frontiers | Research Topics

Current trends and approaches in the comprehensive evaluation of coronary artery disease

Edited by
Dobrin Vassilev, Robert Gil and Gianluca Rigatelli

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-3883-8
DOI 10.3389/978-2-8325-3883-8

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Current trends and approaches in the comprehensive evaluation of coronary artery disease

Topic editors

Dobrin Vassilev — University of Ruse, Bulgaria

Robert Gil — Invasive `Department of the Centre of Postgraduate Medical Education, Poland

Gianluca Rigatelli — Hospital Santa Maria della Misericordia of Rovigo, Italy

Citation

Vassilev, D., Gil, R., Rigatelli, G., eds. (2023). *Current trends and approaches in the comprehensive evaluation of coronary artery disease*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3883-8

Table of contents

06 Editorial: Current trends and approaches in the comprehensive evaluation of coronary artery disease
Gianluca Rigatelli, Dobrin Vassilev and Robert Gil

08 Complete Blood Count-Derived Indices as Prognostic Factors of 5-Year Outcomes in Patients With Confirmed Coronary Microvascular Spasm
Jacek Bil, Natalia Pietraszek, Robert J. Gil, Leszek Gromadziński, Dariusz Onichimowski, Rakesh Jalali and Adam Kern

16 The role of blood CXCL12 level in prognosis of coronary artery disease: A meta-analysis
Shunrong Zhang, Yu Ding, Fei Feng and Yue Gao

31 Association of endothelial glycocalyx shedding and coronary microcirculation assessed by an angiography-derived index of microcirculatory resistance in patients with suspected coronary artery disease
Yang Liu, Si Chen, Shaoyan Liu, Guoqiang Sun, Zhijun Sun and Hongbin Liu

43 Colchicine and coronary heart disease risks: A meta-analysis of randomized controlled clinical trials
Zijun Ma, Jun Chen, Kaiqin Jin and Xin Chen

60 Soluble ST2 in coronary artery disease: Clinical biomarkers and treatment guidance
Junyan Zhang, Zhongxiu Chen, Min Ma and Yong He

67 Prognostic impact of incident left ventricular systolic dysfunction after myocardial infarction
Goro Yoshioka, Atsushi Tanaka, Nozomi Watanabe, Kensaku Nishihira, Masahiro Natsuaki, Atsushi Kawaguchi, Yoshisato Shibata and Koichi Node

78 Using artificial intelligence in the development of diagnostic models of coronary artery disease with imaging markers: A scoping review
Xiao Wang, Junfeng Wang, Wenjun Wang, Mingxiang Zhu, Hua Guo, Junyu Ding, Jin Sun, Di Zhu, Yongjie Duan, Xu Chen, Peifang Zhang, Zhenzhou Wu and Kunlun He

89 The impact of coronary microvascular dysfunction on the discordance between fractional flow reserve and resting full-cycle ratio in patients with chronic coronary syndromes
Jacek Legutko, Lukasz Niewiara, Bartlomiej Guzik, Piotr Szolc, Jakub Podolec, Marcin Nosal, Marta Diachyshyn, Krzysztof Zmudka and Paweł Kleczynski

97 Anomalous left coronary artery from the pulmonary artery: Outcomes and management of mitral valve
Juemin Yu, Qiushi Ren, Xiaobing Liu, Tianyu Chen, Rong Liufu, Shusheng Wen, Jimei Chen, Jianzheng Cen and Jian Zhuang

105 Provisional stenting with side branch rescue stenting is associated with increased 3-year target lesion failure in patients with acute coronary syndrome and coronary bifurcation lesions
Imad Sheiban, Zhen Ge, Jing Kan, Jun-Jie Zhang, Teguh Santoso, Muhammad Munawar, Fei Ye, Nailiang Tian and Shao-Liang Chen on behalf of DKCRUSH Investigators

117 Association between plasma vitamin B5 and coronary heart disease: Results from a case-control study
Pengfei Sun, Haoyu Weng, Fangfang Fan, Nan Zhang, Zhihao Liu, Ping Chen, Jia Jia, Bo Zheng, Tieci Yi, Yuxi Li, Yan Zhang and Jianping Li

127 Timing of angiography and outcomes in patients with non-ST-segment elevation myocardial infarction: Insights from the evaluation and management of patients with acute chest pain in China registry
Yu Han, Shukun Sun, Bao Qiao, Han Liu, Chuanxin Zhang, Bailu Wang, Shujian Wei and Yuguo Chen

137 Left vs. right radial approach for coronary catheterization: Relation to age and severe aortic stenosis
Maximilian Will, Thomas W. Weiss, Michael Weber, Chun Shing Kwok, Josip A. Borovac, Gudrun Lamm, Markus Unterdechler, Simone Aufhauser, Jim Nolan, Julia Mascherbauer and Konstantin Schwarz

145 Predictors of adherence of enhanced external counterpulsation in patients with coronary heart disease after discharge: A mixed-methods study
Yuhuan Yin, Qinli He, Rong Zhang, Hu Cheng, Yiyin Zhang and Juxia Zhang

155 Evaluation of risk stratification program based on trajectories of functional capacity in patients with acute coronary syndrome: The REACP study
Dongze Li, Xiaoli Chen, Fanghui Li, Yu Jia, Zhilin Li, Yi Liu, Lei Ye, Yongli Gao, Wei Zhang, Hong Li, Rui Zeng, Zhi Wan, Zhi Zeng and Yu Cao

167 Construction and evaluation of nomogram model for individualized prediction of risk of major adverse cardiovascular events during hospitalization after percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction
Caoyang Fang, Zhenfei Chen, Jinig Zhang, Xiaoqin Jin and Mengsi Yang

179 Prognostic impact of white blood cell counts on clinical outcomes in patients with chronic renal insufficiency undergoing percutaneous coronary intervention
Wei Yan, Mengyao Li, Yumeng Lei, Shuaiyong Zhang, Fengfeng Lv, Jiawang Wang, Qian Yang, Na Yu, Ming Chen, Xufen Cao and Liqiu Yan

190 Left atrial function index predicts poor outcomes in acute myocardial infarction patients treated with percutaneous coronary intervention
Yijin Tang, Siling Peng, Hui-ling Yao, Zhibin Liu, Liang Zhang, Changqing Zhong, Chang She, Wei Liu, Yi Tang, Qinghua Fu and Yi Zhang

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 23 October 2023
DOI 10.3389/fcvm.2023.1306413

OPEN ACCESS

EDITED AND REVIEWED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

*CORRESPONDENCE
Gianluca Rigatelli
gianluca.rigatelli@aulss6.veneto.it

RECEIVED 03 October 2023
ACCEPTED 09 October 2023
PUBLISHED 23 October 2023

CITATION
Rigatelli G, Vassilev D and Gil R (2023) Editorial: Current trends and approaches in the comprehensive evaluation of coronary artery disease.
Front. Cardiovasc. Med. 10:1306413.
doi: 10.3389/fcvm.2023.1306413

Editorial: Current trends and approaches in the comprehensive evaluation of coronary artery disease

Gianluca Rigatelli[1]*, Dobrin Vassilev[2] and Robert Gil[3]

[1]UOS Emodinamica e Cardiologia Interventistica, Ospedali Riuniti Padova Sud, AULSS6 Euganea, Monselice, Italy, [2]Department of Cardiology, University of Ruse, Ruse, Bulgaria, [3]Invasive Department, Centre of Postgraduate Medical Education, Warsaw, Poland

KEYWORDS

coronary artery disease, atherosclerosis, diagnostic, therapy, pathophysiology

Editorial on the Research Topic
Current trends and approaches in the comprehensive evaluation of coronary artery disease

Coronary artery disease (CAD) continues to be a significant cause of mortality worldwide in the field of chronic degenerative diseases. For this reason, any attempt aimed to understanding its pathophysiologic basis, proper management, and therapy is worthy of efforts in order to improve both diagnosis and treatment outcomes. The present focused issue of Frontiers in Cardiovascular Medicine aims to provide an insight on the current evaluation of CAD by compiling the latest and most up-to-date research studies. The included papers can be broadly categorized as follows: (a) studies pertaining to molecules and biomarkers associated with CAD that are useful for an early diagnosis and understanding of its pathophysiology; (b) studies examining the prognostic factors capable of predicting clinical outcomes; and (c) practical clinical studies focusing on treatment methods such as drugs and percutaneous interventions.

Among the initial set of papers, Sun et al. explored the relationships between plasma Vitamin B5 and CAD, suggesting that plasma vitamin B5 has an L-shaped relationship with CAD, with a threshold at approximately 40.95 ng/ml. Intriguingly, the observed association was influenced by smoking. Zhang et al. reviewed the role of suppression of tumorigenicity 2 (ST2), a member of the interleukin 1 (IL-1) receptor family, and formally known as interleukin 1 receptor-like 1 (IL1RL-1), as a potential biomarker and prognostic factor in the diagnosis and management of CAD. This biomarker is indicative of the extent of plaque accumulation and has the potential to predict the occurrence of no-reflow events, as well as the prognosis of patients. Bil et al. investigated the role of distribution width (DW) and red cell distribution width (RDW) in the diagnosis of coronary microvascular spasm in patients undergoing acetylcholine test. The findings of the study indicated a correlation between both DW and RDW and poor prognosis in patients over a 5-year period.

In an elegant meta-analysis, Zhang et al. showed how an elevated blood CXCL12 level was associated with an increased occurrence of MACEs in patients with CAD, and could potentially serve as an important prognostic index for CAD. Similarly, Yan et al. demonstrated that high white blood cell (WBC) count was associated with the risk of

occurrence of all-cause mortality and cardiac mortality, myocardial infarction, stroke, unplanned revascularization, and major adverse cardiovascular and cerebrovascular events following PCI. On the contrary, Liu et al. utilized an angiography-derived index of microcirculatory resistance to demonstrate that elevated levels of syndecan-1, a component of endothelial glycocalyx (EG) that plays a crucial role in maintaining microvascular homeostasis, are independently associated with the presence of coronary microvascular dysfunction and an impaired microvascular vasodilatory capacity in patients with suspected CAD.

In the second group of papers, Yoshioka et al. explored the prognostic impact of incident left ventricular systolic dysfunction following myocardial infarction, suggesting how incident LV systolic dysfunction during the chronic phase following acute myocardial infarction (AMI) was significantly associated with long-term adverse outcomes. Similarly, Tang et al. showed that LAFI was a strong and independent predictor of adverse events and can be used for risk stratification in patients with AMI treated with PCI. In a retrospective study conducted by Fang et al., it was suggested that urea nitrogen, Killip class II–IV, LVEF, and NT-ProBNP are independent factors associated with in-hospital MACE after PCI in STEMI patients, and nomogram models constructed based on the aforementioned factors have high predictive efficacy and feasibility.

The third and last group of papers included more clinically oriented studies. Sheiban et al. provided an insight of the treatment of coronary bifurcation using either one or two stent strategy. The rescue salvaging of the side branch in their patients was found to be associated with a higher rate of 3-year target lesion failure (TLF), particularly when predilated. Han et al. reported the results of the China Registry on NSTEMi patients, suggesting that the early invasive strategy did not reduce the incidence of MACEs and mortality within 30 days compared with the delayed invasive strategy. Will et al. confirmed that the left transradial angiography is associated with a higher first-pass catheter success rate for coronary artery angiography compared with the right transradial approach. Legutko et al. suggested that in discrepant resting full-cycle ratio (RFR)/flow fractional reserve (FFR) vessels, coronary microvascular dysfunction is more prevalent than in concordant RFR/FFR measurements. According to a study of Li et al., the implementation of a risk stratification program utilizing the Barthel index during hospitalization has the potential to predict outcomes in acute coronary syndrome (ACS) patients.

In terms of CAD treatment, Yin et al. confirmed that enhanced external counter pulsation has poor compliance. Conversely, a meta-analysis conducted by Ma et al. has demonstrated that Colchicine has a positive effect in reducing the incidence of MACE, MI, stroke, and revascularization, but may increase the risk of gastrointestinal complications and diarrhea. Yu et al. have presented an interesting insight on the anomalous origin of the coronary artery from the pulmonary artery in patients who have undergone mitral valve surgery. In addition to the aforementioned studies, Wang et al. conducted a review of the available evidence pertaining to the use of artificial intelligence in developing diagnostic models for coronary artery disease with imaging markers.

The studies presented are intriguing and surely able to stimulate the interest of readers. The clinical insights provided in each publication are anticipated to be incorporated into the research and clinical practices of cardiovascular professionals around the world.

Author contributions

GR: Writing – Original draft. DV: Supervision, Writing – Review and editing. RG: Supervision, Writing – Review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 30 June 2022
doi: 10.3389/fcvm.2022.933374

Complete Blood Count-Derived Indices as Prognostic Factors of 5-Year Outcomes in Patients With Confirmed Coronary Microvascular Spasm

*Jacek Bil[1], Natalia Pietraszek[2], Robert J. Gil[1,2], Leszek Gromadziński[3], Dariusz Onichimowski[4,5], Rakesh Jalali[6,7] and Adam Kern[3,8]**

[1] Department of Invasive Cardiology, Center of Postgraduate Medical Education, Warsaw, Poland, [2] Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland, [3] Department of Cardiology and Internal Medicine, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland, [4] Department of Anesthesiology and Intensive Care, School of Medicine, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland, [5] Clinical Department of Anesthesiology and Intensive Care, Regional Specialist Hospital in Olsztyn, Olsztyn, Poland, [6] Emergency Medicine Department, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland, [7] Clinical Emergency Department, Regional Specialist Hospital in Olsztyn, Olsztyn, Poland, [8] Department of Cardiology, Regional Specialist Hospital in Olsztyn, Olsztyn, Poland

OPEN ACCESS

Edited by:
Turgay Celik, VM Medical Park Ankara (Kecioren), Turkey

Reviewed by:
Hiroki Teragawa, JR Hiroshima Hospital, Japan
Tommaso Gori, Johannes Gutenberg University Mainz, Germany

***Correspondence:**
Adam Kern
adamkern@mail.com
orcid.org/0000-0003-3341-3701

Specialty section:
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

Received: *30 April 2022*
Accepted: *15 June 2022*
Published: *30 June 2022*

Citation:
Bil J, Pietraszek N, Gil RJ, Gromadziński L, Onichimowski D, Jalali R and Kern A (2022) Complete Blood Count-Derived Indices as Prognostic Factors of 5-Year Outcomes in Patients With Confirmed Coronary Microvascular Spasm. Front. Cardiovasc. Med. 9:933374. doi: 10.3389/fcvm.2022.933374

Background: Coronary microcirculatory dysfunction is a meaningful factor in the development of ischemic heart disease. We investigated the relationship between coronary microvascular spasm and complete blood count indices.

Methods: Between 2010 and 2013, we performed acetylcholine test (AChT) in subjects with suspicion of angina evoked by epicardial coronary spasm or coronary microvascular spasm according to COVADIS criteria. We administered acetylcholine in increasing doses of 25, 50, and 75 μg into the right coronary artery and 25, 50, and 100 μg into the left coronary artery. Patients were followed up for 60 months.

Results: In total, 211 patients (60.5 ± 7.8 years, 67.8% women) were included in the study. The AChT revealed angina due to epicardial coronary spasm in 99 patients (46.9%) and coronary microvascular spasm in 72 (34.1%). White blood cell (WBC), red blood cell distribution width (RDW), platelets (PLT), mean platelet volume (MPV), and platelet distribution width (PDW) values were significantly higher in patients with coronary microvascular spasm than in patients from the other two groups, i.e., epicardial coronary spasm and negative AChT. PDW showed the highest sensitivity (65%) and specificity (72%) at the cutoff value of 15.32% [area under the curve, 0.723; 95% confidence interval (CI) 0.64–0.83; $P < 0.001$]. Independent risk factors for coronary microvascular spasm diagnosis using AChT were as follows: female sex (OR, 1.199), PDW (OR, 2.891), and RDW (OR, 1.567).

Conclusion: PDW and RDW are significantly associated with the diagnosis of coronary microvascular spasm in patients undergoing AChT as well as with poor prognosis in such patients at 5 years.

Keywords: RDW, PDW, MPV, acetylcholine test, coronary microcirculation

INTRODUCTION

Coronary microcirculatory dysfunction is a meaningful factor in the development of ischemic heart disease (IHD). The long-term prognosis of coronary microcirculatory dysfunction is often thought to be relatively benign. Nevertheless, standard medical management including vasodilators is often ineffective and sometimes cannot prevent myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) or fatal arrhythmias (1–3).

Although angiographic provocation testing for epicardial coronary spasm or coronary microcirculatory dysfunction is available, still many clinicians concentrate only on atherosclerotic stenoses, with less emphasis on other potential causes like coronary spasm. Therefore, it is vital to raise more awareness on epicardial coronary spasm or coronary microcirculatory dysfunction in clinicians, but also to identify reliable markers for screening patients who may be candidates for a more proactive clinical investigation embracing provocative acetylcholine test (AChT) (4–6).

Interestingly, the red blood cell (RDW) and platelet (PDW) distribution widths reportedly are strong predictors of the frequency as well as the outcomes of various cardiovascular diseases (CVD) (7–10). The mechanism for the links between increased RDW or PDW values and the CVD prognosis remain unclear. Nevertheless, recent studies indicated that an interplay between endothelial dysfunction, chronic inflammatory response as well as oxidative stress might explain this association (2, 3, 11).

In the literature not many studies have assessed this issue, such as those evaluating RDW's predictor role in cardiac syndrome X (12), RDW in vasospastic angina (13), RDW and plateletcrit (Pct) in slow flow phenomenon assessment (14), and neutrophil-to-lymphocyte ratio (NLR) and index of microcirculatory resistance in patients with ST-segment elevation MI undergoing primary percutaneous coronary intervention (15). To our knowledge, there is no data on the association of complete blood count indices with microvascular spasm evaluated in coronary invasive provocative tests or in MINOCA patients. Therefore, we assessed complete blood count indices as potential markers for long-term outcomes in patients with coronary microvascular spasm. We compared systemic inflammatory markers such as NLR and platelet-to-lymphocyte ratio (PLR) as well as various red blood cells and platelet (PLT) indices such as RDW, mean PLT volume (MPV), PDW, and Pct.

MATERIALS AND METHODS

Study Population and Study Plan

It was a prospective observational study. We included patients enrolled to the AChPOL Registry between December 2010 and March 2013 (**Figure 1**) (16). We performed AChT in patients who underwent diagnostic coronary angiography, had non-obstructive coronary arteries (no epicardial stenosis $\geq$ 50%), and were referred for further investigation due to suspicion of angina evoked by epicardial coronary spasm or coronary microcirculatory dysfunction according to Coronary Vasomotion Disorders International Study Group (COVADIS) criteria (17). The exclusion criteria were as follows: (1) severe chronic obstructive pulmonary disease, (2) chronic kidney disease with serum creatinine $>$ 2.0 mg/dL, (3) observed spontaneous spasm, (4) PLTs were $<$ 100,000/μL, (5) active malignancy or (6) active infection.

The institutional review board approved the registry protocol, and all patients provided written informed consent before enrollment to the AChPOL Registry. Study reporting conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement along with references to the STROBE statement and the broader Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines (18).

Interventional Procedure and Concomitant Medications

All patients underwent intracoronary provocation with acetylcholine (ACh) according to a standardized protocol. We administered increasing ACh doses over a period of 3 min into the coronary arteries *via* a diagnostic catheter [25, 50, and 100 μg for the left coronary artery (LCA), 25, 50, and 75 μg for the right coronary artery (RCA)] (17, 19, 20). We judged the AChT as positive for epicardial coronary spasm when we observed focal or diffuse reduction of epicardial coronary diameter $\geq$ 90% comparing to baseline view (following intracoronary nitroglycerine infusion) together with evoking patient's symptoms and ischemic electrocardiographic (ECG) changes. We also recorded the location and type of epicardial coronary spasm. Focal spasm was defined as vessel narrowing within one isolated or two adjacent coronary segments according to the segment definition of the American Heart Association. Diffuse spasm was recognized when present in $\geq$ two neighboring coronary segments. Coronary microvascular spasm was recognized when typical ischemic ST-segment changes and angina developed with epicardial coronary spasm $<$ 90% in diameter reduction. Patients with no angina, spasm, or ST-segment changes were judged to have a negative AChT response (normal coronary vasoreactivity) (17, 21, 22). In coronary arteries with stenoses of $>$ 40% the fractional flow reserve was done, mostly during the initial coronary angiography (20).

Clinical Follow-Up and Endpoints

All patients were discharged on optimal medical treatment, including calcium channel blockers (CCB) uptitrated at the highest tolerated doses. Adverse events were recorded throughout the follow-up period. Follow-up was performed at 12, 24, 36, 48, and 60 months by telephone and/or at clinical visits.

We assessed the rates of death from any cause, cardiac death, recurrent acute coronary syndrome (ACS), and recurrent angina requiring hospitalization. Cardiac death was defined as death from an acute MI, sudden cardiac death, and death due to heart failure and cardiac procedures. All death cases were deemed cardiac unless proven otherwise. MI was defined according to the third universal definition (23).

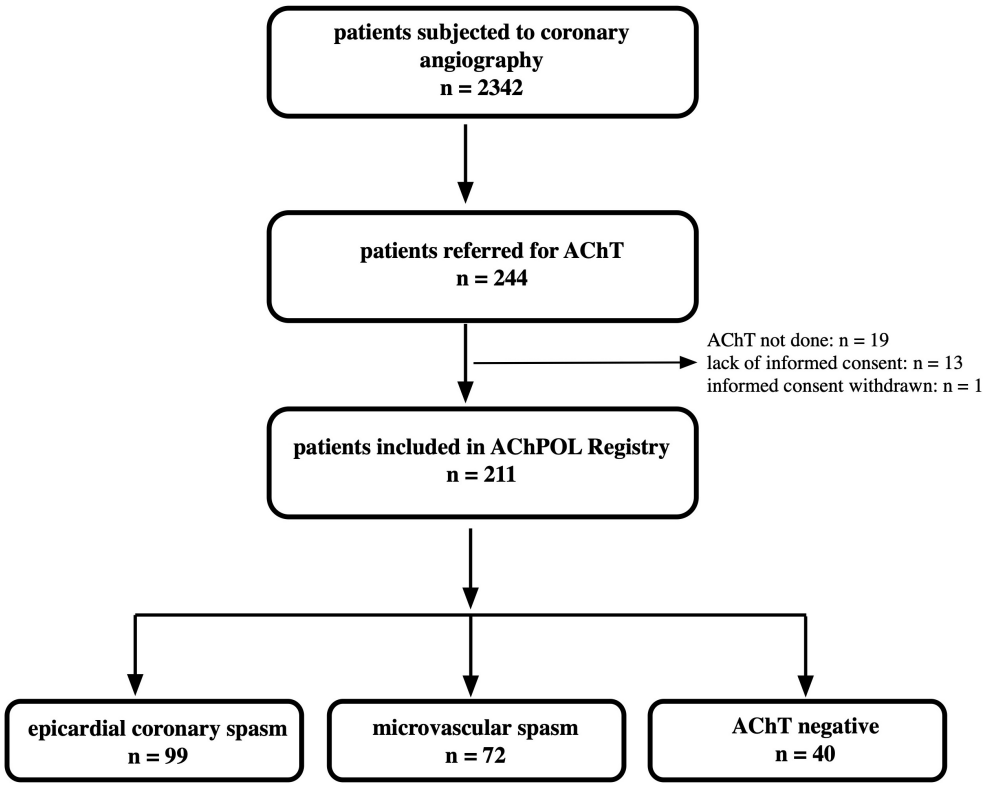


FIGURE 1 | The study flowchart. AChT, acetylcholine test.

Laboratory Tests

For complete blood count measurement, venous blood samples were collected in K2-ethylenediaminetetraacetic acid (EDTA) tubes at admission before performing catheterization and AChT. The neutrophil, lymphocyte, PLT, MPV, PDW, and RDW values were analyzed on an automated hematologic analyzer (Sysmex Corporation, Kobe, Japan) within 60 min after sample collection. The laboratory reference values were as follows: PLT 150 to 400 $\times$ 10^9/L; MPV 9.4–12.4 fL; PDW 9.0–17.0 fL, RDW 11.5%–15%, NLR 1.2–4, and PLR 75–199.

Statistical Analysis

We present the data as means [standard deviation (SD)] or median [interquartile range (IQR)] or percentage. We used the χ^2 or Fisher's exact test in all categorical variables, while one-way analysis of variance or the Kruskal–Wallis *H* test was used for all continuous variables. *Post hoc* analyses using 2-tailed Tukey's honestly significant difference test were conducted to verify the differences between the groups. No corrections for multiple comparisons were applied.

In the next step, univariable and multivariable logistic regression analyses were conducted to evaluate the impact of potential risk factor on odds of microvascular spasm diagnosis. The stepwise backward regression with AIC minimization procedure was used on full multivariable model in variables selection for reduced multivariable model. Then, we used receiver-operating characteristic (ROC) curves to assess the diagnostic values of analyzed parameters.

Finally, the time to event data was investigated with the Kaplan–Meier estimator of survival curve, and a log-rank test was applied to evaluate the survival distributions between groups according to AChT results. To identify independent predictors of MI/chest pain hospitalizations in coronary microvascular spasm group at 5 years we used Cox proportional hazard regression models. Demographic, clinical and laboratory parameters that significantly differed between subgroups according to the AChT result were included into the model.

Level of statistical significance was set as 0.05. Two-sided tests were applied. We performed statistical analyses with R 3.0.2 for OS (R Foundation, Vienna, Austria). As stated previously, no formal sample size calculation was performed, as the study had explorative character and the patients' number was restricted by the number of patients referred for the AChT and length of enrollment period (16).

RESULTS

The enrollment period was from December 2010 to March 2013. We analyzed 211 patients [mean age 60.5 $\pm$ 7.8 years, 143 women (67.8%)] who underwent the AChT and for whom all required laboratory tests were available. Relatively high hypertension

(62.6%, n = 132) and dyslipidemia (45.5%, n = 96) rates were observed. **Table 1** presents the detailed characteristics. The AChT revealed angina due to epicardial coronary spasm in 99 patients (46.9%) and coronary microvascular spasm in 72 (34.1%). In 40 (18.9%) patients, the AChT was negative (no symptoms, no ECG changes, no epicardial spasm, no increased blush).

Table 2 presents 20 complete blood count parameters in three groups. The following parameters were significantly higher in patients with coronary microvascular spasm than in patients from the other two groups, i.e., epicardial coronary spasm and negative AChT: white blood cell (WBC) count, RDW, PLT count, MPV, and PDW. **Figure 2** shows plots for RDW and PDW in all three groups.

Next, we performed univariable and multivariable logistic regression analysis to identify ultimately independent predictors of coronary microvascular spasm diagnosis in AChT. In the multivariable logistic regression analysis, the independent risk factors were female sex [odds ratio (OR), 1.199, 95% CI 1.001–1.329, p = 0.04], PDW (OR, 2.891, 95% CI 1.672–3.932, $p < 0.001$), and RDW (OR, 1.567; 95% CI 1.382–1.987, $p < 0.01$, **Table 3**). No significant findings were shown in angina due to epicardial coronary spasm or negative AChT groups (data not shown).

TABLE 1 | Baseline clinical characteristics.

Parameter	Microvascular spasm N = 72	Epicardial coronary spasm N = 99	Negative AChT N = 40	P
Age [years]	58.4 ± 8.9 ^	59 ± 9.6 ^	68.1 ± 10.8	0.02
Females	60 (83.3) ^	67 (67.7) ^	16 (40)	0.03
Angina:				
Exertional	53 (73.6)	30 (30.3) ^,&	29 (72.5)	0.01
At rest	44 (61.1) ^	71 (71.7) ^	16 (40)	0.02
At night	39 (54.2) ^	62 (62.6) ^	9 (22.5)	0.01
Arterial hypertension	51 (70.8) ^	62 (62.6)	19 (47.5)	0.04
Diabetes type 2	4 (5.6) ^	5 (5.1) ^	7 (17.5)	0.04
Dyslipidemia	46 (63.9) ^,&	35 (35.4)	15 (37.5)	0.01
Prior MI	23 (31.9) ^,&	19 (19.2)	3 (7.5)	0.04
Atrial fibrillation	4 (5.6) ^	7 (7.1) ^	16 (40)	0.02
Thyroid disease	19 (26.4) ^	23 (23.2) ^	1 (2.5)	0.04
Autoimmune disease	5 (6.9)	7 (7.1)	0	0.52
Peptic ulcer disease	12 (16.7)	13 (13.1)	10 (25)	0.19
Smoking	11 (15.3) ^	22 (22.2) ^	2 (5)	0.04
Medications at discharge:				
ASA	57 (79.2)	64 (64.5) ^	26 (65.0)	0.02
β-blocker	36 (50.0)	7 (7.1)*, ^	21 (52.5)	0.00
Calcium blocker	42 (58.3) ^	99 (100.0) ^	9 (22.5)	0.00
ACEI/ARB	51 (70.8)	61 (61.6)	29 (72.5)	0.56
Statins	65 (90.3)	77 (77.8)	35 (87.5)	0.23
Nitrates	9 (12.5)	32 (32.3) ^	2 (5.0)	0.03
Trimetazidine	23 (31.9) ^	22 (22.2) ^	8 (20.0)	0.01
VKA	4 (5.6) ^	7 (7.1) ^	16 (40)	0.02

**Nebivolol; ^p < 0.05 angina due to epicardial coronary spasm/microvascular spasm vs. AChT negative; &p < 0.05 angina due to epicardial coronary spasm vs. microvascular spasm. ACEI, inhibitor of angiotensin convertase enzyme; AChT, provocative test with acetylcholine; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; MI, myocardial infarction; VKA, vitamin K antagonist.*

TABLE 2 | Comparison of values of 20 complete blood count parameters between groups.

Parameter	Microvascular spasm N = 72	Epicardial coronary spasm N = 99	Negative AChT N = 40	P
WBC [x10^3/μL]	9.11 ± 3.34&, ^	8.52 ± 2.68	8.11 ± 3.22	0.04
RBC [x10^6/μL]	4.55 ± 0.62	4.68 ± 0.54	4.43 ± 0.36	0.732
HGB [g/dL]	13.92 ± 1.83	14.08 ± 1.54	14.19 ± 1.21	0.652
HCT [%]	40.82 ± 4.54	41.75 ± 4.07	41.79 ± 5.04	0.783
MCV [fL]	88.45 ± 4.77	89.79 ± 5.03	90.01 ± 4.67	0.689
MCH [pg]	30.13 ± 4.37	30.66 ± 5.00	30.78 ± 3.63	0.723
MCHC [g/dL]	33.04 ± 1.09	33.74 ± 1.14	33.90 ± 1.25	0.451
RDW [%]	14.95 ± 2.01&, ^	13.77 ± 2.43	13.23 ± 1.89	< 0.001
PLT [x10^3/μL]	267 ± 89	231 ± 125	245 ± 145	0.003
MPV [fL]	11.92 ± 0.89 ^	10.88 ± 1.10	10.11 ± 0.78	< 0.001
PCT [%]	0.23 ± 0.08	0.18 ± 0.23	0.18 ± 0.09	0.122
PDW [%]	16.76 ± 5.33 ^	14.15 ± 9.28	13.91 ± 6.39	< 0.001
LYM [x10^3/μL]	3.34 ± 1.95	3.19 ± 2.38	3.01 ± 2.55	0.09
MON [x10^3/μL]	0.48 ± 0.11	0.43 ± 0.01	0.46 ± 0.12	0.442
NEU [x10^3/μL]	5.05 ± 2.34	4.78 ± 2.02	4.44 ± 2.87	0.549
EOS [x10^3/μL]	0.20 ± 0.08	0.11 ± 0.07	0.15 ± 0.02	0.244
BASO [x10^3/μL]	0.04 ± 0.01	0.01 ± 0.01	0.05 ± 0.01	0.577
NLR	1.58 ± 0.29	1.49 ± 0.57	1.40 ± 0.34	0.06
PLR	79.94 ± 44.90	72.41 ± 35.62	81.3 ± 43.54	0.192

^p < 0.05 angina due to epicardial coronary spasm/microvascular spasm vs AChT negative; &p < 0.05 angina due to epicardial coronary spasm vs microvascular spasm. BASO, basophil count; EOS, eosinophil count; HCT, hematocrit; HGB, hemoglobin; LYM, lymphocyte count; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; MON, monocyte count; MPV, mean platelet volume; NEU, neutrophil count; NLR, neutrophil-lymphocyte ratio; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet-lymphocyte ratio; PLT, platelet count; RBC, red blood cell count; RDW, red cell distribution width; WBC, white blood cell count.

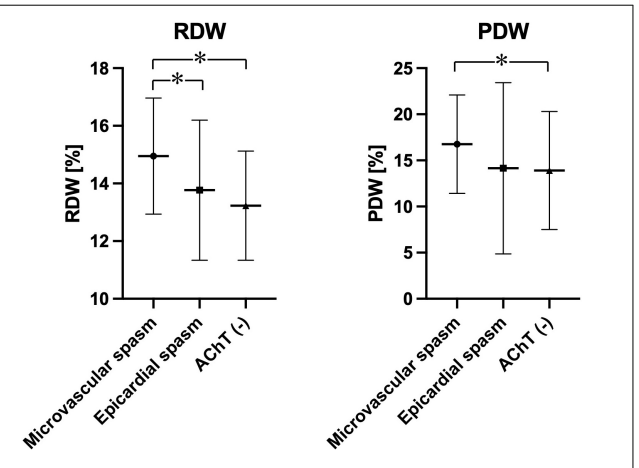


FIGURE 2 | Plots showing RDW and PDW in the study population depending on the AChT result. *$p < 0.05$.

Furthermore, a ROC analysis was performed for PDW and RDW as markers in predicting coronary microvascular spasm. PDW showed the highest sensitivity (65%) and specificity (72%) at the cutoff value of 15.32% [area under the curve (AUC), 0.723; 95% confidence interval (CI) 0.64–0.83; $P < 0.001$], and RDW characterized the following parameters: sensitivity (61%) and

TABLE 3 | Independent predictors in multivariable logistic regression analysis and Cox regression analysis.

Variable	Multivariable analysis	
	OR (95% CI)	***P***
Independent predictors of coronary microvascular spasm		
Female sex	1.199 (1.001–1.329)	0.04
MPV	1.112 (0.988–1.342)	0.06
PDW	2.891 (1.672–3.932)	< 0.001
RDW	1.567 (1.382–1.987)	0.0043
	HR (95% CI)	**P**
Independent predictors of MI/chest pain hospitalizations in coronary microvascular spasm group at 5 years		
Female sex	1.433 (1.288–1.782)	0.03
MPV	1.101 (1.002–1.345)	0.04
PDW	2.923 (1.789–3.332)	< 0.001
RDW	1.732 (1.431–2.344)	0.003

MPV, mean platelet volume; PDW, platelet distribution width; RDW, red cell distribution width.

specificity (69%) at the cut-off value of 14.12% (AUC 0.642; 95% CI 0.543–0.738; $P < 0.001$).

At the 5-year follow-up (median, 55 months; range, 48–60 months), in the coronary microvascular spasm group, there were two non-cardiac deaths (2.8%), while six MIs (5.6%) and recurrent chest pain requiring hospitalization were observed in 19 patients (26.4%) (**Figure 3**). In all patients with MI control angiography was performed. In case of recurrent chest pain requiring hospitalization, control angiography was mainly performed after 18–24 months since the baseline AChT. Only in two patients (after 48 months and after 54 months) significant stenoses developed, and in one patient, after fractional flow reserve assessment, percutaneous coronary intervention with stent deployment was performed. In **Table 4** we present data of clinical outcomes at 5 years in all three groups. Patients with microvascular spasm characterized the highest rate of recurrent chest pain leading to hospitalization, i.e., 26.4% vs. 12.1% in epicardial coronary spasm vs. 7.5% in AChT negative group ($p = 0.02$).

In consequence, we performed Cox regression analysis to identify independent predictors of MI/chest pain hospitalization in the coronary microvascular spasm group: female sex (HR, 1.433, 95% CI 1.288–1.782, $p = 0.03$), MPV (HR, 1.101, 95% CI 1.002–1.345, $p = 0.04$), PDW (HR, 2.923, 95% CI 1.789–3.332, $p < 0.001$) and RDW (HR, 1.732; 95% CI 1.431–2.344, $p = 0.003$, **Table 3**).

DISCUSSION

To the best of our knowledge, our study is the first to investigate the predictive value of complete blood count indices in patients with coronary microvascular spasm. We showed that PDW and RDW were significantly associated with the diagnosis of coronary microvascular spasm in patients undergoing AChT as well as with poor prognosis in such patients at the 5-year follow-up.

The RDW is a measure of red blood cell volume variations (anisocytosis) and can be easily obtained during a routine complete blood count (24). In general, RDW is used in the differential diagnosis of anemia, especially that caused by deficiencies in mineral and vitamin levels, i.e., vitamin B_{12}, folate, and iron. However, many reports have shown that elevated RDW level can be associated with CVDs and might be used as a predictor of high mortality in IHD patients (25), heart failure (26), and acute MI and also in the general population (27).

Although MPV was always considered a good predictor in cardiac patients, PDW currently is considered a more specific PLT reactivity factor (28). The PDW is a parallel measure

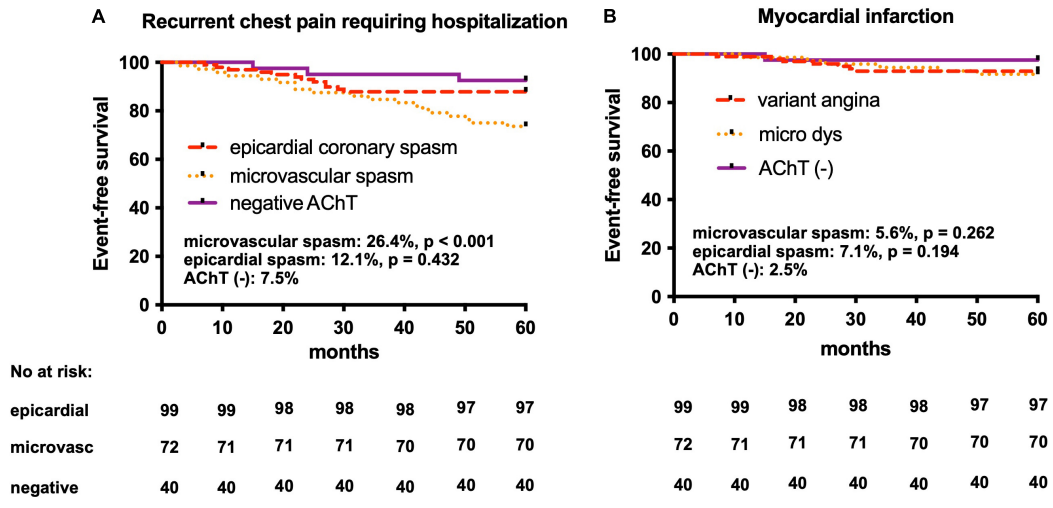


FIGURE 3 | Kaplan–Meier curves in the AChPOL population. **(A)** Event-free survival from recurrent chest pain events requiring hospitalization at 5-year follow-up in three groups: epicardial coronary spasm, microvascular spasm and negative AChT **(B)** Event-free survival form myocardial infarction at 5-year follow-up in three groups: epicardial coronary spasm, microvascular spasm and negative AChT. AChT, provocative test with acetylcholine. Log-rank test: epicardial spasm vs. AChT negative groups and microvascular spasm vs. AChT negative groups.

TABLE 4 | 5-year clinical outcomes based on AChT.

Outcome N (%)	Total population *N* = 211	Microvascular spasm *N* = 72	Epicardial coronary spasm *N* = 99	Negative AChT *N* = 40	*P*
Recurrent chest pain requiring hospitalization	34 (16.1)	19 (26.4)	12 (12.1)	3 (7.5)	0.02
Myocardial infarction	14 (6.6)	6 (5.6)	7 (7.1)	1 (2.5)	0.23
Cardiac death	1 (0.5)	0	1 (1.0)	0	0.89
Death	4 (1.9)	2 (2.8)	2 (2.0)	0	0.67

AChT, acetylcholine provocative test.

to RDW because it shows PLT volume variations (PLTs vary in size and number of pseudopodia) (29). Elevated PDW indicates coagulation activation. PDW is valuable in predicting left ventricular dysfunction in ACS patients undergoing percutaneous coronary interventions (28). PDW has also been associated with the IHD severity in ACS patients (30).

Recently, Bekler et al. investigated that higher PDW (>17%) can be connected to the severity of CAD in patients with acute cardiac syndrome (30). According to the study, the higher the PDW, the higher also the Gensini score (a scoring system that determines the severity of CAD) (OR, 1.91; 95% CI, 1.27–2.88; $P = 0.002$). However, higher Gensini score also was associated with diabetes mellitus and MI (OR, 2.85; 95% CI, 1.91–4.25; $P < 0.001$ and OR, 2.67; 95% CI, 1.74–4.1; $P < 0.001$, respectively). Nevertheless, no correlation between PDW or MPV and the prevalence and severity of CAD (OR 0.99; 95% CI, 0.90–1.09; $P = 0.87$ and OR, 1.05; 95% CI, 0.95–1.16; $P = 0.3$; and adjusted OR, 0.97; 95% CI, 0.87–1.08; $P = 0.63$; respectively) was found in a large cohort study by De Luca et al. (31).

One key equivalent of coronary microcirculatory dysfunction is slow coronary flow (SCF) phenomenon, which can be recognized as a postponed distal vessel opacification without significant stenosis on coronary angiography. The mechanism of this angiographic phenomenon persists unclear, although a couple of concepts have been suggested, such as endothelial dysfunction, changes in blood rheological properties, inflammatory state, elevated uric acid concentration or conditions linked with an increased PLT volume. RDW and PDW were investigated to be predictors of the SCF phenomenon. In a retrospective study on 17,315 patients who underwent coronary angiography, Akpinar et al. found that elevated levels of those parameters may contribute to the microvascular blood flow resistance as the deformability of the cells is impaired (14). PDW also was associated with the presence and extent of SCF as reported by Seyyed-Mohammadzad et al. ($P = 0.005$) (32). Similar observations were proved in our study except for the role of Pct value.

Additionally, in our study, although the WBC count was within the normal limits in all groups, WBCs and neutrophils were observed in significantly higher numbers in the coronary microvascular spasm group compared to the other groups. These findings along with the increased RDW suggested that coronary microvascular spasm might be a subclinical inflammatory condition. However, other indices, such as NLR or PLR did not have a significant role. Altogether, the markers of increased inflammatory state which hamper the endothelial dysfunction as well as markers of procoagulant activity may predict ischemic events in coronary microcirculation. This may manifest benign as recurrent chest pain decreasing quality of life. However, it may lead to acute coronary syndromes or malignant ventricular arrhythmias.

Limitations

The number of enrolled patients as well as the number of adverse events at follow-up were relatively low. Also, not enrolling consecutive patients could have been a source of bias. Moreover, high-sensitivity C-reactive protein or other inflammatory markers were not evaluated routinely in subjects undergoing AChT and was not included to verify the inflammatory status. Moreover, due to the limited population only chosen variables were used in the regression model.

CONCLUSION

To the best of our knowledge, our study is the first to investigate the predictive value of complete blood count indices in patients with coronary microvascular spasm. PDW and RDW were significantly associated with the diagnosis of coronary microvascular spasm in patients undergoing AChT as well as with poor prognosis in such patients at 5-year follow-up.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee at the Central Clinical Hospital of the Ministry of Interior and Administration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors planned and performed the study and took active role in manuscript preparation and final approval.

REFERENCES

1. Bil J, Pawlowski T, Gil RJ. Coronary spasm revascularized with a bioresorbable vascular scaffold. *Coron Artery Dis.* (2015) 26:634–6.
2. Sabe SA, Feng J, Sellke FW, Abid MR. Mechanisms and clinical implications of endothelium-dependent vasomotor dysfunction in coronary microvasculature. *Am J Physiol Heart Circ Physiol.* (2022) 322:H819–41. doi: 10.1152/ajpheart.00603.2021
3. Sucato V, Corrado E, Manno G, Amata F, Testa G, Novo G, et al. Biomarkers of coronary microvascular dysfunction in patients with microvascular angina: a narrative review. *Angiology.* (2022) 73:395–406. doi: 10.1177/00033197211034267
4. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, et al. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicentre registry study of the Japanese coronary spasm association. *Eur Heart J.* (2013) 34:258–67. doi: 10.1093/eurheartj/ehs199
5. Spione F, Arevalos V, Gabani R, Sabate M, Brugaletta S. Coronary microvascular angina: a state-of-the-art review. *Front Cardiovasc Med.* (2022) 9:800918. doi: 10.3389/fcvm.2022.800918
6. Perera D, Berry C, Hoole SP, Sinha A, Rahman H, Morris PD, et al. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British heart foundation/National institute for health research partnership. *Heart.* (2022). doi: 10.1136/heartjnl-2021-320718 [Epub ahead of print].
7. Arbel Y, Shacham Y, Finkelstein A, Halkin A, Milwidsky A, Berliner S, et al. Red blood cell distribution width (RDW) and long-term survival in patients with ST elevation myocardial infarction. *Thromb Res.* (2014) 134:976–9.
8. Hou H, Sun T, Li C, Li Y, Guo Z, Wang W, et al. An overall and dose-response meta-analysis of red blood cell distribution width and CVD outcomes. *Sci Rep.* (2017) 7:43420. doi: 10.1038/srep43420
9. Su C, Liao LZ, Song Y, Xu ZW, Mei WY. The role of red blood cell distribution width in mortality and cardiovascular risk among patients with coronary artery diseases: a systematic review and meta-analysis. *J Thorac Dis.* (2014) 6:1429–40. doi: 10.3978/j.issn.2072-1439.2014.09.10
10. Kern A, Gil RJ, Bojko K, Sienkiewicz E, Januszko-Giergielewicz B, Gorny J, et al. Platelet distribution width as the prognostic marker in coronary bifurcation treatment. *Eur J Clin Invest.* (2017) 47:524–30. doi: 10.1111/eci.12773
11. Bil J, Pietraszek N, Pawlowski T, Gil RJ. Advances in mechanisms and treatment options of MINOCA caused by vasospasm or microcirculation dysfunction. *Curr Pharm Des.* (2018) 24:517–31.
12. Demirkol S, Balta S, Celik T, Arslan Z, Unlu M, Cakar M, et al. Assessment of the relationship between red cell distribution width and cardiac syndrome X. *Kardiol Pol.* (2013) 71:480–4. doi: 10.5603/KP.2013.0094
13. Jung MH, Shin DI, Choi IJ, Seo SM, Choi S, Park MW, et al. Association between the red cell distribution width and vasospastic angina in Korean patients. *Yonsei Med J.* (2016) 57:614–20. doi: 10.3349/ymj.2016.57.3.614
14. Akpinar I, Sayin MR, Gursoy YC, Aktop Z, Karabag T, Kucuk E, et al. Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon. *J Cardiol.* (2014) 63:112–8. doi: 10.1016/j.jjcc.2013.07.010
15. Lee MJ, Park SD, Kwon SW, Woo SI, Lee MD, Shin SH, et al. Relation between neutrophil-to-lymphocyte ratio and index of microcirculatory resistance in patients with st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol.* (2016) 118:1323–8. doi: 10.1016/j.amjcard.2016.07.072
16. Bil J, Mozenska O, Segiet-Swiecicka A, Gil RJ. Revisiting the use of the provocative acetylcholine test in patients with chest pain and nonobstructive coronary arteries: a five-year follow-up of the AChPOL registry, with special focus on patients with MINOCA. *Transl Res.* (2021) 231:64–75. doi: 10.1016/j.trsl.2020.11.009
17. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J.* (2017) 38:2565–8.
18. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *Eur J Clin Invest.* (2010) 40:35–53.
19. Group JCSJW. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008): digest version. *Circ J.* (2010) 74:1745–62. doi: 10.1253/circj.cj-10-74-0802
20. Bil J, Tyczynski M, Modzelewski P, Gil RJ. Acetylcholine provocation test with resting full-cycle ratio, coronary flow reserve, and index of microcirculatory resistance give definite answers and improve health-related quality of life. *Kardiol Pol.* (2020) 78:1291–2. doi: 10.33963/KP.15619
21. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol.* (2012) 59:655–62. doi: 10.1016/j.jacc.2011.11.015
22. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation.* (2014) 129:1723–30.
23. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation.* (2012) 126:2020–35.
24. Karakas MS, Korucuk N, Tosun V, Altekin RE, Koc F, Ozbek SC, et al. Red cell distribution width and neutrophil-to-lymphocyte ratio predict left ventricular dysfunction in acute anterior ST-segment elevation myocardial infarction. *J Saudi Heart Assoc.* (2016) 28:152–8. doi: 10.1016/j.jsha.2015.07.001
25. Osadnik T, Strzelczyk J, Hawranek M, Lekston A, Wasilewski J, Kurek A, et al. Red cell distribution width is associated with long-term prognosis in patients with stable coronary artery disease. *BMC cardiovascular disorders.* (2013) 13:113. doi: 10.1186/1471-2261-13-113
26. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M, et al. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation.* (2008) 117:163–8.
27. Uyarel H, Ergelen M, Cicek G, Kaya MG, Ayhan E, Turkkan C, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coron Artery Dis.* (2011) 22:138–44.
28. Kowara M, Grodecki K, Huczek Z, Puchta D, Paczwa K, Rymuza B, et al. Platelet distribution width predicts left ventricular dysfunction in patients with acute coronary syndromes treated with percutaneous coronary intervention. *Kardiol Pol.* (2017) 75:42–7. doi: 10.5603/KP.a2016.0137
29. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. *Hippokratia.* (2010) 14:28–32.
30. Bekler A, Ozkan MT, Tenekecioglu E, Gazi E, Yener AU, Temiz A, et al. Increased platelet distribution width is associated with severity of coronary artery disease in patients with acute coronary syndrome. *Angiology.* (2015) 66:638–43. doi: 10.1177/0003319714545779
31. De Luca G, Secco GG, Verdoia M, Cassetti E, Schaffer A, Coppo L, et al. Combination between mean platelet volume and platelet distribution width to predict the prevalence and extent of coronary artery disease: results from a large cohort study. *Blood Coagul Fibrinolysis.* (2014) 25:86–91. doi: 10.1097/MBC.0b013e32836577a8
32. Seyyed-Mohammadzad MH, Khademvatani K, Kerachian A, Eskandari R, Rezaei Y. Slow coronary flow phenomenon

and increased platelet volume indices. *Korean Circ J.* (2014) 44:400–5.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 27 July 2022
DOI 10.3389/fcvm.2022.938540

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Madhumita Chatterjee,
University of Tübingen, Germany
Donato Santovito,
National Research Council (CNR), Italy

*CORRESPONDENCE
Yue Gao
gy9821@sina.com

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 07 May 2022
ACCEPTED 29 June 2022
PUBLISHED 27 July 2022

CITATION
Zhang S, Ding Y, Feng F and Gao Y (2022) The role of blood CXCL12 level in prognosis of coronary artery disease: A meta-analysis. *Front. Cardiovasc. Med.* 9:938540. doi: 10.3389/fcvm.2022.938540

The role of blood CXCL12 level in prognosis of coronary artery disease: A meta-analysis

Shunrong Zhang[1], Yu Ding[2], Fei Feng[1] and Yue Gao[1]*

[1]Department of Geriatrics, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2]Central Laboratory, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Objective: The role of C-X-C motif chemokine 12 (CXCL12) in atherosclerotic cardiovascular diseases (ASCVDs) has emerged as one of the research hotspots in recent years. Studies reported that the higher blood CXCL12 level was associated with increased major adverse cardiovascular events (MACEs), but the results were inconsistent. The objective of this study was to clarify the prognostic value of the blood CXCL12 level in patients with coronary artery disease (CAD) through meta-analysis.

Methods: All related studies about the association between the blood CXCL12 level and the prognosis of CAD were comprehensively searched and screened according to inclusion criteria and exclusion criteria. The quality of the included literature was evaluated using the Newcastle-Ottawa Scale (NOS). The heterogeneity test was conducted, and the pooled hazard risk (HR) or the odds ratio (OR) with a 95% confidence interval (CI) was calculated using the fixed-effect or random-effects model accordingly. Publication bias was evaluated using Begg's funnel plot and Egger's test. Sensitivity analysis and subgroup analysis were also conducted.

Results: A total of 12 original studies with 2,959 CAD subjects were included in the final data combination. The pooled data indicated a significant association between higher CXCL12 levels and MACEs both in univariate analysis (HR 5.23, 95% CI 2.48–11.04) and multivariate analysis (HR 2.53, 95% CI 2.03–3.16) in the CXCL12 level as the category variable group. In the CXCL12 level as the continuous variable group, the result also indicated that the higher CXCL12 level significantly predicted future MACEs (multivariate OR 1.55, 95% CI 1.02–2.35). Subgroup analysis of the CXCL12 level as the category variable group found significant associations in all acute coronary syndrome (ACS) (univariate HR 9.72, 95% CI 4.69–20.15; multivariate HR 2.47, 95% CI 1.79–3.40), non-ACS (univariate HR 2.73, 95% CI 1.65–4.54; multivariate HR 3.49, 95% CI 1.66–7.33), Asian (univariate HR 7.43, 95% CI 1.70–32.49; multivariate HR 2.21, 95% CI 1.71–2.85), Caucasian (univariate HR 3.90, 95% CI 2.73–5.57; multivariate HR 3.87, 95% CI 2.48–6.04), short-term (univariate HR 9.36, 95% CI 4.10–21.37; multivariate HR 2.72, 95% CI 1.97–3.76), and long-term (univariate HR 2.86, 95% CI 1.62–5.04; multivariate HR 2.38, 95% CI 1.76–3.22) subgroups. Subgroup analysis of the CXCL12 level as the continuous

variable group found significant associations in non-ACS (multivariate OR 1.53, 95% CI 1.23–1.92), Caucasian (multivariate OR 3.83, 95% CI 1.44–10.19), and long-term (multivariate OR 1.62, 95% CI 1.37–1.93) subgroups, but not in ACS (multivariate OR 1.36, 95% CI 0.67–2.75), Asian (multivariate OR 1.40, 95% CI 0.91–2.14), and short-term (multivariate OR 1.16, 95% CI 0.28–4.76) subgroups. No significant publication bias was found in this meta-analysis.

Conclusion: The higher blood CXCL12 level is associated with increased MACEs in patients with CAD, and the blood CXCL12 level may serve as an important prognostic index for CAD. Integrating the blood CXCL12 level into CAD risk assessment tools may provide more comprehensive messages for evaluating and managing patients with CAD.

KEYWORDS

CXCL12, coronary artery disease, acute coronary syndrome, prognosis, MACEs, meta-analysis

Introduction

Heart disease is the leading cause of death worldwide. As the most common type of heart disease, coronary artery disease (CAD) also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD) affects around 126 million individuals globally, which is estimated to be 1.72% of the world's population in 2017 (1). In China, with the aging of the population, the prevalence and mortality of CAD have been increasing continuously within the past two decades (2). Although with the progress of medical care, the prognosis of CAD is still not optimistic, especially in acute coronary syndrome (ACS) (3) and elderly patients (4). Thus, in addition to diagnosis and therapy, evaluation of prognosis or risk stratification for patients with CAD is a clinical matter of great concern.

In fact, many risk stratification tools, such as the GRACE and CRUSADE scores for assessing the risk of patients with non-STEMI ACS (5), have been generated for risk classification for CAD. Although each may have its respective merits, these risk stratification tools are not comprehensive or have some limitations. Thus, exploring new strategies or indicators guiding more precise evaluation of CAD prognosis and directing more optimized treatment of CAD is of great clinical significance. In recent years, the clinical prognostic value of novel biomarkers in CAD has increasingly aroused people's attention (6).

The C-X-C motif chemokine 12 (CXCL12), also known as stromal cell-derived factor-1 (SDF-1), is a chemokine protein that exerts multifaceted roles in atherosclerosis and other cardiovascular diseases through its classical C-X-C motif chemokine receptor 4(CXCR4) and atypical ACKR3 (atypical chemokine receptor 3, also CXCR7) receptors (7, 8). The role of the CXCL12/CXCR4/ACKR3 system in the pathogenesis of cardiovascular diseases was a research hotspot in recent years. Studies reported that CXCL12 gene polymorphisms are associated with an increased risk of CAD (9, 10), and a high blood CXCL12 level predicted high coronary events in diabetes patients (10).

Other studies reported that an increased level of blood CXCL12 predicted adverse clinical outcomes in CAD. Chang et al. first reported that a higher serum CXCL12 level positively predicted 30-day major adverse clinical outcomes in patients with acute myocardial infarction (AMI) (11). Thereafter, several studies supported the positive correlation between higher blood CXCL12 levels and increased risk of future (both short and long terms) adverse clinical outcomes in patients with CAD (12–14). However, negative or even opposite results were also reported, which found no significant correlation between blood CXCL12 levels and CAD prognosis (15), or even higher serum CXCL12 levels predicting lower future cardiovascular events in patients with CAD (16). Thus, the association between blood CXCL12 levels and future major adverse cardiovascular events (MACEs) in patients with CAD seems to be controversial.

A good method to resolve the contradictions between individual studies is meta-analysis. To evaluate the predicting role of the blood CXCL12 level in the prognosis of CAD objectively, we reviewed all the related literature comprehensively and conducted a meta-analysis.

Methods

Search strategy

All related studies about the correlation between blood CXCL12 level and CAD prognosis were identified by comprehensive computer-based searches. The retrieved databases included PubMed, EMBASE, ScienceDirect, Web of Science, and the China National Knowledge Infrastructure

(CNKI) database. The keywords used for the literature search were combined as follows: ("CXCL12" OR "C-X-C motif chemokine ligand 12" OR "SDF-1" OR "stromal cell-derived factor-1 ") and ("coronary artery disease" OR "coronary heart disease" OR "CAD" OR "CHD" OR "ischemic heart disease" OR "myocardial infarction" OR "angina" OR "acute coronary syndrome" OR "STEMI" OR "non-STEMI") and ("prognosis" OR "MACE" OR "major adverse cardiovascular events" OR "adverse outcome"). The last search was updated on 8 June 2022, and the literature language was limited to English and Chinese.

Data inclusion and exclusion criteria

Data inclusion criteria

The inclusion criteria for eligible studies were as follows: (1) studies evaluated the association between the blood CXCL12 level and the prognosis of CAD. (2) The CAD diagnostic criteria were angiographically confirmed CAD or ACS diagnosed with general standard criteria. (3) Studies were published in prospective cohort studies. (4) The follow-up duration was at least 30 days. (5) The actual number of MACEs was presented, or the hazard ratio (HR)/odds ratio (OR) and 95% confidence interval (CI) of blood CXCL12 level and MACEs were provided.

Data exclusion criteria

Exclusion criteria included (1) conference abstracts or reviews; (2) unpublished data; (3) studies with duplicated publications or studies with partially replicated populations; (4) primary endpoints and secondary endpoints were not about death or adverse cardiovascular events; and (5) Newcastle-Ottawa Scale (NOS) score was <6 scores.

Data extraction

Three reviewers (Zhang, Ding, and Feng) extracted key data from each included original study independently, and the extracted data included the name of the first author, publication year, study type, sample size, region, ethnicity of the study population, diagnostic criteria for patients with CAD, methods for measuring CXCL12 level, cutoff or comparison of CXCL12 level, follow-up duration, measurement of clinical outcomes, and covariables adjusted in the multivariate model. For studies in which the CXCL12 level was presented as a continuous variable, we standardized the group-level exposure estimates to single units, thereby allowing for combining the effects of different CXCL12 values in different studies. All the independently extracted data were compared, and disagreements were settled by consensus. If these three authors could not reach a consensus, the results were further arbitrated by the fourth author (Gao).

Literature quality assessment

The quality was assessed and scored using the Newcastle-Ottawa Quality Assessment Scale (NOS) (17) system by two authors independently. The NOS uses a "star" rating system ranging from zero (worst) to nine stars (best) to judge the quality of observational studies, and studies with a total score of ≥7 were generally regarded as high quality. Any disagreements about study quality assessment between the two authors were settled by consensus or consulted by the third author.

Statistical analysis

STATA 16.0 (STATA Corp., College Station, TX, USA) was used to carry on the statistical analysis. The pooled HRs or ORs and 95% CIs were used as the effect indicator to evaluate the predicting role of the blood CXCL12 level in CAD prognosis. According to the different variable types of the CXCL12 level used in each original study, all the included studies were divided into the CXCL12 level as the category variable group and the CXCL12 level as the continuous variable group, and the overall effects were combined separately. Heterogeneity between studies was assessed using the I^2 test, and $I^2 > 50\%$ and $P < 0.1$ were considered existing significant heterogeneity (18). If significant heterogeneity was found, the random-effects pooling model (I-V heterogeneity) was used to evaluate the pooled HRs or ORs (with 95% CIs); otherwise, the fixed-effect pooling model (inverse variance) was used to calculate pooled HRs or ORs (with 95% CIs). The significance of overall effects was tested using the Z-test (19). Subgroup analysis was performed based on different ethnicities, CAD types, and follow-up durations to explore the predicting role of the blood CXCL12 level in the CAD prognosis more comprehensively. Sensitivity analysis was conducted to observe the influence of any single study on the pooled HRs or ORs to evaluate the robustness of overall effects. The potential publication bias was assessed using Begg's funnel plot and Egger's test. Except for the I^2 test for assessing heterogeneity, a 2-tailed $P < 0.05$ was considered to be statistically significant.

Results

Literature search and study characteristics

A total of 1,815 potentially relevant articles were initially identified according to the search criteria described above. After screening titles and abstracts, 1,779 studies were excluded for duplicates, reviews, or being irrelevant. The left 36 articles were entered full-text assessment for eligibility, and 25 articles were further excluded for duplicate data, endpoints not about death or cardiovascular events, study subjects were not patients with

CAD, detected CXCL12 level not in serum/plasma, or could not get outcome measurement data. As a result, a total of 11 articles (12 studies) with 2,959 patients with CAD were included in this meta-analysis for the final data combination. The study screening process is shown in Figure 1.

Of the included 12 studies, four studies enrolled patients with STEMI as study subjects, four studies enrolled patients with CAD as study subjects, and the left four studies enrolled patients with the acute coronary syndrome. As for the methods for measuring the CXCL12 level, all the included original studies detected the CXCL12 level by enzyme-linked immunosorbent assay (ELISA), with seven studies detected in serum and the left 5 studies in plasma. According to the variable type of the CXCL12 level adopted by the authors, the included studies were divided into two groups: one group incorporated 6 studies with the CXCL12 level as the category variable, and the other group consisted of the left sixstudies with the CXCL12 level as the continuous variable. The pooled data of the two groups were calculated separately. The main characteristics of the included studies are presented in Table 1.

CXCL12 level and future clinical outcomes in patients with CAD

According to the variable type of CXCL12 level adopted in the original studies, all the included original studies were divided into CXCL12 level as the category variable group and CXCL12 level as the continuous variable group, and we pooled the data of the two groups separately. Before calculating pooled HRs/ORs, a heterogeneity test was conducted. In CXCL12 level as category group, heterogeneity was found in univariate analysis (I^2 = 91.7%, $P < 0.001$) but not in multivariate analysis (I^2 = 49.4%, $P = 0.095$) (Figures 2, 3). In the CXCL12 level as the continuous variable group, heterogeneity was found in multivariate analysis (I^2 = 78%, $P < 0.001$) (Figure 4), while univariate analysis data could not be pooled for only one study presented univariate OR and 95% CI. Thus, a random-effects model was used to merge HRs/ORs in univariate analysis of CXCL12 level as category variable group and in CXCL12 level as the continuous variable group, while a fixed-effect model was used to merge HRs in multivariate analysis of CXCL12 level as the category group. A positive association between higher blood CXCL12 level and future MACEs was found in both CXCL12 level as category variable group (univariate HR 5.23, 95% CI 2.48–11.04, $P <$ 0.001; multivariate HR 2.53, 95% CI 2.03–3.16, $P < 0.001$) (Figures 2, 3) and CXCL12 level as continuous variable group (multivariate OR 1.55, 95%CI 1.02–2.35, $P = 0.039$) (Figure 4).

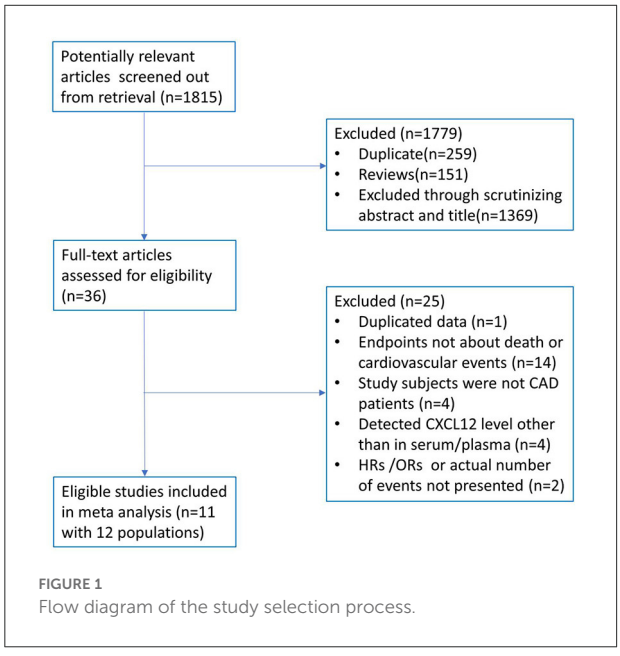


FIGURE 1
Flow diagram of the study selection process.

Publication bias

The Egger's (26) test and Begg's funnel plot were used to evaluate the publication bias of the included studies in both the CXCL12 level as the category group and the CXCL12 level as the continuous group. Begg's test found no significant publication in all the univariate analysis of CXCL12 level as category group ($Z = 1.13$, $P = 0.26$), the multivariate analysis of CXCL12 level as category group ($Z = 1.71$, $P = 0.086$), and the multivariate analysis of CXCL12 level as continuous group ($Z = 0.75$, $P = 0.452$). No obvious asymmetry was found in Begg's funnel plots for all these three analyses (Figure 5). Since Egger's test has a higher sensitivity than Begg's test, Egger's test was further conducted. In addition, Egger's test also found no significant publication in all the univariate analysis of CXCL12 level as category group ($t = 0.61$, $P = 0.577$), the multivariate analysis of CXCL12 level as category group ($t = 2.71$, $P = 0.073$), and the multivariate analysis of CXCL12 level as continuous group ($t = 0.04$, $P = 0.969$).

Subgroup analysis

To evaluate the influences of CAD type, ethnicity, and follow-up duration on the role of the CXCL12 level in predicting CAD adverse outcomes, a subgroup analysis was conducted. According to the CAD type of study subjects, the included studies were divided into ACS subgroup and non-ACS subgroup; according to the ethnicity of study subjects, the included studies were divided into Asian subgroup and Caucasian subgroup; whereas based on different follow-up durations, the included studies were divided into short-term subgroup and long-term subgroup, respectively. The results of

TABLE 1 Clinical characteristics of the included original studies.

Study	Region	Subjects	Study design	Sample size	Follow up (month)	Methods for measuring SDF-1 level	CXCL12 Cutoff or comparison (pg/ml)	Outcome endpoints	HR/OR (95%CI)		Adjusted covariates in multivariate analysis	NOS score
									Univariate	Multivariate		
Matsuoka et al. (20)	Japan	OMI	Prospective study	192	90	Detected with ELISA in plasma	≥2,162 vs. <2,162	Cardiac death, non-fatal MI, refractory unstable angina pectoris (UAP), decompensated heart failure	1.87 (1.35–2.60)	1.98 (1.38–2.85)	Age, gender, smoking, hypertension, diabetes, multivessel disease, BMI, heart rate, LDL, HDL, HbA1c, LVEF, GFR, BNP, CRP, aspirin, thienopyridines, b-Blocker, ACEI/ARB, statin	7
Ghasemzadeh et al. (12)	USA	CAD	Prospective study	186	67.7	Detected with ELISA in plasma	>1,734 vs. <1,734	CV death, MI	3.01 (1.68–5.40)	6.24 (2.61–14.91)	Age, gender, diabetes, hypertension, smoking, acute MI, serum creatinine, LVEF, history of CABG, statin use, aspirin use, presence of at least 50% stenosis in at least one major epicardial vessel, LDL	7
Ghasemzadeh et al. (12)	USA	CAD	Prospective study	599	19.2	Detected with ELISA in plasma	>2,679 vs. <2,679	CV death, MI	4.27 (2.30–7.91)	4.36 (2.05–9.28)	Age, gender, diabetes, hypertension, smoking, acute MI, serum creatinine, LVEF, history of CABG, statin use, aspirin use, presence of at least 50% stenosis in at least one major epicardial vessel, LDL	7

(Continued)

10.3389/fcvm.2022.938540

TABLE 1 Continued

Study	Region	Subjects	Study design	Sample size	Follow up (month)	Methods for measuring SDF-1 level	CXCL12 Cutoff or comparison (pg/ml)	Outcome endpoints	HR/OR (95%CI)		Adjusted covariates in multivariate analysis	NOS score
									Univariate	Multivariate		
Tong et al. (13)	China	ACS	Prospective study	678	18	Detected with ELISA in plasma	>2175.1 vs. <2175.1	Death, recurrent MI, advanced HF	10.879 (7.635–15.499)	2.45 (1.71–3.50)	Age, gender, BMI, smoking, diabetes, hypercholesterolemia, hypertension, MI, chronic HF, revascularization, ST-depression ≥0.1 mV, troponin I, GFR, delay time, admission to balloon time, Killip class, left main artery disease, triple vessel disease, NT-proBNP, hs-CRP, ACEI, ARB, β-blocker, statin, aspirin, clopidogrel, tirofiban	7
Chang et al. (11)	China (Taiwan)	AMI	Prospective study	129	1	Detected with ELISA in serum	>1,500 vs. ≤1,500	Advanced Killip score, mortality	26.00 (7.20–93.93)	NA	NA	7
Peir' (14)	Spain	ACS	Prospective study	254	60	Detected with ELISA in plasma	Three tertile vs. 1+2 tertile	All-cause death	4.90 (2.53–9.50)	2.53 (1.24–5.16)	Age, medical history of myocardial infarction, diabetes, chronic kidney disease, GRACE score, troponin I peak, three vessels stenosis, LVEF≤40%, NSTEMI or unstable angina	7
Cai et al. (21)	China	CAD	Prospective study	130	1	Detected with ELISA in serum	Continuous variable	CV death, recurrent MI, advanced HF	NA	3.683 (1.131–11.989)	White blood cell, mean platelet volume, erythrocyte mean volume, hs-CRP, CTnI, BNP, LVEF, apolipoprotein A,	6

(Continued)

10.3389/fcvm.2022.938540

TABLE 1 Continued

Study	Region	Subjects	Study design	Sample size	Follow up (month)	Methods for measuring SDF-1 level	CXCL12 Cutoff or comparison (pg/ml)	Outcome endpoints	HR/OR (95%CI)		Adjusted covariates in multivariate analysis	NOS score
									Univariate	Multivariate		
										apolipoprotein B, lipoprotein a, TG, TC, HDL, LDL		
Zhang et al. (22)	China	ACS	Prospective study	214	6	Detected with ELISA in serum	Continuous variable	Total death, CV death, recurrent MI, recurrent angina, stroke, advanced HF	NA	1.812 (1.187–2.767)	Age, gender, BMI, smoking, diabetes, hypertension, hyperlipidemia, CAD family history, LVEF, hs-CRP	6
Yang et al. (23)	China	CHD	Prospective study	189	12	Detected with ELISA in serum	Continuous variable	CV death, recurrent MI, revascularization, in-stent thrombosis	NA	1.484 (1.183–1.863)	Hypertension, hyperlipidemia, diabetes, number of coronary artery lesions, length of coronary artery lesions, Gensini scores, LVEF, CRP, TNF-α	6
Yang et al. (24)	China	AMI	Prospective study	94	12	Detected with ELISA in serum	Continuous variable	CV death, recurrent angina, advanced HF, malignant ventricular arrhythmia	NA	1.733 (1.317–2.281)	Age, gender, BMI, smoking, alcohol consumption, diabetes, blood pressure, TC, TG, HDL, LDL	6
Cai et al. (16)	China	STEMI	Prospective study	122	10	Detected with ELISA in serum	Continuous variable	CV death, recurrent MI, recurrent angina, advanced HF, malignant	NA	0.246(0.1–0.603)	Age, hypertension, diabetes, TC, TG, HDL, LDL, creatinine level, cTnI, white blood cell, fast glucose level	6

(Continued)

10.3389/fcvm.2022.938540

TABLE 1 Continued

Study	Region	Subjects	Study design	Sample size	Follow up (month)	Methods for measuring SDF-1 level	CXCL12 Cutoff or comparison (pg/ml)	Outcome endpoints	HR/OR (95%CI)		Adjusted covariates in multivariate analysis	NOS score
									Univariate	Multivariate		
								ventricular arrhythmia				
Fortunato et al. (25)	Italy	AMI	Prospective study	172	12	Detected with ELISA in serum	For 1,000 U increase	Death, repeat AMI, new-onset heart failure	3.4(1.6–9.99)	3.83(1.44–10.19)	Age, gender, the presence of ST elevation, and diabetes	6

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; cTnI, cardiac troponin I; CV, cardiovascular; ELISA, enzyme-linked immunosorbent assay; GFR, glomerular filtration rate; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; HF, heart failure; hs-CRP, hypersensitive C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; NOS, Newcastle-Ottawa Scale; NT-proBNP, N-terminal pro-B type natriuretic peptide; OMI, old myocardial infarction; TC, total cholesterol; TG, triglyceride; STEMI, ST-segment elevation myocardial infarction; TNF-α, tumor necrosis factor-α; UAP, unstable angina pectoris.

subgroup analysis stratified by CAD type, ethnicity, and follow-up duration are presented in Table 2. In the CXCL12 level as the category variable group, all subgroups stratified by CAD type, ethnicity, and follow-up duration (both in univariate and multivariate analyses) have significant correlations. However, in the CXCL12 level as the continuous variable group, the correlations of the ACS subgroup, Asian subgroup, and short-term subgroup were not statistically significant, though the correlations of non-ACS, Caucasian, and long-term subgroups were significant.

Sensitivity analysis

To test the robustness of the pooled data of our meta-analysis, a sensitivity analysis was conducted. As a result, in the CXCL12 level as the category variable group, omitting any single study had no significant influence on the pooled HRs in both univariate analysis and multivariate analysis, indicating the robustness of pooled estimates (Figures 6A,B). However, in the CXCL12 level as the continuous variable group, each study except for the study by Cai X et al. had a significant influence on the overall effect (Figure 6C), suggesting the unstableness of the pooled estimate in this group.

Discussion

CXCL12 (also referred to as SDF-1) is a member of the CXC chemokine family and plays a prominent role in hematopoiesis, angiogenesis, immunogenesis, stem cell mobilization, and tissue regeneration through its receptors CXCR4 and ACKR3 (7, 27). In the past two decades, the role of CXCL12 and CXCR4/ACKR3 systems in the pathogenesis of cardiovascular diseases emerged to be one of the research hotspots of this field (28). CXCL12 as a chemokine plays multifaceted roles in the pathogenesis of coronary atherosclerotic heart disease, both beneficial and detrimental roles of CXCL12 were reported (7, 29). A variety of studies reported that CXCL12 was cardioprotective after myocardial infarction, attenuated adverse ventricular remodeling, and preserved ventricular function after myocardial infarction (30, 31). Exogenous CXCL12 administration significantly alleviated myocardial ischemia/reperfusion injury (IRI) and improved post-ischemic myocardial functional recovery (32). In fact, considering the critical role of CXCL12 in promoting tissue repair and myocardial protection, a clinical trial aimed to improve cardiac function with the treatment of CXCL12 has been conducted. The STOP-HF randomized Phase II trial evaluated the safety and efficacy of a single treatment of plasmid CXCL12 delivered *via* endomyocardial injection to patients with ischemic heart failure and demonstrated the potential for attenuating left ventricular remodeling and improving ejection fraction (EF) in

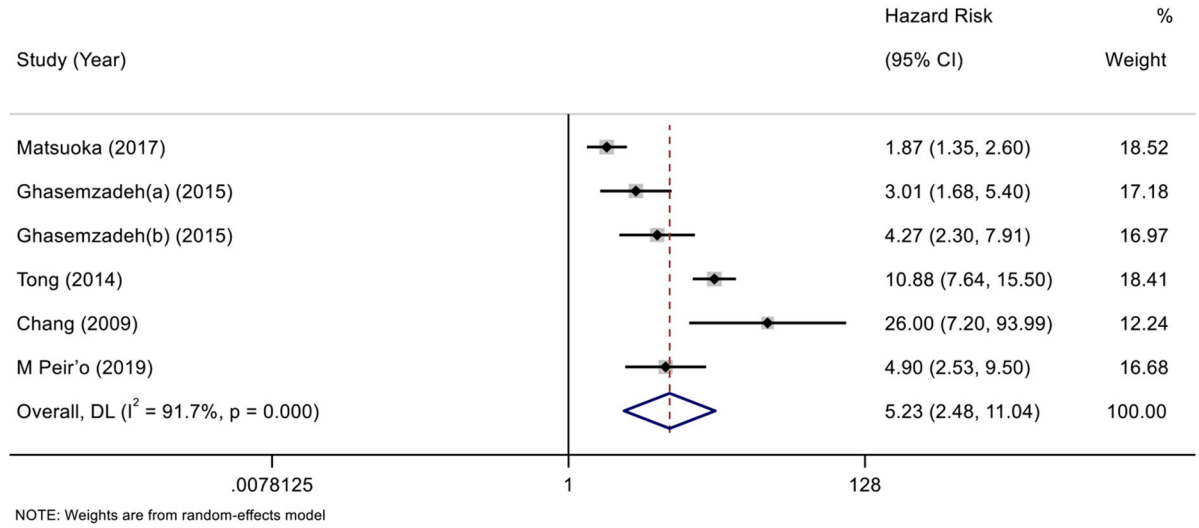


FIGURE 2
Forest plot of the association between C-X-C motif chemokine 12 (CXCL12) level as category variable and major adverse cardiovascular events (MACEs) in patients with coronary artery disease (CAD) (univariate analysis).

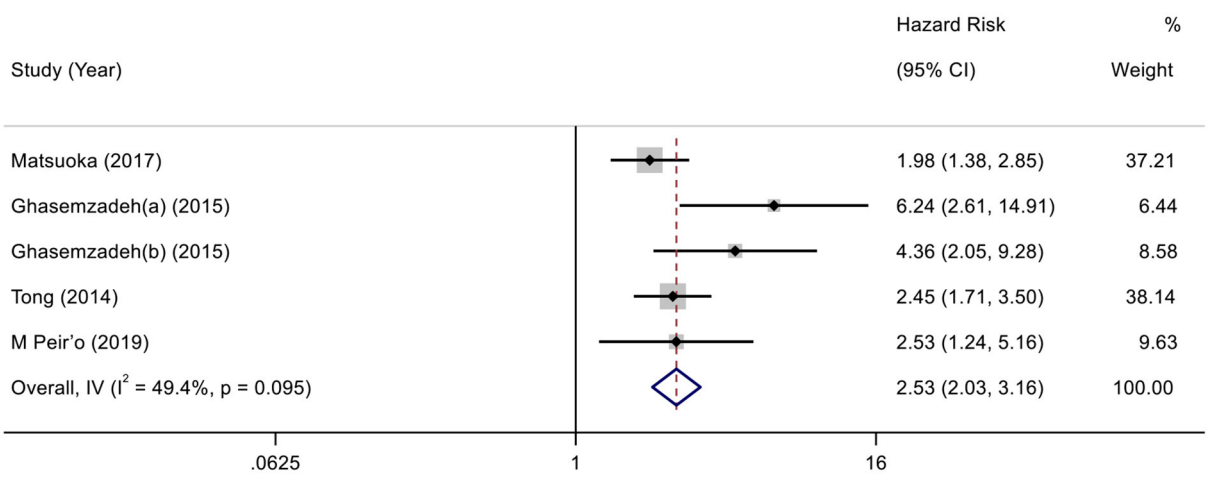


FIGURE 3
Forest plot of the association between CXCL12 level as category variable and MACEs in patients with CAD (multivariate analysis).

high-risk ischemic cardiomyopathy (33), further supporting the cardioprotective role of CXCL12.

However, other studies reported that the higher blood CXCL12 level correlated with the severity of coronary artery lesions and predicted adverse clinical outcomes in patients with stable CAD or acute coronary syndrome, though the underlying mechanism is unclear. Chang et al. (11) first reported that the higher serum CXCL12 level predicted 30-day major adverse clinical outcomes in patients with AMI. Thereafter, other studies also reported the correlation between higher blood CXCL12 levels and increased risk of future adverse clinical outcomes in patients with CAD (12–14). In contrast, negative or even opposite results were also reported (16). Thus, to evaluate the correlation between the blood CXCL12 level and the prognosis of CAD comprehensively and objectively, we conducted this meta-analysis.

By strict screening, 12 original studies with a total of 2,959 CAD subjects were entered into the final data combination. For different studies that assigned blood CXCL12 levels as different variable types, we first divided all the included studies into CXCL12 level as the category variable group and CXCL12 level as the continuous variable group and pooled the estimates,

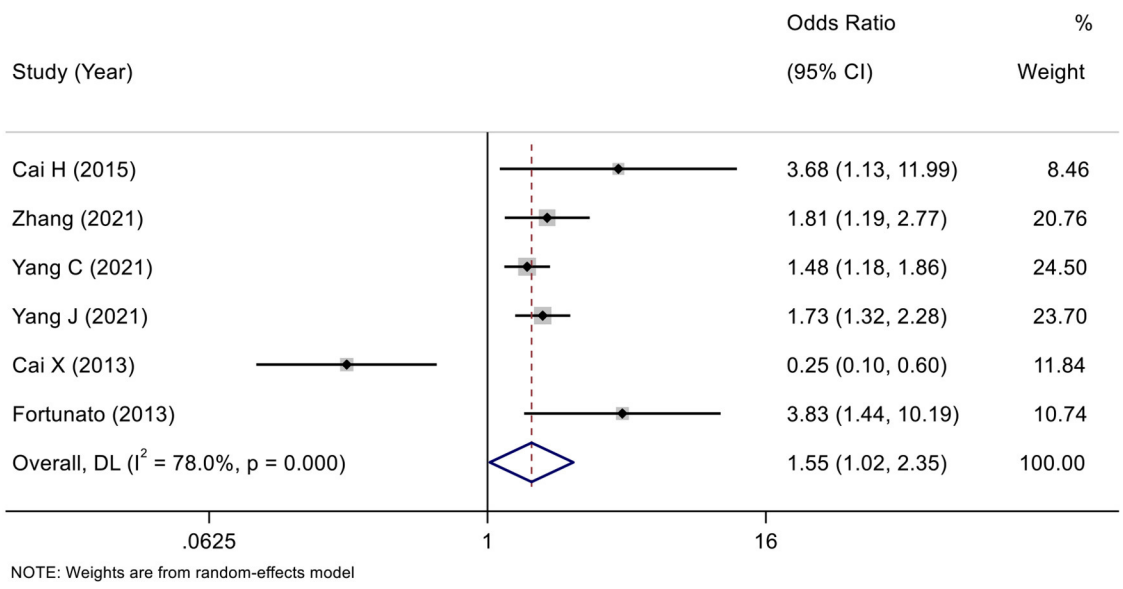


FIGURE 4
Forest plot of the association between CXCL12 level as continuous variable and MACEs in patients with CAD (multivariate analysis).

respectively. As a result, the pooled data indicated a significant association between higher CXCL12 levels and future adverse clinical events both in univariate analysis (pooled HR 5.23, 95% CI 2.48–11.04, $P < 0.001$) and multivariate analysis (pooled HR 2.53, 95% CI 2.03–3.16, $P < 0.001$) in CXCL12 level as category variable group. In the CXCL12 level as the continuous variable group, univariate data were available only in one study, so we only pooled the multivariate estimates, and the result also indicated that the higher CXCL12 level significantly predicted future adverse clinical events (pooled OR 1.55, 95% CI 1.02–2.35, $P = 0.039$). These results suggested that the blood CXCL12 level may be a valuable prognostic index for MACEs in patients with CAD.

Pathophysiologically, there are some differences between stable CAD and ACS (34), and different races may exert influences on the clinical characteristics and prognosis of CAD (35). In addition, the blood CXCL12 level may have different roles in predicting the short-term or long-term prognosis of CAD. So, the subgroup analysis stratified by CAD type, ethnicity, and follow-up duration was conducted to evaluate the influence of these three covariables on the overall effects. In the CXCL12 level as the category variable group, each subgroup (non-ACS or ACS, Caucasian or Asian, and short-term or long-term) showed a significant association between blood CXCL12 level and future MACEs. But in the CXCL12 level as the continuous variable group, the results were only significant in non-ACS, Caucasian, and long-term subgroups, suggesting the unstableness of the pooled OR in this group. In fact, sensitivity analysis also suggested that the pooled OR in the CXCL12 level as the continuous variable group was unstable, for several single studies, all had a significant influence on the overall pooled estimate (Figure 6C). In contrast, sensitivity analysis indicated that the pooled estimates were robust in the CXCL12 level as the category variable group, and no single study was indispensable for the significant overall HRs (Figures 6A,B).

Although all the included original studies measured CXCL12 level with ELISA, the detecting substrates were different. In the CXCL12 level as the continuous variable group, all the included studies detected CXCL12 level in serum, while in the CXCL12 level as the category group, only one in serum (the other five studies detected CXCL12 level in plasma) was detected. The composition of serum and plasma has a small difference, but the pooled estimates in both groups are all significant, indicating the consistency of the predicting role of CXCL12 level in serum and plasma.

Publication bias is a serious problem in the meta-analysis, which may affect the reliability and generalization of conclusions (36). In this meta-analysis, both Begg's and Egger's tests showed no significant publication bias in univariate and multivariable analyses of CXCL12 level as category variable group and multivariable analysis of CXCL12 level as the continuous variable group, indicating the authenticity and validity of the conclusions.

As for the mechanism underlying the association between higher blood CXCL12 levels and poor prognosis of CAD, it remains to be elucidated. But, existing clues indicated that higher blood CXCL12 level was associated with more severe coronary artery lesions (37), and CXCL12 promoted atherosclerosis to

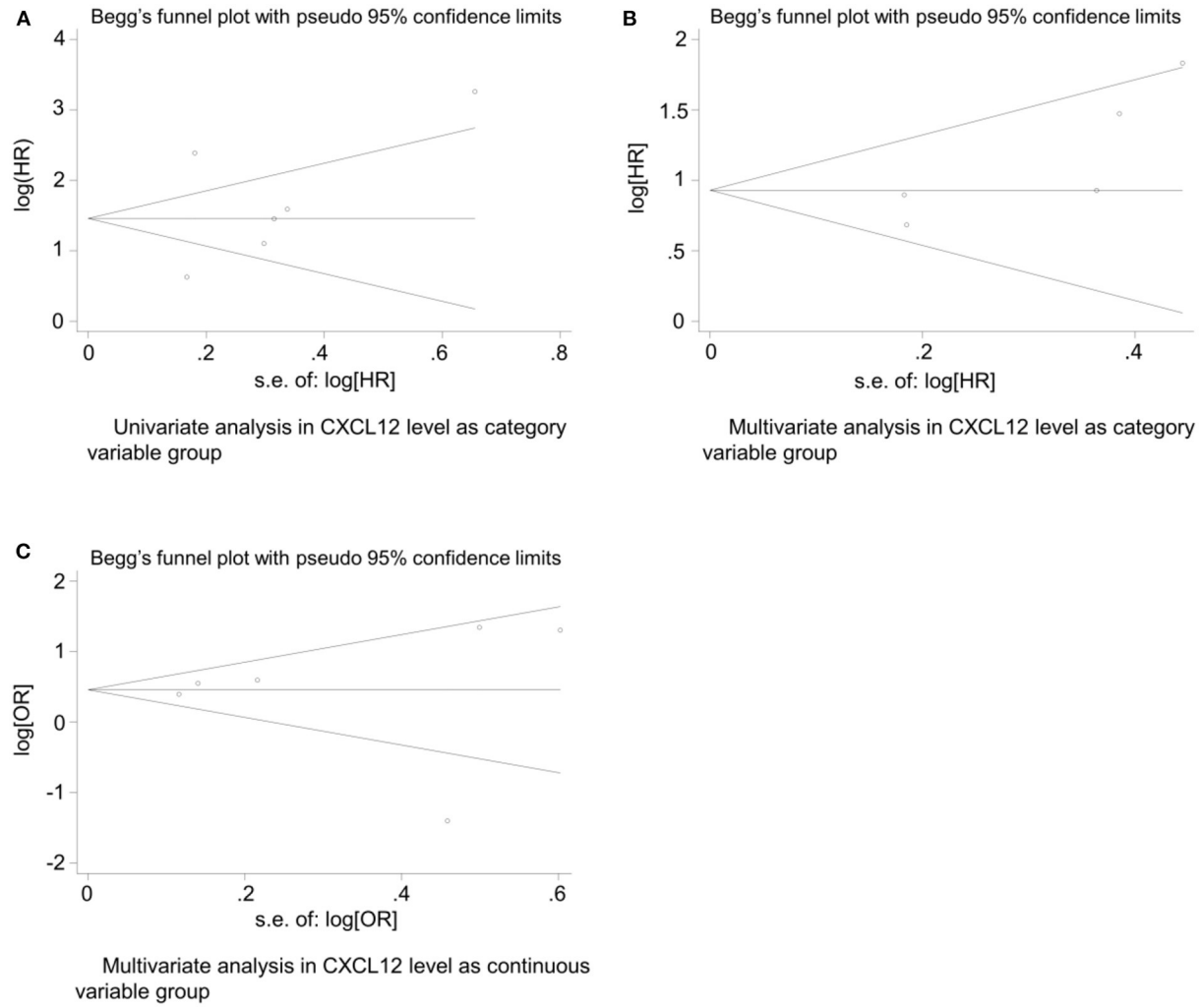


FIGURE 5
Begg's funnel plot for evaluating publication bias of included studies. **(A)** Univariate analysis in CXCL12 level as category variable group ($Z = 1.13$, $P = 0.26$); **(B)** multivariate analysis in CXCL12 level as category variable group ($Z = 1.71$, $P = 0.086$); **(C)** and multivariate analysis in CXCL12 level as continuous variable group ($Z = 0.75$, $P = 0.452$).

drive CAD progress (38), which may lead to a higher incidence of adverse cardiovascular events. This may partly account for the mechanism of the association between higher blood CXCL12 levels and poor prognosis of CAD.

Recently, Leberzammer et al. reported that CXCL12 augments platelet aggregation by activating its receptor CXCR4, while inhibition of CXCR4 attenuates platelet aggregation, and platelet-specific CXCL12 deficiency in mice limits arterial thrombosis, indicating the pro-thrombotic function of platelet-derived CXCL12 (39). In addition, an earlier study reported that platelet-derived CXCL12 can activate platelets thromboxane A2-dependently through its receptor CXCR4 (40). In contrast, higher expression of CXCL12 in platelets is associated with worse clinical outcomes in patients with CAD (41). In the CXCL12 level as the continuous variable group of this meta-analysis, all the original studies detected the CXCL12 level in serum, as much of serum CXCL12 may potentially be derived from circulating platelets activated during blood clotting, so the platelet-derived CXCL12 in serum may have exerted pro-thrombotic role to trigger adverse cardiovascular events. This further supports the role of higher blood CXCL12 levels in predicting the poor prognosis of CAD mechanistically.

CXCR4 and ACKR3 are the two receptors of CXCL12 known so far. CXCR4 is a G protein-coupled receptor (GPCR) and serves as an amplifier to increase CXCL12-associated signaling (42). ARKR3 does not couple with G protein; however, it has a much higher affinity for CXCL12 than CXCR4 and is initially considered a negative regulator of CXCL12 expression and function for the primary role of ACKR3 is to internalize and deliver CXCL12 for lysosomal degradation (43). ACKR3 has also been reported to be involved in signaling independent of G-protein (44). CXCR4 and ACKR3 perform both proatherogenic

TABLE 2 Subgroup analysis stratified by CAD type, ethnicity, and follow-up duration.

Subgroups	Category variable ($n = 2,038$)				Continuous variable ($n = 921$)	
	Univariate analysis		Multivariate analysis		Multivariate analysis	
	HR (95% CI)	I^2 (%)	HR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)
ACS	9.72 (4.69–20.15)	70.4	2.47 (1.79–3.40)	0	1.36 (0.67–2.75)	85.3
Non-ACS	2.73 (1.65–4.54)	67.4	3.49 (1.66–7.33)	74.5	1.53 (1.23–1.92)	54.5
Asian	7.43 (1.70–32.49)	96.6	2.21 (1.71–2.85)	0	1.40 (0.91–2.14)	79.5
Caucasian	3.90 (2.73–5.57)	0	3.87 (2.48–6.04)	23.5	3.83 (1.44–10.19)	0
Short term*	9.36 (4.10–21.37)	78.5	2.72 (1.97–3.76)	45.3	1.16 (0.28–4.76)	89.1
Long term*	2.86 (1.62–5.04)	72.5	2.38 (1.76–3.22)	65	1.62 (1.37–1.93)	47

*In the CXCL12 level as the category variable group, the short-term subgroup was defined as a follow-up period <24 months, while the long-term subgroup was defined as ≥24 months; in the CXCL12 level as the continuous variable group, the short-term subgroup was defined as a follow-up period <12 months, while long-term subgroup defined as ≥12 months.

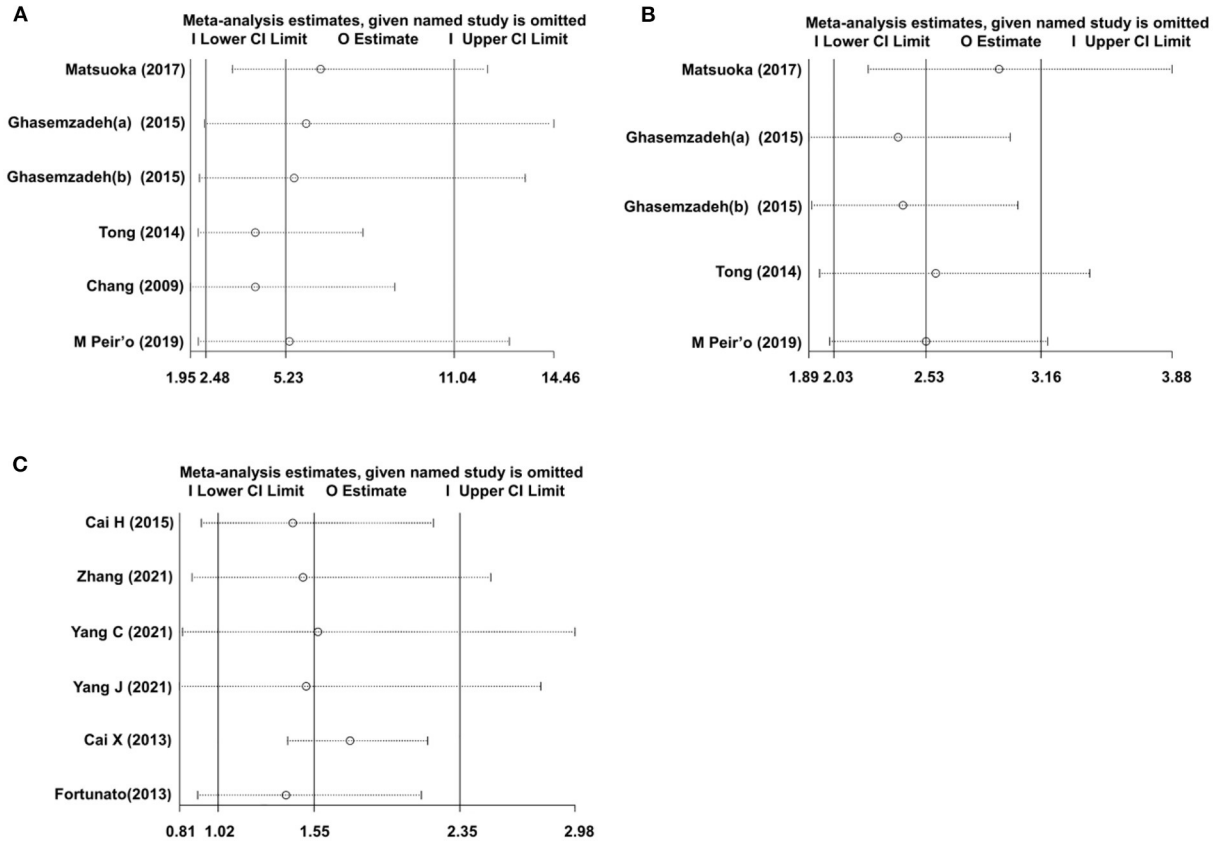


FIGURE 6
Sensitivity analysis evaluating the influence of any single study on the overall effects. **(A)** Univariate analysis data of the CXCL12 level as category variable group. **(B)** Multivariate analysis data of the CXCL12 level as category variable group; **(C)** Multivariate analysis data of the CXCL12 level as the continuous variable group.

and athero-protective functions dependent on various cell types. Both CXCR4 and ACKR3 in macrophages are proatherogenic (45, 46), and CXCR4 in platelets was also reported to be proatherogenic (47). However, activation of CXCR4 or ACKR3 in vascular cells limits atherosclerosis progress (48, 49). We assumed that the proatherogenic role of CXCR4 in both macrophages and platelets and ACKR3 in macrophages is accountable for the association between higher blood CXCL12 levels and worse outcomes of CAD.

Atherosclerosis is an inflammatory disease (50), and CXCL12 was once considered a pro-inflammatory molecule (51), which may promote the progress of CAD and lead to a

poor prognosis. However, later findings indicated that CXCL12 may have the opposite role in inflammation (52, 53). So, the actual mechanism underlying the correlation between higher blood CXCL12 levels and poor prognosis of CAD is complicated and warranted to be further explored.

To the best of our knowledge, this is the first meta-analysis assessing the association between blood CXCL12 levels and the prognosis of CAD. Inevitably, there are some limitations in our meta-analysis. First, as aforementioned, sensitivity analysis indicated the unstableness of pooled OR in the CXCL12 level as the continuous variable group, suggesting that using the CXCL12 level as the continuous variable to conduct multivariate logistic regression to assess the role of the CXCL12 level in predicting the prognosis of CAD maybe not a good method. Second, although we conducted subgroup analysis stratified by CAD clinical type, ethnicity, and follow-up duration, subgroup analysis stratified by different MACEs could not be conducted for lack of enough related data. Third, the sample size of a few included studies was small.

In summary, our meta-analysis illustrated that the higher blood CXCL12 level is associated with increased MACEs in patients with CAD, and the blood CXCL12 level may serve as an important prognostic index for CAD. Integrating blood CXCL12 levels into CAD risk assessment tools may provide more comprehensive messages for evaluating and managing patients with CAD, which are very beneficial for clinical workers. However, in considering the limitations of our meta-analysis, further large-scaled multicentered prospective studies are warranted to demonstrate the predicting role of the blood CXCL12 level in CAD prognosis, especially to elucidate its role in predicting specific MACEs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SZ: literature search, data collection, funds collection, and manuscript writing. YD and FF: data collection and interpretation. YG: study design, statistical analysis, and funds collection. All authors contributed to the article and approved the submitted version.

Funding

This study was financially supported by the Zhejiang Medical and Health Science and Technology Project (Grant No. 2021KY234), the Hangzhou Medical and Health Science and Technology Project (Grant No. A20200804), and the Construction Fund of Key Medical Disciplines of Hangzhou (No. OO20200055).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi S, AlKatheeri R, et al. Global epidemiology of ischemic heart disease: results from the global burden of disease study. *Cureus.* (2020) 12:e9349. doi: 10.7759/cureus.9349

2. Ma LY, Chen WW, Gao RL, Liu LS, Zhu ML, Wang YJ, et al. China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol.* (2020) 17:1–8. doi: 10.11909/j.issn.1671-5411.2020.01.001

3. Bhatt DL, Lopes RD, Harrington RA. Diagnosis and treatment of acute coronary syndromes: a review. *Jama.* (2022) 327:662–75. doi: 10.1001/jama.2022.0358

4. Madhavan MV, Gersh BJ, Alexander KP, Granger CB, Stone GW. Coronary artery disease in patients ≥80 years of age. *J Am Coll Cardiol.* (2018) 71:2015–40. doi: 10.1016/j.jacc.2017.12.068

5. Tscherny K, Kienbacher C, Fuhrmann V, van Tulder R, Schreiber W, Herkner H, et al. Risk stratification in acute coronary syndrome: evaluation of the GRACE and CRUSADE scores in the setting of a tertiary care centre. *Int J Clin Pract.* (2020) 74:e13444. doi: 10.1111/ijcp.13444

6. Freitas IA, Lima NA, Silva GBD Jr, Castro RL Jr, Patel P, Lima CCV, et al. Novel biomarkers in the prognosis of patients with atherosclerotic coronary artery disease. *Rev Port Cardiol.* (2020) 39:667–72. doi: 10.1016/j.repc.2020.05.010

7. Murad HAS, Rafeeq MM, Alqurashi TMA. Role and implications of the CXCL12/CXCR4/CXCR7 axis in atherosclerosis: still a debate. *Ann Med.* (2021) 53:1598–612. doi: 10.1080/07853890.2021.1974084

8. Subramanian S, Liu C, Aviv A, Ho JE, Courchesne P, Muntendam P, et al. Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk. *Arterioscler Thromb Vasc Biol.* (2014) 34:2100–5. doi: 10.1161/ATVBAHA.114.303579

9. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin

therapy: an analysis of primary and secondary prevention trials. *Lancet.* (2015) 385:2264–71. doi: 10.1016/S0140-6736(14)61730-X

10. Sjaarda J, Gerstein H, Chong M, Yusuf S, Meyre D, Anand SS, et al. Blood CSF1 and CXCL12 as causal mediators of coronary artery disease. *J Am Coll Cardiol.* (2018) 72:300–10. doi: 10.1016/j.jacc.2018.04.067

11. Chang LT, Yuen CM, Sun CK, Wu CJ, Sheu JJ, Chua S, et al. Role of stromal cell-derived factor-1alpha, level and value of circulating interleukin-10 and endothelial progenitor cells in patients with acute myocardial infarction undergoing primary coronary angioplasty. *Circ J.* (2009) 73:1097–104. doi: 10.1253/circj.CJ-08-0497

12. Ghasemzadeh N, Hritani AW, De Staercke C, Eapen DJ, Veledar E, Al Kassem H, et al. Plasma stromal cell-derived factor 1α/CXCL12 level predicts long-term adverse cardiovascular outcomes in patients with coronary artery disease. *Atherosclerosis.* (2015) 238:113–8. doi: 10.1016/j.atherosclerosis.2014.10.094

13. Tong G, Wang N, Zhou Y, Leng J, Gao W, Tong X, et al. Role of stromal cell-derived factor-1 in patients with non-ST elevation acute coronary syndrome. *Int Heart J.* (2014) 55:219–27. doi: 10.1536/ihj.13-289

14. Peiró Ó M, Farré N, Cediel G, Bonet G, Rojas S, Quintern V, et al. Stromal cell derived factor-1 and long-term prognosis in acute coronary syndrome. *Biomark Med.* (2019) 13:1187–98. doi: 10.2217/bmm-2019-0133

15. Pizzolo F, Castagna A, Olivieri O, Girelli D, Friso S, Stefanoni F, et al. Basophil blood cell count is associated with enhanced factor ii plasma coagulant activity and increased risk of mortality in patients with stable coronary artery disease: not only neutrophils as prognostic marker in ischemic heart disease. *J Am Heart Assoc.* (2021) 10:e018243. doi: 10.1161/JAHA.120.018243

16. Cai X, Li Y, Ma G. Role of stromal cell-derived factor-1α in patients with acute ST-elevation myocardial infarction. *Jiangsu Med J.* (2013) 39:791–3. doi: 10.19460/j.cnki.0253-3685.2013.07.016

17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of non-randomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

18. Lin L. Comparison of four heterogeneity measures for meta-analysis. *J Eval Clin Pract.* (2020) 26:376–84. doi: 10.1111/jep.13159

19. Zaykin DV. Optimally weighted Z-test is a powerful method for combining probabilities in meta-analysis. *J Evol Biol.* (2011) 24:1836–41. doi: 10.1111/j.1420-9101.2011.02297.x

20. Matsuoka S, Uematsu M, Nakamura T, Shimizu T, Futamata M, Obata JE, et al. High levels of stromal cell-derived factor-1α predict secondary cardiac events in stable patients with a history of myocardial infarction. *J Cardiol.* (2017) 69:320–5. doi: 10.1016/j.jjcc.2016.06.011

21. Cai H, Chen J, Gu Y, Shan Y, Lu J, Li Y. The clinical significance of serum MCP-1, SDF-1 expression in patients with coronary heart disease. *J Nantong Univ Med Sci.* (2015) 35:563–5. doi: 10.16424/j.cnki.cn32-1807/r.2015.06.024

22. Zhang J, Zhong C, Xin M. Correlation analysis of serum CXCL4 and CXCL12 levels with prognosis in patients with acute coronary syndrome. *Guangdong Med J.* (2021) 42:298–302. doi: 10.13820/j.cnki.gdyx.20200352

23. Yang C, Yin Y, Xu H, Guo H, Li Y, Lu L. Study on the relationship between serum CXCR3, CXCL5, CXCL12 levels and the severity of coronary artery disease and prognosis in patients with coronary heart disease. *Prog Mod Biomed.* (2021) 21:4713–8. doi: 10.13241/j.cnki.pmb.2021.24.023

24. Yang J, Ren S, Wang L, Liu W, Zheng J. The relationship between serum SDF-1, CXCR4 expression and platelet activation in patients with acute myocardial infarction and its influence on prognosis. *Chin J Health Lab Tec.* (2021) 31:1580–3. Available online at: https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjIwNDE1EhF6Z3dzanl6ejIwMjExMzAxNBoIcWNxMTZpb3I=

25. Fortunato O, Spinetti G, Specchia C, Cangiano E, Valgimigli M, Madeddu P. Migratory activity of circulating progenitor cells and serum SDF-1α predict adverse events in patients with myocardial infarction. *Cardiovasc Res.* (2013) 100:192–200. doi: 10.1093/cvr/cvt153

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

27. Cheng JW, Sadeghi Z, Levine AD, Penn MS, von Recum HA, Caplan AI, et al. The role of CXCL12 and CCL7 chemokines in immune regulation, embryonic development, and tissue regeneration. *Cytokine.* (2014) 69:277–83. doi: 10.1016/j.cyto.2014.06.007

28. Döring Y, Pawig L, Weber C, Noels H. The CXCL12/CXCR4 chemokine ligand/receptor axis in cardiovascular disease. *Front Physiol.* (2014) 5:212. doi: 10.3389/fphys.2014.00212

29. Gao JH Yu XH, Tang CK, CXC. chemokine ligand 12 (CXCL12) in atherosclerosis: An underlying therapeutic target. *Clin Chim Acta.* (2019) 495:538–44. doi: 10.1016/j.cca.2019.05.022

30. Saxena A, Fish JE, White MD Yu S, Smyth JW, Shaw RM, et al. Stromal cell-derived factor-1alpha is cardioprotective after myocardial infarction. *Circulation.* (2008) 117:2224–31. doi: 10.1161/CIRCULATIONAHA.107.694992

31. Frederick JR, Fitzpatrick JR. 3rd, McCormick RC, Harris DA, Kim AY, Muenzer JR, et al. Stromal cell-derived factor-1alpha activation of tissue-engineered endothelial progenitor cell matrix enhances ventricular function after myocardial infarction by inducing neovasculogenesis. *Circulation.* (2010) 122:S107–17. doi: 10.1161/CIRCULATIONAHA.109.930404

32. Huang C, Gu H, Zhang W, Manukyan MC, Shou W, Wang M. SDF-1/CXCR4 mediates acute protection of cardiac function through myocardial STAT3 signaling following global ischemia/reperfusion injury. *Am J Physiol Heart Circ Physiol.* (2011) 301:H1496–505. doi: 10.1152/ajpheart.00365.2011

33. Chung ES, Miller L, Patel AN, Anderson RD, Mendelsohn FO, Traverse J, et al. Changes in ventricular remodeling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic Ischaemic heart failure patients: the STOP-HF randomized Phase II trial. *Eur Heart J.* (2015) 36:2228–38. doi: 10.1093/eurheartj/ehv254

34. Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the mechanisms of acute coronary syndromes. *Circ Res.* (2019) 124:150–60. doi: 10.1161/CIRCRESAHA.118.311098

35. Rossello X, Ferreira JP, Caimari F, Lamiral Z, Sharma A, Mehta C, et al. Influence of sex, age and race on coronary and heart failure events in patients with diabetes and post-acute coronary syndrome. *Clin Res Cardiol.* (2021) 110:1612–24. doi: 10.1007/s00392-021-01859-2

36. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics.* (2018) 74:785–94. doi: 10.1111/biom.12817

37. Tavakolian Ferdousie V, Mohammadi M, Hassanshahi G, Khorramdelazad H, Khanamani Falahati-Pour S, Mirzaei M, et al. Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary artery disease and coronary artery occlusion. *Int J Cardiol.* (2017) 233:23–8. doi: 10.1016/j.ijcard.2017.02.011

38. Döring Y, van der Vorst EPC, Duchene J, Jansen Y, Gencer S, Bidzhekov K, et al. CXCL12 derived from endothelial cells promotes atherosclerosis to drive coronary artery disease. *Circulation.* (2019) 139:1338–40. doi: 10.1161/CIRCULATIONAHA.118.037953

39. Leberzammer J, Agten SM, Blanchet X, Duan R, Ippel H, Megens RTA, et al. Targeting platelet-derived CXCL12 impedes arterial thrombosis. *Blood.* (2022) 139:2691–705. doi: 10.1182/blood.2020010140

40. Walsh TG, Harper MT, Poole AW. SDF-1α is a novel autocrine activator of platelets operating through its receptor CXCR4. *Cell Signal.* (2015) 27:37–46. doi: 10.1016/j.cellsig.2014.09.021

41. Rath D, Chatterjee M, Bongartz A, Müller K, Droppa M, Stimpfle F, et al. Platelet surface expression of SDF-1 is associated with clinical outcomes in the patients with cardiovascular disease. *Platelets.* (2017) 28:34–9. doi: 10.1080/09537104.2016.1203399

42. De La Luz Sierra M, Yang F, Narazaki M, Salvucci O, Davis D, Yarchoan R, et al. Differential processing of stromal-derived factor-1alpha and stromal-derived factor-1beta explains functional diversity. *Blood.* (2004) 103:2452–9. doi: 10.1182/blood-2003-08-2857

43. Koenen J, Bachelerie F, Balabanian K, Schlecht-Louf G, Gallego C. Atypical Chemokine receptor 3 (ACKR3): a comprehensive overview of its expression and potential roles in the immune system. *Mol Pharmacol.* (2019) 96:809–18. doi: 10.1124/mol.118.115329

44. Torossian F, Anginot A, Chabanon A, Clay D, Guerton B, Desterke C, et al. CXCR7 participates in CXCL12-induced CD34+ cell cycling through β-arrestin-dependent Akt activation. *Blood.* (2014) 123:191–202. doi: 10.1182/blood-2013-05-500496

45. Ma W, Liu Y, Ellison N, Shen J. Induction of C-X-C chemokine receptor type 7 (CXCR7) switches stromal cell-derived factor-1 (SDF-1) signaling and phagocytic activity in macrophages linked to atherosclerosis. *J Biol Chem.* (2013) 288:15481–94. doi: 10.1074/jbc.M112.445510

46. Gupta SK, Pillarisetti K, Lysko PG. Modulation of CXCR4 expression and SDF-1alpha functional activity during differentiation of human monocytes and macrophages. *J Leukoc Biol.* (1999) 66:135–43. doi: 10.1002/jlb.66.1.135

47. Chatterjee M, von Ungern-Sternberg SN, Seizer P, Schlegel F, Büttcher M, Sindhu NA, et al. Platelet-derived CXCL12 regulates monocyte function, survival, differentiation into macrophages and foam cells through differential involvement of CXCR4-CXCR7. *Cell Death Dis.* (2015) 6:e1989. doi: 10.1038/cddis.2015.233

48. Döring Y, Noels H, van der Vorst EPC, Neideck C, Egea V, Drechsler M, et al. Vascular CXCR4 limits atherosclerosis by maintaining arterial integrity: evidence from mouse and human studies. *Circulation*. (2017) 136:388–403. doi: 10.1161/CIRCULATIONAHA.117.027646

49. Hao H, Hu S, Chen H, Bu D, Zhu L, Xu C, et al. Loss of Endothelial CXCR7 Impairs Vascular homeostasis and cardiac remodeling after myocardial infarction: implications for cardiovascular drug discovery. *Circulation*. (2017) 135:1253–64. doi: 10.1161/CIRCULATIONAHA.116.023027

50. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. *Nat Rev Drug Discov*. (2021) 20:589–610. doi: 10.1038/s41573-021-00198-1

51. De Klerck B, Geboes L, Hatse S, Kelchtermans H, Meyvis Y, Vermeire K, et al. Pro-inflammatory properties of stromal cell-derived factor-1 (CXCL12) in collagen-induced arthritis. *Arthritis Res Ther*. (2005) 7:R1208–20. doi: 10.1186/ar1806

52. O'Boyle G, Mellor P, Kirby JA, Ali S. Anti-inflammatory therapy by intravenous delivery of non-heparan sulfate-binding CXCL12. *FASEB J*. (2009) 23:3906–16. doi: 10.1096/fj.09-134643

53. McCandless EE, Wang Q, Woerner BM, Harper JM, Klein RS. CXCL12 limits inflammation by localizing mono-nuclear infiltrates to the perivascular space during experimental autoimmune encephalomyelitis. *J Immunol*. (2006) 177:8053–64. doi: 10.4049/jimmunol.177.11.8053

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 08 September 2022
DOI 10.3389/fcvm.2022.950102

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Francesco Tona,
University of Padua, Italy
David Astapenko,
University Hospital Hradec Králové, Czechia
Gordana Krljanac,
University Clinical Centre of Serbia, Belgrade, Serbia

*CORRESPONDENCE
Hongbin Liu
Cardiology301_lhb@126.com

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 22 May 2022
ACCEPTED 23 August 2022
PUBLISHED 08 September 2022

CITATION
Liu Y, Chen S, Liu SY, Sun GQ, Sun ZJ and Liu HB (2022) Association of endothelial glycocalyx shedding and coronary microcirculation assessed by an angiography-derived index of microcirculatory resistance in patients with suspected coronary artery disease.
Front. Cardiovasc. Med. 9:950102.
doi: 10.3389/fcvm.2022.950102

Association of endothelial glycocalyx shedding and coronary microcirculation assessed by an angiography-derived index of microcirculatory resistance in patients with suspected coronary artery disease

Yang Liu[1,2,3], Si Chen[4], Shaoyan Liu[5], Guoqiang Sun[6], Zhijun Sun[6] and Hongbin Liu[1,2,3,7]*

[1]Medical School of Chinese People's Liberation Army, Beijing, China, [2]Department of Cardiology, Second Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China, [3]National Clinical Research Center for Geriatric Diseases, Beijing, China, [4]Department of Cardiology, First Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China, [5]Department of Cardiology, Yantai Municipal Laiyang Central Hospital, Yantai, China, [6]Department of Cardiology, Sixth Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China, [7]Beijing Key Laboratory of Chronic Heart Failure Precision Medicine, Beijing, China

Background: The endothelial glycocalyx (EG) is essential for maintaining microvascular homeostasis. However, the relationship between the EG and coronary microcirculation remains to be elucidated. One of the main components of EG is syndecan-1, and its shedding has been claimed to represent the state of the EG. In this study, we aimed to analyze the association between syndecan-1 and the coronary microcirculation.

Methods: We enrolled suspected coronary artery disease (CAD) patients who consecutively underwent coronary angiography (CAG) and angiography-based analysis of physiological indices in the left anterior descending artery (LAD). Serum syndecan-1 was measured by enzyme-linked immunosorbent assay (ELISA). The coronary microcirculation was evaluated by the presence of coronary microvascular dysfunction (CMD) and an impaired microvascular vasodilatory capacity (IMVC), which were quantified by an angiography-derived index of microcirculatory resistance (IMRangio) in the maximum hyperemic state (H-IMRangio) induced by adenosine triphosphate and the ratio (RRRangio) of IMRangio in the non-hyperemic phase to H-IMRangio, respectively.

Results: A total of 528 patients were enrolled in this study. There was no difference in epicardial coronary complexity between patients with high syndecan-1 (HSG) and low syndecan-1 (LSG) levels grouped by the median concentration of syndecan-1 (SYNTAX: 7[3, 10] vs. 9[4, 12], $P = 0.15$). However, H-IMRangio and RRRangio were different between the LSG and HSG groups (H-IMRangio: 23.64 ± 6.28 vs. 27.67 ± 5.59, $P < 0.01$; RRRangio: 1.74[1.46, 2.08] vs. 1.55[1.34, 1.72], $P < 0.01$). Patients with CMD (H-IMRangio > 25) and patients with IMVC (RRRangio below the median value) both had higher syndecan-1 levels (CMD: 86.44 ± 54.15 vs. 55.2 ± 43.72, $P < 0.01$; IMVC: 83.86 ± 55.41 vs. 59.68 ± 45.06, $P < 0.01$). After adjustment for confounding factors, HSG remained associated with the presence of CMD and IMVC (CMD: odds ratio [OR]: 2.769, $P < 0.01$; IMVC: OR: 1.908, $P < 0.01$).

Conclusion: High levels of syndecan-1 are independently associated with the presence of CMD and IMVC among patients with suspected CAD.

KEYWORDS

endothelial glycocalyx, syndecan-1, coronary microcirculation, coronary microvascular dysfunction, impaired microvascular vasodilatory capacity, angiography-derived index of microcirculatory resistance

Introduction

The diagnosis and treatment of coronary artery disease (CAD) mostly focus on epicardial vessels. With the development of coronary interventions, the tools used to address epicardial vascular stenosis are becoming increasingly abundant and advanced. However, various studies have shown that among patients who are undergoing clinically indicated coronary angiography, up to 49% do not have significant stenosis. Of these patients, up to 60% may have coronary microvascular dysfunction (CMD) (1–3). Over the past 2 decades, understanding of the pathophysiology of CMD has increased. The incidence of major adverse cardiovascular events (MACEs) was found to be significantly higher among patients with CMD than among patients with normal endothelial function (4–8). One study found that 18, 10, and 5% of patients with severe, moderate and mild CMD, respectively, had adverse cardiovascular events (9).

Coronary microvascular functional and structural abnormalities disrupt vasodilation, thereby limiting increased coronary blood flow in response to increased myocardial oxygen demand. Endothelial function is essential for coronary microcirculation. Functionally intact endothelium, influenced by local metabolic activity, promotes relaxation that adapts to the increase in myocardial oxygen demand (10).

The endothelial glycocalyx (EG) is a polymeric sugar-rich network covering the surface of the vascular endothelium, consisting of glycosaminoglycans, glycoproteins, glycolipids, and proteoglycans, including the syndecan family. The vast majority of the glycocalyx volume is located in the microcirculation, particularly the capillaries. The EG is essential for maintaining microvascular homeostasis by modulating vascular resistance, regulating signals, and exerting a protective effect against circulating cytokines and cells, which all trigger alterations in microcirculation (11). Consequently, the EG is essential for the endothelium to be functionally intact. However, the relationship between an impaired EG and the development of CMD has not been confirmed.

The index of microvascular resistance (IMR), obtained by the fractional flow reserve (FFR) system with the temperature dilution method, is supposed to be the gold standard for the evaluation of CMD (12, 13). However, due to the high costs and operation time requirements, the application of IMR has certain limitations, especially for consecutive clinical observation and patients with mild epicardial vascular stenosis. Quantitative flow ratio (QFR) is a new technique for evaluating coronary physiological indices without a guidewire based on coronary angiography images. A novel pressure wire-free and angiography-based index of microcirculatory resistance (IMR_{angio}) based on QFR has been demonstrated to be a viable alternative to IMR obtained by the FFR system and temperature dilution method, with the potential to significantly simplify the assessment of CMD in patients with acute and chronic coronary syndromes regardless of epicardial stenosis (14, 15). With this technique, the measurement of IMR_{angio} is clearly easier to carry out in a more general population.

Based on this new technology, we aimed to investigate the association between the status of the EG and coronary

microcirculation by assessing serum levels of syndecan-1, a core component of the EG, and correlate the findings with those of IMR_{angio}.

Materials and methods

Study design and subjects

This was a single-center, prospective study. We enrolled consecutive patients who were admitted to the Department of Cardiology of Yantai Municipal Laiyang Central Hospital for suspected CAD, which including suspected stable angina pectoris or asymptomatic myocardial ischemia detected by physiological assessment or scintigraphy. Patients with a history of coronary intervention and other heart diseases (cardiomyopathy, heart valve disease, myocarditis, congenital heart disease), hematological system disease, cancers, and hepatic or renal insufficiency as well as patients who had undergone an invasive operation or had a severe infection within the previous 3 months were excluded from the study. In addition, patients with asthma or sick sinus syndrome and atrial-ventricular block were excluded because of contraindications to adenosine triphosphate (ATP). The study was approved by the Ethics Committee of Yantai Municipal Laiyang Central Hospital, and all patients provided informed consent.

Anthropometric and laboratory analysis

On the morning after admission, fasting venous blood samples were collected from the median cubital vein among all enrolled patients and tested for routine blood and biochemical indices. These indicators included fasting blood glucose, creatinine, total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL), which were all measured with an automatic analyzer (7600P, HITACHI, Tokyo, Japan).

The serum specimens were also used for the measurement of the syndecan-1 concentration, which was performed with a commercially available immunoassay (Human Syndecan-1 ELISA Kit, Abcam, United Kingdom) according to the manufacturer's recommendations.

Angiographic analysis and evaluation of the coronary microcirculation

The interventional doctors at the hospital used the standard Judkins technique to perform coronary angiography and angiographic analysis. A standard dose of 200 μg of nitroglycerine was intravenously administered to each studied artery to minimize changes in coronary volume. Ioversol (50 ml: 33.9 g; Hengrui Pharmaceutical Co., Jiangsu, China), the contrast agent, was injected at a rate of 3–4 ml/s and 2–3 ml/s for the left and right coronary arteries, respectively. Images of the left and right coronary arteries were obtained from at least 2 views. All angiographies were recorded at a rate of 15 frames/s. Three experienced cardiologists were responsible for performing and analyzing the angiograms.

All enrolled patients underwent coronary angiography-based analysis of wire-free physiological indices in the left anterior descending artery (LAD) by a validated system, AngioPlus (Pulse Medical Imaging Technology, Shanghai, China) (16). The coronary angiography images were exported in DICOM format and transferred to the AngioPlus system in the Department of Cardiology of the Chinese PLA General Hospital. Two angiographic images from different angles ($\geq 25°$) with minimal vessel overlap were acquired. The proximal ends were located at the most proximal segment of the imaged vessel. The distal ends were located at the most distal anatomical landmarks, such as side branches. The software reconstructed a 3D anatomical vessel model without its side branches for the computation of QFR. The algorithms used for QFR assessment were described previously (16). Brief description as follows. The reconstructed vessel segment was automatically divided into several subsegments along the arterial centreline, with each three consecutive centreline points forming a subsegment. Typically, a subsegment has a length of 6 mm. The pressure drop (ΔP) for each subsegment was calculated using the stenosis geometry and contrast-flow velocity (CFV), which can be formulated as follows:

$$\Delta P = c1 \times CFV + c2 \times CFV\text{^}2$$

Where c1 and c2 are viscosity and expansion loss coefficients that were determined by the stenosis geometry characterized by the diseased lumen sizing with respect to the reference sizing. The computation of CFV was as follow. According to the length of the centerline, the length of the vessel was calculated. Considering the frame rate, the curve of vessel length variation over time (length/time curve) could be derived. The flow velocity could then be easily calculated by fitting a straight line to the length/time curve during the phase of contrast injection, using the least-square method. The slope of this fitting line defined the rate of length change over time, and hence the flow velocity.

ΔP at every position with respect to the most proximal position is calculated by integrating the pressure drop of all subsegments proximal to that interrogated location. Thus, the QFR at the interrogated position can be derived by the following formula:

$$QFR = \frac{Pa - \int \Delta P dx}{Pa}$$

Where Pa is the aorta pressure and x represents the distance from the most proximal position to the interrogated position.

The evaluation of coronary microcirculation was performed according to IMR_{angio}, which was derived from the calculation formula of IMR referred to the study of De Maria, G. L. et which is calculated as follows (15, 17):

$$IMR_{angio} = Pa \times QFR \times \frac{Nframes}{fps}$$

Where Pa is the mean baseline aortic pressure; Nframes is the number of frames for contrast dye traveling from the tip of the guide catheter to the distal reference; and fps is the frame rate (prespecified as 15). **Figure 1** shows the 3D anatomical vessel model reconstruction and its automatic analyses of QFR in the LAD, which was carried out by the AngioPlus system and the derived calculation of IMR_{angio}. With reference to the optimal cut-off values determined by previous studies, coronary microvascular dysfunction (CMD) in this study was defined as an H-IMR_{angio} value greater than 25 (15).

Physiological indices were obtained in the non-hyperemic and maximum hyperemic states. A maximal hyperemic state was achieved with intravenous infusion of ATP at a rate of 140 μg/kg/min. The angiography-based resistive reserve ratio (RRR_{angio}) was calculated for enrolled patients as the ratio of IMR_{angio} in the non-hyperemic state (NH- IMR_{angio}) and the maximum hyperemic state (H-IMR_{angio}) as follows:

$$RRR_{angio} = \frac{NH{-}IMR_{angio}}{H{-}IMR_{angio}}$$

RRRangio is a measurement of coronary microvascular vasodilatory capacity, describing the ability of the microcirculation to respond to a vasodilatory stimulus regardless of epicardial stenosis (15, 18, 19). Due to the lack of reference on the optimal cut-off value to define impaired coronary vasodilator capacity (IMVC) using RRRangio, referring to the methods of previous studies (15, 18, 19), we used RRRangio below the median value was used to define IMVC.

Statistics

Data are expressed as frequencies and percentages for categorical variables and as the means ± standard deviations (if normally distributed) or as medians with interquartile ranges (if non-normally distributed) for continuous variables. Continuous variables were compared using Student's *t* test or the Mann–Whitney *U* test. Variables relevant to the multivariable models were selected by their clinical significance and a threshold *P* value < 0.1 from the univariate analyses. Binary logistic regression analysis was performed to assess independent factors associated with CMD or IMVC. The area under the receiver-operating characteristic curve (AUC) was calculated to evaluate the predictive ability of syndecan-1 for CMD or IMVC. Analyses were performed using GraphPad Prism (version 5.0.1, San Diego, CA, United States). A *P* value < 0.05 was considered statistically significant.

Results

Enrolled patient characteristics

A total of 528 patients were consecutively enrolled in this study. The median age of the enrolled patients was 68 years, and the proportion of males was 49.2%. Using the median syndecan-1 level of the enrolled patients as the cutoff value (52.9 ng/ml), all subjects were divided into two groups: a high syndecan-1 group (HSG) and a low syndecan-1 group (LSG). The baseline characteristics are listed in **Table 1**. Patients in the HSG were older than those in the LSG. A higher prevalence of diabetes mellitus was observed in the HSG. Four hundred and twenty patients were enrolled in this study due to suspected angina pectoris and there was no significant difference between LSG and HSG. The other demographic factors did not differ significantly. Other than serum albumin, the two groups showed no significant differences in laboratory tests. The levels of serum albumin were higher in the HSG than in the LSG (51.06 ± 6.27 ng/ml vs. 44.38 ± 5.64 ng/ml, $P < 0.01$).

Angiographic findings and physiological indices

Angiographic findings and physiological indices are presented in **Table 2**. Coronary complexity, which was reflected by the SYNTAX score, was not significantly different between the LSG and HSG (7[3, 10] vs. 9[4, 12], $P = 0.15$). There was no difference in the proportion of one-vessel disease and 3-vessel disease between the two groups (one-vessel disease: 39.8 vs. 35.6%, $P = 0.37$; 3-vessel disease: 8.3 vs. 9.47%, $P = 0.76$).

Physiological indices of the LAD were evaluated. A total of 146 patients had ischemic stenosis (QFR < 0.8) in the LAD, and a total of 280 patients were diagnosed with CMD. The proportion of patients with an ischemic LAD in the HSG was 23.9%, which was not different from that in the LSG (23.9 vs. 31.4%, $P = 0.06$). Among all the enrolled patients, there was no significant difference in the IMR_{angio} between patients with ischemic stenosis in the LAD compared and patients without ischemic stenosis (26.26 ± 6.61 vs. 25.44 ± 6.14, $P = 0.18$). The mean resting flow velocity of the two groups was not different (0.19 ± 0.1 m/s vs. 0.17 ± 0.1 m/s, $P = 0.78$). After ATP infusion, the mean flow velocities in the LSG significantly increased (0.42 ± 0.09 m/s vs. 0.28 ± 0.1 m/s, $P < 0.01$). Referring to the evaluation of coronary microcirculation, the NH-IMR_{angio} showed no difference between the HSG and LSG (32.95 [26.06, 41.48] vs. 34.78 [27.76, 41.68], $P = 0.1$). However, the H-IMR_{angio} was significantly lower in the LSG (23.64 ± 6.28 vs. 27.67 ± 5.59, $P < 0.01$). Moreover, we found that the proportion of CMD in the HSG was significantly higher than that in the LSG (66.7% vs. 39.4%, $P < 0.01$). In addition, this study found that RRR_{angio} was significantly higher in the

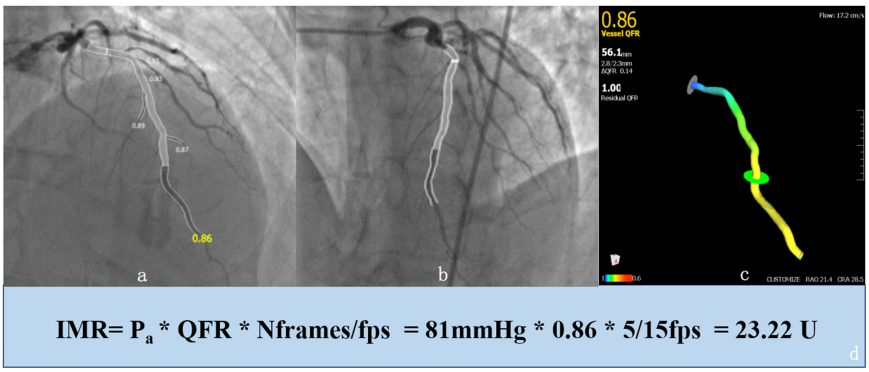


FIGURE 1
Example of an enrolled 65-year-old patient who was analyzed with the AngioPlus System to obtain the value of the quantitative flow ratio (QFR) and derivation of the angiography-based index of microcirculatory resistance (IMRangio). First, we obtained a 3D anatomical vessel model without its side branches **(c)** for the computation of the QFR by two angiographic images with different angles (≥ 25°) and minimal vessel overlap **(a,b)**. Second, the value of IMRangio was derived according to the mean baseline aortic pressure (Pa), the number of frames for contrast dye traveling from the tip of the guiding catheter to the distal reference (Nframes) and the value of the QFR **(d)**.

LSG (1.74[1.46, 2.08] vs. 1.55[1.34, 1.72], $P < 0.01$), and the proportion of patients with IMVC in the LSG was higher than that in the HSG (60.6% vs. 41.67%, $P < 0.01$).

Association of coronary microcirculation and the endothelial glycocalyx

The serum syndecan-1 concentration was significantly different when enrolled patients were grouped according to the presence of CMD and IMVC (CMD vs. non-CMD: 86.44 ± 54.15 vs. 55.2 ± 43.72 ng/ml, $P < 0.01$, **Figure 2A**; IMVC vs. non-IMVC: 83.86 ± 55.41 vs. 59.68 ± 45.06 ng/ml, $P < 0.01$, **Figure 2B**). It has been reported that syndecan-1 was significantly elevated in patients with diabetes (20, 21). Among enrolled patients, there was significant different between patients with DM and without DM (DM vs. non-DM:84.81 ± 53.51 vs. 61.14 ± 48.05 ng/ml, $P < 0.01$). To further clarify the association between EG shedding and coronary microcirculation in patients without DM, we further analyzed the difference of syndecan-1 among patients without DM (CMD vs. non-CMD: 77.36 ± 55.27 vs. 45.9 ± 33.79 ng/ml, $P < 0.01$, **Figure 2C**; IMVC vs. non-IMVC: 73.58 ± 57.23 vs. 51.51 ± 36.92 ng/ml, $P < 0.01$, **Figure 2D**). Logistic regression analysis was applied to screen out the independent factors associated with the presence of CMD and IMVC (**Table 3**). When variables with $P < 0.1$ in univariable regression analysis were tested in a multivariable model, high syndecan-1 levels and diabetes mellitus (DM) were found to be independently associated with the presence of CMD (high syndecan-1 level: odds ratio (OR) = 2.769, 95% confidence interval (95% CI): 1.817–4.22, $P < 0.01$; DM: OR = 1.79, 95% CI: 1.167–2.744, $P = 0.01$) and IMVC (high syndecan-1 level: OR = 1.908, 95% CI: 1.261–2.888, $P < 0.01$; DM: OR = 1.466, 95% CI: 1.018–2.112, $P = 0.04$).

Receiver operating characteristic (ROC) analysis of syndecan-1 to identify CMD and impaired microvascular vasodilatory capacity

Receiver operating characteristic curves were constructed to assess the ability of the syndecan-1 value to identify CMD and IMVC. As shown in **Figure 3A**, the area under the curve (AUC) of syndecan-1 for CMD was 0.7 (95% CI: 0.65–0.74, $P < 0.01$), with a cutoff value of 46.99 ng/ml (sensitivity 60.89% and specificity 71.43%). As shown in **Figure 3B**, the AUC of syndecan-1 for IMVC was 0.64 (95% CI: 0.59–0.68, $P < 0.01$), with a cutoff value of 54.11 ng/ml (sensitivity 59.85% and specificity 62.12%).

Discussion

To assess the relationship between the EG and coronary microcirculation, we quantitatively evaluated coronary microcirculation using an angiographic-based functional analysis of the LAD and applied the measurement of serum syndecan-1 to reflect the state of the EG. The main findings of this study are that a high serum syndecan-1 level was independently associated with the presence of CMD and an impaired microvascular vasodilatory capacity.

Recently, the important role of CMD in cardiovascular disease has been increasingly recognized. Up to 14% of patients with myocardial infarction are found to have non-obstructive coronary arteries (MINOCA) (22), which represents

TABLE 1 Differences in baseline characteristics of patients grouped by the median syndecan-1 level.

Clinical characteristics	ALL (n = 528)	HSG (n = 264)	LSG (n = 264)	P
Age, y	68 (61, 76)	67 (59, 74)	70 (62, 78)	0.01
Male, n (%)	260 (49.24%)	126 (47.73%)	134 (50.76%)	0.54
Body mass index, kg/m^2	28.65 ± 3.65	28.72 ± 0.23	28.58 ± 0.22	0.68
Diabetes mellitus, n (%)	237 (44.89%)	84 (31.82%)	153 (57.95%)	<0.01
Hypertension, n (%)	396 (75.00%)	193 (73.11%)	203 (76.89%)	0.37
Hypercholesterolemia, n (%)	200 (37.88%)	104 (39.39%)	96 (36.36%)	0.53
Current smoker, n (%)	110 (20.83%)	50 (18.94%)	60 (22.73%)	0.34
Total cholesterol, mg/dl	4.52 (3.52, 6.4)	4.64 (3.54, 6.39)	4.43 (3.52, 6.43)	0.86
HDL-C, mg/dl	1.1 (0.92, 1.29)	1.13 (0.94, 1.35)	1.08 (0.91, 1.25)	0.13
Total triglyceride, mg/dl	2.37 (1.21, 4.05)	2.33 (1.14, 4.1)	2.43 (1.32, 3.96)	0.74
LDL-C, mg/dl	2.97 ± 1.13	2.94 ± 0.07	2.99 ± 0.06	0.60
Creatinine, μmol/L	87.7 (71.46, 115.84)	87.96 (72.33, 116.87)	87.1 (68.92, 112.93)	0.40
Albumin, g/L	47.72 ± 6.83	51.06 ± 6.27	44.38 ± 5.64	<0.01
White blood cells (109/L)	7.29 (5.05, 9.26)	7.1 (5.1, 9.38)	7.36 (5.03, 9.20)	0.58
Red blood cells (109/L)	4.21 (3.45, 4.81)	4.17 (3.45, 4.78)	4.24 (3.46, 4.82)	0.86
Platelet count (109/L)	215 (143, 295)	216 (143, 292)	215 (143, 296)	0.58
Hemoglobin (g/L)	116.5 (103, 133.75)	119 (103, 134)	115 (103, 132)	0.19
Aspirin, n (%)	192 (36.36%)	95 (35.98%)	97 (36.74%)	0.93
ACEI/ARB, n (%)	238 (45.08%)	125 (47.35%)	113 (42.80%)	0.34
Beat receptor blocker, n (%)	104 (19.70%)	47 (17.80%)	57 (21.59%)	0.33
CCB, n (%)	108 (20.45%)	49 (18.56%)	59 (22.35%)	0.33
Statin, n (%)	318 (60.23%)	150 (56.82%)	168 (63.64%)	0.13
Suspected symptomatic CAD, n (%)	420 (79.55%)	202 (76.52%)	218 (82.85%)	0.08

Continuous variables are reported as the means ± standard deviations (if normally distributed) or as medians with interquartile ranges for continuous variables (if non-normally distributed); categorical variables are expressed as numbers (percentages). HSG, high syndecan-1 group; LSG, low syndecan-1 group; HDL-C, high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blocker.

a diagnostic and therapeutic dilemma since many patients are discharged without a clear etiology for its clinical presentation (23, 24). As a result, patients may be treated inappropriately or not treated at all. In addition, heart failure with preserved ejection fraction (HFpEF) is viewed as the most intractable fortress in the battle against the prevention and treatment of cardiovascular disease (25). CMD was found to be closely associated with the development and progression of HFpEF. Amelioration of CMD may be a breakthrough in improving the prognosis of HFpEF (26, 27).

However, the exploration on risk factors for CMD is relatively limited. Among the recognized risk factors, female sex was once considered an important factor affecting its occurrence, except for DM. CDM related disease, such as MINOCA, is even once called "female-pattern" cardiovascular disease (28). But several real-world studies in recent years have found that men and women actually differ little in the incidence of CMD (5, 29, 30). In this study population, we similarly did not find an independent association between gender and the occurrence of CMD. Therefore, there were much work remained to be done to unearth the factors associated with CMD.

The EG is an important component in the maintenance of microcirculation (31). Syndecan-1 is a specific core component of the glycocalyx, and elevated serum concentration of syndecan-1 are highly sensitive and specific for reflecting the degree of EG disruption. However, there is still a lack of recognized normal reference range. The largest study to date on concentration of serum syndecan-1 showed that the median of serum syndecan-1 was 19.3 ng/ml (Quartile: 13.7–27.3 ng/ml), which was significantly lower than 48.81 ng/ml (Quartile: 25.34–91.19 ng/ml) in our study (32). We supposed that it may be due to aging and a relatively high proportion of complications in our enrolled patients. Another informative study on syndecan-1 in CAD patients suggested the median of serum syndecan-1 was 99 ng/ml, which was also significantly different from our data (33). According to the published research on serum syndecan-1, the fluctuation range of syndecan-1 is largely varied. The structural variability of EG is large, which ranges from 200 to 2,000 nm in thickness. The instability of its structure may be the main reason for large diversity of serum syndecan-1 (34). We expect more studies with large samples to emerge, helping us to further clarify the reference range of serum syndecan-1.

The concentration of serum syndecan-1 has been found to be significantly elevated in patients with systemic microcirculatory changes, such as sepsis, diabetes and advanced age (20, 21, 35–37). In our study, the shedding of the glycocalyx,

TABLE 2 Angiographic findings and physiological indices between the patients grouped by the median syndecan-1 level.

	HSG (n = 264)	LSG (n = 264)	P
Angiographic findings			
1-vessel disease, n (%)	94 (35.6%)	105 (39.8%)	0.37
2-vessel disease, n (%)	145 (54.9%)	137 (52%)	0.54
3-vessel disease, n (%)	25 (9.47%)	22 (8.3%)	0.76
SYNTAX score	13 (6, 18)	7 (3, 10)	< 0.01
Physiological indices of LAD			
QFR	0.85 (0.75, 0.91)	0.88 (0.80, 0.94)	0.02
QFR < 0.8, n (%)	83 (31.4%)	63 (23.9%)	0.06
Resting flow velocity, m/s	0.17 ± 0.1	0.19 ± 0.1	0.78
Hyperemic flow velocity, m/s	0.28 ± 0.1	0.42 ± 0.09	< 0.01
CFR	1.98 ± 0.62	2.32 ± 0.43	< 0.01
H-IMR$_{angio}$	27.67 ± 5.59	23.64 ± 6.28	< 0.01
NH- IMR$_{angio}$	34.78 (27.76, 41.68)	32.95 (26.06, 41.48)	0.1
RRR$_{angio}$	1.55 (1.34, 1.72)	1.74 (1.46, 2.08)	< 0.01
IMVC, n (%)	160 (60.6%)	110 (41.67%)	< 0.01
CMD, n (%)	176 (66.7%)	104 (39.4%)	< 0.01

Continuous variables are reported as the means ± standard deviations (if normally distributed) or as medians with interquartile ranges for continuous variables (if non-normally distributed); categorical variables are expressed as numbers (percentages). HSG, high syndecan-1 group; LSG, low syndecan-1 group; SYNTAX scores, synergy between percutaneous coronary intervention with taxus and cardiac surgery scores; QFR, quantitative flow ratio; CFR, coronary flow reserve which computed as the ratio of hyperemic flow velocity and resting flow velocity; H-IMRangio, angiography-derived index of microcirculatory resistance in the maximum hyperemic state; NH-IMRangio, angiography-derived index of microcirculatory resistance in the non-hyperemic state; RRRangio, angiography-based resistive reserve ratio.

syndecan-1, differed significantly between patients with and without diabetes among the enrolled patients and between patients grouped according to the median age, which was consistent with previous studies. However, in our cohort, there was no significant difference in the proportion of patients with symptoms between HSG and LSG. This may be related to the relatively stable condition of the enrolled patients. It has no effect on the shedding of EG by the stimulation of a state of relative no stress. In addition, asymptomatic patients were with older age and more diabetes, which promoting the shedding of EG and making up for the elevation of syndecan-1 caused by uncomfortable symptoms. Notably, a significant difference in albumin levels was found between patients grouped by syndecan-1 levels. This may be relevant to the protective function of albumin in the EG. Plasma albumin is physiologically bound within the EG, thus contributing to the stability of the layer. Preclinical studies have illustrated the mechanism of albumin and its effects in models of hemorrhagic shock, endotoxemia, vascular permeability and ischemia. The results from *in vitro* and *in vivo* experiments illustrate the multifunctional nature of albumin, including the maintenance of glycocalyx integrity, partial restoration of impaired vascular permeability and improvement of the microcirculation (38). This result provides a new perspective on strategies for EG-related diseases in the future.

The current study addressed an additional controversial question regarding whether EG shedding, syndecan-1, is associated with lesions of coronary epicardial arteries. Nemoto et al. considered EG impairment to be of little relevance to the complexity of epicardial lesions (33), while an earlier study performed by Xiangjun Xue et al. found a certain association between the shedding of the glycocalyx and the extent of coronary lesions (39). The results of the current study are similar to previous findings obtained by Nemoto et al. on this issue. However, the reasons for the different results of various studies need to be further studied. The author supposed that the different proportions of the endothelial barrier in the formation of coronary atherosclerotic plaques may determine the different strengths of the relationship between the EG and coronary lesions.

With the abundance of evaluation methods for coronary microcirculation, we have had an increasing understanding of CMD. These methods include calculation of IMR by FFR systems and evaluation by non-invasive methods such as CFR evaluated by ultrasound, Cardiac magnetic resonance, PET/CT or dynamic myocardial perfusion computer tomography. However, traditional non-invasive evaluation methods can only evaluate surrogate markers of coronary function. Moreover, contrary to obstructive CAD in which perfusion abnormalities have regional distribution, myocardial impairment in CMD may be a generalized process resulting in diffuse myocardial perfusion abnormalities (40). Therefore, non-invasive ischemia tests may be normal. CMD exists regardless of epicardial stenosis. One of the most important features of IMR in assessing coronary microcirculation is that it is not affected by the degree of epicardial vascular stenosis, which is one

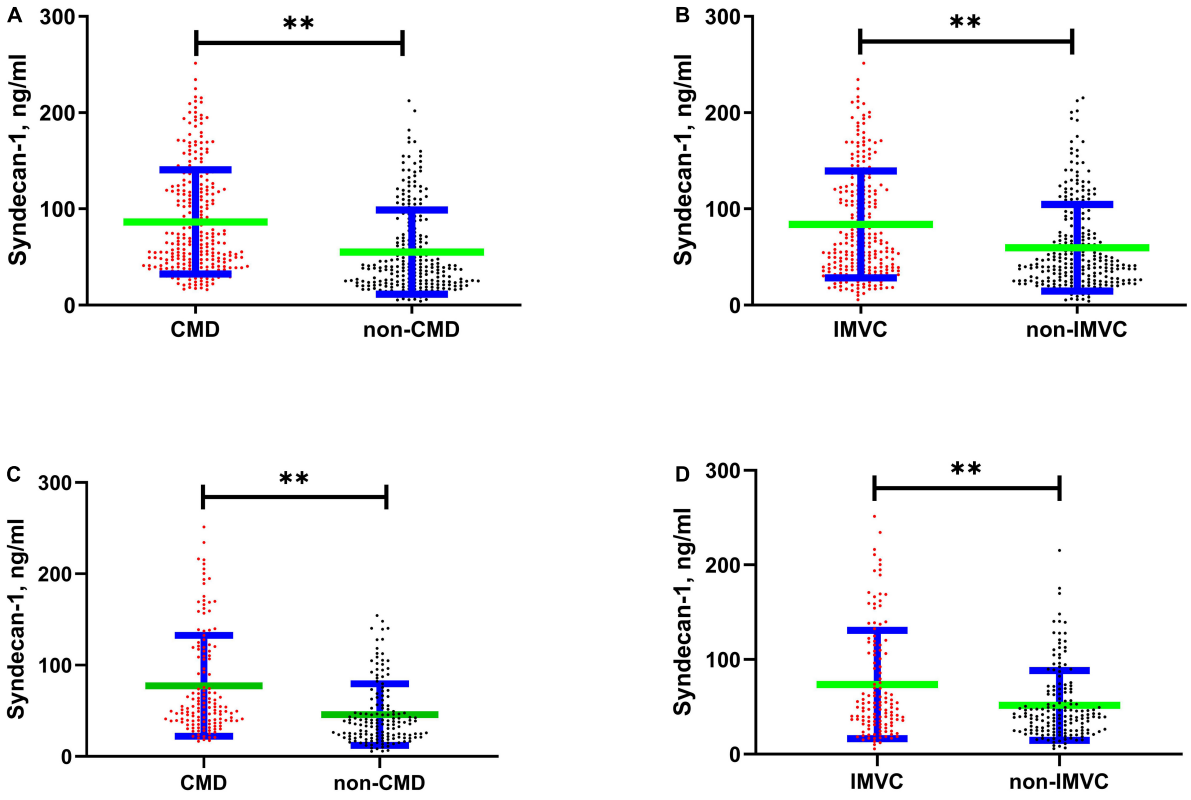


FIGURE 2
Scatter Plot showed difference in serum syndecan-1 concentration between different groups. The green horizontal line reflects the average value, and the blue horizontal line reflects the standard error. **(A)** Shows the difference between CMD and non-CMD (86.44 ± 54.15 vs. 55.2 ± 43.72, $P < 0.01$). **(B)** Shows the difference between IMVC and non-IMVC (83.86 ± 55.41 vs. 59.68 ± 45.06, $P < 0.01$). **(C)** Shows the difference between CMD and non-CMD among patients without diabetes mellites (77.36 ± 55.27 vs. 45.9 ± 33.79, $P < 0.01$). **(D)** Shows the difference between IMVC and non-IMVC among patients without diabetes mellites (IMVC vs. non-IMVC: 73.58 ± 57.23 vs. 51.51 ± 36.92, $P < 0.01$). CMD, coronary microvascular dysfunction; IMVC, impaired microvascular vasodilatory capacity. $^{**}P < 0.01$.

of the greatest advantages of IMR measurement (41, 42). Measurement of IMRangio has the both advantages invasional methods and non-invasional ones, which is regarded as a highly potential and effective way to evaluate CMD. Regarding the measurement of physiological indices in coronary arteries, we chose to conduct these in the LAD because the IMR had poor numerical agreement among different coronary arteries (43). All analyses conducted in the LAD would be more comparable among all the enrolled patients. In addition, stenosis in vessels could not affect the determination of the IMR. Consequently, measuring it in the LAD was not affected by the presence of lesions in the LAD (41). Our study similarly confirmed that the IMR of patients grouped by whether the QFR was less than 0.8 was not significantly different.

Based on analysis of the relationship between the endothelium and glycocalyx, the impact of the glycocalyx on microcirculation is two-sided (34). On the one hand, glycocalyx disruption promotes endothelial apoptosis and endothelial-to-mesenchymal transition and then affects the myocardial microvessel density (27, 44). On the other hand, the glycocalyx is not accessible for flowing red blood cells and greatly hinders plasma flow in the axial direction, causing a reduction in functionally perfused capillary volume (45). In the state of non-hyperemia, the data from our study show no association between the EG and NH-IMR$_{angio}$. It is possible that the positive and negative factors that affect microcirculation resistance have reached a certain balance in long-term adaptation. However, the flow velocity in the LAD showed differences, leading to differences in H-IMR$_{angio}$ and the presence of IMVC between patients grouped by syndecan-1 in the hyperemic state obtained by injection of ATP. One of the mechanisms of the ATP-induced increase in microcirculatory flow is achieved by reducing glycocalyx exclusion properties (45). Therefore, in good condition, the EG fully contributed to the expansion effect of ATP on the microcirculation. We supposed that the flow velocity difference in the state of hyperemia may be related to impairments in the EG and the resulting limited space for adenosine to exert its effects on glycocalyx exclusion property reduction.

TABLE 3 Association of coronary microvascular dysfunction and impaired microvascular vasodilatory capacity with other independent variables determined by the multivariable logistic regression models.

	Odd ratio	95% CI	SE	*P*
Factors related to coronary microvascular dysfunction. Variables selected by univariable regression analysis included high syndecan-1 level, age, male sex, current smoker, body mass index, hypertension, total cholesterol, diabetes mellitus, albumin				
High syndecan-1 level	2.769	1.817, 4.22	0.215	<0.01
Age	1.001	0.982, 1.021	0.010	0.90
Male	1.023	0.678, 1.545	0.210	0.91
Current smoker	1.262	0.754, 2.112	0.263	0.38
Body mass index	0.968	0.920, 1.018	0.026	0.21
Diabetes mellitus	1.790	1.167, 2.744	0.218	0.01
Total cholesterol	1.139	0.781, 1.661	0.193	0.50
Albumin	1.090	0.926, 1.283	0.083	0.30
Factors related to impaired microvascular vasodilatory capacity. Variables selected by univariable regression analysis included syndecan-1, age, male sex, body mass index, low-density lipoprotein cholesterol, creatinine, diabetes mellitus, albumin				
High syndecan-1 level	1.908	1.261, 2.888	0.211	<0.01
Age	1.001	0.982, 1.019	0.009	0.94
Male	0.885	0.62, 1.264	0.182	0.50
Body mass index	0.961	0.915, 1.010	0.025	0.12
low density lipoprotein cholesterol	0.93	0.793, 1.091	0.081	0.38
Creatinine	0.996	0.99, 1.002	0.003	0.15
Diabetes mellitus	1.466	1.018, 2.112	0.186	0.04
Albumin	0.098	0.952, 1.008	0.015	0.16

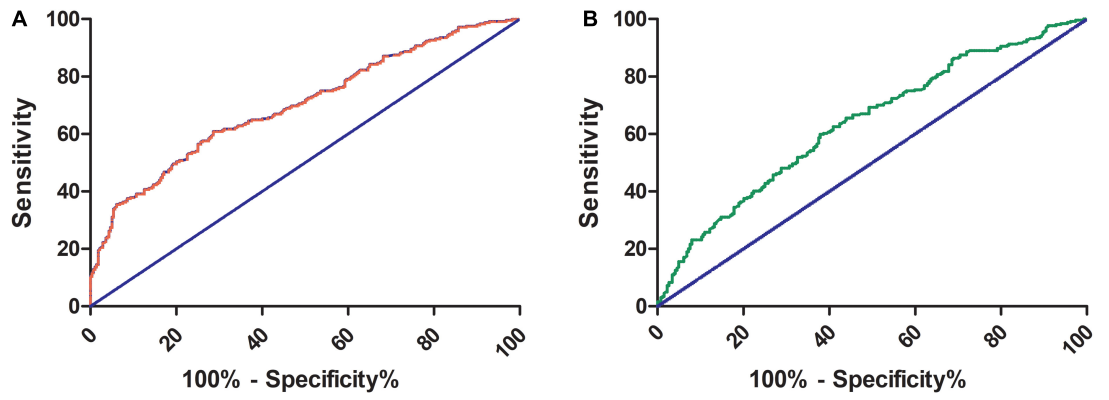


FIGURE 3
Receiver operating characteristic (ROC) curve of serum syndecan-1 for the prediction of CMD and IMVC. The areas under the ROC curve for CMD **(A)** and IMVC **(B)** were 0.7 (95% CI: 0.65–0.74, $P < 0.01$) and 0.64 (95% CI: 0.59–0.68, $P < 0.01$), respectively. For the prediction of CMD and IMVC, the cutoff values of syndecan-1 were 46.99 ng/ml (sensitivity 60.89% and specificity 71.43%) and 54.11 ng/ml (sensitivity 59.85% and specificity 62.12%), respectively. CMD, coronary microvascular dysfunction; IMVC, impaired microvascular vasodilatory capacity.

The impact of EG impairment caused by COVID-19 on the microcirculation has been repeatedly demonstrated as the epidemic spread. EG protection has regained a focus in the domain of panvascular disease (46). Our study focuses on the association between the EG and coronary microcirculation, finding that increased EG shedding is independently associated with the presence of CMD, and the impact of the EG on CMD may mainly be achieved by decreasing microvascular vasodilatory capacity. CMD, which is independent of the occurrence of epicardial coronary artery disease, accounts for a large proportion of patients with angina. Although mature interventional techniques to relieve the stenosis of epicardial vessels, the means to prevent and relieve CMD are relatively scarce. Therapy, such as sulodexide has been attracted great attention for its protective effects on the EG (47). This

study may provide a new direction for the management of patients with angina caused by CMD from the perspective of glycocalyx protection.

Study limitations

Some limitations of our study must be noted. First, the enrolled patients had suspected CAD. The included population was relatively limited. Expanding the inclusion criteria may yield different results. Second, we did not collect data pertaining to the long-term serial coronary microvascular changes of the enrolled patients. There was no further analysis of whether syndecan-1 had an impact on the changes in coronary microcirculation. Third, limited by the inclusion criteria, we could not exclude selection bias for patients who underwent angiography, especially with a low proportion of patients with a higher stage of CKD. Fourth, the gold standard for evaluating coronary microcirculation is the IMR measured by the temperature dilution method and pressure wire. Although there was good accuracy of coronary angiography-based analysis of wire-free physiological indices in the evaluation of coronary microcirculation, there might be deviation in the results.

Conclusion

A high level of syndecan-1, which reflects impairment of the EG, is independently associated with the presence of CMD and IMVC among patients with suspected CAD. This finding suggests an association between EG disruption and impaired coronary microcirculation. Further studies are required to demonstrate the causal relationship of the EG in the initiation and development of CMD. Furthermore, this study may provide new insight into improving the prognosis of CMD-related diseases from the perspective of EG protection.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Yantai Municipal Laiyang Central Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YL was responsible for the study design, statistical analysis, manuscript writing, and the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analyses. SL was responsible for screening and informed notification of patients and performance of CAG. SC and GS were responsible for the measurement of QFR and IMRangio by AngioPlus. ZS performed the major revisions of the manuscript. HL was responsible for the conception, funding, and study design and corrected and approved the revisions and final version of the manuscript. All authors have discussed the manuscript contents.

Funding

This study was funded by the National Key Research and Development Program of China (2020YFC2008304). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Acknowledgments

We thank all the clinical staff and members who participated in this trial for their assistance with the execution and completion of the clinical trial.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bradley SM, Maddox TM, Stanislawski MA, O'Donnell CI, Grunwald GK, Tsai TT, et al. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (veterans affairs clinical assessment reporting and tracking). *J Am Coll Cardiol.* (2014) 63:417–26. doi: 10.1016/j.jacc.2013.09.055

2. Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. *J Am Coll Cardiol.* (2021) 78:1352–71. doi: 10.1016/j.jacc.2021.07.042

3. Farrehi PM, Bernstein SJ, Rasak M, Dabbous SA, Stomel RJ, Eagle KA, et al. Frequency of negative coronary arteriographic findings in patients with chest pain is related to community pr actice patterns. *Am J Manag Care.* (2002) 8:643–8.

4. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation.* (2012) 126:1858–68. doi: 10.1161/CIRCULATIONAHA.112.120402

5. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation.* (2014) 129:2518–27. doi: 10.1161/CIRCULATIONAHA.113.008507

6. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol.* (2010) 55:2825–32. doi: 10.1016/j.jacc.2010.01.054

7. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation.* (2000) 101:948–54. doi: 10.1161/01.cir.101.9.948

8. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation.* (2015) 131:19–27. doi: 10.1161/CIRCULATIONAHA.114.011939

9. Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis.* (2004) 15:259–64. doi: 10.1097/01.mca.0000134590.99841.81

10. Pries AR, Badimon L, Bugiardini R, Camici PG, Dorobantu M, Duncker DJ, et al. Coronary vascular regulation, remodelling, and collateralization: mechanisms and clinical implications on behalf of the working group on coronary pathophysiology and microcirculation. *Eur Heart J.* (2015) 36:3134–46. doi: 10.1093/eurheartj/ehv100

11. Zhang X, Sun D, Song JW, Zullo J, Lipphardt M, Coneh-Gould L, et al. Endothelial cell dysfunction and glycocalyx - A vicious circle. *Matrix Biol.* (2018) 71-72:421–31. doi: 10.1016/j.matbio.2018.01.026

12. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* (2020) 41:407–77. doi: 10.1093/eurheartj/ehz425

13. Xu J, Lo S, Juergens CP, Leung DY. Impact of targeted therapies for coronary microvascular dysfunction as assessed by the index of microcirculatory resistance. *J Cardiovasc Transl Res.* (2021) 14:327–37. doi: 10.1007/s12265-020-10062-z

14. Fernandez-Peregrina E, Garcia-Garcia HM, Sans-Rosello J, Sanz-Sanchez J, Kotronias R, Scarsini R, et al. Angiography-derived versus invasively-determined index of microcirculatory resistance in the assessment of coronary microcirculation: a systematic review and meta-analysis. *Catheter Cardiovasc Interv.* (2022) 99:2018–25. doi: 10.1002/ccd.30174

15. Scarsini R, Shanmuganathan M, Kotronias RA, Terentes-Printzios D, Borlotti A, Langrish JP, et al. Angiography-derived index of microcirculatory resistance (IMRangio) as a novel pressure-wire-free tool to assess coronary microvascular dysfunction in acute coronary syndromes and stable coronary artery disease. *Int J Cardiovasc Imaging.* (2021) 37:1801–13. doi: 10.1007/s10554-021-02254-8

16. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol.* (2017) 70:3077–87. doi: 10.1016/j.jacc.2017.10.035

17. De Maria GL, Scarsini R, Shanmuganathan M, Kotronias RA, Terentes-Printzios D, Borlotti A, et al. Angiography-derived index of microcirculatory resistance as a novel, pressure-wire-free tool to assess coronary microcirculation in ST elevation myocardial infarction. *Int J Cardiovasc Imaging.* (2020) 36:1395–406. doi: 10.1007/s10554-020-01831-7

18. Toya T, Ahmad A, Corban MT, Zcan I, Sara JD, Sebaali F, et al. Risk stratification of patients with nonobstructive coronary artery disease using resistive reserve ratio. *J Am Heart Assoc.* (2021) 10:e020464. doi: 10.1161/JAHA.120.020464

19. Layland J, Carrick D, McEntegart M, Ahmed N, Payne A, McClure J, et al. Vasodilatory capacity of the coronary microcirculation is preserved in selected patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv.* (2013) 6:231–6. doi: 10.1161/CIRCINTERVENTIONS.112.000180

20. Kaur G, Rogers J, Rashdan NA, Cruz-Topete D, Pattillo CB, Hartson SD, et al. Hyperglycemia-induced effects on glycocalyx components in the retina. *Exp Eye Res.* (2021) 213:108846. doi: 10.1016/j.exer.2021.108846

21. Neri AK, da S Junior GB, Meneses GC, Martins AM, Silva RP, Psf Nunes M, et al. Cardiovascular risk assessment and association with novel biomarkers in patients with Type 2 diabetes mellitus. *Biomark Med.* (2021) 15:561–76. doi: 10.2217/bmm-2020-0611

22. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation.* (2015) 131:861–70. doi: 10.1161/CIRCULATIONAHA.114.011201

23. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J.* (2017) 38:143–53. doi: 10.1093/eurheartj/ehw149

24. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* (2020) 17:559–73. doi: 10.1038/s41569-020-0363-2

25. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res.* (2019) 124:1598–617. doi: 10.1161/CIRCRESAHA.119.313572

26. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* (2013) 62:263–71. doi: 10.1016/j.jacc.2013.02.092

27. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. *Circ Res.* (2021) 128:1451–67. doi: 10.1161/CIRCRESAHA.121.318159

28. Nelson MD, Wei J, Bairey Merz CN. Coronary microvascular dysfunction and heart failure with preserved ejection fraction as female-pattern cardiovascular disease: the chicken or the egg? *Eur Heart J.* (2018) 39:850–2. doi: 10.1093/eurheartj/ehx818

29. Rush CJ, Berry C, Oldroyd KG, Rocchiccioli JP, Lindsay MM, Touyz RM, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol.* (2021) 6:1130–43. doi: 10.1001/jamacardio.2021.1825

30. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J.* (2018) 39:840–9. doi: 10.1093/eurheartj/ehx721

31. Fu L, Kim HN, Sterling JD, Baker SM, Lord MS. The role of the cell surface glycocalyx in drug delivery to and through the endothelium. *Adv Drug Deliv Rev.* (2022) 184:114195. doi: 10.1016/j.addr.2022.114195

32. Oda K, Okada H, Suzuki A, Tomita H, Kobayashi R, Sumi K, et al. Factors enhancing serum syndecan-1 concentrations: a large-scale comprehensive medical examination. *J Clin Med.* (2019) 8:1320. doi: 10.3390/jcm8091320

33. Nemoto T, Minami Y, Yamaoka-Tojo M, Kato A, Katsura A, Sato T, et al. Endothelial glycocalyx and severity and vulnerability of coronary plaque in patients with coronary artery disease. *Atherosclerosis.* (2020) 302:1–7. doi: 10.1016/j.atherosclerosis.2020.04.014

34. Villalba N, Baby S, Yuan SY. The endothelial glycocalyx as a double-edged sword in microvascular homeostasis and pathogenesis. *Front Cell Dev Biol.* (2021) 9:711003. doi: 10.3389/fcell.2021.711003

35. Nam EJ, Ham JY, Song KE, Won DI, Lee NY. Age-related variation of syndecan-1 levels in saliva and plasma of healthy individuals. *Clin Lab.* (2021) 67:210113. doi: 10.7754/Clin.Lab.2021.210113

36. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care.* (2019) 23:16. doi: 10.1186/s13054-018-2292-6

37. Wang JB, Zhang YJ, Zhang Y, Guan J, Chen LY, Fu CH, et al. Negative correlation between serum syndecan-1 and apolipoprotein A1 in patients with type 2 diabetes mellitus. *Acta Diabetol.* (2013) 50:111–5. doi: 10.1007/s00592-010-0216-2

38. Aldecoa C, Llau JV, Nuvials X, Artigas A. Role of albumin in the preservation of endothelial glycocalyx integrity and the microcirculation: a review. *Ann Intensive Care.* (2020) 10:85. doi: 10.1186/s13613-020-00697-1

39. Xue XJ, Jiang Y, Chen L, Chen SL. Relationship between the endothelial glycocalyx and the extent of coronary atherosclerosis. *Microcirculation.* (2018) 25:e12504. doi: 10.1111/micc.12504

40. Vancheri F, Longo G, Vancheri S, Henein M. Coronary microvascular dysfunction. *J Clin Med.* (2020) 9:2880. doi: 10.3390/jcm9092880

41. Aarnoudse W, Fearon WF, Manoharan G, Geven M, van de Vosse F, Rutten M, et al. Epicardial stenosis severity does not affect minimal microcirculatory resistance. *Circulation.* (2004) 110:2137–42. doi: 10.1161/01.CIR.0000143893.18451.0E

42. Yong AS, Ho M, Shah MG, Ng MK, Fearon WF. Coronary microcirculatory resistance is independent of epicardial stenosis. *Circ Cardiovasc Interv.* (2012) 5:S1–2. doi: 10.1161/CIRCINTERVENTIONS.111.966556

43. Kobayashi Y, Lee JM, Fearon WF, Lee JH, Nishi T, Choi DH, et al. Three-vessel assessment of coronary microvascular dysfunction in patients with clinical suspicion of ischemia: prospective observational study with the index of microcirculatory resistance. *Circ Cardiovasc Interv.* (2017) 10:e005445. doi: 10.1161/CIRCINTERVENTIONS.117.005445

44. Cancel LM, Ebong EE, Mensah S, Hirschberg C, Tarbell JM. Endothelial glycocalyx, apoptosis and inflammation in an atherosclerotic mouse model. *Atherosclerosis.* (2016) 252:136–46. doi: 10.1016/j.atherosclerosis.2016.07.930

45. VanTeeffelen JW, Brands J, Vink H. Agonist-induced impairment of glycocalyx exclusion properties: contribution to coronary effects of adenosine. *Cardiovasc Res.* (2010) 87:311–9. doi: 10.1093/cvr/cvq114

46. Lambadiari V, Mitrakou A, Kountouri A, Thymis J, Katogiannis K, Korakas E, et al. Association of COVID-19 with impaired endothelial glycocalyx, vascular function and myocardial deformation 4 months after infection. *Eur J Heart Fail.* (2021) 23:1916–26. doi: 10.1002/ejhf.2326

47. Broekhuizen LN, Lemkes BA, Mooij HL, Meuwese MC, Verberne H, Holleman F, et al. Effect of sulodexide on endothelial glycocalyx and vascular permeability in patients with type 2 diabetes mellitus. *Diabetologia.* (2010) 53:2646–55. doi: 10.1007/s00125-010-1910-x

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 12 September 2022
DOI 10.3389/fcvm.2022.947959

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Genmao Cao,
Second Hospital of Shanxi Medical University, China
Gani Bajraktari,
University of Pristina, Albania

*CORRESPONDENCE
Xin Chen
hb-chenxin@126.com
Jun Chen
chenjun0121@126.com

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 19 May 2022
ACCEPTED 05 August 2022
PUBLISHED 12 September 2022

CITATION
Ma Z, Chen J, Jin K and Chen X (2022) Colchicine and coronary heart disease risks: A meta-analysis of randomized controlled clinical trials.
Front. Cardiovasc. Med. 9:947959.
doi: 10.3389/fcvm.2022.947959

Colchicine and coronary heart disease risks: A meta-analysis of randomized controlled clinical trials

Zijun Ma[1], Jun Chen[1]*, Kaiqin Jin[2] and Xin Chen[1]*

[1]Sinopharm Dongfeng General Hospital, Hubei University of Medicine, Shiyan, China, [2]Department of Cardiology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China

Background: Several trials have considered the safety and clinical benefits of colchicine as a treatment option for secondary prevention in patients with coronary atherosclerotic heart disease (CAD), but its safety and clinical benefits remain controversial. The purpose of this study was to explore the clinical benefits of colchicine, focusing on certain subgroups of patients.

Methods: Randomized controlled trials (RCTs) of colchicine in subjects with acute or chronic CAD compared with controls were included to assess all-cause mortality, non-cardiovascular mortality, gastrointestinal adverse effects, diarrhea, MACE, cardiovascular mortality, MI, stroke, and revascularization. We analyzed the association of cardiovascular, mortality, and gastrointestinal risk with colchicine in all subjects. We also focused on the cardiovascular risk of colchicine in subgroups with different drug doses, different treatment durations, age, gender, and associated comorbidities.

Results: This meta-analysis included 15 clinical RCTs, including 13,539 subjects. Colchicine reduced the risk of MACE (RR: 0.65; 95% CI: 0.38–0.77, p for heterogeneity < 0.01; I2 = 70%; $p < 0.01$), stroke (RR: 0.48; 95% CI: 0.30–0.76; p heterogeneity = 0.52; I2 = 0%; $p < 0.01$), MI by 40% (RR: 0.60; 95% CI: 0.43–0.83; p for heterogeneity = 0.01; I2 = 59%; $p < 0.01$) and risk of revascularization (RR: 0.68; 95% CI: 0.56–0.83; p for heterogeneity = 0.17; I2 = 40%; $p < 0.01$), but had no significant effect on risk of cardiovascular death and risk of all-cause mortality. In addition, colchicine increased the risk of gastrointestinal side effects and diarrhea. In a subgroup analysis, low-dose colchicine and treatment duration > 1 month reduced the risk of MACE, MI, stroke, and revascularization. Also, the cardiovascular benefits of colchicine were observed in subjects up to 65 years of age. The results showed that hypertension and diabetes did not have a specific effect on colchicine and MACE risk.

Conclusion: Colchicine has a positive effect in reducing the incidence of MACE, MI, stroke, and revascularization, but can increase the risk of gastrointestinal and diarrhea events. Low-dose colchicine significantly

reduces the risk of MACE more than high-dose colchicine, and the benefits of long-term treatment are higher than those of short-term treatment. Long-term low-dose colchicine treatment may significantly reduce the risk of cardiovascular events. Furthermore, colchicine significantly reduced the risk of cardiovascular events in patients up to 65 years of age, but it did not appear to reduce cardiovascular risk in patients over 65 years of age or in preoperative PCI patients.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/], identifier [CDR42022332170].

KEYWORDS

coronary heart disease, secondary prevention, colchicine, dose, randomized controlled trial

Introduction

In recent years, there has been increasing evidence that inflammation plays a key role in the development of atherosclerosis and other cardiovascular diseases (1, 2). Colchicine is a drug with potent anti-inflammatory effects (3). At low doses, it inhibits microtubule growth, while at high doses it supports microtubule depolymerization. Colchicine's effect on microtubule protein disruption inhibits the action of the NLRP3 inflammasome, resulting in reduced secretion of pro-inflammatory cytokines and inhibition of neutrophil extracellular traps (NETs) formation (4–6). In this context, colchicine has emerged as a new treatment option for cardiovascular diseases.

Clinical trials on the effects of colchicine on cardiovascular-related outcomes in patients with coronary artery disease continue to emerge, Many clinical studies have shown that colchicine significantly reduces the risk of cardiovascular events in patients with coronary artery disease (7, 8), and Several meta-analyses have also shown that colchicine reduces inflammation levels in patients with unstable coronary atherosclerotic heart disease (CAD) (9) and may be considered as a first-line treatment for secondary prevention in patients with coronary artery disease (10). Few meta-analyses, however, have focused on the long-term cardiovascular risk of colchicine in patients of varied ages, as well as the cardiovascular outcomes of PCI pre-operative treatment. Therefore, we conducted a meta-analysis to evaluate the clinical efficacy and safety of colchicine in the secondary prevention of coronary heart disease, We also focused on the differences in cardiovascular events between studies based on follow-up duration and age, as well as the relationship between colchicine and cardiovascular events in terms of dose, gender, and associated comorbidities.

Materials and methods

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (11). The protocol of this meta-analysis was registered on the PROSPERO database[1] with Registration Number 42022332170.

Search strategy

The search strategy was conducted in accordance with the Participant, Intervention, Comparison, Outcome, and Study Design (PICOS) format as follows: P = adults at least 18 years old with CAD or diagnosed CAD; I = Colchicine; C = control group with or without placebo; O = primary outcome was cardiovascular outcomes, including major cardiovascular events (MACEs), coronary revascularization and all-cause death. Secondary outcomes were non-cardiovascular mortality, gastrointestinal adverse events, and diarrhea; MACEs refer to cardiovascular death, myocardial infarction (MI), and non-fatal ischemic stroke. S = Randomized controlled trials (RCT).

We searched databases including PubMed, Cochrane library, and Clinicaltrial.gov to screen all the eligible RCTs published before 2022.4.20, Language is limited to English. The keyword terms used were "colchicine" and "coronary heart disease" or "coronary syndrome" or "myocardial infarction" or "STEMI" or "stable angina" or "PCI" or "percutaneous coronary intervention" and "randomized controlled trial" (see **Supplementary Material** for detailed database search strategies). Trials were included if they met the following criteria. If multiple reports described the same trial, the most recent full text was selected for inclusion in this study.

1 https://www.crd.york.ac.uk/prospero/

Inclusion criteria

The RCTs enrolled adults over the age of 18 with coronary artery disease, regardless of whether they had undergone PCI. No restrictions on country/region, language, or race.

The RCT was designed to compare colchicine treatment with a control group with or without a placebo.

The outcomes of the RCT included one of the following events: MACE; cardiovascular death; MI; stroke; and revascularization; all-cause death; non-cardiovascular death; gastrointestinal adverse effects; diarrhea.

Data extraction

In each RCT, we extracted the first author, publication year, trial location, participant characteristics, a dose of colchicine, treatment duration, subject number of colchicine treatment group and control group, Mean age of subjects, the sex ratio of colchicine treatment and control groups, number of diabetes and non-diabetes, follow-up time, reported endpoints, and study design.

CAD is defined as an acute or chronic coronary syndrome (CCS). (i) Acute coronary syndromes (ACS) include unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). (ii) CCS, also called stable angina or stable ischemic heart disease, which includes a history of angina symptoms, asymptomatic myocardial ischemia, or myocardial revascularization in patients with stable angina.

The final results of the included studies were completed independently by the two researchers, and any disagreements were resolved through consultation.

Assessment of methodological quality

We assessed the risk of bias for inclusion in the methodological quality of RCTs based on the Cochrane Collaboration risk of bias tool (11): Elements of the Cochrane Collaboration risk of bias tool for assessment included random sequence generation, allocation concealment, participant and personnel blinding, blinding of outcome assessment, incomplete outcome data, no selective outcome reporting and other sources of bias. Any disagreements in the quality assessment are resolved through discussion between the two evaluators and, if necessary, the involvement of a third reviewer to reach a consensus.

Subgroup analysis

Several RCTs showed that the most common side effect of oral colchicine is gastrointestinal discomfort (12, 13). This effect is dose-dependent and can resolve during continued treatment or after withdrawal of colchicine (14). To identify the effect of colchicine dose on acute or chronic CAD, we divided the included studies into low-dose studies with a dose of 0.5 mg and high-dose studies with a dose of 1 mg.

To further analyze the effect of study follow-up time on the outcome endpoints, we performed subgroup analyses according to the length of follow-up in three subgroups: $\leq$ 1 month, $>$ 1 month and $<$ 1 year, and $\geq$ 1 year (median follow-up time). In addition, we analyzed a study on the preoperative treatment of PCI with colchicine, A meta-regression analysis of age was also conducted to determine the correlation between the variables and the results, we performed meta-regression analyses of age to find correlations between variables and outcomes, we also conducted subgroup analyses of age (mean age), sex, and associated comorbidities to find out the factors influencing colchicine on cardiovascular outcomes.

Statistical analysis

We analyzed the number of endpoint events and the number of patients in the included RCT and subgroup data. We assessed the risk of bias using Peter's test and regression test for funnel plot asymmetry. I2 and *p*-values were used to test for heterogeneity in each RCT. A fixed effects model was used when I2 $<$ 50% and $P > 0.10$. A random-effects model was used if I2 $>$ 50% or $P < 0.10$. We performed sensitivity analyses to reduce and exclude sources of heterogeneity: (1) When at least three RCTs were combined for the same endpoint outcome, we removed each study in turn and measured the change in I2. If omitting a particular RCT resulted in a significant decrease in I2, that RCT was the cause of heterogeneity. (2) The meta-regression method was used to investigate the relationship between subject age, nationality, and outcome. We performed subgroup analyses according to colchicine dose, study follow-up time, age, the timing of dosing, smoking, hypertension, diabetes or not, and gender. In this meta-analysis, $p < 0.05$ was considered statistically significant. R (version 4.1.2) was used to calculate statistical tests [relative risk (RR), confidence intervals, sensitivity analysis, and I2 tests]. Tables, regression plots, and forest plots generated by R (version 4.1.2) were used to display the data.

Results

This study retrieved 648 articles, and 432 studies were identified after eliminating duplicates. Subsequently, after excluding non-RCTs, intervention subjects, outcome indicators that did not match, and ongoing clinical trials with preliminary results, we included 15 RCTs in our meta-analysis. including 13,543 subjects(**Figure 1**). These subjects included patients with both acute and CCS, and a proportion of the population had

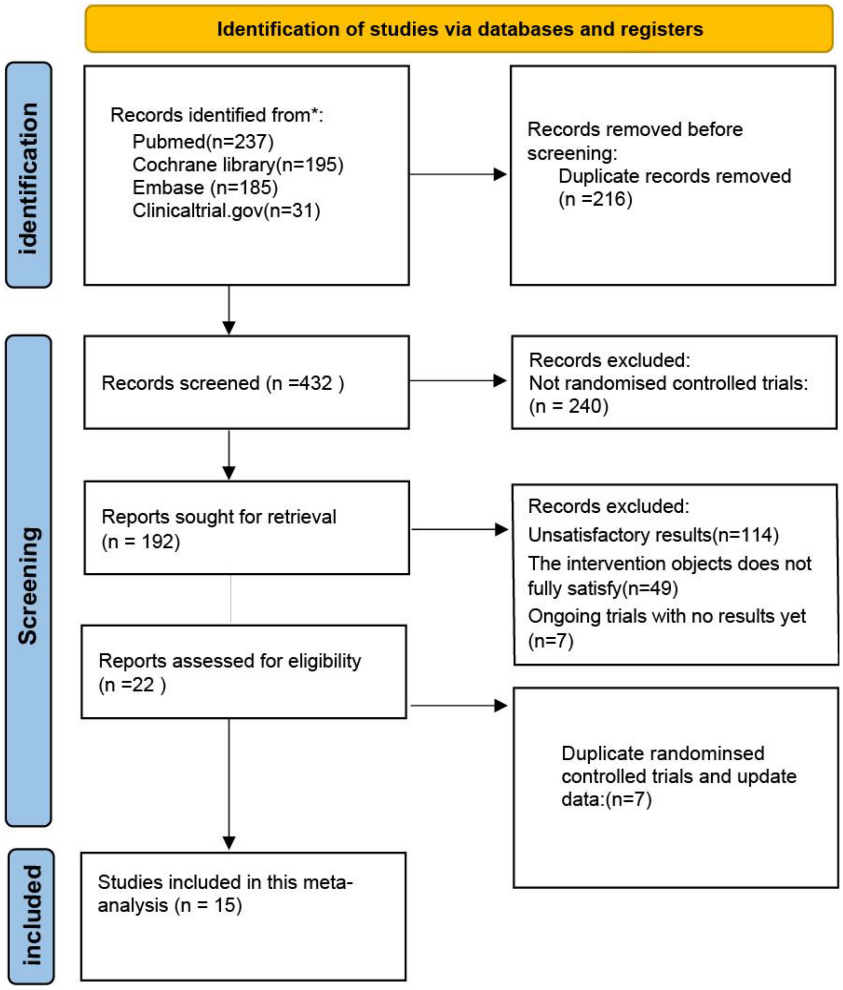


FIGURE 1
Flow diagram of the study selection process.

undergone PCI. A total of 6,817 subjects were treated with colchicine, whereas 6,726 subjects were in the control trial. Figure 1 displays the determination of relevant RCTs and finally retrieved the process of obtaining the final literature. Table 1 shows the characteristics of the finally included 15 RCTs (see Supplementary Material).

According to the design of each RCT, we used the Cochrane tool to score 15 RCTs for risk of bias. Figure 2 demonstrates the methodological quality for each RCT and showed the risk of bias of RCTs included in our meta-analysis was low (Figure 2).

Endpoints

Cardiovascular outcomes

Among the included RCTs, a total of seven studies reported MACE, defined as a composite of cardiovascular death, non-fatal ischemic stroke, and non-fatal MI), with nine RCTs reporting cardiovascular death, six RCTs reporting stroke, and nine RCTs reporting MI, and five RCTs reporting revascularization, respectively. Compared with controls, treatment with colchicine reduced the risk of MACE by 46% (RR: 0.65; 95% CI: 0.38–0.77, p for heterogeneity < 0.01; I2 = 70%; $p < 0.01$) and stroke by 52% (RR: 0.48; 95% CI: 0.30–0.76; p for heterogeneity = 0.52; I2 = 0%; $p < 0.01$), a 40% reduction in risk of MI (RR: 0.60; 95% CI: 0.43–0.83; p for heterogeneity = 0.01; I2 = 59%; $p < 0.01$), a 32% reduction in risk of incidence of revascularization (RR: 0.68; 95% CI: 0.56–0.83; p for heterogeneity = 0.17; I2 = 40%; $p < 0.01$). However, colchicine did not reduce the risk of cardiovascular death compared with controls(RR: 0.77; 95% CI: 0.53–1.12; p for heterogeneity = 0.18; I2 = 34%; $p = 0.17$) (Figure 3).

All-cause and non-cardiovascular deaths

All-cause mortality was reported in 13 trials (n = 13,288) and colchicine did not reduce the risk of death from any

TABLE 1 Main characteristics of included RCTs.

Study	Country	Study design	Characteristics	Participants, *n* (%) (treatment/ control)		Mean age (years) (treatment/ control)		Male (treatment/ control)		Diabetes mellitus, *n* (%) (treatment/ control)		Dose	Endpoints assessed	Follow-up duration (months)
O'Keefe et al. (24)	America	Single center, double-blind RCTs	CCS patients undergoing angioplasty	130	67		62	111	58	16	8	0.5 mg twice daily	1. Mean coronary artery lumen diameter 2. Recurrent ischemia 3. Adverse reactions 4. All-cause death	5.5
Raju et al. (17)	Australia	Single center, double-blind RCTs	ACS patients	40	40	59	57.2	34 (85%)	37 (92.5%)	7 (17.5%)	6 (15%)	1 mg per day	1. The blood level of hs-CRP 2. platelet function 3. Death 4. myocardial infarction 5. stroke 6. Adverse events	1.03
Nidorf et al. (13)	Australia	Single center, triple-blind RCTs	Stable coronary disease	282	250	66 ± 9.6	67 ± 9.2	222 (89%)	251 (89%)	69 (28%)	92 (33%)	0.5 mg per day	1. Acute coronary syndrome 2. Out-of-hospital cardiac arrest 3. Non-cardiac ischemic stroke 4. Death	36
Deftereos et al. (25)	Greece	Single center, double-blind RCTs	Diabetic ACS and CCS patients undergoing PCI with BMS	100	96	63.6 ± 6.9	63.7 ± 7.2	63 (63%)	65 (68%)	100 (100%)	96 (100%)	0.5 mg twice daily	1. Angio-ISR 2, IVUS-ISR 3, angiographic and IVUS parameters of lumen loss and in-stent neointimal hyperplasia 4. Death events 5. Coronary revascularization 6. Adverse reactions	6
Gianno poulos et al. (18)	Greece	Single center, triple-blind RCTs	ACS and CCS patients undergoing CABG	30	29	64.9 ± 10.1	65.6 ± 9.5	21 (70%)	20 (69%)	11 (38%)	14 (47%)	0.6 mg twice daily	1. Maximal hsTnT concentration within 48 h after surgery 2. Maximal CK-MB levels and area 3. Adverse reactions	8 days after surgery.
Deftereos et al. (19)	Greece	Single center, triple-blind RCTs	ACS patients	77	74	58	58	52 (68%)	52 (70%)	19 (26%)	13 (17%)	0.5 mg twice daily	1. CK-MB 2. hs-TnT 3. Left ventricular ejection fraction 4. Adverse reactions 5. Death events	Lasting 5 days
Zarpelon et al. (20)	Brazil	Single center, double-blind RCTs	ACS and CCS patients undergoing AF-POMR	71	69	61.5 ± 10.3	60.3 ± 8.1	49 (69%)	46 (66.7%)	42 (59.2%)	30 (43.5%)	0.5mg twice daily	1, AF-POMR rate 2, death from any cause 3, hospital length of stay 4, postoperative infection.	Hospitalization time
Akodad et al. (15)	France	Single center, double-blind RCTs	ACS patients undergoing PCI	23	21	60.1 ± 13.1	59.7 ± 11.4	19 (82.5%)	16 (76.2%)	3 (13%)	3 (14.3%)	1 mg per day	1, CRP peak value during the index hospitalization 2, troponin peak 3, tolerance of colchicine 4, hospitalization duration, 5, major adverse cardiac events	1

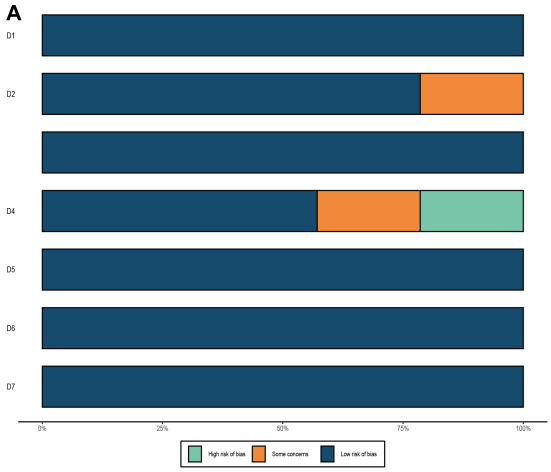
(Continued)

10.3389/fcvm.2022.947959

TABLE 1 (Continued)

Study	Country	Study design	Characteristics	Participants, *n* (%) (treatment/control)		Mean age (years) (treatment/control)		Male (treatment/control)		Diabetes mellitus, *n* (%) (treatment/control)		Dose	Endpoints assessed	Follow-up duration (months)
Hennessy et al. (23)	Australia	Single center, double-blind RCTs	ACS patients	119	118	61	61	89 (75%)	93 (79%)	27 (23%)	25 (21%)	0.5 mg per day	1. The proportion of patients with a residual CRP level ≥ 2 mg/L at 30 days 2. 30-day CRP changes 3. The proportion of recruited patients completing the study; 4. Adverse events; 5. Participant-reported compliance with study medications; 6. Death and major cardiovascular events	1
Mewton et al. (26)	Iran	Single center, double-blind RCTs	ACS patients undergoing PCI	101	91	NC	NC	NC	NC	NC	NC	NC	1, Thrombolysis in myocardial infarction (TIMI) score; 2, TMPG; 3, TFC; 4, MACE	1
Tardif et al. (8)	Canada	Multicenter, triple-blind RCTs	ACS and CCS patients undergoing PCI	2,366	2,379	60.6 ± 10.7	60.5 ± 10.6	1,894 (80.1%)	1,942 (81.6%)	462 (19.5%)	497 (20.9%)	0.5 mg per day	1. The proportion of patients with a residual CRP level ≥ 2 mg/L at 30 days 2. 30 days CRP change 3. the proportion of recruited patients completing the study; 4. adverse events; 5. participant-reported compliance with study medications; 6. death and major cardiovascular events	22.6
Tong et al. (22)	Australia	Multicenter, triple-blind RCTs	ACS or CCS patients	396	399	59.7 ± 10.2	60.0 ± 10.4	322 (81%)	310 (78%)	75 (19%)	76 (19%)	0.5 mg per day	A residual CRP level ≥ 2 mg/L at 30 days 2. 30 days CRP change 3. the proportion of recruited patients completing	12
Shah et al. (16)	Germany	Single center, triple-blind RCTs	ACS or suspected ischemic heart disease patients with possible PCI	206	194	65.9 ± 9.9	66.6 ± 10.2	193 (93.7%)	181 (93.3%)	114 (55.3%)	117 (60.3%)	1.8 mg before under went PCI	The study; 4. adverse events; 5. participant-reported	1
Nidorf et al. (7)	Australia	Multicenter, triple-blind RCTs	ACS or CCS patients	2,762	2,760	65.8 ± 8.4	65.9 ± 8.7	2,305 (83.5%)	2,371 (85.9%)	492 (17.8%)	515 (18.7%)	0.5mg per day	Compliance with study medications; 6. death and	28.6
Akrami et al. (12)	Iran	Single center, triple-blind RCTs	ACS patients undergoing PCI or medical treatment	120	129	56.9 ± 7.56	56.89 ± 7.45	86 (71.7%)	87 (67.4%)	27 (22.5%)	32 (24.8%)	0.5 mg per day	Major cardiovascular events	6

10.3389/fcvm.2022.947959



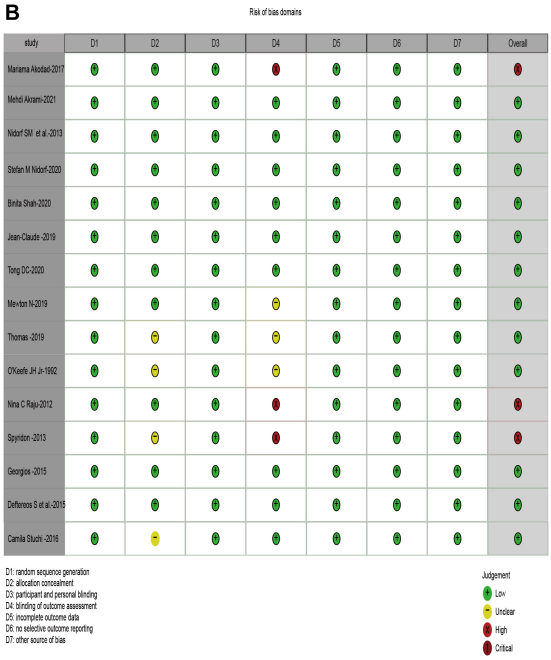


FIGURE 2
Risk of bias plot. **(A)** Risk of bias summary; **(B)** risks of bias of each included study.

cause compared with controls (RR: 1.07; 95% CI: 0.85–1.36; p for heterogeneity $p = 0.56$; I2 = 19%; $p = 0.27$), Seven studies reported non-cardiovascular mortality, and similarly, colchicine was not significantly associated with the risk of non-cardiovascular mortality compared with controls (RR: 1.38; 95% CI: 1.00–1.90; p for heterogeneity $p = 0.36$; I2 = 7%; $p = 0.05$) (**Figure 4**).

Gastrointestinal adverse events and diarrhea

All 14 RCT ($n = 13,311$) reported gastrointestinal adverse events, with a significantly higher incidence in the colchicine treatment group than in the control group (RR: 2.07; 95% CI: 1.45–2.95; p for heterogeneity $p < 0.01$; I2 = 76%; $p = 0.04$). Also, the risk of diarrhea was higher in the colchicine treated group compared to the control group (RR: 3.26; 95% CI: 1.29–8.25; p for heterogeneity $p < 0.01$; I2 = 83%; $p = 0.01$) (**Figure 5**).

Depending on the heterogeneity of the included RCT, we used either a random effects model or a fixed effects model for data analysis, and we used the Peters test and funnel plot for testing the risk of bias at $p < 0.05$, which was symmetrical from the point of view of the geometry in **Figure 6**. This indicates that the risk of bias was low for the RCT included in our meta-analysis. we also performed a meta-regression analysis to determine outcome-related variables (**Figure 7**).

Subgroup analysis

Duration of follow-up visits

Among the included studies, 7 studies had a follow-up time of ≤ 1 month (15–21), 5 studies had a follow-up time of > 1 month and ≤ 1 year (12, 22–25), and 3 studies had a follow-up time of > 1 year (7, 8, 13). First, regardless of the length of follow-up, we found no significant effect of colchicine on cardiovascular mortality, non-cardiovascular mortality, and all-cause mortality compared to controls. Secondly, we found that colchicine treatment significantly increased the incidence of gastrointestinal adverse events compared to the control group when the follow-up period was < 1 year but had no significant effect on the incidence of gastrointestinal adverse events compared to the control group when the follow-up period was > 1 year (RR: 1.06; 95% CI: 0.94–1.20; p for heterogeneity $p = 0.01$; I2 = 78%; $p = 0.55$); In addition, when follow-up was ≤ 1 month, the colchicine treatment group had no significant effect on cardiovascular outcomes, all-cause mortality, and non-cardiovascular mortality, whereas when follow-up was > 1 month in the study, colchicine administration reduced the risk of MACE, MI, stroke, revascularization, and non-cardiovascular mortality (**Figure 8**).

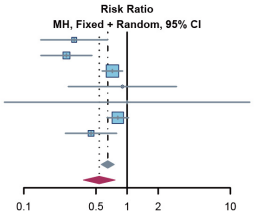
Dose of colchicine

Six RCTs applied low doses of colchicine (dose = 0.5 mg) to 13,165 subjects (7, 8, 12, 13, 22, 23),and eight other RCTs applied high doses of colchicine (dose ≥ 1 mg) to 1,295 subjects (7, 15–18, 20, 24, 25), One trial did not report a definitive dose (21). In our study, a subgroup analysis was conducted to establish the relationship between colchicine and cardiovascular risk. No significant differences were demonstrated in CV mortality and all-cause mortality compared to controls for either low or high dose colchicine; low dose colchicine significantly reduced the risk of MACE (RR: 0.65; 95% CI: 0.56–0.75; p for heterogeneity $p < 0.01$; I2 = 80%; $p < 0.01$), MI (RR: 0.66;95%CI:0.56–0.79;p for heterogeneity $p < 0.01$; I2 = 71%; $p < 0.01$), stroke (RR:0.45;95%CI:0.28–0.73;p for heterogeneity $p = 0.55$; I2 = 0%; $p < 0.01$), and revascularization in subjects

A MACE

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Mehdi Akrami−2012	8	120	28	129	6.3%	12.3%	0.31 [0.15, 0.65]
Nidorf SM, et al.−2013	14	282	48	250	12.0%	15.8%	0.26 [0.15, 0.46]
Stefan M Nidorf−2020	119	2762	165	2760	38.8%	24.1%	0.72 [0.57, 0.91]
Mewton N−2019	5	101	5	91	1.2%	6.5%	0.90 [0.27, 3.01]
Nina C Raju−2012	1	40	1	40	0.2%	1.6%	1.00 [0.06, 15.44]
Jean−Claude Tardif−2019	114	2366	141	2379	33.0%	23.9%	0.81 [0.64, 1.03]
Tong DC−2020	16	396	36	399	8.4%	15.8%	0.45 [0.25, 0.79]
Total (fixed effect, 95% CI)		**6067**		**6048**	**100.0%**	**--**	**0.65 [0.56, 0.75]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.54 [0.38, 0.77]**

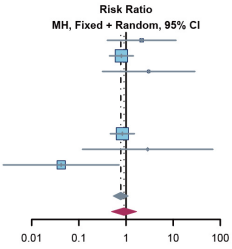
Heterogeneity: $Tau^2 = 0.122$; $Chi^2 = 20.03$, df = 6 (P < 0.01); $I^2 = 70\%$
Test for overall effect (fixed effect): Z = −5.76 (P < 0.01)
Test for overall effect (random effects): Z = −3.43 (P < 0.01)



B CV death

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Mehdi Akrami−2021.12	4	120	2	129	3.0%	10.8%	2.15 [0.40, 11.53]
Stefan M Nidorf−2020	20	2762	25	2760	39.4%	37.6%	0.80 [0.45, 1.44]
Tong DC−2020	3	396	1	399	1.6%	6.5%	3.02 [0.32, 28.94]
Mewton N−2019	0	101	0	91	0.0%	0.0%	
Raju NC−2012	0	40	0	40	0.0%	0.0%	
Thomas Hennessy −2019	0	119	0	118	0.0%	0.0%	
Jean−Claude Tardif−2019	20	2366	24	2379	37.7%	37.3%	0.84 [0.46, 1.51]
Spyridon Deftereos−2013	1	100	0	96	0.8%	3.5%	2.88 [0.12, 69.87]
Nidorf−2013	0	282	10	250	17.5%	4.3%	0.04 [0.00, 0.72]
Total (fixed effect, 95% CI)		**6286**		**6262**	**100.0%**	**--**	**0.77 [0.53, 1.12]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.91 [0.49, 1.68]**

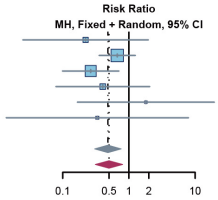
Heterogeneity: $Tau^2 = 0.171$; $Chi^2 = 7.61$, df = 5 (P = 0.18); $I^2 = 34\%$
Test for overall effect (fixed effect): Z = −1.36 (P = 0.17)
Test for overall effect (random effects): Z = −0.31 (P = 0.76)



C Stroke

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Nidorf SM, et al.−2013	1	282	4	250	7.7%	4.8%	0.22 [0.02, 1.97]
Stefan M Nidorf−2020	16	2762	24	2760	43.9%	57.1%	0.67 [0.35, 1.25]
Jean−Claude Tardif−2019	5	2366	19	2379	34.6%	23.4%	0.26 [0.10, 0.71]
Tong DC−2020	2	396	5	399	9.1%	8.5%	0.40 [0.08, 2.07]
Mewton N−2019	2	101	1	91	1.9%	4.0%	1.80 [0.17, 19.54]
Nina C Raju−2012	0	40	1	40	2.7%	2.3%	0.33 [0.01, 7.95]
Total (fixed effect, 95% CI)		**5947**		**5919**	**100.0%**	**--**	**0.48 [0.30, 0.76]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.50 [0.31, 0.80]**

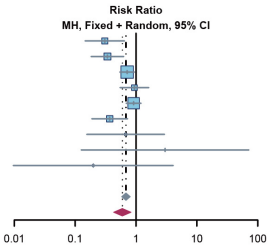
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.20$, df = 5 (P = 0.52); $I^2 = 0\%$
Test for overall effect (fixed effect): Z = −3.09 (P < 0.01)
Test for overall effect (random effects): Z = −2.85 (P < 0.01)



D MI

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Mehdi Akrami−2021	8	120	28	129	8.0%	11.0%	0.31 [0.15, 0.65]
Nidorf SM, et al.−2013	13	282	34	250	10.7%	13.3%	0.34 [0.18, 0.63]
Stefan M Nidorf−2020	83	2762	116	2760	34.4%	21.2%	0.71 [0.54, 0.94]
Binita Shah−2020	23	206	23	194	7.0%	14.9%	0.94 [0.55, 1.62]
Jean−Claude Tardif−2019	89	2366	98	2379	28.9%	21.1%	0.91 [0.69, 1.21]
Tong DC−2020	11	396	30	399	8.9%	12.2%	0.37 [0.19, 0.73]
Mewton N−2019	3	101	4	91	1.2%	4.2%	0.68 [0.16, 2.94]
Nina C Raju−2012	1	40	0	40	0.1%	1.0%	3.00 [0.13, 71.51]
Thomas Hennessy −2019	0	119	2	118	0.7%	1.1%	0.20 [0.01, 4.09]
Total (fixed effect, 95% CI)		**6392**		**6360**	**100.0%**	**--**	**0.68 [0.58, 0.81]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.60 [0.43, 0.83]**

Heterogeneity: $Tau^2 = 0.113$; $Chi^2 = 19.56$, df = 8 (P = 0.01); $I^2 = 59\%$
Test for overall effect (fixed effect): Z = −4.57 (P < 0.01)
Test for overall effect (random effects): Z = −3.08 (P < 0.01)



E Revasularization

Study	colchicine Events	colchicine Total	control Events	control Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
Mehdi Akrami−2020	135	2762	177	2760	72.6%	53.1%	0.76 [0.61, 0.95]
Binita Shah−2020	0	206	0	194	0.0%	0.0%	
Jean−Claude Tardif−2019	25	2366	50	2379	20.4%	31.6%	0.50 [0.31, 0.81]
Tong DC−2020	3	396	12	399	4.9%	7.8%	0.25 [0.07, 0.89]
Spyridon Deftereos−2013	4	112	5	110	2.1%	7.5%	0.79 [0.22, 2.85]
Total (fixed effect, 95% CI)		**5842**		**5842**	**100.0%**	**--**	**0.68 [0.56, 0.83]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.61 [0.42, 0.89]**

Heterogeneity: $Tau^2 = 0.056$; $Chi^2 = 5.02$, df = 3 (P = 0.17); $I^2 = 40\%$
Test for overall effect (fixed effect): Z = −3.86 (P < 0.01)
Test for overall effect (random effects): Z = −2.55 (P = 0.01)

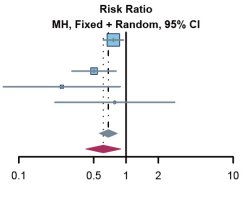


FIGURE 3
Comparison of colchicine treatment vs. control group on the risks of **(A)** MACE, **(B)** CV death, **(C)** stroke, **(D)** MI, **(E)** Revascularization. MACE, major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction.

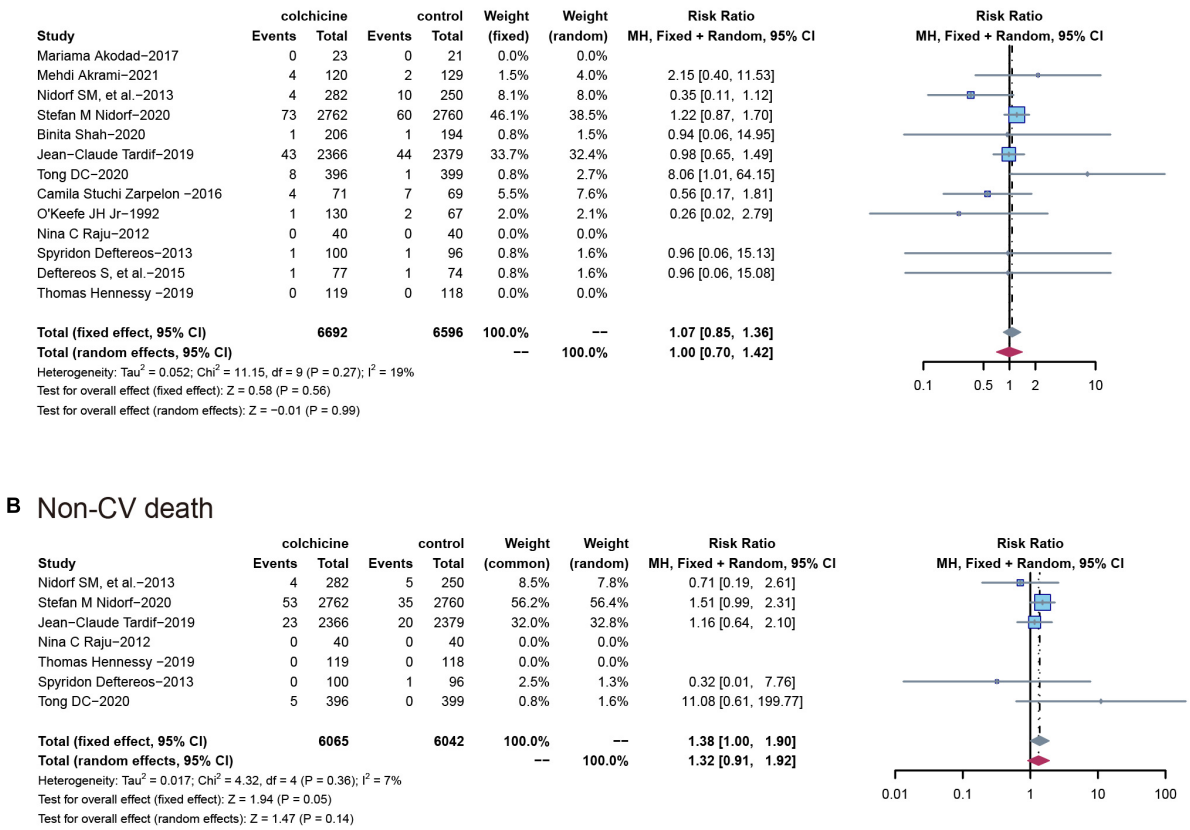


FIGURE 4
Comparison of colchicine treatment vs. control group on the risks of **(A)** All-cause death; **(B)** non-CV death. Non-CV death, Non-cardiovascular death.

(RR:0.68;95%CI:0.56–0.83;p for heterogeneity p = 0.08; I2 = 60%; p = 0.02). However, high-dose colchicine did not show similar benefits for MACE, MI, stroke, or revascularization. Finally, both high and low doses of colchicine increased the risk of gastrointestinal events compared to the control group, but low-dose colchicine treatment was not significantly associated with the occurrence of diarrhea (RR: 1.15; 95% CI: 0.96–1.37; p for heterogeneity p = 0.02; I2 = 84%; p = 0.33) (**Figure 9**).

Age

The mean age of subjects in 11 RCTs was ≤ 65 years (8, 12, 15, 17, 19–22, 24–26) and the age of subjects in the other 4 RCTs was > 65 years (7, 13, 16, 18),For all-cause deaths, CV deaths and non-CV deaths, colchicine had no effect at all age groups, In contrast, colchicine treatment significantly reduced the risk of MACE(RR: 0.69; 95% CI: 0.56–0.84; p for heterogeneity p = 0.06; I2 = 54%; p = 0.02), stroke(RR: 0.35; 95% CI: 0.16–0.74; p for heterogeneity p = 0.54; I2 = 0%; p < 0.01), MI(RR: 0.73; 95% CI: 0.59–0.91; p for heterogeneity p = 0.03; I2 = 62%; p = 0.03) and revascularization(RR: 0.69; 95% CI: 0.57–0.83; p for heterogeneity p = 0.17; I2 = 40%; p < 0.01) in subjects up to 65 years of age, but did not show significant differences in subjects over 65 years of age (**Figure 10**).

Dosing before percutaneous coronary intervention

Two RCTs (15, 16) reported the number of MACE events in patients after pre-PCI dosing. Pre-PCI colchicine did not have a significant effect on improving the risk of cardiovascular MACE in patients compared to the control group (RR: 0.90; 95% CI: 0.54–1.51; p for heterogeneity p = 0.99; I2 = 0%; p = 0.70) (**Figure 11**).

Related comorbidities

Two RCTs reported the number of MACE events in patients with diabetes and hypertension (7, 8) colchicine reduces the risk of MACE in patients with or without diabetes or hypertension. (diabetes: RR: 0.77; 95% CI: 0.60–0.99; p heterogeneity p = 0.27; I2 = 16%; p = 0.03; non-diabetes: RR: 0.73; 95% CI: 0.61–0.86; p heterogeneity p = 0.14; I2 = 55%; p = 0.02;hypertension: RR: 0.71; 95% CI: 0.59–0.86; p heterogeneity p = 0.44; I2 = 0%; p < 0.01; non-hypertension: RR: 0.76; 95% CI: 0.62–0.94; p heterogeneity

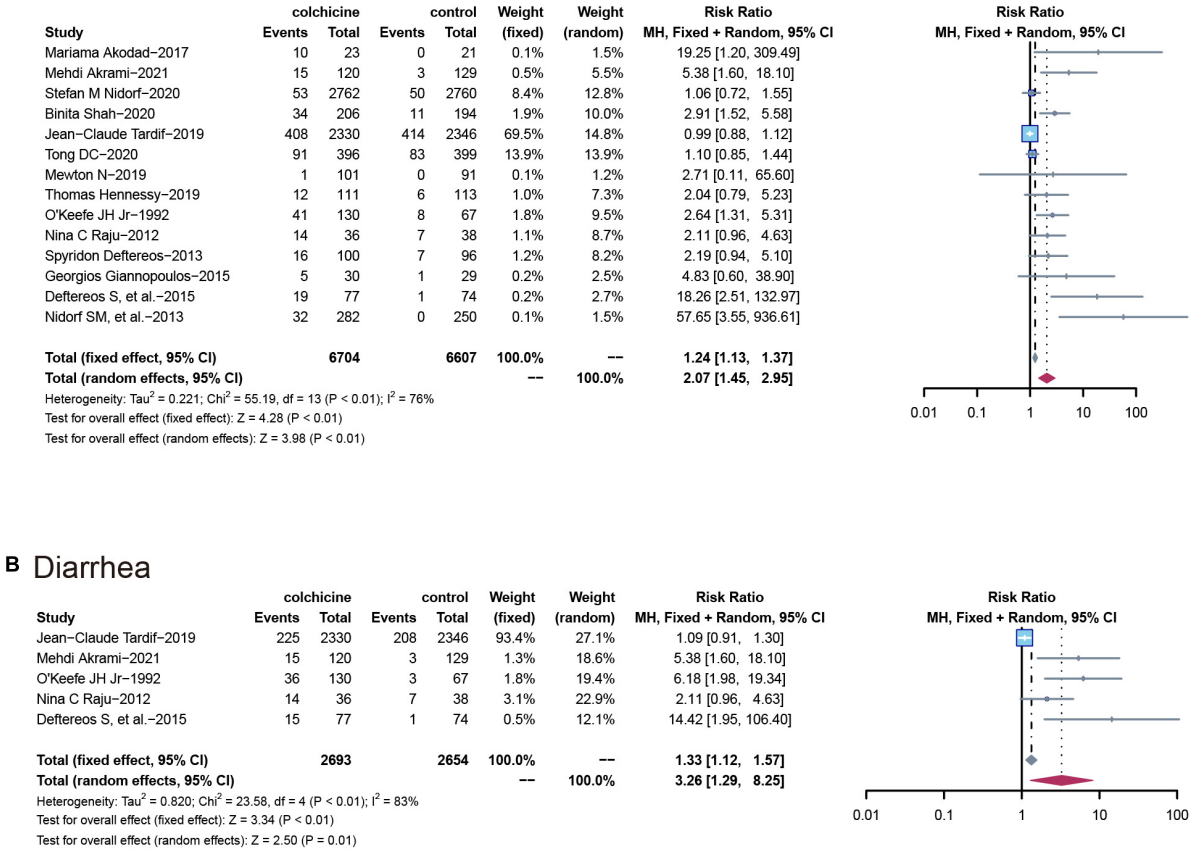


FIGURE 5
Comparison of colchicine treatment vs. control group on the risks of **(A)** GI side effect; **(B)** diarrhea. GI side effect, gastrointestinal side effects.

p = 0.78; I2 = 0%; p = 0.01) (**Figure 12**). Two RCTs reported the number of MACE events in patients with previous PCI or CABG (7, 8).,Patients with a reduced risk of MACE after colchicine compared to controls, regardless of whether PCI or CABG had been performed previously(prior PCI or GABG: RR: 0.74; 95% CI: 0.62–0.88; p heterogeneity p = 0.24; I2 = 28%; p < 0.01; non-PCI or GABG: RR: 0.73; 95% CI: 0.58–0.93; p heterogeneity p = 0.96; I2 = 0%; p < 0.01) (**Figure 12**).

Sex and smoking

Two RCTs reported the number of MACE events in male and female subjects (7, 8). The results showed that colchicine treatment significantly reduced the risk of MACE in men (RR: 0.70; 95% CI: 0.60–0.82; p heterogeneity p = 0.86; I2 = 0%; p < 0.01), but had no significant effect on the risk of events in women (RR: 0.24; 95% CI: 0.19–0.32; p heterogeneity p < 0.01; I2 = 99%; p = 0.31) (**Figure 12**). Two RCTs reported the number of MACE events in smoking and non-smoking subjects (7, 8),Colchicine significantly reduced the risk of MACE in non-smoking subjects compared with controls (RR: 0.70; 95% CI: 0.60–0.81; p for heterogeneity p = 0.69; I2 = 0%; p < 0.01), but had no significant effect on the risk of events in smoking subjects(RR:0.94; 95% CI:0.67–1.31; p for heterogeneity p = 0.92; I2 = 0%; p = 0.72) (**Figure 12**).

Discussion

This study aimed to analyze the effect of colchicine on cardiovascular risk by pooling available clinical trials. The study indicates that when compared with the control group (with or without placebo), the colchicine treatment group reduced the risk of MACE, MI, non-fatal stroke, and revascularization in patients with coronary artery disease; however, it did not reduce the risk of all-cause death, cardiovascular death, or non-cardiovascular death in patients with coronary artery disease. Long-term low-dose Colchicine significantly increases cardiovascular benefits in patients with coronary artery disease compared to high-dose Colchicine, interestingly, colchicine reduced cardiovascular risk in patients under the age of 65, but there was no significant correlation in patients over the age of 65. At the same time, when given before surgery to a

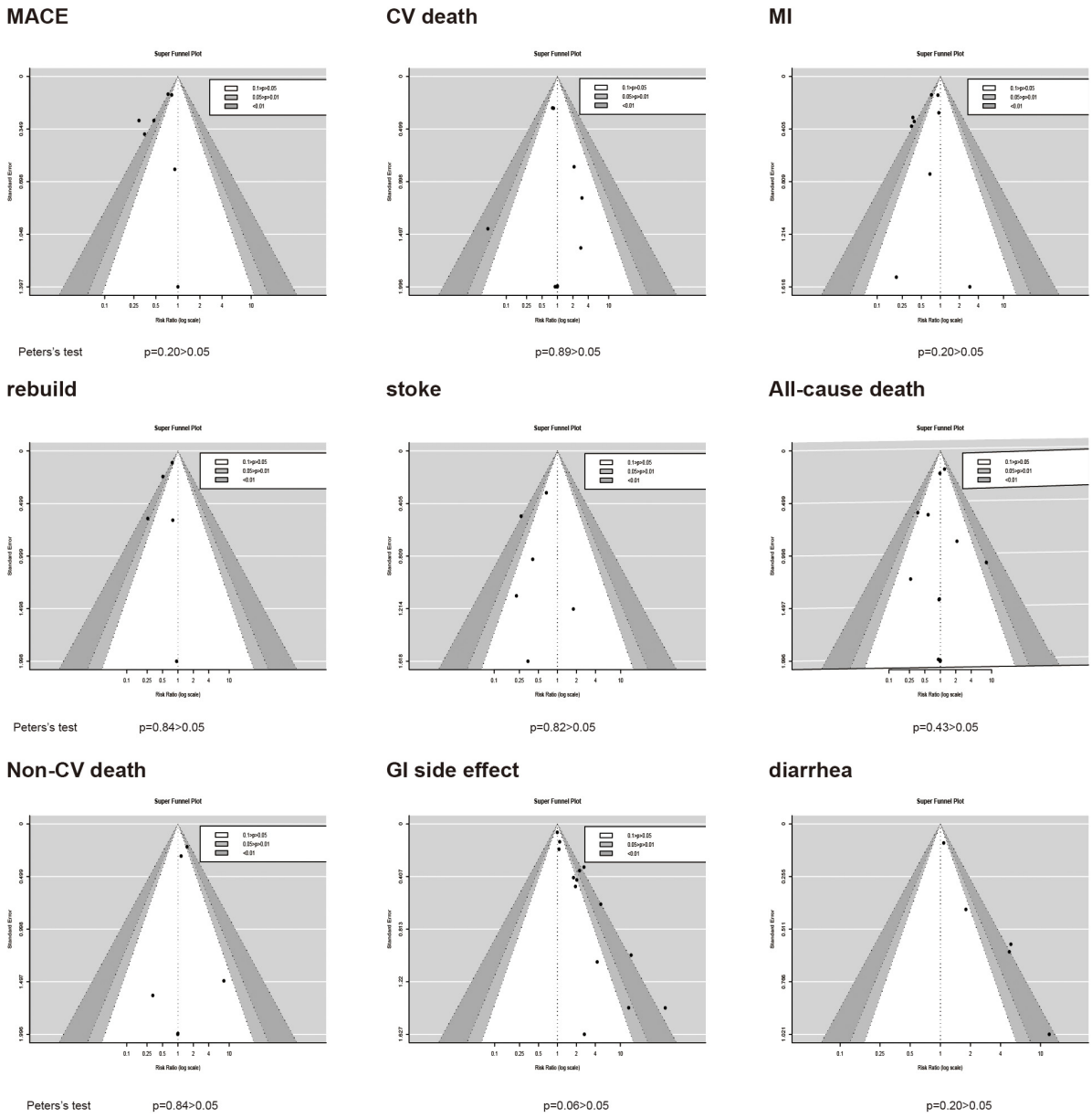


FIGURE 6
The detection of publication bias. Funnel chart.

group of patients with PCI, colchicine did not have any long-term effects.

We showed that the colchicine treatment group had a lower risk of MACE, MI, non-fatal stroke, and revascularization than the control group (with or without placebo). However, colchicine did not improve all-cause mortality or cardiovascular mortality in patients with coronary artery disease, nor did it reduce the risk of non-cardiovascular mortality in patients, as previous meta-analyses had found (10). However, The non-cardiovascular death rate was higher in the colchicine group compared to the control group in two large RCT (n = 5,522; n = 4,745) (7, 8). We were surprised to discover that colchicine may increase the risk of non-cardiovascular mortality when we excluded the Tong DC-2020 (n = 795) study from the meta-analysis(RR:1.42; 95% CI:1.01–1.98; p for heterogeneity; p = 0.44; I2 = 0%; p = 0.04) (22). Therefore, we think that

10.3389/fcvm.2022.947959

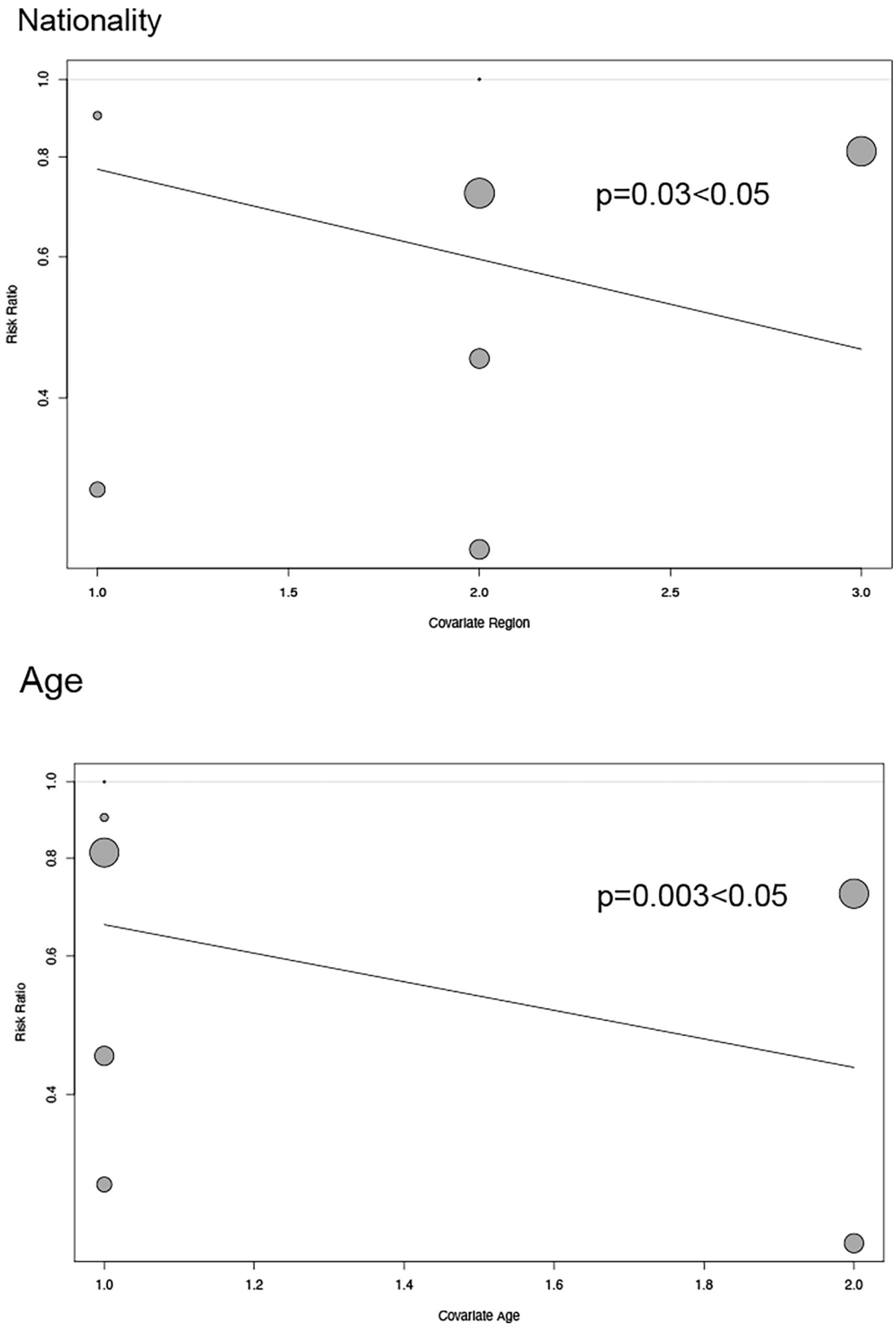


FIGURE 7
Regression plot exhibiting association between age and nationality of patients and major adverse cardiovascular events.

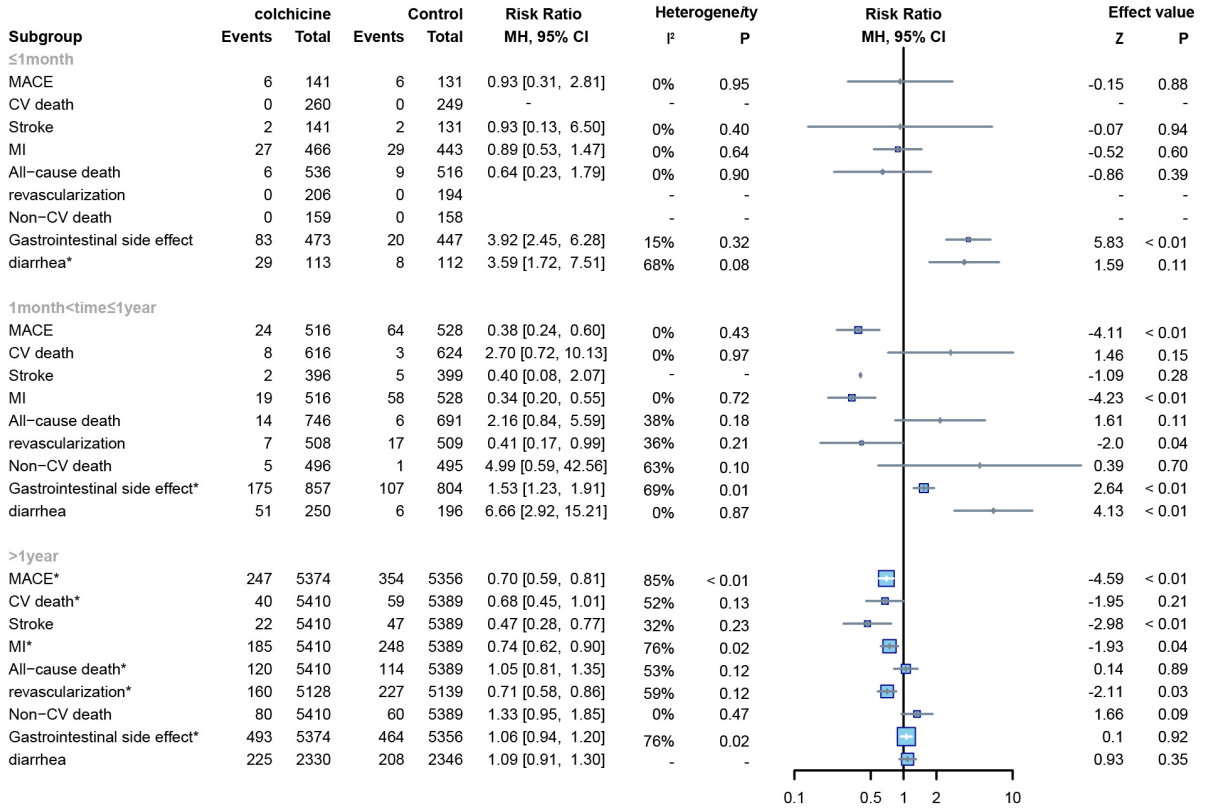


FIGURE 8
Forest plot of subgroup of study with different follow-up duration. MACE, major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction; Non-CV death, Non-cardiovascular death. *Random-effect model.

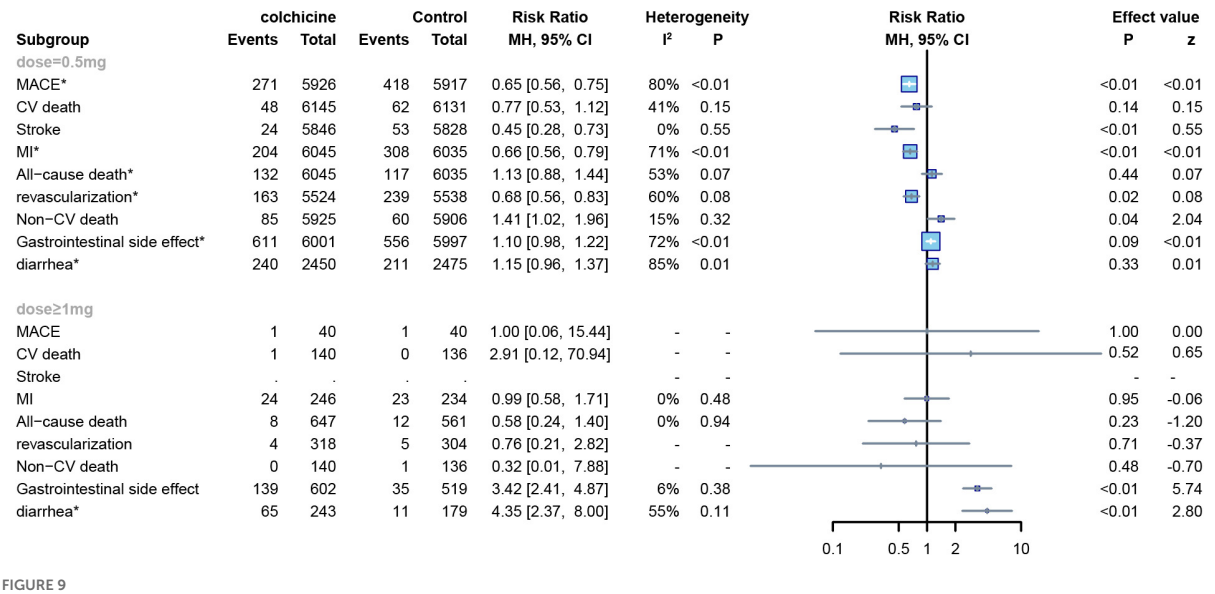


FIGURE 9
Forest plot of subgroup of the application dose of colchicine. MACE, major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction; Non-CV death, Non-cardiovascular death. *Random-effect model.

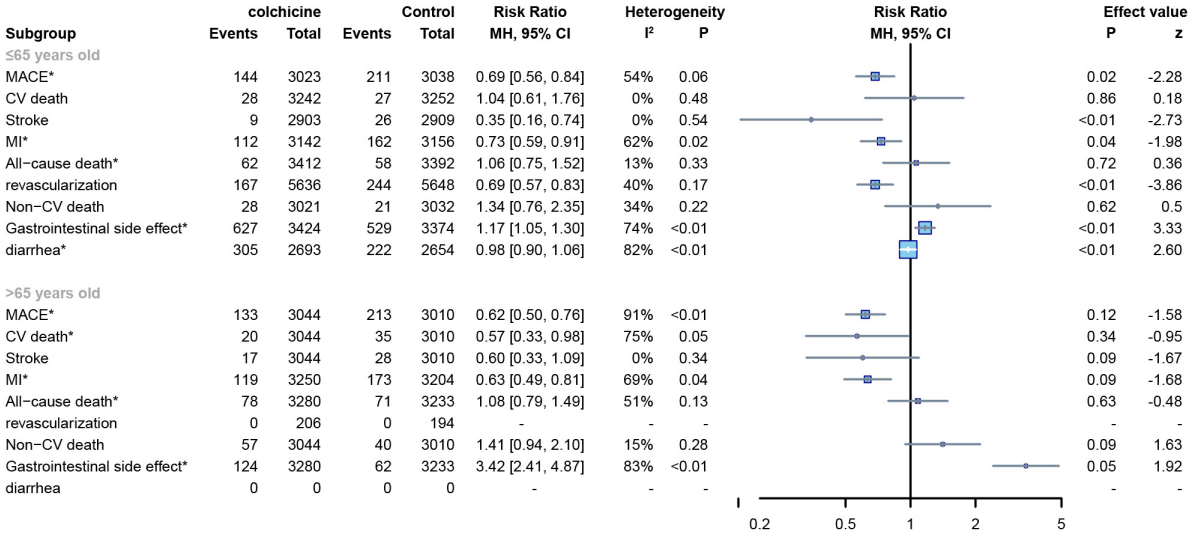


FIGURE 10
Forest plot of subgroup of subjects with varied age. MACE, major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction; Non-CV death, Non-cardiovascular death. *Random-effect model.

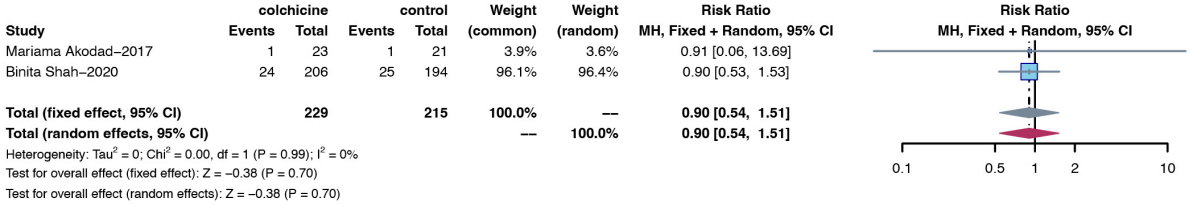


FIGURE 11
Forest plot of subgroups of MACE from studies with pre-surgical colchicine treatment. MACE, major adverse cardiovascular events.

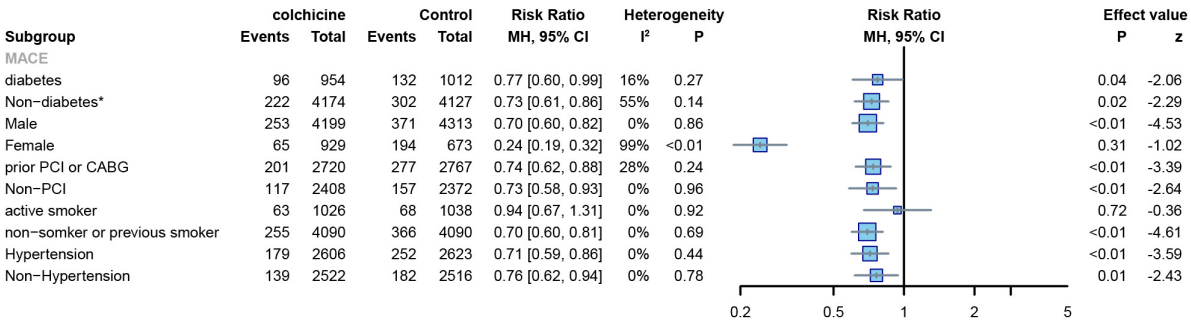


FIGURE 12
Forest plot of subgroup of the diabetes or not, sex, prior PCI or not, hypertension or not, and frequency of smoking. MACE, major adverse cardiovascular events. *Random-effect model.

colchicine's effects on non-cardiovascular mortality should be interpreted with care. To verify this reliability, more substantial RCTs are required.

At the same, subgroup analysis by colchicine dose showed that lower doses of colchicine reduced the risk of cardiovascular outcomes (MACE, MI, stroke, revascularization), whereas higher doses did not show a significant advantage in reducing the risks of cardiovascular outcomes. In a meta-analysis conducted by Thomas et al., a subgroup analysis was performed according to the colchicine dose used in each of

the included studies, reporting outcomes including all-cause death, cardiovascular death, stroke/TIA, MI, and ischemia-driven revascularization, contradicting our findings in that they concluded that there was no significant difference between high and low doses regarding the incidence of stroke/TIA and ischemia-driven revascularization (27). This could be because we have clearly defined stroke as a non-fatal stroke, with both deaths from stroke and non-fatal stroke included in their outcome indicators. At the same time, we found that colchicine increased the risk of gastrointestinal symptoms at both high and low doses, but the effect was less at low doses than at high doses (high dose RR: 1.10, low dose RR: 3.42), confirming previous findings (14, 28, 29).

In addition, we discovered that differences in the duration of study follow-up contributed to differences in outcomes, as colchicine is frequently used as a lifelong treatment for chronic disease and the duration of treatment affects long-term benefits and harms. A meta-analysis by Xia et al. showed that colchicine treatment with a follow-up of more than 6 months significantly reduced the incidence of major adverse cardiovascular events in patients with coronary artery disease (30). Which is consistent with our results, but they did not specify the efficacy of short-term colchicine treatment; Tien et al. previously reported an association between colchicine and the incidence of treatment-time MI in patients with coronary artery disease after PCI (31), but some subjects who had not undergone PCI were excluded from their study, which may have led to some bias. Their meta-analysis revealed that short-term (less than 6 months) treatment with colchicine significantly reduced the risk of MI after PCI compared to long-term treatment. To reduce bias, we included all patients with acute and chronic CAD in our study and divided the follow-up into three subgroups: 1 month, > 1 month and 1 year, and 1 year. In studies with less than 1 month of follow-up, we discovered that colchicine was not associated with a benefit in cardiovascular outcomes; however, in studies with longer follow-up, colchicine produced a more notable cardiovascular benefit when compared to controls. Gastrointestinal adverse events are colchicine's most common side effects (32). We found that the effects of colchicine on gastrointestinal side effects were less noticeable with longer follow-up. This could also be because the COLCOT (8) and LoDoCo2 trials (7), which had large sample sizes, were included in the subgroup of units that were followed for more than a year. As a result, more data are required to determine the risk of adverse gastrointestinal events over the duration of the study's follow-up. In addition, colchicine did not affect improving all-cause and cardiovascular mortality in coronary artery disease patients, regardless of dose or duration of follow-up.

Inflammation is a major factor in atherosclerosis (33, 34). In theory, reducing inflammation levels could be a therapeutic option to reduce cardiovascular risk in patients with CAD. Bytyçi et al. recently conducted a meta-analysis that found that giving colchicine for 24 h reduced inflammatory markers (hs-CRP, IL-1, IL-6, and IL-18) in patients with unstable CAD (9). Meanwhile, the COPE-PCI trial by Cole et al. showed that when colchicine was given before PCI, it was associated with a reduction in perioperative myocardial injury and lower levels of pre-PCI Inflammation (35). Colchicine's anti-inflammatory effect in CAD patients is well known. Surprisingly, we conducted a subgroup analysis of MACE events in subjects who had received preoperative colchicine for PCI and discovered that preoperative colchicine treatment did not affect the incidence of distant MACE events in patients. As far as we know, this study is the first to analyze the efficacy of colchicine in patients after preoperative administration of PCI. Unfortunately, due to the limited number of articles and the lack of substantial data to make definitive recommendations, this conclusion should be considered exploratory and further future studies are needed to demonstrate the long-term cardiovascular benefits of colchicine in patients after PCI.

When the included RCT studies were categorized by age, we discovered that colchicine had no correlation with age for all-cause, cardiovascular, and non-cardiovascular mortality. Colchicine produced a greater cardiovascular benefit in subjects up to 65 years of age compared to controls, whereas no significant differences were observed in subjects over 65 years of age. In the CARDIA study, Lloyd-Jones et al. (36) demonstrated that the occurrence of cardiovascular disease is closely related to a person's age group. The over-65 age group is at higher risk than other age groups, with approximately 60–80% of people facing subclinical cardiovascular disease, this may explain the result, in subjects of the aging population, the cardiovascular benefits of colchicine were outweighed by risk factors associated with their age.

This study encounters some limitations. (1)The majority of the RCTs included in this study were conducted in Western countries, and there was a lack of data on Asians, which may have resulted in bias. (2)Although we included as many RCTs that met the inclusion criteria as possible, the number of studies included in some subgroup analyses was relatively small. More research is still required to support our results. (3)When performing subgroup analyses for age, we chose the mean age of the study for analysis, which may have been biased. (4)There was considerable heterogeneity in comparing some outcome indicators (MI, MACE) and we tried to eliminate this heterogeneity by sensitivity analysis and subgroup analysis. (5) Differences in sample size between large and small trials may affect our results. The previously mentioned limitations require more large-scale RCTs to investigate further.

Conclusion

In this study, a meta-analysis of 15 RCTs was conducted to explore the clinical benefits and safety of colchicine after

its treatment for coronary heart disease. We found that colchicine treatment reduced the risk of MACE, MI, stroke, and revascularization but had no significant effect on all-cause mortality, cardiovascular, or non-cardiovascular mortality. In addition, colchicine may increase the risk of gastrointestinal adverse effects, and long-term low-dose colchicine treatment may reduce the incidence of cardiovascular events compared to higher doses, but colchicine does not appear to reduce cardiovascular risk in patients over 65 years of age or preoperative PCI, which needs to be evaluated and explored in more large sample RCTs.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Author contributions

ZM and JC conceptualized the study and performed screening, data extraction, and data analysis by R software. KJ assessed the risk of bias. ZM, JC, and KJ performed original draft preparation, reviewing, and editing. XC supervised and funded the work. All authors contributed to the article, approved, read, and agreed to the submitted version of the manuscript.

Funding

This research was funded by the Project of Sinopharm Dongfeng General Hospital (2022S01).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.947959/full#supplementary-material

References

1. Wilhelmsen L. Inflammation, infection, and coronary heart disease. *Eur Heart J.* (2002) 23:343–4. doi: 10.1053/euhj.2001.2956

2. von Hundelshausen P, Weber C. [Chronic inflammation and atherosclerosis]. *Dtsch Med Wochenschr.* (2013) 138:1839–44. doi: 10.1055/s-0033-1349426

3. Nerlekar N, Beale A, Harper RW. Colchicine–a short history of an ancient drug. *Med J Austr.* (2014) 201:687–8. doi: 10.5694/mja14.00846

4. Ozen S, Kone-Paut I, Gül A. Colchicine resistance and intolerance in familial mediterranean fever: definition, causes, and alternative treatments. *Semin Arthritis Rheum.* (2017) 47:115–20. doi: 10.1016/j.semarthrit.2017.03.006

5. Ravelli RBG, Gigant B, Curmi PA, Jourdain I, Lachkar S, Sobel A, et al. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature.* (2004) 428:198–202. doi: 10.1038/nature02393

6. Hastie SB. Interactions of colchicine with tubulin. *Pharmacol Ther.* (1991) 51:377–401. doi: 10.1016/0163-7258(91)90067-v

7. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med.* (2020) 383:1838–47. doi: 10.1056/NEJMoa2021372

8. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* (2019) 381:2497–505. doi: 10.1056/NEJMoa1912388

9. Bytyçi I, Bajraktari G, Penson PE, Henein MY, Banach M, Lipid and Blood Pressure Meta-Analysis Collaboration (Lbpmc) Group, et al. Efficacy and safety of colchicine in patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol.* (2022) 88:1520–8. doi: 10.1111/bcp.15041

10. Chen Y, Zhang H, Chen Y, Li M, Luo W, Liu Y, et al. Colchicine may become a new cornerstone therapy for coronary artery disease: a meta-analysis of randomized controlled trials. *Clin Rheumatol.* (2022) 41:1873–87. doi: 10.1007/s10067-022-06050-0

11. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

12. Akrami M, Izadpanah P, Bazrafshan M, Hatamipour U, Nouraein N, Drissi HB, et al. Effects of colchicine on major adverse cardiac events in next 6-month period after acute coronary syndrome occurrence; a randomized placebo-control trial. *BMC Cardiovasc Disord.* (2021) 21:583. doi: 10.1186/s12872-021-02393-9

13. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol.* (2013) 61:404–10. doi: 10.1016/j.jacc.2012.10.027

14. Robinson PC, Terkeltaub R, Pillinger MH, Shah B, Karalis V, Karatza E, et al. Consensus statement regarding the efficacy and safety of long-term low-dose colchicine in gout and cardiovascular disease. *Am J Med.* (2022) 135:32–8. doi: 10.1016/j.amjmed.2021.07.025

15. Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, et al. COLIN trial: value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. *Arch Cardiovasc Dis.* (2017) 110:395–402. doi: 10.1016/j.acvd.2016.10.004

16. Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, et al. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. *Circ Cardiovasc Interv.* (2020) 13:e008717. doi: 10.1161/CIRCINTERVENTIONS.119.008717

17. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. *J Thromb Thrombolysis.* (2012) 33:88–94. doi: 10.1007/s11239-011-0637-y

18. Giannopoulos G, Angelidis C, Kouritas VK, Dedeilias P, Filippatos G, Cleman MW, et al. Usefulness of colchicine to reduce perioperative myocardial damage in patients who underwent on-pump coronary artery bypass grafting. *Am J Cardiol.* (2015) 115:1376–81. doi: 10.1016/j.amjcard.2015.02.036

19. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation.* (2015) 132:1395–403. doi: 10.1161/CIRCULATIONAHA.115.017611

20. Zarpelon CS, Netto MC, Jorge JCM, Fabris CC, Desengrini D, Jardim Mda S, et al. Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization. *Arq Bras Cardiol.* (2016) 107:4–9. doi: 10.5935/abc.20160082

21. Talasaz AH, Jenab Y, Hosseini SH. P4611Colchicine before percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J.* (2019) 40(Suppl. 1):ehz745.0994. doi: 10.1093/eurheartj/ehz745.0994

22. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. *Circulation.* (2020) 142:1890–900. doi: 10.1161/CIRCULATIONAHA.120.050771

23. Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, et al. The low dose colchicine after myocardial infarction (LoDoCo-MI) study: a pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. *Am Heart J.* (2019) 215:62–9. doi: 10.1016/j.ahj.2019.06.003

24. O'Keefe JH, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol.* (1992) 19:1597–600. doi: 10.1016/0735-1097(92)90624-v

25. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol.* (2013) 61:1679–85. doi: 10.1016/j.jacc.2013.01.055

26. Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, et al. Effect of colchicine on myocardial injury in acute myocardial infarction. *Circulation.* (2021) 144:859–69. doi: 10.1161/CIRCULATIONAHA.121.056177

27. Kofler T, Kurmann R, Lehnick D, Cioffi GM, Chandran S, Attinger-Toller A, et al. Colchicine in patients with coronary artery disease: a systematic review and meta-analysis of randomized trials. *J Am Heart Assoc.* (2021) 10:e021198. doi: 10.1161/JAHA.121.021198

28. Andreis A, Imazio M, Piroli F, Avondo S, Casula M, Paneva E, et al. Efficacy and safety of colchicine for the prevention of major cardiovascular and cerebrovascular events in patients with coronary artery disease: a systematic review and meta-analysis on 12 869 patients. *Eur J Prev Cardiol.* (2022) 28:1916–25. doi: 10.1093/eurjpc/zwab045

29. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* (2010) 62:1060–8. doi: 10.1002/art.27327

30. Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. *Am J Cardiol.* (2021) 140:33–8. doi: 10.1016/j.amjcard.2020.10.043

31. Tien YY, Huang HK, Shih MC, Tu YK. Drug repurposing? Cardiovascular effect of colchicine on patients with coronary artery disease: a systematic review and meta-analysis. *J Cardiol.* (2021) 77:576–82. doi: 10.1016/j.jjcc.2020.11.010

32. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol.* (2010) 48:407–14. doi: 10.3109/15563650.2010.495348

33. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res.* (2019) 124:315–27. doi: 10.1161/CIRCRESAHA.118.313591

34. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* (2017) 377:1119–31. doi: 10.1056/NEJMoa1707914

35. Cole J, Htun N, Lew R, Freilich M, Quinn S, Layland J. COlchicine to prevent periprocedural myocardial injury in percutaneous coronary intervention (COPE-PCI): a descriptive cytokine pilot sub-study. *Cardiovasc Revasc Med.* (2022) 39:84–9. doi: 10.1016/j.carrev.2021.09.006

36. Lloyd-Jones DM, Lewis CE, Schreiner PJ, Shikany JM, Sidney S, Reis JP. The coronary artery risk development in young adults (CARDIA) study: JACC focus seminar. *J Am Coll Cardiol.* (2021) 78:260–77. doi: 10.1016/j.jacc.2021.05.022

frontiers | Frontiers in Cardiovascular Medicine

TYPE Mini Review
PUBLISHED 26 September 2022
DOI 10.3389/fcvm.2022.924461

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
Udhaya Kumar S.,
Vellore Institute of Technology, India

*CORRESPONDENCE
Yong He
heyong_huaxi@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 20 April 2022
ACCEPTED 22 August 2022
PUBLISHED 26 September 2022

CITATION
Zhang J, Chen Z, Ma M and He Y (2022) Soluble ST2 in coronary artery disease: Clinical biomarkers and treatment guidance.
Front. Cardiovasc. Med. 9:924461.
doi: 10.3389/fcvm.2022.924461

Soluble ST2 in coronary artery disease: Clinical biomarkers and treatment guidance

Junyan Zhang†, Zhongxiu Chen†, Min Ma and Yong He*

Department of Cardiology, West China Hospital of Sichuan University, Chengdu, China

The IL-33/ST2 L signaling pathway is involved in the pathophysiological processes of several diseases and mainly exerts anti-inflammatory and antifibrotic effects. Soluble suppression of tumorigenicity 2 (sST2), which serves as a competitive inhibitory molecule of this pathway, is a member of the interleukin (IL)-1 family, a decoy receptor for IL33, thought to play a role in cardiac remodeling and the inflammatory process. However, the association between sST2 and coronary artery disease (CAD), one of the most common causes of heart failure, is still being explored. We therefore reviewed the research on sST2 in the field of CAD, including reflecting the atherosclerosis burden, predicting no-reflow, predicting prognosis, responding to myocardial remodeling, and guiding management, hoping to provide cardiologists with new perspectives.

KEYWORDS

sST2, coronary artery disease, myocardial infarction, LVR, management

Introduction

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin 1 (IL-1) receptor family and is formally known as interleukin 1 receptor-like 1 (IL1RL-1). It was first described in 1989 but remained an orphan receptor mainly related to immune and inflammatory diseases for years (1). In 2005, ST2 was reported to be expressed in cardiac cells in response to myocardial stress, and interleukin 33 (IL-33) was reported to be the ligand of ST2 (2). Since then, its role in cardiovascular diseases has been of great concern. The ST2 gene is located on human chromosome 2q12 and encodes two main protein isoforms: transmembrane receptor (ST2 L) and truncated soluble receptor (sST2). The interaction between IL-33 and ST2 L mediates anti-inflammatory and antifibrotic effects (3). For instance, the activation of mitogen-activated protein kinase (MAPK) and nuclear factor (NF-kB) signaling originates from the binding of IL-33 to ST2 L, which produces various downstream effects in target cells in the presence of additional interleukin-1 receptor accessory protein (IL-1RacP) receptor protein molecules. In contrast, when IL-33 binds to sST2, it prevents and blocks these effects (4). While sST2 can be secreted into the circulation and functions as a decoy receptor for IL-33, it is unavailable to ST2 L, which abolishes the cardioprotective effects of IL-33/ST2. Meanwhile, ST2 is established as a selective marker of T helper type 2 (Th2) lymphocytes, which are also expressed on mast cells, epithelial cells, endothelial cells, smooth muscle cells, neonatal cardiac fibroblasts, and cardiac myocytes. More specifically, sST2 can serve as a non-invasive

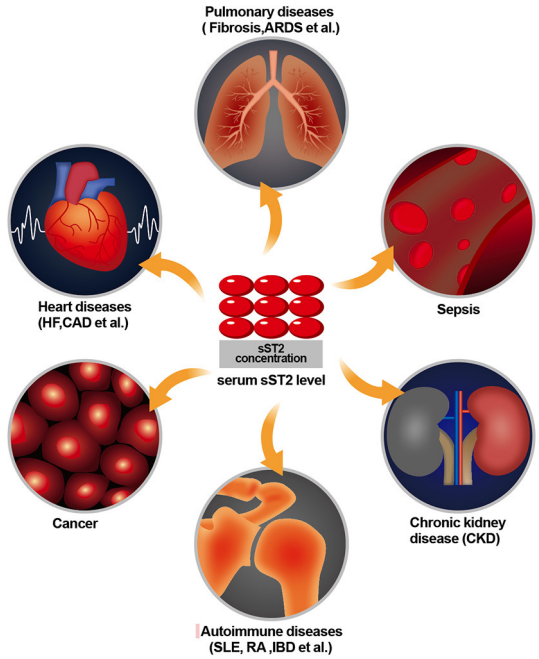


FIGURE 1
Role of sST2 in diseases of various systems.

diagnostic and prognostic marker for lung, gastric, breast, pancreatic, colon, and other cancers (5–7); can be present in diseases associated with a predominantly Th2 response, such as asthma, pulmonary fibrosis, and rheumatoid arthritis (8, 9); can be useful for risk stratification and prediction of prognosis in patients with suspected sepsis (10, 11); and can enhance the development of fibrosis, hypertrophy, remodeling of the heart muscle, and progression of heart failure (12, 13) (Figure 1). Although sST2 is involved in the pathophysiology of several diseases, an increasing number of recent studies have focused on heart disease, especially heart failure. Since sST2 is less influenced by age and renal insufficiency than N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) (14, 15), it has been entered into guidelines in heart failure and considered to provide additive prognostic value and as a guide to therapy decision-making of heart failure (16).

Coronary artery disease (CAD), especially acute coronary syndrome (ACS), is one of the most common causes of mortality throughout the world, despite technological improvements, new drugs, and an increasing level of awareness (17, 18). In fact, timely diagnosis allows physicians to stratify their patients by risk and consequently provide them with the opportunity to select appropriate treatments. Biomarkers that help refine diagnosis, risk stratification, and prognostic assessment are needed. In recent years, the role of ST2 in the pathophysiology of CAD and the clinical value of this biomarker in acute ST-segment elevation myocardial infarction (STEMI) have broadly expanded. In this study, we aimed to reappraise the current knowledge on sST2 in CAD (Figure 2).

Association with coronary atherosclerotic burden

The "inflammatory hypothesis" of atherosclerosis postulates that inflammatory cell signaling drives the formation, growth, and ultimately the instability of atherosclerotic plaques, setting up the substrate for the thrombotic response that causes myocardial damage or infarction (19). In the arterial wall, the interaction between IL-33 and ST2 L directs the immune response toward a T helper 2, macrophage 2 phenotype, limiting plaque inflammation and evolution. In contrast, sST2 blocks the protective effects of IL-33 on atherosclerotic plaques by sequestering IL-33 (20).

Pfetsh et al. observed a strong correlation between elevated sST2 levels and inflammatory markers (hs-CRP and IL-6) that may reflect the presence of chronic inflammation in the pathophysiology of atherosclerosis (21). In addition to being closely related to the progression of atherosclerotic lesions, sST2 has been reported as a biomarker for the stability and complexity of coronary atherosclerosis. Previous studies have shown that an increased sST2 level is a strong marker of increased risk for mortality and adverse cardiac events, such as recurrent MI and stroke, in patients with AMI (22). Zhang et al. revealed that plasma sST2 levels were significantly higher in ACS patients with complex lesions than in those with simple lesions, which indicated that sST2 may be a new marker for assessing the stability and complexity of atherosclerotic plaques (23). However, the above study also showed that there were no correlations between plasma sST2 level and stenosis severity, measured by the number of culprit vessels and Gensini score. Dieplinger et al. came to the same conclusion as above, which elucidated that sST2 was not related to the angiographic severity of CAD (24). The reason for higher sST2 levels in patients with complex lesions than in patients with simple lesions in ACS was explained in the study of Demyanet et al., which showed that sST2 may play a role in the development of vulnerability and plaque rupture, which occurs most predominantly in the ACS population (25).

Based on the above studies, Luo et al. prospectively enrolled 120 patients to assess plaque vulnerability by coronary computed tomography angiography (CCTA) (26). Their study showed that higher serum sST2 levels were associated with higher plaque vulnerability. However, the two prevailing intracoronary imaging techniques in clinical practice, IVUS, which allows macroscopic visualization of the structure of the entire vessel wall, and OCT, which allows microscopic visualization of the subtle structure of the wall, complement each other and can be

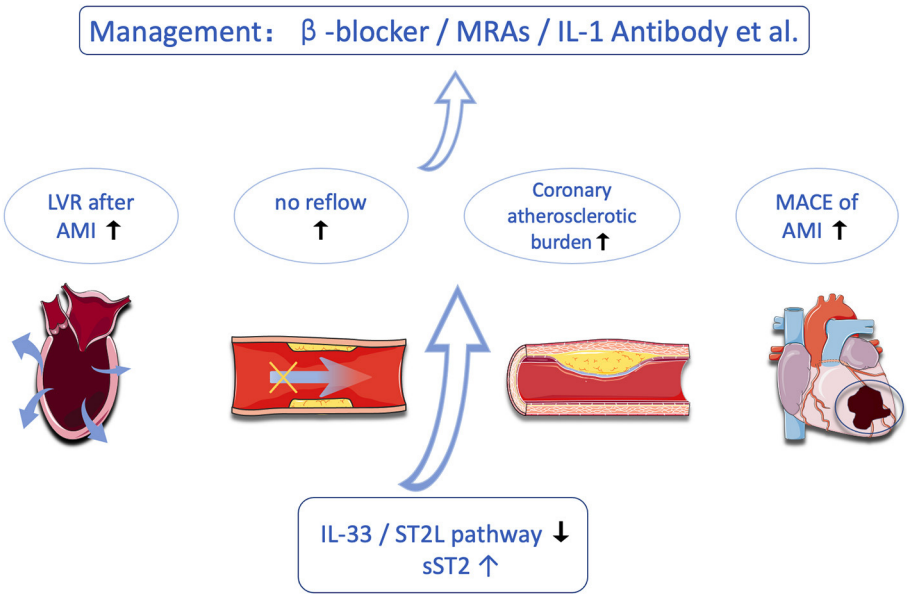


FIGURE 2
Research progress on sST2 in the field of coronary heart disease.

used as an important tool for identifying vulnerable plaques (27–29). Therefore, studies using IVUS and OCT as outcomes should be conducted to further validate the correlation between sST2 and plaque vulnerability.

Meanwhile, the coronary artery calcium score (CACS) is a marker of atherosclerotic plaque burden and an independent predictor of coronary events. In the study by Oh et al. (30), researchers enrolled 456 subjects to illustrate that, compared with hsCRP, sST2 does not improve net reclassification for predicting a high-risk CACS, defined as CACS ≥300 Agatston units. Overall, sST2 may reflect the atherosclerotic burden in unstable, complex atherosclerotic lesions, but further studies are needed to focus on this issue.

Predict no-reflow phenomenon after percutaneous coronary intervention

The no-reflow phenomenon is defined as insufficiency of myocardial perfusion despite the mechanically responsible lesion being opened. The no-reflow phenomenon rate can reach as high as 50% in ACS patients (31) and restrain the positive effects of percutaneous coronary intervention (PCI). As there is limited treatment of no-reflow, it is more important to prevent it from occurring (32). Clinicians are committed to finding markers or clinical conditions that can predict no-reflow. It was demonstrated that sST2, a biomarker related to inflammatory activity, is one of the independent predictors of the no-reflow phenomenon in STEMI patients undergoing primary PCI. Somuncu et al. (33) included 379 patients who underwent PCI treatment for STEMI to determine the relationship between sST2 and the no-reflow phenomenon. Higher levels of sST2 patients had a significantly higher level of no-reflow compared with lower levels of sST2 (OR: 2.741 CI 95% 1.433–5.244, $p = 0.002$). Furthermore, after adjustment for potential confounders, it was found that being in a high-sST2 group was one of the independent predictors of no-reflow [area under the curve (AUC), 0.699; 95% confidence interval (CI), 0.65–0.75; $P < 0.001$].

Since the above study showed that sST2 can predict the no-reflow phenomenon in STEMI patients, experts then turned their attention to non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Zhang et al. (34) revealed similar results, which pointed out that although the predictive ability was low, sST2 had a predictive value for no-reflow [area under the curve (AUC), 0.662; 95% confidence interval (CI), 0.53–0.79; $P = 0.015$]. It also had independent predictive value after adjusting for confounding factors [odds ratio (OR), 3.802; 95% CI, 1.03–14.11; $P = 0.046$]. However, both studies were single-center studies, and the number of patients included was relatively small. More importantly, they only detected the sST2 level of patients at the time of admission but did not observe subsequent changes. Thus, more high-quality trials should be carried out to determine the relationship between sST2 and no-reflow.

As a prognostic biomarker of CAD

Shimpo et al. demonstrated that sST2 levels can predict mortality and heart failure in MI patients by extracting sST2

from the serum of 810 AMI patients (35). Then, Sabatine et al. measured ST2 at baseline in 1,239 patients with STEMI from the CLARITY-TIMI 28 trial, which showed that a high baseline ST2 level, irrespective of baseline features and NT-proBNP, is a strong predictor of cardiovascular mortality and heart failure in STEMI, and the combination of ST2 and NT-proBNP greatly enhances risk stratification (36). At the same time, studies have shown that sST2 is also an independent predictor of future death or heart failure in patients with acute chest pain in the emergency department (37). In contrast, sST levels did not predict the occurrence of MACEs in STEMI patients in the study by Kim et al. (38). The reason for this phenomenon may be that sST2 levels begin to rise at 3 h after STEMI and peak at 12 h. The length of time after AMI onset to reperfusion affects myocardial injury, which is associated with an increase in biomechanical strain, leading to higher sST2 levels. The median time from onset to PCI for patients in this study was 2.7–2.8 h, which is shorter than in other studies (38). These patients, on the one hand, had a short period of myocardial ischemia and may not have been severely injured; on the other hand, they may have had an earlier measurement of sST2, resulting in sST2 not yet being elevated to the desired level. As in STEMI patients, the prognostic predictive role of sST2 in patients with chronic coronary artery disease (SCAD) remains controversial. The 13-year follow-up results of the KAROLA study suggest that sST2 levels can be an independent predictor of mortality in SCAD patients but do not predict non-fatal cardiovascular events (21). Similarly, the results from the Ludwigshafen Risk and Cardiovascular Health Study also elucidated that increased sST2 levels were an independent predictor of long-term all-cause mortality in patients with SCAD (24). However, Demyanets et al. came to the opposite conclusion, stating that sST2 was not associated with mortality in SCAD patients, despite a strong relationship with mortality in STEMI patients (25). Hughes et al. also showed that sST2 does not function as a predictor of cardiovascular events in the general population (39). The reason for this discrepancy may be because the latter study included not only patients with unstable coronary plaque but also patients with stable coronary artery disease, which interfered with the results.

Although many studies have confirmed that sST2 has a strong predictive effect on the prognosis of heart failure, the number of studies on sST2 and the prognosis of CAD, both in ACS and chronic coronary syndrome (CCS), is limited, and their findings are controversial. Therefore, more studies should be conducted in the future to further explore the prognostic effect of sST2 on CAD.

Reflect left ventricular remodeling after acute myocardial infarction

Left ventricular remodeling (LVR) refers to changes in the shape and size of the whole left ventricle after acute myocardial infarction (AMI). Important pathological features of postinfarction LV remodeling include infarct expansion, myocardial hypertrophy, cardiac fibrosis, and ventricular dilation, which are mainly due to inflammatory responses and neuroendocrine activation (40, 41). The development of adverse LVR after AMI remains a significant problem despite current achievements in invasive and pharmacological treatment (40).

Meanwhile, ST2 regulates the expression of proinflammatory cytokines from macrophages and prevents uncontrolled inflammatory reactions in the MI region. The sST2 level could be responsible for myocardial fibrosis and LVR, which could affect the prognosis after MI (40, 42). By constructing a mouse model of MI, Ghali et al. illustrated that IL-33 administration was associated with deterioration of cardiac function and ventricular remodeling. This study validated the role of the IL-33/ST2 axis in LVR after MI and laid the theoretical foundation for subsequent clinical studies (42). Thus, several studies using cardiac magnetic resonance (CMR) or echocardiography (ECHO) as a measure of LVR have been performed to demonstrate the relationship between sST2 and LVR after MI. Weir et al. included 100 patients with AMI for whom serum biomarkers were measured and CMR scans were performed and demonstrated a direct relationship between sST2 and LVR (43). It was also shown that sST2 was higher in individuals with microvascular obstruction (MVO), which is related to a more significant LVR and a poorer cardiovascular prognosis following AMI (44, 45). Kercheva et al. reached a similar conclusion from ECHO endpoints that the rise in serum sST2 was strongly associated with LVR after 6 months (46). Another similar study also found that sST2 levels correlated with both early LVR (<3 months) and late LVR (>3 months) (47). Based on these studies, using novel drugs that may antagonize this pathway, e.g., novel interleukin-1 monoclonal antibodies to antagonize the process of LVR, becomes theoretically possible, but this builds on more experiments demonstrating the causal relationship between sST2 and LVR (47).

Currently, mainly instrumental markers, such as the parameters of ECHO and CMR, are used to indicate the development of adverse LVR (48). The quest for a practical and reliable biomarker of adverse LVR, which would allow us to predict this disease in its early stages based on an exact assessment date, appears to be promising (49). Since both hemodynamic stress and an inflammatory nature are involved in the pathophysiological process of LVR, indicators that might reflect this process, such as NT-proBNP and hsCRP, have been of interest to cardiologists (36). Unlike NT-ProBNP, which responds to cardiac mechanical stress, sST2 reflects the degree of necrosis and inflammatory response of cardiomyocytes (50). Meanwhile, the dynamics of serum levels are different, which affects the timing and purpose of their clinical application. The level of sST2 decreased rapidly during the 7 days after MI; however, the level of NT-proBNP decreased effectively after the first 7 days (46). Then, Pecherina et al. performed a correlation

analysis of echocardiographic parameters and serum biomarkers in patients with STEMI and preserved left ventricular ejection fraction, which showed that sST2 predicted LVR better than NT-proBNP (AUC 0.8 and 0.7, respectively), and several other biomarkers, such as matrix metalloproteinases (MMPs) and galectin-3, were also included in the study, illustrating that biomarkers combined with imaging findings can better predict the occurrence of LVR (51).

Moreover, several studies have found a link between sST2 and circulating aldosterone, implying that the IL-33/sST2 signaling system and the RAAS are linked (43). This raises the possibility of a direct role for the IL-33/sST2 system in the pathogenesis of postinfarction remodeling. Studies are already underway in this area, and the effects of drugs such as eplerenone, spironolactone, and beta-blockers on the IL-33/sST2 axis are gradually being discovered by cardiologists (52, 53), but more research is still needed in this area to find an optimal strategy to detect and cope with ventricular remodeling in an early stage after MI.

As help for management of myocardial infarction

The IL-33/ST2 signaling pathway is involved in various adverse pathophysiological processes after infarction, such as fibrosis, inflammation, and hypertrophy, which are important targets for a variety of neuroendocrine antagonists currently available to improve the prognosis of MI patients. Xia et al. demonstrated that beta-blockers could inhibit fibrosis, reduce infarct size, and improve cardiac function by enhancing the IL-33/ST2 signaling pathway through the construction of an AMI mouse model and that this effect results in a decrease in serum sST2 levels (54). It is possible that measurement of serum sST2 levels may reflect the efficacy of beta-blockers in patients with AMI. Next, Gaggin et al. performed a *post-hoc* analysis of the PROTECT study in which the group of patients who received high-dose beta-blockers with low sST2 levels had the best prognosis, suggesting that sST2 levels can assist cardiologists in selecting the best treatment option for patients with MI (53). Like beta-blockers, mineralocorticoid receptor antagonists (MRAs) are also widely used as neuroendocrine antagonists that can inhibit myocardial remodeling and improve prognosis in patients with MI. Other studies have also shown that both eplerenone and spironolactone antagonize aldosterone and are able to enhance the IL-33/ST2 signaling pathway while decreasing serum sST2 levels. Therefore, the detection of serum sST2 levels can also reflect the efficacy of these drugs (52, 55).

Conclusion and clinical perspectives

Soluble ST2 is a promising biomarker in cardiology, not only in heart failure but also in CAD. As a biomarker related to inflammation and fibrosis, sST2 has important clinical value in CAD, which may guide prognosis prediction, treatment plan selection, risk assessment, and long-term management of MI patients. In this article, we reviewed the use of sST2 in coronary artery disease, including reflecting plaque burden, predicting no-reflow events, predicting the prognosis of patients, reflecting LVR, and guiding the management of patients with MI. We hope that, in the near future, new studies will be conducted to better characterize and understand the relationship between sST2 and CAD.

Author contributions

JZ and ZC wrote the manuscript. MM and YH conceived, instructed, reviewed, and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding

This work was supported by the Fellowship of China Postdoctoral Science Foundation (No. 2020M683325), the Postdoctoral Research Project, West China Hospital, Sichuan University (No. 2020HXBH048), and the Innovative Scientific Research Project of Medical Youth in Sichuan Province (No. Q20061).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Iwahana H, Yanagisawa K, Ito-Kosaka A, Kuroiwa K, Tago K, Komatsu N, et al. Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. *Eur J Biochem.* (1999) 264:397–406. doi: 10.1046/j.1432-1327.1999.00615.x

2. Pascual-Figal DA, Januzzi JL. The biology of ST2: the International ST2 Consensus Panel. *Am J Cardiol.* (2015) 115:3B–7B. doi: 10.1016/j.amjcard.2015.01.034

3. Homsak E, Gruson D. Soluble ST2: a complex and diverse role in several diseases. *Clin Chim Acta.* (2020) 507:75–87. doi: 10.1016/j.cca.2020.04.011

4. Lingel A, Weiss TM, Niebuhr M, Pan B, Appleton BA, Wiesmann C, et al. Structure of IL-33 and its interaction with the ST2 and IL-1RAcP receptors–insight into heterotrimeric IL-1 signaling complexes. *Structure.* (2009) 17:1398–410. doi: 10.1016/j.str.2009.08.009

5. Lu DP, Zhou XY, Yao LT, Liu CG, Ma W, Jin F, et al. Serum soluble ST2 is associated with ER-positive breast cancer. *BMC Cancer.* (2014) 14:198. doi: 10.1186/1471-2407-14-198

6. Wang C, Chen Z, Bu X, Han Y, Shan S, Ren T, et al. IL-33 signaling fuels outgrowth and metastasis of human lung cancer. *Biochem Biophys Res Commun.* (2016) 479:461–8. doi: 10.1016/j.bbrc.2016.09.081

7. Zhang Y, Davis C, Shah S, Hughes D, Ryan JC, Altomare D, et al. IL-33 promotes growth and liver metastasis of colorectal cancer in mice by remodeling the tumor microenvironment and inducing angiogenesis. *Mol Carcinog.* (2017) 56:272–87. doi: 10.1002/mc.22491

8. Boga S, Alkim H, Koksal AR, Ozagari AA, Bayram M, Tekin Neijmann S, et al. Serum ST2 in inflammatory bowel disease: a potential biomarker for disease activity. *J Investig Med.* (2016) 64:1016–24. doi: 10.1136/jim-2016-000062

9. Pei C, Barbour M, Fairlie-Clarke KJ, Allan D, Mu R, Jiang HR. Emerging role of interleukin-33 in autoimmune diseases. *Immunology.* (2014) 141:9–17. doi: 10.1111/imm.12174

10. Hur M, Kim H, Kim HJ, Yang HS, Magrini L, Marino R, et al. Soluble ST2 has a prognostic role in patients with suspected sepsis. *Ann Lab Med.* (2015) 35:570–7. doi: 10.3343/alm.2015.35.6.570

11. Kim H, Hur M, Moon HW, Yun YM, Di Somma S, Network G. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. *Ann Intensive Care.* (2017) 7:27. doi: 10.1186/s13613-017-0252-y

12. De la Fuente M, MacDonald TT, Hermoso MA. The IL-33/ST2 axis: role in health and disease. *Cytokine Growth Factor Rev.* (2015) 26:615–23. doi: 10.1016/j.cytogfr.2015.07.017

13. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation.* (2002) 106:2961–6. doi: 10.1161/01.CIR.0000038705.69871.D9

14. Aimo A, Januzzi JL Jr, Vergaro G, Richards AM, Lam CSP, Latini R, et al. Circulating levels and prognostic value of soluble ST2 in heart failure are less influenced by age than N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T. *Eur J Heart Fail.* (2020) 22:2078–88. doi: 10.1002/ejhf.1701

15. Kim MS, Jeong TD, Han SB, Min WK, Kim JJ. Role of soluble ST2 as a prognostic marker in patients with acute heart failure and renal insufficiency. *J Korean Med Sci.* (2015) 30:569–75. doi: 10.3346/jkms.2015.30.5.569

16. Aimo A, Januzzi JL Jr, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, et al. Clinical and prognostic significance of sst2 in heart failure: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74:2193–203. doi: 10.1016/j.jacc.2019.08.1039

17. Madhavan MV, Gersh BJ, Alexander KP, Granger CB, Stone GW. Coronary artery disease in patients >/=80 years of age. *J Am Coll Cardiol.* (2018) 71:2015–40. doi: 10.1016/j.jacc.2017.12.068

18. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S, et al. Review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol.* (2019) 234:16812–23. doi: 10.1002/jcp.28350

19. Kobiyama K, Ley K. Atherosclerosis. *Circ Res.* (2018) 123:1118–20. doi: 10.1161/CIRCRESAHA.118.313816

20. Aimo A, Migliorini P, Vergaro G, Franzini M, Passino C, Maisel A, et al. The IL-33/ST2 pathway, inflammation and atherosclerosis: trigger and target? *Int J Cardiol.* (2018) 267:188–92. doi: 10.1016/j.ijcard.2018.05.056

21. Pfetsch V, Sanin V, Jaensch A, Dallmeier D, Mons U, Brenner H, et al. Increased plasma concentrations of soluble ST2 independently predict mortality but not cardiovascular events in stable coronary heart disease patients: 13-year follow-up of the KAROLA study. *Cardiovasc Drugs Ther.* (2017) 31:167–77. doi: 10.1007/s10557-017-6718-1

22. Dhillon OS, Narayan HK, Khan SQ, Kelly D, Quinn PA, Squire IB, et al. Pre-discharge risk stratification in unselected STEMI: is there a role for ST2 or its natural ligand IL-33 when compared with contemporary risk markers? *Int J Cardiol.* (2013) 167:2182–8. doi: 10.1016/j.ijcard.2012.05.073

23. Zhang Y, Fan Z, Liu H, Ma J, Zhang M. Correlation of plasma soluble suppression of tumorigenicity-2 level with the severity and stability of coronary atherosclerosis. *Coronary Artery Dis.* (2020) 2020:851. doi: 10.1097/MCA.0000000000000851

24. Dieplinger B, Egger M, Haltmayer M, Kleber ME, Scharnagl H, Silbernagel G, et al. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. *Clin Chem.* (2014) 60:530–40. doi: 10.1373/clinchem.2013.209858

25. Demyanets S, Speidl WS, Tentzeris I, Jarai R, Katsaros KM, Farhan S, et al. Soluble ST2 and interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome. *PLoS ONE.* (2014) 9:e95055. doi: 10.1371/journal.pone.0095055

26. Luo G, Qian Y, Sheng X, Sun J, Wu Z, Liao F, et al. Elevated serum levels of soluble ST2 are associated with plaque vulnerability in patients with non-ST-elevation acute coronary syndrome. *Front Cardiovasc Med.* (2021) 8:688522. doi: 10.3389/fcvm.2021.688522

27. Tian J, Ren X, Vergallo R, Xing L, Yu H, Jia H, et al. Distinct morphological features of ruptured culprit plaque for acute coronary events compared to those with silent rupture and thin-cap fibroatheroma: a combined optical coherence tomography and intravascular ultrasound study. *J Am Coll Cardiol.* (2014) 63:2209–16. doi: 10.1016/j.jacc.2014.01.061

28. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. *In vivo* diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol.* (2013) 62:1748–58. doi: 10.1016/j.jacc.2013.05.071

29. Jia H, Dai J, Hou J, Xing L, Ma L, Liu H, et al. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J.* (2017) 38:792–800. doi: 10.1093/eurheartj/ehw381

30. Oh J, Park S, Yu HT, Chang HJ, Lee SH, Kang SM, et al. Lack of superiority for soluble ST2 over high sensitive C-reactive protein in predicting high risk coronary artery calcium score in a community cohort. *Yonsei Medical J.* (2016) 57:1347–53. doi: 10.3349/ymj.2016.57.6.1347

31. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no reflow. *Int J Cardiol.* (2015) 187:273–80. doi: 10.1016/j.ijcard.2015.03.359

32. Rezkalla SH, Stankowski RV, Hanna J, Kloner RA. Management of no-reflow phenomenon in the catheterization laboratory. *JACC Cardiovasc Intervent.* (2017) 10:215–23. doi: 10.1016/j.jcin.2016.11.059

33. Somuncu MU, Akgun T, Cakir MO, Akgul F, Serbest NG, Karakurt H, et al. The elevated soluble ST2 predicts no-reflow phenomenon in ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Atheroscler Thromb.* (2019) 26:970–8. doi: 10.5551/jat.48413

34. Zhang Q, Hu M, Ma S. Association of soluble suppression of tumorigenicity with no-reflow phenomenon and long-term prognosis in patients with non-ST-segment elevation acute coronary syndrome after percutaneous coronary intervention. *J Atheroscler Thromb.* (2021) 28:1289–97. doi: 10.5551/jat.59832

35. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation.* (2004) 109:2186–90. doi: 10.1161/01.CIR.0000127958.21003.5A

36. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. *Circulation.* (2008) 117:1936–44. doi: 10.1161/CIRCULATIONAHA.107.728022

37. Aldous SJ, Richards AM, Troughton R, Than M. ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the emergency department with chest pain. *J Card Fail.* (2012) 18:304–10. doi: 10.1016/j.cardfail.2012.01.008

38. Kim M, Lee DI, Lee JH, Kim SM, Lee SY, Hwang KK, et al. Lack of prognostic significance for major adverse cardiac events of soluble suppression of tumorigenicity 2 levels in patients with ST-segment elevation myocardial infarction. *Cardiol J.* (2021) 28:244–54. doi: 10.5603/CJ.a2020.0028

39. Hughes MF, Appelbaum S, Havulinna AS, Jagodzinski A, Zeller T, Kee F, et al. ST2 may not be a useful predictor for incident cardiovascular events, heart failure and mortality. *Heart.* (2014) 100:1715–21. doi: 10.1136/heartjnl-2014-305968

40. Dorn GW. Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. *Nat Rev Cardiol.* (2009) 6:283–91. doi: 10.1038/nrcardio.2009.12

41. Yousef ZR, Redwood SR, Marber MS. Postinfarction left ventricular remodelling: where are the theories and trials leading us? *Heart.* (2000) 83:76–80. doi: 10.1136/heart.83.1.76

42. Bayes-Genis A, de Antonio M, Galan A, Sanz H, Urrutia A, Cabanes R, et al. Combined use of high-sensitivity ST2 and NTproBNP to improve the prediction of death in heart failure. *Eur J Heart Fail.* (2012) 14:32–8. doi: 10.1093/eurjhf/hfr156

43. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol.* (2010) 55:243–50. doi: 10.1016/j.jacc.2009.08.047

44. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation.* (1996) 93:223–8. doi: 10.1161/01.CIR.93.2.223

45. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation.* (1998) 97:765–72. doi: 10.1161/01.CIR.97.8.765

46. Kercheva M, Ryabova T, Gusakova A, Suslova TE, Ryabov V, Karpov RS. Serum soluble ST2 and adverse left ventricular remodeling in patients with ST-segment elevation myocardial infarction. *Clin Med Insights Cardiol.* (2019) 13:1179546819842804. doi: 10.1177/1179546819842804

47. Biere L, Garcia G, Guillou S, Larcher F, Furber A, Willoteaux S, et al. ST2 as a predictor of late ventricular remodeling after myocardial infarction. *Int J Cardiol.* (2018) 259:40–2. doi: 10.1016/j.ijcard.2018.02.058

48. Galli A, Lombardi F. Postinfarct left ventricular remodelling: a prevailing cause of heart failure. *Cardiol Res Pract.* (2016) 2016:2579832. doi: 10.1155/2016/2579832

49. Ciccone MM, Cortese F, Gesualdo M, Riccardi R, Di Nunzio D, Moncelli M, et al. Novel cardiac bio-marker: ST2: a review. *Molecules.* (2013) 18:15314–28. doi: 10.3390/molecules181215314

50. Yu J, Oh PC, Kim M, Moon J, Park YM, Lee K, et al. Improved early risk stratification of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention using a combination of serum soluble ST2 and NT-proBNP. *PLoS ONE.* (2017) 12:e0182829. doi: 10.1371/journal.pone.0182829

51. Pecherina T, Kutikhin A, Kashtalap V, Karetnikova V, Gruzdeva O, Hryachkova O, et al. Serum and echocardiographic markers may synergistically predict adverse cardiac remodeling after ST-segment elevation myocardial infarction in patients with preserved ejection fraction. *Diagnostics.* (2020) 10:50301. doi: 10.3390/diagnostics10050301

52. Chen B, Geng J, Gao SX, Yue WW, Liu Q. Eplerenone modulates interleukin-33/sST2 signaling and IL-1beta in left ventricular systolic dysfunction after acute myocardial infarction. *J Interferon Cytokine Res.* (2018) 38:137–44. doi: 10.1089/jir.2017.0067

53. Gaggin HK, Motiwala S, Bhardwaj A, Parks KA, Januzzi JL Jr. Soluble concentrations of the interleukin receptor family member ST2 and beta-blocker therapy in chronic heart failure. *Circ Heart Fail.* (2013) 6:1206–13. doi: 10.1161/CIRCHEARTFAILURE.113.000457

54. Xia J, Qu Y, Yin C, Xu D. Preliminary study of beta-blocker therapy on modulation of interleukin-33/ST2 signaling during ventricular remodeling after acute myocardial infarction. *Cardiol J.* (2017) 24:188–94. doi: 10.5603/CJ.a2016.0096

55. Lax A, Sanchez-Mas J, Asensio-Lopez MC, Fernandez-Del Palacio MJ, Caballero L, Garrido IP, et al. Mineralocorticoid receptor antagonists modulate galectin-3 and interleukin-33/ST2 signaling in left ventricular systolic dysfunction after acute myocardial infarction. *JACC Heart Fail.* (2015) 3:50–8. doi: 10.1016/j.jchf.2014.07.015

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 29 September 2022
DOI 10.3389/fcvm.2022.1009691

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Ratko Lasica,
Clinical Center of Serbia, University of Belgrade, Serbia
Olof Gidlöf,
Lund University, Sweden

*CORRESPONDENCE
Goro Yoshioka
s04211090s@gmail.com
Atsushi Tanaka
tanakaa2@cc.saga-u.ac.jp

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 02 August 2022
ACCEPTED 14 September 2022
PUBLISHED 29 September 2022

CITATION
Yoshioka G, Tanaka A, Watanabe N, Nishihira K, Natsuaki M, Kawaguchi A, Shibata Y and Node K (2022) Prognostic impact of incident left ventricular systolic dysfunction after myocardial infarction.
Front. Cardiovasc. Med. 9:1009691.
doi: 10.3389/fcvm.2022.1009691

Prognostic impact of incident left ventricular systolic dysfunction after myocardial infarction

Goro Yoshioka[1]*, Atsushi Tanaka[1]*, Nozomi Watanabe[2], Kensaku Nishihira[3], Masahiro Natsuaki[1], Atsushi Kawaguchi[4], Yoshisato Shibata[3] and Koichi Node[1]

[1]Department of Cardiovascular Medicine, Saga University, Saga, Japan, [2]Department of Cardiovascular Physiology, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan, [3]Miyazaki Medical Association Hospital Cardiovascular Center, Miyazaki, Japan, [4]Center for Comprehensive Community Medicine, Saga University, Saga, Japan

Introduction: We sought to investigate the prognostic impact of incident left ventricular (LV) systolic dysfunction at the chronic phase of acute myocardial infarction (AMI).

Materials and methods: Among 2,266 consecutive patients admitted for AMI, 1,330 patients with LV ejection fraction (LVEF) $\geq$ 40% during hospitalization who had LVEF data at 6 months after AMI were analyzed. Patients were divided into three subgroups based on LVEF at 6 months: reduced-LVEF (<40%), mid-range-LVEF ($\geq$ 40% and < 50%) and preserved-LVEF ($\geq$ 50%). Occurrence of a composite of hospitalization for heart failure or cardiovascular death after 6 months of AMI was the primary endpoint. The prognostic impact of LVEF at 6 months was assessed with a multivariate-adjusted Cox model.

Results: Overall, the mean patient age was 67.5 $\pm$ 11.9 years, and LVEF during initial hospitalization was 59.4 $\pm$ 9.1%. The median (interquartile range) duration of follow-up was 3.0 (1.5–4.8) years, and the primary endpoint occurred in 35/1330 (2.6%) patients (13/69 [18.8%] in the reduced-LVEF, 9/265 [3.4%] in the mid-range-LVEF, and 13/996 [1.3%] in the preserved-LVEF category). The adjusted hazard ratio for the primary endpoint in the reduced-LVEF vs. mid-range-LVEF category and in the reduced-LVEF vs. preserved-LVEF category was 4.71 (95% confidence interval [CI], 1.83 to 12.13; $p < 0.001$) and 14.37 (95% CI, 5.38 to 38.36; $p < 0.001$), respectively.

Conclusion: Incident LV systolic dysfunction at the chronic phase after AMI was significantly associated with long-term adverse outcomes. Even in AMI survivors without LV systolic dysfunction at the time of AMI, post-AMI reassessment and careful monitoring of LVEF are required to identify patients at risk.

KEYWORDS

acute myocardial infarction, left ventricular ejection fraction, left ventricular systolic dysfunction, prognosis, reassessment

Introduction

In the primary percutaneous coronary intervention (PCI) era, an increased risk of late-onset heart failure (HF) and mortality as post-acute myocardial infarction (AMI) events is still an important clinical issue. Hence, a better risk stratification system to prevent those adverse events at the remote phase of AMI is of clinical importance. At the acute phase of acute coronary syndrome (ACS) including AMI, several established risk scores, such as TIMI (1) and GRACE (2), are universally used to predict prognosis. In addition, previous reports have suggested that some clinical manifestations, such as lack of reperfusion therapy (3), frailty (4), nutritional status (5), and a combination of multiple blood variables (6, 7) obtained at the acute-phase of AMI could predict adverse events after AMI. Thus, while the prognostic value of several clinical indicators in the acute phase of AMI has been established, predictors of long-term prognosis in the chronic phase of AMI have not yet been fully established.

Left ventricular ejection fraction (LVEF) is one of the most general indicators of left ventricular (LV) systolic function and is widely available in clinical settings. Existence of LV systolic dysfunction at the acute phase of AMI is well-known as a strong predictor for adverse prognosis after AMI (8). On the other hand, LVEF often changes dynamically through chronic LV remodeling after AMI (9), and this change in LVEF during the post-AMI period also has prognostic impact (10, 11). Thus, a chronic transition to LV systolic dysfunction can occur even in patients with AMI without systolic dysfunction at the acute phase of AMI, possibly adding to the risk of adverse events at the remote phase of AMI. However, the detailed clinical features and prognostic impact of incident reduced LVEF at the remote phase of AMI remain poorly elucidated. Focusing on newly developed LV systolic dysfunction at the chronic phase of AMI may help in understanding this clinical unmet need better. Herein, we sought to clarify the clinical features of incident LV systolic dysfunction at the remote phase of AMI and its prognostic impact among AMI survivors without LV systolic dysfunction at the acute phase of AMI.

Materials and methods

Design and population

This was a single-center, retrospective, observational study performed at Miyazaki Medical Association Hospital in Japan. A total of 2,266 consecutive patients admitted for AMI, with either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), from February 2008 to January 2016 were eligible. Exclusion criteria were history of myocardial infarction, death within 6 months after AMI, admission due to worsening HF within 6 months after AMI, LVEF $< 40\%$ during index hospitalization, and no follow-up LVEF data at 6 months after AMI. According to LVEF at 6 months after AMI (within 1 month either side of 6 months), patients were divided into three subgroups: reduced-LVEF ($< 40\%$), mid-range-LVEF ($\geq 40\%$ and $< 50\%$), and preserved-LVEF ($\geq 50\%$).

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. All patients provided informed consent for both the procedure and the subsequent data collection and analysis for research purposes. Ethics approval was obtained from the Institutional Review Board of Miyazaki Medical Association Hospital (2019-23).

Definition and diagnosis of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction

Diagnosis of STEMI and NSTEMI, based on the 2007 universal definitions (12), was made by each cardiologist. STEMI and NSTEMI were defined as follows: for STEMI, patients had to have chest symptoms, ST-segment elevation in 2 contiguous leads or left bundle branch block, and an elevated biochemical marker of myocardial necrosis (high-sensitivity troponin T $>$ 0.032 ng/mL or creatine phosphokinase [CPK] at least two times the upper limit of normal), whereas for NSTEMI, patients had to have chest symptoms, ST-segment depression or T-wave inversion in 2 contiguous leads, and an elevated biochemical marker of myocardial necrosis. The therapeutic strategies for AMI treatment depended on the practice of each individual cardiologist, but all treatments followed the guidelines set forth by the Japanese Circulation Society and the American College of Cardiology/American Heart Association for the diagnosis and treatment of AMI (13).

Data collection and endpoints

Data collected included clinical characteristics and demographics during initial hospitalization, such as medical history, presenting signs and symptoms, results of blood tests, electrocardiography, cardiac procedures, and clinical outcomes. Transthoracic echocardiography was also carried out during index hospitalization and at around 6 months after AMI, and LVEF was estimated by the standard biplane Simpson method. In addition, all blood biomarkers were measured within 24 h after admission as acute phase data. Clinical follow-up was carried out through clinic visits, telephone calls, and records from hospital admissions.

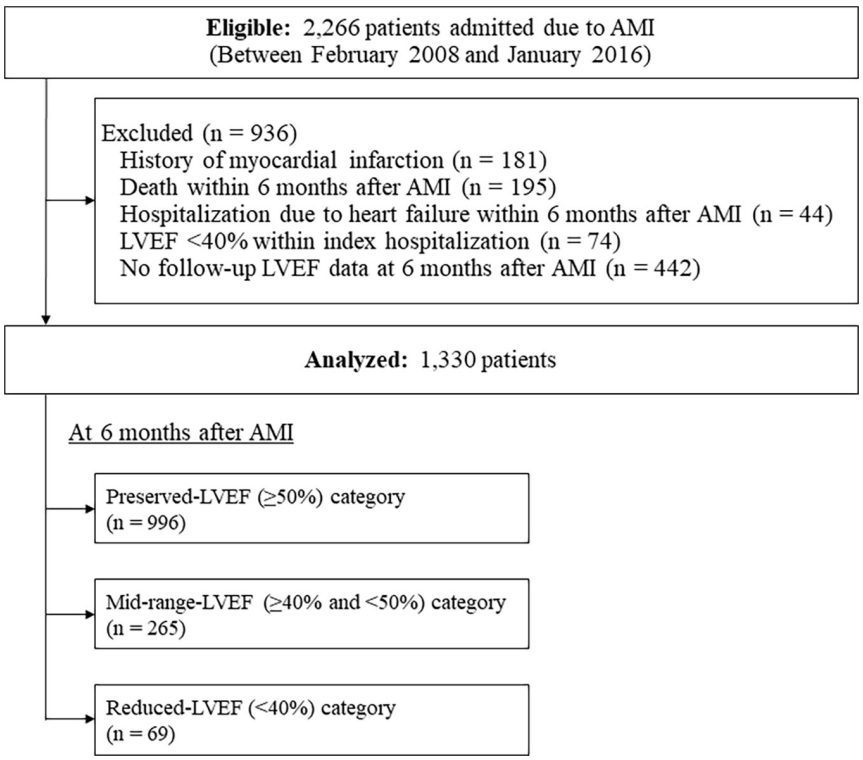


FIGURE 1
Flow diagram of the study cohort. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

The primary endpoint was a composite of hospitalization for HF or cardiovascular death occurred after 6 months of AMI. The diagnosis of HF was made based on the latest local guidelines, in which HF is diagnosed by the presence of at least one sign (rales, peripheral edema, ascites, or radiographic evidence of pulmonary congestion) and one symptom (dyspnea, orthopnea or edema), regardless of ejection fraction (14). Cardiovascular death was defined as the primary cause of death determined to be atherosclerotic cardiovascular disease, arrhythmia, heart failure, or sudden cardiac death. The secondary endpoints included the individual components of the primary endpoint and all-cause death.

Statistical analysis

For continuous variables, normally distributed data are reported as the mean ± standard deviation; non-parametric data are reported as the median and interquartile range (IQR). For categorical variables, data are presented as count and percentage. Comparisons of continuous variables between groups were performed with the Wilcoxon-test or Kruskal Wallis tests, as appropriate. Comparisons of categorical variables were assessed with the chi-square or Fisher's exact test, as appropriate. A paired sample t-test was used to compare LVEF at index hospitalization and 6 months after AMI. LVEF trajectories from index hospitalization for AMI to 6 months post-AMI were demonstrated using parallel plots. Clinical factors associated with LVEF category decline over the 6 months after AMI were assessed by logistic regression analysis adjusting for confounding factors (age, sex, STEMI, Killip class, culprit lesions (left anterior descending artery or left main trunk), use of mechanical support, maximum CPK [natural log-transformed], estimated glomerular filtration rate [eGFR], LVEF during index hospitalization and use of each medication at discharge; angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin II receptor blocker [ARB] and β-blocker). The cumulative incidence of each endpoint was also calculated according to the Kaplan–Meier method, and the effects of LVEF 6 months after AMI on primary and secondary endpoints were determined with a multivariate Cox proportional hazards regression model adjusting for confounding factors (age, sex, STEMI, use of mechanical support, max CPK [natural log-transformed], eGFR, LVEF during index hospitalization and use of each medication at discharge; ACE-I or ARB and β-blocker). Time at risk was defined starting on the day of the 6-month LVEF measurement. A two-sided P value < 0.05 was considered statistically significant. All statistical analyses were performed with JMP® 15 (SAS Institute Inc., Cary, NC, USA).

TABLE 1 Patient background characteristics, procedural information, and medications at discharge.

Variable	Overall $n = 1,330$	LVEF category 6 months after AMI			*P*-value (among LVEF categories)
		Preserved-LVEF (≥ 50%) $n = 996$	Mid-range-LVEF (≥ 40% and < 50%) $n = 265$	Reduced-LVEF (< 40%) $n = 69$	
Age, years	67.5 ± 11.9	67.5 ± 11.9	67.7 ± 11.7	68.0 ± 11.7	0.928
Male	986 (74.1)	717 (72.0)	213 (80.4)	56 (81.2)	0.007
Body mass index, kg/m^2	24.2 ± 3.6	24.2 ± 3.8	24.0 ± 3.4	24.1 ± 3.1	0.579
eGFR, mL/min/1.73 m^2	68.0 ± 22.0	68.8 ± 21.3	66.5 ± 23.0	61.6 ± 26.7	0.025
Medical history					
Hypertension	928 (69.8)	713 (71.6)	165 (62.3)	50 (72.5)	0.014
Dyslipidemia	695 (52.3)	536 (53.8)	126 (47.6)	33 (47.8)	0.145
Diabetes mellitus	413 (31.1)	311 (31.2)	84 (31.7)	18 (26.1)	0.642
STEMI	911 (68.5)	649 (65.2)	213 (80.4)	49 (71.0)	< 0.001
NSTEMI	419 (31.5)	347 (34.8)	52 (19.6)	20 (29.0)	
Onset-to-admission time, min	180 (120-420)	180 (120-420)	180 (60-420)	240 (120-870)	0.108
Delayed arrival (≥ 48 h after onset)	35 (3.0)	27 (3.0)	7 (2.9)	1 (1.7)	0.804
Killip class ≥ 3	55 (4.2)	31 (3.1)	16 (6.0)	8 (11.6)	0.003
Culprit lesion					< 0.001
LMT	27 (2.0)	18 (1.8)	8 (3.0)	1 (1.4)	
LAD	566 (42.6)	396 (39.7)	132 (49.8)	38 (55.1)	
LCX	165 (12.4)	124 (12.8)	32 (12.1)	9 (13.0)	
RCA	483 (36.3)	383 (38.5)	86 (32.5)	14 (20.2)	
MVD and others	89 (6.7)	75 (8.3)	7 (2.6)	7 (10.1)	
Revascularization	1,266 (95.1)	949 (95.3)	253 (95.5)	64 (93.0)	0.676
PCI	1,227 (92.3)	922 (92.6)	242 (91.3)	63 (91.3)	0.765
CABG	39 (2.8)	27 (2.7)	11 (4.2)	1 (1.4)	0.481
Mechanical support	108 (8.1)	69 (6.9)	29 (10.9)	10 (14.5)	0.045
IABP	108 (8.1)	69 (6.9)	29 (10.9)	10 (14.5)	0.045
ECMO	8 (0.6)	6 (0.6)	2 (0.8)	0	0.629
Peak CPK, IU/L	1,417 (471-3,152)	1,124 (376-,367)	3,253 (1,159-5,319)	2,625 (981-5,764)	< 0.001
Hospital stay, days	15 (12-19)	14 (12–)	17 (14-22)	17 (14-23)	< 0.001

(Continued)

10.3389/fcvm.2022.1009691

10.3389/fcvm.2022.1009691

TABLE 1 (Continued)

Variable	Overall $n = 1,330$	LVEF category 6 months after AMI			*P*-value (among LVEF categories)
		Preserved-LVEF (≥ 50%) $n = 996$	Mid-range-LVEF (≥ 40% and < 50%) $n = 265$	Reduced-LVEF (< 40%) $n = 69$	
Medication at discharge					
ACE-I or ARB	933 (70.2)	719 (72.2)	175 (66.0)	39 (56.5)	0.007
β-blocker	619 (46.5)	442 (44.4)	137 (51.7)	40 (58.0)	0.016
MRA	108 (8.1)	55 (5.5)	42 (15.9)	11 (15.9)	< 0.001
Statin	1,165 (88.0)	886 (90.0)	223 (84.2)	60 (87.0)	0.113
Antiplatelet	1,300 (97.8)	979 (98.3)	255 (96.2)	66 (95.7)	0.181
LVEF during index hospitalization,%	59.4 ± 9.1	61.6 ± 8.4	53.6 ± 7.9	50.2 ± 7.7	< 0.001
LVEF at 6 months after AMI,%	49.0 ± 13.5	60.1 ± 6.5	45.5 ± 2.7	35.3 ± 4.0	< 0.001

Data for categorical variables given as number (%); data for continuous variables given as mean ± standard deviation for normal distribution or median (interquartile range) for skewed distribution. ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CPK, creatine phosphokinase; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pumping; IU, international units; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MVD, multi-vessel disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

Results

Patient clinical characteristics during index hospitalization for acute myocardial infarction

Among a total of 2,266 consecutive patients eligible for this study, a total of 936 patients were excluded; thus, a total of 1,330 patients were analyzed (**Figure 1**). Their background characteristics, procedural information during index hospitalization, and medications at discharge are shown in **Table 1**. The mean patient age was 67.5 ± 11.9 years, with 74.1% being male. Electrocardiography revealed that 68.5% were STEMI, and almost all patients (95.1%) received primary revascularization (92.3% for PCI). Most patients received standard medical therapies after AMI at discharge.

Left ventricular ejection fraction trajectories from index hospitalization for acute myocardial infarction to 6 months post-acute myocardial infarction

Overall, mean LVEF during index hospitalization and 6 months after AMI was 59.4 ± 9.1% and 49.0 ± 13.5% ($p < 0.001$), respectively (**Table 1**). The detailed trajectories of LVEF from index hospitalization to 6 months after AMI are shown in **Figure 2A**. A total of 69 patients (28/1,110 [2.5%] initially in the preserved-LVEF and 41/220 [18.6%] initially in the mid-range-LVEF categories) newly developed reduced-LVEF at 6 months, and a total of 170/1,100 (15.5%) patients initially in the preserved-LVEF category declined to the mid-range-LVEF category at 6 months (**Figure 2B**). Conversely, a total of 84/220 (38.2%) patients initially in the mid-range-LVEF category climbed from that to the preserved-LVEF category at 6 months. The LVEF categories in the other patients remained unchanged at 6 months after AMI.

Detailed clinical information at the time of index hospitalization in the three subgroups stratified by LVEF category at 6 months after AMI is also provided in **Table 1**. The subgroups with mid-range- and reduced-LVEF at 6 months after discharge, relative to the preserved-LVEF subgroup, were more likely to have a higher proportion of males, a lower eGFR, and a more severe clinical course of AMI.

The multivariate logistic regression analysis revealed that among 239 patients whose LVEF category declined at 6 months after AMI, male sex and peak CPK were independently associated with the decline, while LVEF during index hospitalization and use of ACE-I or ARB at discharge were inversely associated with a decline (**Table 2**). Among those factors, the use of ACE-I or ARB at discharge

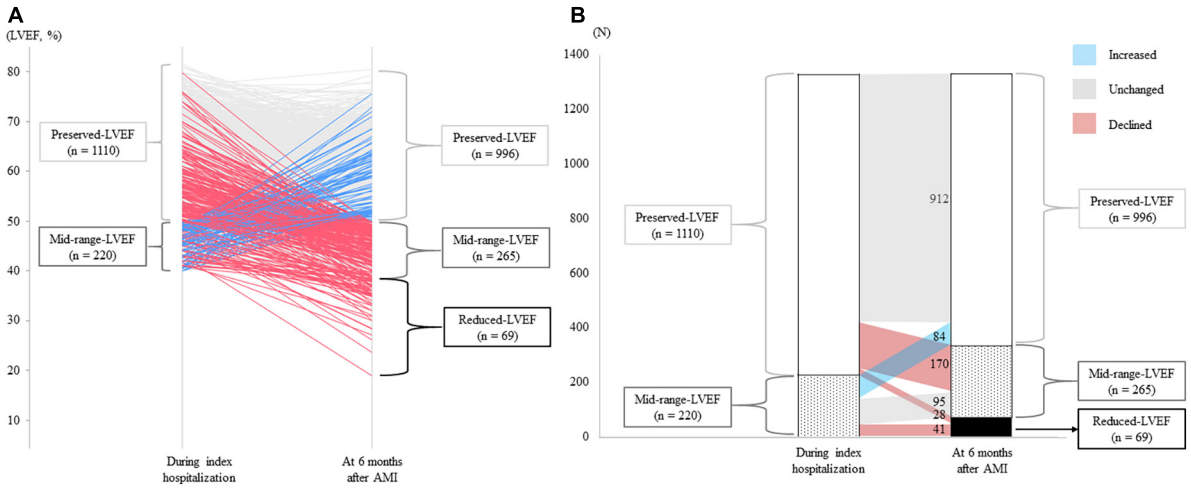


FIGURE 2
LVEF trajectories from index hospitalization for AMI to 6 months post-AMI. **(A)** Individual trajectories of LVEF over the 6 months after AMI. Blue, gray, red lines indicate patients with increased, unchanged, and declined LVEF, respectively. **(B)** Changes in LVEF categories. The numbers in the figure indicate the number of patients whose LVEF category changed or did not change 6 months after AMI. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

was solely an independent negative predictor of a two-step LVEF category decline (Table 3). Notably, ACE-I or ARB therapy was not an independent predictor of improved LVEF at 6 months, but female sex and LVEF during hospitalization were found to be associated (Supplementary Table 1).

Clinical endpoints

The median (interquartile range) duration of follow-up 6 months after AMI was 3.0 (1.5–4.8) years. Overall, the primary composite endpoint of hospitalization for HF or cardiovascular death occurred in 35/1,330 (2.6%) patients (13/996 [1.3%] in the preserved-LVEF, 9/265 [3.4%] in the mid-range-LVEF, and 13/69 [18.8%] in the reduced-LVEF categories, Log-rank $p < 0.001$); individual components of the primary composite endpoint occurred in 21/1,330 (1.6%) patients for hospitalization for HF and 19/1,330 (1.4%) patients for cardiovascular death (Table 4). The adjusted hazard ratio (HR) for the primary endpoint in the reduced-LVEF vs. mid-range-LVEF categories and in the reduced-LVEF vs. preserved-LVEF categories was 4.71 (95% confidence interval [CI], 1.83 to 12.13; $p < 0.001$) and 14.37 (95% CI, 5.38 to 38.36; $p < 0.001$), respectively (Figure 3A). These were almost consistent across the individual components of primary composite endpoint; hospitalization for HF and cardiovascular death (Figures 3B,C). All-cause death occurred in 50/1,330 (3.8%) patients in the overall cohort (23/996 [2.3%] in the preserved-LVEF, 15/265 [5.7%] in the mid-range-LVEF, and 12/69 [17.4%] in the reduced-LVEF categories, Log-rank $p < 0.001$). The adjusted HR for all-cause death in the reduced-LVEF vs. mid-range-LVEF categories and in the reduced-LVEF vs. preserved-LVEF categories was 2.16 (95% CI, 0.89 to 5.25; $p = 0.087$) and 6.13 (95% CI, 2.38 to 15.81; $p < 0.001$), respectively (Figure 3D).

Discussion

This is the report to demonstrate the clinical features of chronic transit of LVEF and incident LV systolic dysfunction at the chronic phase of AMI and its long-term prognostic impact in AMI survivors. Our findings underscore the clinical importance of monitoring LVEF through the post-AMI phases, even in survivors without LV systolic dysfunction at the acute phase of AMI.

In the past two decades, widespread technical innovations in primary coronary revascularization for AMI have dramatically increased the number of AMI survivors. Accordingly, an increased risk of HF and mortality at the post-AMI phase has become an emerging clinical issue of concern, urgently requiring accurate and reliable risk stratification to predict such remote-phase adverse events (15). Traditionally, some risk prediction models, such as GRACE and TIMI, both of which consist of indicators obtained at the acute phase of AMI, have been universally used to predict the prognosis of patients with AMI (1, 2). On the other hand, such indicators obtained during the acute phase are highly variable, depending on the individual clinical situation and the course of treatment during the acute to post-AMI phases. Therefore, risk stratification based on the clinical index obtained at the chronic phase and its change from the acute

TABLE 2 Logistic regression analysis to identify clinical factors associated with LVEF category decline over the 6 months after AMI.

Variable	Odds ratio	95% CI	*P*-value
Age, per 1 year	1.01	0.99-1.03	0.075
Male	1.76	1.19-2.63	0.005
STEMI	0.73	0.49-1.10	0.135
Killip class ≥ 3	1.07	0.51-2.23	0.853
Culprit lesion: LAD or LMT	1.27	0.93-1.74	0.131
Use of mechanical support	0.90	0.51-1.60	0.735
Peak CPK, ln U/L	1.64	1.40-1.93	< 0.001
eGFR, per 1 mL/min/1.73 m^2	0.99	0.99-1.00	0.205
LVEF during index hospitalization, per 1%	0.96	0.94-0.98	< 0.001
Use of ACE-I or ARB at discharge	0.62	0.44-0.86	0.004
Use of β-blocker at discharge	1.10	0.80-1.51	0.548

CI, confidence interval; other abbreviations, see Table 1.

TABLE 3 Logistic regression analysis to identify clinical factors associated with a decline in LVEF category over the 6 months after AMI.

Variable	One-step LVEF category decline*			Two-step LVEF category decline**		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age, per 1 year	1.01	0.99-1.03	0.071	1.00	0.97-1.04	0.897
Male	1.77	1.16-2.69	0.008	1.42	0.51-4.00	0.503
STEMI	0.82	0.53-1.26	0.359	0.47	0.18-1.23	0.125
Killip class ≥ 3	1.09	0.50-2.34	0.833	0.93	0.18-4.81	0.935
Culprit lesion: LAD or LMT	1.23	0.88-1.70	0.222	1.39	0.63-3.08	0.421
Use of mechanical support during procedures	0.74	0.40-1.36	0.328	2.28	0.76-6.88	0.142
Peak CPK, ln U/L	1.63	1.37-1.93	< 0.001	1.45	0.98-2.16	0.057
eGFR, per 1 mL/min/1.73 m^2	0.99	0.99-1.00	0.158	0.99	0.98-1.02	0.843
LVEF during index hospitalization, per 1%	0.96	0.94-0.98	< 0.001	0.99	0.95-1.04	0.696
Use of ACE-I or ARB at discharge	0.70	0.49-0.99	0.044	0.39	0.17-0.86	0.020
Use of β-blocker at discharge	1.07	0.77-1.49	0.697	1.23	0.55-2.76	0.613

*For 211 patients whose LVEF declined from preserved- to mid-range-LVEF or mid-range- to reduced-LVEF at 6 months after AMI. **For 28 patients whose LVEF declined from preserved- to reduced-LVEF at 6 months after AMI. Abbreviations, see Tables 1, 2.

TABLE 4 Clinical events.

Outcomes	Overall *n* = 1,330	LVEF category 6 months after AMI			*P*-value (Log-rank)
		Preserved-LVEF (≥ 50%) n = 996	Mid-range-LVEF (≥ 40% and < 50%) n = 265	Reduced-LVEF (< 40%) n = 69	
Composite outcome	35 (2.6)	13 (1.3)	9 (3.4)	13 (18.8)	< 0.001
Hospitalization for heart failure	21 (1.6)	7 (0.7)	6 (2.3)	8 (11.6)	< 0.001
Cardiac death	19 (1.4)	6 (0.6)	5 (1.9)	8 (11.6)	< 0.001
All-cause death	50 (3.8)	23 (2.3)	15 (5.7)	12 (17.4)	< 0.001

Data are shown as number (%). Abbreviations, see Table 1.

to the chronic phase may contribute to the improvement of a longer-term prognostic ability for patients who have experienced AMI. However, there are few studies on long-term prognostic prediction based on the clinical data obtained at the chronic phase.

LVEF is an established indicator of LV systolic function, and LV systolic dysfunction (reduced LVEF) at the acute phase of AMI is also well-recognized as an independent predictor of adverse outcomes (16, 17). However, it is still clinically controversial whether the sole use of LVEF measured only at the

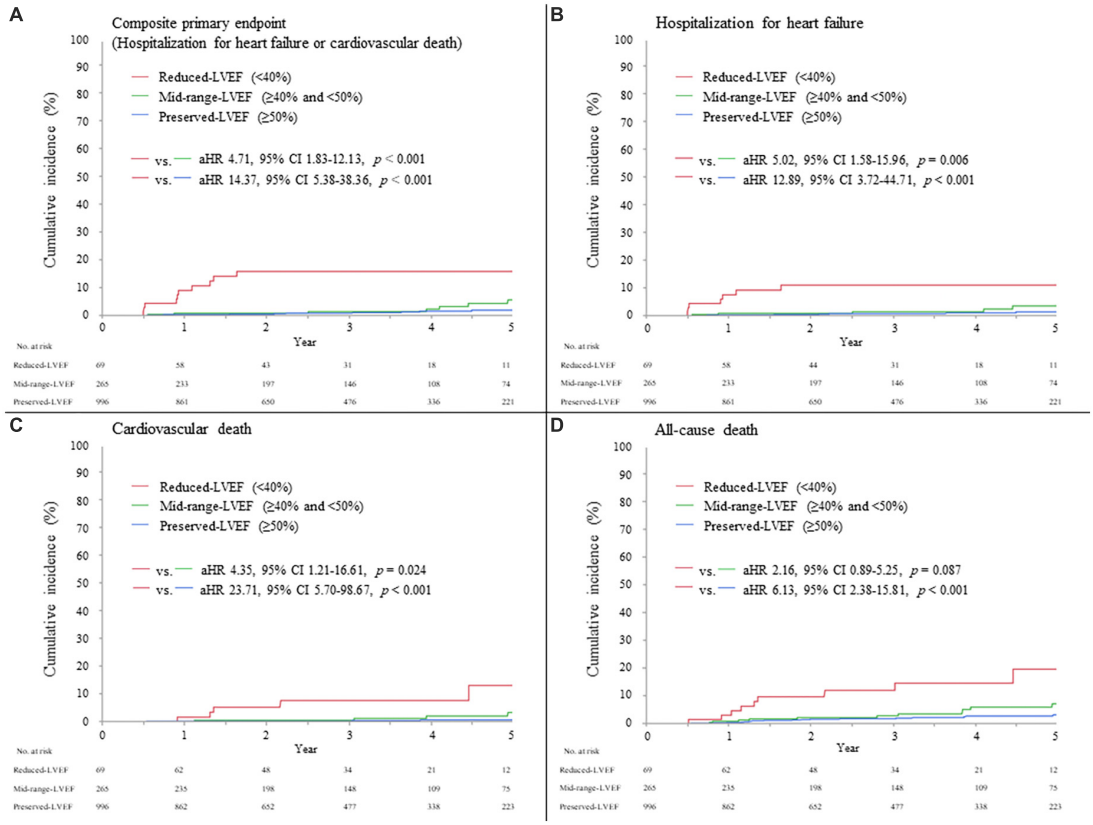


FIGURE 3
Clinical events during follow-up, according to LVEF category 6 months after AMI. **(A)** Composite primary endpoint (hospitalization for heart failure or cardiovascular death). **(B)** Hospitalization for heart failure. **(C)** Cardiovascular death. **(D)** All-cause death. The hazard ratio was adjusted by age, sex, STEMI, maximum creatine phosphokinase (natural log-transformed), LVEF during index hospitalization, eGFR, use of mechanical support, and use of each medication (ACE-I, ARB, and β-blockers) at discharge. ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CI, confidence interval; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction.

acute phase is sufficient to predict the long-term prognosis (18). Moreover, substantial patients often exhibit mildly reduced- or preserved-LVEF immediately following AMI, and the majority of adverse events after AMI develop in that patient population without overt LV dysfunction at the acute-phase (19, 20). Therefore, it is clinically important to assess the mechanism by which patients without LV systolic dysfunction at the acute phase of AMI develop adverse events at the remote phase. In this context, we hypothesized that LVEF at the chronic phase would be a predictor of subsequent events in survivors with preserved LVEF at the acute phase, and then evaluated the long-term prognostic impact according to LVEF at the chronic phase and its trajectory from the acute to the chronic phases.

After the onset of AMI, immediate coronary revascularization and subsequent optimal medical therapies help to prevent adverse LV remodeling and thereby improve LV systolic function. To date, several studies of subjects with reduced LVEF at the time of AMI have demonstrated that chronic LVEF recovery was associated with better outcomes in comparison with survivors without LVEF recovery (11, 21). Chew et al. followed patients with only reduced EF during the acute phase of myocardial infarction (22). They demonstrated that the absence of LVEF recovery is associated with an increased risk of death. This suggests that patterns of chronic change in LVEF following AMI can further discriminate AMI survivors who are at increased risk of death. However, it is uncertain how the LVEF status in patients with preserved LVEF at the time of AMI transitions over time. Further, the clinical characteristics of the trajectory pattern of LVEF are unknown. Compared to a study in which AMI patients with preserved LVEF in the acute phase were excluded, the present study excluded AMI patients with reduced LVEF in the acute phase, and focused on chronic changes in AMI patients with preserved LVEF.

Our findings underscore that careful post-AMI reassessments are required to monitor the LVEF trajectory and identify potential patients who need additional medical and/or device therapies, even in patients with preserved LVEF

at the time of AMI. However, despite guideline-directed recommendations (23, 24), previous studies have shown that the frequency of post-AMI LVEF reassessment was relatively low in patients with LV systolic dysfunction at the time of AMI (25, 26). A recent cohort study from Canada also demonstrated that approximately 1 in 3 patients with mildly reduced LVEF following AMI did not undergo LVEF reassessment within 6 months after AMI (27). The low frequency of post-AMI LVEF reassessment indicates a missed opportunity for appropriate care, especially for LV systolic dysfunction. Importantly, few data on the rate of post-AMI LVEF reassessment in patients with preserved LVEF at the time of AMI are currently available, and it is likely even less frequent for such patients. In addition, given our findings that incident LV systolic dysfunction 6 months after AMI was associated with poor outcomes, improvements in the quality of post-AMI management are urgently needed, including post-AMI LVEF reassessment, irrespective of LVEF status at index AMI.

The development of HF remains a major issue in AMI patients. Several clinical features, such as elevated levels of natriuretic peptides and a clinically severe AMI disease course are known to be risk factors (28). Delayed arrival causes a delay in reperfusion therapy, which often results in a larger infarct size and increased risk of HF (29). In the present study cohort, the frequency of delayed arrival after AMI onset in the subgroup with EF $\geq$ 40% and $<$ 50% at 6 months after AMI was higher than that in the subgroup with reduced LVEF ($<$ 40%) at 6 months. This might be associated with the higher peak CPK levels in the former subgroup. Several previous reports have addressed the potential risk predictors for the occurrence of early- and late-onset HF after AMI. However, the factors were diverse (30), and no specific factor was identified for either early- or late-onset HF (31, 32). In terms of echocardiographic parameters, there have been also several reports on the evaluation of chronic LVEF at a single point in time and the development of HF (33). However, LVEF dynamics and the assessment of late-onset HF according to their trajectories in the remote phase of AMI have not yet been fully studied.

In the present study, we found that the prevalence of incident LV systolic dysfunction 6 months after AMI was 5.2% among AMI survivors without LV systolic dysfunction at the time of AMI, and such patients were associated with poor long-term prognosis compared to subjects without it. This indicates the clinical need for early identification of patients at risk for LVEF decline during the chronic phase of AMI. In this context, male sex, peak CPK level, LVEF at the time of AMI, and use of ACE-I or ARB at discharge were independent predictors of LVEF decline 6 months after AMI. In particular, the use of ACE-I or ARB at discharge was solely an independent negative predictor of a two-step decline in LVEF category. In the previous PREAMI (Perindopril and Remodeling in Elderly With Acute Myocardial Infarction) study, Ferrari et al. also demonstrated that 12 months of ACE-I perindopril therapy rescued adverse LV remodeling in elderly patients with a LVEF 40% or more following AMI (34). This is likely comparable to our findings from multivariate regression analyses. Although no relationship between the prevention of adverse LV remodeling and better clinical outcomes was observed in that study, the short observation period (12 months) might have affected the outcome. Compared to that study, the strength of our study is that we reassessed the LVEF 6 months after AMI and then had a longer follow-up period (median 3 years). On the other hand, Park et al. reported that the dose of ARB had no impact on LV remodeling in patients with mid-range LVEF following AMI (35). Taken together, these findings suggest the importance of administering ACE-I or ARB, even in the absence of LV systolic dysfunction immediately after AMI.

Limitations

Some limitations must be taken into account. First, this was a retrospective, observational study carried out in a relatively small number of subjects at a single center, which limits the generalizability of our findings. It should also be noted that primary coronary revascularization and subsequent oral medication delivery were performed based on the latest local treatment guidelines. However, decision-making regarding hospitalization for HF was the choice of each physician; therefore, relevant endpoints were partly based on physicians' subjective judgment. Second, because the study cohort included only survivors 6 months after AMI to collect remote data on LVEF, a potential selection bias should be noted. Accordingly, the occurrence of composite clinical events (hospitalization for HF and cardiovascular death) was low (2.3%) during the follow-up duration. Additionally, patients with reduced LVEF at 6 months already had worsening of some clinical indicators, such as lower EF and eGFR levels and a higher proportion of patients with Killip class $\geq$ 3, at index hospitalization, and this patient subgroup was therefore not entirely representative of the overall cohort. Third, our study cohort included both STEMI and NSTEMI, with two-thirds of subjects showing STEMI; this rate is higher relative to a contemporary cohort for AMI in Japan (36, 37). The prognostic impact of LVEF at the chronic phase was not investigated separately between STEMI and NSTEMI due to the limited small sample size in our cohort. Fourth, the rate of prescribing optimal drug therapy after AMI was lower than expected in our cohort. Specifically, a relatively small proportion of subjects was treated with β-blockers due mainly to tolerability, and this was similar to previous reports in Japan (36, 37). However, we cannot exclude the possibility that such incomplete implementation of optimal medical therapy after AMI might have affected the patients' prognosis and our findings. Finally, the present analysis did not account for any

clinical information that may have affected long-term prognosis in survivors of AMI, including biomarkers, at the chronic phase other than LVEF. Therefore, further studies are needed to investigate the clinical parameters related to LVEF dynamics and assess the prognostic relationships between their trajectories in the remote phase of AMI.

Conclusion

Our findings suggest that incident LV systolic dysfunction at the chronic phase after AMI was significantly associated with long-term adverse outcomes. Therefore, even in AMI survivors without LV systolic dysfunction at the time of AMI, post-AMI reassessment and careful monitoring of LVEF are required to identify patients at risk. Patient with risk factor, such as male sex and higher peak CPK should be followed more carefully.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of Miyazaki Medical Association Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GY and AT designed the research, project conception, development of overall research plan, study oversight, and wrote the manuscript. GY, KNi, NW, YS, and MN conducted the research, hands-on conduct of the experiments, and data collection. GY, AT, and AK analyzed the data or performed statistical analysis. MN and KNo revised the manuscript. GY and AT had primary responsibility for the final content. All authors read and approved the final manuscript.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science KAKENHI Grant Number: JP21K08130 and Takeda Science Foundation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1009691/full#supplementary-material

References

1. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern. Med.* (2003) 163:2345–53. doi: 10.1001/archinte.163.19.2345

2. Abu-Assi E, Ferreira-Gonzalez I, Ribera A, Marsal JR, Cascant P, Heras M, et al. Do GRACE (Global Registry of Acute Coronary events) risk scores still maintain their performance for predicting mortality in the era of contemporary management of acute coronary syndromes? *Am Heart J.* (2010) 160:826-834.e1-3. doi: 10.1016/j.ahj.2010.06.053

3. Boersma E, Mercado N, Poldermans D, Gardien M, Vos J, Simoons ML. Acute myocardial infarction. *Lancet.* (2003) 361:847–58. doi: 10.1016/S0140-6736(03)12712-2

4. Nishihira K, Yoshioka G, Kuriyama N, Ogata K, Kimura T, Matsuura H, et al. Impact of frailty on outcomes in elderly patients with acute myocardial infarction who undergo percutaneous coronary intervention. *Eur Heart J Qual Care Clin Outcomes.* (2021) 7:189–97. doi: 10.1093/ehjqcco/qcaa018

5. Yoshioka G, Tanaka A, Nishihira K, Shibata Y, Node K. Prognostic impact of serum albumin for developing heart failure remotely after acute myocardial infarction. *Nutrients.* (2020) 12:2637. doi: 10.3390/nu12092637

6. Goriki Y, Yoshioka G, Natsuaki M, Shinzato K, Nishihira K, Kuriyama N, et al. Simple risk-score model for in-hospital major bleeding based on multiple blood variables in patients with acute myocardial infarction. *Int J Cardiol.* (2022) 346:1–7. doi: 10.1016/j.ijcard.2021.11.046

7. Goriki Y, Tanaka A, Nishihira K, Kawaguchi A, Natsuaki M, Watanabe N, et al. A novel predictive model for in-hospital mortality based on a combination of multiple blood variables in patients with ST-segment-elevation myocardial infarction. *J Clin Med.* (2020) 9:852. doi: 10.3390/jcm9030852

8. Shimizu A. What are the most useful predictors of cardiac mortality in patients post myocardial infarction? *Circ J.* (2013) 77:319–20. doi: 10.1253/circj.CJ-12-1542

9. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Fail Rev.* (2011) 16:13–21. doi: 10.1007/s10741-010-9181-7

10. Nienhuis MB, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, et al. Comparative predictive value of infarct location, peak CK, and ejection fraction after primary PCI for ST elevation myocardial infarction. *Coron Artery Dis.* (2009) 20:9–14. doi: 10.1097/MCA.0b013e32831bd875

11. Chew DS, Heikki H, Schmidt G, Kavanagh KM, Dommasch M, Bloch Thomsen PE, et al. Change in left ventricular ejection fraction following first myocardial infarction and outcome. *JACC Clin Electrophysiol.* (2018) 4:672–82. doi: 10.1016/j.jacep.2017.12.015

12. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* (2007) 50:2173–95. doi: 10.1016/j.jacc.2007.09.011

13. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* (2013) 127:e362–425.

14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC)developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128

15. Smith LN, Makam AN, Darden D, Mayo H, Das SR, Halm EA, et al. Acute myocardial infarction readmission risk prediction models: a systematic review of model performance. *Circ Cardiovasc Qual Outcomes.* (2018) 11:e003885. doi: 10.1161/CIRCOUTCOMES.117.003885

16. Halkin A, Stone GW, Dixon SR, Grines CL, Tcheng JE, Cox DA, et al. Impact and determinants of left ventricular function in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction. *Am J Cardiol.* (2005) 96:325–31. doi: 10.1016/j.amjcard.2005.03.069

17. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation.* (2005) 111:3411–9. doi: 10.1161/CIRCULATIONAHA.104.508093

18. Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *Eur Heart J.* (2013) 34:1964–71. doi: 10.1093/eurheartj/eht109

19. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest–the relevance of heart failure. The maastricht circulatory arrest registry. *Eur Heart J.* (2003) 24:1204–9. doi: 10.1016/S0195-668X(03)00191-X

20. Mäkikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J.* (2005) 26:762–9. doi: 10.1093/eurheartj/ehi188

21. Parodi G, Memisha G, Carrabba N, Signorini U, Migliorini A, Cerisano G, et al. Prevalence, predictors, time course, and long-term clinical implications of left ventricular functional recovery after mechanical reperfusion for acute myocardial infarction. *Am J Cardiol.* (2007) 100:1718–22. doi: 10.1016/j.amjcard.2007.07.022

22. Chew DS, Wilton SB, Kavanagh K, Southern DA, Tan-Mesiatowsky LE, Exner DV. Left ventricular ejection fraction reassessment post-myocardial infarction: current clinical practice and determinants of adverse remodeling. *Am Heart J.* (2018) 198:91–6. doi: 10.1016/j.ahj.2017.11.014

23. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* (2013) 127:529–55.

24. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J.* (2018) 39:119–77.

25. Miller AL, Gosch K, Daugherty SL, Rathore S, Peterson PN, Peterson ED, et al. Failure to reassess ejection fraction after acute myocardial infarction in potential implantable cardioverter/defibrillator candidates: insights from the translational research investigating underlying disparities in acute myocardial infarction patients' health status (TRIUMPH) registry. *Am Heart J.* (2013) 166:737–43. doi: 10.1016/j.ahj.2013.07.019

26. Pokorney SD, Miller AL, Chen AY, Thomas L, Fonarow GC, de Lemos JA, et al. Reassessment of cardiac function and implantable cardioverter-defibrillator use among medicare patients with low ejection fraction after myocardial infarction. *Circulation.* (2017) 135:38–47. doi: 10.1161/CIRCULATIONAHA.116.022359

27. Wilton SB, Bennett MT, Parkash R, Kavanagh K, Jolicoeur EM, Halperin F, et al. Variability in reassessment of left ventricular ejection fraction after myocardial infarction in the acute myocardial infarction quality assurance canada study. *JAMA Netw Open.* (2021) 4:e2136830. doi: 10.1001/jamanetworkopen.2021.36830

28. Haeck JD, Verouden NJ, Kuijt WJ, Koch KT, Van Straalen JP, Fischer J, et al. Comparison of usefulness of N-terminal pro-brain natriuretic peptide as an independent predictor of cardiac function among admission cardiac serum biomarkers in patients with anterior wall versus nonanterior wall ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol.* (2010) 105:1065–9. doi: 10.1016/j.amjcard.2009.12.003

29. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* (2004) 109:1223–5. doi: 10.1161/01.CIR.0000121424.76486.20

30. López de Sá E. [Late-onset heart failure following myocardial infarction: putting the jigsaw together]. *Rev Esp Cardiol.* (2005) 58:1258–60. doi: 10.1016/S1885-5857(06)60411-8

31. Choi H, Seo JY, Shin J, Choi BY, Kim YM. A long-term incidence of heart failure and predictors following newly developed acute myocardial infarction: a 10 years retrospective cohort study with Korean national health insurance data. *Int J Environ Res Public Health.* (2021) 18:6207. doi: 10.3390/ijerph18126207

32. Sulo G, Igland J, Nygård O, Vollset SE, Ebbing M, Cerqueira C, et al. Trends in the risk of early and late-onset heart failure as an adverse outcome of acute myocardial infarction: a cardiovascular disease in Norway project. *Eur J Prev Cardiol.* (2017) 24:971–80. doi: 10.1177/2047487317698568

33. Huang H, Liu J, Lei M, Yang Z, Bao K, Li Q, et al. A universal new definition of heart failure with improved ejection fraction for patients with coronary artery disease. *Front Physiol.* (2021) 12:770650. doi: 10.3389/fphys.2021.770650

34. Ferrari R. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. *Arch Intern Med.* (2006) 166:659–66. doi: 10.1001/archinte.166.6.659

35. Park K, Kim YD, Kim KS, Lee SH, Park TH, Lee SG, et al. The impact of a dose of the angiotensin receptor blocker valsartan on post-myocardial infarction ventricular remodelling. *ESC Heart Fail.* (2018) 5:354–63. doi: 10.1002/ehf2.12249

36. Miyachi H, Takagi A, Miyauchi K, Yamasaki M, Tanaka H, Yoshikawa M, et al. Current characteristics and management of ST elevation and non-ST elevation myocardial infarction in the Tokyo metropolitan area: from the Tokyo CCU network registered cohort. *Heart Vessels.* (2016) 31:1740–51. doi: 10.1007/s00380-015-0791-9

37. Natsuaki M, Morimoto T, Watanabe H, Nakagawa Y, Furukawa Y, Kadota K, et al. Ischemic and bleeding risk after percutaneous coronary intervention in patients with prior ischemic and hemorrhagic stroke. *J Am Heart Assoc.* (2019) 8:e013356. doi: 10.1161/JAHA.119.013356

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 04 October 2022
DOI 10.3389/fcvm.2022.945451

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Natallia Maroz-Vadalazhskaya,
Belarusian State Medical University, Belarus
Antonis Sakellarios,
University of Ioannina, Greece
Filippo Cademartiri,
Gabriele Monasterio Tuscany Foundation (CNR), Italy

*CORRESPONDENCE
Kunlun He
kunlunhe@301hospital.com.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 16 May 2022
ACCEPTED 31 August 2022
PUBLISHED 04 October 2022

CITATION
Wang X, Wang J, Wang W, Zhu M, Guo H, Ding J, Sun J, Zhu D, Duan Y, Chen X, Zhang P, Wu Z and He K (2022) Using artificial intelligence in the development of diagnostic models of coronary artery disease with imaging markers: A scoping review. *Front. Cardiovasc. Med.* 9:945451. doi: 10.3389/fcvm.2022.945451

Using artificial intelligence in the development of diagnostic models of coronary artery disease with imaging markers: A scoping review

Xiao Wang[1,2,3†], Junfeng Wang[4†], Wenjun Wang[1,2,3†], Mingxiang Zhu[1,2,3], Hua Guo[5], Junyu Ding[5], Jin Sun[1,2,3], Di Zhu[1,2,3], Yongjie Duan[1,2,3], Xu Chen[1,2,3], Peifang Zhang[6], Zhenzhou Wu[6] and Kunlun He[1,2,3*]

[1]Key Laboratory of Ministry of Industry and Information Technology of Biomedical Engineering and Translational Medicine, Chinese PLA General Hospital, Beijing, China, [2]Beijing Key Laboratory for Precision Medicine of Chronic Heart Failure, Chinese PLA General Hospital, Beijing, China, [3]Medical Big Data Research Center, Chinese PLA General Hospital, Beijing, China, [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands, [5]Department of Pulmonary and Critical Care Medicine, Chinese PLA General Hospital, Beijing, China, [6]BioMind Technology, Zhongguancun Medical Engineering Center, Beijing, China

Background: Coronary artery disease (CAD) is a progressive disease of the blood vessels supplying the heart, which leads to coronary artery stenosis or obstruction and is life-threatening. Early diagnosis of CAD is essential for timely intervention. Imaging tests are widely used in diagnosing CAD, and artificial intelligence (AI) technology is used to shed light on the development of new imaging diagnostic markers.

Objective: We aim to investigate and summarize how AI algorithms are used in the development of diagnostic models of CAD with imaging markers.

Methods: This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline. Eligible articles were searched in PubMed and Embase. Based on the predefined included criteria, articles on coronary heart disease were selected for this scoping review. Data extraction was independently conducted by two reviewers, and a narrative synthesis approach was used in the analysis.

Results: A total of 46 articles were included in the scoping review. The most common types of imaging methods complemented by AI included single-photon emission computed tomography (15/46, 32.6%) and coronary computed tomography angiography (15/46, 32.6%). Deep learning (DL) (41/46, 89.2%) algorithms were used more often than machine learning algorithms (5/46, 10.8%). The models yielded good model performance in terms of accuracy, sensitivity, specificity, and AUC. However, most of the primary studies used a relatively small sample ($n < 500$) in model development, and only few studies (4/46, 8.7%) carried out external validation of the AI model.

Conclusion: As non-invasive diagnostic methods, imaging markers integrated with AI have exhibited considerable potential in the diagnosis of CAD. External validation of model performance and evaluation of clinical use aid in the confirmation of the added value of markers in practice.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022306638], identifier [CRD42022306638].

KEYWORDS

coronary artery disease, artificial intelligence, diagnosis, prediction model, imaging, scoping review

Introduction

Cardiovascular disease (CVD), with a broad definition, refers to a group of disorders of the heart and blood vessels and is the main reason of death globally. CVD has several subtypes, among which coronary artery disease (CAD) is the most prevalent and remains one of the main causes of morbidity and mortality (1). CAD, including heart attack, acute myocardial infarction (MI), stable and unstable angina pectoris (AP), and sudden cardiac death (2), can affect heart functioning and brain processing (3) and further lead to cognitive impairment (4). As a result, CAD became one of the major global economic burdens in healthcare.

Invasive coronary angiography (ICA) is the reference standard for the diagnosis of CAD, especially obstructive disease; however, people who underwent ICA may suffer from complications (5) such as bleeding, pseudoaneurysm, and hematoma. Medical imaging, as a non-invasive technique, has developed from lesion recognition to functional imaging like diagnosis and evaluation of disease, especially radiological methods (6). Previous studies showed that the diagnostic accuracy of coronary computed tomographic angiography (CCTA) for coronary atherosclerosis is comparable to that of invasive techniques due to its potential to identify and describe plaques (7), and the clinical use of MRI techniques in CAD is now widely available in many aspects of CAD (8). The rapid growth of medical imaging data accelerates the discovery of new imaging markers for diagnosis, prediction, or stratification of CAD, which is also known as radiomics. Artificial intelligence (AI), as a technology to enable problem-solving by simulating human intelligence (9), plays an important role in imaging marker derivation and model development in this field.

The application of AI in medical imaging is an interdisciplinary work and involves researchers from different backgrounds. Thus, there are significant differences in study design, medical imaging technique, AI algorithm, and performance evaluation in diagnostic models of CAD. In this scoping review, we aim to investigate and summarize how AI algorithms are used in the development of diagnostic models of CAD with imaging markers and to discover the knowledge gaps to point out the direction for future research.

Methods

This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline (10), and a completed PRISMA-ScR checklist was provided in the **Supplementary Material 1**. The protocol of the systematic review and methodological quality assessment was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with the registry number CRD42022306638.

This scoping review is part of the project, aiming to provide an understanding of the role of medical imaging markers integrated with AI for the diagnosis of CAD. For the purpose of this scoping review, the term CAD includes AP, coronary artery disease, coronary stenosis, myocardial infarction, coronary artery atherosclerosis, and coronary artery vulnerable plaque, which can completely or partially block the blood flow of the major arteries of the heart, as these are the terms used to describe the same medical condition that causes lesions in blood vessels supplying the heart and lead to ischemic heart disease in the International Classification of Diseases (ICD-10) (**Supplementary Material 2**).

Inclusion and exclusion criteria

Publications of primary research on the development of diagnostic models of CAD using AI techniques based on imaging, regardless of targeted patients, data sources, or study design, were included in the review. Exclusion criteria were (1) publications not in English or not using human data or not imaging tests, (2) models not developed for diagnosis, (3) meta-research studies (e.g., reviews of prediction models), (4) conference abstracts, (5) studies that are only focused on automatic segmentation of images or extraction of medical

image parameters, and (6) diagnostic models developed or validated not associated with CAD.

Identification of eligible publications

Eligible publications for this scoping review were selected from a systematic review and methodological quality assessment on the image-based diagnostic models with AI in CVD performed by the same research group. The systematic literature search was conducted in PubMed and Embase, and the search strategy information can be found in the public online protocol.

Studies identified by the search strategy were imported into EndNote for checking duplicates. After removing duplicates, titles and abstracts were screened independently by two authors to identify eligible studies. The potentially eligible studies were independently checked with full text by the same two researchers for final inclusion. As the last step, models for the diagnosis of CAD were selected for this scoping review.

Data extraction

Data were collected on general information of articles (first author, year of publication, title, journal, and DOI), study characteristics (date of submission, acceptance, publication, country of author, and study), population characteristics (age-group, clinical setting, and participant inclusion), AI technique characteristics (purpose/use of the AI technique and AI models/algorithms), data set characteristics (data set size, data types, type of imaging, number of image features, reference/gold standard, competitor, data sources, study design, internal validation, and external validation), and diagnostic model characteristics (clinical effectiveness). We then performed a double data extraction for all included articles on the basis of detailed explanations for each item (**Supplementary Material 3**). If multiple models were established in an article, only one model was selected based on the following criteria in order: (1) the one with the largest total sample size, (2) the one with the largest number of events, and (3) the one with the highest predictive performance. A total of two reviewers (two of WW, HG, JD, JS, YD, MZ, DZ, and XW) independently extracted data from each article using a data extraction form designed for this review. Disagreements were resolved through discussion, and if necessary, the final judgment was made by a third reviewer (JW).

Data synthesis

On account of the heterogeneity in selected studies, a narrative synthesis of the extracted data was performed. Numbers and percentages were used to describe categorical data, and the distribution of continuous data was assessed and described using median and IQR. We also summarized the characteristics of the included articles in this scoping review by descriptive statistics and data visualization. In the process of analysis, all the statistical analyses were performed by R version 3.6.1 and RStudio version 1.2.5001, and graphic charts and tables were used to present the results.

Results

Selection of publications

After removing duplicates, screening titles and abstracts, and checking the full text, a total of 110 eligible articles were identified for the systematic review and methodological quality assessment on the image-based diagnostic models with AI in CVD, of which 46 were about the diagnosis of CAD and thus were selected for this scoping review. A complete list of the included studies and their characteristics is available in the **Supplementary Material 4**.

Characteristics of the included studies

Coronary artery disease is a progressive disease and also a general term for a class of diseases. Of the 46 studies included, 54.4% were specifically for CAD (11–35) as the research disease, and the other specific diseases were named coronary artery atherosclerosis (10.8%) (36–40), coronary artery stenosis (15.3%) (41–47), coronary artery calcium (4.3%) (48, 49), MI (10.8) (50–54), myocardial ischemia (2.1%) (55), and regional wall motion abnormalities (2.1%) (56) (**Figure 1**).

Approximately, half of the included studies were conducted in years 2020 (12/46, 26.0%) (14, 15, 17, 19, 20, 25, 26, 30, 36, 37, 45, 56) and 2021 (12/46, 26.0%) (13, 16, 21, 24, 29, 33, 39, 40, 43, 46, 50, 53) (**Figure 2**). The corresponding authors of the included studies were from 13 countries, including the United States (14/46, 30.3%) (12, 16, 21, 22, 29, 31, 34, 36, 39, 41, 42, 48, 49, 53), China (11/46, 23.9%) (15, 19, 20, 35, 37, 38, 40, 45, 46, 52, 54), Japan (8/46, 17.3%) (17, 23, 25, 27, 28, 32, 55, 56), Greece (2/46, 4.3%) (13, 14), and Netherlands (2/46, 4.3%) (44, 47), whereas Italy (26), Canada (11), India (30), Korea (24), New Zealand (50), Russia (43), Sweden (51), Turkey (18), and the United Kingdom (33) each had only one study (1, 2.1%). In most of the articles, corresponding authors and study cohorts were from unified countries. Only one study involved cross-country collaborations, with the authors of the article being from India, while the study cohort was from China. **Supplementary Table 1** shows the all characteristics of the studies included in our review.

Of all the included articles, 44 articles mentioned the date of submission and date of acceptance, and the time from submission to acceptance varied from 19 days to 466 days, with the median of 105 days and the interquartile range of [66.25, 162.75]. Except for six articles being published in journals not

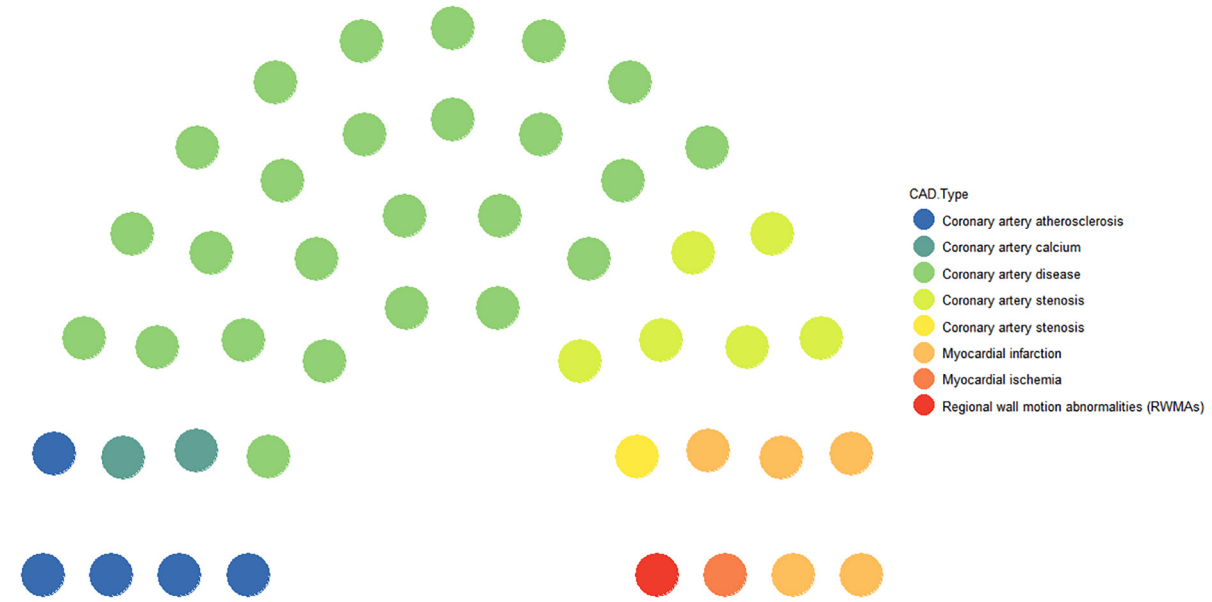


FIGURE 1
CAD types in the included publications.

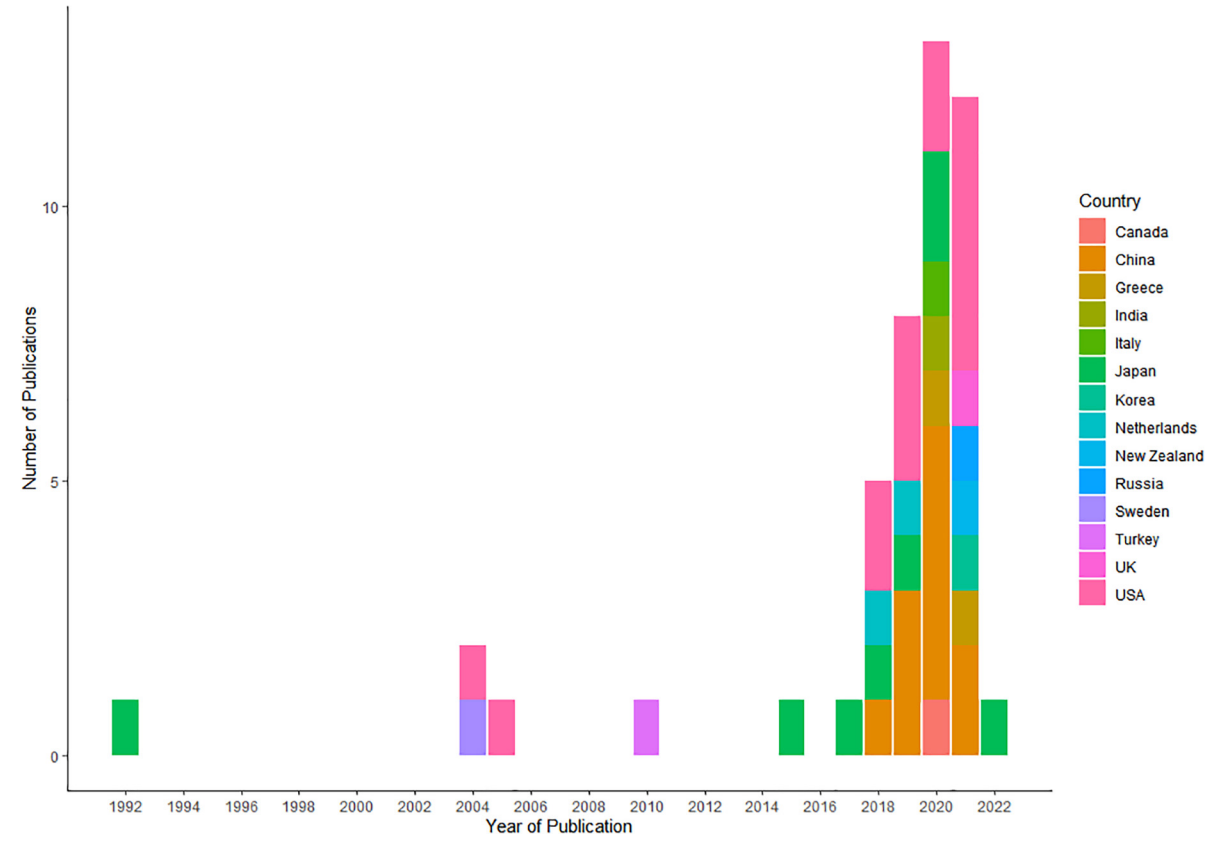


FIGURE 2
Number of publications by year and country.

having an impact factor (IF) yet, the IF of the other 40 articles ranged from 0.785 to 22.673, with the median of 3.6645 and the interquartile range of [2.52775, 7.887]. As can be seen in **Figure 3**, the time needed for a decision of acceptance was positively correlated with the journal IF (Spearman rank correlation = 0.24). **Supplementary Table 2** shows the time from submission to acceptance and the IF of all included articles.

The colors represent the sample size of the model training data set, and the AUC of each model is presented as the radius of the bubble.

Data sources and study designs in the included studies

For data sources, private data (data collected by centers) (35/46, 76.0%) (11–21, 23, 24, 27, 33–50, 53, 54, 56) were the most commonly used data sources for the development of AI models. Except for one article for which the data source is unclear (28), public data (10/46, 21.7%) were the other sources of data for AI models (22, 25, 26, 29–32, 51, 52, 55). Most studies were single-center studies, accounting for 76.0% (35/46), and 19.5% (9/46) were multi-center studies (16, 20, 29, 33, 41, 42, 51, 53, 55). There were three major types of study designs: cohort study (30/46, 65.2%) (11–28, 36–38, 40–43, 46–50), case–control (8/46, 17.3%) (34, 35, 39, 44, 52–54, 56), and nested case–control (1/46, 2.1%) (33), whereas for the other 15.3% of the studies (7/46) (29–32, 45, 51, 55), the type of study design could not be determined based on the information in the article.

Of the 41 (89.2%) studies that reported sample size on patient level, eight (17.3%) studies used data sets of less than 100 samples (11, 12, 19, 34, 35, 37, 43, 46), 20 (43.5%) studies used data sets with 100–500 samples (14–16, 18, 23, 26, 31, 32, 36, 39, 40, 44, 47, 48, 51–56), five (10.8%) studies used data sets with 500–1,000 samples (13, 24, 25, 30, 33), and eight (17.3%) studies used data sets with more than 1,000 samples (20–22, 27–29, 41, 42). The other five (10.8%) studies directly selected relevant medical imaging scans or videos as training samples with a sample size between 63 and 4,664 (17, 38, 45, 49, 50) (**Figure 3**).

Population characteristics in the included studies

Across the populations studied, most studies had no age restrictions on the study population (39/46, 86%), while other studied populations included people older than 18 years (4/46, 8.6%) (19, 35, 39, 45), people older than 40 years (1/46, 2.1%) (15), or older adults (above the age of 65 years) (2/46, 4.3%) (32, 55). In the included articles, most of the study population was patients who were hospitalized (34/46, 74.1%), and some studies included the general population (3/46, 6.5%) (24, 26, 27) or outpatients (3/46, 6.5) (25, 31, 39), while one study dealt with coronial postmortem examination (1/46, 2.1%) (50), and the population of the rest of the studies was unclear (5/46, 10.8%) (22, 38, 45, 49, 52).

Outcome and reference standards in the included studies

The main outcome of the diagnostic models was classified into three formats: binary (e.g., the status of CAD, yes or no) (34/46, 74.1%), ordinal (e.g., severity grading of CAD) (8/46, 17.3%) (16, 19, 29–33, 55), and multinomial (e.g., multiple diseases or classification of CAD) (4/46, 8.6%) (18, 46, 50, 51).

Reference standards for determining the outcomes were only mentioned in 36 of the 46 studies. Experts (11/46, 23.9%) (11, 16, 20, 21, 36, 38, 39, 45, 48, 49, 52), such as cardiologists or radiologists, and coronary angiography (13/46, 28.3%) (12–15, 17–19, 33, 41–43, 46, 53) were the two main reference standards. Coronary angiograms and experienced physicians (6/46, 13.0%) (28, 29, 31, 32, 51, 55), fractional flow reserve (FFR) (4/46, 8.6%) (34, 35, 44, 47), and clinical characteristics, electrocardiogram, and laboratory test index (2/46, 4.3%) (40, 54) were used as the reference standards for CAD in other studies.

Types of medical imaging and artificial intelligence algorithms in the included studies

The included studies demonstrate 10 types of medical imaging that have been used to diagnose CAD with AI techniques. The most common medical imaging used was computed tomography (CT), comprising 73.9% (34/46) of the studies, which included single-photon emission computed tomography (SPECT) (15/46, 32.6%) (12–14, 17, 18, 21, 27–29, 31, 32, 41, 42, 51, 55), coronary computed tomography angiography (CCTA) (15/46, 32.6%) (15, 16, 19, 23, 26, 30, 34–36, 39, 40, 44, 46–48), optical coherence tomography (OCT) (3/46, 6.5%) (11, 37, 38), and non-contrast CT (1/46, 2.1%) (49). Other more commonly used medical imaging techniques were ultrasonography (5/46, 10.8%) (22, 24, 33, 53, 56), MR (2/46,4.3%) (52, 54), and X-ray (2/46, 4.3%) (43, 45). In contrast, the least commonly used images were coronary angioscopy (1/46, 2.1%) (25), histological slides (1/46, 2.1%) (50), and facial photo (1/46, 2.1%) (20). In the process of model development, the majority of the studies focused only on using various characteristics of medical imaging of participants, although few articles clearly defined the image features. Other combinations of data in some included studies, such as demographic data (5/46, 10.8%) (18, 20, 21, 29, 30), clinical data (2/46, 4.3%) (13, 27), and laboratory data (1/46, 2.1%) (31), were also used to

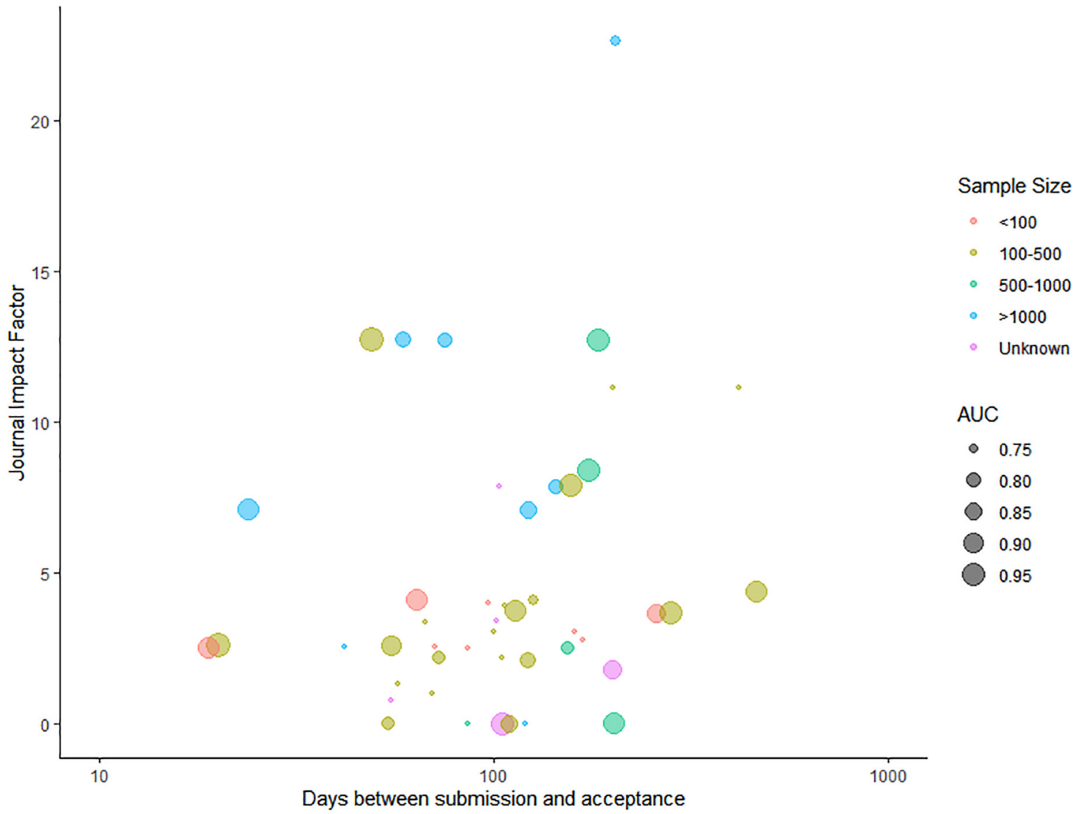


FIGURE 3
Relationship between the time needed for acceptance for publication and the journal impact factor.

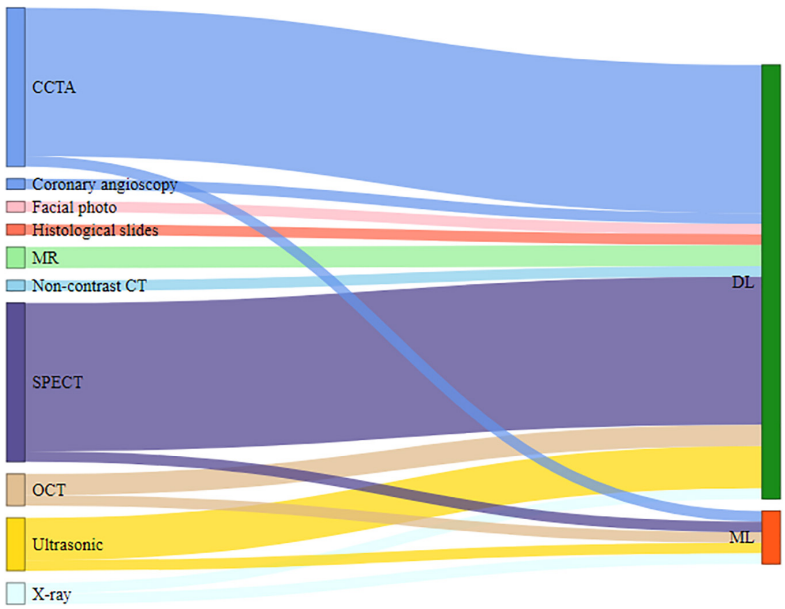


FIGURE 4
Imaging types and AI methods.

evaluate their effect on the performance of the AI technology to predict the diagnosis of CAD.

Many different AI algorithms were applied to explore the diagnostic value of information from images. AI algorithms were classified into deep learning (DL) (41/46, 89.2%) (12, 14–29, 31, 32, 34–42, 44–56) and machine learning (ML) (5/46, 10.8%) (11, 13, 30, 33, 43), as shown in **Figure 4**.

Model performance measures used in the included studies

Different indicators were used in the validation process of different models, and we only summarized the commonly used validation indicators: accuracy, sensitivity, specificity, and the area under the curve (AUC).

The accuracy of the diagnostic models was reported in 26 studies, and the accuracy level ranged from 57 to 100%. The accuracy level was < 70% in three studies (18, 26, 28), 70–90% in 12 studies (13, 14, 19, 20, 32, 35, 38, 40, 45, 47, 48, 53), and > 90% in 11 studies (11, 15, 16, 22, 24, 36, 39, 46, 49, 50, 52).

Sensitivity was reported in 32 studies and ranged from 47 to 97.14%. The sensitivity level was < 70% in five studies (26, 32, 36, 42, 53), 70–90% in 19 studies (13, 14, 18–21, 29, 31, 33, 34, 39–41, 43–47, 54), and > 90% in eight studies (11, 12, 15, 16, 35, 48, 52, 55). Moreover, specificity was reported in only 30 studies and ranged from 48.4 to 99.8%. The specificity level was < 70% in nine studies (15, 18, 20, 29, 31, 40–42, 44), 70–90% in 11 studies (12–14, 19, 21, 26, 32, 33, 35, 47, 48), and > 90% in 10 studies (11, 16, 34, 36, 39, 46, 52–55).

The area under the curve was only reported in 29 studies, ranging from 0.74 to 0.98 (**Figure 3**). In seven studies, the AUC was below 0.80 (13, 15, 18, 20, 44, 47, 53); in nine studies, it was between 0.8 and 0.9 (19, 21, 23, 29, 32, 33, 38, 41, 42); and in 13 studies, it was above 0.9 (24, 25, 27, 33–36, 39, 49, 51, 54–56). However, among all the included articles, only four carried out external validation of the AI model, accounting for a proportion of 8.6% (20, 29, 33, 39).

Competitor and clinical effectiveness of developed models in the included studies

After the AI models were developed, 11 articles compared the performance of the model with clinicians, including experts (10/46, 21.7%) (12–18, 33, 53, 56) and less experienced clinicians (1/46, 2.1%) (49). Some models in the included studies (13/46, 28.3%) were compared with previously existing or published models (20–23, 27, 28, 37, 38, 43, 45, 47, 52, 54). Other methods used for comparison with models in the included studies include total perfusion deficit (2/46, 4.3%) (41, 42), CCTA (1/46, 2.1%) (19), and conventional 120 kVp images (1/46, 2.1%) (46), and the rest of the studies (18/46, 39.1%) (11, 24–26, 29–32, 34–36, 39, 40, 44, 48, 50, 51, 55) have no information about competitors of the AI models.

However, few developed models of CAD have been used in clinical practice or prospective studies to prove their clinical applicability. Only one article (1/46, 2.1%) (51) mentioned that some physicians of the invited hospitals used the model system and generally found it easy to use and of value in their clinical practice.

Discussion

Principal findings and the implications for practice and research

In this review, we explored the use of imaging disease markers in the diagnosis of CAD with AI. This review has highlighted a few salient points and some research gaps which have the potential to guide future research and enhance the value of new imaging disease markers for medical decisions.

First, in a total of 46 included studies, it is obvious that the number of studies increased in the past 20 years, especially in the recent 2 years (12 in 2020 and 12 in 2021), which is not surprising given that the use of AI technology in medical care, especially the diagnosis of common diseases, became a hot topic. Some developed countries have a long history of carrying out research on AI-based diagnostic prediction models of CAD, such as Japan (1992) and the United States (2004). In recent years (2018–2021), China is the fastest growing country in the establishment of AI models, and the final proportion of articles included is 26.0%, second to the United States (30.3%).

Second, there is significant heterogeneity in the study design. The study design of more than half of the articles was a cohort study as the primary studies we included are predominantly retrospective in nature. The common data sources are mostly private data and single-center studies, mainly from different clinical settings in different hospitals in different countries, which cannot be shared by the general public. The performance of models based on these data cannot be effectively verified, so it cannot be widely applied to other sources of data. It is important to emphasize that the generalizability of data and reproducibility of methods (57) are crucial to making new imaging disease markers interpretable and translatable to clinical care for an AI diagnostic model.

Third, most included studies used experts, such as cardiologists or radiologists, and coronary angiography as the reference standards. CAD, the most common clinical heart disease, is a progressive pathological process with varying degrees of severity and clinical symptoms for different patients. Although coronary angiography was often used as the gold standard for CAD in clinical settings, it may be invalid,

especially in patients who have intermediate severity of stenosis (58–60). In the process of establishing CAD diagnostic models using imaging as disease markers, we should carefully select the appropriate reference standard so that the model can obtain more accurate diagnostic performance in prospective research or clinical practice.

Fourth, the most often used outcome is binary (disease versus no disease) in studies using imaging markers integrated with AI techniques, without classifying diseases or grading their level of severity. This explains the rapid and single application of imaging disease markers developed with AI in the reviewed studies. Future research should explore the fusion methods of image features and AI technology to attain higher prediction accuracy in terms of the coronary lesions that occur in the patient and the severity of CAD.

Fifth, we identified the features of AI techniques as observed in the literature. For AI models, DL techniques were used much more than ML techniques. DL can learn from unstructured data, and the information obtained in the learning process is of great help to the interpretation of image data. Therefore, it is understandable that most researchers used DL techniques as they achieved far more results in image recognition than using other related technologies.

Sixth, in this scoping review, a variety of imaging types can be used together with AI in the diagnosis of CAD. Ordinarily, experts in different hospitals make their own judgments about CAD based on the types of medical imaging they specialize in. Thus, it may be related to the strengths of different imaging tests in different hospitals or the professional habits of each doctor. Based on our findings, CCTA and SPECT were the most used non-invasive imaging modality for AI applications. One explanation for this is that radiomics features extracted by CCTA and SPECT showed good diagnostic accuracy for the identification of coronary lesions, coronary plaques, and coronary stenosis.

Seventh, less than one-fifth of the articles used data other than image features in the process of model development, such as clinical data and demographic data, which can contribute to the early prediction of CAD. Furthermore, we should also evaluate the potential of laboratory data and genetic data, as a combination of data with image features, in the early diagnostic prediction of CAD. The earlier the diagnostic prediction time, the more effective a medical or surgical treatment that the physicians can give the patients with CAD, which can significantly reduce the risk of death.

Eighth, the sample size was less than 1,000 in most of the included articles, regardless of whether the research subjects were patients or relevant medical imaging scans or videos. Sample size plays a more important role than model performance in determining the impact of the study, quantified by the journal IF (**Figure 3**). In future studies, AI models should be trained and validated on a larger data set and have a larger healthy control sample, preferably from public sources.

Ninth, several articles claimed that their AI models had a higher performance than existing models or methods (20–22, 27, 28, 38, 45–47, 49, 52, 54). Furthermore, some articles compared with experts (experienced radiologists) and readers (board-certified radiologists) indicated that image-based AI improved the non-invasive diagnosis of CAD (12–16, 23, 33, 53, 56). Although most of the included diagnostic models were verified internally, different model performance measures were used in the validation process of different models. As we calculated, nearly 90% of the AI diagnostic prediction models using imaging as a marker for diagnosing CAD in our included articles were not externally validated. So, we suggest that clinicians and researchers should conduct external validation or prospective studies to explore the use of imaging markers integrated with AI in clinical settings and compare the performance of different imaging models used to diagnose CAD by using relatively uniform indicators.

Last and interestingly, a positive correlation was observed between the time needed for acceptance for publication and the journal IF: the higher the IF of the journal, the longer the review and decision time required. The IF is calculated from how many times articles in the same journal have been cited and usually is seen as an indicator of influence. One possible explanation might be that low-impact journals were less strict than high-impact journals; thus, the decision of acceptance was given fast. Researchers who aim to publish their models in high-impact journals need to take the risk of not being published timely.

Strengths and limitations

The present review was conducted to address the use of all types of imaging disease markers developed with AI in the diagnosis of CAD, with no restrictions on targeted patients, data sources, or study design. Simultaneously, we also explored the features of AI techniques and data sources that were used to develop these models.

Recent reviews focused on the detection of CAD using AI techniques (61) or on machine learning quantitation of CVD (including CAD) (62). The previous review assessed the clinical effectiveness of the use of medical imaging, such as computed tomography angiography (CTA), instead of ICA (63). This review explored and summarized the application of new imaging disease markers developed with AI in the diagnosis of CAD, which gives a deeper insight into the fusion of imaging and AI in medicine.

We have included any primary research publication (in English) related to image-based diagnostic models with AI of CAD for reducing the selection bias. Furthermore, study selection and data extraction involved two reviewers working independently, and disagreements in the process were resolved through discussion, and if necessary, the final judgment was given by a third senior reviewer.

This review included only PubMed and Embase databases, which led to the loss of some gray literature and other potentially relevant studies in other databases. The exclusion of non-English studies may lead to an oversight of relevant articles in other languages. In some of the included articles, we could not extract all the information from the description and reporting of the diagnostic model according to the contents in the data extraction form. Adherence to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement (64, 65) and the Standards for Reporting of Diagnostic Accuracy Studies (STARD) Statement (66, 67) should be recommended for authors. In this scoping review, we only summarized the types of imaging disease markers developed with AI, but not compared models using different types of imaging or the performance of different models using the same type of imaging. As it is part of our overall systematic review project, the assessment of the possible methodological quality and risk of bias in the included literature will be reserved for later research studies.

Conclusion

The current scoping review included 46 studies that focused on the use of imaging markers integrated with AI as diagnostic methods for CAD in all clinical settings. We explored and summarized the types of images and the classification of AI in these models. We have also provided information about the data source and study design commonly used in the diagnostic models and strongly recommend external validation of the models and prospective clinical studies in the future. With the advance in medical imaging data, AI has exhibited considerable potential in clinical decision support and analysis in multiple medical fields. The integrated development of imaging and AI can assist clinicians to make more accurate medical decisions for different diseases, including CAD, which can improve clinical efficiency while avoiding the wastage of medical resources and reducing the economic burden on patients.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Author contributions

XW, JW, WW, and KH contributed to the conception and design of the study. XW, WW, MZ, HG, JD, JS, DZ, and YD organized the database. XW and JW performed the statistical analysis and wrote the first draft of the manuscript. WW, XC, PZ, and ZW wrote sections of the manuscript. KH supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by the Science and Technology Innovation 2030 - Major Project (2021ZD0140406) and the Ministry of Industry and Information Technology of China (2020-0103-3-1).

Conflict of interest

Authors PZ and ZW were employed by the company BioMind Technology.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.945451/full#supplementary-material

References

1. WHO. *Cardiovascular-Diseases-(CVDs)*. (2017). Available online at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed May 17, 2017)

2. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol.* (2014) 11:276–89. doi: 10.1038/nrcardio.2014.26

3. Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, et al. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev.* (2014) 18:41–52. doi: 10.1016/j.arr.2014.07.003

4. Barekatain M, Askarpour H, Zahedian F, Walterfang M, Velakoulis D, Maracy MR, et al. The relationship between regional brain volumes and the extent of coronary artery disease in mild cognitive impairment. *J Res Med Sci.* (2014) 19:739–45.

5. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* (2020) 41:407–77.

6. Xukai, MO, Lin M, Liang J, Center MI. Coronary artery disease and myocardial perfusion imaging evaluation of coronary heart disease meta-analysis. *J Clin Radiol.* (2019):1020–24.

7. Murgia A, Balestrieri A, Crivelli P, Suri JS, Conti M, Cademartiri F, et al. Cardiac computed tomography radiomics: an emerging tool for the non-invasive assessment of coronary atherosclerosis. *Cardiovasc Diagn Ther.* (2020) 10:2005–17. doi: 10.21037/cdt-20-156

8. Vick GW III. The gold standard for noninvasive imaging in coronary heart disease: magnetic resonance imaging. *Curr Opin Cardiol.* (2009) 24:567–79. doi: 10.1097/HCO.0b013e3283315553

9. Chartrand G, Cheng PM, Vorontsov E, Drozdzal M, Turcotte S, Pal CJ, et al. Deep learning: a primer for radiologists. *Radiographics.* (2017) 37:2113–31. doi: 10.1148/rg.2017170077

10. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* (2018) 169:467–73. doi: 10.7326/M18-0850

11. Abdolmanafi A, Cheriet F, Duong L, Ibrahim R, Dahdah N. An automatic diagnostic system of coronary artery lesions in Kawasaki disease using intravascular optical coherence tomography imaging. *J Biophotonics.* (2020) 13:e201900112. doi: 10.1002/jbio.201900112

12. Allison JS, Heo J, Iskandrian AE. Artificial neural network modeling of stress single-photon emission computed tomographic imaging for detecting extensive coronary artery disease. *Am J Cardiol.* (2005) 95:178–81. doi: 10.1016/j.amjcard.2004.09.003

13. Apostolopoulos ID, Apostolopoulos DI, Spyridonidis TI, Papathanasiou ND, Panayiotakis GS. Multi-input deep learning approach for cardiovascular disease diagnosis using myocardial perfusion imaging and clinical data. *Phys Med.* (2021) 84:168–77. doi: 10.1016/j.ejmp.2021.04.011

14. Apostolopoulos ID, Papathanasiou ND, Spyridonidis T, Apostolopoulos DJ. Automatic characterization of myocardial perfusion imaging polar maps employing deep learning and data augmentation. *Hell J Nucl Med.* (2020) 23:125–32.

15. Chen M, Wang X, Hao G, Cheng X, Ma C, Guo N, et al. Diagnostic performance of deep learning-based vascular extraction and stenosis detection technique for coronary artery disease. *Br J Radiol.* (2020) 93:20191028. doi: 10.1259/bjr.20191028

16. Choi AD, Marques H, Kumar V, Griffin WF, Rahban H, Karlsberg RP, et al. CT evaluation by artificial intelligence for atherosclerosis, stenosis and vascular morphology (CLARIFY): a multi-center, international study. *J Cardiovasc Comput Tomogr.* (2021) 15:470–6. doi: 10.1016/j.jcct.2021.05.004

17. Fujita H, Katafuchi T, Uehara T, Nishimura T. Application of artificial neural network to computer-aided diagnosis of coronary artery disease in myocardial SPECT bull's-eye images. *J Nucl Med.* (1992) 33:272–6.

18. Guner LA, Karabacak NI, Akdemir OU, Karagoz PS, Kocaman SA, Cengel A, et al. An open-source framework of neural networks for diagnosis of coronary artery disease from myocardial perfusion SPECT. *J Nucl Cardiol.* (2010) 17:405–13. doi: 10.1007/s12350-010-9207-5

19. Han D, Liu J, Sun Z, Cui Y, He Y, Yang Z. Deep learning analysis in coronary computed tomographic angiography imaging for the assessment of patients with coronary artery stenosis. *Comput Methods Programs Biomed.* (2020) 196:105651. doi: 10.1016/j.cmpb.2020.105651

20. Lin S, Li Z, Fu B, Chen S, Li X, Wang Y, et al. Feasibility of using deep learning to detect coronary artery disease based on facial photo. *Eur Heart J.* (2020) 41:4400–11. doi: 10.1093/eurheartj/ehaa640

21. Liu H, Wu J, Miller EJ, Liu C, Yaqiang, Liu, et al. Diagnostic accuracy of stress-only myocardial perfusion SPECT improved by deep learning. *Eur J Nucl Med Mol Imaging.* (2021) 48:2793–800. doi: 10.1007/s00259-021-05202-9

22. Madani A, Ong JR, Tibrewal A, Mofrad MRK. Deep echocardiography: data-efficient supervised and semi-supervised deep learning towards automated diagnosis of cardiac disease. *NPJ Digit Med.* (2018) 1:59. doi: 10.1038/s41746-018-0065-x

23. Masuda T, Nakaura T, Funama Y, Oda S, Okimoto T, Sato T, et al. Deep learning with convolutional neural network for estimation of the characterisation of coronary plaques: validation using IB-IVUS. *Radiography.* (2022) 28:61–7. doi: 10.1016/j.radi.2021.07.024

24. Min HS, Ryu D, Kang SJ, Lee JG, Yoo JH, Cho H, et al. Prediction of coronary stent underexpansion by pre-procedural intravascular ultrasound-based deep learning. *JACC Cardiovasc Interv.* (2021) 14:1021–9. doi: 10.1016/j.jcin.2021.01.033

25. Miyoshi T, Higaki A, Kawakami H, Yamaguchi O. Automated interpretation of the coronary angioscopy with deep convolutional neural networks. *Open Heart.* (2020) 7:e001177. doi: 10.1136/openhrt-2019-001177

26. Muscogiuri G, Chiesa M, Trotta M, Gatti M, Palmisano V, Dell'Aversana S, et al. Performance of a deep learning algorithm for the evaluation of CAD-RADS classification with CCTA. *Atherosclerosis.* (2020) 294:25–32. doi: 10.1016/j.atherosclerosis.2019.12.001

27. Nakajima K, Kudo T, Nakata T, Kiso K, Kasai T, Taniguchi Y, et al. Diagnostic accuracy of an artificial neural network compared with statistical quantitation of myocardial perfusion images: a Japanese multicenter study. *Eur J Nucl Med Mol Imaging.* (2017) 44:2280–9. doi: 10.1007/s00259-017-3834-x

28. Nakajima K, Matsuo S, Wakabayashi H, Yokoyama K, Bunko H, Okuda K, et al. Diagnostic performance of artificial neural network for detecting ischemia in myocardial perfusion imaging. *Circ J.* (2015) 79:1549–56. doi: 10.1253/circj.CJ-15-0079

29. Otaki Y, Singh A, Kavanagh P, Miller RJH, Parekh T, Tamarappoo BK, et al. Clinical deployment of explainable artificial intelligence of SPECT for diagnosis of coronary artery disease. *JACC Cardiovasc Imaging.* (2021). 15:1091–102. doi: 10.1016/j.jcmg.2021.04.030

30. Saikumar K, Rajesh V, Hasane Ahammad SK, Sai Krishna M, Sai Pranitha G, Ajay Kumar Reddy R. CAB for heart diagnosis with RFO artificial intelligence algorithm. *Int J Res Pharm Sci.* (2020) 11:1199–205. doi: 10.26452/ijrps.v11i1.1958

31. Scott JA, Aziz K, Yasuda T, Gewirtz H. Integration of clinical and imaging data to predict the presence of coronary artery disease with the use of neural networks. *Coron Artery Dis.* (2004) 15:427–34. doi: 10.1097/00019501-200411000-00010

32. Shibutani T, Nakajima K, Wakabayashi H, Mori H, Matsuo S, Yoneyama H, et al. Accuracy of an artificial neural network for detecting a regional abnormality in myocardial perfusion SPECT. *Ann Nucl Med.* (2019) 33:86–92. doi: 10.1007/s12149-018-1306-4

33. Upton R, Mumith A, Beqiri A, Parker A, Hawkes W, Gao S, et al. Automated echocardiographic detection of severe coronary artery disease using artificial intelligence. *JACC Cardiovasc Imaging.* (2021). doi: 10.1016/j.jcmg.2021.10.013

34. von Knebel Doeberitz PL, De Cecco CN, Schoepf UJ, Duguay TM, Albrecht MH, van Assen M, et al. Coronary CT angiography-derived plaque quantification with artificial intelligence CT fractional flow reserve for the identification of lesion-specific ischemia. *Eur Radiol.* (2019) 29:2378–87. doi: 10.1007/s00330-018-\break5834-z doi: 10.1007/s00330-018-5834-z

35. Wang ZQ, Zhou YJ, Zhao YX, Shi DM, Liu YY, Liu W, et al. Diagnostic accuracy of a deep learning approach to calculate FFR from coronary CT angiography. *J Geriatr Cardiol.* (2019) 16:42–8.

36. Candemir S, White RD, Demirer M, Gupta V, Bigelow MT, Prevedello LM, et al. Automated coronary artery atherosclerosis detection and weakly supervised localization on coronary CT angiography with a deep 3-dimensional convolutional neural network. *Comput Med Imaging Graph.* (2020) 83:101721. doi: 10.1016/j.compmedimag.2020.101721

37. He C, Wang J, Yin Y, Li Z. Automated classification of coronary plaque calcification in OCT pullbacks with 3D deep neural networks. *J Biomed Opt.* (2020) 25:095003. doi: 10.1117/1.JBO.25.9.095003

38. Liu R, Zhang Y, Zheng Y, Liu Y, Zhao Y, Yi L. Automated detection of vulnerable plaque for intravascular optical coherence tomography images. *Cardiovasc Eng Technol.* (2019) 10:590–603. doi: 10.1007/s13239-019-00425-2

39. White RD, Erdal BS, Demirer M, Gupta V, Bigelow MT, Dikici E, et al. Artificial intelligence to assist in exclusion of coronary atherosclerosis during CCTA evaluation of chest pain in the emergency department: preparing an application for real-world use. *J Digit Imaging.* (2021) 34:554–71. doi: 10.1007/s10278-021-00441-6

40. Zhao H, Yuan L, Chen Z, Liao Y, Lin J. Exploring the diagnostic effectiveness for myocardial ischaemia based on CCTA myocardial texture features. *BMC Cardiovasc Disord.* (2021) 21:416. doi: 10.1186/s12872-021-02206-z

41. Betancur J, Commandeur F, Motlagh M, Sharir T, Einstein AJ, Bokhari S, et al. Deep learning for prediction of obstructive disease from fast myocardial perfusion SPECT: a multicenter study. *JACC Cardiovasc Imaging.* (2018) 11:1654–63. doi: 10.1016/j.jcmg.2018.01.020

42. Betancur J, Hu LH, Commandeur F, Sharir T, Einstein AJ, Fish MB, et al. Deep learning analysis of upright-supine high-efficiency SPECT myocardial perfusion imaging for prediction of obstructive coronary artery disease: a multicenter study. *J Nucl Med.* (2019) 60:664–70. doi: 10.2967/jnumed.118.213538

43. Danilov VV, Klyshnikov KY, Gerget OM, Kutikhin AG, Ganyukov VI, Frangi AF, et al. Real-time coronary artery stenosis detection based on modern neural networks. *Sci Rep.* (2021) 11:7582. doi: 10.1038/s41598-021-87174-2

44. van Hamersvelt RW, Zreik M, Voskuil M, Viergever MA, Išgum I, Leiner T. Deep learning analysis of left ventricular myocardium in CT angiographic intermediate-degree coronary stenosis improves the diagnostic accuracy for identification of functionally significant stenosis. *Eur Radiol.* (2019) 29:2350–9. doi: 10.1007/s00330-018-5822-3

45. Wu W, Zhang J, Xie H, Zhao Y, Zhang S, Gu L. Automatic detection of coronary artery stenosis by convolutional neural network with temporal constraint. *Comput Biol Med.* (2020) 118:103657. doi: 10.1016/j.compbiomed.2020.103657

46. Yi Y, Xu C, Guo N, Sun J, Lu X, Yu S, et al. Performance of an artificial intelligence-based application for the detection of plaque-based stenosis on monoenergetic coronary CT angiography: validation by invasive coronary angiography. *Acad Radiol.* (2021) 29 Suppl. 4:S49–58. doi: 10.1016/j.acra.2021.10.027

47. Zreik M, Lessmann N, van Hamersvelt RW, Wolterink JM, Voskuil M, Viergever MA, et al. Deep learning analysis of the myocardium in coronary CT angiography for identification of patients with functionally significant coronary artery stenosis. *Med Image Anal.* (2018) 44:72–85. doi: 10.1016/j.media.2017.11.008

48. Fischer AM, Eid M, De Cecco CN, Gulsun MA, van Assen M, Nance JW, et al. Accuracy of an artificial intelligence deep learning algorithm implementing a recurrent neural network with long short-term memory for the automated detection of calcified plaques from coronary computed tomography angiography. *J Thorac Imaging.* (2020) 35(Suppl. 1):S49–57. doi: 10.1097/RTI.0000000000000491

49. Huo Y, Terry JG, Wang J, Nath V, Bermudez C, Bao S, et al. Coronary calcium detection using 3D attention identical dual deep network based on weakly supervised learning. *Proc SPIE Int Soc Opt Eng.* (2019) 10949:1094917. doi: 10.1117/12.2512541

50. Garland J, Hu M, Duffy M, Kesha K, Glenn C, Morrow P, et al. Classifying microscopic acute and old myocardial infarction using convolutional neural networks. *Am J Forensic Med Pathol.* (2021) 42:230–4. doi: 10.1097/PAF.0000000000000672

51. Ohlsson M. WeAidU-a decision support system for myocardial perfusion images using artificial neural networks. *Artif Intell Med.* (2004) 30:49–60. doi: 10.1016/S0933-3657(03)00050-2

52. Xu C, Xu L, Gao Z, Zhao S, Zhang H, Zhang Y, et al. Direct delineation of myocardial infarction without contrast agents using a joint motion feature learning architecture. *Med Image Anal.* (2018) 50:82–94. doi: 10.1016/j.media.2018.09.001

53. Zaman F, Ponnapureddy R, Wang YG, Chang A, Cadaret LM, Abdelhamid A, et al. Spatio-temporal hybrid neural networks reduce erroneous human "judgement calls" in the diagnosis of Takotsubo syndrome. *EClinicalMedicine.* (2021) 40:101115. doi: 10.1016/j.eclinm.2021.101115

54. Zhang N, Yang G, Gao Z, Xu C, Zhang Y, Shi R, et al. Deep learning for diagnosis of chronic myocardial infarction on nonenhanced cardiac cine MRI. *Radiology.* (2019) 291:606–17. doi: 10.1148/radiol.2019182304

55. Nakajima K, Okuda K, Watanabe S, Matsuo S, Kinuya S, Toth K, et al. Artificial neural network retrained to detect myocardial ischemia using a Japanese multicenter database. *Ann Nucl Med.* (2018) 32:303–10. doi: 10.1007/s12149-018-1247-y

56. Kusunose K, Abe T, Haga A, Fukuda D, Yamada H, Harada M, et al. A deep learning approach for assessment of regional wall motion abnormality from echocardiographic images. *JACC Cardiovasc Imaging.* (2020) 13(2 Pt 1):374–81. doi: 10.1016/j.jcmg.2019.02.024

57. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American heart association. *Circulation.* (2009) 119:2408–16. doi: 10.1161/CIRCULATIONAHA.109.192278

58. Miller DD, Donohue TJ, Younis LT, Bach RG, Aguirre FV, Wittry MD, et al. Correlation of pharmacological 99mTc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. *Circulation.* (1994) 89:2150–60. doi: 10.1161/01.CIR.89.5.2150

59. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* (1996) 334:1703–8. doi: 10.1056/NEJM199606273342604

60. White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med.* (1984) 310:819–24. doi: 10.1056/NEJM198403293101304

61. Alizadehsani R, Khosravi A, Roshanzamir M, Abdar M, Sarrafzadegan N, Shafie D, et al. Coronary artery disease detection using artificial intelligence techniques: a survey of trends, geographical differences and diagnostic features 1991-2020. *Comput Biol Med.* (2021) 128:104095. doi: 10.1016/j.compbiomed.2020.104095

62. Boyd C, Brown G, Kleinig T, Dawson J, McDonnell MD, Jenkinson M, et al. Machine learning quantitation of cardiovascular and cerebrovascular disease: a systematic review of clinical applications. *Diagnostics.* (2021) 11:551. doi: 10.3390/diagnostics11030551

63. Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess.* (2008) 12:iii–iv, ix-143. doi: 10.3310/hta12170

64. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ.* (2015) 350:g7594. doi: 10.1136/bmj.g7594

65. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med.* (2015) 162:W1–73. doi: 10.7326/M14-0698

66. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ.* (2015) 351:h5527. doi: 10.1136/bmj.h5527

67. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open.* (2016) 6:e012799. doi: 10.1136/bmjopen-2016-012799

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 05 October 2022
DOI 10.3389/fcvm.2022.1003067

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
Junji Matsuda,
Tokyo Medical and Dental University, Japan
Rada Vucic,
University of Kragujevac, Serbia

*CORRESPONDENCE
Paweł Kleczynski
kleczu@interia.pl

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 25 July 2022
ACCEPTED 29 August 2022
PUBLISHED 05 October 2022

CITATION
Legutko J, Niewiara L, Guzik B, Szolc P, Podolec J, Nosal M, Diachyshyn M, Zmudka K and Kleczynski P (2022) The impact of coronary microvascular dysfunction on the discordance between fractional flow reserve and resting full-cycle ratio in patients with chronic coronary syndromes. *Front. Cardiovasc. Med.* 9:1003067. doi: 10.3389/fcvm.2022.1003067

The impact of coronary microvascular dysfunction on the discordance between fractional flow reserve and resting full-cycle ratio in patients with chronic coronary syndromes

Jacek Legutko[1,2], Lukasz Niewiara[2,3], Bartlomiej Guzik[1,2], Piotr Szolc[1,2], Jakub Podolec[1,2], Marcin Nosal[4], Marta Diachyshyn[2], Krzysztof Zmudka[1,2] and Paweł Kleczynski[1,2]*

[1]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland, [2]Clinical Department of Interventional Cardiology, John Paul II Hospital, Krakow, Poland, [3]Department of Emergency Medicine, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland, [4]Center of Invasive Cardiology, Angiology and Electrotherapy, Krosno, Poland

Background: Resting full-cycle ratio (RFR) is an alternative to fractional flow reserve (FFR) for the evaluation of borderline coronary artery lesions. Although FFR and RFR results are discordant in some cases, factors associated with the discordance remain unclear. The role of coronary microvascular dysfunction (CMD) is discussed as a potential mechanism to explain these discrepancies.

Aim: The study aimed to assess concordance between RFR and FFR in a real-life cohort from a high-volume center regarding the role of CMD.

Methods: Consecutive patients with borderline coronary lesions undergoing coronary functional testing for chronic coronary syndromes were included in the study. Measurements of RFR and FFR were performed alongside additional coronary flow reserve (CFR), resistance reserve ratio (RRR), and an index of microcirculatory resistance (IMR) measurements. CMD was defined according to the current guideline by either IMR $\geq$25 or CFR $\leq$2.0 in vessels with no significant stenosis.

Results: Measurements were performed in 157 coronary arteries, in 101 patients, with a median age of 66 y., 74% male, with prior history of arterial hypertension (96%), dyslipidaemia (91%), and diabetes (40%). The median value of vessel diameter stenosis was 45% according to QCA.

Overall, FFR and RFR values were significantly correlated ($r = 0.66$, $p < 0.001$), where positive FFR/negative RFR and negative FFR/positive RFR were observed in 6 (3.8%) and 38 (24.2%) of 157 vessels. The RFR/FFR discrepancy was present in 44 (28%) of measurements. CMD was confirmed in 28 (64%) of vessels with discrepant RFR/FFR and in 46 (41%) of vessels with concordant results

($p = 0.01$). In discordant RFR/FFR vessels, as compared to concordant ones, significantly lower values of CFR [median 1.95 (IQR: 1.37, 2.30) vs. 2.10 (IQR: 1.50, 3.00), $p = 0.030$] and RRR [median 2.50 (IQR: 1.60, 3.10) vs. 2.90 IQR (1.90, 3.90), $p = 0.048$] were observed.

Main predictors of RFR/FFR discrepancy in a univariate regression analysis were: higher age of patients [OR = 1.06 (1.01; 1.10), $p = 0.010$], presence of CMD [OR = 2.51 (1.23; 5.25), $p = 0.012$], lower CFR [OR = 1.64 (1.12; 2.56), $p = 0.018$], and lower RRR values [OR = 1.35 (95% CI: 1.03; 1.83), $p = 0.038$].

Conclusion: In discrepant RFR/FFR vessels, CMD is more prevalent than in concordant RFR/FFR measurements, which can be driven by lower CFR or RRR values. Further research is needed to confirm this observation.

KEYWORDS

coronary microvascular dysfunction (CMD), fractional flow reserve (FFR), resting-full cycle ratio, borderline lesions, coronary artery disease, chronic coronary syndromes, concordance

Introduction

Fractional flow reserve measurement (FFR) is a gold standard to obtain information about ischemia in an invasive setting (1). Nevertheless, full stable hyperaemia is an absolute necessity to get adequate FFR results (2–6).

To avoid this inconvenience, new non-hyperemic invasive indices calculated in different cardiac cycle phases, are being developed and introduced to contemporary practice (7–10). Resting full cycle ratio (RFR) is one of the new non-hyperemic indices, assessed during the whole cardiac cycle, with performance confirmed in real-world practice (9, 11).

Unfortunately, not all measurements of RFR and FFR provide concordant results, and there is a considerable number of discrepancies between those two indices.

Several clinical and angiographic risk factors for this discrepancy have been reported (11–15). A few pathomechanisms of RFR/FFR discrepancy are discussed, however precise data are scarce.

Coronary microvascular dysfunction (CMD) is highly prevalent in patients presenting with chronic coronary syndromes (CCS), and as RFR is a non-hyperemic index, some concerns may arise about the potential role of CMD in a discrepancy between hyperemic FFR assessment and RFR-based decision on revascularization. However, RFR-related data in this context are scarce.

The CMD may be a potential contributor to differences in CFR and RRR values reported in the context of discordance between FFR and another non-hyperemic pressure-derived index, i.e., iFR (16). Similarly, microvascular dysfunction was discussed in terms of RFR and FFR discrepancy, nevertheless, this issue was not directly measured and reported in contemporary literature (15).

Aim

To assess concordance between RFR and FFR in a real-life cohort from a high-volume center regarding the role of coronary microcirculatory function.

Materials and methods

The study was a prospective registry of patients with CCS undergoing coronary angiography. All procedures were performed with Helsinki Declaration and were approved by the local bioethics committee. Quantitative coronary angiography (QCA) was performed by an independent core lab analyst blinded to the results of FFR/RFR. Using the guide catheter for calibration and an edge detection system (CAAS 5.7 QCA system, Pie Medical, Maastricht, The Netherlands), the reference vessel diameter and minimum lumen diameter were measured, and the percent diameter stenosis was calculated.

Physiologic measurements

In all vessels with borderline lesions (i.e., 40–90% of diameter stenosis) both resting (Pd/Pa, resting full-cycle ratio) and hyperemic (FFR) indices were assessed using pressure wire (PressureWire X, Abbott US), with hyperaemia induced by constant infusion of adenosine i.v. according to body weight (140 ug/kg/min) (17, 18). Resting full-cycle ratio was defined as lowered filtered P_d/P_a value during 4 cardiac cycles. Coronary flow reserve and index of myocardial resistance were assessed by room-temperature intracoronary saline infusion and calculated using Coroflow ver. 3 software (Abbott, US).

FFR/RFR assessment was performed by an independent analyst, blinded to clinical and angiographic data.

Cut-off values

Values of FFR ≤0.80 and RFR ≤0.89 were assumed hemodynamically significant, also CFR <2.0 and IMR >25 U were considered abnormal (1).

Coronary microcirculatory dysfunction was defined according to current ESC guidelines as IMR >25U or CFR <2.0 where the lesion was assessed to be hemodynamically non-significant (1).

Statistical analysis

Continuous data were presented as a mean value with standard deviation for normally distributed variables or by a median with an interquartile range for non-normally distributed values. Categorical data were presented as a percentage of the full group. A comparison of continuous variables was performed using the t-Student test or U-Mann Whitney test according to normality status by the Shapiro-Wilk test. Correlation between continuous values was assessed with Pearson R. Receiver operating curve for RFR to detect FFR <0.80 was analyzed, using Youden criteria to calculate the best RFR threshold.

Logistic regression was used to determine independent RFR/FFR discrepancy predictors, those with $p < 0.1$ in univariate analysis were included in multivariate models. In all analyses, a level of $p < 0.05$ was considered significant.

All analyses were performed in R statistical language (R core group, Vienna, AU), using R-studio ver 1.3, tidyverse packages ecosystem, and ggstatsplot package for graphical presentation of results.

Results

The analysis included 101 patients with chronic coronary syndromes and a median age of 66 years, of which 26% were women, mostly overweight [median BMI 28.1 kg/m^2 (IQR 26.0; 31.8)], 44% were current or former smokers, 25 patients had a history of prior myocardial infarction.

The discrepancy between RFR and FFR ischemia assessment in at least one vessel was present in 27 patients (27%).

Most of the patients were treated with ACE inhibitors/ARB and beta-blockers, and 40% had a history of diabetes. Detailed patient characteristics are presented in Table 1.

TABLE 1 Baseline clinical data.

Characteristic	$N = 101$[a]
Age, (years)	66 (59, 73)
Sex	
Female	26 (26%)
Male	75 (74%)
BMI, (kg/m^2)	28.1 (26.0, 31.8)
Medical history	
Diabetes	42 (42%)
Smoking status	
Never	52 (56%)
Current	19 (20%)
In the past	22 (24%)
Arterial hypertension treatment	97 (96%)
Dyslipidemia treatment	92 (91%)
Prior AMI	25 (24.7%)
Echocardiography	
LVEF (%)	55 (50, 60)
LVMI g/m2	108 (89.4; 128)
Laboratory parameters	
LDL (mmol/l)	2.22 (1.79, 2.86)
HGB (g/dl)	13.9 (13.1; 15.1)
Serum creatinine (μmol/l)	82.0 (71.0; 93.0)
Pharmacotherapy	
ASA	91 (90%)
Beta-blockers	86 (85%)
DHP-Ca clockers	33 (33%)
Non-DHP Ca blockers	9 (9.0%)
ACEI or ARB	91 (91%)
Patient level RFR/FFR concordance	
RFR and FFR discordant at least one vessel	27 (27%)
RFR and FFR concordant	74 (73%)

[a]Median (IQR); *n* (%); ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; DHP, dihydropyridine; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction.

Per vessel analysis—RFR performance

The analysis included 157 vessels, predominantly left anterior descending arteries (88 vessels), with median artery stenosis of 45% (IQR: 40.50%) and a median FFR of 0.84 (IQR: 0.78, 0.91). Overall, FFR and RFR values showed a good correlation ($R = 0.66$, $p < 0.001$, Figure 1 left panel), while positive FFR with negative RFR and negative FFR with positive RFR were seen in 6 (3.8%) and 38 (24.2%) of 157 vessels, respectively. The discrepancy between RFR and FFR-based decisions on revascularization was present in 44 (28%) of measurements. Discordance was present in 30% of LAD lesions and 26% of non-LAD lesions ($p = 0.6$).

Bland-Altman plot confirmed the moderate agreement of RFR with FFR values, with a median difference between both

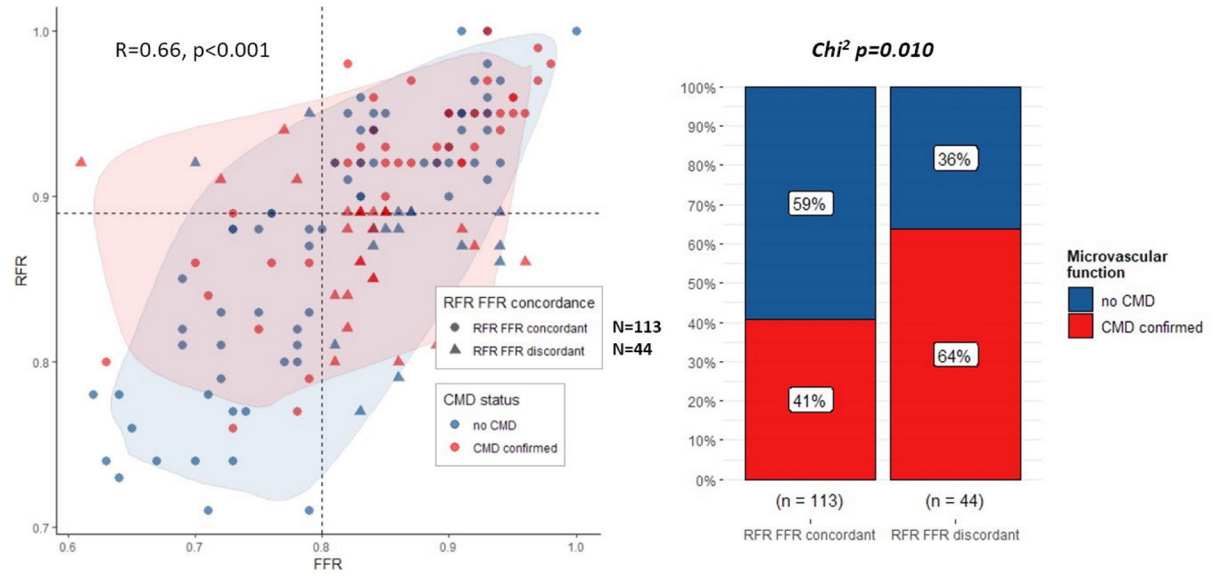


FIGURE 1
Correlation between RFR and FFR **(left panel)**, coronary microvascular dysfunction prevalence **(right panel)**.

indices of 0.04 (95% CI 0.02, 0.09, Supplementary Figure 1 Right panel).

AUC for RFR to detect FFR ≤0.80 was 0.865 (95% CI: 0.805–0.925), with an optimal cut-point RFR of 0.88 (see Supplementary Figure 1 Left panel). The diagnostic accuracy of RFR was good, with a sensitivity of 75.9% and specificity of 81.6%.

Coronary physiology analysis

The presence of CMD was confirmed in 28 (64%) of vessels with discrepant RFR/FFR results and in 46 (41%) of vessels with concordant results ($p = 0.01$, Figure 1 panel right). In discordant RFR/FFR vessels, as compared to concordant ones, significantly lower values of CFR [median 1.95 (IQR: 1.37, 2.30) vs. 2.10 (IQR: 1.50, 3.00), $p = 0.030$] and RRR [median 2.50 (IQR: 1.60, 3.10) vs. 2.90 IQR (1.90, 3.90), $p = 0.048$] were observed. There was no significant difference between discordant and concordant vessels in terms of IMR value [median 22 (IQR: 16, 30) vs. 19 (IQR: 13, 26), $p = 0.082$, respectively]. Detailed results of the angiographic and functional coronary assessment are presented in Table 2.

RFR/FFR discrepancy predictors

Main predictors of RFR/FFR discrepancy in a univariate regression analysis were: higher age of patients [OR = 1.06 (1.01; 1.10) for additional year, $p = 0.010$], presence of CMD [OR = 2.51 (1.23; 5.25), $p = 0.012$], lower CFR [OR = 1.64 (1.12; 2.56) for decrease of 1 unit, $p = 0.018$], and lower RRR values [OR = 1.35 (95% CI: 1.03; 1.83) for decrease of 1 unit, $p = 0.038$].

Lower CFR values, lower RRR values, and the presence of CMD in the analyzed territory, after adjustment for sex and age, remained independent predictors of discordance between RFR and FFR in multivariate regression analysis with $OR_{adjusted} = 1.69$ (95% CI: 1.15; 2.70, $p = 0.016$), $OR_{adjusted} = 1.37$ (95% CI: 1.04; 1.89, $p = 0.024$) and $OR_{adjusted} = 2.40$ (95% CI: 1.15, 5.14, $p = 0.019$), respectively. Detailed results of uni- and multivariate regression analysis are presented in Table 3.

Discussion

Resting full-cycle ratio is one of several new, non-hyperemic physiological indices, assessed during a whole cardiac cycle, providing convenient, on-table proof of ischemia.

Several studies showed a significant level of discrepancy between RFR and FFR-based decisions on revascularization (12, 15, 19–21). These studies explored angiographic and clinical markers of this discrepancy. Noteworthy, none of them analyzed the coronary microcirculatory status of patients.

In the current study, we provide additional data validating RFR as a non-hyperemic index in a real-life cohort of patients with chronic coronary syndromes and present evidence for the higher prevalence of coronary microcirculatory dysfunction

TABLE 2 Angiographic and functional characteristics of analyzed vessels.

Characteristic	Overall ($N = 157$)	RFR FFR concordant ($N = 113$)	RFR FFR discordant ($N = 44$)	P-value[a]
Artery tested				0.8
LAD	88 (57%)	62 (56%)	26 (60%)	
LCx	39 (25%)	28 (25%)	11 (26%)	
RCA	27 (18%)	21 (19%)	6 (14%)	
Angiographic analysis				
QCA DS [%] (IQR)	45 (40, 50)	45 (40, 50)	44 (39, 48)	0.3
Reference diameter [mm] (IQR)	2.7 (2.4; 3.0)	2.7 (2.4; 3.0)	2.6 (2.4; 2.98)	>0.9
Lesion length [mm] (IQR)	17.1 (10.9; 24.7)	17.4 (10.7; 25.0)	16.8 (11.5; 22.5)	0.9
Epicardial artery stenosis assessment				
RFR, median (IQR)	0.89 (0.84, 0.94)	0.92 (0.83, 0.95)	0.88 (0.85, 0.89)	**<0.001**
FFR, median (IQR)	0.84 (0.78, 0.91)	0.84 (0.76, 0.91)	0.84 (0.82, 0.86)	0.6
Coronary microcirculation assessment				
CMD status, *n* (%)				**0.010**
CMD confirmed	74 (47%)	46 (41%)	28 (64%)	
No CMD	83 (53%)	67 (59%)	16 (36%)	
CFR (IQR)	2.10 (1.50, 2.70)	2.10 (1.50, 3.00)	1.95 (1.37, 2.30)	**0.031**
Tmn resting [s]	0.63 [0.45; 1.01]	0.63 [0.45; 1.00]	0.62 [0.44; 0.97]	0.565
IMR (IQR)	20 (13, 28)	19 (13, 26)	22 (16, 30)	0.082
RRR (IQR)	2.70 (1.80, 3.70)	2.90 (1.90, 3.90)	2.50 (1.60, 3.10)	**0.048**

[a]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. CMD, coronary microcirculatory dysfunction; CFR, coronary flow reserve; FFR, fractional flow reserve; RFR, resting full-cycle ratio; RRR, relative reserve ratio; QCA, qualitative coronary analysis.

in patients with discordant RFR and FFR-based decision on revascularization as compared to those with concordant RFR/FFR results.

RFR performance in intermediate coronary stenosis

Overall, our data confirm a particularly good correlation between RFR and FFR values. A similar, good correlation was described by Svanerud et al. with $R^2 = 0.557$ (9). Consistently, Ohashi et al. showed an even better RFR to FFR positive correlation ($r = 0.774$, $p < 0.001$) (14). The ICC value showed moderate concordance between RFR and FFR values, however, one needs to remember that RFR, as a non-hyperemic index, records systematically higher values.

An optimal cut-off value of 0.89 to detect significant lesions was originally reported by Svanerud (9), however other authors suggested different values ranging up to 0.90–0.92 (13, 14). In our analysis, the optimal cut-off for RFR was calculated on 0.88, which is similar and concurs with available data.

Regardless of the report, all authors agree there is a considerable level of discrepancy between RFR and FFR-based decisions on revascularization. In our cohort in over one-fourth of measurements, both indices suggested different classifications of lesions. Goto et al. reported a similar level of discrepant measurements, reported in over 19.6% of cases (15). A big-scale retrospective analysis performed by Lee et al. and including 1,024 vessels, suggested a lower number of discrepancies between RFR and FFR measurements, observed in 13.1% of cases.

Clinical and angiographic risk factors of discrepancy

Reasons for RFR/FFR discrepancies were analyzed by Goto, who suggested, that end-stage renal disease with hemodialysis and the presence of peripheral artery disease were risk factors for low RFR/high FFR phenotype of discrepancy (15). Muroya et al. compared both phenotypes of RFR/FFR discrepancy and reported anemia as a risk factor for high FFR/low RFR phenotype compared to low FFR/high RFR patients (12).

In our analysis, only the higher age of patients remained an independent clinical risk factor for discrepancy.

Currently published data suggest an association between the analyzed vessel and the level of discordance, especially when comparing LAD and non-LAD lesions (14, 15). In our

TABLE 3 Univariate and multivariate regression analysis of RFR/FFR discordance predictors.

Characteristic	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age (+ year)	1.06 (1.01, 1.10)	0.009	1.05 (1.01, 1.10)[#]	0.023
Male sex	0.52 (0.24, 1.14)	0.10	0.68 (0.30, 1.55)[##]	0.400
BMI (+1 kg/m^2)	0.95 (0.86, 1.03)	0.20	—	—
Diabetes	1.36 (0.67, 2.75)	0.40	—	—
Smoking		0.19	—	—
Never	Reference		—	—
Current	1.61 (0.60, 4.14)		—	—
In the past	2.19 (0.92, 5.20)		—	—
PAD	0.46 (0.02, 2.96)	0.53	—	—
LVEF (+5% increase)	0.88 (0.73, 1.06)	0.17	—	—
LDL (+1 mmol/l)	0.94 (0.68, 1.26)	0.69	—	—
ACEI or ARB use	0.60 (0.21, 1.87)	0.36	—	—
Beta-blockers use	2.28 (0.81, 8.20)	0.13	—	—
Vessel tested		0.75	—	—
LAD	Reference		—	—
LCx	0.94 (0.40, 2.13)		—	—
RCA	0.68(0.23, 1.80)		—	—
RFR (0.05 lower)	1.30 (1.01, 1.67)	0.049	1.22 (0.94, 1.61)[###]	0.130
FFR (0.05 lower)	0.93 (0.75,1.14)	0.44	NA	
CFR (1 unit decrease)	1.66 (1,13, 2.56)	0.007	1.69 (1.15, 2.70)[###]	0.016
IMR_calc_Yong (1 unit increase)	1.02 (0.99, 1.04)	0.17		
RRR (1 unit decrease)	1.35 (1.04, 1.85)	0.38	1.37 (1.04, 1.89)[###]	0.024
CMD confirmed	2.55 (1.25, 5.33)	0.010	2.40 (1.15, 5.14)[###]	0.019

—Not applicable; # adjusted for sex only; ## adjusted for age only; ### adjusted for sex and age; ACEI, angiotensin; ARB, angiotensin receptor blockers; BMI, body mass index; CFR-coronary flow reserve; DHP dihydropyridine, CMD, coronary microcirculatory dysfunction; FFR, fractional flow reserve; LAD, left anterior descending, LCx, left circumflex; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction; PAD, peripheral artery disease; RCA, right coronary artery; RFR, resting full-cycle ratio; RRR, relative reserve ratio.

analysis discordance was also numerically more often when LAD lesions were assessed, however, there was no statistically significant difference. Noteworthy, neither percent diameter stenosis, lesion length nor a reference diameter was associated with the discordance, which is consistent with data presented by Goto et al. (15). On the contrary, Wienemann et al. reported focal lesion as a potential risk factor for RFR/FFR discordance (21).

Coronary microcirculation dysfunction as a potential mechanism of discrepancy

In our study presence of CMD was an independent predictor of RFR/FFR discordance, driven rather by decreased CFR values than elevated coronary microcirculatory resistance.

This is a unique observation regarding RFR validation, as available data focus on clinical and angiographic factors influencing agreement between RFR and FFR assessment (13, 15).

Lower CFR measured by the thermodilution method, as observed in our study in discrepant RFR/FFR cases, can be attributed to both higher baseline flow velocity (meaning the presence of baseline hyperaemia) and decreased ability to accelerate coronary flow (i.e., microvascular dysfunction). Similar reasoning may be referred to low RRR values in discrepant cases. Both mechanisms may be a reason to develop a low RFR/high FFR phenotype of discrepancy.

Our analysis revealed no change in baseline transit time and the observed difference in CFR is probably due to decreased coronary microvascular reactivity. It is particularly important to emphasize a need for resting baseline conditions to perform any functional coronary physiology testing.

On the other hand, high resting index/low FFR discrepancy phenotype may be caused by hyperactivity of coronary microcirculation, a high amount of myocardium supplied by the artery, or a particularly low baseline coronary flow in a specific area (16). In our analysis, neither vessel bed nor increased microvascular reactivity was observed in the discordant RFR/FFR group. Neither of those proposed pathomechanisms

was sufficiently researched in terms of RFR/FFR concordance and are only hypotheses to be checked. Further research is needed, as our study was not powered to verify them.

Finally, one should note, that the potential influence of coronary microvascular dysfunction may be less pronounced when the highest-pressure gradient is calculated during the whole cardiac cycle, compared to diastolic-part only calculations, as in the case of iFR.

Study limitations

Our study has some limitations. Firstly, this is a single-center analysis. Nevertheless, it was performed in a high-volume referral center and included 157 vessels in over 100 patients, showing a real-life population undergoing functional assessment of intermediate coronary lesions.

Secondly, coronary microcirculation was assessed by an invasive thermodilution method. This approach was driven both by pragmatic reasons and by current chronic coronary syndrome guidelines.

Thirdly, the analyzed group consisted only of patients with chronic coronary syndrome. Therefore, obtained results cannot be used in an acute coronary syndrome setting, where coronary microcirculatory dysfunction may be even more prevalent than in a stable group of patients.

Finally, a sparse number of patients in the low FFR/high RFR cohort precluded an in-depth comparison of discrepant phenotypes, which can be improved by extending the study group.

Conclusion

In discrepant RFR/FFR vessels, CMD is more prevalent than in concordant RFR/FFR arteries. The observed discrepancy may be driven by lower CFR or RRR values rather than elevated IMR levels. Further research on a wider population, in a multi-center setting, is needed to confirm our observation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Jagiellonian University Bioethics Commetee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The research was funded by Jagiellonian University statutory grant (No. K/ZDS/006435).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1003067/full#supplementary-material

SUPPLEMENTARY FIGURE 1
ROC analysis for RFR to detect FFR ≤0.80 **(left panel)**, Bland-Altman plot for RFR-FFR difference **(right panel)**.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* (2019) 41:407–77. doi: 10.1093/eurheartj/ehz425

2. Ferrari M, Schnell B, Werner GS, Figulla HR. Safety of deferring angioplasty in patients with normal coronary flow velocity reserve. *J Am Coll Cardiol.* (1999) 33:82–7. doi: 10.1016/S0735-1097(98)00552-X

3. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F. van 't Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* (2009) 360:213–24. doi: 10.1056/NEJMoa0807611

4. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease. *J Am Coll Cardiol.* (2010) 56:177–84. doi: 10.1016/j.jacc.2010.04.012

5. van Nunen LX, Zimmermann FM, Tonino PAL, Barbato E, Baumbach A, Engstrøm T, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet.* (2015) 386:1853–60. doi: 10.1016/S0140-6736(15)00057-4

6. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* (2012) 367:991–1001. doi: 10.1056/NEJMoa1205361

7. Maini R, Moscona J, Katigbak P, Fernandez C, Sidhu G, Saleh Q, et al. Instantaneous wave-free ratio as an alternative to fractional flow reserve in assessment of moderate coronary stenoses: a meta-analysis of diagnostic accuracy studies. *Cardiovasc Rev Med.* (2018) 19:613–20. doi: 10.1016/j.carrev.2017.12.014

8. Lee JM, Rhee T-M, Choi KH, Park J, Hwang D, Kim J, et al. Clinical outcome of lesions with discordant results among different invasive physiologic indices — resting distal coronary to aortic pressure ratio, resting full-cycle ratio, diastolic pressure ratio, instantaneous wave-free ratio, and fractional flow res. *Circ J.* (2019) 83:2210–21. doi: 10.1253/circj.CJ-19-0230

9. Svanerud J, Ahn J-M, Jeremias A. van 't Veer M, Gore A, Maehara A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *Euro Interv.* (2018) 14:806–14. doi: 10.4244/EIJ-D-18-00342

10. Kogame N, Ono M, Kawashima H, Tomaniak M, Hara H, Leipsic J, et al. The impact of coronary physiology on contemporary clinical decision making. *JACC Cardiovasc Interv.* (2020) 13:1617–38. doi: 10.1016/J.JCIN.2020.04.040

11. Kumar G, Desai R, Gore A, Rahim H, Maehara A, Matsumura M, et al. Real world validation of the nonhyperemic index of coronary artery stenosis severity-resting full-cycle ratio-RE-VALIDATE. *Catheter Cardiovasc Interv.* (2020) 96:E53–8. doi: 10.1002/CCD.28523

12. Muroya T, Kawano H, Hata S, Shinboku H, Sonoda K, Kusumoto S, et al. Relationship between resting full-cycle ratio and fractional flow reserve in assessments of coronary stenosis severity. *Catheter Cardiovasc Interv.* (2020) 96:E432–8. doi: 10.1002/CCD.28835

13. Kato Y, Dohi T, Chikata Y, Fukase T, Takeuchi M, Takahashi N, et al. Predictors of discordance between fractional flow reserve and resting full-cycle ratio in patients with coronary artery disease: Evidence from clinical practice. *J Cardiol.* (2021) 77:313–9. doi: 10.1016/j.jjcc.2020.10.014

14. Ohashi H, Takashima H, Ando H, Suzuki A, Sakurai S, Nakano Y, et al. Clinical feasibility of resting full-cycle ratio as a unique non-hyperemic index of invasive functional lesion assessment. *Heart Vessels.* (2020) 35:1518–26. doi: 10.1007/S00380-020-01638-5

15. Goto R, Takashima H, Ohashi H, Ando H, Suzuki A, Sakurai S, et al. Independent predictors of discordance between the resting full-cycle ratio and fractional flow reserve. *Heart Vessels.* (2021) 36:790–8. doi: 10.1007/s00380-020-01763-1

16. Lee SH, Choi KH, Lee JM, Hwang D, Rhee TM, Park J, et al. Physiologic Characteristics and Clinical Outcomes of Patients With Discordance Between FFR and iFR. *JACC Cardiovasc Interv.* (2019) 12:2018–31. doi: 10.1016/J.JCIN.2019.06.044

17. Legutko J, Kleczyński P, Dziewierz A, Rzeszutko Ł, Dudek D. Adenosine intracoronary bolus dose escalation versus intravenous infusion to induce maximum coronary hyperemia for fractional flow reserve assessment. *Kardiol Pol.* (2019) 77:610–7. doi: 10.5603/*KP.a2019.0060

18. Legutko J, Dziewierz A, Rzeszutko L, Dudek D, Kleczynski P. Comparison of hyperemic efficacy between femoral and antecubital fossa vein adenosine infusion for fractional flow reserve assessment. *Adv Int Cardiol /Post Kardiol Int.* (2019) 15:52–8. doi: 10.5114/AIC.2019.83652

19. Hoshino M, Yonetsu T, Sugiyama T, Kanaji Y, Hamaya R, Kanno Y, et al. All resting physiological indices may not be equivalent: comparison between the diastolic pressure ratio and resting full-cycle ratio. *Circ J.* (2020) 84:1147–54. doi: 10.1253/circj.CJ-19-1110

20. Lee JM, Choi KH, Park JJ, Hwang D, Rhee TM, Kim J, et al. Physiological and clinical assessment of resting physiological indexes: resting full-cycle ratio, diastolic pressure ratio, and instantaneous wave-free ratio. *Circulation.* (2019) 139:889–900. doi: 10.1161/CIRCULATIONAHA.118.037021

21. Wienemann H, Meyer A, Mauri V, Baar T, Adam M, Baldus S, et al. Comparison of resting full-cycle ratio and fractional flow reserve in a german real-world cohort. *Front Cardiovasc Med.* (2021) 8:1973. doi: 10.3389/fcvm.2021.744181

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 06 October 2022
DOI 10.3389/fcvm.2022.953420

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
Hao Lai,
Fudan University, China
Giovanni Battista Luciani,
University of Verona, Italy

*CORRESPONDENCE
Jian Zhuang
zhuangjian5413@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 26 May 2022
ACCEPTED 07 September 2022
PUBLISHED 06 October 2022

CITATION
Yu J, Ren Q, Liu X, Chen T, Liufu R, Wen S, Chen J, Cen J and Zhuang J (2022) Anomalous left coronary artery from the pulmonary artery: Outcomes and management of mitral valve. *Front. Cardiovasc. Med.* 9:953420. doi: 10.3389/fcvm.2022.953420

Anomalous left coronary artery from the pulmonary artery: Outcomes and management of mitral valve

Juemin Yu[1,2†], Qiushi Ren[1,2†], Xiaobing Liu[1†], Tianyu Chen[1], Rong Liufu[1], Shusheng Wen[1], Jimei Chen[1], Jianzheng Cen[1] and Jian Zhuang[1*]

[1]Department of Cardiovascular Surgery, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China, [2]School of Medicine, South China University of Technology, Guangzhou, China

Objective: Use of concomitant mitral valve repair remains controversial in the anomalous left coronary artery from the pulmonary artery (ALCAPA) with mitral regurgitation (MR). This study aimed to evaluate postoperative mitral valve function and explore the indication for concomitant mitral valve repair.

Materials and methods: The medical records of 111 patients with ALCAPA and MR who underwent ALCAPA surgery between April 2006 and November 2020 were reviewed. The patients were categorized into three groups for comparison, namely, group I consisted of 38 patients with trivial or mild MR who underwent ALCAPA repair only; group II consisted of 37 patients with moderate or severe MR who similarly had only surgery of the ALCAPA performed; and group III consisted of 36 patients who had concomitant mitral valve repair for moderate or severe MR.

Result: Overall mortality was 7.2% (8 of 111). The mortality of group II (16.2%, 6 of 37) was higher than those of groups I (5.3%, 2 of 38) and III (0%, 0 of 36) (p = 0.027). All three patients who underwent mitral valve reintervention were in group II. At the last follow-up, none of the patients had more than moderate MR in group I. The percentage of patients with improved MR grade was 79.4% (27 of 34) in group III and 51.4% (19 of 37) in group II (p = 0.001). The multivariate logistic regression revealed that concomitant mitral valve repair (adjusted odds ratio = 4.492, 95% CI: 1.909–12.794; $p < 0.001$) was the major factor influencing MR grade improvement.

Conclusion: The long-term outcomes after ALCAPA repair were favorable. For mild MR, ALCAPA repair only can be performed. For moderate and severe MR, we suggest concomitant mitral valve repair.

KEYWORDS

congenital heart disease, anomalous left coronary artery from the pulmonary artery (ALCAPA), mitral regurgitation, concomitant mitral valve repair, outcome

Introduction

The anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital anomaly of coronary anatomy, with an incidence of approximately 1 in 300,000 births (1, 2). In the first few weeks of life due to the closure of the ductus arteriosus, pressure in the pulmonary arteries decreases, pulmonary vascular resistance decreases, and LCA perfusion decreases. These changes are associated with a range of adverse outcomes, such as left ventricular dysfunction, left ventricular dilatation, and mitral regurgitation (MR).

Currently, surgical treatment of ALCAPA has positive outcomes. However, whenever MR is present, the decision to intervene has always been controversial. Brown et al. (3) argued that concurrent mitral valve intervention is unnecessary for patients with ALCAPA. However, Biçer et al. (4) noted that despite the low rate of mitral valve reintervention, more than moderate preoperative MR required attention. Similarly, Weixler et al. (5) believed that patients with more than moderate MR had a higher risk of reintervention after surgery. This study aimed to evaluate the long-term outcome of mitral valve repair and explore the indications for mitral valve intervention by reviewing cases at our center.

Materials and methods

From April 2006 to November 2020, 128 patients underwent ALCAPA repair at Guangdong Provincial People's Hospital. After reviewing the medical records of all potential cases, 111 cases were obtained for this study. Two patients who underwent mitral valve repair due to MR prior to ALCAPA repair were excluded. In addition, two other patients without preoperative echocardiographic records were excluded. Seven patients had normal mitral valve function before the operation, two patients had undergone the Takeuchi procedure, three patients had undergone left coronary ligation with coronary bypass surgery, and one patient had undergone left coronary ligation without coronary bypass surgery. The following data were retrieved from the clinical records: demographic variables, preoperative and postoperative transthoracic echocardiographic findings, surgical findings, and further interventions required after the initial operation. This study was approved by the ethics committee of Guangdong Provincial People's Hospital on 12 September 2019 [Approval ID No.: GDREC2019338H(R2)]. The approval included a waiver of informed consent.

Based on the severity of MR and the surgical procedures performed, the patients were categorized into three groups for comparison. Group I consisted of 38 patients with trivial or mild MR who underwent ALCAPA repair only. Group II consisted of 37 patients with moderate or severe MR who similarly had only surgery of the ALCAPA performed. Group III consisted of 36 patients who had moderate or severe MR and underwent concomitant mitral valve repair in addition to ALCAPA repair.

Echocardiogram Z-scores of MR, left ventricular ejection fraction (LVEF), and left ventricular end-diastolic diameter (LVEDD) were obtained (6). The degree of MR was graded as none, trivial, mild, moderate, or severe (7). Echocardiography was performed before operation, 1 week before discharge, and 3 and 6 months after the operation to evaluate coronary and pulmonary artery stenosis, ventricular function, and MR. Subsequently, all patients underwent regular echocardiography examinations annually. The severity of MR at the last follow-up was used in the outcome analysis. Improvement in the degree of MR was defined as a reduction in the degree of MR at the most recent follow-up compared with the preoperative MR. Early postoperative death was defined as predischarge hospital death, and long-term death was defined as postdischarge death.

All patients underwent surgical correction by median sternotomy. The aorta was cross-clamped, and the right and left pulmonary arteries, superior vena cava, and inferior vena cava were snared. Cardioplegia was induced in the aortic root and main pulmonary artery. The right atrium was incised, the pulmonary artery was transected, the orifice of the LCA was determined, and the LCA position was observed. The LCA button was clipped from the pulmonary artery, and an appropriate size was cut in an appropriate aortic location for coronary reimplantation. For patients with moderate or severe MR, the decision to perform concomitant mitral valve intervention was made according to surgeons' preferences and MR degree. A total of 36 (32.4%) patients underwent concomitant mitral valve intervention. Patients in group III underwent different techniques for mitral valve repair (**Table 1**).

Continuous variables are expressed as mean and standard deviation for normally distributed data or median and range for non-normally distributed data. Data were assessed for normality of distribution using the Shapiro–Wilk test. Differences in normally distributed variables among the three groups were determined using a one-way analysis of variance with *post-hoc* comparisons using the Bonferroni test. Furthermore, analysis of non-normally distributed data was performed using the Kruskal–Wallis test with *post-hoc* comparisons using Dunn's multiple comparison test. The classification variables are represented by appropriate frequencies or percentages, and the intergroup differences of variables were analyzed using Fisher's exact test. Confounders were controlled using multivariate logistic regression. A p-value of < 0.05 was considered statistically significant. All reported p-values were

TABLE 1 MV pathology and operative techniques of MV repair in all 36 patients of group III.

MV pathology	No. of patients	MV repair technique
Ring dilatation	22	Annuloplasty with mattress
Prolapse of anterior leaflet, ring dilatation	5	Annuloplasty with mattress
Prolapse of anterior leaflet	1	Annuloplasty with mattress
Prolapse of A2 and A3	1	Mitral valvuloplasty with Gore-Tex suture as an artificial chordae tendineae
Ring dilatation, Ischemia of papillary muscle	1	Annuloplasty with mattress
Ischemia of papillary muscle	1	Annuloplasty with mattress
prolapse of mitral valve	1	Annuloplasty with mattress
Partial adhesion of subvalvular chordae tendon	2	Mechanical Valve Implantation
N/A	2	N/A

MV, mitral valve; N/A, not applicable.

bilateral. All data were analyzed using SPSS version 26.0 (Chicago, Illinois SPSS).

Results

Baseline characteristics

The preoperative characteristics of all patients are summarized in Table 2. The median age at surgery was 9 months (range: 1 month to 44 years), and the median follow-up period was 5.5 years (range: 0.5–15.03 years). Patients in group I were older and heavier than those in group II ($p = 0.007$, $p = 0.009$). Group I had the lowest LVEDD Z-score among the three groups ($p = 0.003$). Fewer patients in group I required preoperative inotropic support than in group III ($p = 0.008$). Age at the time of surgery, weight at the time of surgery, preoperative LVEF, and preoperative LVEDD were comparable between groups II and III.

Surgical outcome

The surgical outcomes of all patients are summarized in Table 3. No differences in cardiopulmonary bypass time and aortic occlusion time were found among the three groups ($p = 0.208$, $p = 0.130$). The postoperative mechanical ventilation time of group I was less than those of groups II and III ($p = 0.032$). However, no significant difference existed between group II and group III. No difference in ICU time existed among the three groups ($p = 0.096$). Postoperative hospital stay length was shorter in group I than those in other groups ($p = 0.009$). Six patients, including one patient in group I, one patient in group III, and four patients in group II, were assisted with extracorporeal membrane oxygenation (ECMO) after surgery ($p = 0.319$).

The median follow-up period was 5.49 years (range: 0.5–15.03 years). A total of six early deaths and two late deaths were recorded, with a total mortality rate of 7.2%. Two patients each in groups I and III were lost to follow-up during the follow-up period. One patient had mild MR preoperatively in group I and died postoperatively on the 7th day due to severe low cardiac output syndrome. One patient died after 158 days. This outcome was obtained by telephone follow-up; therefore, the specific cause of death was not ascertained. In addition, none of the patients had mitral valve reintervention. In group II, five patients died early, three patients died postoperatively within 5 days due to low cardiac output syndrome, and two patients died postoperatively on the 7th and 9th days due to sudden cardiac arrest secondary to ventricular fibrillation. Among the patients who died early, three patients had severe MR preoperatively, two patients had moderate MR preoperatively, and one patient had mild MR preoperatively. One patient died after 359 days during follow-up; this outcome was obtained by telephone follow-up. Three patients underwent mitral valve surgery due to severe MR at 2, 3, and 4 years after the initial surgery. From the intraoperative, postoperative, and follow-up echocardiography, none of the patients had coronary artery stenosis and pulmonary artery stenosis. Group III had no deaths and reinterventions. Group II had a higher mortality rate than group III (6/37 vs. 0/34; $p = 0.027$), and group II had a higher rate of long-term mitral valve reintervention than group III (3/31 vs. 0/34; $p = 0.031$).

Left ventricular function

In group I, the median LVEF was 62% (range = 16–78%) before surgery, 56% (range = 12–73%) before discharge, and 69% (range = 32–82%) at the last follow-up. LVEF at the most recent follow-up was better than those recorded preoperatively and before discharge ($p < 0.001$; $p < 0.001$). Compared with preoperative LVEF, postoperative LVEF decreased ($p = 0.003$). The preoperative median LVEDD Z-score, 1.69 (range = –3.97 to 7.32), was poorer than the postoperative median LVEDD Z-score, 0.24 (range = –3.46 to 7.56) ($p < 0.001$).

In group II, the median LVEF was 44.5% (range = 20–86%) before surgery, 56% (range = 15–80%) before discharge, and 69% (range = 32–82%) at the last follow-up. LVEF at the most recent follow-up was better than those recorded preoperatively and before discharge ($p < 0.001$; $p < 0.001$). Compared with the preoperative

TABLE 2 The preoperative characteristics of all patients.

Characteristic	All (n = 111)	Group I (n = 38)	Group II (n = 37)	Group III (n = 36)	p-value
Female gender, n	69 (62.2)	23 (60.5)	23 (62.2)	23 (63.9)	0.969
Age at surgery, years	0.75 (0.08, 49)	3.5 (0.08, 42)[a]	0.58 (0.17, 37)[b]	0.67 (0.08, 44)[a,b]	0.007
Weight at surgery, kg	7.5 (3.5, 67)	12.75 (3.5, 67)[a]	6.5 (3.8, 48.5)[b]	6.75 (4.2, 50.5)[a,b]	0.009
Positive inotropic drugs, n	54 (48.6)	11 (28.9)[a]	20 (54.1)[a,b]	23 (63.9)[b]	0.08
Mechanical ventilation, n	7 (6.3)	3 (7.9)	3 (8.1)	1 (2.8)	0.696
LVEDD Z-score	3.93 (–3.97, 7.89)	1.68 (–3.97, 7.32)[a]	4.67 (–1.09, 7.64)[b]	4.29 (0.25, 7.89)[b]	0.003
LVEF (%)	53 (16, 86)	62 (16, 78)	44 (20, 86)	58.5 (21, 78)	0.118
MR					< 0.001
Trivial	11 (9.9)	11 (28.9)	0[b]	0[b]	
Mild	27 (24.3)	27 (71.1)			
Moderate	45 (40.5)	0[a]	27 (73.0)[b]	18 (450)[c]	
Server	28 (25.2)	0[a]	10 (27)[b]	18 (50)[c]	

Values are presented as median (range), n (%). Each superscript letter indicates a subset of group categories whose column proportions do not differ significantly from each other at the 0.05 level. LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

TABLE 3 Surgical outcomes.

Variable	Group I	Group II	Group III	p-value
Aortic cross-clamping time (min)	78 (38, 250)	75 (25, 149)	76 (53, 135)	0.130
Cardiopulmonary bypass time (min)	144.5 (66, 517)	136 (58, 532)	159.5 (76.354)	0.208
Mechanical ventilation time (h)	16 (3, 528)[a]	57.25 (4, 476)[b]	50.25 (5, 696)[b]	0.032
Intensive care unit stay (d)	3 (1, 38)	4 (1, 47)	4 (1, 41)	0.096
Postoperative hospital stays (d)	8 (2, 45)[a]	14 (5, 55)[b]	15 (4, 65)[b]	0.009
Mortality	2 (5.6)[a,b]	6 (16.2)[a]	0[b]	0.027
Reoperation	0[a]	3 (9.4)[b]	0[a]	0.031

Values are presented as median (range), n (%). Each superscript letter indicates a subset of group categories whose column proportions do not differ significantly from each other at the 0.05 level.

LVEF, the median LVEF at discharge was not different (p = 0.068). The preoperative median LVEDD Z-score, 4.67 (range = –1.09 to 7.64), was poorer than the postoperative median LVEDD Z-score, 1.32 (range = –3.67 to 5.61) ($p < 0.001$).

In group III, the median LVEF was 58.5% (range = 21–78%) before surgery, 54.5% (range = 11–79%) before discharge, and 68% (range = 19–85%) at the last follow-up. LVEF at the recent follow-up was better than those recorded preoperatively and before discharge ($p < 0.001$; p = 0.004). Compared with preoperative LVEF, postoperative LVEF decreased (p = 0.042). The preoperative median LVEDD Z-score, 4.297 (range = 0.25–7.89), was poorer than the postoperative median LVEDD Z-score, 1.57 (range = –4.26 to 4.61) ($p < 0.001$).

No significant differences in LVEF were observed among the three groups preoperatively and at the last follow-up (p = 0.085; p = 0.774; p = 0.638). Patients in group I had lower LVEDD Z-scores than those in other two groups (p = 0.003), and no significant differences in LVEDD Z-scores were observed among the three groups after surgery.

Mitral valve function

Preoperatively, the MR grade was trivial in 11 (28.9%) patients and mild in 27 (71.1%) patients in group I. At the last follow-up, none of the patients in group I had more than moderate MR and underwent reintervention for MR. Figures 1, 2 illustrate the changes in MR among the preoperative, postoperative, and last follow-up periods for groups II and III. Preoperatively, 27 and 18 patients had moderate MR in groups II and III, respectively. A total of 10 and 18 patients had severe MR in groups II and III, respectively. At the last follow-up, three patients had trivial MR, 13 patients had mild MR, nine patients had moderate MR, and three patients had severe MR in group II. Three patients had no MR, three patients had mild MR, 14 patients had moderate MR, and three patients had severe MR in group III. The percentage of patients with improved MR grades was 79.4% (27 of 34 patients) in group III and 51.4% (19 of 37 patients) in group II (p = 0.001). Multivariate logistic regression findings for independent risk factors for the MR grade improvement are provided in Table 4. From the multivariate logistic regression analysis, concomitant

10.3389/fcvm.2022.953420

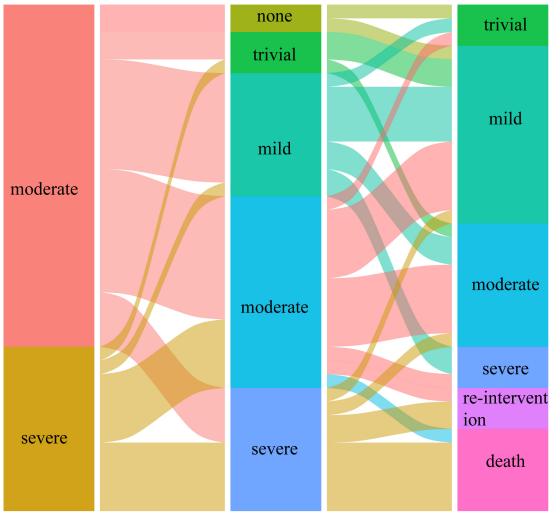


FIGURE 1
The changes in mitral regurgitation among preoperative, postoperative, and last follow-up periods in group II.

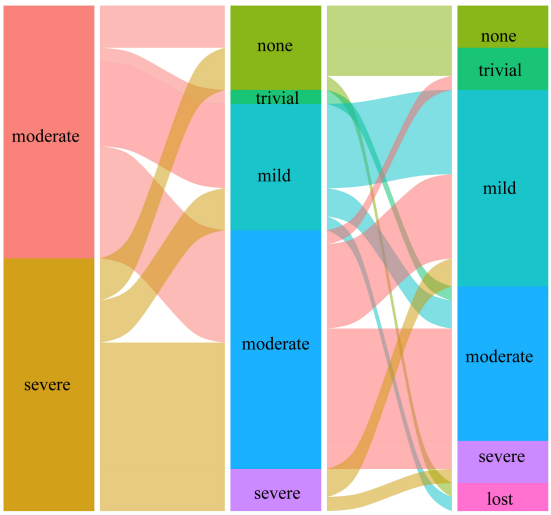


FIGURE 2
The changes in mitral regurgitation among preoperative, postoperative, and last follow-up periods in group III.

mitral valve repair (adjusted odds ratio = 4.492, 95% CI: 1.909–12.794; $p < 0.001$) was the major factor influencing MR grade improvement.

Discussion

The main finding of this study is that for patients with ALCAPA and moderate or severe MR, concomitant mitral valve repair in ALCAPA repair is feasible. Our data suggest that concomitant mitral valve repair should be performed in patients with ALCAPA and moderate and severe MR. The reasons are as follows:

TABLE 4 Multivariate analysis for the degree of mitral regurgitation improved after the operation.

Variable	Odds ratio	95% CI	*p*-value
Age	0.943	0.844–1.054	0.300
Weight	1.045	0.974–1.121	0.217
Concomitant MV repair	5.889	2.132–16.263	0.001
LVEF	1.008	0.973–1.044	0.656
LVEDD *Z*-score	1.131	0.853–1.499	0.394
MR*			
Mild	1.042	0.227–4.779	0.958
Moderate	2.049	0.421–9.986	0.374
Server	3.013	0.523–17.366	0.217

MV, mitral valve; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation. *Odds ratios for patients with preoperative MR of other grades compared with preoperative MR of trivial.

1. For mild MR, even without mitral valve intervention, no MR function deterioration or MR reintervention was needed.
2. Mitral function was better in patients who underwent concomitant mitral valve repair than in those who underwent ALCAPA repair only (79.4% vs. 51.4%; $p = 0.008$).
3. Patients who underwent concomitant mitral valve repair had higher survival rate and reintervention exclusion rate (83.8% vs. 100%, $p = 0.027$; 90.6% vs. 100%, $p = 0.031$; respectively).

Our data suggest that concomitant mitral valve repair for ALCAPA with moderate or severe MR had no poor early outcomes than ALCAPA repair only. However, some clinicians (3, 8) believe that concomitant mitral valve repair will prolong the aortic occlusion time, increasing postoperative mortality and postoperative complications. In our cohort, the aortic occlusion time and cardiopulmonary bypass time of patients who underwent concomitant mitral valve intervention were similar to those of other patients who underwent ALCAPA repair only. No significant differences in postoperative mechanical ventilation time and postoperative ICU time existed between groups II and III. In addition, no mortality was recorded in group III. According to Triglia et al. (9), Alexi et al. (10), and Isomatsu et al. (11), concomitant mitral valve repair does not result in adverse consequences after the operation. Other studies reported that mitral valve repair can improve the early postoperative cardiac output and can be conducive to early recovery of cardiac function (12, 13). Concomitant mitral valve

repair for moderate or severe MR does not result in poor outcomes in the early postoperative period and has similar perioperative recovery.

Our data suggest that patients with ALCAPA and moderate or severe MR who did not undergo concomitant mitral valve intervention had higher mortality and reintervention rates than those who underwent concomitant mitral valve intervention. In our study, the total mortality was 7.2%, of which 5.4% occurred prior to discharge from the hospital. This finding is similar to findings from studies reported in recent years (14–17). The long-term reintervention rate was 3%. One case of moderate MR and two cases of severe MR were recorded among patients who underwent reintervention. Before reintervention, these patients had severe MR, suggesting that some patients with moderate MR may progress even after ALCAPA repair only. In our cohort, postoperative death and mitral valve reintervention were both present in group II, and no cases of death and reintervention were reported in group III. Weixler et al. (5) reported an early mortality rate of 6.9% and a mitral valve reintervention rate of 10.25% in patients who underwent ALCAPA repair only. Furthermore, no death and mitral valve reintervention were reported in the surgical group during the same period. Zhang et al. (18) indicated that concurrent mitral valve repair could result in better postoperative recovery and higher survival rate.

The MR improvement in concomitant mitral valve repair was significantly higher than in ALCAPA repair only. The number of patients with improved MR in group III was more than that in group II. Moreover, more patients with severe preoperative MR in group III underwent concomitant mitral valve repair. These data suggest an association between concomitant mitral valve repair and mitral valve improvement. Furthermore, our multivariate analysis of MR grade improvement revealed that concomitant mitral valve repair was a major factor influencing the long-term improvement of MR degree, which further confirmed our inference. We speculate that for moderate and severe MR, the extent of damage to the mitral valve is high that the mere correction of anomalous coronary arteries and recovery of the double coronary flow are insufficient for the functional recovery of the mitral valve, requiring a concomitant mitral valve repair. In addition, Weixler et al. (5) reported similar improvements in mitral valve function, with 89% in the concomitant mitral valve repair group and 41% in the no mitral valve repair group.

In this study, no significant differences in the recovery of ventricular function existed among the three groups. After ALCAPA repair, the left ventricular function of most patients returned to normal regardless of concomitant mitral valve intervention, which is similar to that reported in most literature (19–21). In addition, we found that the left ventricular diameter of most patients improved significantly before discharge, and the LVEF did not improve immediately. This may mean that ventricular morphology recovery is faster than function recovery after ALCAPA repair. However, this study was retrospective, and this conclusion needs verification by further studies. Cochrane et al. (22) and Imamura et al. (23) reported similar results on left ventricular recovery. In group III, the early postoperative LVEF was lower than the preoperative LVEF. We considered this because MR was reduced, and LV afterload, ejection resistance, and LV myocardial contractility were restored after concomitant mitral valve repair, resulting in a corresponding decrease in ejection fraction.

This study had some limitations which should be noted. The critical limitation was that this study was retrospective and participant selection was non-randomized. In this study, we could not preclude results being influenced by differences between the surgical period and surgeon, which may limit meaningful comparison of outcomes between concomitant mitral valve repair and no repair. In addition, some patients failed to complete the examinations on time when they were followed up. Therefore, some data were missing.

Conclusion

Surgical treatment of ALCAPA has good efficacy, with acceptable mortality and an expected reintervention rate. Postoperative cardiac function mostly recovers, but ventricular diameter recovers faster than ejection fraction. For the management of the mitral valve, we recommend concomitant mitral valve repair for moderate or severe MR and ALCAPA repair only for mild and trivial MR.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangdong Provincial People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JY, XL, and QR wrote the manuscript and performed the statistical analysis. TC and RL performed the data inspection and validation. JMC and SW provided funding support and supervision. JZC and JZ revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Science and Technology Planning Project of Guangdong Province (2019B020230003 and 2018B090944002), the Guangdong Peak Project (DFJH201802), and the National Key Research and Development Program (2018YFC100168).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Keith JD. The anomalous origin of the left coronary artery from the pulmonary artery. *Br Heart J.* (1959) 21:149–61. doi: 10.1136/hrt.21.2.149

2. Askenazi J, Nadas AS. Anomalous left coronary artery originating from the pulmonary artery. Report on 15 cases. *Circulation.* (1975) 51:976–87. doi: 10.1161/01.cir.51.6.976

3. Brown JW, Ruzmetov M, Parent JJ, Rodefeld MD, Turrentine MW. Does the degree of preoperative mitral regurgitation predict survival or the need for mitral valve repair or replacement in patients with anomalous origin of the left coronary artery from the pulmonary artery? *J Thorac Cardiovasc Surg.* (2008) 136:743–8. doi: 10.1016/j.jtcvs.2007.12.065

4. Biçer M, Korun O, Yurdakök O, Çiçek M, Dedemoğlu M, Özdemir F, et al. Anomalous left coronary artery from the pulmonary artery repair outcomes: preoperative mitral regurgitation persists in the follow-up. *J Card Surg.* (2021) 36:530–5. doi: 10.1111/jocs.15247

5. Weixler VHM, Zurakowski D, Baird CW, Guariento A, Piekarski B, Del Nido PJ, et al. Do patients with anomalous origin of the left coronary artery benefit from an early repair of the mitral valve? *Eur J Cardiothorac Surg.* (2020) 57:72–7. doi: 10.1093/ejcts/ezz158

6. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr.* (2008) 21:922–34. doi: 10.1016/j.echo.2008.02.006

7. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European association of echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr.* (2010) 11:307–32. doi: 10.1093/ejechocard/jeq031

8. Radman M, Mastropietro CW, Costello JM, Amula V, Flores S, Caudill E, et al. Intermediate outcomes after repair of anomalous left coronary artery from the pulmonary artery. *Ann Thorac Surg.* (2020) 112:1307–15. doi: 10.1016/j.athoracsur.2020.06.130

9. Triglia LT, Guariento A, Zanotto L, Zanotto L, Cattapan C, Hu R, et al. Anomalous left coronary artery from pulmonary artery repair: outcomes from the European congenital heart surgeons association database. *J Card Surg.* (2021) 36:1910–6. doi: 10.1111/jocs.15448

10. Alexi-Meskishvili V, Nasseri BA, Nordmeyer S, Schmitt B, Weng YG, Böttcher W, et al. Repair of anomalous origin of the left coronary artery from the pulmonary artery in infants and children. *J Thorac Cardiovasc Surg.* (2011) 142:868–74. doi: 10.1016/j.jtcvs.2011.04.006

11. Isomatsu Y, Imai Y, Shin'oka T, Aoki M, Iwata Y. Surgical intervention for anomalous origin of the left coronary artery from the pulmonary artery: the Tokyo experience. *J Thorac Cardiovasc Surg.* (2001) 121:792–7. doi: 10.1067/mtc.2001.112834

12. Mongé MC, Eltayeb O, Costello JM, Sarwark AE, Carr MR, Backer CL. Aortic implantation of anomalous origin of the left coronary artery from the pulmonary artery: long-term outcomes. *Ann Thorac Surg.* (2015) 100:154–60;discussion 60–1. doi: 10.1016/j.athoracsur.2015.02.096

13. Zhang C, Luo Q, Li Y, Wu X, Hao Z, Li S, et al. Predictors of short-term outcomes following repair of anomalous origin of the left coronary artery from the pulmonary artery in Chinese children: a case-control study. *J Cardiothorac Vasc Anesth.* (2018) 32:2644–51. doi: 10.1053/j.jvca.2018.04.008

14. Azakie A, Russell JL, McCrindle BW, Van Arsdell GS, Benson LN, Coles JG, et al. Anatomic repair of anomalous left coronary artery from the pulmonary artery by aortic reimplantation: early survival, patterns of ventricular recovery and late outcome. *Ann Thorac Surg.* (2003) 75:1535–41. doi: 10.1016/s0003-4975(02)04822-1

15. Kudumula V, Mehta C, Stumper O, Desai T, Chikermane A, Miller P, et al. Twenty-year outcome of anomalous origin of left coronary artery from pulmonary artery: management of mitral regurgitation. *Ann Thorac Surg.* (2014) 97:938–44. doi: 10.1016/j.athoracsur.2013.11.042

16. Lange R, Cleuziou J, Krane M, Ewert P, Pabst von Ohain J, Beran E, et al. Long-term outcome after anomalous left coronary artery from the pulmonary artery repair: a 40-year single-centre experience. *Eur J Cardiothorac Surg.* (2018) 53:732–9. doi: 10.1093/ejcts/ezx407

17. Naimo PS, Fricke TA, d'Udekem Y, Cochrane AD, Bullock A, Robertson T, et al. Surgical intervention for anomalous origin of left coronary artery from the pulmonary artery in children: a long-term follow-up. *Ann Thorac Surg.* (2016) 101:1842–8. doi: 10.1016/j.athoracsur.2015.11.020

18. Zhang W, Hu R, Zhu Y, Zhang W, Yu X, Sun Y, et al. Surgical outcomes for anomalous left coronary artery from the pulmonary artery: influence of late presentation. *J Thorac Cardiovasc Surg.* (2020) 159:1945–52.e1. doi: 10.1016/j.jtcvs.2019.09.179

19. Cavalcanti LRP, Sa M, Escorel Neto AC, Salerno PR, Lima RC. Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) in adults: collateral circulation does not preclude direct reimplantation. *J Card Surg.* (2021) 36:731–4. doi: 10.1111/jocs.15238

20. Kanoh M, Inai K, Shinohara T, Tomimatsu H, Nakanishi T. Outcomes from anomalous origin of the left coronary artery from the pulmonary artery repair: long-term complications in relation to residual myocardial abnormalities. *J Cardiol.* (2017) 70:498–503. doi: 10.1016/j.jjcc.2017.03.008

21. Qiu J, Li S, Yan J, Wang Q, Song Y, Sun H, et al. Repair of anomalous coronary artery from the pulmonary artery: a-signal center 20-year experience. *Int J Cardiol.* (2016) 223:625–9. doi: 10.1016/j.ijcard.2016.08.221

22. Cochrane AD, Coleman DM, Davis AM, Brizard CP, Wolfe R, Karl TR. Excellent long-term functional outcome after an operation for anomalous left coronary artery from the pulmonary artery. *J Thorac Cardiovasc Surg.* (1999) 117:332–42. doi: 10.1016/s0022-5223(99)70431-9

23. Imamura M, Dossey AM, Jaquiss RD. Reoperation and mechanical circulatory support after repair of anomalous origin of the left coronary artery from the pulmonary artery: a twenty-year experience. *Ann Thorac Surg.* (2011) 92:167–72;discussion 172–3. doi: 10.1016/j.athoracsur.2011.02.074

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 11 October 2022
DOI 10.3389/fcvm.2022.910313

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
Plinio Cirillo,
University of Naples Federico II, Italy
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

*CORRESPONDENCE
Shao-Liang Chen
chmengx@126.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 01 April 2022
ACCEPTED 15 August 2022
PUBLISHED 11 October 2022

CITATION
Sheiban I, Ge Z, Kan J, Zhang J-J, Santoso T, Munawar M, Ye F, Tian N and Chen S-L (2022) Provisional stenting with side branch rescue stenting is associated with increased 3-year target lesion failure in patients with acute coronary syndrome and coronary bifurcation lesions. *Front. Cardiovasc. Med.* 9:910313. doi: 10.3389/fcvm.2022.910313

Provisional stenting with side branch rescue stenting is associated with increased 3-year target lesion failure in patients with acute coronary syndrome and coronary bifurcation lesions

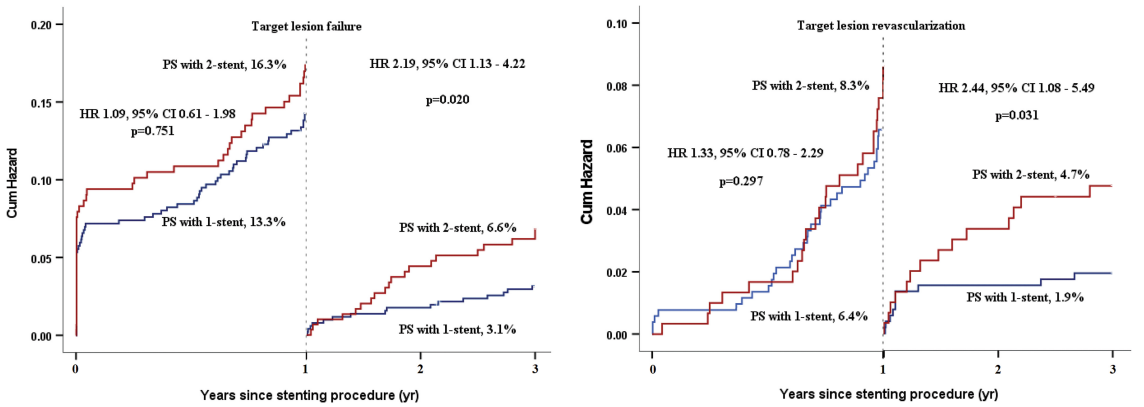
Imad Sheiban[1†], Zhen Ge[2†], Jing Kan[2†], Jun-Jie Zhang[2], Teguh Santoso[3], Muhammad Munawar[4], Fei Ye[2], Nailiang Tian[2] and Shao-Liang Chen[2*] on behalf of DKCRUSH Investigators

[1]Division of Cardiology, Pederzoli Hospital-Peschiera del Garda, Verona, Italy, [2]Division of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China, [3]Division of Cardiology, Medistra Hospital, University of Indonesia Medical School, Jakarta, Indonesia, [4]Division of Cardiology, Binawaluya Cardiac Center, Jakarta, Indonesia

Background: Provisional stenting (PS) is the main treatment for a majority of coronary bifurcation lesion and includes PS with 1-stent and PS with 2-stent. However, the treatment difference between PS with 1-stent and with 2-stent remains unclear in patients with the acute coronary syndrome (ACS) and coronary bifurcation lesions.

Materials and methods: Overall, 820 ACS patients with Medina 1,1,1 or 0,1,1 coronary bifurcation lesion who had completed 3-year follow-up were included and assigned to the PS with 1-stent (n = 519) or the PS with 2-stent (n = 301) according to the use of final stenting technique. The primary endpoint was the target lesion failure (TLF) at 3 years since stenting procedures.

Results: At 3-year follow-up, TLF occurred in 85 (16.4%) patients in the PS with 1-stent group and 69 (22.9%) in the PS with 2-stent group (hazard ratio [HR] 1.52, 95% confidence interval [CI] 1.06–2.17, p = 0.021), mainly driven by a higher rate of target lesion revascularization (TLR) in the PS with 2-stent group (13.0% vs. 8.3%, HR 1.65, 95% CI 1.04–2.61, p = 0.033). Complex bifurcations, side branch (SB) pretreatment, intravascular imaging guidance, and hyperlipidemia were the four predictors for 3-year TLF. SB pretreatment was associated with increased 3-year TLR, leading to an extremely higher 3-year TLF.



GRAPHICAL ABSTRACT

Landmark analysis of target lesion failure and target lesion revascularization.

Conclusion: Provisional with 2-stent for patients with ACS is associated with a higher rate of 3-year TLF, mainly due to increased requirement of revascularization. SB pretreatment should be avoided for simple bifurcation lesion.

KEYWORDS

acute coronary syndrome (ACS), coronary artery bifurcation lesions, provisional stenting, drug-eluting stent, target lesion failure

Introduction

Coronary artery bifurcation lesions involve three vessel segments (proximal main vessel [MV], distal MV, and side branch [SB]), leading to technical challenging of bifurcation stenting and suboptimal clinical outcomes (1, 2). While upfront two-stent approach (like DK crush stenting) has been demonstrated to be associated with less rate of target lesion failure (TLF) for the treatment of patients with bifurcation lesions localizing at distal left main (LM) or having higher complexity (3, 4), provisional stenting (PS) is still accepted to be a major technique for simple bifurcation lesions (2, 5–7). PS requires a jailed wire or balloon in the SB, which could rescue an SB at risk of occlusion after stenting MV. Thus, PS could be shifted to PS with 1-stent or PS with 2-stent, with a rate of crossover to 2-stent varying from 2 to 40% (2, 4–9), depending on the performance of SB pretreatment and final kissing balloon inflation (KBI), lesions' complexity, flow-limiting dissection, severely compromised ostial SB induced by plaque or carina shifting, and criteria for treating SB in clinical trials. As a result, PS with SB rescue stenting is unavoidable for complex bifurcations (4, 9). However, there is a paucity of data showing the difference in clinical outcomes between PS with 1-stent and PS with 2-stent among patients with acute coronary syndrome (ACS) and bifurcation lesions. Accordingly, this study includes all ACS patients with bifurcations who underwent the PS approach and had completed 3-year clinical follow-up from previous four trials (4, 9–11) with a view to identify the rate of crossover to 2-stent, the difference in 3-year TLF between PS with 1-stent and with 2-stent, and the independent factors of 3-year TLF.

Abbreviations: PS, provisional stenting; ACS, acute coronary syndrome; TLF, target lesion failure; TVF, target vessel failure; TLR, target lesion revascularization; SB, side branch; MV, main vessel; DK crush, double kissing crush; KBI, kissing balloon inflation; TIMI, thrombolysis in myocardial infarction; POT, proximal optimization technique; QCA, quantitative coronary analysis; TVMI, target vessel myocardial infarction; ST, stent thrombus; DAPT, dual antiplatelet therapy; PMI, periprocedural myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Materials and methods

Study design

We included data of the following clinical trials with only Medina 1,1,1 and 0,1,1 bifurcation lesions in patients with ACS: DKCRUSH II (10), DKCRUSH V (9), DKCRUSH VI (11), and DEFINITION II (4; **Figure 1**). All patients were prospectively followed up till January 1, 2022. The

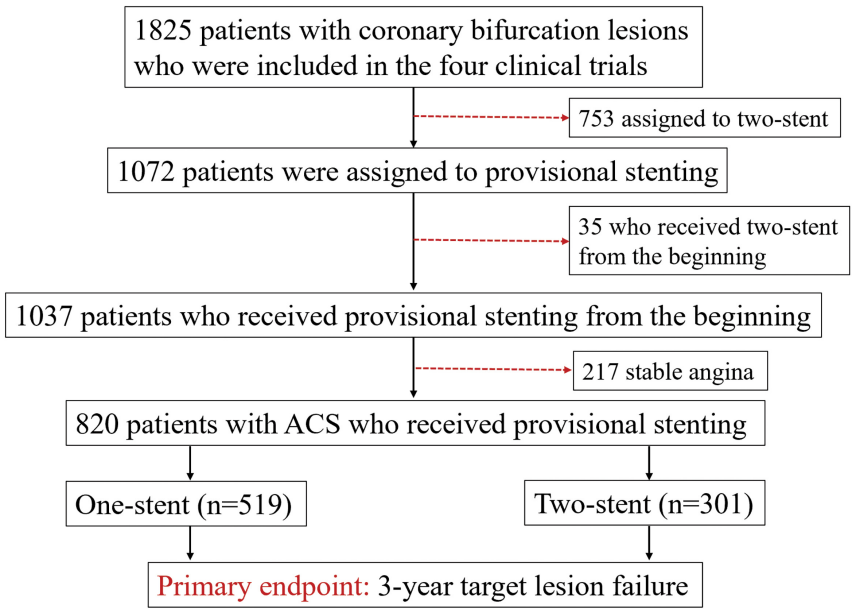


FIGURE 1
Study flowchart. Description: 820 patients with acute coronary syndrome (ACS) were assigned to the provisional stenting (PS) with 1-stent and the PS with 2-stent groups.

study protocol was approved by the ethics committee at each participating center and complied with the Declaration of Helsinki. All patients provided written informed consent for participation in the respective trials. All authors had free access to the database.

Patient population

Overall, 1,825 patients with coronary bifurcation lesions from the four clinical trials were screened. We excluded 1,005 patients because of upfront 2-stent (n = 753) at randomization, SB pretreatment leading to the urgent requirement of stenting SB before stenting the MV (n = 35), and stable angina patients (n = 217). Finally, 820 patients with ACS who underwent PS were included (**Figure 1**), with 519 patients assigned to the PS with 1-stent group and 301 patients assigned to the PS with 2-stent group.

Provisional stenting procedures

The PS approach has been previously described (4, 9–11). In brief, the MV and SB are wired. Predilation was left to the operator's discretion, although predilating the SB is discouraged. A new-generation drug-eluting stent was used in the bifurcation lesions. A stent with a stent/artery ratio of 1.1:1 was implanted in the MV, and then the proximal optimization technique (POT) using non-compliant balloons (balloon/stent ratio of 1:1, > 18 atm) was performed. Ballooning or stenting the SB after MV stenting is performed only if the SB ostium is severely compromised or has a Type B/C dissection or thrombolysis in myocardial infarction (TIMI) flow < 3. If SB dilatation or stenting is required, the SB is rewired through a distal cell of the MV stent, followed by re-POT, KBI, and final POT using non-compliant balloons with a suggested inflation pressure of >18 atm.

Medications and follow-up

All patients were treated with aspirin preprocedure and 300 mg loading dose of clopidogrel or 180 mg ticagrelor if they were not under chronic dual antiplatelet therapy (DAPT). After the intervention, they received 100 mg/day aspirin indefinitely and 75 mg/day clopidogrel or 180 mg (90 mg, bid) ticagrelor for at least 12 months. A clinical follow-up was performed at 1 and 12 months and annually subsequently through 3 years.

Follow-up coronary angiography was scheduled at 13 months (after ascertainment of the primary clinical endpoint) unless performed earlier for clinical indications. Quantitative coronary analysis (QCA) was analyzed at a central core laboratory using the Cardiovascular Angiographic Analysis System (CAAS) II software (Pie Medical Imaging, The Netherlands), as previously described (4). Restenosis was defined as a QCA DS > 50% at follow-up.

Endpoints and definitions

The primary endpoint was TLF at 3 years, defined as the composite of cardiac death, target vessel MI (TVMI), or clinically driven TLR. Death from cardiac causes was defined as any death without a clear non-cardiac cause. Protocol-defined periprocedural MI (within 48 h) was defined as a creatine kinase-MB (CK-MB) > 10 × upper reference limit (URL) of the assay or > 5 × URL plus either (1) new pathological Q waves in ≥ 2 contiguous leads or new left bundle branch block (LBBB); (2) angiographically documented graft or coronary artery occlusion or new severe stenosis with thrombosis; (3) imaging evidence of new loss of viable myocardium; or (4) new regional wall motion abnormality. Spontaneous MI (after 48 h) was defined as a clinical syndrome consistent with MI with a CK-MB or troponin > 1 × URL and new ST-segment elevation or depression or other findings as above. All MIs were considered TVMI unless there was clear evidence that they were attributable to a non-target vessel (4, 12). Clinically driven TLR was defined as angina or ischemia referable to the target lesion requiring repeat PCI or coronary artery bypass graft. Secondary endpoints included cardiac death, TVMI, clinically driven TLR, and stent thrombus (ST). Definite or probable ST according to the Academic Research Consortium (13) was the major safety endpoint. All events were adjudicated by a central committee using original source documents blinded to the treatment.

Statistical analysis

Baseline characteristics are reported as counts and percentages or mean ± standard deviation (SD). The chi-squared or Fisher's exact test was used to compare categorical variables. Student's *t*-test or Wilcoxon rank-sum scores for non-normally distributed data were used to compare continuous variables. Time-to-first event curves were generated using Kaplan–Meier analysis and compared using the log-rank test. Cox regression was also used to compare the differences in both primary and secondary endpoints, with outputs of hazard ratio (HR), 95% confidence interval (CI), and *p*-value. Multivariate analysis was performed to identify the independent factors of 3-year TLF. All statistical tests were two-sided, and a *p*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (SPSS Institute Inc., Chicago, Illinois, USA).

Results

Baseline clinical characteristics

Baseline clinical characteristics were well comparable between the groups (**Table 1**), except for unstable angina (85.0% in the 2-stent group vs. 75.3% in the 1-stent group, $p = 0.001$) and ST-segment elevation MI (4.7% in the 2-stent group vs. 12.1% in the 1-stent group, $p < 0.001$). Diabetes was present in 27.6% of patients.

Lesion characteristics and procedures

Multivessel disease was present in 52.2% of patients, and the mean SYNTAX score was 26 (**Table 2**). Notably, 37.4% of the lesions were localized in the distal LM. Complex bifurcation lesions were seen in 59.1% of patients in the 2-stent group, compared to 43.0% in the 1-stent group ($p < 0.001$), with an extremely higher rate of SB lesion length ≥ 10 mm in the 2-stent group (42.9% vs. 32.2%, $p = 0.002$), as confirmed by the QCA analysis (**Table 3**).

The trans-radial approach was predominantly used (82%, **Table 2**). In the 2-stent group, SB pretreatment was used in 56.8%, significantly different from 32.2% in the 1-stent group ($p < 0.001$), resulting in more frequent use of KBI in the 2-stent group (95.3 vs. 41.4%, $p < 0.001$). Final POT was only used in 89.4% of patients in the 2-stent group, lower than 94.8% in the 1-stent group ($p < 0.001$). Complete revascularization was achieved in 68.4% of patients in the 2-stent group, compared to 62.0% in the 1-stent group ($p < 0.001$). IVUS guidance was only used in <30.0% of patients, without a significant difference between the groups. The two-stent strategy was associated with longer procedural time and more contrast volume compared with the PS with 1-stent approach.

Quantitative coronary analysis

Except for longer SB lesion length, the 2-stent group also had a more severe SB diameter stenosis (54.1 vs. 44.7%, $p < 0.001$) at baseline. At 3 years since procedures, a total of 427 (52.1%) patients underwent repeat angiography, with 246 (30.0%) at 13 months and 181 (22.1%) after 13 months. The in-stent restenosis (ISR) rate in the MV was non-significantly different between the 2 groups (**Table 3**). In the 2-stent group, the rate of ISR at the ostial SB was 13.3%, compared to 29.4% in the 1-stent group ($p < 0.001$).

Clinical outcomes

At 3 years, DAPT was prescribed to 203 (39.1%) patients in the PS with 1-stent and 198 (65.8%) in the PS with 2-stent ($p < 0.001$). Ticagrelor (90 mg; twice a day) was administered in 58.6% of patients in the PS with 2-stent group and 38.2% in the PS with 1-stent group ($p < 0.001$).

TABLE 1 Baseline characteristics.

	PS with 1-stent (n = 519)	PS with 2-stent (n = 301)	P-value
Age, year	64.6 ± 9.8	64.4 ± 10.1	0.721
Male, n (%)	399 (76.9)	228 (75.7)	0.733
Hypertension, n (%)	343 (66.1)	203 (67.4)	0.702
Systolic blood pressure, mmHg	133 ± 16	134 ± 18	0.384
Diastolic blood pressure, mmHg	79 ± 10	79 ± 10	1.000
Heart rate, beats per minute	73 ± 12	73 ± 10	0.706
Hyperlipidemia, n (%)	214 (41.2)	111 (36.9)	0.236
Diabetes, n (%)	147 (28.3)	81 (26.9)	0.687
Current smoker, n (%)	101 (19.6)	63 (21.1)	0.601
Renal dysfunction, n (%)	15 (2.9)	10 (3.3)	0.834
Previous PCI, n (%)	92 (17.7)	55 (18.3)	0.851
Previous CABG, n (%)	3 (0.6)	1 (0.3)	1.000
Previous MI, n (%)	69 (13.3)	50 (16.6)	0.217
Stroke, n (%)	45 (8.7)	22 (7.3)	0.597
Peripheral arterial disease, n (%)	21 (4.0)	16 (5.3)	0.390
Heart failure, n (%)	58 (11.2)	37 (12.3)	0.651
Atrial fibrillation, n (%)	10 (1.9)	8 (2.7)	0.623
eGFR < 60 ml/min/1.73m^2	77 (14.8)	37 (12.3)	0.310
Presentation, n (%)			
Unstable angina	388 (75.3)	256 (85.0)	0.001
STEMI > 24 h	63 (12.1)	14 (4.7)	<0.001
NSTEMI > 24 h	68 (13.1)	31 (10.3)	0.235

PS, provisional stenting; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; STEMI, ST-segment elevation myocardial infarction; NSTEMI, ST-segment elevation myocardial infarction.

A 1-year clinical follow-up was completed in all patients. The primary endpoint of TLF at 1 year occurred in 69 (13.3%) patients in the PS with 1-stent group and 49 (16.3%) patients in the PS with 2-stent group (HR 1.09, 95% CI 0.61–1.98, p = 0.751) (Table 4). The rates of TVMI, cardiac death, TLR, and ST at 1 year were also non-significantly different between the two groups.

At 3 years, 12 (1.6%) patients were lost to the follow-up, with 7 (2.3%) in the PS with 2-stent group and 5 (0.9%) in the PS with 1-stent group. TLF at 3 years occurred in 85 (16.4%) patients in the PS with 1-stent group and 69 (22.9%) in the PS with 2-stent group (HR 1.52, 95% CI 1.06–2.17, p = 0.021, Table 4 and Figure 2A), mainly driven by increased TLR (8.3% vs. 13.0%, HR 1.65, 95% CI 1.04–2.61, p = 0.033, Table 4 and Figure 2B), without statistical differences in cardiac death, TVMI, and ST. By landmark analysis (Graphic Abstract), the rates of TLF and TLR at 1 year were comparable between PS with 1-stent and PS with 2-stent; however, the increased rate of TLR from year 1 to year 3 was 3.5% in the PS with 2-stent group (4.7 vs. 1.9%, HR 2.44, 95% CI 1.08–5.49, p = 0.031, Graphic Abstract), resulted in a significant difference in TLF after 1 year between the PS with 2-stent (6.6%) and the PS with 1-stent (3.1%, HR 2.19, 95% CI 1.13–4.22, p = 0.020).

By multivariate analysis, SB pretreatment (HR 1.66, 95% CI 1.19–2.31, p = 0.003), complex bifurcation lesions (HR 2.76, 95% CI 1.42–5.38, p = 0.003), without intravascular imaging (HR 1.51, 95% CI 1.07–2.14, p = 0.020), and hyperlipidemia (HR 1.15, 95% CI 1.04–1.88, p = 0.006) were the four independent factors of 3-year TLF. SB pretreatment was performed because operators were worried about the abrupt closure of an SB after ballooning or stenting MV. Supplementary Table 1 shows that the SB pretreatment subgroup had a longer lesion length (mean length of 14.47 vs. 12.25 mm, p = 0.001) and more severe disease (mean diameter stenosis of 51.99 vs. 42.96%) in the SB compared to those in the non-pretreatment subgroup. Subsequent clinical follow-up demonstrated a higher rate of 30-day PMI (8.6%) in the SB pretreatment subgroup, compared to 4.8% (p = 0.036) in the non-pretreatment subgroup. At 1- and 3-year follow-up, the increased rates of TVMI and TLR in the PS with 2-stent group led to significantly different TLF rates in the pretreatment subgroup (18.9 and 24.6%) when compared with 11.2% (p = 0.002) and 14.7% (p = 0.001) in the non-pretreatment subgroup, respectively (Supplementary Figure 1).

Discussion

This analysis for the first time compared the difference in clinical outcome between the PS with 1-stent and the PS with 2-stent for patients with ACS. The major findings

TABLE 2 Lesions and procedural characteristics.

	PS with 1-stent (n = 519)	PS with 2-stent (n = 301)	P-value
Multiple vessel disease, n (%)	282 (54.3)	151 (50.2)	0.276
SYNTAX Score, scores	25.68 ± 10.9	26.27 ± 11.2	0.458
≤22 scores, n (%)	213 (41.0)	117 (38.9)	0.541
23∼32 scores, n (%)	167 (32.3)	95 (31.6)	0.855
≥32 scores, n (%)	139 (26.8)	89 (29.6)	0.391
Lesion location, n (%)			0.429
LAD-LCX	178 (34.3)	122 (40.5)	
LAD-D	265 (51.1)	140 (46.5)	
LCX-OM	54 (10.4)	28 (9.3)	
Distal RCA	22 (4.2)	11 (3.7)	
True bifurcation lesions, n (%)	464 (89.6)	280 (93.0)	0.104
Complex bifurcation lesion, n (%)	223 (43.0)	178 (59.1)	<0.001
No. lesion, n	2.20 ± 0.91	2.24 ± 0.95	0.642
No. treated lesion, n	1.96 ± 0.81	2.02 ± 0.86	0.481
SB lesion length ≥ 10 mm, n (%)	167 (32.2)	129 (42.9)	0.002
≥Moderate calcification, n (%)	156 (30.1)	85 (28.2)	0.633
Chronic total occlusion, n (%)	37 (7.1)	32 (10.6)	0.119
Thrombus-containing lesion, n (%)	22 (4.2)	6 (2.0)	0.110
TIMI flow < 3 prior-to PCI, n (%)			
Main vessel	99 (9.1)	62 (20.6)	0.172
Side branch	40 (7.7)	27 (9.0)	0.859
Trans-radial approach, n (%)	368 (83.1)	216 (82.8)	0.427
MV pretreatment, n (%)	216 (41.6)	59 (19.6)	<0.001
SB pretreatment, n (%)	167 (32.2)	171 (56.8)	<0.001
IVUS guidance, n (%)	123 (23.7)	66 (21.9)	0.606
MV stent			
No. stent, n	1.65 ± 0.68	1.55 ± 0.67	0.054
Average diameter, mm	3.05 ± 0.61	3.09 ± 0.39	0.327
Average length, mm	43.66 ± 20.09	41.91 ± 21.37	0.241
Proximal optimization technique, n (%)	492 (94.8)	269 (89.4)	0.005
Balloon diameter, mm	3.79 ± 0.61	3.86 ± 0.43	0.689
Inflation pressure, atm	17.97 ± 3.21	17.73 ± 3.99	0.812
Final kissing inflation, n (%)	215 (41.4)	287 (95.3)	<0.001
Complete revascularization, n (%)	322 (62.0)	206 (68.4)	<0.001
Contrast volume, ml	158 ± 79	183 ± 84	<0.001
Procedural time, min	55.8 ± 37.2	65.3 ± 36.0	<0.001

PS, provisional stenting; LAD, left anterior descending artery; LCX, left circumflex; D, diagonal; OM, obtuse marginal; RCA, right coronary artery; SB, side branch; PCI, percutaneous coronary intervention; MV, main vessel; IVUS, intravascular ultrasound.

are (1) PS with 2-stent is associated with a higher rate of TLF at 3-year follow-up, largely driven by an increased 3-year rate of TLR, compared to those in the PS with 1-stent group; (2) by multivariate analysis, SB pretreatment, complex bifurcation lesions, without intravascular imaging, and hyperlipidemia were the four independent factors of 3-year TLF; and (3) the rate of TLF at 3-year follow-up in the SB pretreatment subgroup is significantly higher than that in the no pretreatment subgroup, mainly induced by the extreme increments in TVMI and TLR.

The PS with 2-stent is a rescue strategy for SB and reduces the incidence of SB occlusion and PMI and is required in 2–40% of bifurcation lesion treated by provisional approach (2, 4–9). This wide discrepancy in the rate of cross-over to two stents is due to the different criteria for treating SB from previous trials (4–9). For example, SB TIMI flow < 3 was the only criterion for stenting SB in the BBC ONE trial (6), and composite criteria of TIMI flow < 3, Type B or C dissection, and severely compromised in the SB after stenting MV were more commonly used in others (2–5, 7, 9–11). While a few risk stratifications have

TABLE 3 Quantitative angiographic analysis.

	PS with 1-stent (n = 286)	PS with 2-stent (n = 141)	P-value
MV lesion length, mm	32.34 ± 16.79	27.52 ± 16.58	0.003
Proximal MV	12.66 ± 9.56	10.89 ± 10.32	0.016
Distal MV	19.43 ± 12.92	17.86 ± 14.21	0.118
SB lesion length, mm	12.04 ± 7.75	15.11 ± 7.18	<0.001
Distal bifurcation angle, 0°			
Prior-to	72.2 ± 39.5	82.8 ± 41.8	0.001
Post-stenting	69.5 ± 38.2	77.1 ± 42.3	0.020
Follow-up	73.9 ± 40.3	70.9 ± 40.7	0.462
Proximal MV reference diameter, mm			
Prior-to	3.19 ± 0.49	3.16 ± 0.51	0.385
Post-stenting	3.28 ± 0.49	3.39 ± 0.47	0.002
Follow-up	3.26 ± 0.49	3.29 ± 0.46	0.491
Proximal MV MLD, mm			
Prior-to	1.78 ± 0.82	1.77 ± 0.79	0.888
Post-stenting	2.89 ± 0.55	3.08 ± 0.49	<0.001
Acute gain	1.11 ± 0.79	1.32 ± 0.74	<0.001
Follow-up	2.81 ± 0.58	2.83 ± 0.58	0.658
Late loss	0.11 ± 0.38	0.19 ± 0.39	0.019
Proximal MV diameter stenosis, %			
Prior-to	45.0 ± 22.9	43.6 ± 23.1	0.421
Post-stenting	12.1 ± 9.9	9.3 ± 6.8	<0.001
Follow-up	11.8 ± 9.8	11.4 ± 9.3	0.588
Restenosis, n (%)	3 (1.0)	2 (1.3)	0.667
Distal MV reference diameter, mm			
Prior-to	2.65 ± 0.46	2.69 ± 0.51	0.231
Post-stenting	2.74 ± 0.43	2.82 ± 0.42	0.023
Follow-up	2.77 ± 0.44	2.77 ± 0.40	0.943
Distal MV MLD, mm			
Prior-to	1.21 ± 0.59	1.15 ± 0.63	0.214
Post-stenting	2.37 ± 0.46	2.46 ± 0.43	0.003
Acute gain	1.15 ± 0.61	1.31 ± 0.63	0.001
Follow-up	2.26 ± 0.54	2.23 ± 0.54	0.570
Late loss	0.13 ± 0.38	0.22 ± 0.44	0.013
Distal MV diameter stenosis, %			
Prior-to	53.8 ± 21.4	56.9 ± 22.9	0.050
Post-stenting	14.5 ± 10.8	12.9 ± 8.8	0.033
Follow-up	17.5 ± 14.4	18.6 ± 15.3	0.383
Restenosis, n (%)	12 (4.2)	8 (5.7)	0.244
SB reference diameter, mm			
Prior-to	2.37 ± 0.44	2.47 ± 0.43	0.002
Post-stenting	2.27 ± 0.46	2.58 ± 0.37	<0.001
Follow-up	2.28 ± 0.47	2.50 ± 0.39	<0.001
SB MLD, mm			
Prior-to	1.29 ± 0.39	1.29 ± 0.57	0.997
Post-stenting	1.42 ± 0.59	2.16 ± 0.40	<0.001
Acute gain	0.12 ± 0.54	0.99 ± 0.54	<0.001
Follow-up	1.43 ± 0.59	1.83 ± 0.61	<0.001
Late loss	0.04 ± 0.43	0.29 ± 0.52	<0.001

(Continued)

TABLE 3 (Continued)

	PS with 1-stent (n = 286)	PS with 2-stent (n = 141)	P-value
SB diameter stenosis, %			
Prior-to	44.7 ± 20.6	54.1 ± 18.9	<0.001
Post-stenting	37.2 ± 20.6	13.8 ± 10.1	<0.001
Follow-up	33.8 ± 23.1	24.8 ± 20.9	<0.001
Restenosis, n (%)	90 (31.5)	22 (15.6)	<0.001
Ostial SB	84 (29.4)	19 (13.5)	<0.001

PS, provisional stenting; MV, main vessel; MLD, minimal lumen diameter; SB, side branch.

TABLE 4 Clinical results.

	PS with 1-stent (n = 519)	PS with 2-stent (n = 301)	Adjusted		
			HR	95% CI	p
30 days, n (%)					
TLF	34 (6.6)	24 (8.0)	1.24	0.83–1.85	0.296
Cardiac death	5 (1.0)	1 (0.3)	0.34	0.04–2.95	0.329
TVMI	30 (5.8)	22 (7.3)	1.29	0.73–2.27	0.388
PMI	16 (3.1)	8 (2.7)			
TLR	4 (0.8)	1 (0.3)	0.43	0.05–3.86	0.450
Stent thrombosis	6 (1.2)	5 (1.7)	1.44	0.44–4.77	0.547
1-year, n (%)					
TLF	69 (13.3)	49 (16.3)	1.09	0.61–1.98	0.751
Cardiac death	11 (2.1)	5 (1.7)	0.78	0.27–2.27	0.648
TVMI	33 (6.4)	29 (9.6)	1.57	0.93–2.64	0.089
STEMI	2 (0.4)	4 (1.3)			
TLR	33 (6.4)	25 (8.3)	1.33	0.78–2.29	0.296
Stent thrombosis	11 (2.1)	10 (3.3)	1.59	0.66–3.78	0.297
Definite	3 (0.6)	4 (1.3)			
Probable	8 (1.6)	6 (2.0)			
3-year, n (%)					
TLF	85 (16.4)	69 (22.9)	1.52	1.06–2.17	0.021
Cardiac death	19 (3.7)	12 (4.0)	1.09	0.52–2.28	0.814
TVMI	41 (7.9)	36 (12.0)	1.58	0.99–2.54	0.056
TLR	43 (8.3)	39 (13.0)	1.65	1.04–2.61	0.033
Stent thrombosis	16 (3.1)	16 (5.3)	1.77	0.87–3.58	0.116
Definite	5 (1.0)	6 (1.8)			
Probable	11 (2.1)	9 (2.7)			

PS, provisional stenting; HR, hazard ratio; CI, confidence interval; TLF, target lesion failure; TVMI, target vessel myocardial infarction; PMI, periprocedural myocardial infarction; TLR, target lesion revascularization.

been proposed to predict the occurrence of clinical events after the PS or upfront two-stent techniques (3, 14–16), the difference in treatment effect between the PS with 1-stent and the PS with 2-stent remained understudied. To echo this issue, Song et al. (17, 18) for the first time randomized 258 patients with a coronary bifurcation lesion to the conservative and aggressive groups according to the criteria for SB intervention after MV stenting (for non-LM bifurcations, the criterion for SB treatment was TIMI < 3 [conservative] or diameter stenosis > 75% [aggressive]; for LM bifurcation lesions, the criterion for SB treatment was diameter stenosis > 75% [conservative] or > 50% [aggressive]). The study reported that at a 3-year follow-up, the primary endpoint (target vessel failure [TVF]) occurred in 11.7% of the conservative group vs. 20.8% of the aggressive group (p = 0.049). Although no significant differences were observed in the incidence of TVF between groups at 1 year, landmark analysis between 1 and 3 years showed significantly less TVF in patients assigned to the conservative strategy (2.6 vs. 12.7%; p = 0.004). Conservative treatment for SB obviously had a less requirement of additional SB stent. However, the real

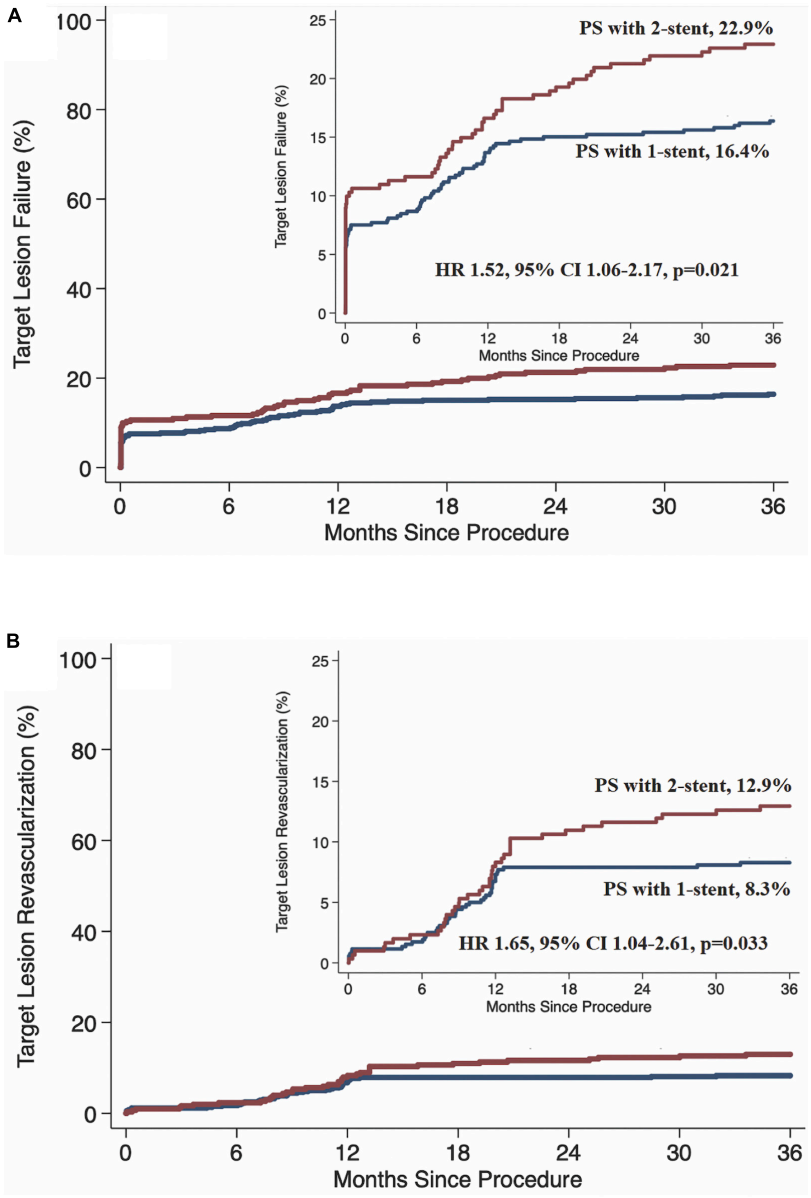


FIGURE 2
Kaplan–Meier survival rate. PS, provisional stenting; HR, hazard ratio; CI, confidence interval. **(A)** Target lesion failure. **(B)** Target lesion revascularization.

difference in TVF between the PS with 1-stent and 2-stent could not be directly derived from that study with a small sample size. In this study, we found that a higher rate of 3-year TLF in the PS with 2-stent group was predominantly induced by the increased requirement of TLR after 1-year follow-up, which indicated the reduction in the durability of the second stent in the SB. While the crossover to the 2-stent technique was an independent predictor of TVF (4, 17, 18), we further found that complex bifurcation lesions, SB pretreatment, IVUS use, and hyperlipidemia were the four predictors of 3-year TLF. In this study, IVUS was only used in less than 30% of procedures; although it was equally used in the two groups, the results still recommended the importance of routine use of IVUS in improving the clinical outcome after the PS approach (19–21). In contrast, complex bifurcation defined by DEFINITION criteria (3, 4, 8) was associated with a higher rate of crossover to two stents and a subsequent increased rate of MI and TLR. As a result, an upfront two-stent approach may be an appropriate option for real complex bifurcation lesions.

Side branch pretreatment mirrors the complexity of a given bifurcation lesion, particularly in the SBs having a higher grade of diameter stenosis, as shown by our data. To answer the correlation of the SB pretreatment with increased TVF, Song et al. (22) reported that an additional SB stent was frequently

required in the SB pretreatment group and that SB pretreatment increased the rate of TLR and TVF at 24-month follow-up, similar to our results. Recently, a meta-analysis (23) including the four studies demonstrated that bifurcation lesions stented without SB predilation demonstrated lower OR of requiring further SB intervention compared with lesions receiving upfront SB predilation. In fact, our result showed a prediction of SB pretreatment for PMI. More recently, Sheiban et al. (12) reported that PMI was positively correlated with TLF at 1-year follow-up after stenting bifurcation lesions. Conclusively, the routine performance of SB pretreatment before the PS procedures was not recommended by the current consortium (24) and previous clinical trials (4–9). SB pretreatment should be avoided for simple bifurcation lesions (short lesion length and less severe disease in the SB).

Acute coronary syndrome is a stage where coronary plaques become unstable (25). The COBIS Registry showed a lower rate of 3-year TLF after the PS approach for patients with ACS but no difference between the PS and upfront 2-stent for patients without ACS (26), confirmed by another study of Korean team which further found that SB lesion length was an independent factor of TLF (27). The underlying mechanisms for a higher rate of TLF in patients with ACS were multifactorial, of them DAPT might be one major reason (25). However, this study reported more frequent prescription of DAPT in the PS with 2-stent group and DAPT was not the factor for predicting TLF. This may again address the critical importance of intravascular imaging in guiding SB treatment.

Limitations

This study has some limitations. First, the non-randomized feature raised concerns about the exact different treatment effects between the PS with 1-stent and the PS with 2-stent as SB rescue stenting was performed in the scenario that SB was severely compromised or had complications induced by pretreatment. Thus, a randomized study using physiological assessment as the sole criterion for treating SB after stenting MV is crucial. Second, we did not compare the difference in clinical outcome between the PS with T and the PS with T-and-Protrusion (TAP) (4, 9, 10, 24) when a second stent was required in the SB. When an SB needed to be dilated after MV stenting, rewire was recommended across the distal cell of the MV stent (24). However, a very narrow space at the ostial SB after stenting MV did not allow precisely rewiring (from proximal or distal cell) so long as successfully crosses the struts to restore the SB flow, particularly for complex bifurcations (4). Finally, intravascular imaging was not routinely used because imaging guidance was not recommended in the studies (4, 9–11). Therefore, an intravascular imaging-guided stenting bifurcation is highly recommended. For this issue, two ongoing studies (28, 29) would launch their results, demonstrating the advantage of intravascular imaging guidance in treating a bifurcation lesion.

Conclusion

Provisional stenting with 2-stent is associated with a higher rate of 3-year TLF, mainly due to increased requirement of revascularization. A further study identifying the underlying mechanisms correlated with stent failure is warranted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Nanjing First Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

S-LC and IS made substantial contributions to the initial conception and design of the whole study and to the revision of the manuscript. IS and ZG wrote the first draft. JK contributed to data management and statistical expertise. J-JZ, TS, MM, FY, and NT provided comments and suggestions in critical revision of the manuscript. All authors approved the final version of the article.

Funding

This study was funded by grants from the National Science Foundation of China (Grant numbers: NSFC 91639303 and NSFC 81770441) and jointly supported by the Jiangsu Provincial Special Program of Medical Science (BE2019615) and Microport (Shanghai, China).

Acknowledgments

We thank Professor Feng Chen for his thorough statistical analysis. We also acknowledge Dr. Spencer B. King (Director of Clinical Event Committee), Dr. Tanveer S. Rab, and Dr. Tak W. Kwan for their meticulous work assessing all events. S-LC is a Fellow at the Collaborative Innovation Center for Cardiovascular Disease Translational Medicine, Nanjing Medical University, Nanjing, China.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.910313/full#supplementary-material

References

1. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused on update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* (2014) 64:1929–49. doi: 10.1161/CIR.0000000000000095

2. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation.* (2006) 114:1955–61. doi: 10.1161/CIRCULATIONAHA.106.664920

3. Chen SL, Sheiban I, Xu B, Jepson N, Paiboon C, Zhang JJ, et al. Impact of the complexity of bifurcation lesions treated with drug-eluting stents: the DEFINITION study (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts). *JACC Cardiovasc Interv.* (2014) 7:1266–76. doi: 10.1016/j.jcin.2014.04.026

4. Zhang JJ, Ye F, Xu K, Kan J, Tao L, Santoso T, et al. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial. *Eur Heart J.* (2020) 41:2523–36.

5. Colombo A, Bramucci E, Saccà S, Violini R, Lettieri C, Zanini R, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary bifurcations: application of the crushing technique using sirolimus-eluting stents) study. *Circulation.* (2009) 119:71–8. doi: 10.1161/CIRCULATIONAHA.108.808402

6. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation.* (2010) 121:1235–43. doi: 10.1161/CIRCULATIONAHA.109.888297

7. Hildick-Smith D, Egred M, Banning A, Brunel P, Ferenc M, Hovasse T, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). *Eur Heart J.* (2021) 42:3829–39. doi: 10.1093/eurheartj/ehab283

8. Di Gioia G, Sonck J, Ferenc M, Chen SL, Colaiori I, Gallinoro E, et al. Clinical outcomes following coronary bifurcation PCI techniques: a systematic review and network meta-analysis comprising 5,711 patients. *JACC Cardiovasc Interv.* (2020) 13:1432–44. doi: 10.1016/j.jcin.2020.03.054

9. Chen X, Li X, Zhang JJ, Han Y, Kan J, Chen L, et al. 3-year outcomes of the DKCRUSH-V Trial comparing DK crush with provisional stenting for left main bifurcation lesions. *JACC Cardiovasc Interv.* (2019) 12:1927–37. doi: 10.1016/j.jcin.2019.04.056

10. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double kissing crush versus provisional stenting technique for treatment of coronary bifurcation lesions) trial. *J Am Coll Cardiol.* (2011) 57:914–20. doi: 10.1016/j.jacc.2010.10.023

11. Chen SL, Ye F, Zhang JJ, Ye F, Xu YW, Fu Q, et al. Randomized comparison of FFR-guided and angiography-guided provisional stenting of true coronary bifurcation lesions: the DKCRUSH-VI trial (Double kissing crush versus provisional stenting technique for treatment of coronary bifurcation lesions VI). *JACC Cardiovasc Interv.* (2015) 8:536–46.

12. Sheiban I, Ge Z, Kan J, Nie S, Zhang JJ, Santoso T, et al. Association of peri-procedural myocardial infarction with mortality after stenting true coronary bifurcation lesions: a pooled individual participant data analysis from four randomized controlled trials. *Catheter Cardiovasc Interv.* (2022) 99:617–26. doi: 10.1002/ccd.29946

13. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med.* (2007) 356:1020–9. doi: 10.1056/NEJMoa067731

14. Vassilev D, Mileva N, Collet C, Nikolov P, Sokolova K, Karamfiloff K, et al. Bifurcation functional significance score as predictor of mortality: a validating study. *Sci Rep.* (2021) 11:24308. doi: 10.1038/s41598-021-03815-6

15. Chen SL, Chen JP, Mintz G, Xu B, Kan J, Ye F, et al. Comparison between the NERS (new risk stratification) score and the SYNTAX (Synergy between percutaneous coronary intervention with taxus and cardiac surgery) score in outcome prediction for unprotected left main stenting. *JACC Cardiovasc Interv.* (2010) 3:632–41. doi: 10.1016/j.jcin.2010.04.006

16. Chen SL, Han YL, Zhang YJ, Ye F, Liu HW, Zhang JJ, et al. The anatomic- and clinical-based NERS (new risk stratification) score II to predict clinical outcomes after stenting unprotected left main coronary artery disease: results from a multicenter, prospective, registry study. *JACC Cardiovasc Interv.* (2013) 6:1233–41. doi: 10.1016/j.jcin.2013.08.006

17. Song YB, Hahn JY, Song PS, Yang JH, Choi JH, Choi SH, et al. Randomized comparison of conservative versus aggressive strategy for provisional side branch intervention in coronary bifurcation lesions: results from the SMART-STRATEGY (Smart angioplasty research team-optimal strategy for side branch intervention in coronary bifurcation lesions) randomized trial. *JACC Cardiovasc Interv.* (2012) 5:1133–40. doi: 10.1016/j.jcin.2012.07.010

18. Song YB, Park TK, Hahn JY, Yang JH, Choi JH, Choi SH, et al. Optimal strategy for provisional side branch intervention in coronary bifurcation lesions: 3-year outcomes of the SMART-STRATEGY randomized trial. *JACC Cardiovasc Interv.* (2016) 9:517–26. doi: 10.1016/j.jcin.2015.11.037

19. Zhang J, Gao X, Kan J, Ge Z, Han L, Lu S, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol.* (2018) 72:3126–37. doi: 10.1016/j.jacc.2018.09.013

20. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA.* (2015) 314:2155–63. doi: 10.1001/jama.2015.15454

21. Hong SJ, Zhang JJ, Mintz GS, Ahn CM, Kim JS, Kim BK, et al. Improved 3-year cardiac survival after IVUS-guided long DES implantation: a patient-level analysis from 2 randomized trials. *JACC Cardiovasc Interv.* (2022) 15:208–16. doi: 10.1016/j.jcin.2021.10.020

22. Song PS, Song YB, Yang JH, Hahn JY, Choi SH, Choi JH, et al. The impact of side branch predilatation on procedural and long-term clinical outcomes in coronary bifurcation lesions treated by the provisional approach. *Rev Esp Cardiol (Engl Ed).* (2014) 67:804–12. doi: 10.1016/j.rec.2014.01.032

23. Mirzaee S, Isa M, Thakur U, Cameron JD, Nicholls SJ, Dundon BK. Impact of side-branch predilation on angiographic outcomes in non-left main coronary bifurcation lesions. *J Invasive Cardiol.* (2020) 32:42–8.

24. Burzotta F, Lassen JF, Lefèvre T, Banning AP, Chatzizisis YS, Johnson TW, et al. Percutaneous coronary intervention for bifurcation coronary lesions: the 15th consensus document from the European Bifurcation Club. *EuroIntervention.* (2021) 16:1307–17. doi: 10.4244/EIJ-D-20-00169

25. Tomaniak M, Katagiri Y, Modolo R, de Silva R, Khamis RY, Bourantas CV, et al. Vulnerable plaques and patients: state-of-the-art. *Eur Heart J.* (2020) 41:2997–3004. doi: 10.1093/eurheartj/ehaa227

26. Kim MC, Ahn Y, Sun Sim D, Joon Hong Y, Han Kim J, Ho Jeong M, et al. Comparison of the planned one- and elective two-stent techniques in patients with coronary bifurcation lesions with or without acute coronary syndrome from the COBIS II Registry. *Catheter Cardiovasc Interv.* (2018) 92:1050–60. doi: 10.1002/ccd.27551

27. Sang Song P, Ryeol Ryu D, Choi SH, Yang JH, Song YB, Hahn JY, et al. Impact of acute coronary syndrome classification and procedural technique on clinical outcomes in patients with coronary bifurcation lesions treated with drug-eluting stents. *Clin Cardiol.* (2012) 35:610–8. doi: 10.1002/clc.22020

28. Holm NR, Andreasen LN, Walsh S, Kajander OA, Witt N, Eek C, et al. Rational and design of the European randomized optical coherence tomography optimized bifurcation event reduction trial (OCTOBER). *Am Heart J.* (2018) 205:97–109. doi: 10.1016/j.ahj.2018.08.003

29. Ge Z, Kan J, Gao XF, Kong XQ, Zuo GF, Ye F, et al. Comparison of intravascular ultrasound-guided with angiography-guided double kissing crush stenting for patients with complex coronary bifurcation lesions: rationale and design of a prospective, randomized, and multicenter DKCRUSH VIII trial. *Am Heart J.* (2021) 234:101–10.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 13 October 2022
DOI 10.3389/fcvm.2022.906232

OPEN ACCESS

EDITED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

REVIEWED BY
Cornelie Nienaber-Rousseau,
North-West University, South Africa
Zahra Khorasanchi,
Mashhad University of Medical Sciences, Iran

*CORRESPONDENCE
Yan Zhang
drzhy1108@163.com
Jianping Li
lijianping03455@pkufh.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 28 March 2022
ACCEPTED 26 September 2022
PUBLISHED 13 October 2022

CITATION
Sun P, Weng H, Fan F, Zhang N, Liu Z, Chen P, Jia J, Zheng B, Yi T, Li Y, Zhang Y and Li J (2022) Association between plasma vitamin B5 and coronary heart disease: Results from a case-control study. *Front. Cardiovasc. Med.* 9:906232. doi: 10.3389/fcvm.2022.906232

Association between plasma vitamin B5 and coronary heart disease: Results from a case-control study

Pengfei Sun[1†], Haoyu Weng[1†], Fangfang Fan[1], Nan Zhang[1], Zhihao Liu[1], Ping Chen[2], Jia Jia[1], Bo Zheng[1], Tieci Yi[1], Yuxi Li[1], Yan Zhang[1,3*‡] and Jianping Li[1,3*‡]

[1]Department of Cardiology, Peking University First Hospital, Beijing, China, [2]School of Pharmacy, Jinan University, Guangzhou, China, [3]Key Laboratory of Molecular Cardiovascular Science of Ministry of Education, Peking University, Beijing, China

Aim: The relationship of vitamin B5 and coronary heart disease (CHD) is still uncertain. This case–control study was performed to evaluate the relationship between the plasma vitamin B5 concentration and the risk of CHD.

Materials and methods: The study involved 429 patients with >70% stenosis of the coronary arteries on coronary angiography and 429 matched controls were included for age ± 2 years, gender, and date of coronary angiography examination ± 180 days. Logistic regression analyses were performed to evaluate the association between plasma vitamin B5 and the risk of CHD.

Results: An L-shaped relationship was found between the plasma vitamin B5 concentration and CHD. Compared with patients with low vitamin B5 (first quartile, <27.6 ng/ml), the odds ratio (OR) and 95% confidence interval (CI) for participants in the third quartile (34.9–44.0 ng/ml) and fourth quartile (≥44.0 ng/ml) were 0.42 (95% CI, 0.26–0.70) and 0.49 (95% CI, 0.29–0.82), respectively. In the threshold effect analysis, the risk of CHD significantly decreased as the vitamin B5 concentration increased (per 10 ng/ml increment: OR, 0.71; 95% CI, 0.57–0.89) in participants with a plasma vitamin B5 concentration of <40.95 ng/ml; however, an increased plasma vitamin B5 concentration was no longer associated with a decreased risk of CHD (per 10 ng/ml increment: OR, 1.00; 95% CI, 0.87–1.14) in participants with a plasma vitamin B5 concentration of ≥40.95 ng/ml. The association between vitamin B5 and CHD was stronger in ever or current smokers than non-smokers (p-interaction = 0.046).

Conclusion: Plasma vitamin B5 has an L-shaped relationship with CHD, with a threshold around 40.95 ng/ml. This association was modified by smoking.

KEYWORDS

vitamin B5 (pantothenic acid), coronary heart disease, smoking, case control, L-shaped relationship

Introduction

In spite of the improvements in prevention and treatment, coronary heart disease (CHD) remains one of the most common non-communicable diseases and leading cause of death globally (1). The burden of CHD is also increasing in Chinese population in recent decades (2). The prevalence of ischemic heart disease (IHD) nearly doubled since 1990, reaching approximately 23 million in 2016 (2).

At present, identification and management of traditional risk factors for CHD are the main focus of the clinical guidelines, including smoking, dyslipidemia, hypertension, obesity, diabetes, and physical inactivity (3–6). However, in light of rising CHD prevalence and recognition of residual risk despite the effort to control traditional risk factors, there is a clear need to explore non-traditional risk or protective factors. In this regard, a better understanding the role of micronutrients is highlighted by the US precision nutrition initiative (7).

Along this line, vitamin B5 is of considerable interest. It belongs to the family of water-soluble B vitamin, also known as pantothenic acid or pantothenate or "anti-stress vitamin" (8, 9). Vitamin B5 was first discovered by Williams et al. (10) in 1933 as an essential nutrient for yeast. One important fact is that vitamin B5 must be obtained from various dietary sources or intestinal bacteria, because human body cannot synthesize B5 (11). The vitamin B5 obtained from food is in the form of coenzyme A (12). Therefore, clinicians infrequently encounter vitamin B5 deficiency, the clinical manifestations of which include generalized malaise, burning foot syndrome (13), insomnia, and autoimmune arthritis (14). Vitamin B5 can also be obtained from intestinal bacterial sources, suggesting that the intestinal microbiome might impact the concentration of vitamin B5 in plasma (12, 15).

The importance of vitamin B5 is dictated by its role in cellular metabolism. It is the key precursor to the biosynthesis of coenzyme A, which is important in the synthesis and degradation of fatty acids, synthesis of phospholipids, synthesis of heme, and operation of the tricarboxylic acid cycle (16, 17). Furthermore, pantethine, the disulfide derivative of vitamin B5, can reduce the concentrations of low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL), total cholesterol, triglyceride, and apolipoprotein B and increase the concentrations of high-density lipoprotein cholesterol and apolipoprotein A-1 (18). Therefore, it has been regarded as a nutritional supplement in the United States since 1992 (15). Pantethine is well-tolerated and has a low occurrence (3.6%) of mild gastrointestinal adverse effects (19). Pantethine can also reportedly improve the function of platelet, exert an antioxidant effect, protect the endothelium (20, 21), modify lipid deposition, and reduce fatty streak formation in major arteries (18, 22). Vitamin B5 deficiency may be related to a relative "hyperadrenergic" state, increasing the risk of hypertension, arrhythmia, stroke, and some other diseases (14). Moreover, dexpanthenol, the precursor to vitamin B5, is reportedly beneficial in rats with ischemia–reperfusion injury of the brain and cardiovascular system (23). According to several studies, vitamin B5 might also be related to obesity (24) and visceral fat accumulation (VFA) (25). There are also reports on the association between B5 and hypertension (26, 27). Previous study had also stated a dietary multivitamin, multimineral and phytonutrient supplement, which contained vitamin B5, could lower homocysteine level (28).

When it comes to CHD, there are many unsettled questions regarding the role of vitamin B5. This case-control study sought to advance our understanding on the association of vitamin B5 with risk of CHD in Chinese men and women undergoing coronary angiography by involving patients with CHD and matched controls from hospital, with a particular attention to the effect modification by or joint effects with traditional CVD risk factors.

Materials and methods

Study participants

Participants were enrolled from 1 January 2016 to 31 December 2019 in Peking University First Hospital, Beijing, China. A case-control study design was used. The inclusion criteria were examination by coronary angiography, provision of written informed consent, and storage of frozen blood samples in the Peking University First Hospital biorepository. Exclusion criteria were as follows: a history of physician diagnosed CHD; serum cardiac troponin (cTnI) $\geq$ 0.04 ng/ml; inability to provide informed consent; refusal to supply a venous blood sample. One thousand nine hundred and sixty six individuals were included. Then a CHD case was defined as a patient with >70% stenosis of the coronary arteries on coronary angiography and non-CHD controls were defined as a patient with <30% coronary stenosis. In total, we matched 429 patients with CHD with an equal number of controls for age $\pm$ 2 years, gender, and date of coronary angiography examination $\pm$180 days. **Figure 1** showed the flow chat of the enrollment. All participants provided written informed consent, and the study protocol was approved by the ethics committee of both Peking University and Peking University First Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Measurement of vitamin B5 and covariates

The plasma vitamin B5 concentration was measured using liquid chromatography tandem mass spectrometry. The linear

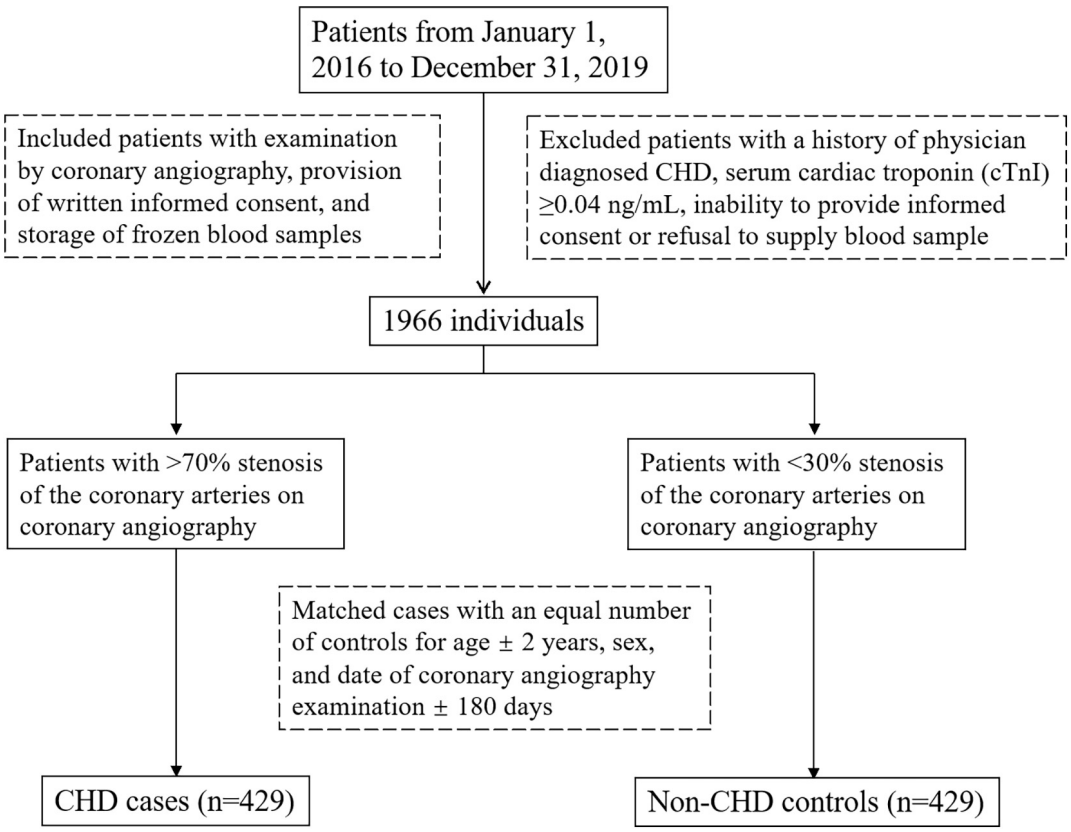


FIGURE 1
The flow chat of the enrollment.

range for plasma vitamin B5 was 2.5–1,000 ng/ml. The precision within and between batches was <15%.

For each participant, we reviewed the medical records and abstracted the following variables: gender; age; height; weight and body mass index (BMI); date of coronary angiography examination; systolic blood pressure (SBP); fasting plasma glucose (FPG) concentration; plasma creatinine concentration; plasma LDL-C concentration; plasma homocysteine concentration; smoking status (current, never, or ever); drinking status (current, never, or ever); diagnosis of hypertension, diabetes, and dyslipidemia; and use of antihypertensive, hypoglycemic, and lipid-lowering drugs.

Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range) for non-normally distributed variables. Categorical variables are presented as number and percentage. Differences between two groups were compared using *t*-tests for normally distributed continuous variables including age, BMI, SBP, LDL-C, FPG, Crea; Mann–Whitney U-test for non-normally distributed continuous variables including homocysteine, VB5; and χ^2 tests for categorical variables including smoking status, drinking status, diagnosis of disease, medication.

Odds ratios (ORs) and 95% confidence intervals (CIs) of CHD were estimated by modeling the plasma vitamin B5 concentration as continuous as well as categorical variables using conditional logistic regression, conditioned on the matching factors of age, gender, and operation time with and without adjusting for BMI; SBP; FPG; smoking status; drinking status; discharge diagnosis of hypertension, diabetes, and dyslipidemia; use of antihypertensive, hypoglycemic, and lipid-lowering drugs; LDL-C concentration, and plasma creatinine concentration. We also assessed the possible modifications of the association between the plasma vitamin B5 concentration and CHD by including interaction terms in the logistic regression models. Interactions between subgroups and the vitamin B5 concentration were examined by likelihood ratio testing. A smoothing function and two-piecewise linear regression model were used to examine the threshold effect of the plasma vitamin B5 concentration on CHD. A two-tailed *p*-value of <0.05 was considered statistically

TABLE 1 Characteristics of cases and controls.

Characteristics[a]	Total	Non-CHD controls	CHD cases	*P*-value[b]
N	858	429	429	
Female, *n* (%)	456 (53.1)	228 (53.1)	228 (53.1)	1
Age, years	63.5 ± 10.4	63.1 ± 10.3	63.9 ± 10.5	0.241
BMI, kg/m^2	26.1 ± 3.7	26.2 ± 3.7	25.9 ± 3.7	0.298
SBP, mm Hg	133.0 ± 15.8	132.4 ± 15.6	133.6 ± 16.1	0.262
LDL-C, mmol/l	2.3 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	0.05
FPG, mmol/l	7.0±3.0	6.5 ± 2.5	7.5 ± 3.4	<0.001
Crea, μmoI/l	82.0 ± 49.3	80.2 ± 53.3	83.8 ± 45.0	0.276
Homocysteine, μmoI/l	13.4 (10.3, 17.3)	13.5 (10.0, 17.7)	13.4 (10.5, 16.9)	0.859
Smoking status, *n* (%)				0.005
Never	499 (59.4)	272 (64.6)	227 (54.2)	
Ever	158 (18.8)	64 (15.2)	94 (22.4)	
Current	183 (21.8)	85 (20.2)	98 (23.4)	
Drinking status, *n* (%)				0.988
Never	590 (70.9)	297 (70.7)	293 (71.1)	
Ever	82 (9.9)	42 (10.0)	40 (9.7)	
Current	160 (19.2)	81 (19.3)	79 (19.2)	
Diagnosis of disease, *n* (%)				
Hypertension	600 (69.9)	280 (65.3)	320 (74.6)	0.003
Diabetes	361 (42.1)	139 (32.4)	222 (51.7)	<0.001
Dyslipidemia	669 (78.0)	317 (73.9)	352 (82.1)	0.004
Medication, *n* (%)				
Antihypertensive	476 (55.5)	226 (52.7)	250 (58.3)	0.099
Hypoglycemia	263 (30.7)	97 (22.6)	166 (38.7)	<0.001
Lipid-lowering	411 (47.9)	171 (39.9)	240 (55.9)	<0.001
VB5, ng/ml	34.9 (27.6, 44.0)	36.9 (29.2, 44.7)	33.3 (26.7, 42.7)	0.006

[a]Normally distributed variables were presented as mean ± standard deviation, non-normally were presented as median (interquartile range) and categorical variables are presented as number and percentage. [b]Differences between two groups were compared using *t*-tests for normally distributed continuous variables, Mann–Whitney U-test for non-normally distributed continuous variables and χ^2 tests for categorical variables. VB5, vitamin B5; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; FPG, fast plasma glucose; Crea, plasma creatinine; HTD, hypertension drugs.

significant in all analyses, which were performed using R software version 3.6.3.

Results

Patient characteristics

This case–control study involved 429 cases and 429 matched controls and the characteristics of both groups were showed in Table 1. The median plasma vitamin B5 concentration was 33.3 ng/ml (interquartile range, 26.7–42.7 ng/ml) among CHD cases, and 36.9 ng/ml (interquartile range, 29.8–45.1 ng/ml) among controls. CHD cases had a higher FPG concentration, lower frequency of current smoking, lower plasma vitamin B5 concentration, and higher frequency of hypertension, diabetes, plasma homocysteine levels and hyperlipidemia. Participants' characteristics at different plasma vitamin B5 concentrations are shown Supplementary Table 1, and participants' characteristics stratified by smoking status are shown Supplementary Table 2.

Association between plasma vitamin B5 and coronary heart disease

In Figure 2 we showed the smoothing curve between the plasma vitamin B5 concentration and CHD in overall sample (Figure 2A) and stratified by smoking status (Figure 2B), adjusted for gender; age; BMI; SBP; FPG concentration; drinking status; discharge diagnosis of hypertension, diabetes, and dyslipidemia; LDL-C concentration; and plasma creatinine concentration. The smooth curve shows an L-shaped relationship between the plasma vitamin B5 concentration and CHD in overall sample.

In Table 2 we summarized the univariate and multivariate OR (95% CI) of CHD in relation to the plasma vitamin B5 concentration (as a categorical variable and in quartiles) in overall sample and stratified by gender. In overall sample,

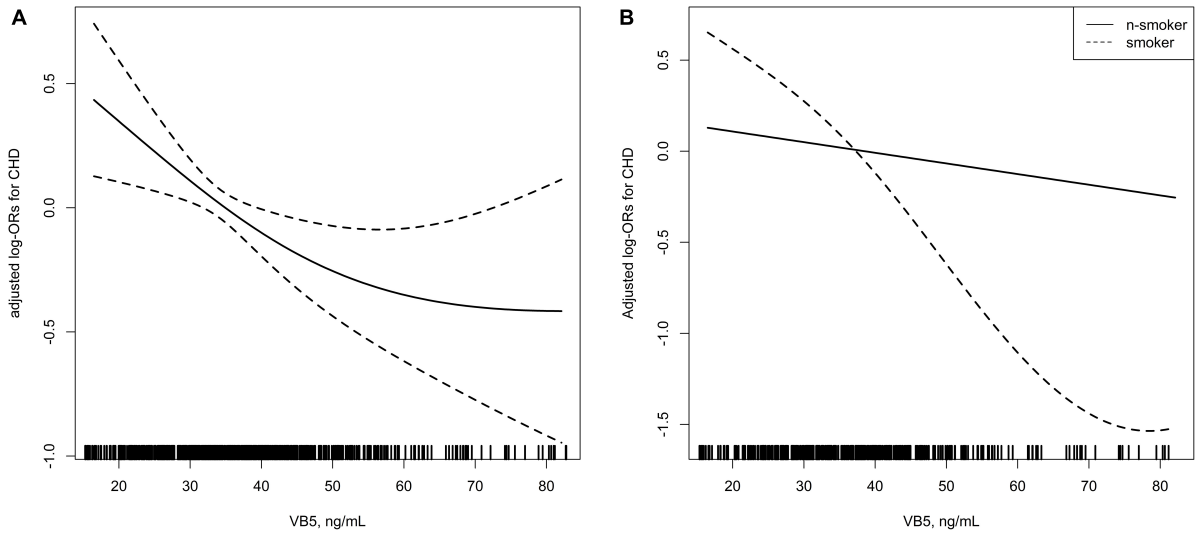


FIGURE 2
(A) Smoothing curve showing the effects of plasma vitamin B5 on the risk of coronary heart disease (CHD). **(B)** Smoothing curve showing the effects of plasma vitamin B5 on the risk of CHD stratified by smoking status.

compared with patients with a low vitamin B5 concentration (first quartile, <27.6 ng/ml), the OR (95% CI) for participants in the third quartile (34.9–44.0 ng/ml) and fourth quartile (≥44.0 ng/ml) was 0.42 (95% CI, 0.26–0.70) and 0.49 (95% CI, 0.29–0.82), respectively. In males, compared with patients with a low vitamin B5 concentration (first quartile, <27.6 ng/ml), the OR (95% CI) for participants in the third quartile (34.9–44.0 ng/ml) and fourth quartile (≥44.0 ng/ml) was 0.27 (95% CI, 0.12–0.62) and 0.29 (95% CI, 0.13–0.66), respectively. In females, this association was insignificant, although the gender interaction effect was insignificant ($p = 0.067$).

Although higher plasma vitamin B5 quartiles were associated with a lower frequency of CHD, a threshold effect was found for this association. In the threshold effect analysis, the risk of CHD significantly decreased as the plasma vitamin B5 concentration increased (per-10 ng/ml increment: OR, 0.71; 95% CI, 0.57–0.89) in participants with a plasma vitamin B5 concentration of <40.95 ng/ml; however, increased plasma vitamin B5 was no longer associated with a decreased risk of CHD (per 10 ng/ml increment: OR, 1.00; 95% CI, 0.87–1.14) in participants with a plasma vitamin B5 concentration of ≥40.95 ng/ml. The p of the log likelihood ratio test comparing the two-piecewise model with the linear logistic regression model was 0.026 (Table 3).

Subgroup and interaction analyses

In the stratified analyses to assess the relationship between the plasma vitamin B5 concentration (<27.6 vs. ≥27.6 ng/ml) and CHD in the various subgroups, none of the following variables significantly modified the association between vitamin B5 and CHD: age (<60 vs. ≥60 years, p-interaction = 0.346); gender (p-interaction = 0.067); BMI (<24, 24–28, and ≥28 kg/m^2, p-interaction = 0.698); alcohol drinking status (never, ever, or current; p-interaction = 0.402); plasma creatinine concentration (<82 vs. ≥82 μmol/l, p-interaction = 0.238); and diagnosis of hypertension (no or yes, p-interaction = 0.837), diabetes (no or yes, p-interaction = 0.686), and dyslipidemia (no or yes, p-interaction = 0.807). However, the smoking status modified the association between vitamin B5 and the risk of CHD, the association between vitamin B5 and CHD was stronger in ever or current smokers than non-smokers (p-interaction = 0.046, Table 4). Participants' characteristics stratified by smoking status are shown Supplementary Table 2.

Discussion

To our knowledge, there are limited studies that specifically examined vitamin B5 and CHD. From mechanistic perspective, our study findings are biologically plausible. The possible mechanism between vitamin B5 and CHD can be postulated to involve inflammatory events. It is widely accepted that CHD manifests with chronic low-grade inflammation, while vitamin B5 has an antioxidant effect in the inflammatory process underlying the pathogenesis of atherosclerosis (8). Jung et al. (29) reported that high dietary vitamin B5 intake was significantly related to a lower serum C-reactive protein (CRP) concentration at the 5 years follow-up in South Korea; CRP

TABLE 2 Association of vitamin B5 with risk of coronary heart disease (CHD).

VB5, ng/ml	Cases (%)	Model 1[a]		Model 2[b]	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Overall sample					
Quartiles					
Q1 (<27.6 ng/ml)	126 (58.6)	Ref		Ref	
Q2 (27.6–34.9 ng/ml)	110 (51.4)	0.77 (0.53, 1.11)	0.161	0.70 (0.42, 1.15)	0.155
Q3 (34.9–44.0 ng/ml)	94 (43.9)	0.55 (0.38, 0.81)	0.003	0.42 (0.26, 0.70)	<0.001
Q4 (=44.0 ng/ml)	99 (46.0)	0.61 (0.41, 0.89)	0.010	0.49 (0.29, 0.82)	0.007
Categories					
Q1 (<27.6 ng/ml)	126 (58.6)	Ref		Ref	
Q2–Q4 (≥27.6 ng/ml)	303 (47.1)	0.64 (0.47, 0.88)	0.005	0.53 (0.35, 0.80)	0.002
Male					
Quartiles					
Q1 (<27.6 ng/ml)	71 (65.1)	Ref		Ref	
Q2 (27.6–34.9 ng/ml)	50 (50.0)	0.54 (0.31, 0.95)	0.034	0.40 (0.19, 0.87)	0.020
Q3 (34.9–44.0 ng/ml)	39 (41.9)	0.36 (0.20, 0.66)	<0.001	0.27 (0.12, 0.62)	0.002
Q4 (≥44.0 ng/ml)	41 (41.0)	0.36 (0.20, 0.64)	<0.001	0.29 (0.13, 0.66)	0.003
Categories					
Q1 (<27.6 ng/ml)	71 (65.1)	Ref		Ref	
Q2–Q4 (≥27.6 ng/ml)	130 (44.4)	0.42 (0.26,0.68)	<0.001	0.32 (0.17,0.62)	<0.001
Female					
Quartiles					
Q1 (<27.6 ng/ml)	55 (51.9)	Ref		Ref	
Q2 (27.6–34.9 ng/ml)	60 (52.6)	1.04 (0.64, 1.72)	0.865	1.17 (0.56, 2.44)	0.669
Q3 (34.9–44.0 ng/ml)	55 (45.5)	0.77 (0.46, 1.28)	0.317	0.55 (0.27, 1.12)	0.102
Q4 (≥44.0 ng/ml)	58 (50.4)	0.95 (0.57, 1.60)	0.852	0.83 (0.38, 1.80)	0.643
Categories					
Q1 (<27.6 ng/ml)	55 (51.9)	Ref		Ref	
Q2–Q4 (≥27.6 ng/ml)	173 (49.4)	0.91 (0.60, 1.38)	0.673	0.79 (0.44, 1.41)	0.419

[a]Conditioned on the matching factors of age, gender, and operation time. [b]Conditioned on the matching factors of age, gender, and operation time and adjusted for BMI; SBP; fasting plasma glucose concentration; smoking status; drinking status; diagnosis of hypertension, diabetes, and dyslipidemia; LDL-C concentration; plasma creatinine concentration; and use of antihypertensive, hypoglycemic and lipid-lowering medications. VB5, vitamin B5; CHD, coronary heart disease; OR, odds ratio; CI, confidence interval; Ref, reference; BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

TABLE 3 Threshold effect analysis of vitamin B5 (per 10 ng/ml) on coronary heart disease (CHD) using piecewise logistic regression.

Threshold effect analysis	B	SE	Exp (B)	*Z* value	OR (95% CI)	*P*
Model comparison						
Model I						
One line model	−0.12	0.05	0.89	−2.22	0.89 (0.80, 0.99)	0.026
Model II						
VB5 turn point (K)					40.95 ng/ml	
<K, effect 1	−0.34	0.11	0.71	−2.98	0.71 (0.57, 0.89)	0.003
>K, effect 2	0	0.07	1	−0.07	1.00 (0.87, 1.14)	0.945
Log likelihood ratio test *P*-value					0.026	

Adjustment was performed for gender; age; BMI; SBP; fasting plasma glucose concentration; drinking status; diagnosis of hypertension, diabetes, and dyslipidemia; LDL-C concentration; plasma creatinine concentration; and use of antihypertensive, hypoglycemic, and lipid-lowering medications. CHD, coronary heart disease; OR, odds ratio; CI, confidence interval; VB5, vitamin B5; BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol. A smoothing function and two-piecewise logistics regression model were used to examine the threshold effect of the plasma VB5 concentration on CHD. The turning point was determined using trial and error, including selection of turning points along a predefined interval and then choosing the turning point that gave the maximum model likelihood. A log likelihood ratio test was used to compare the two-piecewise model with the linear logistic regression model.

TABLE 4 Subgroup and interaction analyses for the association between vitamin B5 (quartiles 2–4 vs. 1) and coronary heart disease (CHD).

Subgroup	B5 Q1 (<27.6 ng/ml) case (%)	B5 Q2–4 (≥27.6 ng/ml) case (%)	OR (95% CI)	*P*	*P*-interaction
Gender					0.067
Male	71 (65.1)	130 (44.4)	0.39 (0.23, 0.67)	<0.001	
Female	55 (51.9)	173 (49.4)	0.77 (0.47, 1.26)	0.302	
Age, years					0.346
<60	55 (59.1)	76 (41.5)	0.45 (0.25, 0.80)	0.007	
≥60	71 (58.2)	227 (49.3)	0.64 (0.40, 1.01)	0.054	
BMI, Kg/m^2					0.698
<24	38 (58.5)	86 (51.8)	0.69 (0.35, 1.34)	0.271	
24–28	58 (59.2)	134 (46.9)	0.48 (0.28, 0.82)	0.007	
≥28	27 (56.2)	80 (44.2)	0.59 (0.29, 1.22)	0.155	
Crea, μ mol/l					0.238
<82	89 (57.4)	174 (43.7)	0.48 (0.31, 0.74)	<0.001	
≥82	37 (62.7)	128 (52.9)	0.78 (0.40, 1.53)	0.468	
Smoking status					0.046
Never	50 (45.5)	177 (45.5)	0.82 (0.51, 1.31)	0.402	
Ever	29 (74.4)	65 (54.6)	0.26 (0.10, 0.67)	0.006	
Current	42 (70)	56 (45.5)	0.39 (0.19, 0.81)	0.011	
Drinking status					0.402
Never	80 (54.1)	213 (48.2)	0.65 (0.42, 0.99)	0.046	
Ever	14 (70)	26 (41.9)	0.30 (0.09, 1.02)	0.054	
Current	26 (65)	53 (44.2)	0.44 (0.19, 1.01)	0.052	
Hypertension					0.837
No	43 (53.1)	66 (37.3)	0.53(0.29, 0.97)	0.04	
Yes	83 (61.9)	237 (50.9)	0.58(0.37, 0.91)	0.019	
Diabetes					0.686
No	70 (49.3)	137 (38.6)	0.59 (0.38, 0.92)	0.02	
Yes	56 (76.7)	166 (57.6)	0.51 (0.27, 0.96)	0.036	
Dyslipidemia					0.807
No	25 (51)	52 (37.1)	0.52 (0.25, 1.09)	0.084	
Yes	101 (60.8)	251 (49.9)	0.58 (0.38, 0.87)	0.009	

Adjusted, if not stratified, for gender; age; BMI; SBP; fasting plasma glucose concentration; smoking status; drinking status; diagnosis of hypertension, diabetes, and dyslipidemia; LDL-C concentration; plasma creatinine concentration; and use of antihypertensive, hypoglycemic, and lipid-lowering medications. OR, odds ratio; CI, confidence interval; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; Crea, plasma creatinine; Q1, quartile 1; Q2–4, quartile 2–4.

can directly bind LDL-C and is involved in the formation of foam cells in the inflammatory process. Additionally, the findings of Scheurig et al. (30) indicated that multivitamin supplements, including vitamin B5, were associated with lower CRP concentrations among female patients. He et al. (31) stated that vitamin B5 might promote neutrophils to secrete anti-inflammatory cytokines to reduce the recruitment or activation of macrophages in early infection. In this way, vitamin B5 might regulate the macrophages in the early process of atherosclerosis.

In support of our findings, previous studies showed that vitamin B5 is also associated with several risk factors of CHD, such as dyslipidemia, hypertension, and obesity. An association between vitamin B5 and the lipid-regulating effect of pantethine has been supported by some experiments (18, 19). A randomized controlled trial by Evans et al. (15) also suggested that pantethine, synthesized from vitamin B5 in the body, can lower the concentrations of total cholesterol, LDL-C, very-low-density lipoprotein, and triglycerides in patients with a low to moderate risk of CVD. Although the mechanism underlying the ability of pantethine to reduce blood lipids is unclear, dyslipidemia plays a major role in the development of CVD (32). In the present study, the diagnosis of CHD in all participants was based on coronary angiography, which is more accurate than other methods.

Vitamin B5 was also proven to be associated with hypertension in some animal experiments (33–35). Koyanagi et al. (26) reported that residents with lower serum vitamin B5 concentrations living in rice field areas were more likely to be

diagnosed with hypertension than residents with higher serum vitamin B5 concentrations living in upland villages in Japan, this relationship was also confirmed by a survey launched in black South African children (27).

There is also some evidence of a relationship between vitamin B5 and obesity. According to a survey among male adolescents (24), higher dietary vitamin B5 intake was associated with a greater likelihood of obesity prevention in male adolescents. Another study in Japan (25) focused on the relationship between vitamin B5 and VFA, a persuasive predictor of CVD. One of the conclusions was that vitamin B5 was significantly inversely correlated with VFA. These associations between vitamin B5 and CHD risk factors may also help explain the association between vitamin B5 and CHD.

The correlation between B vitamin supplementation and its protective effect against CVD seems to be attributed to a decreased serum homocysteine (Hcy) concentration (28), which is harmful to the myocardium at a high level (36). However, no previous studies have directly investigated the relationship between vitamin B5 and Hcy or CHD. The mechanisms underlying this correlation are not well-established. The above-mentioned study was based on multivitamin supplements which contained vitamin B5. Therefore, the effect of reducing homocysteine may be the joint effect of multiple vitamins supplementation. We further examined the relationship between vitamin B5 and homocysteine, and the results showed that the two were not related. More qualified researches are needed to investigate the relationship of vitamin B5 and homocysteine.

We also observed a stronger correlation in smokers than non-smokers (p for interaction = 0.046). Smoking was related to the increasement of activation of neutrophil and macrophages (37). And vitamin B5 could reduce the recruitment or activation of macrophages (31), which could be an explanation of the interaction of smoking status and vitamin B5.

In order to make the characteristics between CHD cases and controls more differentiated, we included patients with severe coronary artery stenosis (>70% stenosis of the coronary arteries on coronary angiography) as CHD cases. In this way, we hoped to make the relationship between vitamin B5 and coronary heart disease more apparent and easier to discover. The clinical situations of these patients with elevated myocardial enzymes were more complex. These patients may have acute coronary syndrome, cardiomyopathy, or heart failure and the vitamin status could be affected (38, 39). So, we excluded these patients.

Our study findings have several strengths. Vitamin B5 was previously hardly considered to be associated with CHD and our study implied the potential correlations. This could provide us a new point of view to understand the mechanism of CHD. Our study was well-designed by including a relatively large number of patients with comprehensive clinical data, which made the results more credible.

A few limitations of this study require mentioning. First, this is a case–control study, and we can't get a causal relationship between vitamin B5 and CHD. Hence, further epidemiological studies and subsequent clinical trials should be conducted to examine the role of vitamin B5 in the development of CHD. Second, selection bias inevitably exists, although we used strict statistical matching of age, gender, and the date of the coronary angiography examination to minimize confounders and maximize comparability. Third, methodological biases exist. We could not include all the confounders in the regression models. But we looked through all the variables that we could get from the electrical medical records and include variables that could have an effect on vitamin B5 or CHD. Fourth, our study is limited by the lack of long-term observation of the plasma vitamin B5 concentration. Vitamin B5 was measured only once, and potential fluctuation was not taken into account. Fifth, we did not check the vitamin B5 intake in everyday diet, and this might cause the bias. Finally, the study was carried out in a hospital setting containing only Chinese men and women, the generalizability of the study should be assessed when it applies to other populations with different characteristics in future work.

Our findings, if further confirmed by future studies, offers a new venue for preventing or treating CHD, given that vitamin B5 supplementation is simple, safe, and inexpensive. According to NIH website (40), people can obtain pantothenic acid by eating a variety of foods, including beef, poultry, seafood, organ meats, eggs and milk, vegetables such as mushrooms (especially shiitakes), avocados, potatoes, and broccoli, whole grains, such as whole wheat, brown rice and oats, peanuts, sunflower seeds, and chickpeas. If the "L" shaped association is true, it also implies that finding a dose that is appropriate for a patient is needed.

Conclusion

In summary, this hospital-based case-control study showed a significant L-shaped relationship of the plasma vitamin B5 concentration with CHD, with a threshold around 40.95 ng/ml. The smoking status significantly modified this association, which was stronger in ever or currently smoking participants. Our findings provided a new idea for preventing or treating CHD and further studies are needed to confirm.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics review board of Peking University First Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JL and YZ designed the research and had primary responsibility for final content. ZL, JJ, BZ, and TY conducted the research. NZ provided the essential reagents. PS, FF, and YL analyzed the data and performed the statistical analysis. PS and HW wrote the manuscript. PC was responsible for the test of vitamin B5. All authors contributed to the article and approved the submitted version.

Funding

This research was funded by Projects of National Natural Science Foundation of China (grant 82070458), Capital's Funds for Health Improvement and Research (2020-2Z-40714), Beijing Municipal Science and Technology Project (Z191100006619039), Key Laboratory of Molecular Cardiovascular Sciences (Peking University), and the Ministry of Education and NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides.

Acknowledgments

The authors gratefully acknowledge all persons involved in this study, all researchers, and all participants enrolled.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.906232/full#supplementary-material

References

1. World Health Organization. *Global Health Estimates: Life Expectancy and Leading Causes of Death and Disability. The Top 10 Causes of Death*. (2020). Available online at: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed December 9, 2020).

2. Liu S, Li Y, Zeng X, Wang H, Yin P, Wang L, et al. Burden of cardiovascular diseases in China, 1990-2016: findings from the 2016 global burden of disease study. *JAMA Cardiol.* (2019) 4:342–52. doi: 10.1001/jamacardio.2019.0295

3. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. *Ann Intern Med.* (1961) 55:33–50. doi: 10.7326/0003-4819-55-1-33

4. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J.* (2012) 33:1635–701. doi: 10.1093/eurheartj/ehs092

5. Zhu N, Yu C, Guo Y, Bian Z, Han Y, Yang L, et al. Adherence to a healthy lifestyle and all-cause and cause-specific mortality in Chinese adults: a 10-year prospective study of 0.5 million people. *Int J Behav Nutr Phys Act.* (2019) 16:98. doi: 10.1186/s12966-019-0860-z

6. Lv J, Yu C, Guo Y, Bian Z, Yang L, Chen Y, et al. Adherence to healthy lifestyle and cardiovascular diseases in the Chinese population. *J Am Coll Cardiol.* (2017) 69:1116–25. doi: 10.1016/j.jacc.2016.11.076

7. Rodgers GP, Collins FS. Precision nutrition-the answer to "what to eat to stay healthy". *Jama.* (2020) 324:735–6. doi: 10.1001/jama.2020.13601

8. Gheita AA, Gheita TA, Kenawy SA. The potential role of B5: a stitch in time and switch in cytokine. *Phytother Res.* (2020) 34:306–14. doi: 10.1002/ptr.6537

9. Webb ME, Smith AG, Abell C. Biosynthesis of pantothenate. *Nat Prod Rep.* (2004) 21:695–721. doi: 10.1039/b316419p

10. Williams RJ, Lyman CM, Goodyear GH, Truesdail JH, Holaday D. Pantothenic acid," a growth determinant of universal biological occurrence. *J Am Chem Soc.* (1933) 55:2912–27. doi: 10.1021/ja01334a049

11. Wojtczak L, Slyshenkov VS. Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals–the role of glutathione. *Biofactors.* (2003) 17:61–73. doi: 10.1002/biof.5520170107

12. Said HM. Intestinal absorption of water-soluble vitamins in health and disease. *Biochem J.* (2011) 437:357–72. doi: 10.1042/BJ20110326

13. Tahiliani AG, Beinlich CJ. Pantothenic acid in health and disease. *Vitam Horm.* (1991) 46:165–228. doi: 10.1016/s0083-6729(08)60684-6

14. Gominak SC. Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a "pro-inflammatory" state associated with atherosclerosis and autoimmunity. *Med Hypotheses.* (2016) 94:103–7. doi: 10.1016/j.mehy.2016.07.007

15. Evans M, Rumberger JA, Azumano I, Napolitano JJ, Citrolo D, Kamiya T. Pantethine, a derivative of vitamin B5, favorably alters total, LDL and non-HDL cholesterol in low to moderate cardiovascular risk subjects eligible for statin

therapy: a triple-blinded placebo and diet-controlled investigation. *Vasc Health Risk Manag.* (2014) 10:89–100. doi: 10.2147/VHRM.S57116

16. Leonardi R, Jackowski S. Biosynthesis of pantothenic acid and coenzyme A. *EcoSal Plus.* (2007) 2:10.1128/ecosallus.3.6.3.4. doi: 10.1128/ecosalplus.3.6.3.4

17. Liu YT, Jia HM, Chang X, Ding G, Zhang HW, Zou ZM. The metabolic disturbances of isoproterenol induced myocardial infarction in rats based on a tissue targeted metabonomics. *Mol Biosyst.* (2013) 9:2823–34. doi: 10.1039/c3mb70222g

18. Carrara P, Matturri L, Galbussera M, Lovati MR, Franceschini G, Sirtori CR. Pantethine reduces plasma cholesterol and the severity of arterial lesions in experimental hypercholesterolemic rabbits. *Atherosclerosis.* (1984) 53:255–64. doi: 10.1016/0021-9150(84)90126-6

19. Houston MC, Fazio S, Chilton FH, Wise DE, Jones KB, Barringer TA, et al. Nonpharmacologic treatment of dyslipidemia. *Prog Cardiovasc Dis.* (2009) 52:61–94. doi: 10.1016/j.pcad.2009.02.002

20. Qian H, Zhang Y, Wu B, Wu S, You S, Zhang N, et al. Structure and function of HECT E3 ubiquitin ligases and their role in oxidative stress. *J Transl Int Med.* (2020) 8:71–9. doi: 10.2478/jtim-2020-0012

21. Pins JJ, Keenan JM. Dietary and nutraceutical options for managing the hypertriglyceridemic patient. *Prog Cardiovasc Nurs.* (2006) 21:89–93. doi: 10.1111/j.0889-7204.2006.01776.x

22. Houston M. The role of nutraceutical supplements in the treatment of dyslipidemia. *J Clin Hypertens (Greenwich)* (2012) 14:121–32. doi: 10.1111/j.1751-7176.2011.00576.x

23. Demirci B, Demir O, Dost T, Birincioglu M. Protective effect of vitamin B5 (dexpanthenol) on cardiovascular damage induced by streptozocin in rats. *Bratisl Lek Listy.* (2014) 115:190–6. doi: 10.4149/bll_2014_040

24. Gholamalizadeh M, Rastgoo S, Doaei S, Vahid F, Malmir H, Ashoori N, et al. Index of Nutritional Quality (INQ) and the risk of obesity in male adolescents: a case-control study. *Biol Trace Elem Res.* (2021) 199:1701–6. doi: 10.1007/s12011-020-02297-3

25. Ozato N, Saito S, Yamaguchi T, Katashima M, Tokuda I, Sawada K, et al. Association between nutrients and visceral fat in healthy Japanese adults: a 2-year longitudinal study brief title: micronutrients associated with visceral fat accumulation. *Nutrients.* (2019) 11:2698. doi: 10.3390/nu11112698

26. Koyanagi T, Hareyama S, Kikuchi R, Kimura T. Effect of diet on the pantothenic acid content in serum and on the incidence of hypertension among villagers. *Tohoku J Exp Med.* (1966) 88:93–7. doi: 10.1620/tjem.88.93

27. Schutte AE, van Rooyen JM, Huisman HW, Kruger HS, Malan NT, De Ridder JH. Dietary risk markers that contribute to the etiology of hypertension in black South African children: the THUSA BANA study. *J Hum Hypertens.* (2003) 17:29–35. doi: 10.1038/sj.jhh.1001508

28. Isakov VA, Bogdanova AA, Bessonov VV, Sentsova TB, Tutelyan VA, Lin Y, et al. Effects of multivitamin, multimineral and phytonutrient supplementation on nutrient status and biomarkers of heart health risk in a Russian population: a randomized, double blind, placebo controlled study. *Nutrients.* (2018) 10:120. doi: 10.3390/nu10020120

29. Jung S, Kim MK, Choi BY. The long-term relationship between dietary pantothenic acid (vitamin B(5)) intake and C-reactive protein concentration in adults aged 40 years and older. *Nutr Metab Cardiovasc Dis.* (2017) 27:806–16. doi: 10.1016/j.numecd.2017.05.008

30. Scheurig AC, Thorand B, Fischer B, Heier M, Koenig W. Association between the intake of vitamins and trace elements from supplements and C-reactive protein: results of the MONICA/KORA Augsburg study. *Eur J Clin Nutr.* (2008) 62:127–37. doi: 10.1038/sj.ejcn.1602687

31. He W, Hu S, Du X, Wen Q, Zhong XP, Zhou X, et al. Vitamin B5 reduces bacterial growth via regulating innate immunity and adaptive immunity in mice infected with *Mycobacterium tuberculosis*. *Front Immunol.* (2018) 9:365. doi: 10.3389/fimmu.2018.00365

32. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* (2019) 139:e1082–143. doi: 10.1016/j.jacc.2018.11.002

33. Stangl E. Relationship between pantothenic acid, adrenals, and hypertension. *Acta Med Scand Suppl.* (1956) 312:215–21. doi: 10.1111/j.0954-6820.1956.tb16978.x

34. Schwabedal PE, Pietrzik K, Wittkowski W. Pantothenic acid deficiency as a factor contributing to the development of hypertension. *Cardiology.* (1985) 72(Suppl 1):187–9. doi: 10.1159/000173972

35. Lewis LA, Page IH. Pantothenic acid deficiency in experimental renal hypertension in dogs. *Am J Physiol.* (1953) 173:359–63. doi: 10.1152/ajplegacy.1953.173.2.359

36. Kolling J, Scherer EB, Da CAA, Da CMJ, Wyse AT. Homocysteine induces oxidative-nitrative stress in heart of rats: prevention by folic acid. *Cardiovasc Toxicol.* (2011) 11:67–73. doi: 10.1007/s12012-010-9094-7

37. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol.* (2004) 43:1731–7. doi: 10.1016/j.jacc.2003.12.047

38. Angeline T, Jeyaraj N, Tsongalis GJ. MTHFR Gene polymorphisms, B-vitamins and hyperhomocystinemia in young and middle-aged acute myocardial infarction patients. *Exp Mol Pathol.* (2007) 82:227–33. doi: 10.1016/j.yexmp.2007.02.005

39. Azizi-Namini P, Ahmed M, Yan AT, Keith M. The role of B vitamins in the management of heart failure. *Nutr Clin Pract.* (2012) 27:363–74. doi: 10.1177/0884533612444539

40. National Institutes of Health. *Pantothenic Acid: Fact Sheet for Consumers.* (2021). Available online at: https://ods.od.nih.gov/factsheets/PantothenicAcid-Consumer/ (accessed March 22, 2021).

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fcvm.2022.1000554

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
Sri Harsha Patlolla,
Mayo Clinic, United States
Xi Fu,
ShengJing Hospital of China Medical University, China

*CORRESPONDENCE
Shujian Wei
weishujian@sdu.edu.cn
Yuguo Chen
chen919085@sdu.edu.cn

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 22 July 2022
ACCEPTED 06 October 2022
PUBLISHED 20 October 2022

CITATION
Han Y, Sun S, Qiao B, Liu H, Zhang C, Wang B, Wei S and Chen Y (2022) Timing of angiography and outcomes in patients with non-ST-segment elevation myocardial infarction: Insights from the evaluation and management of patients with acute chest pain in China registry. *Front. Cardiovasc. Med.* 9:1000554. doi: 10.3389/fcvm.2022.1000554

Timing of angiography and outcomes in patients with non-ST-segment elevation myocardial infarction: Insights from the evaluation and management of patients with acute chest pain in China registry

Yu Han[1,2,3,4], Shukun Sun[1,2,3,4], Bao Qiao[1,2,3,4], Han Liu[1,2,3,4], Chuanxin Zhang[1,2,3,4], Bailu Wang[5], Shujian Wei[1,2,3,4]* and Yuguo Chen[1,2,3,4]*

[1]Department of Emergency and Chest Pain Center, Qilu Hospital of Shandong University, Jinan, China, [2]Clinical Research Center for Emergency and Critical Care Medicine of Shandong Province, Qilu Hospital of Shandong University, Jinan, China, [3]Key Laboratory of Emergency and Critical Care Medicine of Shandong Province, Qilu Hospital of Shandong University, Jinan, China, [4]Key Laboratory of Cardiopulmonary-Cerebral Resuscitation Research of Shandong Province, Qilu Hospital of Shandong University, Jinan, China, [5]Clinical Trial Center, Qilu Hospital of Shandong University, Jinan, China

Objective: Although an invasive strategy has been recommended within 24 h for patients with non-ST-segment elevation myocardial infarction (NSTEMI), the optimal timing of the invasive strategy remains controversial. We sought to investigate the association between the different timings of invasive strategies and clinical outcomes in patients with NSTEMI.

Materials and methods: Patients admitted with NSTEMI from the Evaluation and Management of Patients with Acute ChesT pain in China (EMPACT) registry between January 2016 and September 2017 were included. The primary outcomes were major adverse cardiac events (MACEs) within 30 days. Multivariable logistic regression was performed to assess independent risk factors for MACEs.

Results: A total of 969 patients with NSTEMI from the EMPACT Registry were eligible for this study. Coronary angiography (CAG) was performed in 501 patients [<24 h, n = 150 (15.5%); ≥ 24 h, n = 351 (36.2%)]. The rate of MACEs at 30 days in all patients was 9.2%, including 54 (5.6%) deaths. Patients who underwent CAG had a lower rate of MACEs and mortality than those who did not receive CAG (MACEs: 5.6% vs. 13.0%, $P < 0.001$; mortality: 1.6% vs. 9.8%, $P < 0.001$). Nonetheless, no statistically significant difference was found in the rates of MACEs and mortality between the early (< 24 h) and delayed

(≥ 24 h) CAG groups. Older age (OR: 1.036, 95% CI: 1.007, 1.065, P = 0.014), and acute heart failure (OR: 2.431, 95% CI: 1.244, 4.749, P = 0.009) increased the risk of MACEs and protective factors were underwent CAG (OR: 0.427, 95% CI: 0.219, 0.832, P = 0.012) or PCI (OR: 0.376, 95% CI: 0.163, 0.868, P = 0.022). In the multilevel logistic regression, older age (OR: 0.944, 95% CI: 0.932, 0.957, $P < 0.001$), cardiogenic shock (OR: 0.233, 95% CI: 0.079, 0.629, P = 0.009), pulmonary moist rales (OR: 0.368, 95% CI: 0.197, 0.686, P = 0.002), and prior chronic kidney disease (OR: 0.070, 95% CI: 0.018, 0.273, $P < 0.001$) was negatively associated with CAG.

Conclusion: This real-world cohort study of NSTEMI patients confirmed that the early invasive strategy did not reduce the incidence of MACEs and mortality within 30 days compared with the delayed invasive strategy in NSTEMI patients.

KEYWORDS

non-ST-segment-elevation myocardial infarction, coronary angiography, percutaneous coronary intervention, major adverse cardiac events, mortality

Introduction

Acute myocardial infarction (AMI) has a significant worldwide health impact and is a leading cause of mortality and disability (1–3). Based on electrocardiogram (ECG) characteristics, AMI can be classified into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). The risk of recurrent cardiovascular events is higher in both STEMI and NSTEMI patients, but NSTEMI patients have higher long-term mortality and greater cardiovascular risk than STEMI patients (4, 5). Furthermore, the proportion of patients with NSTEMI has increased since the 1990s and NSTEMI has become the leading cause of emergency admissions for AMI patients in Europe, the USA, and China (6–10). NSTEMI patients are older and more often female than STEMI patients (11). In addition, the clinical manifestations of NSTEMI patients are diverse, ranging from asymptomatic patients to those with persistent myocardial ischemia, heart failure (HF), cardiogenic shock, and even cardiac arrest. Therefore, the management of NSTEMI is complicated. Recently, an early invasive strategy (within the first 24 h after hospital admission) was recommended for NSTEMI patients, but the optimal timing of the invasive strategy remains to be further explored (12).

Few studies have focused on the optimal timing of invasive strategies for the Chinese NSTEMI population. In the present study, we sought to investigate the association between the different timings of invasive strategies and clinical outcomes in NSTEMI patients using data from the Evaluation and Management of Patients with Acute ChesT pain in China (EMPACT) registry (13).

Materials and methods

Study population

The methods of the EMPACT registry (NCT02536677) have been previously described (13). In short, EMPACT was a multicenter prospective registry collecting the clinical characteristics and outcomes of emergency department (ED) patients experiencing acute chest pain and acute coronary syndrome (ACS)-related symptoms from 22 representative public hospitals in Shandong Province, China. Consecutive NSTEMI cases enrolled in the EMPACT registry from January 1, 2016, to September 30, 2017, were eligible for this study. The diagnosis of NSTEMI has been covered in extensive detail, including European and US clinical practice guidelines (12, 14). In short, cardiac troponin elevation with ischemic symptoms or ECG changes but without new persistent ST-segment elevation are defined as NSTEMI. Elevated troponin is defined as a measurement exceeding the 99th percentile of the upper reference limit. Eventually, 969 patients with NSTEMI were eligible for this study. The Ethics Committee of Qilu Hospital of Shandong University approved the study (No.2015-058), and all patients provided written informed consent.

Timing of angiography and percutaneous coronary intervention

For the present analysis, patients were categorized into 3 groups according to the time of their first coronary angiography (CAG) after admission: no, early (<24 h), or delayed (≥24 h)

CAG. Patients undergoing percutaneous coronary intervention (PCI) were categorized into 2 groups according to the time of their first PCI after admission: the early PCI group (<24 h), and the delayed PCI group (≥24 h).

Follow-up and definitions of outcomes

Follow-up began at discharge and lasted 30 days for outcome confirmation. The primary outcomes were major adverse cardiac events (MACEs) within 30 days, which is a composite of death from all causes, non-fatal myocardial infarction (MI), urgent revascularization, stroke, cardiac arrest, and cardiogenic shock.

Statistical analysis

Categorical variables were expressed as numbers (percentages) and compared by the chi-square test or Fisher's exact test as appropriate. Continuous variables were described as medians (interquartile ranges) and compared by the Mann-Whitney *U*-test.

To evaluate the relationship between the different timings of invasive strategies and the incidence of MACEs, we constructed univariable and multivariate logistic regression modes. Any variables having $P < 0.1$ in the univariate analyses were included in the multivariate regression analysis. Thus, multivariable models included the following variables: undergoing CAG, undergoing PCI, undergoing delayed CAG, undergoing delayed PCI, older age, body mass index (BMI), acute heart failure (HF), systolic blood pressure, cardiogenic shock, diabetes, prior HF, prior stroke, and pulmonary moist rales. Secondary analyses examined the associations between the different timings of invasive strategies and MACEs within prespecified subgroups. Subgroups were selected to focus on the types of patients expected to benefit (or harm) from the early invasive strategy, including age (< 75 years or ≥ 75 years), sex, and the presence of heart failure.

Factors associated with CAG occurrence were assessed by a multiple logistic regression initially including all the variables having $P < 0.1$ in the univariate analyses and then we applied a stepwise backward selection of the variables which remained significant ($P < 0.05$). The following variables were included in the multivariate model: older age, cardiogenic shock, pulmonary moist rales, and prior CKD. Sensitivity analyses were performed to test the stability of results by removing patients with cardiogenic shock, and patients with cardiogenic shock and prior CKD.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, US). Two-sided *P*-values < 0.05 were considered statistically significant.

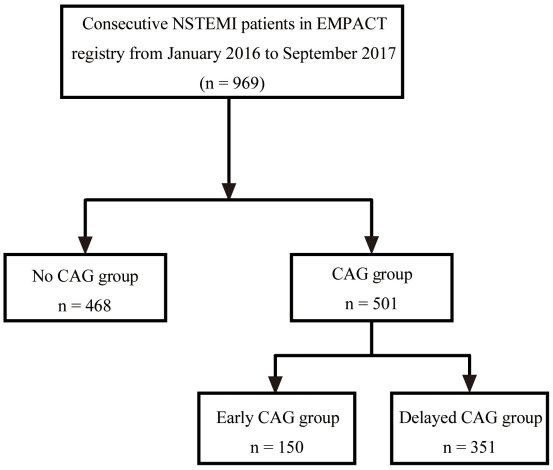


FIGURE 1
Flow diagram of patient selection. AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infarction; CAG, coronary angiography.

Results

Baseline characteristics

A total of 969 NSTEMI patients were eligible from the EMPACT registry according to inclusion and exclusion criteria (**Figure 1**). 150 NSTEMI patients (15.5%) underwent early CAG and 351 NSTEMI patients (36.2%) received delayed CAG (**Supplementary Table 1**). 332 NSTEMI patients (34.3%) underwent PCI. Among them, 103 underwent early PCI and 229 underwent delayed PCI (**Supplementary Table 2**). **Table 1** shows the clinical characteristics of NSTEMI patients. 355 (36.6%) patients were females. The mean age was 67 years old, and 28% of patients were current smokers. Comorbidities of diabetes, hypertension, and hyperlipidemia accounted for 25.5, 60.1, and 9.5% of all patients, respectively. On admission, the mean blood pressure was 146/86 mm Hg and the mean heart rate was 79 beats/min. Of all patients, 12.7% experienced acute HF, and 2.3% experienced cardiogenic shock. Patients who did not undergo CAG were more likely to be female (42.5% vs. 31.1%, $P < 0.001$) and older (71.5 years old vs. 64 years old, $P < 0.001$).

Emergency medication

Aspirin, adenosine diphosphate (ADP) receptor antagonists, and Low molecular weight heparins were given in 49.7, 41.5, and 27.2% of all NSTEMI patients, respectively. NSTEMI patients who did not receive CAG were less likely to receive aspirin (46.8% vs. 52.5%, $P = 0.076$), ADP receptor antagonist (35.9%

TABLE 1 Baseline clinical characteristics for NSTEMI patients.

	All (n = 969)	NO CAG (n = 468)	CAG (n = 501)	P-value
Demographic				
Female sex, *n* (%)	355 (36.6)	199 (42.5)	156 (31.1)	<0.001
Age, mean (*SD*), y	67 (60, 76)	71.5 (63, 80)	64 (55, 71)	<0.001
BMI (*SD*), kg/m^2	24.7 (22.9, 26.9)	24.3 (22.5, 26.3)	25.1 (23.2, 27.3)	<0.001
Current smoker	271 (28.0)	105 (22.4)	166 (33.1)	<0.001
Medical history, *n* (%)				
premature CHD family history	105 (10.8)	38 (8.1)	67 (13.4)	0.009
Prior MI	203 (20.9)	122 (26.1)	81 (16.2)	<0.001
Prior PCI	116 (12.0)	51 (10.9)	65 (13.0)	0.320
Prior CABG	32 (3.3)	22 (4.7)	10 (2.0)	0.019
Diabetes	247 (25.5)	135 (28.8)	112 (22.4)	0.021
Hypertension	582 (60.1)	278 (59.4)	304 (60.7)	0.685
Hyperlipidemia	92 (9.5)	41 (8.8)	51 (10.2)	0.451
Prior HF	35 (3.6)	27 (5.8)	8 (1.6)	0.001
Prior CKD	24 (2.5)	21 (4.5)	3 (0.6)	<0.001
Chronic lung disease	43 (4.4)	31 (6.6)	12 (2.4)	0.001
Peripheral arterial disease	5 (0.5)	5 (1.1)	0 (0)	0.026
Prior stroke	125 (12.9)	79 (16.9)	46 (9.2)	<0.001
On presentation				
Systolic blood pressure (mm Hg), mean (*SD*)	146 (126, 165)	143 (125, 163.5)	148 (127, 166)	0.063
Diastolic blood pressure (mm Hg), mean (*SD*)	86 (74, 98.5)	82 (71, 95.5)	88 (76, 100)	<0.001
Heart rate (beats/min), mean (*SD*)	79 (68, 93)	81 (70, 96)	77 (66, 89)	<0.001
Cardiogenic shock, *n* (%)	22 (2.3)	17 (3.6)	5 (1.0)	0.006
HF, *n* (%)	123 (12.7)	69 (14.7)	54 (10.8)	0.064
Abnormal heart auscultation, *n* (%)	101 (10.4)	62 (13.2)	39 (7.8)	0.005
Pulmonary moist rales, *n* (%)	71 (7.3)	56 (12.0)	15 (3.0)	<0.001
Lower extremity edema, *n* (%)	47 (4.9)	32 (6.8)	15 (3.0)	0.005
Biochemical indices were positive, *n* (%)				
D-dimer	125 (33.4)	85 (49.7)	40 (19.7)	<0.001
BNP	112 (45.0)	59 (49.6)	53 (40.8)	0.163

NSTEMI, non-ST segment elevation myocardial infarction; CAG, coronary angiography; BMI, body mass index; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HF, heart failure; CKD, chronic kidney disease; BNP, brain sodium peptide.

vs. 46.7%, $P = 0.001$), and low molecular weight heparin (22.9% vs. 31.3%, $P = 0.003$) than NSTEMI patients who received CAG. NSTEMI patients who underwent CAG were more likely to receive statins (34.1% vs. 23.9%, $P < 0.001$), nitrate esters (51.1% vs. 48.7%, $P = 0.459$), and Chinese patent drugs (38.5% vs. 31.8%, $P = 0.030$) than NSTEMI patients who did not undergo CAG (Table 2).

Thirty-days outcomes

The rate of MACEs in all patients was 9.2%, including 54 (5.6%) deaths (Table 3). Patients who underwent CAG had a lower rate of MACEs and mortality than those who did not receive CAG (MACEs: 5.6% vs. 13%, $P < 0.001$; mortality: 1.6% vs. 9.8%, $P < 0.001$). However, there was no statistically significant difference in the rates of MACEs and mortality between the early and delayed CAG groups (MACEs: 6.7% vs. 5.1%, $P = 0.492$; mortality: 2.0% vs. 1.4%, $P = 0.701$). Moreover, when 30-day outcomes were compared among patients who received PCI at different times, there were no statistically significant differences either (Supplementary Table 3). There were also no statistically significant differences in the rates of MACEs of NSTEMI patients undergoing early CAG vs. delayed CAG when subgroup analysis was performed according to age, sex, or the presence of HF (Supplementary Table 4).

Bleeding and procedural complications

Bleeding complications were shown in Supplementary Table 5. There was no statistically significant difference in

TABLE 2 Emergency medication for NSTEMI patients in the EDs.

	ALL (n = 969)	NO CAG (n = 468)	CAG				*P*-value (yes vs. no)
			Total (n = 501)	Early CAG (n = 150)	Delayed CAG (n = 351)	*P*-value (Early vs. delayed)	
Aspirin, *n* %	482 (49.7)	219 (46.8)	263 (52.5)	77 (51.3)	186 (53.0)	0.734	0.076
ADP receptor Antagonists, *n* %	402 (41.5)	168 (35.9)	234 (46.7)	72 (48)	162 (46.2)	0.704	0.001
Statins, *n* %	283 (29.2)	112 (23.9)	171 (34.1)	46 (30.7)	125 (35.6)	0.285	<0.001
Nitrate esters, *n* %	484 (49.9)	228 (48.7)	256 (51.1)	69 (46.0)	187 (53.3)	0.136	0.459
LMWH, *n* %	264 (27.2)	107 (22.9)	157 (31.3)	19 (12.7)	138 (39.3)	<0.001	0.003
Chinese patent drug, *n* %	342 (35.3)	149 (31.8)	193 (38.5)	34 (22.7)	159 (45.3)	<0.001	0.030

NSTEMI, non-ST segment elevation myocardial infarction; EDs, emergency departments; CAG, coronary angiography; ADP, adenosine diphosphate; LMWH, low molecular weight heparin.

TABLE 3 30 days outcomes of patients with NSTEMI undergoing CAG.

	ALL (n = 969)	NO CAG (n = 468)	CAG				*P*-value (yes vs. no)
			Total (n = 501)	Early CAG (n = 150)	Delayed CAG (n = 351)	*P*-value (Early vs. delayed)	
All, *n* %	89 (9.2)	61 (13.0)	28 (5.6)	10 (6.7)	18 (5.1)	0.492	<0.001
Death, *n* %	54 (5.6)	46 (9.8)	8 (1.6)	3 (2)	5 (1.4)	0.701	<0.001
Myocardial infarction, *n* %	9 (0.9)	3 (0.6)	6 (1.2)	1 (0.7)	5 (1.4)	0.674	0.508
Emergency revascularization, *n* %	2 (0.2)	0 (0)	2 (0.4)	1 (0.7)	1 (0.3)	0.510	0.500
Cardiogenic shock, *n* %	33 (3.4)	21 (4.5)	12 (2.4)	5 (3.3)	7 (2.0)	0.356	0.073
Cardiac arrest/ventricular Fibrillation, *n* %	36 (3.7)	28 (6)	8 (1.6)	5 (3.3)	3 (0.9)	0.056	<0.001
Stroke, *n* %	10 (1.0)	4 (0.9)	6 (1.2)	2 (1.3)	4 (1.1)	1.000	0.754

NSTEMI, Non-ST segment elevation myocardial infarction; CAG, coronary angiography.

the rates of bleeding complications between the early and delayed CAG groups (11.3% vs. 6.8%, P = 0.109). Moreover, no statistically significant difference was found in the rates of procedural complications between the early and delayed PCI groups (14.6% vs. 10.5%, P = 0.357) (**Supplementary Table 6**).

Independent predictors of the rate of major adverse cardiac events in patients with non-ST-segment elevation myocardial infarction

Table 4 and **Figure 2** show the logistic regression model with the odds ratio (OR) and 95% confidence interval (CI) of the predictors of the rate of MACEs. Older age (OR: 1.036, 95% CI: 1.007, 1.065, P = 0.014) and acute HF (OR: 2.431, 95% CI: 1.244, 4.749, P = 0.009) increased the risk of MACEs and protective factors were associated with CAG (OR: 0.427, 95% CI: 0.219, 0.832, P = 0.012) or PCI (OR: 0.376, 95% CI: 0.163, 0.868, P = 0.022). The timing of undergoing CAG (OR: 0.923, 95% CI: 0.271, 3.149, P = 0.899) or PCI (OR: 0.817, 95% CI: 0.138, 4.833, P = 0.823), BMI (OR: 0.938, 95% CI: 0.859, 1.025, P = 0.159), cardiogenic shock (OR: 2.273, 95% CI: 0.605, 8.535, P = 0.224), diabetes (OR: 1.610, 95% CI: 0.890, 2.916, P = 0.116), prior HF (OR: 1.036, 95% CI: 0.348, 3.086, P = 0.949), prior stroke (OR: 1.389, 95% CI: 0.707, 2.731, P = 0.304), and pulmonary moist rales (OR: 1.460, 95% CI: 0.670, 3.181, P = 0.341) are not independent influences on the rate of MACEs.

Independent predictors of undergoing coronary angiography in patients with non-ST-segment elevation myocardial infarction

Table 5 and **Figure 3** show the logistic regression model with OR (95% CI) of the predictors of undergoing CAG. Older age (OR: 0.944, 95% CI: 0.932, 0.957, P < 0.001), cardiogenic shock (OR: 0.233, 95% CI: 0.079, 0.629, P = 0.009), pulmonary moist rales (OR: 0.368, 95% CI: 0.197, 0.686, P = 0.002), and prior CKD (OR: 0.070, 95% CI: 0.018, 0.273, P < 0.001) were negatively associated with CAG. The OR value of the variables in the three

TABLE 4 Univariate analysis of the rate of MACEs of NSTEMI patients.

Variables	OR	95% CI	*P*-value
CAG	0.246	0.134, 0.452	<0.001
Age	1.062	1.035, 1.088	<0.001
Sex	1.518	0.908, 2.536	0.112
Current smoker	0.588	0.308, 1.120	0.106
BMI	0.898	0.827, 0.976	0.012
Heart rate	1.001	0.990, 1.012	0.823
Systolic blood pressure	0.985	0.976, 0.993	<0.001
Diastolic blood pressure	0.976	0.963, 0.990	0.001
Cardiogenic shock	7.425	2.910, 18.95	<0.001
Abnormal heart auscultation	1.272	0.588, 2.752	0.542
Acute HF	3.626	2.053, 6.404	<0.001
Pulmonary moist rales	3.378	1.708, 6.681	<0.001
Lower extremity edema	0.980	0.296, 3.247	0.973
Prior CABG	1.512	0.448, 5.107	0.506
Prior CKD	2.108	0.611, 7.265	0.238
Chronic lung disease	0.332	0.045, 2.451	0.280
Diabetes	1.885	1.109, 3.204	0.019
Prior HF	2.517	0.942, 6.730	0.066
premature CHD family history	0.695	0.272, 1.773	0.446
Prior MI	1.559	0.882, 2.757	0.127
Prior stroke	2.490	1.364, 4.544	0.003

NSTEMI, non-ST segment elevation myocardial infarction; MACEs, major adverse cardiac events; OR, odds ratio; CI, confidence interval; CAG, coronary angiography; BMI, body mass index; HF, heart failure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MI, myocardial infarction.

models did not change significantly, confirming the stability of the logistic regression model.

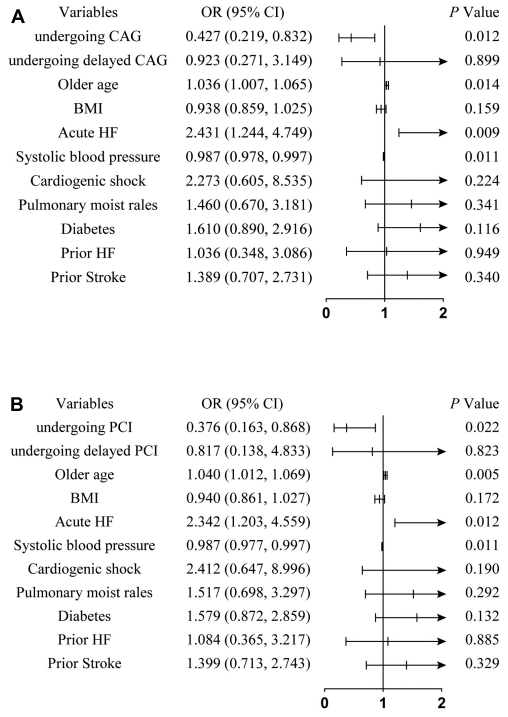


FIGURE 2
Forest plot of odds ratio for the rate of MACEs of NSTEMI patients. **(A)** Represents the independent effects of undergoing CAG on the incidence of MACEs; **(B)** represents the independent effects of undergoing PCI on the incidence of MACEs. NSTEMI, non-ST segment elevation myocardial infarction; MACEs, major adverse cardiac events; OR, odds ratio; CI, conference interval; CAG, coronary angiography; HF, heart failure; BMI, body mass index; PCI, percutaneous coronary intervention.

Discussion

Based on the EMPACT registry, the present study revealed that undergoing CAG or PCI was beneficial in improving the short-term prognosis (30 days) of patients with NSTEMI, while the timing of undergoing CAG or PCI was not associated with the rate of MACEs.

Several randomized, controlled trials (RCTs) have addressed the optimal timing of invasive strategies for NSTEMI patients. Both TIMACS (Timing of Intervention in Acute Coronary Syndromes) and VERDICT (Very Early vs. Deferred Invasive Evaluation Using Computerized Tomography) trials confirmed that an early invasive strategy improved clinical outcomes in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients with a GRACE score > 140 (15, 16). Based on the above evidence, the European society of cardiology (ESC) guideline recommends invasive treatment within 24 h for NSTEMI patients (12). The present study did not specifically focus on the GRACE risk score of NSTEMI patients, but it assessed the association between the timing of invasive strategies and clinical outcomes in unselected NSTEMI cohorts. The results showed that an early invasive strategy did not reduce the incidence of MACEs or mortality within 30 days compared with delayed invasive strategies. A meta-analysis including 10 trials from 2003 to 2016 has compared early (0.5–14 h) and delayed (18.3–86 h) strategies in 6,397 NSTEMI patients with moderate or high risk (17). Similarly, there was no difference in terms of mortality (4.0% vs. 4.7%; OR: 0.85; 95% CI: 0.67–1.09; P = 0.20) or MI (6.7% vs. 7.7%; OR: 0.88; 95% CI: 0.53–1.45; P = 0.62) (17). However, another meta-analysis including 14 RCTs (9,637 patients) showed that the early invasive strategy was associated with a lower incidence of MACEs than the delayed invasive strategy (RR: 0.65; 95% CI: 0.49, 0.87; P = 0.003) (18). Contradictory results were obtained from our and previous studies. The timing of intervention, outcome indicators, and follow-up time varied between studies. The diagnosis and prognosis of NSTEMI have been improved considerably in recent years with the introduction of high-sensitivity troponin, the use of second-generation drug-eluting stents, and advancements in P2Y12 inhibitors (19–21). The results of some trials were based on previous generation stents and antithrombotic therapy, rendering comparisons between studies difficult. Therefore, it is necessary to further explore the optimal timing of invasive treatment for patients with

TABLE 5 Univariate analysis of whether NSTEMI patients undergo CAG.

Variables	OR	95% CI	*P*-value
Age	0.944	0.933, 0.956	<0.001
Sex	0.611	0.470, 0.795	<0.001
Current smoker	1.713	1.287, 2.280	<0.001
BMI	1.078	1.036, 1.123	<0.001
Heart rate	0.987	0.982, 0.993	<0.001
Systolic blood pressure	1.004	0.999, 1.008	0.099
Diastolic blood pressure	1.012	1.005, 1.020	0.001
Cardiogenic shock	0.267	0.098, 0.731	0.010
Abnormal heart auscultation	0.553	0.362, 0.843	0.006
Acute HF	0.699	0.477, 1.022	0.065
Pulmonary moist rales	0.227	0.127, 0.407	<0.001
Lower extremity edema	0.421	0.225, 0.787	0.007
Prior CABG	0.413	0.193, 0.882	0.022
Prior CKD	0.128	0.038, 0.433	0.001
Chronic lung disease	0.346	0.176, 0.682	0.002
Diabetes	0.710	0.531, 0.949	0.021
Prior HF	0.265	0.119, 0.589	0.001
premature CHD family history	1.747	1.148, 2.658	0.009
Prior MI	0.547	0.399, 0.749	<0.001
Prior stroke	0.498	0.338, 0.734	<0.001

NSTEMI, non-ST segment elevation myocardial infarction; CAG, coronary angiography; OR, odds ratio; CI, confidence interval; BMI, body mass index; HF, heart failure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MI, myocardial infarction.

NSTEMI by designing more refined randomized controlled trials in the future.

The OPERA registry reported that HF and age were predictors of 1-year mortality in NSTEMI patients (22). Similarly, the present study showed that older age and acute HF increased the risk of 30-day MACEs. Park et al. reported that diabetes, major bleeding, multivessel disease, post-TIMI flow, Killip class, and left ventricular dysfunction were independently associated with the risk of cardiac mortality (within 30 days) in NSTEMI patients (23). In our study, however, diabetes was not an independent influence on the incidence of MACEs. We did not assess multivessel disease, post-PCI TIMI flow, Killip class, and left ventricular dysfunction in our analysis because related information was not available in the registry. These variables may have an impact on clinical outcomes. Thus, well-designed investigations with other variables should be conducted to corroborate the findings of this study.

In this study, only 51.7% of NSTEMI patients underwent CAG, which is lower than that in France (95.0%), Germany (60.2%), and the US (58.0%) (11, 24, 25). This rate was even lower than the rate of revascularization (58.2%) reported in the Improving CCC Project in Chinese NSTE-ACS patients (26). Previous studies have indicated that the invasive treatment of NSTEMI patients is far from standardized in China (26, 27). Therefore, it is necessary to explore the causes to provide opportunities for improvement. Further analysis demonstrated that older age, cardiogenic shock, pulmonary moist rales, and prior CKD were associated with CAG. The treatment strategy for older patients with NSTEMI can be challenging for clinicians since they are more likely to have atypical symptoms than younger patients (28). A meta-analysis including 3 RCTs with 5-year outcomes showed that patients older than 75 years old benefited from the invasive strategy, while data for patients older than 80 years old were not available (29). Another RCT determined that the invasive strategy was superior to the

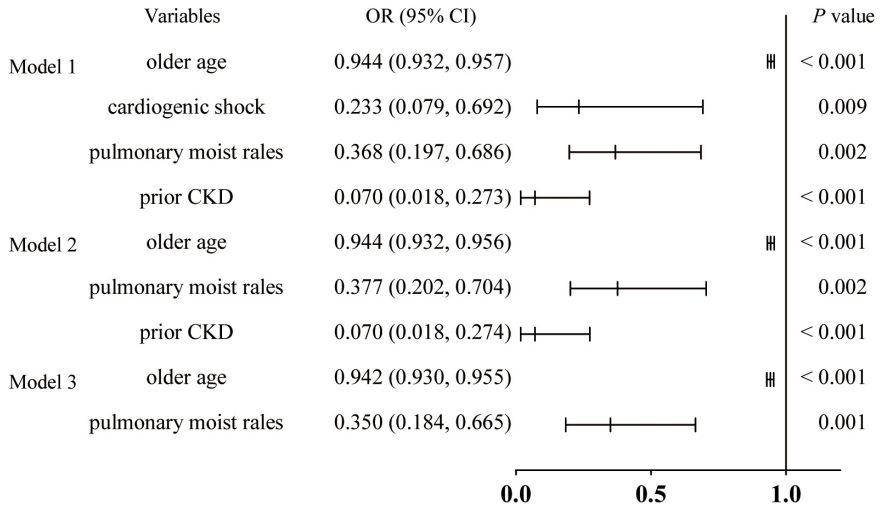


FIGURE 3
Forest plot of odds ratio for risk factors of undergoing CAG. Model 1, all patients; Model 2, remove patients with cardiogenic shock; and Model 3, remove patients with cardiogenic shock and CKD; NSTEMI, non-ST segment elevation myocardial infarction; CAG, coronary angiography; OR, odds ratio; CI, conference interval; CKD, chronic kidney disease.

conservative strategy in reducing combined events in NSTEMI patients older than 80 years old. Moreover, there was no difference between the two strategies in terms of bleeding complications (30). Thus, early invasive treatment represents a safe strategy for the majority of elderly NSTEMI patients.

Current guidelines recommend that NSTEMI patients with CKD undergo appropriate invasive treatment, except for those with advanced CKD (12, 14). However, a smaller proportion of CKD patients underwent invasive treatment, due to previous studies that have shown that NSTEMI patients with CKD or a low glomerular filtration rate were at high risk for surgical complications such as bleeding events, acute kidney injury, and death (31, 32). A study including 12,821 (mean age 86 years old) NSTEMI patients demonstrated that patients undergoing PCI had a significantly lower risk of death than those treated conservatively during the follow-up period (3.2 years), and this finding held in all stages of CKD (33). Therefore, CKD should not be a reason to avoid revascularization for NSTEMI patients.

NSTEMI patients with HF are less likely to receive CAG or PCI than non-HF patients and they have a higher risk of death at 30 days (34). Steg et al. demonstrated a reduction in post-discharge mortality in NSTEMI patients with HF who received invasive therapy, indicating the possibility of widespread use of invasive treatment in this high-risk population (35). Cardiogenic shock is a life-threatening complication in NSTEMI patients (36). In this study, 2.3% of the patients presented with cardiogenic shock. Regardless of the ECG presentation, guidelines recommend early invasive treatment in hemodynamically unstable patients (12, 14). A report from the SHOCK trial showed that approximately two-thirds of NSTEMI patients with cardiogenic shock had triple-vessel lesions (37). Omer et al. explored the clinical outcomes of multivessel vs. culprit vessel-only PCI in NSTEMI patients with multivessel disease and cardiogenic shock (38). The findings indicated that multivessel PCI reduced all-cause in-hospital mortality while leading to more procedural complications (38). The risks associated with perioperative complications could outweigh the benefits of the invasive treatment under some conditions. Therefore, clinicians must consider the patient's comorbidities, life expectancy, and bleeding risk and consequently recognize those patients who might not benefit from the early invasive treatment.

Limitations

Several limitations of the present study are as follows. First, as a retrospective study, it only revealed important correlations and could not prove causality. Second, the present study only provided real-world data for the outcomes of NSTEMI patients who underwent invasive treatment at different times. Further studies integrating propensity matching or risk adjustment and randomized prospective controlled studies are necessary to assess whether the prognosis of NSTEMI patients is better with an early invasive strategy than with a delayed invasive strategy. Third, although we performed multivariate logistic regression analysis to overcome the limitations of this retrospective study, the results were still affected by unobserved confounding factors, such as variables that were not included in the registry.

Conclusion

This real-world cohort study of NSTEMI patients supported that an early invasive strategy did not reduce the incidence of MACEs or mortality within 30 days compared with the delayed invasive strategy in NSTEMI patients.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YH and SW made substantial contributions to the conception of the study. YH, SS, and SW contributed to the design of the work. YH, HL, BW, and SS made substantial contributions to the acquisition and analysis of the data and the interpretation of data. BQ, CZ, and SW drafted the work. SW, YC, and YH revised and edited the draft. All authors approved the submitted version and have agreed to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, were appropriately investigated, resolved, and the resolution documented in the literature, read, and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (82072141), Natural Science Foundation of Shandong Province (ZR2020MH030), and the Clinical Research Foundation of Shandong University (2020SDUCRCC014).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1000554/full#supplementary-material

References

1. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J.* (2011) 32:2999–3054. doi: 10.1093/eurheartj/ehr236

2. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr., et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation.* (2013) 127:e663–828. doi: 10.1161/CIR.0b013e31828478ac

3. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* (2012) 33:2569–619. doi: 10.1093/eurheartj/ehs215

4. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation.* (2009) 119:3110–7. doi: 10.1161/CIRCULATIONAHA.108.799981

5. Vora AN, Wang TY, Hellkamp AS, Thomas L, Henry TD, Goyal A, et al. Differences in short- and long-term outcomes among older patients with ST-elevation versus non-ST-elevation myocardial infarction with angiographically proven coronary artery disease. *Circ Cardiovasc Qual Outcomes.* (2016) 9:513–22. doi: 10.1161/CIRCOUTCOMES.115.002312

6. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med.* (2010) 362:2155–65. doi: 10.1056/NEJMoa0908610

7. Chung SC, Gedeborg R, Nicholas O, James S, Jeppsson A, Wolfe C, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet.* (2014) 383:1305–12. doi: 10.1016/S0140-6736(13)62070-X

8. Jortveit J, Govatsmark RE, Digre TA, Risøe C, Hole T, Mannsverk J, et al. Myocardial infarction in norway in 2013. *Tidsskr Nor Laegeforen.* (2014) 134:1841–6. doi: 10.4045/tidsskr.14.0804

9. Barrabés JA, Bardají A, Jiménez-Candil J, del Nogal Sáez F, Bodí V, Basterra N, et al. Prognosis and management of acute coronary syndrome in Spain in 2012: the DIOCLES study. *Rev Esp Cardiol* (2015) 68:98–106. doi: 10.1016/j.rec.2014.03.010

10. Zhang Q, Zhao D, Xie W. Recent trends in hospitalization for acute myocardial infarction in Beijing: increasing overall burden and a transition from ST-segment elevation to non-ST-segment elevation myocardial infarction in a population-based study. *Medicine.* (2016) 95:e2677. doi: 10.1097/MD.0000000000002677

11. Neumann JT, Goßling A, Sörensen NA, Blankenberg S, Magnussen C, Westermann D. Temporal trends in incidence and outcome of acute coronary syndrome. *Clin Res Cardiol.* (2020) 109:1186–92. doi: 10.1007/s00392-020-01612-1

12. Collet JP, Thiele H, Barbato E. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* (2021) 42:1289–367.

13. Zheng W, Wang J, Xu F, Zheng J, Zhang H, Ma J, et al. Evaluation and management of patients with acute chest pain in China (EMPACT): protocol for a prospective, multicentre registry study. *BMJ Open.* (2018) 8:e017872. doi: 10.1136/bmjopen-2017-017872

14. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr., Ganiats TG, Holmes DR Jr., et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation.* (2014) 130:e344–426. doi: 10.1161/CIR.0000000000000134

15. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation.* (2018) 138:2741–50. doi: 10.1161/CIRCULATIONAHA.118.037152

16. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med.* (2009) 360:2165–75. doi: 10.1056/NEJMoa0807986

17. Bonello L, Laine M, Puymirat E, Lemesle G, Thuny F, Paganelli F, et al. Timing of coronary invasive strategy in non-st-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. *JACC Cardiovasc Interv.* (2016) 9:2267–76. doi: 10.1016/j.jcin.2016.09.017

18. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Chahine A, Haykal T, et al. Meta-analysis of optimal timing of coronary intervention in non-ST-elevation acute coronary syndrome. *Catheter Cardiovasc Interv.* (2020) 95:185–93. doi: 10.1002/ccd.28280

19. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *J Am Coll Cardiol.* (2022) 79:e21. doi: 10.1016/j.jacc.2021.09.006

20. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical outcomes for prasugrel versus clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction: an analysis from the TRITON-TIMI 38 trial. *Eur Heart J Acute Cardiovasc Care.* (2014) 3:363–72. doi: 10.1177/2048872614534078

21. Thygesen K, Alpert JS, Jaffe AS. Fourth universal definition of myocardial infarction. *J Am Coll Cardiol.* (2018) 72:2231–64.

22. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J.* (2007) 28:1409–17. doi: 10.1093/eurheartj/ehm031

23. Park HW, Yoon CH, Kang SH, Choi DJ, Kim HS, Cho MC, et al. Early- and late-term clinical outcome and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. *Int J Cardiol.* (2013) 169:254–61. doi: 10.1016/j.ijcard.2013.08.132

24. Malta Hansen C, Wang TY, Chen AY, Chiswell K, Bhatt DL, Enriquez JR, et al. Contemporary patterns of early coronary angiography use in patients with non-ST-Segment elevation myocardial infarction in the united states: insights from the national cardiovascular data registry acute coronary treatment and intervention outcomes network registry. *JACC Cardiovasc Interv.* (2018) 11:369–80. doi: 10.1016/j.jcin.2017.12.016

25. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (french registry

of acute ST-elevation or non-ST-elevation myocardial infarction) 1995 to 2015. *Circulation.* (2017) 136:1908–19. doi: 10.1161/CIRCULATIONAHA.117.030798

26. Yang Q, Wang Y, Liu J. Invasive management strategies and antithrombotic treatments in patients with non-ST-segment-elevation acute coronary syndrome in china: findings from the improving CCC project (care for cardiovascular disease in China). *Circ Cardiovasc Interv.* (2017) 10:6.

27. Leng W, Yang J, Fan X, Sun Y, Xu H, Gao X, et al. Contemporary invasive management and in-hospital outcomes of patients with non-st-segment elevation myocardial infarction in china: findings from china acute myocardial infarction (CAMI) registry. *Am Heart J.* (2019) 215:1–11. doi: 10.1016/j.ahj.2019.05.015

28. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the global registry of acute coronary events. *Chest.* (2004) 126:461–9. doi: 10.1378/chest.126.2.461

29. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol.* (2010) 55:2435–45. doi: 10.1016/j.jacc.2010.03.007

30. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (after eighty study): an open-label randomised controlled trial. *Lancet.* (2016) 387:1057–65. doi: 10.1016/S0140-6736(15)01166-6

31. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA.* (2013) 309:1022–9. doi: 10.1001/jama.2013.1556

32. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* (2004) 351:1296–305. doi: 10.1056/NEJMoa041031

33. Holzmann MJ, Siddiqui AJ. Outcome of percutaneous coronary intervention during non-ST-segment-elevation myocardial infarction in elderly patients with chronic kidney disease. *J Am Heart Assoc.* (2020) 9:e015084. doi: 10.1161/JAHA.119.015084

34. Bahit MC, Lopes RD, Clare RM, Newby LK, Pieper KS, Van de Werf F, et al. Heart failure complicating non-ST-segment elevation acute coronary syndrome: timing, predictors, and clinical outcomes. *JACC Heart Fail.* (2013) 1:223–9. doi: 10.1016/j.jchf.2013.02.007

35. Steg PG, Kerner A, Van de Werf F, López-Sendón J, Gore JM, Fitzgerald G, et al. Impact of in-hospital revascularization on survival in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. *Circulation.* (2008) 118:1163–71. doi: 10.1161/CIRCULATIONAHA.108.789685

36. Anderson ML, Peterson ED, Peng SA, Wang TY, Ohman EM, Bhatt DL, et al. Differences in the profile, treatment, and prognosis of patients with cardiogenic shock by myocardial infarction classification: a report from NCDR. *Circ Cardiovasc Quality Outcomes.* (2013) 6:708–15. doi: 10.1161/CIRCOUTCOMES.113.000262

37. Jacobs AK, French JK, Col J, Sleeper LA, Slater JN, Carnendran L, et al. Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK trial registry. Should we emergently revascularize occluded coronaries for cardiogenic shock. *J Am Coll Cardiol.* (2000) 36:1091–6. doi: 10.1016/s0735-1097(00)00888-3

38. Omer MA, Brilakis ES, Kennedy KF, Alkhouli M, Elgendy IY, Chan PS, et al. Multivessel versus culprit-vessel percutaneous coronary intervention in patients with non-ST-segment elevation myocardial infarction and cardiogenic shock. *JACC Cardiovasc Interv.* (2021) 14:1067–78. doi: 10.1016/j.jcin.2021.02.021

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 31 October 2022
DOI 10.3389/fcvm.2022.1022415

OPEN ACCESS

EDITED BY
Dobrin Vassilev,
University of Ruse, Bulgaria

REVIEWED BY
ELisabetta Ricottini,
Campus Bio-Medico University, Italy
Marco Zuin,
University Hospital of Ferrara, Italy

*CORRESPONDENCE
Konstantin Schwarz
konstantin.schwarz@stpoelten.lknoe.at

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 18 August 2022
ACCEPTED 26 September 2022
PUBLISHED 31 October 2022

CITATION
Will M, Weiss TW, Weber M, Kwok CS, Borovac JA, Lamm G, Unterdechler M, Aufhauser S, Nolan J, Mascherbauer J and Schwarz K (2022) Left vs. right radial approach for coronary catheterization: Relation to age and severe aortic stenosis. *Front. Cardiovasc. Med.* 9:1022415. doi: 10.3389/fcvm.2022.1022415

Left vs. right radial approach for coronary catheterization: Relation to age and severe aortic stenosis

Maximilian Will[1,2], Thomas W. Weiss[2,3], Michael Weber[4], Chun Shing Kwok[5,6], Josip A. Borovac[7], Gudrun Lamm[1], Markus Unterdechler[8], Simone Aufhauser[1,2], Jim Nolan[5,6], Julia Mascherbauer[1] and Konstantin Schwarz[1]*

[1]Department of Internal Medicine 3, University Hospital St. Pölten, Karl Landsteiner University of Health Sciences, Krems, Austria, [2]Karl Landsteiner Institute for Cardiometabolics, Karl Landsteiner Society, St. Pölten, Austria, [3]Medical School, Sigmund-Freud University, Vienna, Austria, [4]Division Biostatistics and Data Science, Department of General Health Studies, Karl Landsteiner University of Health Sciences, Krems, Austria, [5]Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom, [6]School of Medicine, Keele University, Keele, United Kingdom, [7]Clinic for Heart and Vascular Diseases, University Hospital of Split, Split, Croatia, [8]CDL VaSiCS, LIT CPS Lab, Johannes Kepler University Linz, Linz, Austria

Background: Old age and the presence of aortic stenosis are associated with the unfolding of the intrathoracic aorta. This may result in increased difficulties navigating catheters from the right compared to the left radial approach.

Objective: To investigate whether increasing age or presence of severe aortic stenosis was associated with increased catheterization success rates from left (LRA) compared to right radial artery approach (RRA).

Methods: We compared coronary angiography success rates of RRA and LRA according to different age groups and in a subgroup of patients with severe aortic stenosis.

Results: A total of 21,259 coronary angiographies were evaluated. With increasing age, the first pass success rate from either radial access decreased significantly ($p < 0.001$). In patients aged <85 years, there was no difference between LRA and RRA. However, in patients aged ≥85 years, LRA was associated with significantly higher success rates compared to RRA (90.1 vs. 82.8%, $p = 0.003$). Patients aged ≥85 years received less contrast agent and had shorter fluoroscopy time when LRA was used [86.6 ± 41.1 vs. 99.6 ± 48.7 ml ($p < 0.001$) and 4.5 ± 4.1 min vs. 6.2 ± 5.7 min ($p < 0.001$), mean (±SD)]. In patients with severe aortic stenosis ($n = 589$) better first pass success rates were observed *via* LRA compared to the RRA route (91.9 vs. 85.1%, $p = 0.037$).

Conclusion: LRA, compared to RRA, is associated with a higher first-pass catheter success rate for coronary artery angiography in patients aged ≥85 years and those with severe aortic stenosis.

KEYWORDS

coronary angiography (CAG), radial access, aortic unfolding, elderly patients, aortic stenosis (AS)

Introduction

Coronary angiography and percutaneous coronary intervention (PCI) play a major role in the diagnosis and treatment of coronary artery disease (CAD) (1–3). Since the first transradial procedure in 1989 (4), radial artery replaced femoral approach as the first access site choice for most coronary procedures. The shift toward radial access was possible due to evolution of smaller size equipment and its popularity was driven by its lower bleeding risk compared to femoral access (4).

In current clinical practice, radial access is performed primarily from the right radial artery. The reason is an ergonomic catheterization table setup for right-handed operators. An exception to this practice is coronary angiography in patients with previous coronary artery bypass grafting (CABG) with a left internal mammary artery graft where right-radial approach is associated with low success rates (5). While some authors report shorter fluoroscopy time for LRA when compared to RRA (6, 7), others suggest no significant differences between left and right radial access in terms of success rates, amount of contrast used, or complications (8, 9). Small, randomized trials reported less radiation exposure to the operator with LRA compared to RRA (6, 10).

We hypothesize that specifically in elderly patients an initial LRA, compared to the RRA approach might result in higher success rates.

There are a few anatomical differences between LRA and RRA access routes, which are hypothesized to be a consequence of age-related changes in aortic arch geometry (11). Aortic unfolding is a condition described as the elongation and increased curvature of the aortic arch (Figure 1) (8). It is associated with increasing age, proximal aortic stiffness (11), body surface area, hypertension, and increased coronary artery calcification (9). Furthermore, right subclavian tortuosity was more frequently observed compared to the left side (12, 13). These age-related aortic arch changes could lead to a lower success rate when performing diagnostic angiography from RRA and **one** could assume that it may be easier to overcome aortic unfolding due to better anatomical angulation *via* the LRA route (Figure 1).

To determine whether there is any age-related difference in LRA compared to the RRA approach, we evaluated the success rates of both routes in different age groups and a population with severe aortic stenosis. Our primary hypothesis stated that in the elderly population LRA, compared to RRA will be associated with a higher success rate to engage coronary arteries. Our second hypothesis was that a higher success rate will also be achieved *via* the LRA approach in a population with severe aortic stenosis. If the primary hypotheses were proven correct, we planned further analysis, whether a primary LRA use could be associated with less fluoroscopy time and saving of contrast volume.

Materials and methods

This retrospective observational study was approved by the Karl-Landsteiner Scientific Integrity and Ethics Commission (ethics commission number 1056/2021). The reporting of this study is in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations (14).

All consecutive patients who underwent cardiac catheterization *via* primary radial access between January 2014 and November 2021 were identified from the local database at the Sankt Pölten University Hospital, Austria. Data extraction was done by MaWi and MU independently on two different occasions yielding the same results and a data quality check was independently performed by KS and MaWi.

To compare LRA vs. RRA success rates, we stratified the whole population into subgroups according to their age and compared if there was a difference between the right and left radial approaches in terms of success. A first-pass success was defined as a successful coronary angiography without the need to switch to an alternative access route. The stratification into age groups was set by decades in the younger patients, and in half decades in patients above the age of 70 years, where we hypothesized the impact of aortic elongation on the success rates *via* RRA.

A second analysis compared LRA and RRA first-pass success rates in a population of patients with severe aortic stenosis. These patients were selected from our database under the coding of "Transcutaneous aortic valve replacement (TAVR) evaluation". All these patients were previously diagnosed with severe aortic stenosis by echocardiography and underwent elective coronary angiography prior to heart team discussion regarding the best treatment strategy (transcutaneous aortic valve replacement vs. surgical valve replacement). Most of the aortic stenosis patients received an aortogram to assess iliac and femoral arteries for TAVR access, resulting in extra radiation dose and contrast volume.

For the comparison of fluoroscopy time, contrast volume, and number of used catheters, only patients with diagnostic procedures were included. Contrast volume, fluoroscopy time, and the number of used catheters were compared for all angiographies, which were initially started by either radial artery access (regardless of first pass success and the possible need for switch to an alternative route). All diagnostic procedures, which in the same session were followed by PCI, were excluded. Furthermore, diagnostic procedures in patients with CABG were also excluded.

Statistical analysis

All statistical tests were performed by MiWe using the SPSS software (IBM, Version 27.0, IBM, Armonk, NY). Due

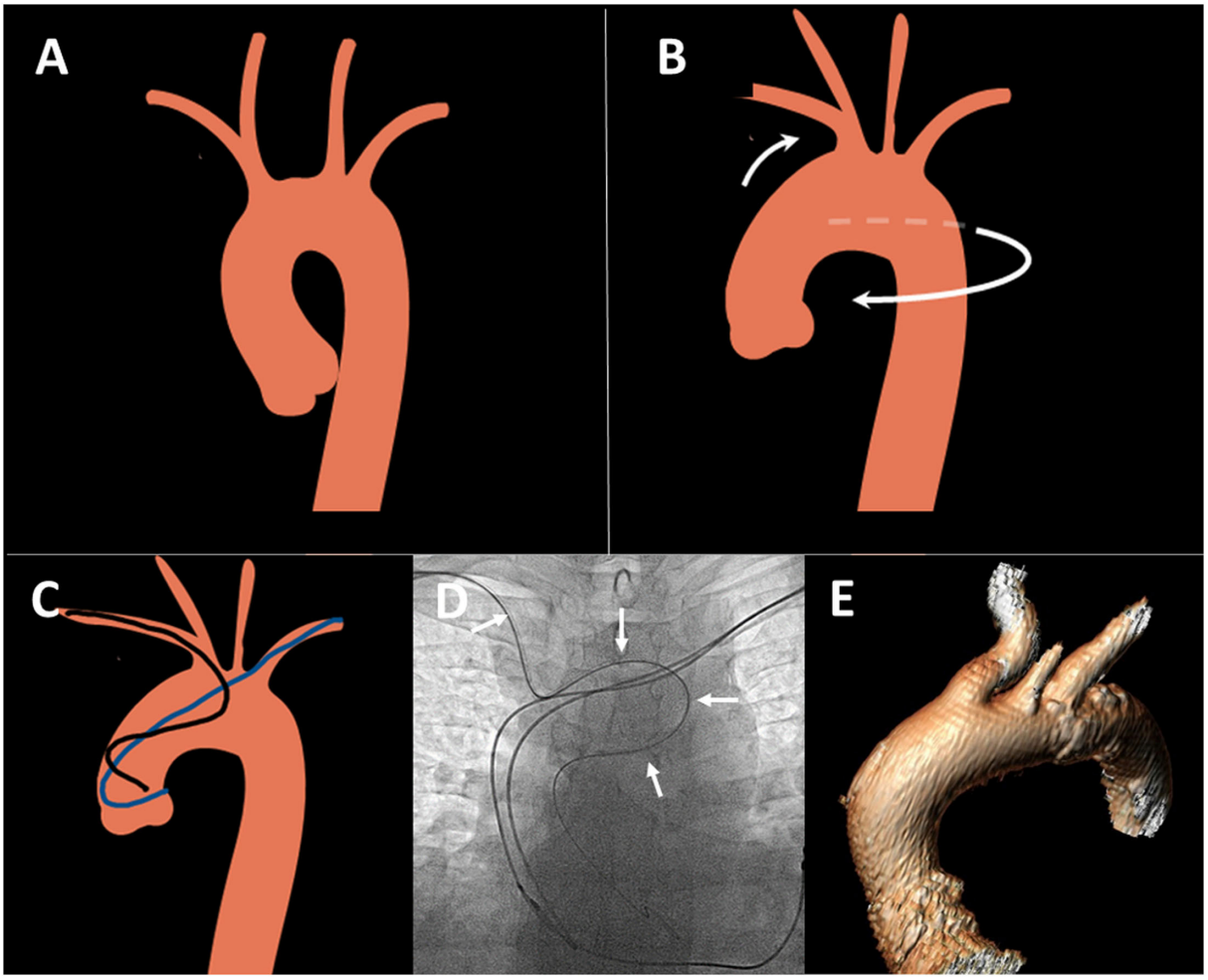


FIGURE 1
Aortic unfolding and its consequences for transradial angiography. **(A)** Normal aortic arch anatomy: **(B)** Aortic unfolding leading to anti-clockwise rotation, elongation of aortic arch, posterior displacement and tortuosity of right radial and innominate artery (white arrows). **(C)** Unfavorable catheter position from right radial (black) compared to left radial (blue) access route in unfolded thoracic aorta. Figures created using smart.servier.com image bank. **(D)** Example of tortuous catheter route in unfolded aorta in elderly patient from right radial route, white arrows: EBU catheter. **(E)** 3D reconstruction of the unfolded aorta and posteriorly displaced innominate artery in a patient with severe aortic stenosis.

to the large sample size, we did not use statistical tests for normal distribution but used histograms and QQ-plots to identify relevant deviations from a normal distribution. In cases of skewed data, we used median as well as first and third quartiles (IQR, interquartile range) as descriptive statistics. Nominal data were described using absolute frequencies and percentages. To compare contrast volumes and fluoroscopy times of the left- vs. right-radial approach, Mann-Whitney U-tests were used due to skewed data. The success rates of the **two** approaches were compared using crosstabs and chi² tests. To identify predictors of success for the left and right radial approach, multiple logistic regressions were used. All tests were two-tailed and $p < 0.05$ was considered statistically significant. Normally distributed data were expressed as mean ±SD and non-normally distributed data as median (IQR).

Results

A total of 21,259 coronary angiographies with primary radial access were included in our analysis. The mean age of the patients was 67.8 ± 11.7 years and 14,024 (66%) were male. The majority were elective cases (16,493, 77.6% respectively), whereas 4,758 (22.4%) angiographies were undertaken due to acute coronary syndrome (ACS).

Multiple binary logistic regression revealed that the first-pass success rate of transradial access was independently affected

TABLE 1 Predictors of transradial success in a logistic regression model.

Independent variable	Odds ratio (95% CI)	*p*
Sex	1.1 (1.0–1.2)	0.028
Side	0.8 (0.8–1.0)	0.017
Age	1.0 (0.9–1.0)	<0.001

by increasing age, gender, and the side of access [$p < 0.001$, $p = 0.028$, $p = 0.017$, respectively (Table 1)]. Increasing age was the strongest predictor of failure to successfully carry out transradial angiography by the first pass, whereas female gender and RRA predicted slightly less successful first-pass success.

Success rates for RRA and LRA stratified by different age groups are shown in Table 2 and Figure 2. The reduction in success rates with RRA was most evident among patients of age 85 or older, whereas success rates *via* LRA remained stable in this age group (Figure 2). For these elderly patients, the rate of first-pass success for LRA compared to RRA was 90.1 vs. 82.8% ($p = 0.003$), respectively. In patients aged <85 years, there was no difference in the first-pass success rate comparing RRA vs. LRA [13,551 (90.0%) vs. 4,614 (90.8 %), $p = 0.11$]. When the study population was divided into more detailed age groups, the age group between 50 and 59 years showed a statistically greater proportion of success with LRA compared to RRA that was statistically significant ($p = 0.031$). We have no explanation for this statistical finding, which is at odds with findings in other similar age groups, but the clinical significance of a 2% side difference is clinically negligible and could be driven by large sample size.

Fluoroscopy time and contrast volume increased with age and were affected by the choice of access side (Table 3).

Patients who underwent LRA received significantly lower median contrast volume (77 vs. 94 ml, $p < 0.001$). Every 1-year age increase was associated with the additional use of a 0.3 ml contrast agent. This increase was more evident in men (9.9 ml more than in women) and with RRA (3.0 ml more than with LRA). In case of **first** pass failure, an additional 17.2 ml was required. These analyses concerning contrast use were adjusted for age, gender, and first-pass failure. In non-adjusted analysis, LRA compared with RRA was associated with an average reduction in contrast volume of 33 ml (95%CI: 5.346–1.330).

Moreover, LRA was associated with a significantly shorter median fluoroscopy time (3.2 vs. 4.4 min, $p < 0.001$) in our study population. On average, an increase in age by one year was associated with a 0.2-min longer fluoroscopy time for the procedure. This increase was pronounced in men (1.0 min more than in women) and with RRA (1.5 min more than with LRA). In case of first pass failure, RRA required a 2.5-min longer fluoroscopy time when compared to LRA. These findings concerning fluoroscopy time were adjusted for age, gender, and first-pass failure. In non-adjusted analysis, LRA compared with RRA was associated with an average reduction of fluoroscopy time of 1.6 min (95%CI: 2.03–1.1).

TABLE 2 Comparison of coronary angiography success rates RRA vs. LRA route—divided by age groups and for severe aortic stenosis population.

Age (y)	RRA success, *n* (total)	RRA success, %	LRA success, *n* (total)	LRA success %	*p*
<39	155 (176)	88.1	69 (77)	89.6	0.832
40–49	842(929)	90.6	294 (321)	91.6	0.654
50–59	2,686 (2,961)	90.7	841(904)	93.0	0.031*
60–69	3,762 (4,133)	91.0	1,210 (1,317)	91.9	0.371
70–74	2,230 (2,494)	89.4	800 (881)	90.8	0.271
75–79	2,377 (2,655)	89.5	846 (948)	89.2	0.806
80–84	1,498 (1,712)	87.5	554 (636)	87.1	0.834
85–90	568 (677)	83.9	214 (238)	89.9	0.025*
>90	112 (144)	77.8	49 (54)	90.7	0.041*
Total	14,232 (15,883)	89.6	4,877 (5,376)	90.7	0.020*
<84	13,551 (15,061)	90.0	4,614 (5,084)	90.8	0.109
85+	680 (821)	82.8	263 (292)	90.1	0.003*
AS	509 (589)	85.1	125 (136)	91.1	0.037*

RRA, Right radial access; LRA, Left radial access; *p < 0.05, AS severe aortic stenosis population.

The number of used diagnostic material was numerically marginally different between right and left radial access groups, favoring the latter [$n = 11,352$, 2.58 (2.57–2.60) vs. 2.52 (2.48–2.56), respectively, $p = 0.002$, mean (95% CI)]. This finding was numerically more pronounced in patients older than 85 years, and probably due to the smaller sample size did not reach statistical significance [$n = 545$, 2.90 (2.82–2.97) vs. 2.75 (2.57–2.93), respectively, $p = 0.127$, mean (95% CI)].

In the subgroup of patients with severe AS, LRA led to significantly higher success rates compared with RRA (91.9 vs. 85.1%, $p = 0.037$ (Figure 3; Table 2). Fluoroscopy time and used contrast volume did not differ between the two groups in this cohort [8.2 (7.5) min vs. 8.5 (10.3) min, $p = 0.716$ and 128.7 (52.4) vs. 129.8 (79.0) ml, $p = 0.861$, respectively, mean (SD)]. In the subgroup of patients with severe aortic stenosis, the mean age was 81.4 [5.6]. On average, the aortic valve area prior to TAVR was 0.72 cm^2 and AV mean was 44.9 mmHg.

Discussion

This study has several key findings. First, left radial access compared to the right radial approach was associated with a higher first pass success rate in the elderly population (≥85 years of age) and in a population with severe aortic stenosis. In the elderly population, the left radial approach resulted in

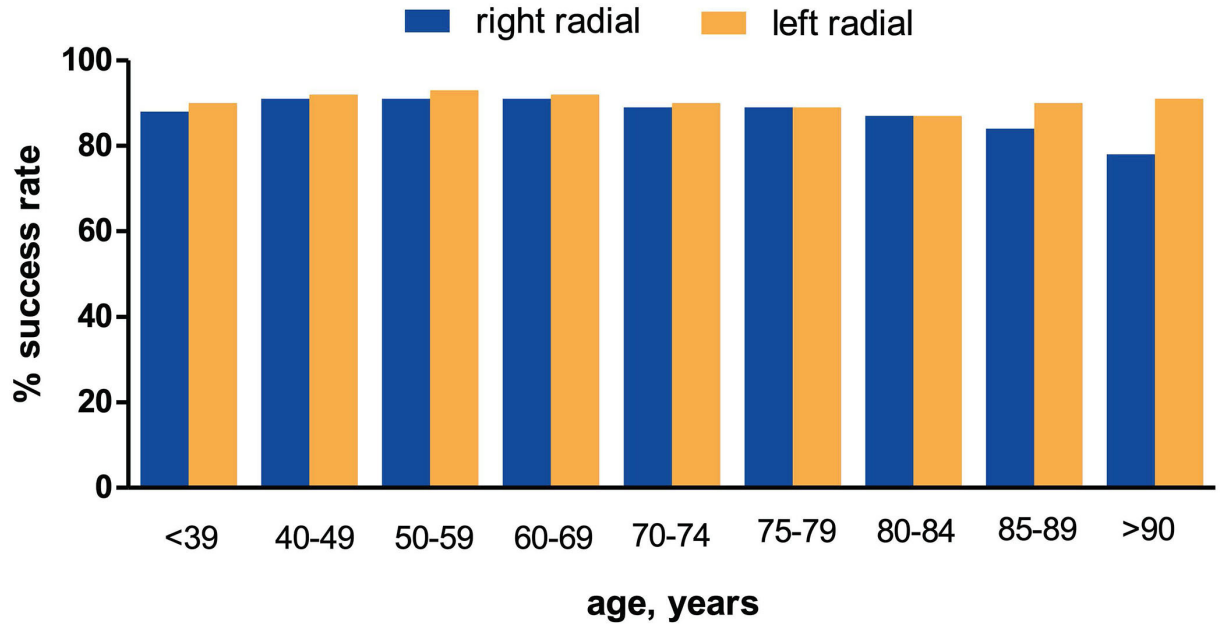


FIGURE 2
Age-dependent comparison of coronary angiography success rates (RRA vs. LRA route).

TABLE 3 Contrast volume and fluoroscopy times*.

>85 years of age	*n*	RRA	LRA	*p*
Contrast volume ml, median (IQR)	586	94 (62–130)	77 (55–110)	<0.001
Fluoroscopy time min, median (IQR)	586	4.4 (2.4–7.8)	3.2 (1.7–5.9)	<0.001
Aortic stenosis		**RRA**	**LRA**	**p**
Contrast volume ml, median (IQR)	671	116.5 (93–14)	116.0 (94–160)	0.861
Fluoroscopy time min, median (IQR)	671	5.3 (3.1–0.4)	6.1 (3.0–10.5)	0.716

*Results after exclusion of PCIs, CABG-angiographies, and statistical outliers (>100 min fluoroscopy time and 500 ml contrast volume); IQR, interquartile range.

shorter fluoroscopy times and lower contrast volume use. Radial approach success rates from either side decreased with older age and were lower in female compared to male patients.

There is strong evidence supporting radial over femoral access safety advantage in the elderly population (15–17). In 2009, Dehghani et al. postulated three independent risk factors of transradial PCI failure: age above 75 years, prior coronary artery bypass graft surgery, and short stature (18). In our study, increasing age was the strongest predictor of failure to successfully navigate cardiac catheter *via* radial access, hence making the aspiration of achieving safe radial access in every geriatric patient potentially more challenging (19).

Notably, congenital coronary artery disease or malformation may have influenced coronary artery catheterization. Unfortunately, there is no available data concerning this topic in our study population. Nevertheless, according to previous literature, the prevalence of coronary anomalies in most populations is quite low and reported only in 0.2–2% of all coronary angiographies (20).

Our findings of worse radial success in women are supported by the findings of existing literature. Radial access in women has been reported to be affected by smaller vessel calibers and higher rates of radial artery spasm, which can result in procedure failure and high crossover rates to femoral access (18, 21). Pandie et al. (22) reported a 2-fold higher failure of first pass radial success in a pre-specified subgroup analysis of the randomized, multicenter RIVAL (Radial vs. Femoral Access for Coronary Intervention) trial (23). Crossover from radial to femoral approach was reported with 11.1% in women and 6.3% in men, and this is a consequence of higher rates of radial artery spasm (9.5% in women vs. 3.3% in men).

We present a novel finding identifying the age of 85 years (or older) as a cut-off age when there was greater coronary artery catheterization success *via* the LRA compared to RRA. In addition, LRA was associated with a decrease in fluoroscopy time and used contrast agents in this population. Previous randomized trials compared the efficacy of the right- vs. left-radial approach for coronary angiography. Dominici et al. demonstrated a reduction of fluoroscopy time and decreased the number of catheters used *via* LRA in a prospective trial including over 1,000 patients (24). Surprisingly, no significant difference in the amount of used contrast agent was observed

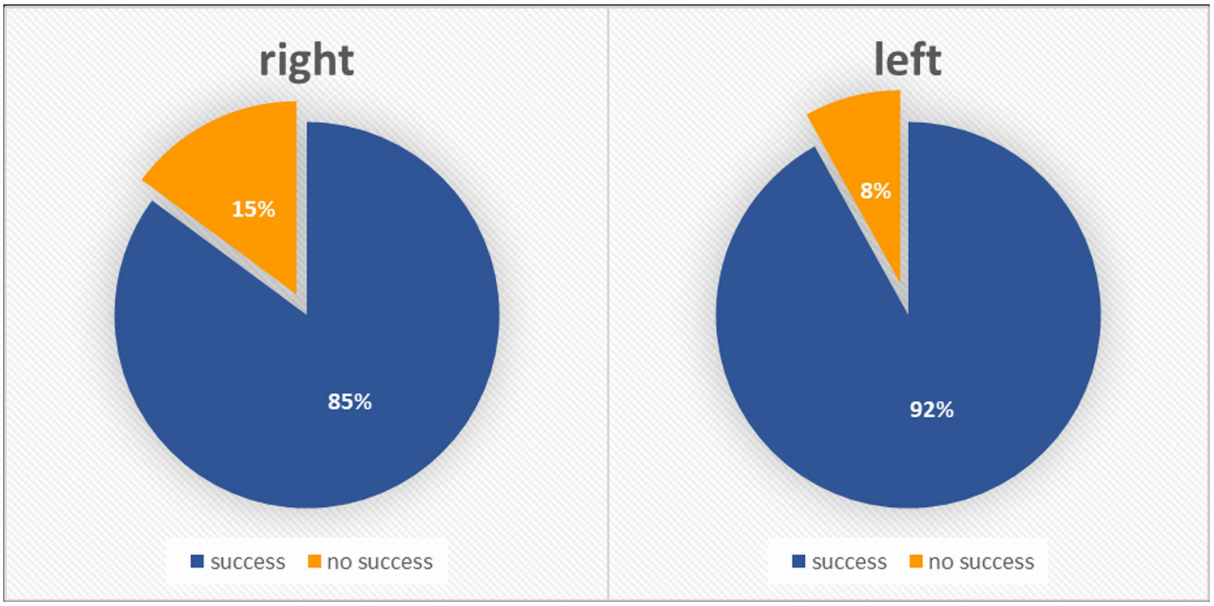


FIGURE 3
Severe aortic stenosis population–radial approach success rates according to initial side choice.

between the groups. Another prospective trial by Norgaz et al. (25) randomized 1,000 patients to RRA or LRA and fluoroscopy time was found to be significantly shorter *via* LRA compared with RRA. However, no significant difference comparing LRA and RRA in terms of success rate, procedural time, amount of contrast used, or the number of diagnostic catheters used In the TALENT-trial (13), left radial access for diagnostic angiography was associated with significantly lower fluoroscopy time and this was more evident among lower experienced operators and elderly patients (>70 years) according to prespecified subgroup analyses. However, the benefits of LRA were not consistent across the literature, and differences in procedural and fluoroscopy times could not be demonstrated in small randomized series of 100 octogenarian patients (26). A large meta-analysis, including 14 studies by Xia et al. (26) on a total of 6,870 patients, reported a significant reduction in fluoroscopy times, less contrast volume, and fewer catheter numbers used *via* the left radial route, but no significant difference in procedural failure or procedural times when comparing the two approaches.

Interestingly, whereas most previous studies concentrated on fluoroscopy times, numbers of catheters used, or contrast volume used, they either rarely reported or failed to demonstrate a difference in first pass success rates comparing the two approaches.

The success rates of the two different radial approaches depending on different age distributions were rarely reported. To the best of our knowledge, our study with over 21,000 coronary angiographies presents by far the largest original data set to date, which addresses the question of the LRA vs. RRA approach for successful coronary angiography in different age groups. We identified that the LRA was superior to the RRA for the patients in the age group of >85 years. The most likely explanation is difficult catheter navigation due to tortuosity in the right subclavian artery, which was previously more frequently reported when compared to the left subclavian artery (13, 26). Thoracic aortic unfolding was described with increasing age (11), and is most likely preventing a smooth path of the catheter on its way from the right radial artery to the aortic root in elderly patients.

Not only age but also calcific aortic disease seems to play a major role in the pathophysiology of aortic unfolding. Aortic stenosis is associated with post-stenotic ascending aorta dilation and geometric changes in intrathoracic aorta (27). This may negatively affect the right radial catheter route. To the best of our knowledge, we are the first group to demonstrate that the right radial success rate decreased, whereas the left radial success rates remained stable in patients with severe aortic stenosis. There was no difference in fluoroscopy time or contrast volume used in the severe aortic stenosis population. We have no explanation for this; however, presume that fluoroscopy times and especially contrast volume comparison in the two groups is somewhat difficult due to varying practice and volumes injected into the abdominal aorta for femoral and iliac arteries assessment prior to femoral TAVR access route planning. The contrast volume injected into descending aorta is frequently altered according to patient size and kidney function, and was recently frequently omitted with good CT angiography planning. In the future, large prospective randomized trials

and other real-world registry data are warranted to confirm our results.

Study limitations

This study has several limitations. First, it is a single-center study and the practice in Austria may not be the same in other countries. Second, the study took place over 7 years and some of the procedures were undertaken at a time when operators were transitioning from a routine femoral to radial approach. Third, there is no data on the experience of the operator performing the procedures as both experienced and training operators carried out the procedures at our institution. However, the experience of operators and their preferred access side choice should not affect the fact that older age would be associated with different outcomes if the operators stuck to their preferred initial side choice across the entire age range.

Another limitation is that our aortic stenosis population data apply to elderly patients with degenerative aortic stenosis and cannot be extrapolated to other etiologies (e.g., bicuspid aortic valve).

Finally, we initially planned to collect data and adjust to the presence of hypertension or body size which may impact the thoracic aorta and subclavian artery anatomy, but these data were incomplete so could not be reliably included.

Despite the limitations mentioned above, our data set offers real-world insight into the practice, avoiding other biases associated with prospective randomized trials, regarding the selection of a certain patient population or certain operator experience. The unselected nature of our documented procedures makes the information obtained generally transferable to most settings.

Conclusion

Compared to the RRA, the use of the LRA approach was associated with the higher success of coronary artery angiography in patients above 85 years of age and those with severe AS. These selected patients may benefit from an initial LRA approach to reduce the need to change the access side.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Kommission für Scientific Integrity und Ethik der Karl Landsteiner Privatuniversität, Krems an der Donau. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MWi and KS designed the study, validated and interpreted the results, wrote and drafted the manuscript, and wrote the final manuscript. MU, KS, and MWi created the database. MWe analyzed the data. GL collected the AS population demographic data. TW, CK, JB, SA, JN, GL, and JM revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

We acknowledge the support of the Open Access Publishing Fund of Karl Landsteiner University of Health Sciences, Krems, Austria.

Acknowledgments

We are grateful to Paul Vock, Gudrun Lamm, Jörg Heindl, Jürgen Nowy, Gunnar Gamper, Simone Hermanek, Mariella Kadnar-Wölken, Monika Steininger, Doris Kerö, Deddo Mörtl, and all other colleagues who over the last years contributed to the cardiac catheterization service at Universitätsklinikum Sankt Pölten.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1022415/full#supplementary-material

References

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. (2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393

2. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. (2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* (2021) 42:1289–367. doi: 10.1093/eurheartj/ehaa909

3. Neumann FJ, Sechtem U, Banning AP, Bonaros N, Bueno H, Bugiardini R, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* (2020) 41:407–77.

4. Incidence P. and Impact on Long-Term Survival Among 17,901 Patients Treated at the Mayo Clinic From 1994 to 2005. *JACC: Cardiovasc Interven.* (2008) 1:202–9. doi: 10.1016/j.jcin.2007.12.006

5. Guédès A, Dangoisse V, Gabriel L, Jamart J, Chenu P, Marchandise B, et al. Low rate of conversion to transfemoral approach when attempting both radial arteries for coronary angiography and percutaneous coronary intervention: a study of 1,826 consecutive procedures. *J Invasive Cardiol.* (2010) 22:391–7.

6. Kado H, Patel AM, Suryadevara S, Zenni MM, Box LC, Angiolillo DJ, et al. Operator radiation exposure and physical discomfort during a right versus left radial approach for coronary interventions: a randomized evaluation. *JACC: Cardiovasc Interven.* (2014) 7:810–6. doi: 10.1016/j.jcin.2013.11.026

7. Sciahbasi A, Romagnoli E, Trani C, Burzotta F, Sarandrea A, Summaria F, et al. Operator radiation exposure during percutaneous coronary procedures through the left or right radial approach: the TALENT dosimetric substudy. *Circ Cardiovasc Interv.* (2011) 4:226–31. doi: 10.1161/CIRCINTERVENTIONS.111.961185

8. Gibson TC. Arterial disease. *Arch Intern Med.* (1965) 116:963. doi: 10.1001/archinte.1965.03870060161045

9. Lee JW, Hur J, Kim YJ, Lee HJ, Nam JE, Kim HY, et al. Aortic unfolding determined using non-contrast cardiac computed tomography: correlations with age and coronary artery calcium score. *PLoS ONE.* (2014) 9:95887. doi: 10.1371/journal.pone.0095887

10. Dominici M, Diletti R, Milici C, Bock C, Placanica A, D'Alessandro G, et al. Operator exposure to x-ray in left and right radial access during percutaneous coronary procedures: OPERA randomised study. *Heart.* (2013) 99:480–4. doi: 10.1136/heartjnl-2012-302895

11. Redheuil A, Yu WC, Mousseaux E, Harouni AA, Kachenoura N, Wu CO, et al. Age-related changes in aortic arch geometry: relationship with proximal aortic function and left ventricular mass and remodeling. *J Am Coll Cardiol.* (2011) 58:1262–70. doi: 10.1016/j.jacc.2011.06.012

12. Cha KS, Kim MH, Kim HJ. Prevalence and clinical predictors of severe tortuosity of the right subclavian artery in patients undergoing transradial coronary angiography. *Am J Cardiol.* (2003) 92:1220–2. doi: 10.1016/j.amjcard.2003.07.038

13. Sciahbasi A, Romagnoli E, Burzotta F, Trani C, Sarandrea A, Summaria F, et al. Transradial approach (left vs right) and procedural times during percutaneous coronary procedures: TALENT study. *Am Heart J.* (2011) 161:172–9. doi: 10.1016/j.ahj.2010.10.003

14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med.* (2007) 4:1623–7. doi: 10.1371/journal.pmed.0040296

15. Achenbach S, Ropers D, Kallert L, Turan N, Krähner R, Wolf T, et al. Transradial versus transfemoral approach for coronary angiography and intervention in patients above 75 years of age. *Cathet Cardiovasc Interven.* (2008) 72:629–35. doi: 10.1002/ccd.21696

16. Louvard Y, Benamer H, Garot P, Hildick-Smith D, Loubeyre C, Rigattieri S, et al. Comparison of transradial and transfemoral approaches for coronary angiography and angioplasty in octogenarians (the OCTOPLUS study). *Am J Cardiol.* (2004) 94:1177–80. doi: 10.1016/j.amjcard.2004.07.089

17. Cantor WJ, Mehta SR, Yuan F, DŽavík V, Worthley M, Niemelä K, et al. Radial versus femoral access for elderly patients with acute coronary syndrome undergoing coronary angiography and intervention: insights from the RIVAL trial. *Am Heart J.* (2015) 170:880–6. doi: 10.1016/j.ahj.2015.08.011

18. Dehghani P, Mohammad A, Bajaj R, Hong T, Suen CM, Sharieff W, et al. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv.* (2009) 2:1057–64. doi: 10.1016/j.jcin.2009.07.014

19. Cao Z, Zhou YJ, Zhao YX, Liu YY, Shi DM, Guo YH, et al. Transradial approach for coronary angioplasty in Chinese elderly patients. *Chin Med J (Engl).* (2008) 121:1126–9. doi: 10.1097/00029330-200806020-00017

20. Yildiz A, Okcun B, Peker T, Arslan C, Olcay A, Bulent Vatan M. Prevalence of coronary artery anomalies in 12,457 adult patients who underwent coronary angiography. *Clin Cardiol.* (2010) 33:E60–4. doi: 10.1002/clc.20588

21. Keeley EC, Cornielle-Caamano VM. Radial artery access in women undergoing percutaneous coronary procedures. *JACC Cardiovasc Interv.* (2015) 8:513–4. doi: 10.1016/j.jcin.2015.03.003

22. Pandie S, Mehta SR, Cantor WJ, Cheema AN, Gao P, Madan M, et al. Radial versus femoral access for coronary angiography/intervention in women with acute coronary syndromes: insights from the RIVAL Trial (Radial Vs femorAL access for coronary intervention). *JACC: Cardiovasc Interven.* (2015) 8:505–12. doi: 10.1016/j.jcin.2014.11.017

23. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet.* (2011) 377:1409–20. doi: 10.1016/S0140-6736(11)60404-2

24. Dominici M, Diletti R, Milici C, Bock C, Garg S, de Paolis M, et al. Left radial versus right radial approach for coronary artery catheterization: a prospective comparison. *J Interv Cardiol.* (2012) 25:203–9. doi: 10.1111/j.1540-8183.2011.00689.x

25. Norgaz T, Gorgulu S, Dagdelen S. A randomized study comparing the effectiveness of right and left radial approach for coronary angiography. *Catheter Cardiovasc Interv.* (2012) 80:260–4. doi: 10.1002/ccd.23463

26. Xia SL, Zhang XB, Zhou JS, Gao X. Comparative efficacy and safety of the left versus right radial approach for percutaneous coronary procedures: a meta-analysis including 6870 patients. *Braz J Med Biol Res.* (2015) 48:743–50. doi: 10.1590/1414-431x20154571

27. Wilton E, Jahangiri M. Post-stenotic aortic dilatation. *J Cardiothorac Surg.* (2006) 1:7. doi: 10.1186/1749-8090-1-7

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 25 November 2022
DOI 10.3389/fcvm.2022.1005958

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Anna Mierzyńska,
Gruca Orthopaedic and Trauma Teaching Hospital, Poland
Ying Li,
First Hospital of Lanzhou University, China

*CORRESPONDENCE
Juxia Zhang
yuhuan6011@163.com

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 28 July 2022
ACCEPTED 03 November 2022
PUBLISHED 25 November 2022

CITATION
Yin Y, He Q, Zhang R, Cheng H, Zhang Y and Zhang J (2022) Predictors of adherence of enhanced external counterpulsation in patients with coronary heart disease after discharge: A mixed-methods study. *Front. Cardiovasc. Med.* 9:1005958. doi: 10.3389/fcvm.2022.1005958

Predictors of adherence of enhanced external counterpulsation in patients with coronary heart disease after discharge: A mixed-methods study

Yuhuan Yin[1†], Qinli He[2†], Rong Zhang[1], Hu Cheng[3], Yiyin Zhang[1] and Juxia Zhang[3*]

[1]School of Nursing, Gansu University of Chinese Medicine, Lanzhou, China, [2]Department of Cardiology, Gansu Provincial Hospital, Lanzhou, China, [3]Clinical Educational Department, Gansu Provincial Hospital, Lanzhou, China

Background: Although enhanced external counter pulsation (EECP) has been included in the cardiac rehabilitation prescription for coronary heart disease (CHD) in China, because the total treatment duration of a course of EECP is 36–36 h, the average hospital stay of CHD patients is short, and the adherence after discharge remains unclear. The purpose of this study is to investigate the adherence to EECP in CHD patients after discharge, and analyze the related influencing factors.

Methods: A retrospective mixed method study combining qualitative and quantitative methods. Quantitative component included CHD patients who had received EECP treatment between March 2020 and August 2021. The qualitative component included in-depth interviews with patients who did not adhere to EECP after discharge. Binary Logistic regression was used to analyze the predictors of EECP adherence after discharge. In-depth interviews with patients were conducted to explore the reasons for dropping out of the EECP after discharge.

Results: Among 1,304 patients, only 24.23% adhered to EECP treatment after discharge. Binary logistic regression results showed that patients with disease duration <2 years (OR = 3.13, 95%CI: 2.31–4.24), high school or below (OR = 2.81, 95%CI: 1.98–4.01), distance between residence and hospital more than 20km (OR = 2.08, 95%CI: 1.47–2.96), age over 60 (OR = 2.00, 95%CI: 1.46–2.74), female (OR = 1.64, 95%CI: 1.78–2.29), and angina pectoris (OR = 1.65, 95%CI: 1.16–2.34) were more likely to not adhere to EECP treatment after discharge. However, patients with monthly family income over 8000¥ (OR = 0.46, 95%CI: 0.28–0.75) were more likely to adhere to EECP treatment after discharge than those with household monthly income below 4,000¥. In the qualitative results, the reasons why patients do not adhere to EECP after discharge mainly include insufficient understanding, restricted objective conditions and psychosocial factors.

Conclusions: The adherence of CHD patients to EECP treatment after discharge was poor. It is necessary to develop effective intervention measures, such as brochures or videos to improve patients' understanding of the importance of adherence to EECP treatment after discharge. In addition, offering EECP treatment during off-hours and weekends may also improve adherence in more young patients.

KEYWORDS

EECP, coronary heart disease, discharge, adherence, factors

Introduction

Cardiovascular disease is the main cause of death worldwide, among which coronary heart disease (CHD) has the highest morbidity and mortality, posing a serious threat to human health (1). As the secondary prevention of cardiovascular diseases, exercise-centered cardiac rehabilitation is an important part of medical care for all patients with heart disease (2). However, about a third of patients have severe lifestyle restrictions that prevent them from exercising (3), which increases the dropout rate from cardiac rehabilitation to some extent. Meta-analysis showed that the drop-out rate for enrolled patients in high-income countries was 12-56% (4). The dropout rate in Iran was reported to be as high as 82% (5). A survey of 283 patients after PCI in China found that the dropout rate of exercise training program was 36.44% (6).

Enhanced external counterpulsation (EECP) is a non-invasive, safe and cost-effective adjunctive therapy approved by the US Food and Drug Administration (7). It can not only be used as an alternative therapy in addition to drugs and surgical treatment of cardiovascular diseases, but also has been included in the prescription of cardiac rehabilitation in China (8). A large number of clinical randomized controlled trials have proven that EECP can improve myocardial ischemia and hypoxia and left ventricular function, reduce angina attacks, and improve exercise tolerance (9–11). Long-term adherence to EECP treatment can significantly improve the endothelial function of patients, thereby inhibiting the occurrence and development of atherosclerotic lesions (12). Moreover, EECP is considered to be a "passive" exercise and thus can significantly benefit patients who are unable to exercise (13).

The expert consensus on EECP treatment in China suggested the course of EECP is 1h per day, and the total duration of a course is 35–36 h (14). However, the average length of hospital stay for CHD patients is about 3–7 days, which requires that most patients to come to the hospital for treatment every day after discharge. EECP has been developed in China for more than 50 years, but it was introduced in Gansu Province in 2020, CHD patients' adherence to EECP treatment after discharge remains unclear. Therefore, the purpose of this study is to investigate the adherence to EECP treatment in CHD patients after discharge, and analyze the related influencing factors, in order to provide reference for healthcare workers to formulate related measures.

Methods

Study design and population

This was a mixed method study with qualitative and quantitative components. The quantitative component was a retrospective cohort analysis based on the medical and rehabilitation records of CHD patients who received EECP treatment during their hospitalization in Gansu Provincial Hospital from March 1, 2020 to August 31, 2021. Inclusion criteria for the retrospective cohort study: (1) Patients who received 5-10h of EECP treatment during hospitalization from March 1, 2020 to August 31, 2021; (2) Patients diagnosed with CHD by coronary angiography; (3) Age 18 years or older.

Adherence criteria for EECP after discharge: The latest expert consensus in China recommends that the course of EECP is 1 h a day, with a total course of 35–36 h. For statistical analysis, we defined the adherence rate as at least 70% (25 h) based on the actual EECP treatment of our patients, which was considered as the patients' adherence to EECP.

The qualitative component was in-depth interviews with key informants who did not adhere to EECP treatment after discharge. We conducted a purposeful sampling, and identified key interviewees based on the sociodemographic characteristics of patients, disease characteristics and geographical location. Because patients had been discharged and were geographically widespread, 19 respondents were selected for semi-structured telephone interviews. To ensure consistency of the collected data, all interviews were conducted by the principal investigator (YYH). The interview consisted of three core questions: "How do you feel after EECP treatment? Has it relieved your symptoms?", "Do you know what benefits EECP can bring to your health?" and "What made you unwilling to adhere to EECP

treatment after discharge?". Participants were encouraged to explain and elaborate on their answers.

Data collection and procedure

Quantitative data

the hostipal numbers of patients receiving EECP treatment was queried through the rehabilitation notebook, and then the baseline characteristics of patients were queried through the electronic medical record system according to the hospital numbers. Baseline characteristics included: (1) Sociodemographic characteristics: sex, age, educational level, monthly family income, health insurance, distance from residence to hospital, BMI, smoking; (2) Clinical characteristics: course of disease, angina pectoris, hypertension and history of PCI surgery. The researchers input the relevant information into the Microsoft Excel, which was double-checked by two researchers.

Qualitative data

All interviews were recorded. After the interview, the researchers transcribed the entire recording word by word, input the original qualitative data into Microsoft Word, and then sorted out, analyzed and classified according to topics and questions to determine common topics.

Data analysis

Quantitative data

SPSS 21.0 was used for statistical analysis of quantitative data. First, frequencies (n) and proportions (%) were used to describe the general characteristics (sociodemographic characteristics and clinical characteristics) in adherence group and non-adherence group. Second, chi-square test and was performed to preliminarily analyse general characteristics related to EECP adherence after discharge (yes/no). Finally, binary logistic regression was used to examine the independent factors associated with EECP adherence after discharge. The dependent variable was EECP adherence treatment after discharge (adherence=0, non-adherence = 1), with the significant factors in univariate analyses included as independent variables. Odd ratio (OR) with 95% confidence intervals (95%CI) were used as the measure of association. OR = 1 indicates that there was no correlation between exposure factors and outcome (EECP non-adherence); OR>1 indicates that exposure factors are risk factors for EECP non-adherence; OR <1 indicates that exposure factors are protective factors for EECP non-adherence. The statistical tests were two-sided, and the effects with $p < 0.05$ were considered to be statistically significant.

Qualitative data

NVivo version 12.0 (QSR International) was used for data transcription and analyzed by thematic analysis. Data were subject to thematic analysis using the framework approach (15). YYH (who has 2 years of qualitative research training) and HQL(teacher of qualitative research training in Department of Cardiology, has 8 years of qualitative research experience) read all recordings carefully and repeatedly to extract relevant statements and meanings, and then look for common conceptual or meaningful features to form topic groups and categories, with topics associated with the raw data. The obtained data were analyzed, summarized and classified. ZJX (who has 2 years of qualitative research training and 6 years of qualitative research experience) reviewed the analysis to reduce bias and increase the credibility of the interpretation.

Ethics approval

This study was approved by the Ethics Committee of Gansu Provincial Hospital (2021-234). The quantitative component was a retrospective analysis of the basic characteristics of the patients, so informed consent was not required. Informed consent was obtained for key interviewees in the qualitative component. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Results

Quantitative results

Patients' characteristics

Among 1,304 patients, only 24.23% adhered to EECP treatment after discharge. 62.12% were male and 61.81% had lower education. Only 13.88% of patients had a monthly income of more than 8,000¥, and more than 70% lived more than 20 km away from the hospital (Table 1).

Factors associated with EECP treatment after discharge

The results of univariate analysis showed that patients with different gender, age, education level, family monthly income, medical insurance, distance, course of disease, angina pectoris and Post-PCI had statistically significant differences in their adherence to EECP after discharge (Table 1).

Binary logistic regression results in Table 2 showed that patients with disease duration <2 years (OR = 3.13, 95%CI: 2.31–4.24), high school or below (OR = 2.81, 95%CI: 1.98–4.01), distance between residence and hospital more than 20 km (OR = 2.08, 95%CI: 1.47–2.96), age over 60 (OR = 2.00, 95%CI: 1.46–2.74), female (OR = 1.64, 95%CI: 1.78–2.29), and angina pectoris (OR = 1.65, 95%CI: 1.16–2.34) were more likely

TABLE 1 Demographic characteristics of coronary heart disease patients.

Characteristics	Overall patients ($N = 1,304$), n (%)	Adherence ($N = 316$), n (%)	Non-adherence ($N = 988$), n (%)	p
Gender				<0.001*
Male	810 (62.12)	244 (77.22)	566 (57.29)	
Female	494 (37.88)	72 (22.78)	422 (42.71)	
Age (years)				<0.001*
<60	730 (55.98)	206 (65.19)	524 (53.04)	
≥60	574 (44.02)	110 (34.81)	464 (46.96)	
Educational level				<0.001*
High school or below (≤12 years)	830 (61.81)	114 (36.08)	716 (72.47)	
College degree or above (≥15 years)	474 (38.19)	202 (63.92)	272 (27.53)	
Monthly family income (¥)				<0.001*
<4,000	566 (43.40)	82 (25.95)	484 (48.99)	
4,000–8,000	564 (43.25)	135 (42.72)	429 (43.42)	
>8,000	174 (13.34)	99 (31.33)	75 (7.59)	
Medical insurance				<0.001*
Medical insurance for urban workers	550 (42.18)	209 (66.14)	341 (34.51)	
Medical insurance for urban residents	224 (17.18)	46 (14.56)	178 (18.02)	
New rural cooperative	380 (29.14)	45 (14.24)	335 (33.91)	
Self pay	150 (11.50)	16 (5.06)	134 (13.56)	
Distance (km)				<0.001*
>20	958 (73.47)	166 (52.53)	792 (80.16)	
≤20	346 (26.53)	150 (47.47)	196 (19.84)	
BMI (kg/m^2)	24.79 ± 3.29	24.92 ± 3.54	24.74 ± 3.20	0.408
Course of disease (year)				<0.001*
<2	864 (66.26)	134 (42.41)	730 (73.89)	
≥2	440 (33.74)	182 (57.59)	258 (26.11)	
Smoking				0.881
No	986 (75.61)	240 (75.95)	746 (75.51)	
Yes	318 (24.39)	76 (24.05)	242 (24.49)	
Angina pectoris				<0.001*
No	922 (70.71)	248 (78.48)	674 (68.22)	
Yes	382 (29.29)	68 (21.52)	314 (31.78)	
Post-PCI				<0.001*
No	1088 (83.44)	216 (68.35)	872 (88.26)	
Yes	216 (16.56)	100 (31.65)	116 (11.74)	
Hypertension				0.246
No	656 (50.31)	168 (53.16)	488 (49.39)	
Yes	648 (49.69)	148 (46.84)	500 (50.61)	

PCI, percutaneous coronary intervention.
Data are reported as n (%) unless otherwise noted; Age data are presented as mean±SD.
*$p < 0.01$.

TABLE 2 Factors associated with EECP adherence after discharge.

Factors	OR (95% CI)	*p*
Gender (female)	1.64 (1.78–2.29)	0.003*
Age (≥60 years)	2.00 (1.46–2.74)	<0.001*
Educational level (high school or below)	2.81 (1.98–4.01)	<0.001*
Monthly family income (¥)		
<4,000		
4,000–8,000	1.04 (0.72–1.52)	0.830
>8,000	0.46 (0.28–0.75)	0.002*
Medical insurance		
Medical insurance for urban workers		
Medical insurance for urban residents	0.97 (0.62–1.50)	0.879
New rural cooperative	1.26 (0.82–1.92)	0.295
Self pay	1.79 (0.97–3.29)	0.062
Distance (>20 km)	2.08 (1.47–2.96)	<0.001*
Course of disease (≤2 years)	3.13 (2.31–4.24)	<0.001*
Angina pectoris (yes)	1.65 (1.16–2.34)	0.005*
Post-PCI (yes)	0.73 (0.51–1.05)	0.093

Dependent variable assignment: adherence = 0, non-adherence = 1.
OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; Ref, Reference group.
*p < 0.01.

to not adhere to EECP treatment after discharge. However, patients with monthly family income over 8,000¥ (OR = 0.46, 95%CI: 0.28–0.75) were more likely to adhere to EECP treatment after discharge than those with household monthly income below 4,000¥.

Qualitative results

Sample characteristics

A total of 19 patients were interviewed, including 11 females and 8 males. The specific characteristics were shown in Table 3.

Barriers to adherence to EECP treatment after discharge

The qualitative results showed that the most important reasons for CHD patients not to adhere to EECP after discharge were insufficient understanding of the efficacy of EECP, distance and transportation, and lack of financial support. In addition, COVID-19, lack of time, negative attitude and lack of awareness of the disease also hinder patients' adherence to EECP treatment after discharge (Figure 1 and Table 4).

Insufficient understanding of EECP

The reason why most patients did not adhere to EECP treatment after discharge was due to insufficient understanding of the efficacy of EECP, especially older and less educated patients. Most patients were unaware of the benefits of adherence to EECP treatment.

> *"I'm a farmer, I do farm work at home, so these exercises don't do much for me".* [Male, 68 years]
>
> *"I have been hospitalized three times this year and each time I have been treated with EECP, but I never recovered. I think it useless to do so"* [Male, 71 years]

However, there were also some patients who believed that although EECP has brought benefits to their health, they thought their disease was much better after discharge than before hospitalization, so there was no need to continue treatment.

> *"EECP is indeed beneficial, but I feel much better after discharge, so I don't think it is necessary to continue treatment".* [Female, 63 years]

Affected by distance and traffic

As EECP was carried out in provincial hospitals, some patients in remote areas cannot continue to receive EECP treatment after discharge due to distance and transportation.

> *"Our home is too far from the hospital to come back every day for treatment".* [Male, 51 years]

TABLE 3 General characteristics of participants in the qualitative study.

Characteristics	All interviews ($N = 19$), n (%)/$\bar{x}\pm$SD (range)
Age (years)	61.33 ± 11.27 (40-81)
Educational level	7 (36.84)
Junior high or below	
High school	5 (26.32)
College or above	7 (36.84)
Occupation	6 (31.58)
Farmers	
Employed	7 (36.84)
Retiree	6 (31.58)
Financial support	5 (26.32)
No	
Yes	14 (73.68)
Distance (km)	9 (47.37)
≤20	
>20	10 (52.63)
Course of disease (years)	9 (47.37)
<2	
≥2	10 (52.63)
Angina pectoris	12 (63.16)
No	
Yes	7 (36.84)
History of surgery	12 (63.16)
No	
PCI	5 (26.32)
CABG	2 (10.53)

PCI, percutaneous coronary intervention; CABG, Coronary Artery Bypass Graft.

Lack of financial support

More than half of patients lacked financial support and considered that the 35-day course was too long and expensive.

> *"I also want to continue to adhere to EECP treatment, but I have no money. My economic situation is so poor that I have spent so much money in hospitalization. If I come to the hospital for treatment every day after discharge, it will be covered by outpatient reimbursement. The outpatient reimbursement rate is too low, which will cost too much".* [Female, 60 years]

In addition to the above three important factors, failure to adhere to EECP after discharge was also associated with the COVID-19, negative attitude, time and the awareness of disease.

> *"I got out of the hospital just as the COVID-19 was getting worse, and I had to give up".* [Male, 62 years]
>
> *"I know that this EECP has a good effect on my disease, but I have no time to hospital for treatment after discharge. I need to work, and the outpatient department of the hospital closes after I get off work in the evening, so I have no choice but to give up the rest of the course".* [Male, 46 years]

Importantly, negative attitude mainly occurred in female and angina patients.

> *"My chest pain has been incurable and has affected my life so much that I don't want treatment. I think I have an incurable disease".* [Female, 52 years]

Discussion

The results of this study showed that the adherence rate of CHD patients to EECP treatment after discharge was only 24.23%, which was similar to the adherence to exercise training programs in cardiac rehabilitation (16, 17). Studies have proved that adhering to a complete course of EECP treatment can not only improve the cardiac function of CHD patients, relieve the onset of angina, but also improve their sleep, anxiety, depression, and thus improve the quality of life (18–21). However, the dropout rate of CHD patients after discharge was quite high in this study. If patients only receive EECP treatment during hospitalization and do not adhere to EECP after discharge, the total duration of EECP treatment is too short, the expected therapeutic effect may not be achieved.

The results of this study showed that education level and disease duration were the two strongest predictors of the adherence of EECP treatment after discharge, which was consistent with Parashar et al.'s findings (22). Importantly, Rosengren et al. showed that education level is also one of the major risks factor for cardiovascular diseases (23). People with lower levels of education may be less aware of the importance of seeking timely care or have reduced access to information on how to access care and overcome existing barriers (23). These patients may often not understand the benefits of EECP for their health or believe that these health problems can be self-managed (4, 24). In the qualitative results, we found that insufficient understanding of the efficacy of EECP was the main reason for patients not to adhere to EECP treatment after discharge. Most of these patients were older and had lower education level, they believed that EECP was no different from exercise. Therefore, patients who could exercise alone had poor adherence after discharge. Meanwhile, some patients have a false perception that they are getting better after discharge and therefore there is no need to continue treatment, especially newly diagnosed patients. However, with longer time to diagnosis, patients' perceived risk

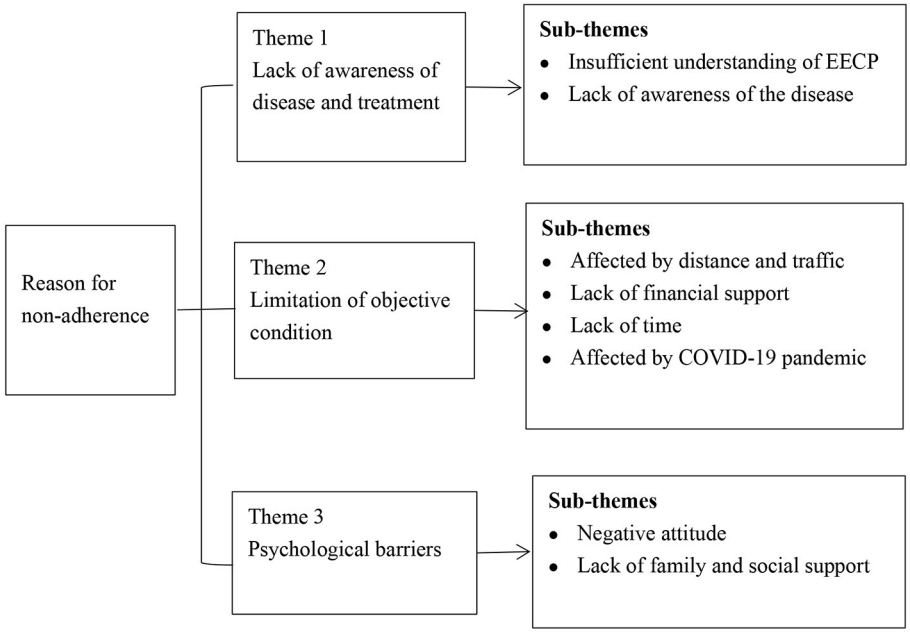


FIGURE 1
Diagrammatic of the themes and subthemes within the thematic framework.

of disease may increase, as well as access to knowledge and programs about cardiac rehabilitation.

Studies found that female patients were more likely to have multiple comorbidities, or believe that their disease was at high risk and that such participation was futile (25, 26), so this perception may be a barrier for patients to adhere to EECP treatment after discharge. Meanwhile, other studies have found that women were more likely to have problems with transportation and family responsibilities (27, 28). Interestingly, in the qualitative results we found that due to the limitations of disease, lack of financial resources and family support, female patients were more likely to have negative emotions, which became an important barrier to adhere to EECP treatment after discharge. Huffman et al. found that optimism and positive emotions can improve patients' adherence to cardiac rehabilitation (29). Therefore, medical workers should pay more attention to the patients' psychological problems, encourage caregivers to provide more family support. Meanwhile, nurses can also encourage patients with good prognosis to share their experiences and the importance of completing 35 h course of EECP, in order to relieve these patient' negative emotions and improve their confidence in disease treatment, thus helping to improve the adherence to EECP treatment after discharge.

In previous studies, distance has been reported as a common factor affecting adherence to cardiac rehabilitation (26, 30, 31). Our study showed that patients who live more than 20 km away from the hospital have poor adherence, which may be related to the fact that EECP treatment is carried out in provincial grade A hospitals, while most patients come from rural areas or other remote areas. Qualitative results showed that even though patients were aware of the importance of EECP adherence after discharge, they could not accept the time and expense of daily trips to and from the hospital, and as the cost of each EECP treatment is 75¥, which exceeds the expected cost of patients. Meanwhile, the reimbursement rate of treatment expenses after discharge is low, which greatly affects patients' adherence to EECP treatment. Therefore, the availability of EECP treatment in smaller tertiary hospitals or community centers and increased health insurance reimbursement rates will help improve patients' adherence to EECP treatment after discharge.

However, we found that patients with angina pectoris had poor adherence after discharge. Previous studies found that patients with angina pectoris were often hindered from participating in exercise training programs due to pain and limited activity, resulting in a higher dropout rate (32, 33). Importantly, in the qualitative results, we also found that patients with angina were more likely to have negative attitude, they had a wrong understanding that angina pectoris is an incurable disease, such practical issues need to be considered. In fact, they did not know that 35 h course of EECP has been shown to relieve angina attacks and reduce the use of nitroglycerin, which may also be related to a lack of physician advice and encouragement (34, 35). The intensity of physician encouragement was reported to be a key factor in determining patients to participate and adhere

TABLE 4 Analysis of causes and representative quotes of non-adherence to EECP in CHD patients after discharge.

Themes	Subthemes	Representative quotes
Lack of awareness of disease and treatment	Insufficient understanding of EECP	*"I'm a farmer, I do farm work at home, so these exercises don't do much for me"*
		"I have been hospitalized three times this year and each time I have been treated with EECP, but I never recovered. I think it useless to do so"
		"EECP is indeed beneficial, but I feel much better after discharge, so I don't think it is necessary to continue treatment"
	Lack of awareness of the disease	*"Only an operation can cure my disease"*
		"I have too many physical diseases, and I think my disease can only be slowly maintained by medication"
Limitation of objective condition	Affected by distance and traffic	*"Our home is too far from the hospital to come back every day for treatment"*
		"My house is not far from the hospital, but I can't drive, so it is not convenient to go to and from the hospital"
	Lack of financial support	*"I also want to continue to adhere to EECP treatment, but I have no money. My economic situation is so poor that I have spent so much money in hospitalization. If I come to the hospital for treatment every day after discharge, it will be covered by outpatient reimbursement. The outpatient reimbursement rate is too low, which will cost too much".*
		"The total duration of a course of EECP is too long and costly"
	Lack of time	*"I know that this EECP has a good effect on my disease, but I have no time to hospital for treatment after discharge. I need to work, and the outpatient department of the hospital closes after I get off work in the evening, so I have no choice but to give up the rest of the course"*
		"I have to take care of the elderly and children in my family, so I don't have time to go to the hospital for treatment every day"
	Affected by the COVID-19 pandemic	*"I got out of the hospital just as the COVID-19 was getting worse, and I had to give up"*
Psychological barriers	Negative attitude	*"My chest pain has been incurable and has affected my life so much that I don't want treatment. I think I have an incurable disease"*
		"I have an incurable disease, and I don't want any more treatment, any more burden on my family"
	Lack of family and social support	*"I did this EECP treatment during the hospital, which was useful for the improvement of my symptoms. After discharge, my family did not allow me to continue to do this treatment"*

to cardiac rehabilitation (36). This may also be due to the fact that EECP treatment has only been carried out in Gansu province in the past 2 years, and there was still a lack of understanding and knowledge of EECP among healthcare workers, so the information transmission to patients was not enough. In addition, due to the large workload and the fast turnover of patients, the health education for patients was not in place, resulting in the patients did not realize the importance of complete the remaining courses of EECP after discharge. Zhang et al. found that developing brochures or making educational videos for illiterate patients might help patients better understand the program (37). Therefore, it is necessary to formulate practical and effective training and health education to improve patients' understanding of the role of EECP and their motivation to adhere to treatment after discharge. In addition, offering EECP treatment during off-hours and weekends may improve compliance in more young patients.

Limitations

Our quantitative study was retrospective and did not cover all factors associated with non-adherence to EECP after discharge due to limited information in the medical record database. More prospective, multi-center studies are needed in the future to further explore the factors and obstacles affecting the EECP adherence in patients with coronary heart disease.

Conclusions

Patients with coronary heart disease had lower adherence to EECP treatment after discharge, especially elderly patients with lower education level. The main barriers include insufficient awareness of the efficacy of EECP, as well as the influence of distance and economic conditions. On the one hand, it is necessary to formulate practical and effective training and health education to improve patients' understanding of the role of EECP and their motivation to adhere to treatment after discharge. On the other hand, the availability of EECP treatment in smaller tertiary hospitals and community centers, with benefits through health insurance, will help improve patients' adherence to EECP treatment after discharge.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Gansu Provincial Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The conception and design of the study: JZ, YY, and QH. Acquisition of data: YY, RZ, YZ, and HC. Analysis and interpretation of data: YY, RZ, and HC. Drafting the article: YY and JZ. Revising the article: JZ, YY, YZ, and QH. Funding acquisition: JZ and QH. Final approval of the version to be submitted: all authors.

Funding

This research was funded by the Natural Science Foundation of Gansu Province (21JR7RA607 and 21JR7RA613), National Natural Science Foundation of China (72264002), the China Medical Education Association Project (2022KTZ010), and Health industry scientific research project of Gansu Province (GSWSKY-2019-50).

Acknowledgments

We thank all the healthcare workers in the Department of Cardiology for providing us with research resources in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action. *J Am Coll Cardiol.* (2020) 76:2980–1. doi: 10.1016/j.jacc.2020.11.021

2. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *Eur J Prev Cardiol.* (2016) 23:1715–33. doi: 10.1177/2047487316657669

3. Shah SA, Shapiro RJ, Mehta R, Snyder JA. Impact of enhanced external counterpulsation on Canadian Cardiovascular Society angina class in patients with chronic stable angina: a meta-analysis. *Pharmacotherapy.* (2010) 30:639–45. doi: 10.1592/phco.30.7.639

4. Turk-Adawi KI, Grace SL. Narrative review comparing the benefits of and participation in cardiac rehabilitation in high-, middle- and low-income countries. *Heart Lung Circ.* (2015) 24:510–20. doi: 10.1016/j.hlc.2014.11.013

5. Moradi B, Esmaeilzadeh M, Maleki M, Sari L. Factors associated with failure to complete phase II cardiac rehabilitation: survey registry in Rajaie

cardiovascular medical and research center. *Int Cardiovasc Res J.* (2011) 5:139–42. doi: 10.5812/icrj.4370

6. Cao Q, Xu L, Wen S, Li F. Investigating the Influence of the Shared Decision-Making Perception on the Patient Adherence of the Home- and Exercise-Based Cardiac Rehabilitation After Percutaneous Coronary Intervention. *Patient Prefer Adherence.* (2021) 15:411–22. doi: 10.2147/PPA.S292178

7. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. *Circulation.* (2002) 106:1237–42. doi: 10.1161/01.CIR.0000028336.95629.B0

8. Wu F, John CH. Cardiovascular disease rehabilitation prescription-enhanced external counterpulsation application international expert consensus. *Chin J Int Med.* (2014) 53:587–90.

9. Holmes DR Jr. Treatment options for angina pectoris and the future role of enhanced external counterpulsation. *Clin Cardiol.* (2002) 25:II22–5. doi: 10.1002/clc.4960251407

10. Braith RW, Casey DP, Beck DT. Enhanced external counterpulsation for ischemic heart disease: a look behind the curtain. *Exerc Sport Sci Rev.* (2012) 40:145–52. doi: 10.1097/JES.0b013e318253de5e

11. Braverman DL. Enhanced external counterpulsation: a novel therapy for angina. *Complement Ther Clin Pract.* (2012) 18:197–203. doi: 10.1016/j.ctcp.2012.06.004

12. Yang DY, Wu GF. Vasculoprotective properties of enhanced external counterpulsation for coronary artery disease: beyond the hemodynamics. *Int J Cardiol.* (2013) 166:38–43. doi: 10.1016/j.ijcard.2012.04.003

13. Manchanda A, Soran O. Enhanced external counterpulsation and future directions: step beyond medical management for patients with angina and heart failure. *J Am Coll Cardiol.* (2007) 50:1523–31. doi: 10.1016/j.jacc.2007.07.024

14. Mi SL, Qian JY, Wu YJ, Zhang JJ, Huo Y, Ge JB. Chinese expert consensus on enhanced extracorporeal counterpulsation therapy for chronic coronary syndrome. *Chin J Interven Cardiol.* (2022) 30:81–7.

15. Braun VB, Clark V. Using thematic analysis in psychology. *Qual Res Psychol.* (2006) 3:77–101. doi: 10.1191/1478088706qp063oa

16. Way KL, Vidal-Almela S, Keast ML, Hans H, Pipe AL, Reed JL. The feasibility of implementing high-intensity interval training in cardiac rehabilitation settings: a retrospective analysis. *BMC Sports Sci Med Rehabil.* (2020) 12:38. doi: 10.1186/s13102-020-00186-9

17. Thompson MP, Yaser JM, Hou H, Syrjamaki JD, DeLucia A. 3rd, Likosky DS, et al. Determinants of hospital variation in cardiac rehabilitation enrollment during coronary artery disease episodes of care. *Circ Cardiovasc Qual Outcomes.* (2021) 14:e007144. doi: 10.1161/CIRCOUTCOMES.120.007144

18. Sardari A, Hosseini SK, Bozorgi A, Lotfi-Tokaldany M, Sadeghian H, Nejatian M. Effects of enhanced external counterpulsation on heart rate recovery in patients with coronary artery disease. *J Tehran Heart Cent.* (2018) 13:13–7.

19. Caceres J, Atal P, Arora R, Yee D. Enhanced external counterpulsation: A unique treatment for the "No-Option" refractory angina patient. *J Clin Pharm Ther.* (2021) 46:295–303. doi: 10.1111/jcpt.13330

20. Shaker SR, Al-Amran F, Fatima G, Al-Aubaid H, Hadi NR. Trimetazidine improves the outcome of EECP therapy in patients with refractory angina pectoris. *Med Arch.* (2020) 74:199–204. doi: 10.5455/medarh.2020.74.199-204

21. Wu E, Desta L, Broström A, Mårtensson J. Effectiveness of enhanced external counterpulsation treatment on symptom burden, medication profile, physical capacity, cardiac anxiety, and health-related quality of life in patients with refractory angina pectoris. *J Cardiovasc Nurs.* (2020) 35:375–85. doi: 10.1097/JCN.0000000000000638

22. Parashar S, Spertus JA, Tang F, Bishop KL, Vaccarino V, Jackson CF, et al. Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction. *Circulation.* (2012) 126:1587–95. doi: 10.1161/CIRCULATIONAHA.111.088799

23. Rosengren A, Smyth A, Rangarajan S, Ramasundarahettige C, Bangdiwala SI, AlHabib KF, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *Lancet Glob Health.* (2019) 7:e748–60. doi: 10.1016/S2214-109X(19) 30045-2

24. Prabhu NV, Maiya AG, Prabhu NS. Impact of cardiac rehabilitation on functional capacity and physical activity after coronary revascularization: a scientific review. *Cardiol Res Pract.* (2020) 2020:1236968. doi: 10.1155/2020/1236968

25. Grace SL, Tan Y, Simpson C, Chessex C. Perceptions of cardiac specialists and rehabilitation programs regarding patient access to cardiac rehabilitation and referral strategies. *J Cardiopulm Rehabil Prev.* (2012) 32:135–40. doi: 10.1097/HCR.0b013e31824e2df2

26. Kotseva K, Wood D, De Bacquer D, EUROASPIRE investigators. Determinants of participation and risk factor control according to attendance in cardiac rehabilitation programmes in coronary patients in Europe: EUROASPIRE IV survey. *Eur J Prev Cardiol.* (2018) 25:1242–51. doi: 10.1177/2047487318781359

27. Chamosa S, Alarcón JA, Dorronsoro M, Madruga FJ, Barrera J, Arrazola X, et al. Predictors of Enrollment in Cardiac Rehabilitation Programs in Spain. *J Cardiopulm Rehabil Prev.* (2015) 35:255–62. doi: 10.1097/HCR.0000000000000126

28. Oosenbrug E, Marinho RP, Zhang J, Marzolini S, Colella TJ, Pakosh M, et al. Sex differences in cardiac rehabilitation adherence: a meta-analysis. *Can J Cardiol.* (2016) 32:1316–24. doi: 10.1016/j.cjca.2016.01.036

29. Huffman JC, Moore SV, DuBois CM, Mastromauro CA, Suarez L, Park ER. An exploratory mixed methods analysis of adherence predictors following acute coronary syndrome. *Psychol Health Med.* (2015) 20:541–50. doi: 10.1080/13548506.2014.989531

30. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. a systematic review. *Int J Cardiol.* (2016) 223:436–43. doi: 10.1016/j.ijcard.2016.08.120

31. Heydarpour B, Saeidi M, Ezzati P, Soroush A, Komasi S. Sociodemographic predictors in failure to complete outpatient cardiac rehabilitation. *Ann Rehabil Med.* (2015) 39:863–71. doi: 10.5535/arm.2015.39.6.863

32. Wittmer M, Volpatti M, Piazzalonga S, Hoffmann A. Expectation, satisfaction, and predictors of dropout in cardiac rehabilitation. *Eur J Prev Cardiol.* (2012) 19:1082–8. doi: 10.1177/1741826711418163

33. Sumner J, Grace SL, Doherty P. Predictors of cardiac rehabilitation utilization in England: results from the national audit. *J Am Heart Assoc.* (2016) 5:e003903. doi: 10.1161/JAHA.116.003903

34. Abdelwahab AA, Elsaied AM. Can enhanced external counter pulsation as a non-invasive modality be useful in patients with ischemic cardiomyopathy after coronary artery bypass grafting? *Egypt Heart J.* (2018) 70:119–23. doi: 10.1016/j.ehj.2018.01.002

35. Sahebjami F, Madani FR, Komasi S, Heydarpour B, Saeidi M, Ezzati K, et al. Refractory angina frequencies during 7 weeks treatment by enhanced external counterpulsation in coronary artery disease patients with and without diabetes. *Ann Card Anaesth.* (2019) 22:278–82. doi: 10.4103/aca.ACA_86_18

36. Grace SL, Shanmugasegaram S, Gravely-Witte S, Brual J, Suskin N, Stewart DE. Barriers to cardiac rehabilitation: DOES AGE MAKE A DIFFERENCE? *J Cardiopulm Rehabil Prev.* (2009) 29:183–7. doi: 10.1097/HCR.0b013e3181a3333c

37. Zhang L, Zhang L, Wang J, Ding F, Zhang S. Community health service center-based cardiac rehabilitation in patients with coronary heart disease: a prospective study. *BMC Health Serv Res.* (2017) 17:128. doi: 10.1186/s12913-017-2036-3

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 20 December 2022
DOI 10.3389/fcvm.2022.1020488

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Roberto Franco Enrico Pedretti,
MultiMedica Scientific and Technological Pole, MultiMedica (IRCCS), Italy
Ana Teresa Timoteo,
Hospital de Santa Marta, Portugal

*CORRESPONDENCE
Yu Cao
caoyu@wchscu.cn
Zhi Zeng
zengzhi2013@qq.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 16 August 2022
ACCEPTED 02 December 2022
PUBLISHED 20 December 2022

CITATION
Li D, Chen X, Li F, Jia Y, Li Z, Liu Y, Ye L, Gao Y, Zhang W, Li H, Zeng R, Wan Z, Zeng Z and Cao Y (2022) Evaluation of risk stratification program based on trajectories of functional capacity in patients with acute coronary syndrome: The REACP study. *Front. Cardiovasc. Med.* 9:1020488. doi: 10.3389/fcvm.2022.1020488

Evaluation of risk stratification program based on trajectories of functional capacity in patients with acute coronary syndrome: The REACP study

Dongze Li[1†], Xiaoli Chen[1†], Fanghui Li[2], Yu Jia[1], Zhilin Li[1], Yi Liu[1], Lei Ye[1], Yongli Gao[1], Wei Zhang[1], Hong Li[1], Rui Zeng[2], Zhi Wan[1], Zhi Zeng[1*] and Yu Cao[1*]

[1]Department of Emergency Medicine and West China School of Nursing, Laboratory of Emergency Medicine, Disaster Medical Center, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China, [2]Department of Cardiology, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

Background: As a validated assessment tool for functional disability (activities of daily living), the Barthel index (BI) assessed initially at admission has the potential to stratify patients with high-risk acute coronary syndrome (ACS). Dynamic trajectory evaluation of functional capacity in hospitals may provide more prognostic information. We aimed to establish a novel dynamic BI-based risk stratification program (DBRP) during hospitalization to predict outcomes among ACS patients.

Methods: A total of 2,837 ACS patients were included from the Retrospective Multicenter Study for Early Evaluation of Acute Chest Pain. The DBRP rating (low, medium, and high-risk categories) was calculated from dynamic BI at admission and discharge. The primary outcome was all-cause mortality, and the secondary outcome was cardiac mortality.

Results: Of all the included patients, 312 (11%) died during a median follow-up period of 18.0 months. Kaplan–Meier analysis revealed that the cumulative mortality was significantly higher in patients in the higher risk category according to the DBRP. Multivariable Cox regression analysis indicated that, compared to the low-risk category, the higher risk category in the DBRP was an independent strong predictor of all-cause mortality after adjusting for confounding factors (medium-risk category: hazard ratio [HR]: 1.756, 95%

confidence interval [95% CI]: 1.214–2.540; $P = 0.003$; high-risk category: HR: 5.052, 95% CI: 3.744–6.817; $P < 0.001$), and the same result was found for cardiac mortality.

Conclusion: The DBRP was a useful risk stratification tool for the early dynamic assessment of patients with ACS.

Clinical trial registration: [http://www.chictr.org.cn], identifier [ChiCTR1900024657].

KEYWORDS

acute coronary syndrome, trajectory, functional capacity, risk stratification, activities of daily living

1 Introduction

Acute coronary syndrome (ACS) is a life-threatening emergent condition of coronary artery disease mainly caused by coronary plaque rupture with relatively high mortality and morbidity (1). Risk stratification in patients with ACS facilitates treatment decisions and improves survival rates (1–4). Current guidelines regarding ACS management emphasize the importance of risk assessment for identifying patients with a higher mortality risk requiring more aggressive care and therapy, selecting the optimal care site, and matching therapeutic intensity with risk (1, 5, 6). Previous studies indicated that risk evaluation based on the Global Registry of Acute Coronary Events (GRACE) or thrombolysis in myocardial infarction (TIMI) risk scores have been well-implemented for and proved to be clinically beneficial to patients with ACS, and the ACS guidelines recommend that the GRACE score should be completed within 24 h and re-evaluated before discharge to guide the management of ACS (5–9).

Nearly 38% of in-hospital deaths occur within the first 24 h of symptom onset in patients with AMI; therefore, early, rapid, and dynamic risk assessment identifying high-risk patients is necessary to guide treatment decisions in the emergency department (ED) (10). However, assessment using these risk scores, including GRACE or TIMI, is relatively time consuming and cannot be completed without a medical examination because these scoring systems consist of components including biomarkers of myocardial and other related organ injuries. In addition, the condition of patients with ACS can change rapidly, and the continuous dynamic assessment of ACS patients may provide more prognostic information during the whole course of ACS (11). With this in mind, current scoring systems cannot also immediately stratify patients out of hospitals or during hospitalization, and realize the timely revision of their risk level. This suggests the need for simpler, more accurate dynamic assessment and better treatment decision tools or algorithms to guide individual healthcare during the pre-hospital, admission, in-hospital, and discharge settings.

Activities of daily living (ADL), as a basic functional capacity marker assessed by the Barthel Index (BI) score based on difficulty degrees of daily activities without any laboratory or imaging examination results, has gained interest in recent years as a prognostic indicator in patients with cardiovascular emergency conditions (12, 13). Performance of the ADL assessment is nowadays feasible in the ambulance and, therefore, the functional capacity assessment can be completely obtained in the pre-hospital, in-hospital, or even discharge settings. A previous study indicated that the initial ADL assessed by the BI at the ED has the potential to stratify high-risk patients with ACS, and independently associated with mortality, however, the accuracy was inferior to that of the GRACE score (12). In addition, patients with ACS would receive optimal drug therapy and/or PCI during hospitalization, patient's ADL should be improved if patients responded well to the treatment therapy, and maybe the elevated change in ADL assessed by BI scores during hospitalization suggested that the improvement of myocardial ischemia or less complications after treatment in hospital. It is possible that the continuous dynamic assessment of functional capacity trajectories may provide more prognostic information for patients with ACS. However, the assessment of functional status at admission or the deterioration in functional status during hospitalization has received little consideration and has not been studied as a potential risk prognostic tool for risk stratification of ACS. Therefore, we conducted this multicenter retrospective cohort study to establish a novel dynamic BI-based risk stratification program (DBRP) based on

Abbreviations: ACS, acute coronary syndrome; ACP, acute chest pain; ADL, activities of daily living; AUC, area under the curve; BI, Barthel index; DBRP, dynamic Barthel index-based risk stratification program; ED, emergency department; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-segment elevation myocardial infarction; NST-ACS, non-ST elevation acute coronary syndrome; REACP, retrospective evaluation of acute chest pain; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UA, unstable angina.

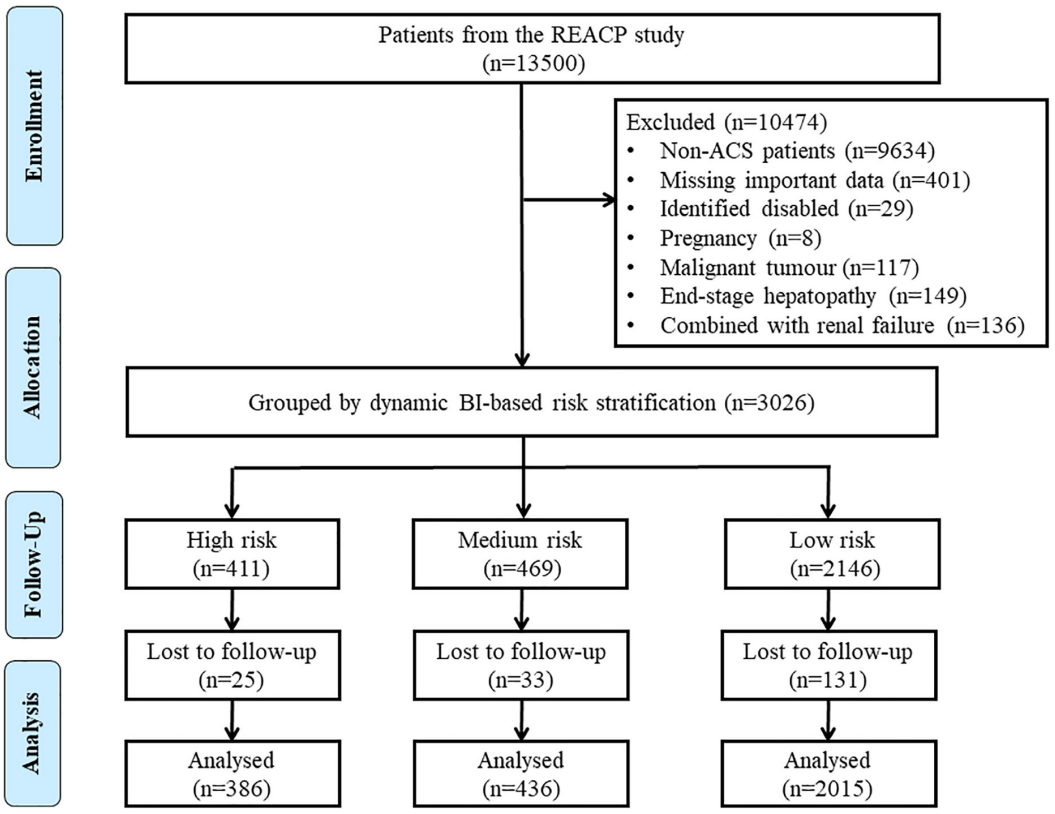


FIGURE 1
Flow chart of the enrollment of participants in the study. ACS, acute coronary syndrome; BI, Barthel index; REACP, the multicentre retrospective evaluation of acute chest pain study.

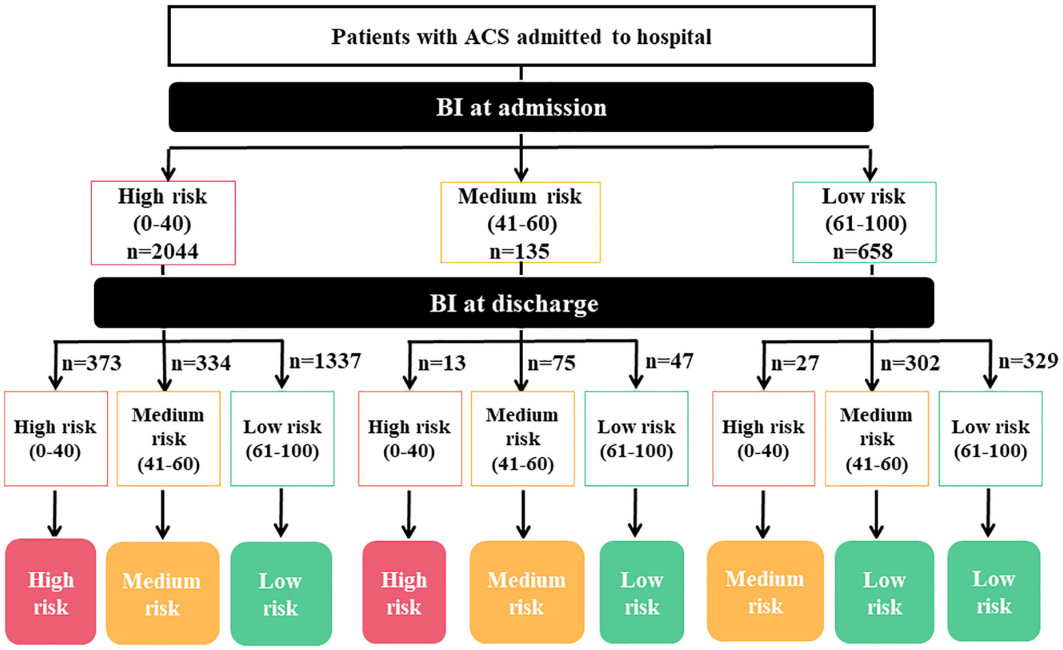


FIGURE 2
Diagram of the detailed rules for dynamic BI-based risk stratification. BI, Barthel index.

TABLE 1 Relationships between baseline clinical characteristics and the DBRP in patients with acute coronary syndrome.

Characteristic	High-risk (*n* = 386)	Medium-risk (*n* = 436)	Low-risk (*n* = 2,015)	*P*-value
Demographic variables				
Age, years	70.5 ± 13.9	69.6 ± 13.1	63.6 ± 12.4	<0.001
Males, n (%)	264 (68.4%)	288 (66.1%)	1569 (77.9%)	<0.001
Smoking, n (%)	181 (46.9%)	204 (46.8%)	1162 (57.7%)	<0.001
Drinking, n (%)	89 (23.1%)	114 (26.3%)	695 (34.5%)	<0.001
Chronic medical conditions				
Hypertension, n (%)	210 (54.4%)	264 (60.6%)	1055 (52.4%)	0.008
Diabetes, n (%)	126 (32.6%)	147 (33.7%)	489 (24.3%)	<0.001
Hyperlipidemia, n (%)	37 (9.6%)	53 (12.2%)	253 (12.6%)	0.260
COPD, n (%)	20 (5.2%)	19 (4.4%)	45 (2.2%)	0.001
Physiological and lab variables				
BMI, kg/m^2	23.4 ± 3.6	23.9 ± 3.6	24.4 ± 3.2	<0.001
Admission SBP, mmHg	123 ± 25.8	131.2 ± 25.3	129.4 ± 23.4	<0.001
Admission DBP, mmHg	74.8 ± 17.1	77.4 ± 15.6	79.5 ± 15.4	<0.001
Heart rate, /min	87.0 ± 22.8	81.9 ± 18.8	79.4 ± 16.8	<0.001
Killip class ≥ 2, n (%)	233 (60.4%)	223 (51.1%)	770 (38.2%)	<0.001
LVEF, (%)	49.0 ± 13.3	53.1 ± 12.1	55.4 ± 11.2	<0.001
WBC, $10^9/L$	10.6 ± 4.3	9.6 ± 3.6	9.2 ± 3.5	<0.001
Neutrophil, $10^9/L$	7.9 ± 3.9	7.7 ± 3.6	7.3 ± 3.5	<0.001
CRP, mg/L	46.5 (15.9–90.2)	5.1 (2.8–12.9)	6.6 (2.7–33.2)	<0.001
IL-6, pg/mL	28.3 (13.3–52.8)	9.5 (5.4–26.3)	12.6 (6.4–43.4)	<0.001
NLR	5.5 (2.9–10.1)	5.5 (3.2–9.0)	5.0 (3.0–8.4)	0.009
Platelet count, $10^9/L$	170.5 (135–213)	174 (138–223)	177 (140–219)	0.755
D-dimer, mg/L	0.8 (0.4–1.9)	0.6 (0.3–1.1)	0.3 (0.2–0.7)	<0.001
Fibrinogen, g/L	3.4 (2.7–4.6)	3.3 (2.7–4.3)	2.9 (2.4–3.7)	<0.001
Blood glucose, mmol/L	8.1 (6.5–11.2)	7.8 (6.4–10.4)	7.4 (6.1–9.7)	<0.001
Creatinine, μmol/L	90 (71.5–130.5)	82 (69–106)	77 (65–91)	
BUN, mmol/L	7.1 (5.3–10.3)	6.2 (5–8.6)	5.6 (4.5–7)	<0.001
Triglycerides, mmol/L	1.2 (0.8–1.6)	1.3 (0.9–2.1)	1.5 (0.9–2.2)	<0.001
Total cholesterol, mmol/L	4.2 ± 1.2	4.3 ± 1.3	4.5 ± 1.3	<0.001
HDL, mmol/L	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	0.006
LDL, mmol/L	2.6 ± 1.1	2.7 ± 1.1	2.8 ± 1.1	0.001
NT-proBNP, pg/mL	2399 (382–6316)	1490 (404–4221)	499 (138–1594)	<0.001
CTn T pg/mL	1020 (191–4322)	387 (60–1872)	301 (31–1517)	<0.001
Creatinine kinase, IU/L	290 (126–1150)	155 (72–627)	172 (87–675)	0.008
CK-MB, U/L	14.3 (4.1–76.9)	7.4 (2.5–32.4)	6.5 (2.1–52.1)	0.083
Stenotic coronary arteries*				
Left main, n (%)	75/374 (20.1%)	94/426 (22.1%)	330/1985 (16.6%)	0.015
LAD, n (%)	249/374 (66.6%)	358/426 (84.0%)	1737/1985 (87.5%)	<0.001
Left circumflex, n (%)	215/374 (57.5%)	299/426 (70.2%)	1305/1985 (65.7%)	0.001
RCA, n (%)	230/374 (61.5%)	331/426 (77.7%)	1546/1985 (77.9%)	<0.001

(Continued)

TABLE 1 (Continued)

Characteristic	High-risk (*n* = 386)	Medium-risk (*n* = 436)	Low-risk (*n* = 2,015)	*P*-value
Risk score				
GRACE score	170.0 ± 45.7	153.2 ± 37.6	139.2 ± 35.7	<0.001
Gensini score*	84 (43–120)	67 (37–107)	56 (29–90)	<0.001
Treatment				0.002
PCI, n (%)	267 (69.2%)	348 (79.8%)	1521 (75.5%)	
Optimal drug therapy, n (%)	119 (30.8%)	88 (20.2%)	494 (24.5%)	

SBP, systolic blood pressure; DBRP, dynamic Barthel index-based risk stratification program; DBP, diastolic blood pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CTn T, cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; CK-MB, creatinine kinase-myocardial band isoenzyme; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; LAD, left anterior descending; NLR, neutrophil-to-lymphocyte ratio; RCA, right coronary artery; GRACE, the Global Registry of Acute Coronary Events score; PCI, percutaneous coronary intervention.
*Two thousand seven hundred and eighty-five patients received coronary angiography, and other 52 patients refuse to undergo coronary angiography.

functional capacity trajectories during hospitalization for long-term outcomes and evaluate the prediction efficiency of this risk assessment tool in patients with ACS.

2 Materials and methods

2.1 Study design and setting

The Retrospective Evaluation of Acute Chest Pain (REACP) study is a multicenter, retrospective study including a cohort of patients with acute chest pain (ACP) who were admitted to EDs from seven tertiary hospitals in China from January 2017 to December 2019 (clinicaltrials.gov, identifier: ChiCTR1900024657) (12, 14). This study was conducted to elucidate the development of fatal chest pain (ACS, aortic dissection, and pulmonary embolism) and the risk factors in the suspected population. This study was conducted in accordance with the Declaration of Helsinki and approved by local or central institutional review.

2.2 Study population

In this study, we aimed to establish a novel DBRP based on admission and hospital-acquired BI score for risk stratification in ACS patients. The inclusion criteria were as follows: age greater than 18 years, first-time diagnosis of ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI), and unstable angina (UA), less than 12 h between the onset of symptoms and ED admission, and treatment with coronary angiography or primary percutaneous coronary intervention in the hospital. The exclusion criteria were as follows: accompanied by the identified disabled (including previous stroke, severe valvular heart disease, heart failure, chronic obstructive pulmonary disease, rheumatological diseases, trauma diseases, and other diseases with possible impact in BI assessment), malignant tumors, pregnancy, end-stage hepatopathy, or renal failure at admission. A diagram demonstrating the election of patients is shown in **Figure 1**.

2.3 Data collection and measures

In this study, the BI scores of ACS patients were assessed by trained nurses at admission and discharge. The details of evaluating BI scores were described in our previous study (12). Briefly, the BI score comprises 10 items: feeding, toilet use, bathing, grooming, dressing, bowel and bladder control, chair transferring, stair climbing, and ambulating. Each item is scored proportionally, and a given number of points are assigned to each level or rank. The admission and discharge BI assessments were conducted according to responses from the ACS patient or a family member. We divided the BI score into three different level categories according to the standard BI grouping method: high disability caused by ADL (0–40), considered high risk, moderate disability caused by ADL (41–60), considered medium risk, low disability caused by ADL (61–100), considered low risk (12).

We obtained demographic data, characteristic details, and clinical features of the patients from the database of the REACP study, including medical histories, vital signs, electrocardiograms, troponin I/T, myocardial enzymes, liver and renal function, coronary angiography (CAG) findings, echocardiography findings, inpatient complications, pre-hospital and in-hospital treatment and discharge medication. Standard case report forms were used to collect these data; the details were described in our previous publications (3, 4, 12, 15, 16).

2.4 Risk stratification score based on dynamic BI scores

In this study, we established a novel DBRP consisting of the low, medium, and high-risk categories, based on admission

BI, discharge BI and the changes between the two. In terms of the BI changes, "largely improved" was defined as two levels of improvement; for example, BI changes from the high risk (0–40) to the low-risk category (61–100); "slightly improved" was defined as one level of improvement; for example, BI changes from the high-risk category (0–40) to the medium-risk category (41–60); "largely declined" was defined as two levels of worsening; for example, BI changes from low risk (61–100) to high risk (0–40); "slightly declined" was defined as one level of worsening; for example, BI changes from the medium risk (41–60) to the high-risk category (0–40); "no change" was defined as the risk group at discharge BI remaining the same as that on admission. In particular, for dead patients within hospitalization, the BI at discharge was signed to high risk (0–40). The detailed rules for risk stratification based on the DBRP are described in **Figure 2**.

2.5 Outcome and follow-up

The primary endpoint of this study was all-cause mortality, confirmed through a combination of hospital medical records and telephone contact with the patient's family members. The secondary outcome was cardiac death, identified based on hospital record reviews for identified hospitalizations and through phone interviews. All reported events were reviewed and verified by the outcome assessment committee of the REACP study.

2.6 Statistical analysis

Parametric continuous variables are expressed as means ± standard deviations (SD) and non-parametric continuous variables as medians with interquartile ranges. Categorical variables are reported as frequencies and percentages. Parametric patient characteristics were compared using one-way analysis and non-parametric variables using the Kruskal–Wallis H test. Categorical variables were compared using Fisher's exact test or chi-square test.

The Kaplan–Meier survival analysis and log-rank tests were performed to calculate and compare the cumulative survival of ACS patients with different risk levels. Cox proportional hazards models were used to investigate the relationship between risk levels according to dynamic BI-based risk stratification and time-to-mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the multivariate Cox regression model after adjusting for potential influencing factors. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and Cohen's Kappa coefficient were calculated to evaluate the predictive efficiency of DBRP and GRACE score. Receiver operating

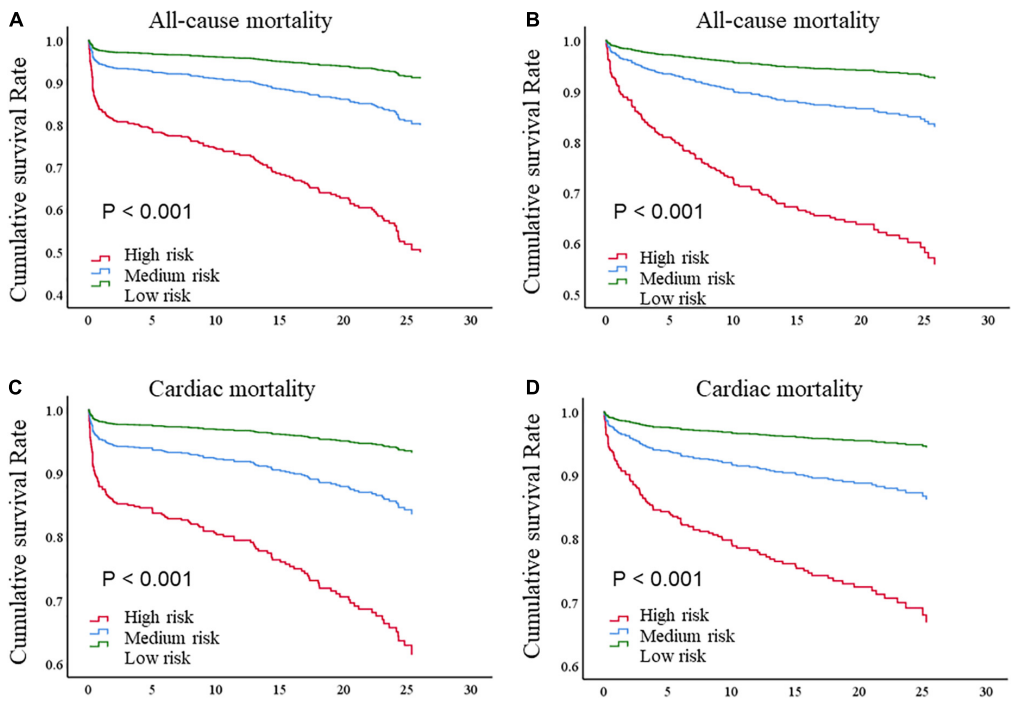


FIGURE 3
Kaplan–Meier survival curve of **(A)** all-cause death for STEMI patients; **(B)** all-cause death for NST-ACS patients; **(C)** cardiac death for STEMI patients; **(D)** cardiac death for NST-ACS patients; by risk levels according to dynamic BI-based risk stratification. BI, Barthel index; STEMI, ST-segment elevation myocardial infarction; NST-ACS, non-ST elevation acute coronary syndrome.

TABLE 2 Cox regression analysis regarding correlations between clinical outcomes and the DBRP.

Variables	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality								
Low-risk	REF.	–	REF.	–	REF.	–	REF.	–
Medium-risk	2.352 (1.721–3.215)	<0.001	1.891 (1.350–2.650)	<0.001	1.959 (1.390–2.759)	<0.001	1.756 (1.214–2.540)	0.003
High-risk	7.499 (5.853–9.606)	<0.001	5.086 (3.842–6.733)	<0.001	5.079 (3.818–6.757)	<0.001	5.052 (3.744–6.817)	<0.001
Cardiac mortality								
Low-risk	REF.	–	REF.	–	REF.	–	REF.	–
Medium-risk	2.536 (1.791–3.592)	<0.001	2.055 (1.427–2.959)	<0.001	2.095 (1.446–3.034)	<0.001	1.865 (1.252–2.779)	0.002
High-risk	7.056 (5.296–9.402)	<0.001	4.865 (3.556–6.656)	<0.001	4.851 (3.529–6.668)	<0.001	4.780 (3.423–6.673)	<0.001

Model 1: adjusted by age, sex, admission systolic blood pressure, smoking, drinking, body mass index, hypertension, diabetes.
Model 2: adjusted by model 1 plus white blood cell count, creatinine kinase-myocardial band isoenzyme, cardiac troponin T, blood urea nitrogen.
Model 3: adjusted by model 2 plus Global Registry of Acute Coronary Events score and Gensini score. CI, confidence interval; DBRP, dynamic Barthel index-based risk stratification program; HR, hazard ratio; REF, reference.

characteristic (ROC) analyses for the DBRP and GRACE score were performed, and differences in mortality between these indicators were compared using the area under the curve (AUC) values with the method of DeLong et al. (17).

Subgroup analysis was performed to test the robustness of the association between the Dynamic BI-based risk stratification score and the all-cause mortality. A two-tailed P-value < 0.05 was considered significant for all tests. Statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA) and R Statistical Software (v4.1.2; R Core Team 2021) (18).

3 Results

3.1 Baseline patient characteristics

A total of 2,837 ACS patients were enrolled with an average age of 65.5 ± 13.0 years. Of these participants, 2,121 (74.7%) were male. According to the dynamic BI-based risk stratification program (DBRP), patients were divided into three groups: the high-risk (n = 386, 13.6%), medium risk (n = 436, 15.4%), and low-risk groups (n = 2,015, 71.0%). During a median follow-up period of 18.0 (10.3–24.2) months, a total of 312 (11.0%) patients died, of whom 237 (8.3%) died due to cardiac causes. The baseline characteristics of patients in these three groups are described and compared in **Table 1**. Compared to those in the low-risk group, participants in the high-risk group were older, had lower body mass indexes (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), triglycerides, total cholesterol, and low-density lipoprotein (LDL), and had higher heart rates, fibrinogen, blood glucose, creatinine, BUN, N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T, creatinine kinase, CK-MB levels, GRACE scores, and Genisini scores, and were more likely to have chronic obstructive pulmonary disease (COPD) and Killip classes ≥ 2. Several common inflammatory and thrombus indicators, namely white blood cells (WBC), neutrophil, C-reactive protein (CRP), interleukin 6, neutrophil-to-lymphocyte ratio (NRL), and D-dimer, were significantly higher in the high-risk category of DBRP than in the low-risk category (NLR, $P = 0.009$; all others, $P < 0.001$).

3.2 The dynamic BI-based risk stratification program and clinical outcomes

Kaplan–Meier analysis (**Figure 3**) revealed that the cumulative mortality was significantly higher in patients in the higher risk category according to the DBRP, regardless of STEMI and non-ST segment elevation acute coronary syndrome (NST-ACS), in both all-cause mortality and cardiac mortality ($P < 0.001$ for all). Multivariable Cox regression

analysis further indicated compared to participants with the low-risk category, the higher risk category in the DBRP was an independent strong predictor of both all-cause mortality and cardiac mortality after eliminating confounding factors (all-cause mortality: medium-risk category: HR: 1.756, 95% CI: 1.214–2.540; $P = 0.003$; high-risk category: HR: 5.052, 95% CI: 3.744–6.817; $P < 0.001$; cardiac mortality: medium-risk category: HR: 1.865, 95% CI: 1.252–2.779; $P = 0.002$; high-risk category: HR: 4.780, 95% CI: 3.423–6.673; $P < 0.001$; Table 2).

3.3 The dynamic BI-based risk stratification program and its predictive efficiency

The sensitivity, specificity, accuracy, PPV, and NPV for mortality of the dynamic BI-based risk stratification, when high-risk was taken as the cut point, were 42.0, 89.9, 84.6, 33.9, and 92.6%, respectively. And the Cohen's Kappa coefficient was 0.289 (95%CI: 0.240–0.338, $P < 0.001$). When medium-risk was used as the cutoff point, the sensitivity, specificity, accuracy, PPV, and NPV for mortality of the dynamic BI-based risk stratification were 60.6, 74.9, 73.4, 23.0, and 93.9%, respectively. The Cohen's Kappa coefficient was 0.207 (95% CI: 0.171–0.242, $P < 0.001$). We also evaluated the predictive efficiency of the GRACE score, using guideline-recommended 140 and 108 as cutoff points, respectively. The specific results were shown in Table 3. The AUC generated using the ROC curve analysis found no significant differences in AUCs for all-cause mortality between the DBRP (low, medium, and high risk) and GRACE score (140 and 108 as cutoff points) (AUC, 0.700 vs. 0.698, $P > 0.05$), however, the AUC of GRACE score (AUC, 0.791, $P < 0.001$) was higher than that of categorical DBRP for all-cause mortality.

3.4 Subgroup analysis

We carried out subgroup analysis by grouping patients according to gender, age, BMI, SBP, DBP, heart rate, WBC, cardiac troponin T, NT-proBNP, Killip class, GRACE score, and ACS type. Patients in the high-risk group had the lowest cumulative survival rates of all-cause mortality in each subgroup (Table 4).

4 Discussion

This study established a novel dynamic BI-based risk stratification program (DBRP) using admission and discharge BI, and the changes between them for risk assessment in ACS patients and investigated whether the DBRP was efficient in predicting the prognosis of patients with ACS. Our findings demonstrated that the DBRP could accurately predict the prognosis of ACS patients. Patients with high and medium risks were correlated with an increased risk of all-cause mortality and cardiac mortality compared to those with low risk. Higher risk independently predicted a worse prognosis in ACS patients.

Our previous study demonstrated that the BI scores assessed at admission were a valuable prognostic predictor for patients with ACS, predicting all-cause mortality and cardiac mortality both in-hospital and during follow-up (12). According to the BI scores at admission, the HR for mortality of patients in the high-risk group is twice that of patients in the low-risk group. One study focusing on older ACS patients (≥85 years) found that the BI scores assessed at discharge were correlated with 1-year mortality in these patients (13). However, the development of the disease process is ever-changing; thus, dynamic assessment may provide more valuable information (11).

The BI score at admission reflects the ADL of patients before medical intervention, which shows the initial status of the patient after the onset of illness, while the BI score assessed at discharge reflects the ADL of patients after receiving medical intervention, indicating the patient's current status. The change between these two indices provided information on disease development and therapeutic effects. The DBRP comprehensively evaluates these three items, which may more accurately predict the prognosis of ACS patients. In addition, the elevated change in ADL assessed by BI scores during

TABLE 3 Predictive efficiency for mortality of the DBRP and GRACE score in acute coronary syndrome patients.

Values	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	Kappa (95% CI)
DBRP						
High risk	42.0	89.9	84.6	33.9	92.6	0.289 (0.240–0.338)
Medium risk	60.6	74.9	73.4	23.0	93.9	0.207 (0.171–0.242)
GRACE score						
140	85.9	52.5	56.2	18.3	96.8	0.146 (0.124–0.168)
108	97.1	18.8	27.4	12.9	98.1	0.041 (0.033–0.049)

AUC, area under the curve; DBRP, dynamic Barthel index-based risk stratification program; PPV, positive predictive value; NPV, negative predictive value; BI, Barthel index; CI, confidence interval; GRACE, the Global Registry of Acute Coronary Events.

hospitalization suggested that the improvement of myocardial ischemia or less complications after treatment in hospital. Therefore, In this study, we took the dynamic changes of ADL functional status into consideration and established a relatively more accurate risk stratification tool for ACS patients.

As described in our previous research, ADL representing patients' physical functional status is correlated with several pathophysiological states, including inflammatory processes, aging status, and frailty (19–23). These factors are all essential considerations in the occurrence and development

TABLE 4 Kaplan–Meier survival analysis of mortality in acute coronary syndrome patients.

Subgroups	Cumulative survival rate			Log rank χ^2	*P*-value
	High-risk	Medium-risk	Low-risk		
Gender					
Male (n = 2,121)	0.488	0.823	0.937	293.382	<0.001
Female (n = 716)	0.497	0.838	0.846	55.749	<0.001
Age[a]					
≤65 (n = 1,345)	0.794	0.923	0.967	79.083	<0.001
>65 (n = 1,492)	0.347	0.786	0.859	187.264	<0.001
BMI,[b] **kg/m^2**					
≤24 (n = 1,508)	0.365	0.763	0.889	186.051	<0.001
>24 (n = 1,329)	0.700	0.891	0.942	88.698	<0.001
SBP,[b] **mmHg**					
≤128 (n = 1,455)	0.432	0.815	0.916	212.282	<0.001
>128 (n = 1,382)	0.593	0.840	0.920	116.962	<0.001
DBP,[b] **mmHg**					
≤78 (n = 1,486)	0.440	0.845	0.907	172.766	<0.001
>78 (n = 1,351)	0.563	0.807	0.930	166.130	<0.001
Heart rate,[b] **/min**					
≤ 78 (n = 1,444)	0.555	0.867	0.934	103.610	<0.001
>78 (n = 1,393)	0.449	0.794	0.901	211.153	<0.001
WBC,[b] **10^9/L**					
≤9 (n = 1,477)	0.639	0.860	0.927	103.938	<0.001
>9 (n = 1,360)	0.412	0.795	0.907	219.677	<0.001
Troponin T,[b] **pg/mL**					
≤453 (n = 1,438)	0.710	0.850	0.930	65.640	<0.001
>453 (n = 1,399)	0.337	0.809	0.902	224.779	<0.001
NT-proBNP,[b] **pg/mL**					
≤745 (n = 1,452)	0.872	0.949	0.956	24.895	<0.001
>745 (n = 1,385)	0.293	0.766	0.865	196.706	<0.001
Killip class[c]					
I (n = 1,611)	0.720	0.894	0.945	56.387	<0.001
II-IV (n = 1,226)	0.330	0.768	0.874	204.638	<0.001
GRACE score[b]					
≤142 (n = 1,443)	0.891	0.900	0.973	28.693	<0.001
>142 (n = 1,394)	0.369	0.781	0.856	205.622	<0.001
ACS type					
STEMI (n = 1,581)	0.452	0.824	0.921	252.327	<0.001
NST-ACS (n = 1,256)	0.327	0.832	0.915	95.472	<0.001

HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; GRACE score, Global Registry of Acute Coronary Events score; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NST-ACS, non-ST elevation acute coronary syndrome.

[a]The cutoff point for age was according to the definition of the elderly (65 years old).

[b]The cutoff points for these variates were medians.

[c]The cutoff point for Killip class was having congestive heart failure (≥II).

of cardiovascular disease (24–28). Also, the results of our study showed that several common inflammatory and thrombus indicators were significantly higher among patients in the high-risk category of DBRP than in the low-risk category, which may further explain an underlying mechanism. Prior studies have demonstrated that the indicators related to the various pathophysiological conditions involved in the pathogenesis of cardiovascular disease or myocardial injury may provide more prognostic information (3, 29–31). Being a validated evaluation tool for ADL, the BI score is highly likely to play a role in the risk stratification and prognosis prediction of ACS patients.

As the performance of the evaluation of ADL is nowadays feasible in the ambulance, the BI score can be completely obtained in the pre-hospital setting. The scale is considered easy to use, with good reliability and sensitivity to change, mainly in predicting the ADL functional status. The DBRP established in the present study is based on the changes between admission and discharge BI scores, and it has been proved that dynamic monitoring may provide more information and guide clinical decision-making, no matter the patient's physiological indices or functional status (32–35). Thus, the continuous dynamic evaluation of BI scores may provide more prognostic information for patients with ACS. According to our results, the risk of mortality was five times greater in the high-risk category than the low-risk category of DBRP. Furthermore, in patients with different levels of cardiovascular risk factors, the DBRP had a stable prognostic value. This result is far better than that of our previous study, in which risk stratification was carried out based on the BI score at admission alone (12).

The GRACE score is a guideline-recommended risk stratification for patients with ACS, comprising several factors, including demographic data, heart and other organ damage related to ACS, and has been widely used in clinical practice (36). The results of this study show that the DBRP had relatively better specificity, accuracy, PPV, and consistency than the GRACE score in predicting mortality in ACS patients, and no significant differences in the AUCs for all-cause mortality were observed between the DBRP and GRACE score (as categorical data). The DBRP provides additional geriatric-related signals reported to predict outcomes beyond age and standard risk factors (37). Currently, the ACS patients with geriatric conditions account for an increasing proportion of total patients, making it all the more important to consider the relevant indicators (38). Thus, the DBRP is indeed necessary because it may provide prognostic information not provided by the GRACE score, and combining these two indicators may illustrate comprehensive and systematic information. Furthermore, the BI score is routinely evaluated orally by nurses in hospital settings in China, which does not increase the burden on doctors, and has been widely accepted by both physicians and patients. Importantly, in the early evaluation of ACS patients, the participation of nurses can promote physician-nurse collaboration, subsequently leading to a more efficient and comprehensive evaluation. The latest European Society of Cardiology consensus statement demonstrated that the active participation of well-trained nurses can be beneficial to the risk stratification of patients (5). In addition, as a ADL assessment tool, the BI score consists of 10 items that relate to ADL without any medical examination results, and is considered easy to use mainly in predicting the functional outcomes.

5 Limitations

There are several limitations to this study. Firstly, retrospective as this study was, large, multicenter, and prospective studies are needed to further verify the validity of these results. Secondly, we only collected BI scores at one time point after admission, while multiple collections may provide more prognostic information. Thirdly, whether subsequent clinical interventions according to the DBRP can improve the prognosis of ACS patients was not investigated in this study, and this would be an interesting point to further explore in the future.

6 Conclusion

This study established a risk stratification tool based on dynamic BI scores and demonstrated that this dynamic BI-based risk stratification program might help identify high-risk patients and provide useful prognostic information for patients with ACS. As such, it could be applied in clinical practice for ACS patients for early risk warning and clinical decision guidance.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

DL, ZZ, and YC conceived the study design. DL, XC, YJ, FL, ZL, YL, WZ, LY, HL, and YG collected the epidemiological and clinical data. DL, XC, YJ, YL, and ZL summarized data and performed the statistical analysis. DL, FL, and YC interpreted the data and drafted the manuscript. ZZ and RZ participated in the design of the study, acquired the data, and helped to revise the manuscript. All authors accepted responsibility for the entire content of this submitted manuscript and approved submission.

Funding

This work was financially supported by grants from National Key Research and Development Program of China (Nos. 2020AAA0105000 and 2020AAA0105005), Sichuan Science and Technology Program (Nos. 2022YFS0279, 2021YFQ0062, and 2022JDRC0148), Sichuan Provincial Health Commission (No. ZH2022-101), and Sichuan University West China Nursing Discipline Development Special Fund Project (Nos. HXHL20017, HXHL20046, and HXHL21016).

Acknowledgments

We thank all the participants of this project and investigators for collecting the data.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393

2. O'Donoghue M, Morrow D, Cannon C, Jarolim P, Desai N, Sherwood M, et al. Multimarker risk stratification in patients with acute myocardial infarction. *J Am Heart Assoc.* (2016) 5:e002586. doi: 10.1161/jaha.115.002586

3. Li F, Li D, Yu J, Jia Y, Jiang Y, Chen X, et al. Prognostic value of the nutritional risk screening 2002 scale in patients with acute myocardial infarction: insights from the retrospective multicenter study for early evaluation of acute chest pain. *J Cardiovasc Nurs.* (2021) 36:546–55. doi: 10.1097/jcn.0000000000000786

4. Yu J, Li D, Jia Y, Li F, Jiang Y, Zhang Q, et al. Nutritional risk screening 2002 was associated with acute kidney injury and mortality in patients with acute coronary syndrome: insight from the REACP study. *Nutr Metab Cardiovasc Dis.* (2021) 31:1121–8. doi: 10.1016/j.numecd.2020.12.028

5. Stepinska J, Lettino M, Ahrens I, Bueno H, Garcia-Castrillo L, Khoury A, et al. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the acute cardiovascular care association. *Eur Heart J Acute Cardiovasc Care.* (2020) 9:76–89. doi: 10.1177/2048872619885346

6. Wong G, Welsford M, Ainsworth C, Abuzeid W, Fordyce C, Greene J, et al. 2019 canadian cardiovascular society/canadian association of interventional cardiology guidelines on the acute management of ST-elevation myocardial infarction: focused update on regionalization and reperfusion. *Can J Cardiol.* (2019) 35:107–32. doi: 10.1016/j.cjca.2018.11.031

7. Tamis-Holland J, Jneid H, Reynolds H, Agewall S, Brilakis E, Brown T, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the american heart association. *Circulation.* (2019) 139:e891–908. doi: 10.1161/cir.0000000000000670

8. Lim M, Eagle K, Gore J, Anderson F Jr., Dabbous O, Mehta R, et al. Treating patients with acute coronary syndromes with aggressive antiplatelet therapy (from the global registry of acute coronary events). *Am J Cardiol.* (2005) 96:917–21. doi: 10.1016/j.amjcard.2005.05.047

9. Hall M, Bebb O, Dondo T, Yan A, Goodman S, Bueno H, et al. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. *Eur Heart J.* (2018) 39:3798–806. doi: 10.1093/eurheartj/ehy517

10. Ohman E, Topol E, Califf R, Bates E, Ellis S, Kereiakes D, et al. An analysis of the cause of early mortality after administration of thrombolytic therapy. The thrombolysis angioplasty in myocardial infarction study group. *Coron Artery Dis.* (1993) 4:957–64. doi: 10.1097/00019501-199311000-00002

11. Chang W, Boersma E, Granger C, Harrington R, Califf R, Simoons M, et al. Dynamic prognostication in non-ST-elevation acute coronary syndromes: insights from GUSTO-IIb and PURSUIT. *Am Heart J.* (2004) 148:62–71. doi: 10.1016/j.ahj.2003.05.004

12. Li F, Li D, Yu J, Jia Y, Jiang Y, Chen T, et al. Barthel index as a predictor of mortality in patients with acute coronary syndrome: better activities of daily living, better prognosis. *Clin Interv Aging.* (2020) 15:1951–61. doi: 10.2147/cia.S270101

13. Higuchi S, Kabeya Y, Matsushita K, Taguchi H, Ishiguro H, Kohshoh H, et al. Barthel index as a predictor of 1-year mortality in very elderly patients who underwent percutaneous coronary intervention for acute coronary syndrome: better activities of daily living, longer life. *Clin Cardiol.* (2016) 39:83–9. doi: 10.1002/clc.22497

14. Li D, Cheng Y, Yu J, Jia Y, Li F, Zhang Q, et al. Early risk stratification of acute myocardial infarction using a simple physiological prognostic scoring system: insights from the REACP study. *Eur J Cardiovasc Nurs.* (2021) 20:147–59. doi: 10.1177/1474515120952214

15. Jia Y, Li H, Li D, Li F, Li Q, Jiang Y, et al. Prognostic value of braden scale in patients with acute myocardial infarction: from the retrospective multicenter study for early evaluation of acute chest pain. *J Cardiovasc Nurs.* (2020) 35:E53–61. doi: 10.1097/jcn.0000000000000735

16. Jia Y, Gao Y, Li D, Cao Y, Cheng Y, Li F, et al. Geriatric nutritional risk index score predicts clinical outcome in patients with acute ST-segment elevation myocardial infarction. *J Cardiovasc Nurs.* (2020) 35:E44–52. doi: 10.1097/jcn.0000000000000674

17. DeLong E, DeLong D, Clarke-Pearson D. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* (1988) 44:837–45.

18. R Core Team. *R: a language and environment for statistical computing.* Vienna: R Foundation for Statistical Computing (2021). Available online at: https://www.R-project.org

19. Noz M, Hartman Y, Hopman M, Willems P, Tack C, Joosten L, et al. Sixteen-week physical activity intervention in subjects with increased cardiometabolic risk shifts innate immune function towards a less proinflammatory State. *J Am Heart Assoc.* (2019) 8:e013764. doi: 10.1161/jaha.119.013764

20. Duggal N, Niemiro G, Harridge S, Simpson R, Lord J. Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? *Nat Rev Immunol.* (2019) 19:563–72. doi: 10.1038/s41577-019-0177-9

21. Bier N, Belchior Pda C, Paquette G, Beauchemin É, Lacasse-Champagne A, Messier C, et al. The instrumental activity of daily living profile in aging: a feasibility study. *J Alzheimers Dis.* (2016) 52:1361–71. doi: 10.3233/jad-150957

22. Costenoble A, Knoop V, Vermeiren S, Vella R, Debain A, Rossi G, et al. Comprehensive overview of activities of daily living in existing frailty instruments:

a systematic literature search. *Gerontologist.* (2021) 61:e12–22. doi: 10.1093/geront/gnz147

23. Op Het Veld L, Beurskens A, de Vet H, van Kuijk S, Hajema K, Kempen G, et al. The ability of four frailty screening instruments to predict mortality, hospitalization and dependency in (instrumental) activities of daily living. *Eur J Ageing.* (2019) 16:387–94. doi: 10.1007/s10433-019-00502-4

24. Swirski F, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science.* (2013) 339:161–6. doi: 10.1126/science.1230719

25. Li D, Zhao L, Yu J, Zhang W, Du R, Liu X, et al. Lipoprotein-associated phospholipase A2 in coronary heart disease: review and meta-analysis. *Clin Chim Acta.* (2017) 465:22–9. doi: 10.1016/j.cca.2016.12.006

26. Veerasamy M, Edwards R, Ford G, Kirkwood T, Newton J, Jones D, et al. Acute coronary syndrome among older patients: a review. *Cardiol Rev.* (2015) 23:26–32. doi: 10.1097/crd.0000000000000016

27. Campo G, Maietti E, Tonet E, Biscaglia S, Ariza-Solè A, Pavasini R, et al. The assessment of scales of frailty and physical performance improves prediction of major adverse cardiac events in older adults with acute coronary syndrome. *J Gerontol A Biol Sci Med Sci.* (2020) 75:1113–9. doi: 10.1093/gerona/glz123

28. Uchmanowicz I, Lisiak M, Wleklik M, Gurowiec P, Kałużna-Oleksy M. The relationship between frailty syndrome and quality of life in older patients following acute coronary syndrome. *Clin Interv Aging.* (2019) 14:805–16. doi: 10.2147/cia.S204121

29. Li D, Ye L, Yu J, Deng L, Liang L, Ma Y, et al. Significance of the thrombo-inflammatory status-based novel prognostic score as a useful predictor for in-hospital mortality of patients with type B acute aortic dissection. *Oncotarget.* (2017) 8:79315–22. doi: 10.18632/oncotarget.18105

30. Du R, Li D, Yu J, Ma Y, Zhang Q, Zeng Z, et al. Association of platelet to lymphocyte ratio and risk of in-hospital mortality in patients with type B acute aortic dissection. *Am J Emerg Med.* (2017) 35:368–70. doi: 10.1016/j.ajem.2016.11.003

31. Li D, Chen Y, Jia Y, Tong L, Tong J, Wang W, et al. CoV-2-induced immune dysregulation and myocardial injury risk in china: insights from the ERS-COVID-19 study. *Circulation Res.* (2020) 127:397–9. doi: 10.1161/circresaha.120.317070

32. Shekelle P, Pane J, Agniel D, Shi Y, Rumball-Smith J, Haas A, et al. Assessment of variation in electronic health record capabilities and reported clinical quality performance in ambulatory care clinics, 2014-2017. *JAMA Netw Open.* (2021) 4:e217476. doi: 10.1001/jamanetworkopen.2021.7476

33. Neoh M, Abu Zaid Z, Mat Daud Z, Md Yusop N, Ibrahim Z, Abdul Rahman Z, et al. Changes in nutrition impact symptoms, nutritional and functional status during head and neck cancer treatment. *Nutrients.* (2020) 12:1225. doi: 10.3390/nu12051225

34. Smith S, Madden A. Body composition and functional assessment of nutritional status in adults: a narrative review of imaging, impedance, strength and functional techniques. *J Hum Nutr Diet.* (2016) 29:714–32. doi: 10.1111/jhn.12372

35. Bowen M. Monitoring functional status using a wearable real-time locating technology. *Nurs Outlook.* (2020) 68:727–33. doi: 10.1016/j.outlook.2020.04.012

36. Granger C, Goldberg R, Dabbous O, Pieper K, Eagle K, Cannon C, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* (2003) 163:2345–53. doi: 10.1001/archinte.163.19.2345

37. Sanchis J, Bonanad C, Ruiz V, Fernández J, García-Blas S, Mainar L, et al. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. *Am Heart J.* (2014) 168:784–91. doi: 10.1016/j.ahj.2014.07.022

38. Chaudhry S, Wang Y, Gill T, Krumholz H. Geriatric conditions and subsequent mortality in older patients with heart failure. *J Am Coll Cardiol.* (2010) 55:309–16. doi: 10.1016/j.jacc.2009.07.066

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 21 December 2022
DOI 10.3389/fcvm.2022.1050785

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Jun Chen,
Hubei University of Medicine, China
Zhaoqing Sun,
Shengjing Hospital of China Medical University, China

*CORRESPONDENCE
Zhenfei Chen
1601994492@qq.com

SPECIALTY SECTION
This article was submitted to Coronary Artery Disease, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 22 September 2022
ACCEPTED 29 November 2022
PUBLISHED 21 December 2022

CITATION
Fang C, Chen Z, Zhang J, Jin X and Yang M (2022) Construction and evaluation of nomogram model for individualized prediction of risk of major adverse cardiovascular events during hospitalization after percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. *Front. Cardiovasc. Med.* 9:1050785. doi: 10.3389/fcvm.2022.1050785

Construction and evaluation of nomogram model for individualized prediction of risk of major adverse cardiovascular events during hospitalization after percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction

Caoyang Fang[1,2], Zhenfei Chen[1]*, Jinig Zhang[1], Xiaoqin Jin[1,2] and Mengsi Yang[1]

[1]Department of Cardiology, The Second People's Hospital of Hefei, Hefei Hospital Affiliated to Anhui Medical University, Hefei, Anhui, China, [2]Department of Cardiology, Hefei Second People's Hospital Affiliated to Bengbu Medical College, Hefei, Anhui, China

Background: Emergency percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) helps to reduce the occurrence of major adverse cardiovascular events (MACEs) such as death, cardiogenic shock, and malignant arrhythmia, but in-hospital MACEs may still occur after emergency PCI, and their mortality is significantly increased once they occur. The aim of this study was to investigate the risk factors associated with MACE during hospitalization after PCI in STEMI patients, construct a nomogram prediction model and evaluate its effectiveness.

Methods: A retrospective analysis of 466 STEMI patients admitted to our hospital from January 2018 to June 2022. According to the occurrence of MACE during hospitalization, they were divided into MACE group (n = 127) and non-MACE group (n = 339), and the clinical data of the two groups were compared; least absolute shrinkage and selection operator (LASSO) regression was used to screen out the predictors with non-zero coefficients, and multivariate Logistic regression was used to analyze STEMI Independent risk factors for in-hospital MACE in patients after emergency PCI; a nomogram model for predicting the risk of in-hospital MACE in STEMI patients after PCI was constructed based on predictive

factors, and the C-index was used to evaluate the predictive performance of the prediction model; the Bootstrap method was used to repeat sampling 1,000 Internal validation was carried out for the second time, the Hosmer-Lemeshow test was used to evaluate the model fit, and the calibration curve was drawn to evaluate the calibration degree of the model. Receiver operating characteristic (ROC) curves were drawn to evaluate the efficacy of the nomogram model and thrombolysis in myocardial infarction (TIMI) score in predicting in-hospital MACE in STEMI patients after acute PCI.

Results: The results of LASSO regression showed that systolic blood pressure, diastolic blood pressure, Killip grade II-IV, urea nitrogen and left ventricular ejection fraction (LVEF), IABP, NT-ProBNP were important predictors with non-zero coefficients, and multivariate logistic regression analysis was performed to analyze that Killip grade II-IV, urea nitrogen, LVEF, and NT-ProBNP were independent factors for in-hospital MACE after PCI in STEMI patients; a nomogram model for predicting the risk of in-hospital MACE after PCI in STEMI patients was constructed with the above independent predictors, with a C-index of 0.826 (95% CI: 0.785–0.868) having a good predictive power; the results of H-L goodness of fit test showed $\chi^2 = 1.3328$, $P = 0.25$, the model calibration curve was close to the ideal model, and the internal validation C-index was 0.818; clinical decision analysis also showed that the nomogram model had a good clinical efficacy, especially when the threshold probability was 0.1–0.99, the nomogram model could bring clinical net benefits to patients. The nomogram model predicted a greater AUC (0.826) than the TIMI score (0.696) for in-hospital MACE after PCI in STEMI patients.

Conclusion: Urea nitrogen, Killip class II-IV, LVEF, and NT-ProBNP are independent factors for in-hospital MACE after PCI in STEMI patients, and nomogram models constructed based on the above factors have high predictive efficacy and feasibility.

KEYWORDS

acute ST-segment elevation myocardial infarction, STEMI, percutaneous coronary intervention, PCI, MACE, nomogram model

1 Introduction

In recent years, the incidence of acute ST-segment elevation myocardial infarction (STEMI) has been increasing, and it has become one of the most common and fatal cardiac emergencies in clinical practice (1). Percutaneous coronary intervention (PCI) is currently one of the most effective treatments for STEMI (2). Although PCI can timely open the infarcted vessel and achieve reperfusion, reperfusion itself aggravates myocardial injury and increases the incidence of major adverse cardiovascular events (MACEs), so it is particularly important to identify high-risk patients with STEMI who have a poor prognosis early in admission (3). Timely risk assessment of STEMI patients has a positive effect on improving patient outcomes. Establishing a convenient and effective prediction model is helpful to assess the risk of in-hospital MACE after emergency PCI in STEMI patients and has a positive effect on the early identification of patients at high risk of in-hospital MACE and timely intervention.

The nomogram is based on the analysis results of COX proportional hazards or logistic regression model, which is graphical and visualized for the prediction of individual disease risk and is more intuitive and easy to be popularized and applied in clinical practice. Compared with traditional risk scoring systems, nomogram models integrate more risk factors and obtain numerical probabilities of target events, more accurately quantify risk, and are more flexible to apply. Its application has been reported in predicting the risk of postoperative heart

failure in patients with acute myocardial infarction (AMI) (4), the risk of in-hospital major cardiovascular events in patients with AMI after PCI (5), and the prognosis of patients with the acute coronary syndrome (6). In this study, we retrospectively analyzed the clinical characteristics of 466 STEMI patients before emergency PCI, and provided a reference for clinical assessment of the patient's condition and guiding treatment by constructing a nomogram model to predict the risk of in-hospital MACE in STEMI patients after emergency PCI.

2 Materials and methods

2.1 Study population

A retrospective analysis of 466 STEMI patients who underwent emergency PCI at the Second People's Hospital of Hefei from January 2018 to June 2022 was performed as the study subjects, all of whom were stented patients. Inclusion criteria (1) aged 18 years or older; (2) no previous history of atrial fibrillation; (3) admitted for emergency PCI within 24 h after onset; (4) demographic characteristics and complete clinical data. Exclusion criteria: (1) combined with malignant tumor; (2) accompanied by non-obstructive coronary heart disease, primary cardiomyopathy; (3) clinical evidence of infection; (4) accompanied by immune system disease; (5) combined with severe liver and kidney dysfunction. Patients were divided into the MACE group (n = 127) and the non-MACE group (n = 339) according to whether MACE occurred in the hospital after PCI. MACE defined the primary endpoint as cardiac death. Secondary endpoints were myocardial reinfarction, malignant arrhythmia, and acute heart failure. Myocardial reinfarction was defined as stent thrombosis in this study. Criteria for stent thrombosis diagnosis were according to those proposed by the Academic Research Consortium (ARC) (7). Diagnosis of acute heart failure: clinical manifestations such as shortness of breath, orthopnea, pulmonary rales, pink foamy sputum; NT-proBNP: >450 ng/L in patients under 50 years old, >900 ng/L in patients over 50 years old, >1,800 ng/L in patients over 75 years old, and >1,200 ng/L in patients with renal insufficiency (glomerular filtration rate <60 ml/min). Malignant arrhythmias include severe sinus bradycardia (≤40 beats/min), high-grade or third-degree atrioventricular block, ventricular tachycardia, ventricular fibrillation, etc., and classify cardiac arrest as a special type of malignant arrhythmia. This study has been approved by the Ethics Committee of the Second People's Hospital of Hefei (Approval No.: 2020-ke-058). All methods were performed following the Declaration of Helsinki. PCI: refers to the treatment of transcatheter techniques to dredge the stenotic or even occluded coronary lumen, thereby improving the blood perfusion of the myocardium, including percutaneous coronary balloon angioplasty (PTCA), coronary stent implantation, coronary rotational atherectomy, intracoronary thrombus aspiration, and cutting balloon angioplasty.

2.2 Study method

2.2.1 Data collection

Demographic characteristics and clinical data of AMI patients at admission were collected through the hospital's electronic case system, including age, gender, smoking history, heart rate at admission, systolic blood pressure, diastolic blood pressure, comorbidities (including hypertension and diabetes), Killip class II-IV, Gensini score, LVEF of echocardiography results, laboratory parameters (including neutrophils, lymphocytes, hemoglobin, platelets, total bilirubin, direct bilirubin, indirect bilirubin, albumin, triglycerides, total cholesterol, LDL-C, HDL-C, Apolipoprotein B, Apolipoprotein A1, urea, creatinine, uric acid, cystatin C, homocysteine, and fasting blood glucose, NT-ProBNP), Intervention-related data (Gensini score, D-to-B time, infarct location, number of diseased vessels, number of implanted stents, tirofiban, thrombus aspiration, IABP), and MACE data during hospitalization.

2.2.2 Nomogram establishment and verification

Least absolute shrinkage and selection operator (LASSO) regression was used to reduce the dimension of 31 clinical data in this study, predictors of non-zero coefficients were selected, and multivariate logistic regression was used to analyze independent predictors affecting in-hospital MACE after PCI in STEMI patients. Predictors were used to construct a nomogram model to predict the risk of in-hospital MACE after PCI in STEMI patients, and C-index was used to assess the predictive efficacy of the nomogram model for in-hospital MACE after PCI in STEMI patients. Bootstrap multiple sampling 1,000 times was used for model internal validation, model fit was evaluated by the Hosmer-Lemeshow test, and calibration curves were plotted to evaluate the calibration of the model. Decision curves were drawn to analyze the net benefit rate of this nomogram model in predicting in-hospital MACE after PCI in STEMI patients. Receiver operating characteristic (ROC) curves were plotted to assess the efficacy of nomogram models and thrombolysis in myocardial infarction (TIMI) scores in predicting in-hospital MACE after acute PCI in STEMI patients.

2.2.3 Statistical methods

Statistics and graphs were performed using SPSS 26.0, R4.2.1, and GraphPad Prism9.0. Kolmogorov-Smirnov normality test was performed on the measurement data, which conformed to the normal distribution and was expressed as mean ± standard deviation, and an independent sample

t-test was used for comparison between the two groups; the measurement data without normal distribution were expressed as median M (P25, P75), and Mann-Whitney U test was used for comparison between the two groups; the adoption rate of enumeration data was expressed, and chi-square test was used for comparison between the two groups; LASSO regression was used to select the predictors of non-zero coefficients, and multivariate logistic regression was used to analyze the independent risk factors affecting MACE during hospitalization after PCI in STEMI patients; C-index, area under ROC curve, calibration curve, and clinical decision curve were calculated. All statistics were performed using two-sided tests, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Comparison of clinical data between MACE group and non-MACE patients

In this study, there were significant age differences, the proportion of women, history of hypertension, systolic and diastolic blood pressure at admission, neutrophils, hemoglobin, total bilirubin, indirect bilirubin, albumin, urea, creatinine, uric acid, cystatin C, fasting blood glucose, NT-ProBNP, LVEF, Killip class II-IV, Gensini score, number of diseased vessels, thrombus aspiration, and IABP between the MACE group and the non-MACE group ($P < 0.05$). There were no significant differences in diabetes history, smoking history, heart rate, lymphocytes, platelets, direct bilirubin, triglycerides, total cholesterol, LDL-C, HDL-C, Apo-B, Apo-A1, homocysteine, D-to-B time, infarct location, number of implanted stents, and tirofiban between the two groups ($P > 0.05$), as shown in **Table 1**.

3.2 Construction of a risk prediction model for in-hospital MACE after PCI in STEMI patients

3.2.1 Predictor variables were filtered by lasso regression

Lasso regression analysis was performed with the presence or absence of MACE (assigned value: NO = 0, YES = 1) during hospitalization after PCI in STEMI patients as the dependent variable and the clinical data and laboratory parameters of the patients as independent variables [categorical variable (assigned value: NO = 0, YES = 1); continuous variable (assigned value: measured value)]. The 39 included variables were dimensionality reduced by Lasso regression, λ values were calculated using 10-fold cross-validation, and finally, λ values within one standard deviation of the least mean square prediction error was selected as optimal values, as shown in Figure. Final Lasso regression analysis screened seven predictors of non-zero coefficients (systolic and diastolic blood pressure at admission, Killip class II-IV, LVEF, urea, NT-ProBNP, IABP) from 39 variables. As shown in **Figure 1**.

3.2.2 Multivariate logistic regression model construction

Seven predictive variables, systolic blood pressure (assigned value: measured value), diastolic blood pressure (assigned value: measured value), Killip class II-IV (assigned value: NO = 0, YES = 1), LVEF (assigned value: measured value), urea (assigned value: measured value), and IABP (assigned value: NO = 0, YES = 1), selected by Lasso regression, were used as dependent variables whether MACE occurred during hospitalization after PCI in STEMI patients (assigned value: NO = 0, YES = 1). The optimal Cut-Off value for MACE prediction according to NT-ProBNP was 700 ng/L, with values assigned as 0 for values less than 700 and 1 for values greater than or equal to 700. Multivariate logistic regression models were constructed using these variables as independent variables, and the results showed that Killip class II-IV, urea nitrogen, LVEF, and NT-ProBNP were independent factors for in-hospital MACE after PCI in STEMI patients ($P < 0.05$) as shown in **Table 2**. A nomogram of the predictive model for the development of in-hospital MACE after PCI in STEMI patients, the Nomogram, was drawn according to the predictive variables and is shown in **Figure 2**. Each predictor variable corresponds to a specific score on the horizontal axis of the nomogram score, and the scores corresponding to the three predictor variables are summed to obtain a total score. Through the total score corresponding to the risk prediction value of adverse cardiovascular events at the bottom of the nomogram, it can be seen from the figure that the patients with higher total scores are more likely to have in-hospital MACE.

3.2.3 Nomogram model validation

The nomogram model concordance index, C-index (equivalent area under the ROC curve AUC), was 0.826 (95% CI: 0.785–0.868); The sensitivity was 0.709, the specificity was 0.802, and the accuracy was 78.7% which had good predictive power. The results of the H-L goodness of fit test of the nomogram model for predicting in-hospital MACE after PCI in STEMI patients showed $\chi^2 = 0.44$, $P = 0.51$, and the model calibration curve was close to the ideal model, as shown in **Figure 3**. The internal validated C-index was 0.818 (95% CI: 0.78–0.87), suggesting that the model had good calibration; The Brier score was 0.137, suggesting that the nomogram model predicted in-hospital MACE occurrence in acute ST-segment elevation myocardial infarction with good correlation and strong calibration with internal sampling. ROC curve analysis results showed that the AUC of the nomogram model for predicting in-hospital MACE after PCI in STEMI patients was

TABLE 1 Comparison of general clinical data between major adverse cardiovascular events (MACE) group and non-MACE group.

Variables	MACE group	Non-MACE group	$t/\chi^2/z$ value	*P*-value
General clinical data				
Age (years)[b]	66 (55,78)	59 (51,71)	4.091	<0.001*
Gender (Female, *n* %)	36 (28.35)	64 (18.88)	4.913	0.027*
Diabetes (*n* %)	37 (29.13)	87 (25.66)	0.57	0.45
Hypertension (*n* %)	82 (64.57)	176 (51.92)	5.982	0.014*
Smoking (*n* %)	67 (52.76)	201 (59.29)	1.615	0.204
Heart rate (beats/min)[b]	80 (66.5, 92.25)	76 (67, 86)	1.598	0.11
SBP (mmHg)[a]	112.61 ± 26.3	126.74 ± 22.31	5.79	<0.001*
DBP (mmHg)[a]	68 ± 15.54	77.69 ± 15.43	6.025	<0.001*
Killip grade II-IV (*n* %)	67 (52.8)	60 (17.7)	52.27	<0.001*
Laboratory data				
Neutrophils ($\times 10^9$/L)[b]	8.9 (6.55, 11.77)	7.16 (5.25, 9.68)	4.902	<0.001*
Lymphocytes ($\times 10^9$/L)[b]	1.3 (0.89, 2.2)	1.49 (1.08, 2.15)	0.974	0.33
Hemoglobin (g/L)[a]	132.26 ± 19.61	138.31 ± 18.4	3.101	0.002*
Platelets ($\times 10^9$/L)[b]	198.2 (160.75, 241.25)	196.5 (154, 238)	0.892	0.372
Total bilirubin (umol/L)[b]	16.6 (11.88, 21.2)	18 (13.4, 24.68)	2.215	0.027*
Direct bilirubin (umol/L)[b]	4.85 (3.6, 6)	5 (3.7, 6.7)	1.272	0.203
Indirect bilirubin (umol/L)[b]	11.85 (8.28, 15.6)	13.4 (9.6, 17.5)	2.799	0.005*
Albumin (g/L)[a]	37.93 ± 4.11	39.59 ± 3.71	4.164	<0.001*
Triglycerides (mmol/L)[b]	1.42 (0.96, 1.99)	1.51 (1.06, 2.23)	1.628	0.103
Total cholesterol (mmol/L)[b]	4.28 (3.69, 4.98)	4.41 (3.84, 5.11)	1.572	0.116
LDL-C (mmol/L)[b]	2.71 (2.15, 3.3)	2.79 (2.29, 3.42)	1.261	0.207
HDL-C (mmol/L)[b]	1.09 (0.92, 1.29)	1.07 (0.91, 1.24)	0.647	0.518
Apolipoprotein B (g/L)[b]	0.86 (0.71, 0.98)	0.87 (0.74, 1.01)	1.13	0.258
Apolipoprotein A1 (g/L)[b]	1.02 (0.91, 1.18)	1.06 (0.94, 1.18)	1.523	0.128
Urea (mmol/L)[b]	6.4 (5.23, 9.27)	5.15 (4.19, 6.38)	6.653	<0.001*
Creatinine (umol/L)[b]	76 (61.95, 103.88)	69 (58, 78.98)	4.52	<0.001*
Uric acid (umol/L)[b]	373.6 (303.5, 437)	346.8 (281.03, 415.3)	2.535	0.011*
Cystatin C (mg/L)[b]	1.11 (0.91, 1.39)	1.01 (0.88, 1.15)	3.24	0.001*
Homocysteine (umol/L)[b]	14.75 (10.8, 18.17)	13.8 (10.72, 17.4)	0.485	0.628
Fasting blood glucose (mmol/L)[b]	7.37 (6.05, 9.56)	6.06 (5.31,7.78)	5.169	<0.001*
LVEF[b]	56 (48, 61)	60 (56, 64)	5.697	<0.001*
NT-ProBNP (ng/L)[b]	774.42 (466.11, 1071.09)	491.95 (328.67, 731.58)	5.602	<0.001*
Interventional data				
Gensini score[b]	80 (42.75, 105)	60 (41, 84)	3.047	0.002*
D-to-B time	61.41 ± 7.88	60.94 ± 7.22	0.608	0.543
Infarct location (*n*, %)	–	–	1.934	0.164
Anterior MI	59 (46.45)	182 (53.69)	–	–
Others	68 (53.55)	157 (46.31)	–	–
Number of diseased vessels (*n*, %)	–	–	3.996	0.046*
1	35 (27.56)	127 (37.46)	–	–
≥2	92 (72.44)	212 (62.54)	–	–
Number of stents implanted[b]	1 (1, 2)	1 (1, 2)	1.294	0.196
Tirofiban, *n* (%)	56 (44.1)	127 (37.46)	1.704	0.192
Thrombus aspiration, *n* (%)	37 (29.13)	53 (15.63)	10.804	0.001*
IABP, *n* (%)	22 (17.32)	9 (2.65)	32.009	<0.001*
In-hospital MACE				
Cardiogenic death (*n*, %)	16 (12.6)		–	
Myocardial reinfarction (*n*, %)	2 (1.6)		–	
Malignant arrhythmia (*n*, %)	71 (55.9)		–	
Acute heart failure (*n*, %)	38 (29.9)		–	

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol C; HDL-C, high-density lipoprotein cholesterol C; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

[a]Normally distributed data are expressed as mean ± standard deviation.

[b]Non-normally distributed data are expressed as median M (P_{25}, P_{75}) 0.1 mmHg = 0.133 kPa; *$P < 0.05$. Mean ± standard deviation, M (P_{25}, P_{75}), number of cases and percentage (*n*, %).

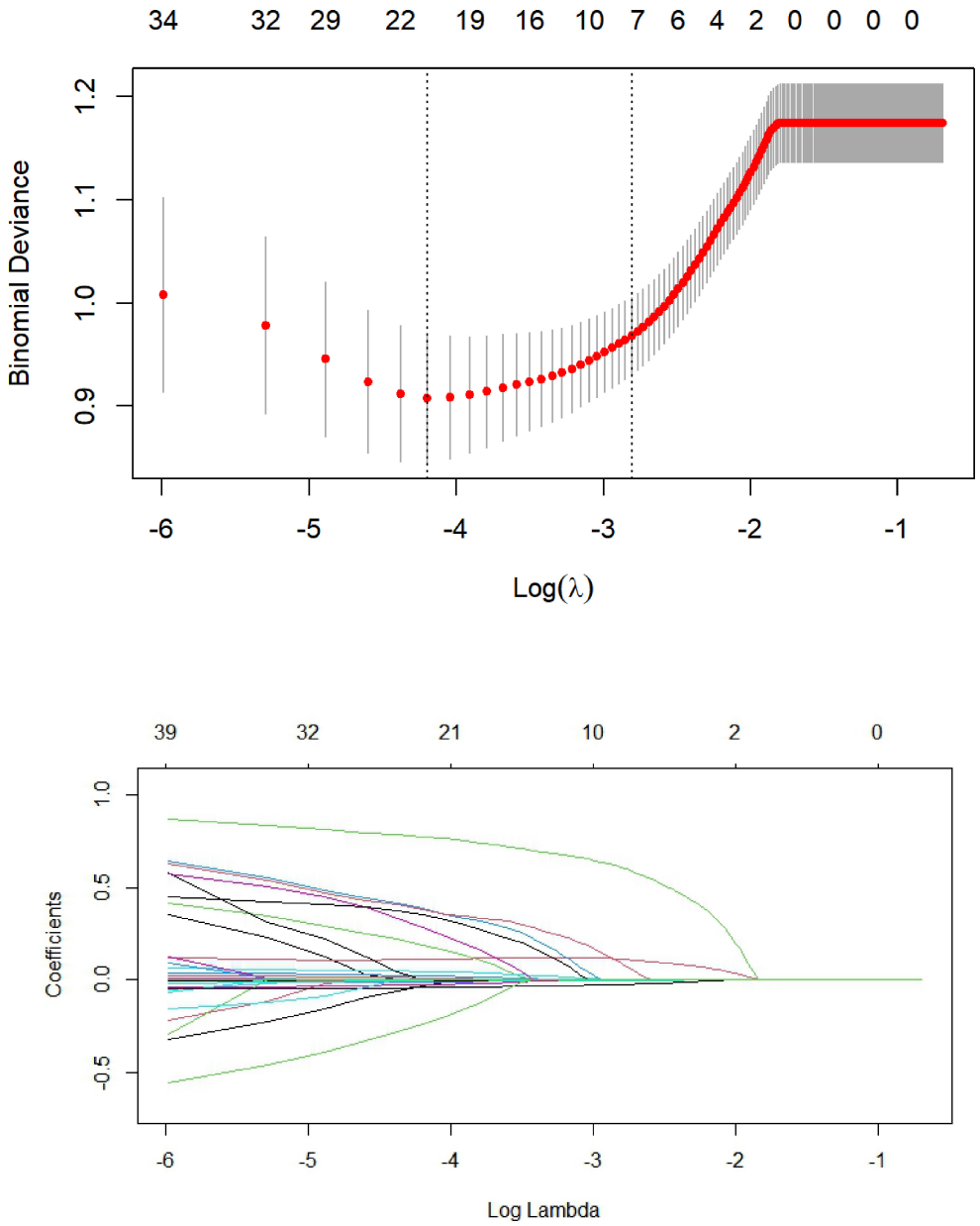


FIGURE 1
Predictor plots screened by least absolute shrinkage and selection operator (LASSO) regression analysis.

TABLE 2 Multivariate logistic regression analysis of influencing factors in major adverse cardiovascular events (MACE) group.

	β	Standard error	*Wald*	OR	95% CI	*P*-value
SBP	0.018	0.009	3.664	0.982	(0.964, 1)	0.056
DBP	0.007	0.015	0.259	0.993	(0.964, 1.021)	0.611
Killip grade II-IV	1.088	0.277	15.411	0.337	(0.922, 0.983)	<0.001*
Urea	0.199	0.055	13.065	0.337	(0.196, 0.58)	<0.001*
LVEF	0.049	0.016	9.03	0.952	(0.922, 0.983)	0.003*
NT-ProBNP	1.485	0.261	32.304	0.226	(0.136, 0.378)	<0.001*
IABP	0.855	0.518	2.726	0.425	(0.154, 1.173)	0.099

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; *$P < 0.05$.

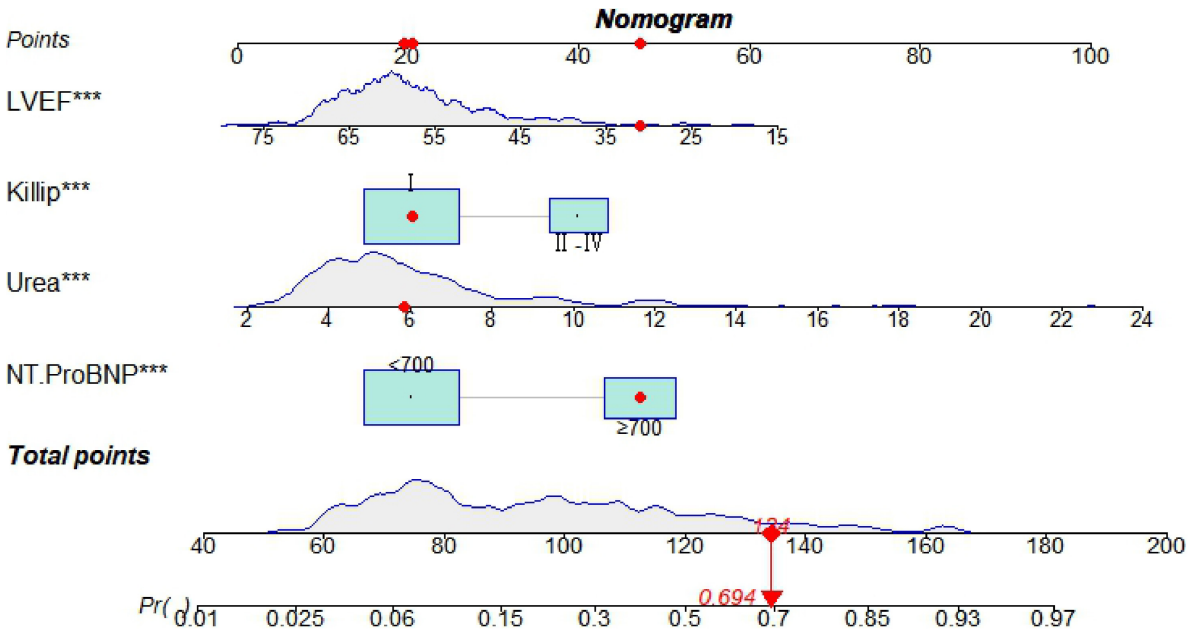


FIGURE 2
A nomogram predicting in-hospital major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). ***$P < 0.05$.

0.826 greater than that of the TIMI score 0.696 (Z =3.567, $P < 0.05$) nomogram model had better predictive performance than TIMI score, as shown in **Figure 4**.

3.2.4 Clinical decision analysis for nomogram models

The clinical decision curve (DCA) was plotted with the probability of the high-risk threshold as the abscissa and the net benefit rate as the ordinate, in which the probability of the high-risk threshold was set at (0, 1), the black solid line represented the net benefit rate of in-hospital MACE in all patients, the gray solid line represented the net benefit rate of in-hospital MACE in all patients, the sky blue curve represented the single model decision curve taking TIMI score as an example, the red curve represented the decision curve of this nomogram model, which was positive or negative relative to all study subjects, and the nomogram predicted the net benefit of the model in the interval of 0.1–0.99 with a threshold probability of 0.1–0.99, suggesting that the nomogram model could bring net clinical benefit to patients when the threshold probability was 0.1–0.99, as shown in **Figure 5**. The clinical impact curve (CIC) can further reflect the use of the nomogram model to predict the risk stratification of 1,000 people, showing the coordinate axis of "loss: benefit," assigned with eight scales, green in the figure is a single factor model represented by TIMI score, red is a nomogram model, gray represents the actual occurrence of in-hospital MACE, it is seen that compared with the single model of TIMI score, the difference between the nomogram model curve and the actual occurrence curve is smaller, suggesting that the nomogram model is more suitable for the actual occurrence of in-hospital MACE in clinical practice, as shown in **Figure 6**.

4 Discussion

This study aimed to investigate the occurrence of MACE during hospitalization in patients with STEMI, so the primary study endpoint in the definition of MACE was cardiac death. Secondary endpoints included myocardial reinfarction, first acute or subacute thrombosis, which could be induced at the site of stent implantation due to intimal injury. In addition, when interventional therapy is performed for major vessels, it can compress branch vessels to a certain extent, resulting in vascular occlusion, and also causing some myocardial necrosis with symptoms of acute myocardial infarction. During the onset of acute myocardial infarction, various arrhythmias, especially ventricular arrhythmias, can occur due to myocardial ischemia, and in severe cases, cardiorespiratory arrest in patients. In patients with inferior myocardial infarction, inhibition of the sinoatrial node and atrioventricular node function can lead to heart rate reduction and atrioventricular block. For patients with longer ischemic events, due to more myocardial cell necrosis, patients still cannot save the necrotic myocardium after opening the vessel, resulting in decreased cardiac pump function during hospitalization, resulting in acute heart failure or even cardiogenic shock. Therefore, in this study, these indicators

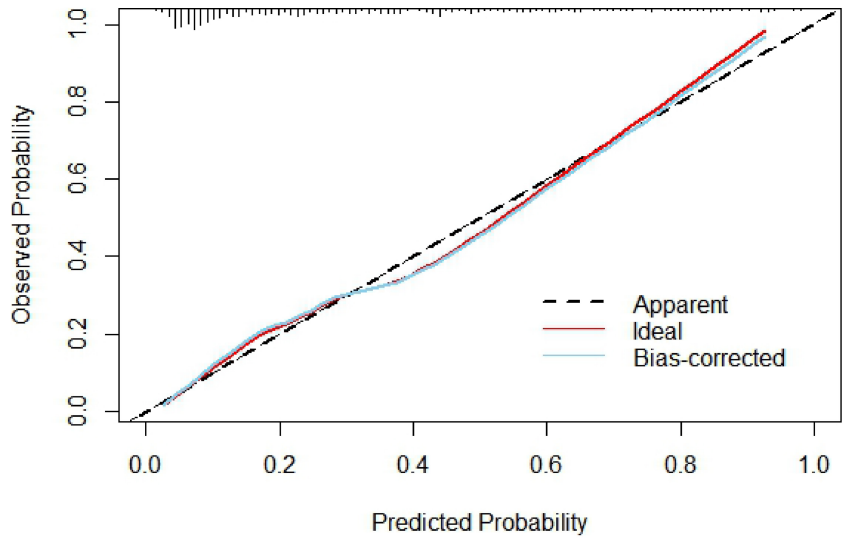


FIGURE 3
Calibration curve.

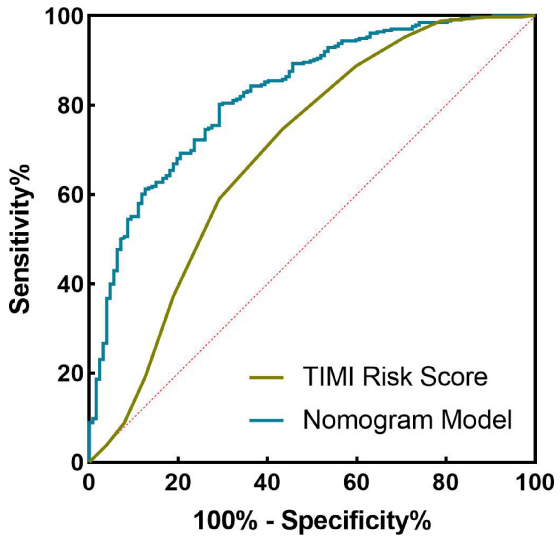


FIGURE 4
Receiver operating characteristic (ROC) curve of nomogram model and thrombolysis in myocardial infarction (TIMI) score in predicting the efficacy of in-hospital major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) patients.

were selected as meeting the endpoints, and predictors were selected to construct a nomogram model to provide a reference for clinical assessment of the patient's condition and guiding treatment.

Acute myocardial infarction (AMI) is a serious and fatal disease with high mortality and poor prognosis. Although PCI can restore myocardial perfusion associated with an infarcted artery as soon as possible and improve the prognosis of patients, the risk of major adverse cardiovascular events in patients after PCI is still very high, mainly including cardiac death, heart failure, stroke, revascularization, malignant arrhythmia, etc. (8–10). Studies have shown that poor prognosis after PCI in patients with acute myocardial infarction is associated with several indicators, such as LVEF, Killip class, Hb, and red blood cell distribution width (11–13).

Therefore, early assessment of short-term risk in STEMI patients, including assessment of the extent of myocardial injury, presence of clinical features at high risk of developing MACE, risk of reperfusion therapy, and success, is important. To obtain more effective prognostic information, the scoring system for patient risk assessment mainly includes the TIMI risk score (14), GRACE risk score (15), PAMI risk score (16), etc., of which TIMI risk score is widely used in clinical practice (14). The TIMI risk score was based on data from the TIMI-II study, which enrolled STEMI patients who presented within 6 h and underwent thrombolytic therapy, taking into account risk factors and reperfusion time, and therefore has important prognostic value for STEMI patients, especially STEMI patients receiving reperfusion therapy. The GRACE risk score model was derived from the Global Registry of Acute Coronary Events (17), which primarily enrolled patients with non-ST-segment elevation acute coronary syndrome, and the score was used to risk stratify patients based primarily on their basic clinical signs and ancillary tests and did not include the impact of reperfusion on prognosis. Therefore, it is generally believed in clinical work that the TIMI risk score is more accurate for risk stratification of STEMI patients, while the GRACE risk score is more reasonable for risk stratification of non-ST-segment

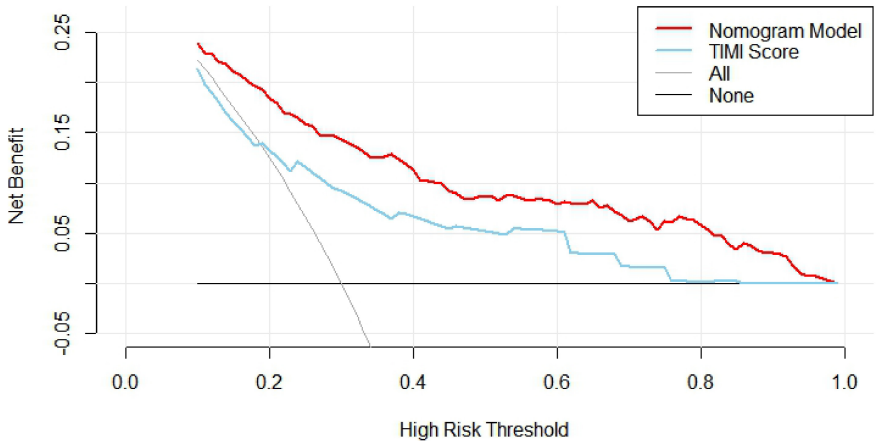


FIGURE 5
Clinical decision curve analysis for nomogram models.

elevation acute coronary syndrome patients. Therefore, early screening of patients at high risk of MACE and individualized management are beneficial to improve patient outcomes.

To better individualize patient outcomes, we used Lasso regression to screen five risk factors most associated with major adverse cardiovascular events during hospitalization: systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, Killip class II-IV, urea, left ventricular ejection fraction (LVEF), IABP, and NT-ProBNP as significant predictors with coefficients that were not zero. Previous studies have shown that blood pressure at admission has also been shown to be a risk factor for in-hospital outcomes in STEMI patients. Acute myocardial infarction patients with hypertension have a poor prognosis (18), while other studies have shown that AMI patients with low SBP and low DBP levels at admission are significantly associated with the risk of in-hospital mortality (19, 20). In this study, we found that SBP and DBP at admission were lower and statistically significantly different in patients affecting the MACE group than in the non-MACE group. We believe that lower SBP and/or lower DBP impacts myocardial perfusion and thus adversely impacts prognosis. In this study, multivariate logistic regression analysis was performed with five predictor variables SBP, DBP, Killip class II-IV, LVEF (assigned value: measured value), and urea selected by Lasso regression as independent variables, and the results showed that Killip class II-IV and urea were independent risk factors for in-hospital MACE after PCI in STEMI patients ($P < 0.05$), and LVEF was an independent protective factor for in-hospital MACE after PCI in STEMI patients ($P < 0.05$).

Killip classification is an index to assess the severity of heart failure after acute myocardial infarction (21). Previous studies have reported that myocardial infarction patients with higher Killip grades tend to have more severe coronary artery disease and larger myocardial infarct size, which means more myocardial cell necrosis and necrotic cells are subsequently replaced by fibrotic scars, which are difficult to reverse once formed, in addition to their effects on cardiac contractility, which interfere with normal cardiac electrical activity and thus lead to arrhythmia, which may be a factor in the poor long-term prognosis of patients with higher Killip grades (22, 23). At the same time, DeGeare et al. (24) reported that patients with a higher Killip class were more likely to develop renal failure after PCI, and some patients required long-term dialysis therapy, which may also be partly responsible.

Patients with acute myocardial infarction complicated by heart failure (HF) or left ventricular dysfunction have a poor prognosis and are at high risk of rehospitalization and death (25). Assessment of left ventricular function using echocardiographic measurements of LVEF after acute myocardial infarction is an important predictor of clinical outcome (26) and can well distinguish between low and high risk of cardiac events after acute myocardial infarction. In a study of 417 patients with AMI, LVEF <40% was an independent predictor of the combined end point of death, congestive heart failure, and recurrent AMI 30 years after AMI (27). In another large prospective cohort study (28), 4,122 patients with acute myocardial infarction undergoing PCI were followed up for 4 years and found to have a significantly increased risk of sudden cardiac death and all-cause mortality in patients with LVEF ≤30 and 30< LVEF ≤40% compared with those with LVEF >40%. Another study (29), involving 28,771 patients with HF, left ventricular dysfunction, or both after acute myocardial infarction, showed that the risk of death increased with decreasing LVEF for all types of death.

NT-proBNP is an endogenous hormone produced by ventricular myocytes, and it has been shown that its peripheral content is not significantly changed in the early stages of ventricular dysfunction, but is significantly increased in patients

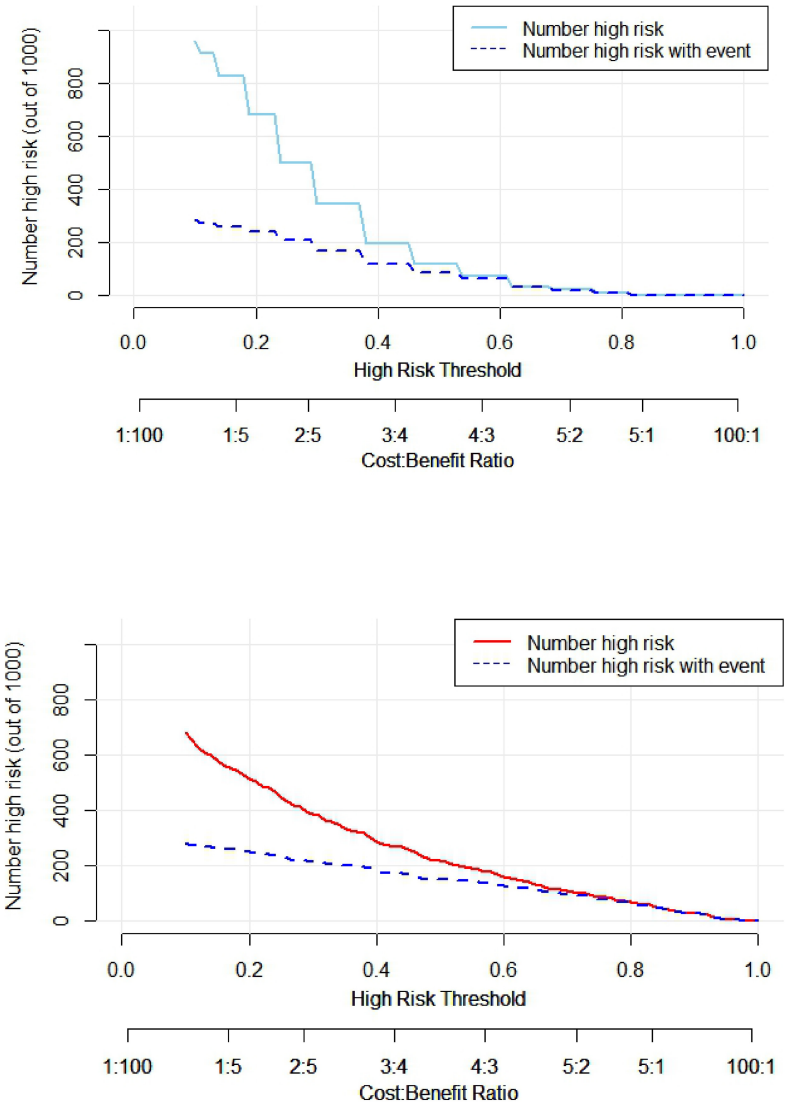


FIGURE 6
Analysis of clinical impact curve between nomogram model and TIMI score single model.

with acute heart failure (30). In clinical practice, LVEF, NYHA functional classification, A-D stage, and other indicators are the main indicators to determine heart failure, but these indicators have a certain subjective color, in reflecting the severity of heart failure, it is bound to be subjectively affected, resulting in a certain degree of inaccuracy. NT-proBNP levels have been reported to more accurately reflect the severity of heart failure and correlate well with NYHA functional class (31). When acute heart failure occurs, NT-ProBNP levels rise dramatically in the patient's plasma. NT-ProBNP levels have a close correlation with left ventricular systolic dysfunction (30, 32) and can be used as a sensitive indicator to determine the ventricular function and the degree of cardiac insufficiency, as well as to evaluate the clinical treatment effect and prognosis (33, 34). This study also found that serum NT-proBNP was significantly increased in patients who developed acute heart failure, consistent with the trend in the above studies.

Previous studies have shown that renal dysfunction in STEMI patients is one of the most important predictors of in-hospital and long-term mortality (35). And serum creatinine levels are closely related to prognosis after treatment (36). This study showed that creatinine and urea levels were significantly higher in the MACE group than in the non-MACE group ($P < 0.05$), while elevated blood urea nitrogen levels were independent risk factors for in-hospital MACE in STEMI patients. Early restoration of effective myocardial reperfusion in STEMI patients is critical to reducing acute mortality and improving prognosis; however, interventional or

medical therapy is often limited by renal function and serum creatinine levels. Therefore, serum creatinine and urea nitrogen levels should be used as important predictors of prognosis when individualizing treatment regimens, and risk stratification should be performed according to renal function status as well as blood urea nitrogen and creatinine levels, which ultimately effectively reduces mortality and improves hospital outcomes.

A nomogram is a visual graph composed of line segments of different lengths that are used to predict the probability of a clinical event, is based on a multivariate regression model, and is drawn after integrating multiple clinical indicators. In this study, we constructed a nomogram model for risk prediction of in-hospital MACE after PCI in STEMI patients based on indicators that were statistically different in multivariate logistic regression analysis. The results showed that the AUC of the nomogram model for predicting in-hospital MACE after PCI in STEMI patients was greater than that of the TIMI score, indicating that the nomogram model constructed in this study had a higher predictive value for in-hospital MACE after PCI in STEMI patients compared with TIMI score. The nomogram model concordance index (C-index) was 0.826 (95% CI: 0.785–0.868), with a sensitivity of 0.709 and a specificity of 0.802, which had good predictive power. The results of the H-L goodness-of-fit test for predicting in-hospital MACE after PCI in STEMI patients showed $\chi^2 = 1.3328$, $P = 0.25$, and the model calibration curve was close to the ideal model, with an internally validated C-index of 0.818 and good discrimination. Clinical decision curve (DCA) analysis showed that the net benefit of the nomogram prediction model was higher in the interval of 0.1–0.99 for threshold probability, suggesting that when the threshold probability was 0.11–0.99, the nomogram model could bring net clinical benefit to patients; clinical impact curve (CIC) analysis showed that compared with the TIMI score single model, the difference between the nomogram model curve and the actual disease curve was smaller, suggesting that the nomogram model was more suitable for the actual occurrence of in-hospital MACE in clinical practice, and the prediction model judged that STEMI patients at high risk of in-hospital MACE were highly matched with STEMI patients who developed in-hospital MACE, confirming that the prediction model had a high clinical effective rate.

This study still has shortcomings: firstly, this study is a single-center study with a limited sample size, the risk factors included in the study are not comprehensive and bias cannot be avoided; secondly, in terms of model validation, only internal validation has been performed. Third, due to the limitation of our medical institution level, all enrolled patients in this study were patients who underwent coronary artery stenting, so the effect of different PCI procedures on MACE still needs further study. Lack of external validation results from other sites. Therefore, in terms of the clinical application and promotion of this model, large-sample, multicenter clinical data are still needed to provide more external evidence to support further exploring the influencing factors of in-hospital MACE after PCI in STEMI patients and optimize the nomogram model.

5 Conclusion

In summary, Killip class II-IV, urea nitrogen, and LVEF NT-ProBNP are independent factors for in-hospital MACE after PCI in STEMI patients, and a nomogram model for in-hospital MACE risk prediction after PCI in STEMI patients constructed based on the above factors has good discrimination, calibration, and clinical effectiveness and can be used as an effective tool for early clinical prediction of in-hospital MACE risk after PCI in STEMI patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Second People's Hospital of Hefei Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CF and ZC wrote the main manuscript text. XJ and MY prepared **Tables 1**, **2** and **Figures 1–6**. All authors reviewed the manuscript and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Çınar T, Çağdaş M, Rencüzoğulları İ, Karakoyun S, Karabağ Y, Yesin M, et al. Prognostic efficacy of C-reactive protein/albumin ratio in ST elevation myocardial infarction. *Scand Cardiovasc J.* (2019). 53:83–90. doi: 10.1080/14017431.2019.1590628

2. Zhang H, Qiu B, Zhang Y, Cao Y, Zhang X, Wu Z, et al. The value of pre-infarction angina and plasma D-dimer in predicting no-reflow after primary percutaneous coronary intervention in st-segment elevation acute myocardial infarction patients. *Med Sci Monit.* (2018) 24:4528–35. doi: 10.12659/MSM.909360

3. Klingenberg R, Aghlmandi S, Räber L, Gencer B, Nanchen D, Heg D, et al. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. *Eur Heart J Acute Cardiovasc Care.* (2018) 7:129–38. doi: 10.1177/2048872616684678

4. Zheng S, Lyu J, Han D, Xu F, Li C, Yang R, et al. Establishment of a prognostic model based on the Sequential Organ Failure Assessment score for patients with first-time acute myocardial infarction. *J Int Med Res.* (2021) 49:3000605211011976. doi: 10.1177/03000605211011976

5. Bai Z, Ma Y, Shi Z, Li T, Hu S, Shi B. Nomogram for the prediction of intrahospital mortality risk of patients with ST-segment elevation myocardial infarction complicated with hyperuricemia: a multicenter retrospective study. *Therap Clin Risk Manag.* (2021) 17:863–75. doi: 10.2147/TCRM.S320533

6. Kong S, Chen C, Zheng G, Yao H, Li J, Ye H, et al. A prognostic nomogram for long-term major adverse cardiovascular events in patients with acute coronary syndrome after percutaneous coronary intervention. *BMC Cardiovasc Disord.* (2021) 21:253. doi: 10.1186/s12872-021-02051-0

7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* (2007) 115:2344–51. doi: 10.1161/CIRCULATIONAHA.106.685313

8. Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol.* (2010) 56:254–63.

9. Krumholz HM, Normand SL, Wang Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011. *Circulation.* (2014) 130:966–75. doi: 10.1161/CIRCULATIONAHA.113.007787

10. Panduranga P, Al-Rashidi M, Al-Hajri F. In-hospital and one-year clinical outcome of percutaneous coronary intervention in a tertiary hospital in Oman: Oman PCI registry. *Oman Med J.* (2017) 32:54–61. doi: 10.5001/omj.2017.10

11. Shiraishi J, Kohno Y, Nakamura T, Yanagiuchi T, Hashimoto S, Ito D, et al. Predictors of in-hospital outcomes after primary percutaneous coronary intervention for acute myocardial infarction in patients with a high Killip class. *Internal Med.* (2014) 53:933–9. doi: 10.2169/internalmedicine.53.1144

12. Saito D, Nakanishi R, Watanabe I, Yabe T, Okubo R, Amano H, et al. Combined assessment of left ventricular end-diastolic pressure and ejection fraction by left ventriculography predicts long-term outcomes of patients with ST-segment elevation myocardial infarction. *Heart Vessels.* (2018) 33:453–61. doi: 10.1007/s00380-017-1080-6

13. Brener SJ, Mehran R, Dangas GD, Ohman EM, Witzenbichler B, Zhang Y, et al. Relation of baseline hemoglobin levels and adverse events in patients with acute coronary syndromes (from the acute catheterization and urgent intervention triage strategY and harmonizing outcomes with revasculariZatiON and stents in acute myocardial infarction trials). *Am J Cardiol.* (2017) 119:1710–6. doi: 10.1016/j.amjcard.2017.02.052

14. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation.* (2000) 102:2031–7. doi: 10.1161/01.cir.102.17.2031

15. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* (2004) 291:2727–33. doi: 10.1001/jama.291.22.2727

16. Addala S, Grines CL, Dixon SR, Stone GW, Boura JA, Ochoa AB, et al. Predicting mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (PAMI risk score). *Am J Cardiol.* (2004) 93:629–32. doi: 10.1016/j.amjcard.2003.11.036

17. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Internal Med.* (2003) 163:2345–53. doi: 10.1001/archinte.163.19.2345

18. Kenchaiah S, Pfeffer MA, St John Sutton M, Plappert T, Rouleau JL, Lamas GA, et al. Effect of antecedent systemic hypertension on subsequent left ventricular dilation after acute myocardial infarction (from the survival and ventricular enlargement trial). *Am J Cardiol.* (2004) 94:1–8. doi: 10.1016/j.amjcard.2004.03.020

19. Yap YG, Duong T, Bland JM, Malik M, Torp-Pederson C, Køber L, et al. Prognostic value of blood pressure measured during hospitalization after acute myocardial infarction: an insight from survival trials. *J Hypertens.* (2007) 25:307–13. doi: 10.1097/HJH.0b013e3280115bae

20. Shiraishi J, Kohno Y, Sawada T, Ito D, Kimura M, Ariyoshi M, et al. Systolic blood pressure at admission, clinical manifestations, and in-hospital outcomes in patients with acute myocardial infarction. *J Cardiol.* (2011) 58:54–60. doi: 10.1016/j.jjcc.2011.04.003

21. Killip T III, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* (1967) 20:457–64. doi: 10.1016/0002-914990023-9

22. Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, et al. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA.* (2003) 290:2174–81. doi: 10.1001/jama.290.16.2174

23. Francis Stuart SD, De Jesus NM, Lindsey ML, Ripplinger CM. The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction. *J Mol Cell Cardiol.* (2016) 91:114–22. doi: 10.1016/j.yjmcc.2015.12.024

24. DeGeare VS, Boura JA, Grines LL, O'Neill WW, Grines CL. Predictive value of the Killip classification in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol.* (2001) 87:1035–8. doi: 10.1016/s0002-914901457-6

25. Metra M, Cotter G, El-Khorazaty J, Davison BA, Milo O, Carubelli V, et al. Acute heart failure in the elderly: differences in clinical characteristics, outcomes, and prognostic factors in the VERITAS study. *J Card Fail.* (2015) 21:179–88. doi: 10.1016/j.cardfail.2014.12.012

26. Prastaro M, Pirozzi E, Gaibazzi N, Paolillo S, Santoro C, Savarese G, et al. Expert review on the prognostic role of echocardiography after acute myocardial infarction. *J Am Soc Echocardiogr.* (2017) 30:431–43.e2. doi: 10.1016/j.echo.2017.01.020

27. Schwammenthal E, Adler Y, Amichai K, Sagie A, Behar S, Hod H, et al. Prognostic value of global myocardial performance indices in acute myocardial infarction: comparison to measures of systolic and diastolic left ventricular function. *Chest.* (2003) 124:1645–51. doi: 10.1378/chest.124.5.1645

28. Shiga T, Hagiwara N, Ogawa H, Takagi A, Nagashima M, Yamauchi T, et al. Sudden cardiac death and left ventricular ejection fraction during long-term follow-up after acute myocardial infarction in the primary percutaneous coronary intervention era: results from the HIJAMI-II registry. *Heart.* (2009) 95:216–20. doi: 10.1136/hrt.2008.145243

29. Hall TS, von Lueder TG, Zannad F, Rossignol P, Duarte K, Chouihed T, et al. Relationship between left ventricular ejection fraction and mortality after myocardial infarction complicated by heart failure or left ventricular dysfunction. *Int J Cardiol.* (2018) 272:260–6. doi: 10.1016/j.ijcard.2018.07.137

30. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension.* (2000) 36:355–9. doi: 10.1161/01.hyp.36.3.355

31. Pizzolo F, Zorzi F, Chiecchi L, Consoli L, Aprili I, Guarini P, et al. NT-proBNP, a useful tool in hypertensive patients undergoing a diagnostic evaluation for primary aldosteronism. *Endocrine.* (2014) 45:479–86. doi: 10.1007/s12020-013-0028-6

32. Chen AA, Wood MJ, Krauser DG, Baggish AL, Tung R, Anwaruddin S, et al. NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnoea in the Emergency Department (PRIDE) echocardiographic substudy. *Eur Heart J.* (2006) 27:839–45. doi: 10.1093/eurheartj/ehi811

33. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *Am J Cardiol.* (2005) 95:948–54. doi: 10.1016/j.amjcard.2004.12.032

34. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart.* (2006) 92:843–9. doi: 10.1136/hrt.2005.071233

35. Zhao L, Wang L, Zhang Y. Elevated admission serum creatinine predicts poor myocardial blood flow and one-year mortality in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. *J Invasive Cardiol.* (2009) 21:493–8.

36. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* (2013) 127:529–55. doi: 10.1161/CIR.0b013e3182742c84

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 09 March 2023
DOI 10.3389/fcvm.2023.1027107

OPEN ACCESS

EDITED BY
Dong Han,
People's Liberation Army General Hospital,
China

REVIEWED BY
Linggen Gao,
People's Liberation Army General Hospital,
China
Hong Qiu,
Chinese Academy of Medical Sciences and
Peking Union Medical College,
China

*CORRESPONDENCE
Liqiu Yan
✉ yanliqiu110@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to
Coronary Artery Disease,
a section of the journal
Frontiers in Cardiovascular Medicine

RECEIVED 24 August 2022
ACCEPTED 14 February 2023
PUBLISHED 09 March 2023

CITATION
Yan W, Li M, Lei Y, Zhang S, Lv F, Wang J, Yang Q, Yu N, Chen M, Cao X and Yan L (2023) Prognostic impact of white blood cell counts on clinical outcomes in patients with chronic renal insufficiency undergoing percutaneous coronary intervention.
Front. Cardiovasc. Med. 10:1027107.
doi: 10.3389/fcvm.2023.1027107

Prognostic impact of white blood cell counts on clinical outcomes in patients with chronic renal insufficiency undergoing percutaneous coronary intervention

Wei Yan[1,2†], Mengyao Li[2†], Yumeng Lei[2†], Shuaiyong Zhang[2], Fengfeng Lv[2], Jiawang Wang[2], Qian Yang[2], Na Yu[2], Ming Chen[2], Xufen Cao[2] and Liqiu Yan[1,2*]

[1]Department of Cardiology and Dongguan Cardiovascular Research Institute, Dongguan Songshan Lake Central Hospital, Guangdong Medical University, Dongguan, China, [2]Department of Cardiology, Cangzhou Central Hospital, Hebei Medical University, Cangzhou, China

Objective: To determine whether the inclusion of white blood cell (WBC) counts in the SYNTAX score (SS) or SS II models could improve the models' performance for risk stratification in individuals with chronic renal insufficiency (CRI) following percutaneous coronary intervention (PCI).

Methods: In total, 2,313 patients with CRI, who were subjected to PCI and had data available on in-hospital WBC (ih-WBC) counts, were recruited. Patients were divided into 3 groups as per their ih-WBC counts (low, medium, and high). The primary endpoints were all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints incorporated myocardial infarction, stroke, unplanned revascularization, and major adverse cardiovascular and cerebrovascular events (MACCEs).

Results: During a median follow-up of 3years, the high WBC group had the highest incidences of CM (2.4% vs. 2.1% vs. 6.7%; $p<0.001$), ACM (6.3% vs. 4.1% vs. 8.2%; $p<0.001$), unplanned revascularization (8.4% vs. 12.4% vs. 14.1%; $p<0.001$), and MACCEs (19.3% vs. 23.0% vs. 29.2%; $p<0.001$) among the three groups. Multivariable Cox regression analysis depicted that the risk of ACM and CM in the high WBC group was 2.577 (95% confidence interval [CI]: 1.504–4.415, $p<0.001$) and 3.850 (95% CI: 1.835–8.080, $p<0.001$) times that in the low WBC group after adjusting for other confounding factors. A combination of ih-WBC counts with SS or SS II significantly improved the risk assessment and prediction of ACM and CM.

Conclusion: The ih-WBC counts was associated with the risk of occurrence of ACM, CM, unplanned revascularization, and MACCEs in individuals with CRI following PCI. It provides an incremental predictive value for the occurrence of ACM and CM when included in SS or SS II models.

KEYWORDS

white blood cell count, SYNTAX score, SYNTAX score II, chronic renal insufficiency, percutaneous coronary intervention

1. Introduction

Inflammation exerts a critical function in the progression as well as plaque destabilization in atherosclerosis (1). Studies have found that downstream biomarkers of inflammation, such as interleukin-6 and the high-sensitivity C-reactive protein (hs-CRP) are linked to a greater risk of cardiovascular events (2, 3).

The white blood cell (WBC) counts are a widely-used and easily available marker of inflammation in clinical practice. Its predictive value as a marker for mortality in individuals with acute coronary syndrome (ACS) is well-established (4–6). Recently, it has also been demonstrated that total, as well as differential in-hospital white blood cell (ih-WBC) counts, are independent prognostic factors for long-term deaths and major adverse cardiovascular and cerebrovascular events (MACCEs). Including ih-WBC counts in SYNTAX score (SS) or SYNTAX score II (SS-II) models can improve mortality predictions in individuals with triple-vessel coronary artery disease (CAD) (7). However, there have been no assessments of the predictive value of ih-WBC counts in patients with CRI after percutaneous coronary intervention (PCI). Chronic renal insufficiency (CRI), which is defined as the presence of kidney damage or reduced kidney function (estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2) for ≥3 months (8), is high-risk comorbidity that increases the risk of cardiovascular mortality and morbidity and is known to be associated with poorer clinical outcomes in patients following PCI (9). In this investigation, we sought to evaluate the utility of including ih-WBC counts as a factor in SS or SS II models for anticipating long-term clinical outcomes in individuals with CRI following PCI.

2. Methods

2.1. Study population

The study design of the risk evaluation of CRI patients following PCI has been described previously (10). Briefly, a total of 2,468 patients with creatinine clearance rates (CrCl) <90 mL/min per 1.73 m^2 who underwent PCI between January 2014 and September 2017 in Cangzhou Central Hospital, Hebei Medical University, were retrospectively enrolled in the study. After excluding 155 patients for whom ih-WBC counts data were not available, 2,313 patients were included in this investigation. Patients were classified into three groups as per tertiles of ih-WBC counts as follows: low WBC group [WBC counts ≤6.18*10^9/L (n = 776)], medium WBC group [WBC counts >6.18*10^9/L but ≤8.14*10^9/L (n = 768)], and high WBC group [WBC counts >8.14*10^9/L (n = 769)] (Figure 1). The study protocol was subjected to approval by the ethics committee of Cangzhou Central Hospital. Written and informed consent was obtained for all subjects.

The clinical and interventional data of the participants were collected from the electronic medical record (EMR) system. The CrCl values were calculated utilizing the simplified Modification of Diet in Renal Disease (MDRD) equation. The ih-WBC counts were defined as the first WBC counts value from the EMR system. Two of three trained cardiologists (who were blinded to the clinical data as well as outcomes) calculated the SS (11) and SS II (12) through the dedicated website.[1] In case of any disagreement, the opinion of a third observer was obtained and resolved by consensus.

2.2. Study endpoints and follow-up

Clinical follow-up was performed *via* clinic visits or telephone conversations. The primary endpoints included all-cause mortality (ACM) as well as cardiac mortality (CM). Deaths that could not be attributed to non-cardiac causes were considered CM. The secondary endpoints included myocardial infarction (MI), stroke, unplanned revascularization, and major adverse cardiovascular and cerebrovascular events (MACCEs), defined as a composite of ACM, MI, stroke, and unplanned revascularization. MI was defined following the consensus document on the fourth universal definition (13). Stroke was defined as neural dysfunction due to a sudden rupture or blockage of a blood vessel, and was diagnosed based on signs of brain dysfunction or imaging evidence (14). Revascularization of PCI or coronary artery bypass grafting (CABG) driven by ischemic symptoms or cardiac events was defined as unplanned revascularization. All endpoints were confirmed by two independent clinicians.

2.3. Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or medians with interquartile ranges (IQR). Categorical variables are presented as frequencies and percentages. Continuous variables were compared utilizing one-way ANOVAs or Kruskal-Wallis tests, when necessary. Chi-square or the Fisher exact tests, on the other hand, carried out comparisons of categorical variables. Patients who were lost to follow-up were deemed at risk until they were censored at the date of the last contact. The cumulative event rates were measured utilizing Kaplan–Meier curves and compared across groups *via* the log-rank test. We assessed the prognostic value of ih-WBC grouping for predicting clinical outcomes using multivariable Cox regression models. While Log[−logS(t)] plots were used to test for proportional hazard assumption. All potential confounders (with $p < 0.1$ in the univariate analyses) were incorporated in the multivariate analyses. By combining ih-WBC counts with SS or SS II values, we assessed the improvements in model performance, risk classification, and discrimination; this was done by comparing the AUC of the two nested models employing the nonparametric deLong approach and computing the net reclassification improvement (NRI) as well as the integrated discrimination improvement (IDI) indices. A two-sided value of $p < 0.05$ was statistically significant. SPSS 24.0 (IBM Corp., Armonk, NY, United States) and R Software Version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria) conducted all the statistical analyses of this investigation.

1 http://www.syntaxscore.com

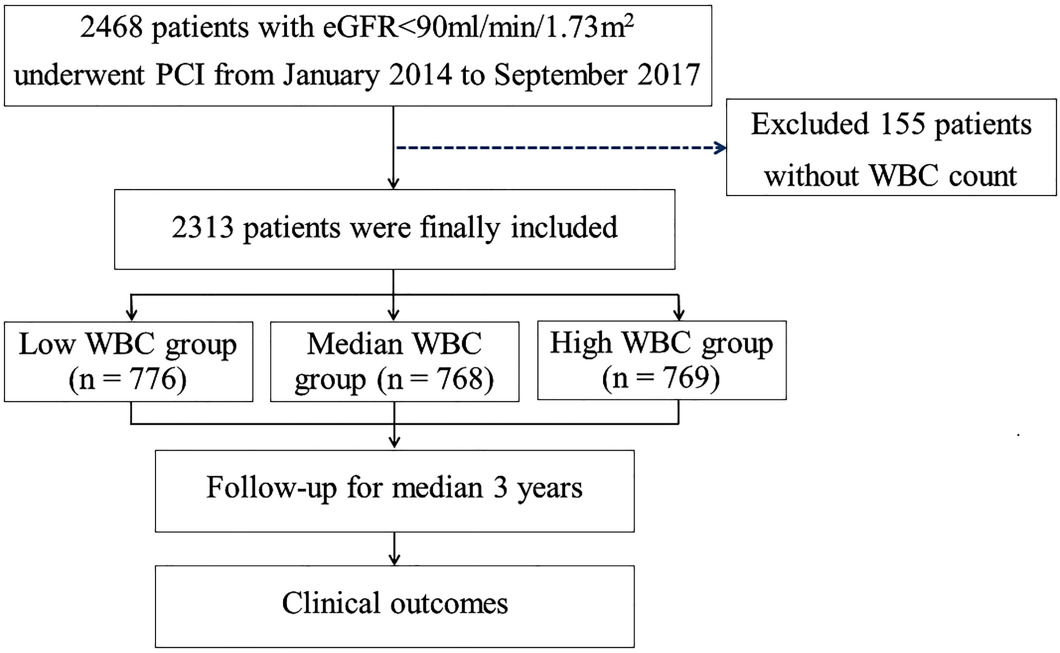


FIGURE 1
Study flow chart. PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft; WBC, white blood cell.

3. Results

3.1. Patients' baseline characteristics

The ih-WBC counts ranged from 2.6*10^9/L to 32.7*10^9/L. The SS values ranged from 1.0 to 47.0, and the SS-II values ranged from 9.7 to 59.6. Patients with high ih-WBC counts were younger and more likely to have current smoker status; clinical presentation of MI; reduced eGFR; lower left ventricular ejection fraction (LVEF); higher left ventricular end-diastolic diameter (LVEDD); and elevated levels of serum creatinine, blood glucose, total cholesterol, triglyceride, and low-density lipoprotein ($p < 0.05$ or $p < 0.001$) than those with low and median ih-WBC counts. Patients with high ih-WBC counts also had higher baseline SS values and were more likely to have thrombus lesions and undergo primary PCI ($p < 0.001$ for all) (Tables 1, 2).

3.2. Association of ih-WBC counts with clinical outcomes

The median follow-up period was 3 years (IQR = 1.5–5.0). Among the three groups, the high ih-WBC counts group had the highest 5-year cumulative event rates of ACM (6.3% vs. 4.1% vs. 8.2%; $p < 0.001$), CM (2.4% vs. 2.1% vs. 6.7%; p < 0.001), unplanned revascularization (8.4% vs. 12.4% vs. 14.1%; $p < 0.001$), and MACCEs (19.3% vs. 23.0% vs. 29.2%; $p < 0.001$) (Table 3 and Figure 2). Univariate Cox regression analyses for different clinical outcomes were shown in Supplementary Table 1. Multivariate Cox regression analyses affirmed that the risk of ACM and CM in the high WBC group was 2.577 (95% confidence interval [CI]: 1.504–4.415, $p < 0.001$) and 3.850 (95% CI: 1.835–8.080, p < 0.001) times that in the low WBC group after adjusting for other confounding factors (Table 4).

3.3. Combination of ih-WBC counts with SS or SS II values for prediction of ACM and CM

The analyses of time-dependent AUCs for ACM showed that the AUCs for SS in combination with ih-WBC counts were significantly larger than those of SS alone ($p < 0.05$) during the 30-month follow-up period. However, the degree of increase tended to decrease with time. There was no remarkable difference between the predictive value of the SS plus ih-WBC counts model and the SS model ($p > 0.05$) when the follow-up times were longer than 30 months. A similar result was observed for the SS-II models, albeit with a cutoff value of 28 months instead of 30 months. In the models used to predict the incidence of CM, though the extent of increase also tended to decrease with time, there was a remarkable difference between the predictive value of the SS plus ih-WBC counts model and the SS model ($p < 0.05$) during the whole follow-up period, and for the SS-II models, the cutoff value was 33 months (Figure 3).

Furthermore, by combining the ih-WBC counts with SS or SS II models, the metrics for risk reclassification and discrimination were significantly improved. The respective NRIs of the SS plus ih-WBC counts model over the SS model were 0.121 for ACM and 0.188 for CM; the NRIs of the SS-II plus ih-WBC counts model over the SS-II model were 0.025 for ACM and 0.135 for CM. The IDI indices of the SS plus ih-WBC counts model over the SS model were 0.019 ($p < 0.01$) for ACM and 0.022 ($p < 0.001$) for CM and the IDI indices of the SS-II

TABLE 1 Baseline clinical characteristics of patients.

	Low ih-WBC count (*n*=776)	Medium ih-WBC count (*n*=768)	High ih-WBC count (*n*=769)	*P*-value
Demographics				
Age, yrs	66.0 (61.0–72.0)	66.0 (60.0–71.0)	65.0 (59.0–70.0)	<0.001
Male	409 (52.7)	471 (61.3)	468 (60.9)	0.001
BMI, kg/m^2	25.7 ± 3.4	26.4 ± 3.3	25.8 ± 3.2	0.012
Previous history				
Diabetes	148 (19.1)	190 (24.7)	189 (24.6)	0.010
Hypertension	521 (67.1)	550 (71.6)	484 (62.9)	0.001
Dyslipidemia	266 (34.3)	341 (44.4)	322 (41.9)	<0.001
Current smoker	61 (7.9)	90 (11.7)	110 (14.3)	<0.001
Prior MI	69 (8.9)	69 (9.0)	58 (7.5)	0.524
Previous PCI	101 (13.0)	116 (15.1)	89 (11.6)	0.121
Previous stroke	82 (10.6)	94 (12.2)	76 (9.9)	0.312
COPD, n (%)	11 (1.4)	12 (1.6)	14 (1.8)	0.815
Clinical presentation				<0.001
Stable angina	428 (55.2)	352 (45.8)	172 (22.4)	
Unstable angina	132 (17.0)	113 (14.7)	56 (7.3)	
NSTEMI	103 (13.3)	143 (18.6)	158 (20.5)	
STEMI	113 (14.6)	160 (20.8)	383 (49.8)	
eGFR, ml/min	79.9 (71.9–85.7)	78.5(69.8–85.0)	77.8(67.3–84.6)	<0.001
LVEF, %	63.0 (59.0–66.0)	62.0 (58.0–66.0)	60.0 (53.0–65.0)	<0.001
LVEDD (mm)	47.0 (45.0–50.0)	47.0 (44.0–51.0)	48.0 (45.0–53.0)	0.006
Baseline laboratory				
WBC, *10^9/L	5.3 (4.8–5.8)	7.1 (6.6–7.6)	10.1 (8.9–11.9)	<0.001
Hemoglobin (mg/dL)	13.1 (12.0–14.0)	13.4 (12.4–14.4)	13.2 (11.9–14.4)	<0.001
Creatinine (mg/dL)	0.93 (0.78–1.02)	0.96 (0.84–1.07)	0.97 (0.85–1.1)	<0.001
Blood glucose (mg/dL)	107.5 (93.6–139.5)	111.6 (95.4–147.7)	132.8 (107.6–187.2)	<0.001
Total cholesterol (mg/dL)	164.4 (143.1–193.4)	170.2 (143.1–196.9)	174.0 (150.0–205.1)	<0.001
TG (mg/dL)	124.0 (93.0–174.5)	139.1 (98.3–195.1)	140.4 (103.6–200.2)	<0.001
HDL (mg/dL)	35.6 (30.2–41.4)	35.2 (29.8–41.0)	36.0 (30.9–41.4)	0.275
LDL (mg/dL)	94.0 (76.2–114.8)	96.3 (77.2–120.4)	102.1 (84.6–123.1)	<0.001

Values are mean ± SD, median (IQR), or n (%). BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

plus ih-WBC counts model over the SS-II model were 0.025 ($p < 0.001$) for ACM and 0.032 ($p < 0.001$) for CM (Table 5).

4. Discussion

This study shows that the ih-WBC counts is associated with the risk of occurrence of ACM, CM, unplanned revascularization, and MACCEs in individuals with CRI following PCI. The ih-WBC counts can be utilized for risk reclassification, especially in secondary prevention among patients with CRI post-PCI. Integrating ih-WBC counts into SS or SS II models also improves the predictive performance of these models and facilitates the identification of patients at risk for future ACM and CM. Therefore, the ih-WBC counts may also be used to flag patients at risk for adverse cardiac events post-PCI, who may warrant more intensive follow-up and preventive treatment.

Inflammation is known to exert an important function not only in atherogenesis but also in atherosclerotic plaque rupture resulting in acute coronary syndrome (ACS) (15–18). Studies have found that biomarkers of inflammation including hs-CRP and interleukin-6 are independent risk factors for cardiovascular events (19). Preprocedural hs-CRP elevation has been linked to a greater risk of adverse cardiac events in people undergoing PCI (20–22). The WBC counts, which can be easily and repeatedly obtained in clinical practice, are one of the most viable inflammatory biomarkers. Cannon et al. (4) have

TABLE 2 Anatomical characteristics of lesions and procedural details.

	Low ih-WBC count (*n*=776)	Medium ih-WBC count (*n*=768)	High ih-WBC count (*n*=769)	*P*-value
CAD extension				0.070
1-vessel disease	187 (24.1)	161 (21.0)	157 (20.4)	
2-vessel disease	265 (34.1)	282 (36.7)	247 (32.1)	
3-vessel disease	324 (41.8)	325 (42.3)	365 (47.5)	
Left main disease	49 (6.3)	50 (6.5)	47 (6.1)	0.950
Lesion characteristics				
Lesion length > 20 mm	445 (57.3)	429 (55.9)	362 (47.1)	<0.001
Bifurcation or trifurcation	241 (31.1)	198 (25.8)	153 (19.9)	<0.001
Aorto-ostial lesion	13 (1.7)	15 (2.0)	24 (3.1)	0.127
Heavy calcification	86 (11.1)	68 (8.9)	49 (6.4)	0.005
Severe tortuosity	46 (5.9)	50 (6.5)	40 (5.2)	0.550
Thrombus	24 (3.1)	40 (5.2)	226 (29.4)	<0.001
Chronic total occlusions	97 (12.5)	133 (17.3)	101 (13.1)	0.014
Target vessel number	1 (1–1)	1 (1–2)	1 (1–1)	0.099
Target lesion location				
LM	27 (3.5)	24 (3.1)	17 (2.2)	0.314
LAD	444 (57.2)	404 (52.6)	391 (50.8)	0.035
LCX	212 (27.3)	247 (32.2)	195 (25.4)	0.010
RCA	307 (39.6)	324 (42.4)	352 (45.8)	0.046
Procedural characteristics				
Stent per patient	2.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.016
Total length of stent, mm	41.0 (25.0–64.0)	38.0 (24.0–64.0)	36.0 (25.0–60.0)	0.151
Stent length > 100 mm	65 (8.4)	48 (6.3)	43 (5.6)	0.074
Mean stent diameter, mm	3.00 (2.75–3.25)	2.95 (2.75–3.25)	3.00 (2.75–3.25)	0.683
Minimum stent diameter, mm	2.75 (2.50–3.00)	2.75 (2.50–4.00)	2.75 (2.50–3.00)	0.266
Maximum stent diameter, mm	3.00 (2.75–3.50)	3.00 (2.75–3.50)	3.00 (2.75–3.50)	0.669
Primary PCI	13 (1.7)	25 (3.3)	191 (24.8)	<0.001
Baseline SYNTAX score	8.0 (13.0–18.5)	8.0 (13.0–18.5)	14.0 (9.0–19.5)	0.004
SYNTAX II score for PCI	28.3 (24.3–32.3)	27.6 (23.6–32.1)	28.2 (23.5–33.0)	0.165

Values are mean ± SD, median (IQR), or n (%). CAD, coronary artery disease; LM, left main; LAD, left anterior descending artery; LCX, left circumflex; RCA, right coronary artery.

reported that WBC counts are linked to an increased rate of mortality after 30 days and 10 months in individuals with acute MI and unstable angina pectoris. The TACTICS-TIMI 18 [Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) Thrombolysis in Myocardial Infarction (TIMI)] sub-study demonstrated that an increased WBC counts predicted extensive CAD and increased mortality at 6 months in people with ACS (5). More recently, Alkhalfan et al. (23) observed that elevated WBC counts were linked to increased major or minor hemorrhage and ischemic events (such as cardiovascular death, MI, and stroke) in patients with ACS.

The SS model is a well-established tool used to predict adverse clinical outcomes to help clinicians decide on optimum revascularization strategies in individuals with complex CAD (11, 24, 25). The SS-II model incorporates the anatomical variables in the SS model with other clinical variables (age, sex, LVEF, CrCl, chronic obstructive pulmonary disease, and peripheral vascular disease), and can predict 4-year mortality with higher accuracy. The SS-II model is also a better guide than the SS model for decisions on PCI and CABG in complex CAD cases (12). Subsequently, several studies have demonstrated the predictive value of the SS-II model for predicting outcomes in different cohorts such as three-vessel and/or unprotected left main coronary artery disease (ULMAD) following PCI (26, 27), ACS (28, 29), and cardiogenic shocks after primary PCI (30).

The SS-II model was created according to a Cox proportional hazards model utilizing the SYNTAX trial findings (12). The baseline features that were strongly associated with 4-year mortality were added to the model. However, the ih-WBC counts, a marker of the inflammatory state, were not included in the SS-II model. A recent study observed that a combination of differential WBC (eosinophil, monocyte, and lymphocyte) counts enhanced the success of risk prediction and reclassification for mortality when combined with SS

TABLE 3 Five-year cumulative incidence of adverse events.

	Low ih-WBC count (a)	Medium ih-WBC count (b)	High ih-WBC count (c)	*P*-value			
				Trend	a vs. b*	b vs. c*	a vs. c*
All-cause mortality	6.3% (49)	4.1% (55)	8.2% (63)	<0.001	0.599	0.006	0.001
Cardiac mortality	2.4% (19)	2.1% (16)	6.7% (52)	<0.001	0.377	<0.001	<0.001
Myocardial infarction	4.7% (36)	5.8% (45)	6.2% (48)	0.328	0.197	0.778	0.313
Unplanned revascularization	8.4% (65)	12.4% (95)	14.1% (108)	0.001	0.024	0.275	0.001
Stroke	6.0% (47)	8.9% (68)	9.5% (73)	0.151	0.510	0.435	0.154
MACCEs	19.3 (150)	23.0% (177)	29.2% (225)	<0.001	0.042	0.008	<0.001

Event rates are Kaplan–Meier estimates, %(n). *Adjusted significance level is 0.017. MACCEs, major adverse cardiovascular and cerebrovascular events.

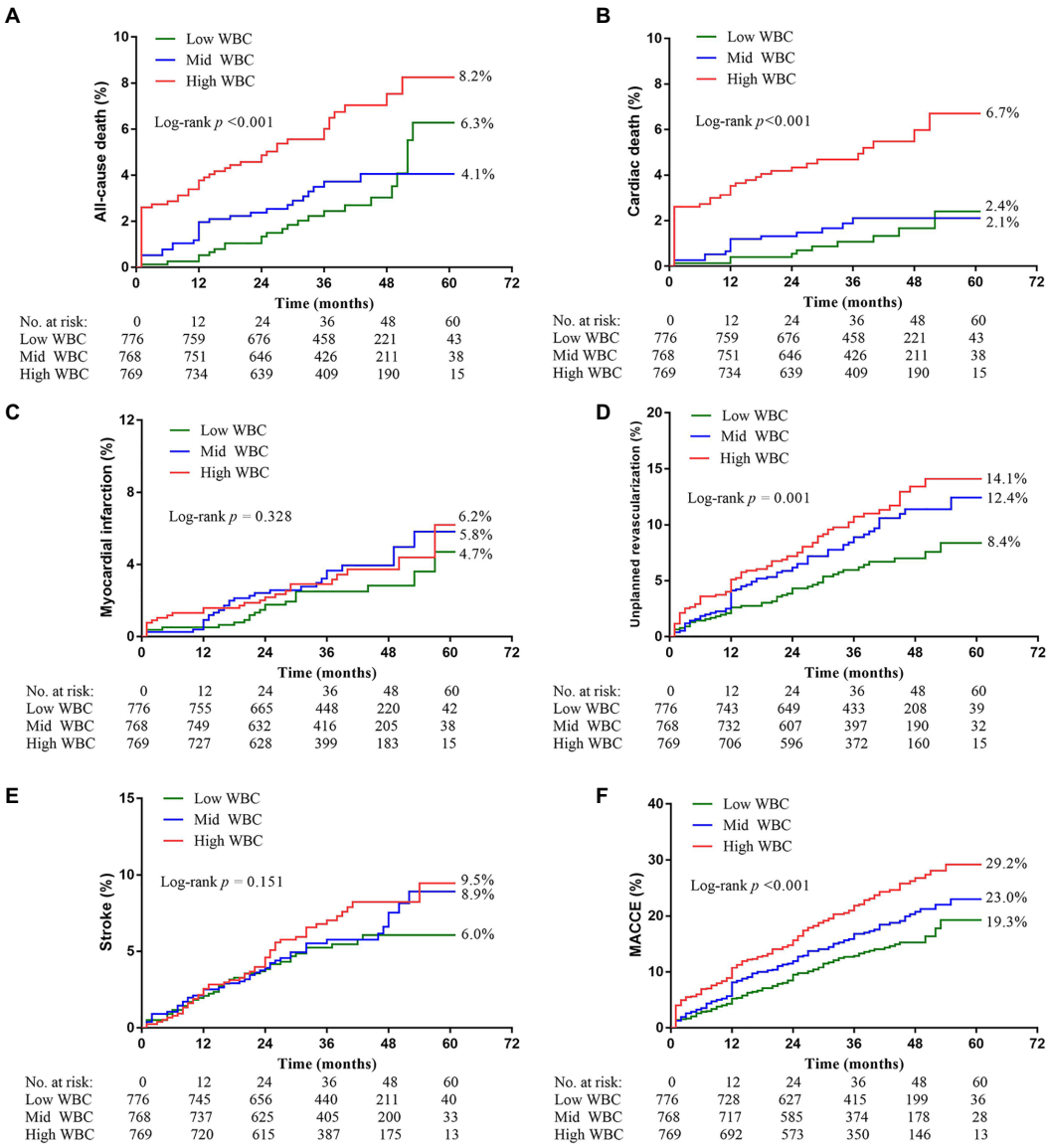


FIGURE 2
Kaplan–Meier curves showing event rates stratified by the WBC counts. **(A)** All-cause death. **(B)** Cardiac death. **(C)** Myocardial infarction. **(D)** Unplanned revascularization. **(E)** Stroke. **(F)** Major adverse cardiovascular and cerebrovascular events (MACCE).

TABLE 4 Multivariate Cox regression analyses for median 3-year clinical outcomes.

Variables	All-cause mortality		Variables	Cardiac mortality	
	Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value
WBC_Low	Ref.		WBC_Low	Ref.	
WBC_Mid	1.293(0.731–2.289)	0.377	WBC_Mid	1.427(0.627–3.247)	0.396
WBC_High	2.577(1.504–4.415)	<0.001	WBC_High	3.850(1.835–8.080)	<0.001
Age	1.097(1.066–1.130)	<0.001	Age	1.079(1.040–1.119)	<0.001
Hypertension	0.667(0.442–1.006)	0.053	Diabetes	1.115(0.622–2.001)	0.715
Dyslipidemia	0.631(0.367–1.085)	0.096	Dyslipidemia	0.617(0.350–1.089)	0.096
COPD	3.395(1.614–7.144)	0.001	COPD	3.953(1.667–9.374)	0.002
Stable angina	Ref.		Stable angina	Ref.	
Unstable angina	2.184(1.372–3.476)	0.491	Unstable angina	1.105(0.657–1.858)	0.708
NSTEMI	0.967(0.576–1.623)	0.598	NSTEMI	1.150(0.605–2.185)	0.670
STEMI	1.200(0.671–2.143)	0.983	STEMI	0.760(0.353–1.637)	0.483
eGFR	0.972(0.948–0.996)	0.023	eGFR	0.966(0.937–0.995)	0.024
LVEF	0.971(0.946–0.998)	0.038	LVEF	0.986(0.950–1.023)	0.445
LVEDD	1.006(0.966–1.048)	0.762	LVEDD	1.032(0.971–1.098)	0.304
Hemoglobin	0.999(0.988–1.012)	0.992	Hemoglobin	0.999(0.984–1.014)	0.878
Creatinine	0.994(0.982–1.006)	0.307	Creatinine	0.992(0.978–1.006)	0.276
Blood glucose	1.030(0.988–1.074)	0.161	Blood glucose	1.035(0.991–1.082)	0.122
TG	0.943(0.716–1.242)	0.675	SYNTAX score	1.024(0.995–1.055)	0.111
SYNTAX score	1.012(0.987–1.037)	0.363			
Variables	Unplanned revascularization		Variables	Stroke	
	Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value
WBC_Low	Ref.		Age	1.034(1.012–1.056)	0.002
WBC_Mid	1.184(0.772–1.818)	0.439	Male	0.585(0.390–0.878)	0.010
WBC_High	1.389(0.915–2.109)	0.123	Hypertension	1.435(0.963–2.140)	0.076
BMI	1.035(0.958–1.118)	0.386	Previous stroke	1.963(1.296–2.975)	0.001
Dyslipidemia	0.846(0.569–1.258)	0.409	eGFR	1.002(0.986–1.018)	0.801
Prior MI	1.132(0.635–2.017)	0.675	Creatinine	1.008(1.004–1.012)	<0.001
Previous PCI	1.145(0.695–1.887)	0.595	Total cholesterol	0.932(0.630–1.379)	0.724
Total cholesterol	0.862(0.570–1.304)	0.483	LDL	0.954(0.569–1.600)	0.859
LDL	0.961(0.567–1.630)	0.883	SYNTAX score	1.019(0.998–1.041)	0.080
SYNTAX score	1.025(1.004–1.047)	0.022			
Variables	Myocardial infarction		Variables	MACCEs	
	Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value
BMI	1.058(0.939–1.192)	0.354	WBC_Low	Ref.	
Diabetes	1.134(0.648–1.984)	0.660	WBC_Mid	1.184(0.772–1.818)	0.552
Prior MI	1.290 (0.532–3.129)	0.049	WBC_High	1.389(0.915–2.109)	0.217
Previous PCI	1.846 (0.943–3.612)	0.010	Age	1.036(1.014–1.059)	0.001
Stable angina	Ref.		Male	0.526(0.347–0.796)	0.002
Unstable angina	2.184(1.372–3.476)	<0.001	BMI	1.029(0.950–1.114)	0.489
NSTEMI	0.967(0.576–1.623)	0.899	Diabetes	1.128(0.721–1.763)	0.598
STEMI	1.200(0.671–2.143)	0.539	Prior MI	1.207(0.675–2.159)	0.525
eGFR	0.991(0.970–1.012)	0.400	Previous PCI	1.062(0.642–1.756)	0.815
LVEDD	1.007(0.955–1.062)	0.792	COPD	1.467(0.462–4.662)	0.516

(Continued)

TABLE 4 (Continued)

Variables	All-cause mortality		Variables	Cardiac mortality	
	Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value
Creatinine	1.000(0.993–1.008)	0.929	Stable angina	Ref.	
Blood glucose	1.018(0.965–1.074)	0.514	Unstable angina	1.134(0.801–1.604)	0.478
TG	1.108(0.940–1.306)	0.220	NSTEMI	1.086(0.745–1.583)	0.667
SYNTAX score	1.025(0.995–1.055)	0.102	STEMI	1.268(0.823–1.952)	0.282
			eGFR	0.996(0.980–1.012)	0.607
			LVEF	1.036(1.004–1.069)	0.025
			LVEDD	0.993(0.949–1.040)	0.776
			Creatinine	1.006(1.003–1.011)	<0.001
			Blood glucose	1.004(0.958–1.053)	0.860
			SYNTAX score	1.020(0.999–1.043)	0.065

CI, confidence interval; WBC, white blood cell; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; TG, triglyceride; LDL, low density lipoprotein; MACCEs, major adverse cardiovascular and cerebrovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

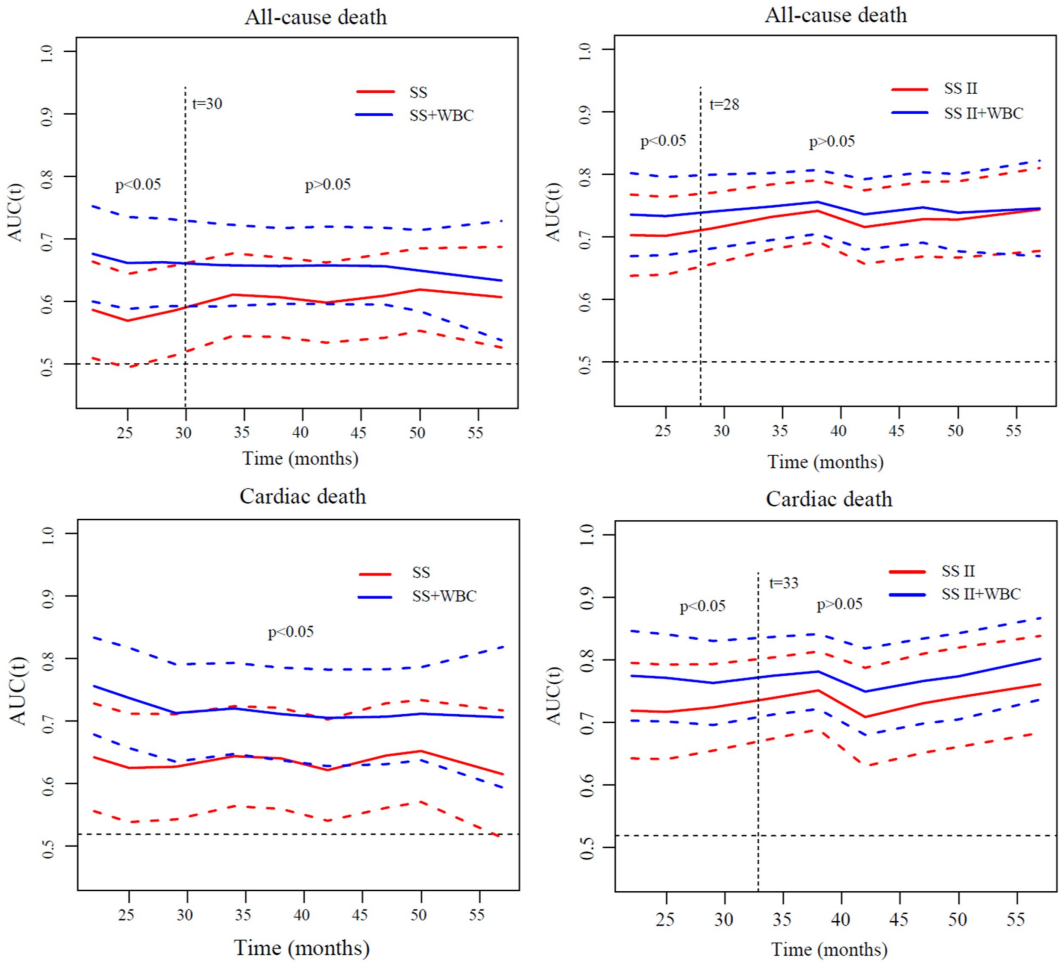


FIGURE 3
Comparisons of time-dependent AUCs of different models for discrimination of all-cause death and cardiac death. AUC, area under curve; SS, SYNTAX score; SS II, SYNTAX score II; WBC, white blood cell; SS II+WBC: SYNTAX score II plus white blood cell.

TABLE 5 Statistics for model improvement of for all-cause mortality and cardiac mortality.

	Discrimination		Risk reclassification				
	IDI [95% CI]	*P*-value	Events		Non-events		NRI [95% CI]
			Risk up	Risk down	Risk up	Risk down	
All-cause mortality							
SS vs. SS + WBC	0.019 (0.004–0.058)	<0.01	0.243	0.092	0.113	0.083	0.121 (−0.003–0.232)
SS II vs. SS II + WBC	0.025 (0.005–0.060)	<0.001	0.119	0.106	0.056	0.069	0.025 (−0.051–0.239)
Cardiac mortality							
SS vs. SS + WBC	0.022 (0.006–0.060)	<0.001	0.256	0.033	0.089	0.045	0.188 (0.023–0.322)
SS II vs. SS II + WBC	0.032 (0.009–0.060)	<0.001	0.209	0.077	0.060	0.057	0.135 (−0.051–0.266)

CI, confidence interval; AUC, area under the curve; SS, SYNTAX score; SS II, SYNTAX score II; WBC, white blood cell; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

or SS II models in patients with triple-vessel CAD (7). Patients with CRI have a hallmark feature of persistent, low-grade inflammation, which is involved in the development of ACM (31). Inflammation plays an important role in the initiation and progression of kidney disease. Recent studies have reported that plasma proinflammatory biomarkers, such as soluble TNF receptors 1 and 2 (TNFR-1 and TNFR2) were associated with the increased risk of progression of diabetic kidney disease, even after adjustment for established clinical risk factors (32, 33). However, not much is known about the predictive value of ih-WBC counts for predicting clinical outcomes in patients with CRI post-PCI. This study demonstrated that elevated ih-WBC counts were associated with increased incidence of ACM, CM, unplanned revascularization, and MACCEs in individuals with CRI following PCI. Furthermore, the addition of ih-WBC counts to the SS or SS II models also improved the predictive performance of these models in predicting ACM and CM events in individuals with CRI following PCI, although the degree of improvement in predictive performance tended to decrease with time.

5. Limitations

Despite these promising results, our results should be viewed in the light of multiple limitations. First, this study is based on data from a single center and is retrospective and observational in nature; therefore, it can only identify associations and cannot ascribe causality to related events. Second, differences in blood collection periods from the occurrence of the index event were not controlled for in this analysis. Third, we did not collect information on differential WBC counts and hs-CRP levels, both of which may be important for clinical outcomes. Finally, in some patients, we believe that the ih-WBC counts data may have been affected by undetected infections or other conditions for which we have no information.

6. Conclusion

In patients with CRI following PCI, an elevated ih-WBC counts was found to be associated with the risk of occurrence of ACM, CM, unplanned revascularization, and MACCEs. A combination of ih-WBC counts with SS or SS II models significantly improved these models' performance in predicting ACM and CM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Cangzhou Central Hospital, Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WY, LY, and ML provided the conception of the idea for the study and analyzed the acquired data. LY, WY, ML, SZ, and YL contributed to the development of the methodology and wrote the manuscript. FL, JW, NY, and MC were responsible for the interpretation of statistical results. XC revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Natural Science Foundation of Hebei Province, China (H2021110008) and Hebei Provence Key Research Projects (172777163).

Acknowledgments

We thank all the study participants whose work made this study possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1027107/full#supplementary-material

References

1. Pedro-Botet, J, Climent, E, and Benaiges, D. Atherosclerosis and inflammation. *New Ther Appr Med Clin*. (2020) 155:256–62. doi: 10.1016/j.medcli.2020.04.024

2. Ziegler, L, Gajulapuri, A, Frumento, P, Bonomi, A, Wallén, H, de Faire, U, et al. Interleukin 6 trans-signalling and risk of future cardiovascular events. *Cardiovasc Res*. (2019) 115:213–21. doi: 10.1093/cvr/cvy191

3. Shimizu, T, Suwa, S, Dohi, T, Wada, H, Miyauchi, K, Shitara, J, et al. Clinical significance of high-sensitivity C-reactive protein in patients with preserved renal function following percutaneous coronary intervention. *Int Heart J*. (2019) 60:1037–42. doi: 10.1536/ihj.18-683

4. Cannon, CP, McCabe, CH, Wilcox, RG, Bentley, JH, and Braunwald, E. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 investigators. *Am J Cardiol*. (2001) 87:a10:636–9, A10. doi: 10.1016/s0002-9149(00)01444-2

5. Sabatine, MS, Morrow, DA, Cannon, CP, Murphy, SA, Demopoulos, LA, DiBattiste, PM, et al. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (treat angina with Aggrastat and determine cost of therapy with an invasive or conservative strategy- thrombolysis in myocardial infarction 18 trial) substudy. *J Am Coll Cardiol*. (2002) 40:1761–8. doi: 10.1016/s0735-1097(02)02484-1

6. Lindahl, B, Toss, H, Siegbahn, A, Venge, P, and Wallentin, L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC study group. Fragmin during instability in coronary artery disease. *N Engl J Med*. (2000) 343:1139–47. doi: 10.1056/nejm200010193431602

7. Zhao, X, Jiang, L, Xu, L, Tian, J, Xu, Y, Zhao, Y, et al. Predictive value of in-hospital white blood cell count in Chinese patients with triple-vessel coronary disease. *Eur J Prev Cardiol*. (2019) 26:872–82. doi: 10.1177/2047487319826398

8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. (2002) 39:S1–S266.

9. Tsai, TT, Messenger, JC, Brennan, JM, Patel, UD, Dai, D, Piana, RN, et al. Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease: a report from the linked CathPCI registry-CMS claims database. *J Am Coll Cardiol*. (2011) 58:1859–69. doi: 10.1016/j.jacc.2011.06.056

10. Yan, L, Li, P, Wang, Y, Han, D, Li, S, Zhang, J, et al. Impact of the residual SYNTAX score on clinical outcomes after percutaneous coronary intervention for patients with chronic renal insufficiency. *Catheter Cardiovasc Interv*. (2020) 95:606–15. doi: 10.1002/ccd.28652

11. Serruys, PW, Morice, MC, Kappetein, AP, Colombo, A, Holmes, DR, Mack, MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. (2009) 360:961–72. doi: 10.1056/NEJMoa0804626

12. Farooq, V, van Klaveren, D, Steyerberg, EW, Meliga, E, Vergouwe, Y, Chieffo, A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. (2013) 381:639–50. doi: 10.1016/s0140-6736(13)60108-7

13. Thygesen, K, Alpert, JS, Jaffe, AS, Chaitman, BR, Bax, JJ, Morrow, DA, et al. Fourth universal definition of myocardial infarction (2018). *Circulation*. (2018) 138:e618–51. doi: 10.1161/CIR.0000000000000617

14. Li, J, Xin, Y, Li, J, Zhou, L, Qiu, H, Shen, A, et al. Association of haemoglobin glycation index with outcomes in patients with acute coronary syndrome: results from an observational cohort study in China. *Diabetol Metab Syndr*. (2022) 14:162. doi: 10.1186/s13098-022-00926-6

15. Ross, R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. (1999) 340:115–26. doi: 10.1056/NEJM199901143400207

16. Wolf, D, and Ley, K. Immunity and inflammation in atherosclerosis. *Circ Res*. (2019) 124:315–27. doi: 10.1161/CIRCRESAHA.118.313591

17. Warnatsch, A, Ioannou, M, Wang, Q, and Papayannopoulos, V. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. *Science*. (2015) 349:316–20. doi: 10.1126/science.aaa8064

18. Zakynthinos, E, and Pappa, N. Inflammatory biomarkers in coronary artery disease. *J Cardiol*. (2009) 53:317–33. doi: 10.1016/j.jjcc.2008.12.007

19. Ridker, PM, Hennekens, CH, Buring, JE, and Rifai, N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. (2000) 342:836–43. doi: 10.1056/NEJM200003233421202

20. Wada, H, Dohi, T, Miyauchi, K, Shitara, J, Endo, H, Doi, S, et al. Preprocedural high-sensitivity C-reactive protein predicts long-term outcome of percutaneous coronary intervention. *Circ. Soc.* (2016) 81:90–5. doi: 10.1253/circj.CJ-16-0790

21. Sabatine, MS, Morrow, DA, Jablonski, KA, Rice, MM, Warnica, JW, Domanski, MJ, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. *Circulation*. (2007) 115:1528–36. doi: 10.1161/circulationaha.106.649939

22. Razzouk, L, Muntner, P, Bansilal, S, Kini, AS, Aneja, A, Mozes, J, et al. C-reactive protein predicts long-term mortality independently of low-density lipoprotein cholesterol in patients undergoing percutaneous coronary intervention. *Am Heart J*. (2009) 158:277–83. doi: 10.1016/j.ahj.2009.05.026

23. Alkhalfan, F, Nafee, T, Yee, MK, Chi, G, Kalayci, A, Plotnikov, A, et al. Relation of white blood cell count to bleeding and ischemic events in patients with acute coronary syndrome (from the ATLAS ACS 2-TIMI 51 trial). *Am J Cardiol*. (2020) 125:661–9. doi: 10.1016/j.amjcard.2019.12.007

24. Sianos, G, Morel, MA, Kappetein, AP, Morice, MC, Colombo, A, Dawkins, K, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. (2005) 1:219–27.

25. Morice, M-C, Serruys, PW, Kappetein, AP, Feldman, TE, Ståhle, E, Colombo, A, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial. *Circulation*. (2010) 121:2645–53. doi: 10.1161/circulationaha.109.899211

26. Song, Y, Gao, Z, Tang, X, Ma, Y, Jiang, P, Xu, J, et al. Usefulness of the SYNTAX score II to validate 2-year outcomes in patients with complex coronary artery disease undergoing percutaneous coronary intervention: a large single-center study. *Catheter Cardiovasc Interv*. (2018) 92:40–7. doi: 10.1002/ccd.27321

27. Xu, B, Généreux, P, Yang, Y, Leon, MB, Xu, L, Qiao, S, et al. Validation and comparison of the long-term prognostic capability of the SYNTAX score-II among 1,528 consecutive patients who underwent left main percutaneous coronary intervention. *J Am Coll Cardiol Intv*. (2014) 7:1128–37. doi: 10.1016/j.jcin.2014.05.018

28. Obeid, S, Frangieh, AH, Räber, L, Yousif, N, Gilhofer, T, Yamaji, K, et al. Prognostic value of SYNTAX score II in patients with acute coronary syndromes referred for invasive management: a subanalysis from the SPUM and COMFORTABLE AMI cohorts. *Cardiol Res Pract*. (2018) 2018:1–11. doi: 10.1155/2018/9762176

29. Salvatore, A, Boukhris, M, Giubilato, S, Tomasello, SD, Castaing, M, Giunta, R, et al. Usefulness of SYNTAX score II in complex percutaneous coronary interventions in the setting of acute coronary syndrome. *J Saudi Heart Assoc*. (2016) 28:63–72. doi: 10.1016/j.jsha.2015.07.003

30. Hayıroğlu, Mİ, Keskin, M, Uzun, AO, Bozbeyoğlu, E, Yıldırımtürk, Ö, Kozan, Ö, et al. Predictive value of SYNTAX score II for clinical outcomes in cardiogenic shock underwent primary percutaneous coronary intervention; a pilot study. *Int J Cardiovasc Imaging*. (2018) 34:329–36. doi: 10.1007/s10554-017-1241-9

31. Mihai, S, Codrici, E, Popescu, ID, Enciu, A-M, Albulescu, L, Necula, LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res*. (2018) 2018:1–16. doi: 10.1155/2018/2180373

32. Schrauben, SJ, Shou, H, Zhang, X, Anderson, AH, Bonventre, JV, Chen, J, et al. Association of multiple plasma biomarker concentrations with progression of prevalent diabetic kidney disease: findings from the chronic renal insufficiency cohort (CRIC) study. *J Am Soc Nephrol*. (2021) 32:115–26. doi: 10.1681/ASN.2020040487

33. Pavkov, ME, Weil, EJ, Fufaa, GD, Nelson, RG, Lemley, KV, Knowler, WC, et al. Tumor necrosis factor receptors 1 and 2 are associated with early glomerular lesions in type 2 diabetes. *Kidney Int*. (2016) 89:226–34. doi: 10.1016/j.kint.2016.06.002

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 01 September 2023
DOI 10.3389/fcvm.2023.1043775

OPEN ACCESS

EDITED BY
Gianluca Rigatelli,
Hospital Santa Maria della Misericordia of Rovigo, Italy

REVIEWED BY
Tingbo Jiang,
The First Affiliated Hospital of Soochow University, China
Aneta Aleksova,
University of Trieste, Italy
Fabrizio D'Ascenzo,
University of Turin, Italy

*CORRESPONDENCE
Yi Tang
✉ da123zhiruoyu@163.com
Qinghua Fu
✉ qing_hua@aliyun.com
Yi Zhang
✉ zhangyi3@medmail.com.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 14 September 2022
ACCEPTED 11 August 2023
PUBLISHED 01 September 2023

CITATION
Tang Y, Peng S, Yao H-l, Liu Z, Zhang L, Zhong C, She C, Liu W, Tang Y, Fu Q and Zhang Y (2023) Left atrial function index predicts poor outcomes in acute myocardial infarction patients treated with percutaneous coronary intervention.
Front. Cardiovasc. Med. 10:1043775.
doi: 10.3389/fcvm.2023.1043775

Left atrial function index predicts poor outcomes in acute myocardial infarction patients treated with percutaneous coronary intervention

Yijin Tang[1†], Siling Peng[1†], Hui-ling Yao[2], Zhibin Liu[1], Liang Zhang[3], Changqing Zhong[3], Chang She[3], Wei Liu[3], Yi Tang[3*], Qinghua Fu[3*] and Yi Zhang[3*]

[1]Department of Cardiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China, [2]Department of General Medicine, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Hunan Normal University, Changsha, China, [3]Department of Cardiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Clinical Medicine Research Center of Heart Failure of Hunan Province, Hunan Normal University, Changsha, China

Background and aims: The left atrial function index (LAFI) is an index that combines the left atrial emptying fraction, adjusted left atrial volume and stroke volume. The prognostic value of LAFI in acute myocardial infarction (AMI) patients treated with percutaneous coronary intervention (PCI) is unknown. This study aims to determine whether LAFI predicts prognosis in AMI patients treated with PCI.

Methods: Patients with newly diagnosed AMI who were treated with PCI at Hunan Provincial People's Hospital from March 2020 to October 2021 were prospectively enrolled. All patients underwent transthoracic echocardiography (TTE) at baseline and follow-up. The endpoint events included rehospitalization due to unstable angina, nonfatal myocardial infarction, rehospitalization due to heart failure and cardiovascular death.

Results: A total of 368 patients with AMI (92 women; mean age, 61.45 ± 11.91 years) were studied with a median follow-up of 14 ± 6.58 months. Sixty-nine patients had endpoint events. Patients who presented with events had a significantly lower LAFI than patients without events (34.25 ± 12.86 vs. 48.38 ± 19.42, $P < 0.0001$). Multivariate Cox analysis demonstrated that LAFI (HR = 0.97 [95% CI: 0.95; 0.99]; $P = 0.012$) and the Killip classification (HR = 1.51 [95% CI: 1.03; 2.22]; $P = 0.034$) were independently predictive of endpoint events. Kaplan–Meier survival curves showed that patients with LAFI ≤ 40.17 cm/ml/m^2 had higher events than patients with LAFI > 40.17 cm/ml/m^2 (HR = 8.53 [95% CI: 4.74; 15.35]; $P < 0.0001$).

Conclusion: LAFI is a strong and independent predictor of adverse events and can be used for risk stratification in patients with AMI treated with PCI.

KEYWORDS

left atrial function index, acute myocardial infarction, transthoracic echocardiography, percutaneous coronary intervention, prognosis

Introduction

Acute myocardial infarction (AMI) remains a leading cause of mortality worldwide, despite substantial improvements in prognosis over the past decade (1). However, some patients still experience adverse events, such as unstable angina, nonfatal myocardial infarction, heart failure after myocardial infarction and death even after receiving percutaneous coronary intervention (PCI). This places a major economic and resource burden on the public health system (2). Therefore, it is important to identify patients with a higher risk of adverse events after AMI in order to treat these patients with intensive drugs at the early stage to improve their prognosis. Transthoracic echocardiography (TTE) is a noninvasive, low-cost, and easily available bedside imaging tool that detects the motion of the myocardial walls, damage extent, functional consequences, and mechanical complications; therefore, TEE is widely used for risk stratification in patients with AMI (3). The left ventricular ejection fraction (LVEF) obtained from echocardiography is often used to assess left ventricular (LV) systolic dysfunction, which can predict poor outcome in patients with AMI. However, LVEF only reflects LV systolic dysfunction, which cannot reveal LV diastolic dysfunction, left atrial (LA) volume, as well as LA function. Meanwhile, several studies have demonstrated that the LA volume index and LA emptying fraction (LAEF), which reflect LA volume and LA function, respectively, could predict morbidity or mortality after AMI (4–6). However, these parameters cannot reflect LV systolic dysfunction. Researchers have attempted to find a better parameter that can reflect both LV systolic and diastolic function, as well as LA function, to predict prognosis in patients with AMI.

The left atrial function index (LAFI) was such a parameter, initially proposed by Liza et al. in 2008 (7) and it is calculated as LAFI = [LAEF × LV outflow tract-velocity time integral (LVOT-VTI)]/LA end-systolic volume index (LAESVi). The LAFI incorporates analogues of cardiac output, atrial reservoir function and LA size, which reflects LV systolic and diastolic function, as well as LA function. Previous studies showed that LAFI was a good predictor of hospitalization for heart failure in patients with preserved ejection fraction and coronary heart disease, and could also predict long-term survival in stable outpatients with systolic heart failure (8, 9). However, whether LAFI could be used to predict the prognosis of patients with AMI treated with PCI is unknown. This study intended to explore the value of the LAFI in the prognostic evaluation of patients with AMI treated with PCI.

Methods

Study population

Patients who were diagnosed with AMI and received PCI in hospital at Hunan Provincial People's Hospital between March 2020 and October 2021 were enrolled. The diagnostic criteria for AMI, including ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI), was based on clinical guidelines (10). Patients who only underwent culprit-lesion PCI all came to our hospital underwent the second PCI for complete revascularization after 1 month. Patients with absent or poor imaging of the atrium and moderate to severe degrees of mitral regurgitation were excluded. This research was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Hunan Provincial People's Hospital. Informed consent was obtained from all enrolled patients.

Echocardiographic methods

We performed resting TTE (GE Vivid E9, America) for all patients within 2 days after they underwent PCI. TTE was performed in the standard left lateral recumbent and supine positions. Routine M-mode and 2-dimensional echocardiography were performed using a standard protocol (11). The maximum LA volume (LAmax) and minimum LA volume (LAmin) were determined by averaging LAmax and LAmin measurements from the apical two- and four-chamber views using the recommended Simpson's biplane summation of disks method. LAEF was calculated as [(LAmax–LAmin)/LAmax] × 100%. The LAESVi was calculated by dividing LA end-systolic volumes by body surface area. LV end-diastolic (LVEDV) and LV end-systolic volumes (LVESV) were measured using Simpson's method in the apical-4 chamber and the apical-2 chamber view. Stroke volume was calculated as (LVEDV-LVESV), and LVEF was calculated as (Stroke volume/LVEDV) × 100%. LVOT-VTI was measured by manually tracing pulsed Doppler velocities in the LV outflow tract in apical 5-chamber views. The final measures were derived by averaging the measurements over ≥3 cardiac cycles. The LAFI was calculated using a previously validated formula: LAFI = (LAEF × LVOT-VTI)/LAESVi (7).

Clinical assessment and follow-up

Basic demographic data, biochemical tests, Killip classification and coronary arteriography were collected at baseline. All enrolled patients were followed up telephonically at 1, 3, 6, 12, and 18 months after discharge, and the endpoint events during this period were recorded. The endpoint events were defined as rehospitalization due to unstable angina, nonfatal myocardial infarction, rehospitalization due to heart failure and cardiovascular death. The follow-up ended on May 1, 2022. The first occurrence of the event, rather than a cumulative event, was taken into consideration in our analysis.

Statistical method

Continuous variables with a normal distribution are expressed as the mean ± standard deviation ($\bar{x} \pm s$), and continuous variables with a nonnormal distribution are represented by the median and

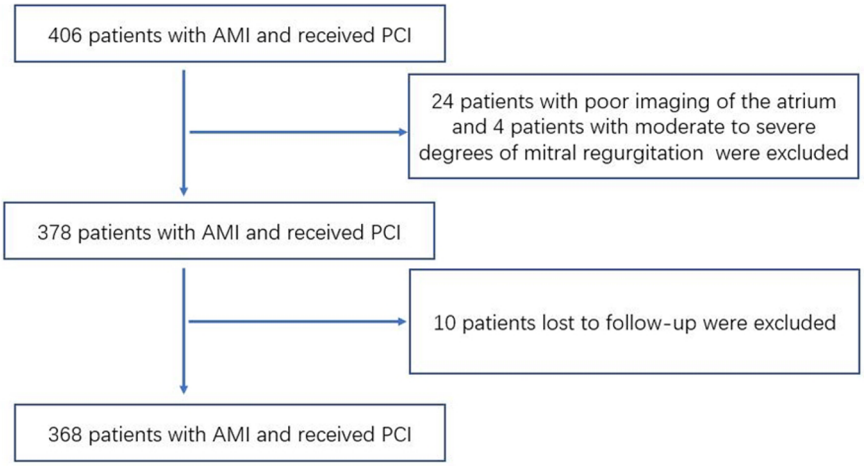


FIGURE 1
Patients' flow-chart in our study.

quartile (IQR). One-way analysis of variance (ANOVA), Student's *t*-test or Mann-Whitney *U* test was used for comparison as appropriate. The categorical variables are expressed as *n* (%), and the Chi-square (χ^2) test was used for categorical variables. Pearson or Spearman correlation coefficients were used for bivariate correlation analysis. Receiver Operating Characteristic (ROC) Curve was used to judge the performance of variables in prognostic prediction and to determine the best cut-off point. Univariate and multivariate Cox proportional hazards model and Kaplan-Meier curve were used for survival analysis. The method of "enter" was used in the multivariable Cox analysis. The ROC curve was analysed using MedCalc v19.3.0, and the rest of the assays were analysed using SPSS 23.0. Two-tailed *P* value <0.05 was statistically significant.

Results

Baseline characteristics and follow-up

Initially, a total of 406 patients were enrolled in our study. Of those, 24 patients had poor imaging of the atrium, 4 patients had moderate to severe degrees of mitral regurgitation and 10 patients lost to follow-up were not included in the analysis. The remaining 368 patients were included in the final analysis of our study (Figure 1). The mean age was 61.45 ± 11.91 years, and 25.0% of patients were women. The median follow-up time was 14.76 ± 6.58 months, and 69 patients developed events during the follow-up period, including 13 patients readmitted due to unstable angina pectoris, 31 patients readmitted due to heart failure, 11 patients with nonfatal myocardial infarction, and 14 patients with cardiovascular death.

Differences in variables between groups

Patients with events had a similar sex distribution and body mass index compared with patients without events (Non-events). However, patients with adverse events are much older, had a higher proportion of type 2 diabetes mellitus (T2DM) and multivessel coronary artery disease (MVD), a poorer Killip classification, higher levels of N-terminal fragment of pro B-type natriuretic peptide (NT-proBNP) and white blood cell count (WBC) compared to patients with non-events. In terms of echocardiography parameters, patients who presented with adverse events had significantly lower LAEF, LAFI, LVEF, and LVOT-VTI and higher LAESVi and LVEDV. In addition, a higher proportion of patients with events were treated with diuretics (Table 1).

Correlation analysis

With the increase in Killip classification, the levels of LAFI were decreased (Figure 2). In our study, 7 patients had atrial fibrillation and 361 patients did not have atrial fibrillation. Compared to patients without atrial fibrillation, LAFI levels were significantly lower in patients with atrial fibrillation (29.47 ± 15.04 vs. 46.05 ± 19.12 cm/ml/m^2, $P = 0.02$). Correlation analysis showed that LAFI levels correlated positively with LVEF and estimated glomerular filtration rate (eGFR) ($r = 0.62$, 0.24, all $P < 0.001$) and negatively with age, NT-proBNP, and LVEDV ($r = -0.21$, -0.50, -0.48, all $P < 0.001$).

Prediction of the composite outcome

LAFI had the highest area under the receiver operator characteristic curve (AUC) value in predicting the events when compared with its individual components LAEF, LAESVi and LVOT-VTI (C-statistics: LAFI 0.73 > LAEF 0.70 > LAESVi 0.64 > LVOT-VTI 0.59). The calculated optimal point of LAFI was 40.17 cm/ml/m^2. The sensitivity and specificity for predicting the events were 78.26% and 66.56%, respectively. The AUC and the

10.3389/fcvm.2023.1043775

TABLE 1 Comparison of baseline data between patients with or without events.

Variables	Events ($n = 69$)	Non-events ($n = 299$)	*P*
Clinical characteristics			
Male, *n* (%)	48 (69.6%)	228 (76.3%)	NS
Age, year	65.42 ± 11.36	60.54 ± 11.87	0.001
BMI, (kg/cm^2)	24.17 ± 3.66	24.33 ± 3.43	NS
Smoking, *n* (%)	41 (59.4%)	206 (68.9%)	NS
Hypertension, *n* (%)	39 (56.5%)	173 (57.9%)	NS
T2DM, *n* (%)	27 (39.1%)	80 (26.8%)	0.042
Previous CI, *n* (%)	8 (11.6%)	29 (9.7%)	NS
Previous MI, *n* (%)	12 (17.4%)	30 (10.1%)	NS
Atrial fibrillation, *n* (%)	2 (2.9%)	5 (1.7%)	NS
The Killip classification, *n* (%)			0.001
I/II	59 (85.5%)	287 (96.0%)	
III/IV	10 (14.5%)	12 (4.0%)	
Biochemical parameters			
WBC, ×10^9/L	10.22 ± 3.98	8.76 ± 2.71	0.012
TC, mmol/L	4.46 ± 1.21	5.16 ± 13.00	NS
LDL, mmol/L	2.69 ± 0.91	2.62 ± 0.96	NS
eGFR, ml/min/1.73m^2	88.22 ± 42.07	93.97 ± 35.70	NS
TB, umol/L	13.29 ± 6.51	14.75 ± 21.10	NS
NT-proBNP, ng/L	6,094.52 ± 8,140.09	2,088.71 ± 4,120.15	<0.0001
Coronary arteriography			
Culprit vessel, *n* (%)			0.85
LAD	39 (56.5%)	172 (57.5%)	
LCX	9 (13.0%)	32 (10.7%)	
RCA	21 (30.4%)	95 (31.7%)	
MVD, *n* (%)	66 (95.7%)	240 (80.3%)	0.002
Echocardiography			
LAESVi, ml/m^2	28.85 ± 8.15	25.56 ± 8.61	<0.001
LAEF, %	50.69 ± 8.39	56.88 ± 10.57	<0.0001
LVOT-VTI, cm	18.18 ± 3.79	19.68 ± 4.19	<0.007
LAFI, cm/ml/m^2	34.25 ± 12.86	48.38 ± 19.42	<0.0001
LVEF, %	44.00 ± 10.29	52.93 ± 10.00	<0.0001
LVEDV, ml	82.72 ± 21.82	77.09 ± 27.47	0.004
Therapeutics			
Aspirin, *n* (%)	68 (98.6%)	297 (99.3%)	NS
P2Y12 inhibitor (clopidogrel or ticagrelor), *n* (%)	69 (100%)	297 (99.3%)	NS
β-blocker, *n* (%)	61 (88.4%)	276 (92.3%)	NS
ACEI/ARB, *n* (%)	60 (87.0%)	263 (88.0%)	NS
Statin, *n* (%)	69 (100%)	296 (99.0%)	NS
Diuretics, *n* (%)	10 (14.5%)	18 (6.0%)	0.017

Continuous data are mean ± standard deviation or median (interquartile range), and categorical variables are *n* (%). ACEI/ARB, angiotensin-converting enzyme inhibit or angiotensin receptor blocker; BMI, body mass index; CI, cerebral infarction; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LAEF, left atrial emptying fraction; LAESVi, left atrial end-systolic volume index; LAFI, left atrial function index; LCX, left circumflex artery; LDL, low density lipoprotein; LVOT-VTI, the left ventricular outflow tract velocity time integral; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MVD, multi-vessel coronary artery disease; NT-proBNP, NT-terminal B-type brain natriuretic peptide precursor; MI, myocardial infarction; RCA, right coronary artery; TC, total cholesterol; TB, total bilirubin;T2DM, type 2 diabetes mellitus; WBC, white blood cell count.

calculated optimal point of LAFI and other important echocardiography parameters were shown in Table 2. Multivariable Cox models, which included LAFI and its components, also revealed that LAFI provided prognostic value incremental to its individual components (Table 3).

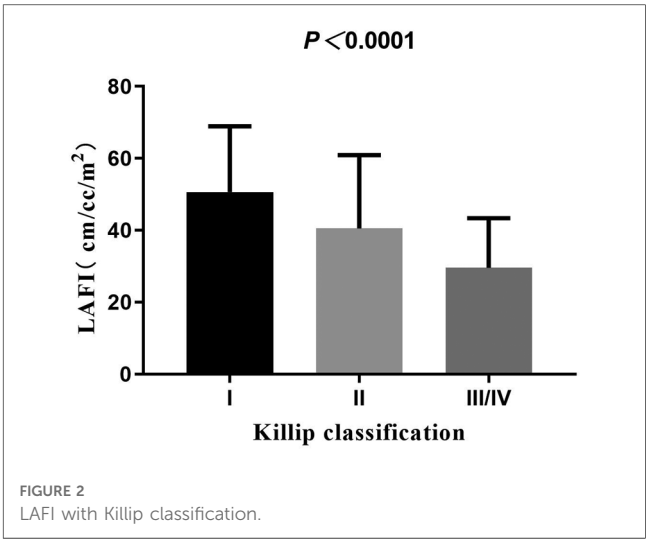


FIGURE 2
LAFI with Killip classification.

On univariate Cox regression analysis, age, T2DM, NT-proBNP, MVD, Killip classification, and variables obtained from echocardiography (LAESVi, LAEF, LVOT-VTI, LAFI, LVEF, LVEDV) were significant predictors of events. Since there were not enough events and LAESVi, LAEF, LVOT-VTI and LAFI exhibited collinearity, we only included age, T2DM, NT-proBNP, Killip Classification, MVD, LAFI, LVEF, LVEDV and diuretics in the multivariable Cox analysis. The results showed that Killip classification (HR = 1.51 [95% CI: 1.03; 2.22]; $P = 0.034$) and LAFI (HR = 0.97 [95% CI: 0.95; 0.99]; $P = 0.012$) were independent predictors of events (Table 4).

Patients with LAFI ≤ 40.17 cm/ml/m^2 had a worse survival rate than patients with LAFI > 40.17 cm/ml/m^2. Kaplan–Meier survival estimates (Figure 3) showed early separation of the event-free survival curves, which continued to diverge throughout follow-up. The unadjusted HR was 8.53 ([95% CI: 4.74; 15.35]; $P < 0.0001$), and after adjustment for age, the HR was 8.06 ([95% CI: 4.46; 14.56]; $P < 0.0001$).

Discussion

We first evaluated the prognostic value of the LAFI in a cohort of 368 AMI patients treated with PCI. We found that LAFI was

TABLE 2 The ROC analysis of important echocardiography parameters.

Variables	AUC (95% CI)	Sensitivity/specificity	Cut-off value
LAEF	0.70 (0.66, 0.75)	66.67%/71.57%	≤52%
LAESVi	0.64 (0.58, 0.68)	63.77%/62.21%	>26.10 ml/m^2
LVOT-VTI	0.59 (0.54, 0.64)	69.13%/78.26%	≤16.4 cm
LAFI	0.73 (0.70, 0.77)	78.26%/66.56%	≤40.17 cm/ml/m^2
LVEDV	0.61 (0.56, 0.66)	60.87%/63.88%	>77.32 ml
LVEF	0.74 (0.69, 0.78)	68.12%/69.90%	≤48%

LAEF, left atrial emptying fraction; LAESVi, left atrial end-systolic volume index; LAFI, left atrial function index; LVOT-VTI, the left ventricular outflow tract velocity time integral; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume.

TABLE 3 Cox analysis of LAFI and its components.

Variables	Wald	HR	95% CI	*P*-value
LAFI	13.67	0.89	0.83–0.94	<0.0001
LAEF	3.75	1.05	1.00–1.10	0.053
LVOT-VTI	3.86	1.14	1.00–1.29	0.050
LAESVi	5.56	0.92	0.86–0.99	0.018

LAEF, left atrial emptying fraction; LAESVi, left atrial end-systolic volume index; LAFI, left atrial function index; LVOT-VTI, the left ventricular outflow tract velocity time integral.

negatively correlated with NT-proBNP and positively correlated with LVEF; furthermore, the results showed that patients with LAFI were associated with poor prognosis. Importantly, the prognostic value of the LAFI was independent of a wide range of clinical risk factors and laboratory and echocardiographic parameters.

LAEF is an indicator of functional LA remodelling, and LAESVi reflects LA structural remodelling. A previous study found that LAEF had a weak correlation with LAESVi (12). By incorporating both LAEF and LAESVi in one formula, LAFI is a more comprehensive indicator of LA remodelling (13). Rigatelli G et al. showed that LAFI was an useful marker of atrial dysfunction severity in patients with patent foramen ovale before and after the interventional procedure (14). LA remodelling can promote the occurrence of atrial fibrillation, and Sardana et al. demonstrated that LAFI, an indicator of LA remodeling, was associated with incidental atrial fibrillation in Framingham Offspring Study participants (15). Meanwhile, atrial fibrillation can decrease LA contractile function and lead to enlargement of the LA, and Nagase et al. also demonstrated that catheter ablation could improve LAFI in patients with atrial fibrillation

TABLE 4 Cox analysis of proportional risks for events.

Variables	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.03	1.01–1.05	0.004	1.01	0.98–1.03	0.613
T2DM	1.73	1.07–2.81	0.026	1.30	0.78–2.16	0.317
The Killip classification	2.28	1.72–3.02	<0.0001	1.51	1.03–2.22	0.034
NT-proBNP	1.00	1.00–1.00	<0.0001	1.00	1.00–1.00	0.277
MVD	5.47	1.72–17.41	0.004	2.70	0.82–8.81	0.101
LAFI	0.95	0.94–0.97	<0.0001	0.97	0.95–0.99	0.012
LVEF	0.93	0.91–0.95	<0.0001	0.97	0.94–1.01	0.112
LVEDV	1.01	1.00–1.02	0.03	0.99	0.98–1.00	0.145
Diuretics	2.40	1.22–4.69	0.011	1.22	0.56–2.62	0.617

HR, hazard ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; NT-proBNP, NT-terminal B-type brain natriuretic peptide precursor; MVD, multi-vessel coronary artery disease; LAFI, left atrial function index; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume.

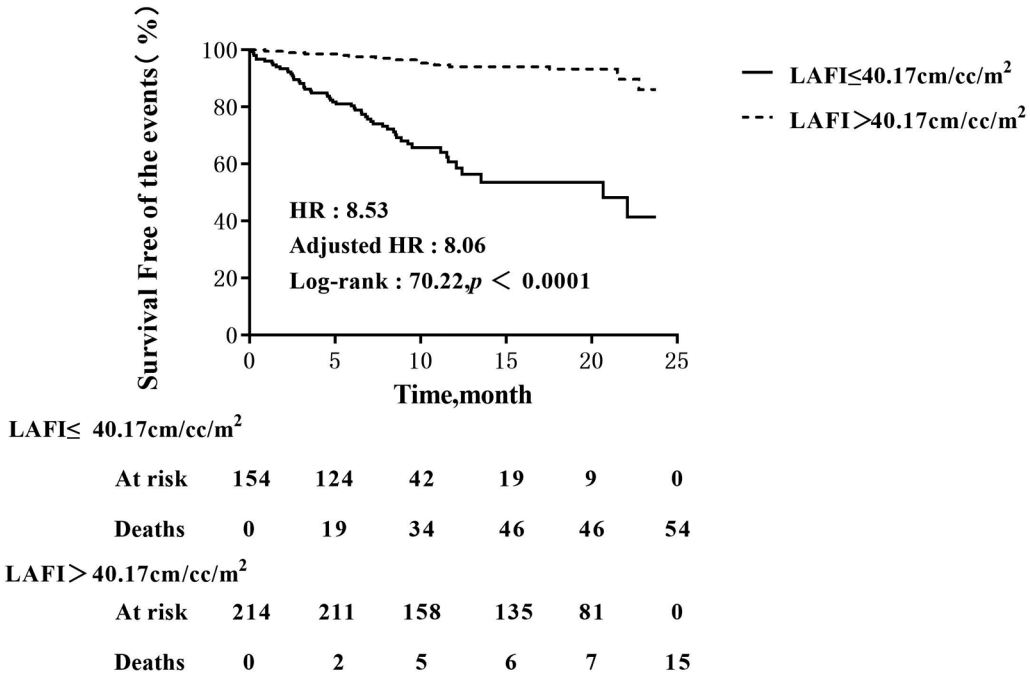


FIGURE 3
Kaplan–Meier analysis of LAFI for events. Adjusted HR indicates hazard ratio (HR) adjusted for age; LAFI, left atrial function index.

(16). The results of our study showed that the LAFI was lower in subjects with atrial fibrillation than in subjects without atrial fibrillation, which are consistent with the results of previous studies (8, 9).

LAFI combines not only LAEF and LAESVi but also LVOT-VTI. In other words, it not only reflects LA structure and function, but also reflects both LV systolic and diastolic function (17). Therefore, LAFI may provide greater prognostic information than a single parameter, such as LVEF, LAESVi or LAEF. Studies have demonstrated that LAFI, superior to other echocardiography parameters, could predict long-term survival in stable systolic heart failure outpatients with LVEF < 40% and patients with preserved ejection fraction and coronary heart disease (8, 9). Shamekhi et al. reported that transcatheter aortic valve replacement (TAVR) could improve LAFI within 12 months after the procedure and a reduced LAFI was an independent predictor of mortality in patients with severe aortic stenosis (18). In addition, Sardana et al. found that LAFI was associated with atrial fibrillation recurrence after catheter ablation in patients with atrial fibrillation (19). The results of our study showed that LAFI had a positive association with LVEF, an indicator of positive cardiac remodelling, and an inverse association with LVEDV, an indicator of adverse cardiac remodelling. Although the AUC value of LVEF was slightly higher than LAFI. However, LAFI showed better performance than LVEF in multivariable Cox analysis. In addition, LAFI, rather than LVEF, could independently predict the events after adjusting for significant confounders, which was consistent with the results of the studies that we mentioned above (8, 9, 18, 19).

In our study, patients with LAFI $\leq$ 40.17 cm/ml/m^2 had a worse survival rate than patients with LAFI > 40.17 cm/ml/m^2, which supported that LAFI was useful in the risk stratification of patients with AMI with PCI. Shamekhi et al. found that severe aortic stenosis patients with a LAFI $\leq$ 13.5 cm/ml/m^2 showed significantly higher rate of 1-year mortality, compared to those with a LAFI > 13.5 cm/ml/m^2 (18). Sargento et al. reported that heart failure with reduced ejection fraction patients with LAFI < 16.57 cm/ml/m^2 had a worse adverse outcomes than patients with LAFI $\geq$ 16.57 cm/ml/m^2 (9). The calculated optimal point of LAFI for predicting the events in our study is different from that in other studies (9, 18). We speculate that the reason is mainly attributed to different study populations, as the LAFI of patients with severe aortic stenosis or reduced ejection fraction heart failure was usually lower than patients with AMI with PCI.

Study limitations

There are several limitations to our study. First, we did not measure LAFI before patients underwent PCI and the day when the patient was discharged. Second, as there was a lack of electrocardiogram recording, we did not record the incidence of atrial fibrillation. Third, our study was a single-center study, and the sample size was relatively small. A multi-center study with a large-scale sample will be required to further validate these results.

Conclusions

LAFI is a strong and independent predictor of events and can be used for risk stratification in patients with AMI treated with PCI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Hunan Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YT, YZ, and QF designed the study. YJT, SP, ZL, LZ, CZ, H-lY, CS, WL collected data and organized the database, YJT and SP wrote the first draft of the manuscript and performed the statistical analysis. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from Scientific research project approved by Hunan Provincial Health Commission (202103012117), Key Project of Hunan Provincial Science and Technology Innovation (2020SK1013), the Science and Technology Innovation Program of Hunan Province (2020SK50922), Renshu Fund project of Hunan Provincial People's Hospital (RS2022A12) and Natural Science Foundation of Hunan Province (2021JJ40294).

Acknowledgments

We thank all subjects and colleagues for participating in the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet*. (2017) 389 (10065):197–210. doi: 10.1016/s0140-6736(16)30677-8

2. Kelly DJ, Gershlick T, Witzenbichler B, Guagliumi G, Fahy M, Dangas G, et al. Incidence and predictors of heart failure following percutaneous coronary intervention in ST-segment elevation myocardial infarction: the Horizons-Ami trial. *Am Heart J*. (2011) 162(4):663–70. doi: 10.1016/j.ahj.2011.08.002

3. Prastaro M, Pirozzi E, Gaibazzi N, Paolillo S, Santoro C, Savarese G, et al. Expert review on the prognostic role of echocardiography after acute myocardial infarction. *J Am Soc Echocardiogr*. (2017) 30(5):431–43.e2. doi: 10.1016/j.echo.2017.01.020

4. Hanada K, Sasaki S, Seno M, Kimura Y, Ichikawa H, Nishizaki F, et al. Reduced left ventricular ejection fraction is a risk for sudden cardiac death in the early period after hospital discharge in patients with acute myocardial infarction. *Circ J*. (2022) 86 (10):1490–8. doi: 10.1253/circj.CJ-21-0999

5. Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, et al. Long-term prognostic significance of left atrial volume in acute myocardial infarction. *J Am Coll Cardiol*. (2004) 44(2):327–34. doi: 10.1016/j.jacc.2004.03.062

6. Modin D, Pedersen S, Fritz-Hansen T, Gislason G, Biering-Sørensen T. Left atrial function determined by echocardiography predicts incident heart failure in patients with stemi treated by primary percutaneous coronary intervention. *J Card Fail*. (2020) 26(1):35–42. doi: 10.1016/j.cardfail.2019.08.014

7. Thomas L, Hoy M, Byth K, Schiller NB. The left atrial function index: a rhythm independent marker of atrial function. *Eur J Echocardiogr*. (2008) 9(3):356–62. doi: 10.1016/j.euje.2007.06.002

8. Welles CC, Ku IA, Kwan DM, Whooley MA, Schiller NB, Turakhia MP. Left atrial function predicts heart failure hospitalization in subjects with preserved ejection fraction and coronary heart disease: longitudinal data from the heart and soul study. *J Am Coll Cardiol*. (2012) 59(7):673–80. doi: 10.1016/j.jacc.2011.11.012

9. Sargento L, Vicente Simões A, Longo S, Lousada N, Palma Dos Reis R. Left atrial function index predicts long-term survival in stable outpatients with systolic heart failure. *Eur Heart J Cardiovasc Imaging*. (2017) 18(2):119–27. doi: 10.1093/ehjci/jew196

10. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. (2018) 72 (18):2231–64. doi: 10.1016/j.jacc.2018.08.1038

11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. (2015) 28 (1):1–39.e14. doi: 10.1016/j.echo.2014.10.003

12. Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, et al. Left atrial structure and function and clinical outcomes in the general population. *Eur Heart J*. (2013) 34(4):278–85. doi: 10.1093/eurheartj/ehs188

13. Sardana M, Nah G, Tsao CW, Ogunsua AA, Vittinghoff E, Thomas RC, et al. Clinical and echocardiographic correlates of left atrial function index: the Framingham offspring study. *J Am Soc Echocardiogr*. (2017) 30(9):904–12.e2. doi: 10.1016/j.echo.2017.05.013

14. Rigatelli G, Zuin M, Braggion G, Lanza D, Aggio S, Adami A, et al. Changing of left atrial function Index in symptomatic patients with patent foramen ovale after device closure. *Turk Kardiyol Dern Ars*. (2022) 50(3):175–81. doi: 10.5543/tkda.2022.21027

15. Sardana M, Lessard D, Tsao CW, Parikh NI, Barton BA, Nah G, et al. Association of left atrial function index with atrial fibrillation and cardiovascular disease: the Framingham offspring study. *J Am Heart Assoc*. (2018) 7(7):e008435. doi: 10.1161/jaha.117.008435

16. Nagase T, Kato R, Nakano S, Shiki Y, Tanaka S, Ikeda Y, et al. Prediction of improvement in left atrial function index after catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol*. (2015) 44(2):151–60. doi: 10.1007/s10840-015-0043-z

17. Longobardo L, Zito C, Khandheria BK. Left atrial function index: did we end up waiting for godot? *Eur Heart J Cardiovasc Imaging*. (2017) 18(2):128–9. doi: 10.1093/ehjci/jew210

18. Shamekhi J, Nguyen TQA, Sigel H, Maier O, Piayda K, Zeus T, et al. Left atrial function index (LAFI) and outcome in patients undergoing transcatheter aortic valve replacement. *Clin Res Cardiol*. (2022) 111(8):944–54. doi: 10.1007/s00392-022-02010-5

19. Sardana M, Ogunsua AA, Spring M, Shaikh A, Asamoah O, Stokken G, et al. Association of left atrial function index with late atrial fibrillation recurrence after catheter ablation. *J Cardiovasc Electrophysiol*. (2016) 27(12):1411–9. doi: 10.1111/jce.13086

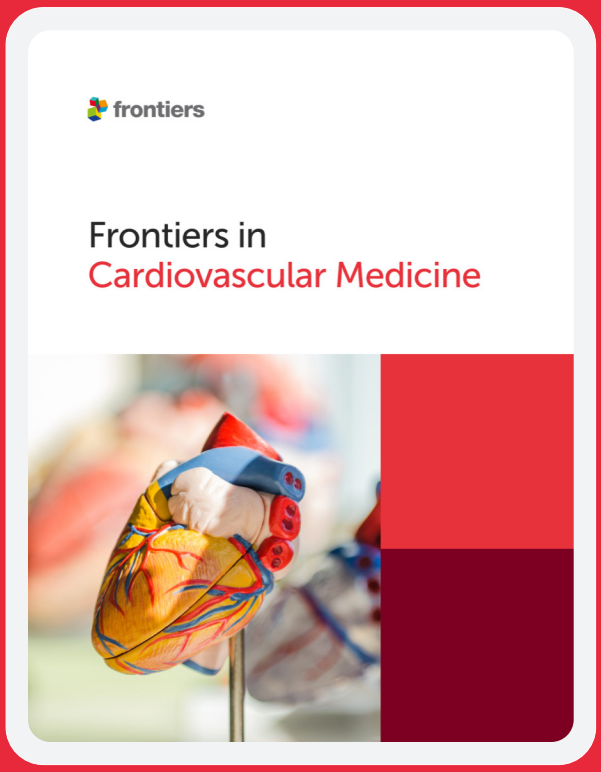
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact