frontiers | Research Topics

Global excellence in cardiovascular medicine: Asia and Australasia

Edited by
Yoshitaka Iso, Zhonghua Sun and Neiko Ozasa

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-6510-0
DOI 10.3389/978-2-8325-6510-0

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

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

Global excellence in cardiovascular medicine: Asia and Australasia

Topic editors

Yoshitaka Iso — Showa University, Japan

Zhonghua Sun — Curtin University, Australia

Neiko Ozasa — Kyoto University Hospital, Japan

Citation

Iso, Y., Sun, Z., Ozasa, N., eds. (2025). *Global excellence in cardiovascular medicine: Asia and Australasia*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-6510-0

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 12 April 2023
DOI 10.3389/fcvm.2023.1144444

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Athanasios Giannoukas,
University of Thessaly, Greece
Bin Lu,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

*CORRESPONDENCE
Jihoon Kim
✉ novolley@naver.com
Sung Mok Kim
✉ sungmok_kim@hanmail.net

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

RECEIVED 14 January 2023
ACCEPTED 28 March 2023
PUBLISHED 12 April 2023

CITATION
Kim H, Kim J, Choe YH and Kim SM (2023) Clinical outcomes of a CT protocol for simultaneous examination of the aorta and coronary artery in patients with aortic aneurysm.
Front. Cardiovasc. Med. 10:1144444.
doi: 10.3389/fcvm.2023.1144444

Clinical outcomes of a CT protocol for simultaneous examination of the aorta and coronary artery in patients with aortic aneurysm

Hoyoung Kim[1], Jihoon Kim[2,3]*, Yeon Hyeon Choe[1,3,4] and Sung Mok Kim[1,3,4]*

[1]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Division of Cardiology, Department of Internal Medicine, Samsung Medical Center, Seoul, Republic of Korea, [3]Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea, [4]Department of Radiology, Samsung Medical Center, Seoul, Republic of Korea

Objectives: In patients with aortic aneurysm (AA), coronary artery disease (CAD) increases the risk of perioperative complications and even asymptomatic CAD is associated with adverse clinical outcomes. We aimed to compare coronary-aorta CT (CACT) with thoracoabdominal CT angiography (Aorta CT) for CAD management and clinical outcomes in these patients.
Methods: We enrolled 479 patients undergoing CACT and 693 patients undergoing Aorta CT as an initial CT scan for AA. The primary outcome was a composite of all-cause death or myocardial infarction (MI) at 3 years after CT. The secondary outcomes were subsequent CAD management and invasive coronary angiography (CAG).
Results: After index CT scan, the CACT group had a significantly higher rate of coronary revascularization compared with the Aorta CT group (10.7% vs. 3.8%, $p < 0.001$) but a lower probability of diagnostic CAG among total invasive CAG (32% vs. 55%, $p < 0.001$). At 3 months after the CT scan, the prescription rates of statins (65.8% vs. 44.6%, $p < 0.001$) and antiplatelet agents (57.6% vs. 43.9%, $p < 0.001$) were higher in the CACT group. During follow-up, the CACT group had a significantly lower incidence of the composite outcome of all-cause death or MI (adjusted HR 1.72, 95% CI 1.07–2.78, $p = 0.027$) than the Aorta CT group.
Conclusion: Among patients with AA, CACT was associated with a higher rate of subsequent CAD management and a lower risk of all-cause death or MI compared to Aorta CT. When evaluating with AA using CT, simultaneous coronary and aortic evaluation using CACT would be recommended over Aorta CT.

KEYWORDS

aortic aneurysm, coronary artery disease, clinical outcomes, multidetector computed tomography, computed tomography angiography

Abbreviations
AA, aortic aneurysm; Aorta CT, thoracoabdominal aorta CT angiography; CACT, coronary-aorta CT; CAD, coronary artery disease; CAG, coronary angiography; CIN, contrast-induced nephropathy; CT, computed tomography; DLP, dose length product; ECG, electrocardiogram; MI, myocardial infarction.

1. Introduction

Patients with aortic aneurysm (AA) are at increased risk of coronary artery disease (CAD) related to traditional cardiovascular risk factors (e.g., smoking, hypertension, and diabetes mellitus) and common pathways (e.g., atherosclerosis and inflammation) (1, 2). The prevalence of CAD has been reported to be up to 65% in this population (3). In patients with AA, CAD increases the risk of perioperative complications such as myocardial ischemia and death (3–5), and even asymptomatic CAD is associated with adverse clinical outcomes (4, 6). Therefore, screening for CAD is clinically important in patients with AA (4). In previous studies, invasive coronary angiography (CAG) was the main modality used to detect CAD (3, 6). Invasive CAG, however, is accompanied by procedural complications including stroke, vascular injury, and local hematoma (7). As an alternative, coronary computed tomography (CT) angiography is a useful technique for evaluating CAD (8, 9).

Thoracoabdominal CT angiography is a standard method for evaluating AA, but non-electrocardiogram (ECG)-gated thoracoabdominal CT angiography has limitations when assessing and evaluating CAD because of motion artifacts. Although traditional ECG-gated coronary CT angiography has high accuracy for detecting CAD (10, 11), the scan field is limited from the carina to the base of the heart, which limits evaluation of the aortic arch and abdominal aorta. There was a previous attempt to evaluate the coronary artery and aorta simultaneously using ECG-gated 64-channel thoracoabdominal CT (12). Although that study demonstrated the feasibility of ECG-gated thoracoabdominal CT scan for coronary evaluation, the sample size was small with 28 patients, and clinical outcomes were not assessed. With the recent increase in transcatheter aortic valve implantation, the dedicated coronary-aorta CT protocol (CACT), which can evaluate the coronary arteries and aorta simultaneously, has been established for pre-procedural evaluation (13). Therefore, we investigated the relationship between CACT and subsequent CAD management and clinical outcomes compared with conventional thoracoabdominal CT angiography (Aorta CT) in patients with AA.

2. Material and methods

2.1. Study population

Between January 2010 and May 2021, a total of 8,491 patients underwent CACT or Aorta CT at Samsung Medical Center. The choice of CT protocol was driven by clinician preference. Patients were divided into two groups based on the first CT scan protocols. Of 8,491 patients, 4,868 underwent CACT, and 3,623 underwent Aorta CT. Subjects without AA (1,940 in the CACT group and 2,193 in the Aorta CT group) were excluded. In this study, the presence of AA was defined as an aortic segment exceeding the certain diameter in specific area: ascending aorta ≥40 mm, aortic arch and descending thoracic aorta ≥30 mm, and abdominal aorta ≥20 mm, which were 1.5 times larger than the patient's normal segment in the aorta (14, 15). Subjects with aneurysms at other sites, including the left ventricle or small arteries including the renal, hepatic, and splenic artery, were also excluded (141 in the CACT group and 114 in the Aorta CT group). Furthermore, patients who had history of AA repair (78 in the CACT group and 174 in the Aorta CT group) or who had underlying diseases including genetic vascular disease, vasculitis, congenital disease, valvular heart disease, heart transplantation status, and aneurysms not caused by atherosclerosis (2,230 in the CACT group and 449 in the Aorta CT group) were excluded. Finally, 479 patients with AA who underwent CACT and 693 patients with AA who underwent Aorta CT were included in this study (**Supplementary Figure S1**).

2.2. CT protocol

CT examinations of the coronary artery and aorta were performed using 2nd or 3rd-generation dual-source CT scanners (Somatom Force or Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Retrospective ECG-gated helical mode with tube current modulation was used for coronary evaluation, followed by prospective ECG-triggered high pitch helical mode for aorta evaluation. The tube voltage and tube current/exposure time product were adjusted according to patient body size as follows: tube voltage, 80–100 kV; tube current/exposure time product, 185–450 mAs; collimation, 2 mm × 192 mm × 0.6 mm or 2 mm × 128 mm × 0.6 mm; gantry rotation time, 250 or 280 ms. A bolus of 50–60 ml of contrast material (Iomeron 400; Bracco, Milan, Italia) was injected into the antecubital vein, followed by 25–30 ml of saline chaser at 4–5 ml/sec for cardiac scan, and a bolus of 60–70 ml of contrast material was injected followed by 40 ml of saline chaser at 4 ml/sec for aorta scan.

CT examinations of the thoracoabdominal aorta were performed using a high-definition CT scanner (Discovery CT 750 HD FREEdom Edition, GE Healthcare, Milwaukee, WI, USA) with a 64 × 0.625 mm detector collimation, Z–coverage 40 mm with an increment of 35 mm and gantry rotation time 350 ms, and field of view of 25 cm. A bolus of 110 to 130 ml of contrast material (Iomeron 300, Bracco; Xeneticx 300, Guerbet, Roissy, France; Omnipaque 300, GE Healthcare, Princeton, NJ, USA; Ultravist 300, Bayer-Schering, Berlin, Germany) was injected into the antecubital vein followed by 40 ml of saline chaser at 3.5–4 ml/sec.

The anatomic coverage for aorta evaluation was the same between the two CT protocols, from the mid clavicle to the symphysis pubis (**Supplementary Figure S2**).

2.3. Clinical data collection

All clinical, laboratory, and image data were collected from medical records. Serum creatinine level was collected before and after CT scans. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (16). The definition of obstructive CAD was

based on CT findings showing 50% or greater stenosis. The outcomes were collected by comprehensive reviewing medical records.

2.4. Outcomes

The primary outcome was a composite of all-cause death or nonfatal myocardial infarction (MI) during 3 years after the CT scan. MI was defined as elevated cardiac enzyme levels, such as troponin I or myocardial band fraction of creatine kinase, greater than the upper limit of the normal range with either ischemic symptoms or electrocardiography changes indicating ischemia and that required subsequent hospitalization.

The secondary outcomes consisted of impacts of CT protocols on subsequent CAD management and safety of CT scans. First, impact of CT protocols on subsequent CAD management included the proportion of diagnostic only CAG among total invasive CAG procedures, incidence of coronary revascularization (percutaneous coronary revascularization or coronary artery bypass graft) during 3 years of follow-up after CT scan, and the prescription rates of statins or antiplatelet agents within 3 months after CT scan. Diagnostic only CAG was defined as an invasive CAG not followed by revascularization. The general indication of coronary revascularization included left main coronary artery with diameter stenosis ≥50% and major epicardial arteries or large side branches with diameter stenosis ≥70% or 50%–70% with ischemic symptoms or signs. Second, the safety of CT scans was assessed by radiation exposure and contrast-induced nephropathy (CIN). Radiation exposure was calculated as the total dose length product (DLP). CIN was defined as either a 25% increase in baseline serum creatinine or a 0.5 mg/dl increase in absolute serum creatinine value within 72 h after CT scan (17).

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical data are presented as frequency or percentage. Shapiro-Wilk test was used to determine whether data were normally distributed. Student's *t*-test was used to determine whether there were significant differences for normally distributed data, whereas the Wilcoxon rank-sum test was used for nonparametric data. Categorical variables were analyzed using Fisher's exact test. Clinical event rates were calculated by Kaplan-Meier censoring estimates and presented with the cumulative incidence. Log-rank tests were used to compare survival curves between CACT and Aorta CT groups. Cox proportional hazard regression was used to calculate hazard ratio (HR) and 95% confidence interval (CI) with adjustments for age, sex, hypertension, diabetes mellitus, medication (statins and antiplatelet agents) before CT scan, and location of the aneurysm.

A sensitivity analysis comparing the primary outcome between the CACT group and the Aorta CT group was conducted, excluding patients who underwent AA repair during follow-up. Subgroup analyses were conducted according to age, sex, diabetes mellitus, medication history before CT scan, and size and location of AA. All probability values are two-sided and statistical significance was defined as p-value <0.05. SPSS version 27 and R version 4.2.0 (R Foundation for Statistical Computing) were used for all statistical analyses.

3. Results

Table 1 shows the baseline characteristics of 479 patients who underwent CACT and 693 patients who underwent Aorta CT. The CACT group was younger (69.9 ± 10.1 vs. 71.3 ± 10.0 years, p = 0.022) and had higher body mass index (24.5 ± 3.3 vs. 24.0 ± 3.2 kg/m^2, p = 0.011) and lower prevalence of abdominal AA (54.1% vs. 71.4%, p < 0.001), but had higher prevalence of hypertension (75.2% vs. 65.2%, p < 0.001) and dyslipidaemia (64.1% vs. 46.3%, p < 0.001) compared with the Aorta CT group.

Obstructive CAD was detected in 215 of 479 patients (44.9%) in the CACT group. During the follow-up period, 90 patients in the CACT group and 156 in the Aorta CT group underwent open repair of AA (18.8% vs. 22.5%, p = 0.143). Among 246 patients who underwent AA open repair, 3 patients developed MI within 30 days of surgery. Two out of 3 patients with MI underwent invasive CAG and had a significant stenosis of 90% or more in major epicardial coronary arteries. All 3 cases were in the Aorta CT group.

3.1. Subsequent CAD management after CT scan

There were 132 invasive CAGs during the 3 years after the index CT scan. The proportion of diagnostic only CAG among total invasive CAG procedures was significantly lower in the CACT group than the Aorta CT group (32.0% vs. 55.2%, p < 0.001) (left panel in Figure 1). During the 3-year follow-up, the

TABLE 1 Baseline characteristics of the patients who underwent CACT or aorta CT.

	CACT (n = 479)	Aorta CT (n = 693)	p value
Age (years)	69.9 ± 10.1	71.3 ± 10.0	0.022
Sex (male, %)	344 (71.8%)	523 (75.5%)	0.161
Height (cm)	163.9 ± 9.1	164.1 ± 9.2	0.747
Weight (kg)	66.3 ± 11.8	65.1 ± 11.3	0.071
BMI (kg/m^2)	24.5 ± 3.3	24.0 ± 3.2	0.011
BSA (m^2)	1.73 ± 0.2	1.71 ± 0.2	0.200
Hypertension (%)	360 (75.2%)	452 (65.2%)	<0.001
Diabetes mellitus (%)	105 (21.9%)	142 (20.5%)	0.555
Dyslipidemia (%)	307 (64.1%)	321 (46.3%)	<0.001
Renal dysfunction (%)[a]	99 (20.7%)	171 (24.7%)	0.121
Location of aneurysm (AAA)	259 (54.1%)	498 (71.4%)	<0.001
Statins	102 (21.3%)	112 (16.2%)	0.025
Antiplatelet agents	79 (16.5%)	116 (16.7%)	0.911
History of coronary revascularization	69 (14.4%)	111 (16.0%)	0.452

Continuous variables are presented as mean ± standard deviation. Categorical data are presented as frequency and percentage. AAA, abdominal aortic aneurysm; Aorta CT, thoracoabdominal aorta computed tomography angiography protocol; BMI, body mass index; BSA, body surface area; CACT, coronary-aorta computed tomography protocol; eGFR, estimated glomerulus filtration rate.
[a]Renal dysfunction was defined as eGFR <60 ml/min/1.73 m^2.

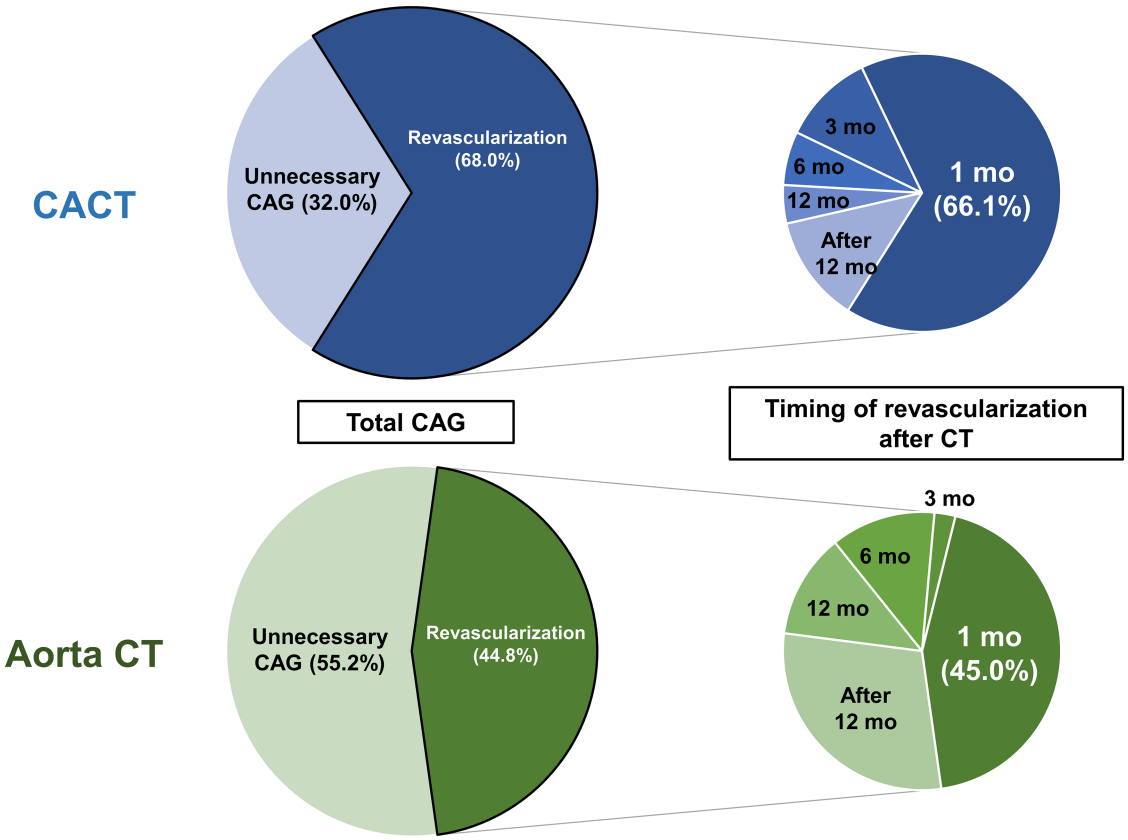


FIGURE 1
Patterns of invasive CAG and timing of coronary revascularization after CT scan. **Left** panels describe the proportions of diagnostic only CAG and coronary revascularization among total invasive CAG after CT scan. **Right** panels describe the timing of coronary revascularization after CT scan. Aorta CT, thoracoabdominal aorta CT angiography protocol; CACT, coronary-aorta CT protocol; CAG, coronary angiography; CT, computed tomography; mo, month.

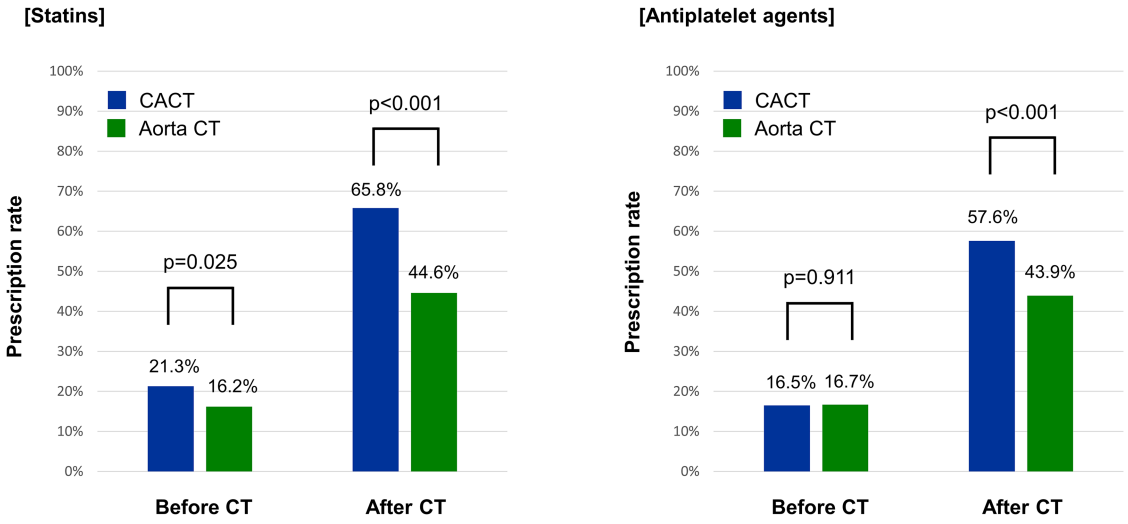
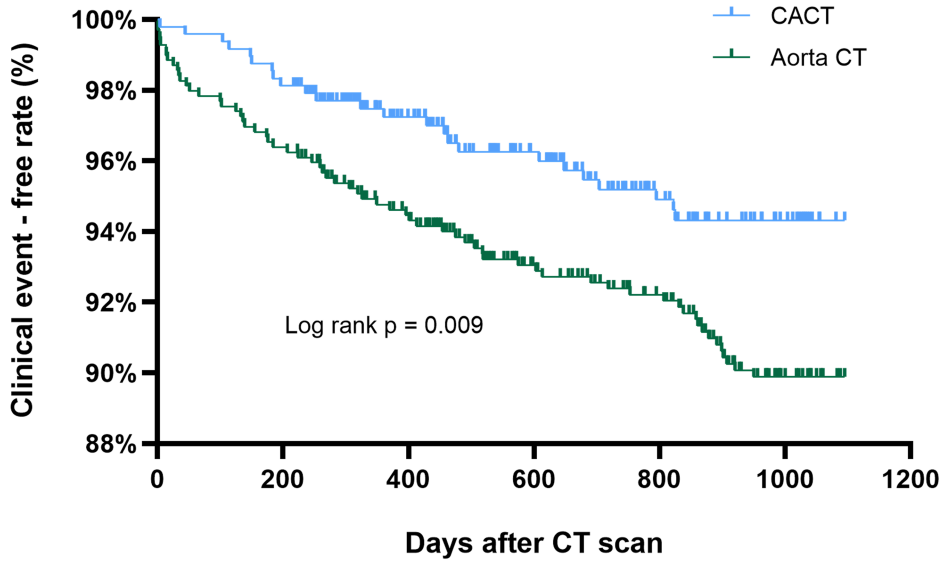


FIGURE 2
Prescription rates of cardiovascular medications before and after CT scan. Aorta CT, thoracoabdominal aorta CT angiography protocol; CACT, coronary-aorta CT protocol; CT, computed tomography.



No. at Risk

	0 mo	1 mo	3 mo	6 mo	12 mo	36 mo
CACT	479	478	477	473	421	283
Aorta CT	693	683	677	668	626	266

FIGURE 3
Incidence of all-cause death or myocardial infarction according to CT protocol. Aorta CT, thoracoabdominal aorta CT angiography protocol; CACT, coronary-aorta CT protocol; CT, computed tomography.

CACT group had a significantly higher incidence of coronary revascularization compared with the Aorta CT group (11.2% vs. 4.0%, $p < 0.001$) (Supplementary Figure S3). Most revascularizations were performed within 1 month after CT scan in the CACT group, but not in the Aorta CT group (66.1% vs. 45.0%, $p < 0.001$) (right panel in Figure 1).

In addition, the CACT group had a significantly higher prescription rate of statins (65.8% vs. 44.6%, $p < 0.001$) and antiplatelet agents (57.6% vs. 43.9%, $p < 0.001$) than the Aorta CT group at 3 months after CT scan (Figure 2).

3.2. Clinical outcomes according to CT protocol

There were 76 deaths and 14 nonfatal MIs (23 deaths and 2 MIs in the CACT group, and 53 deaths and 12 MIs in the Aorta CT group) during the 3 years of follow-up. The incidence of death or nonfatal MI was significantly lower in the CACT group compared with the Aorta CT group (5.7% vs. 9.5%, adjusted HR 1.71, 95% CI 1.06–2.76, $p = 0.028$) (Figure 3).

3.3. Independent predictors of death or nonfatal MI

In multivariable analysis, age, sex, renal dysfunction, and CT protocol were independent predictors of death or nonfatal MI at 3 years (Table 2). Multivariable Cox regression analysis including the medications after CT is presented in Supplementary Table S1.

TABLE 2 Independent predictors for composite of all-cause death or myocardial infarction in patients with aortic aneurysm.

	Hazard ratio (95% CI)	*p* value
Aorta CT (vs. CACT)	1.71 (1.06–2.76)	0.028
Age	1.03 (1.01–1.06)	0.010
Sex	2.51 (1.34–4.72)	0.004
Obesity (BMI ≥ 30 kg/m^2)	0.43 (0.06–3.12)	0.403
Hypertension	1.36 (0.81–2.29)	0.239
Diabetes mellitus	1.29 (0.80–2.08)	0.291
Statin	1.04 (0.53–2.04)	0.916
Antiplatelet agent	1.24 (0.63–2.44)	0.535
Renal dysfunction[a]	2.07 (1.33–3.22)	0.001
History of coronary revascularization	0.60 (0.33–1.11)	0.104
Location of aortic aneurysm	1.10 (0.66–1.83)	0.725

This table shows the results of cox proportional hazard regression. Aorta CT, thoracoabdominal aorta computed tomography angiography protocol; BMI, body mass index; CACT, coronary-aorta computed tomography protocol; CI, confidence interval; eGFR, estimated glomerulus filtration rate.
[a]Renal dysfunction was defined as eGFR <60 ml/min/1.73m^2.

3.4. Subgroup analysis

The lower risk of the primary outcome in patients evaluated with CACT was consistent across subgroups (Figure 4).

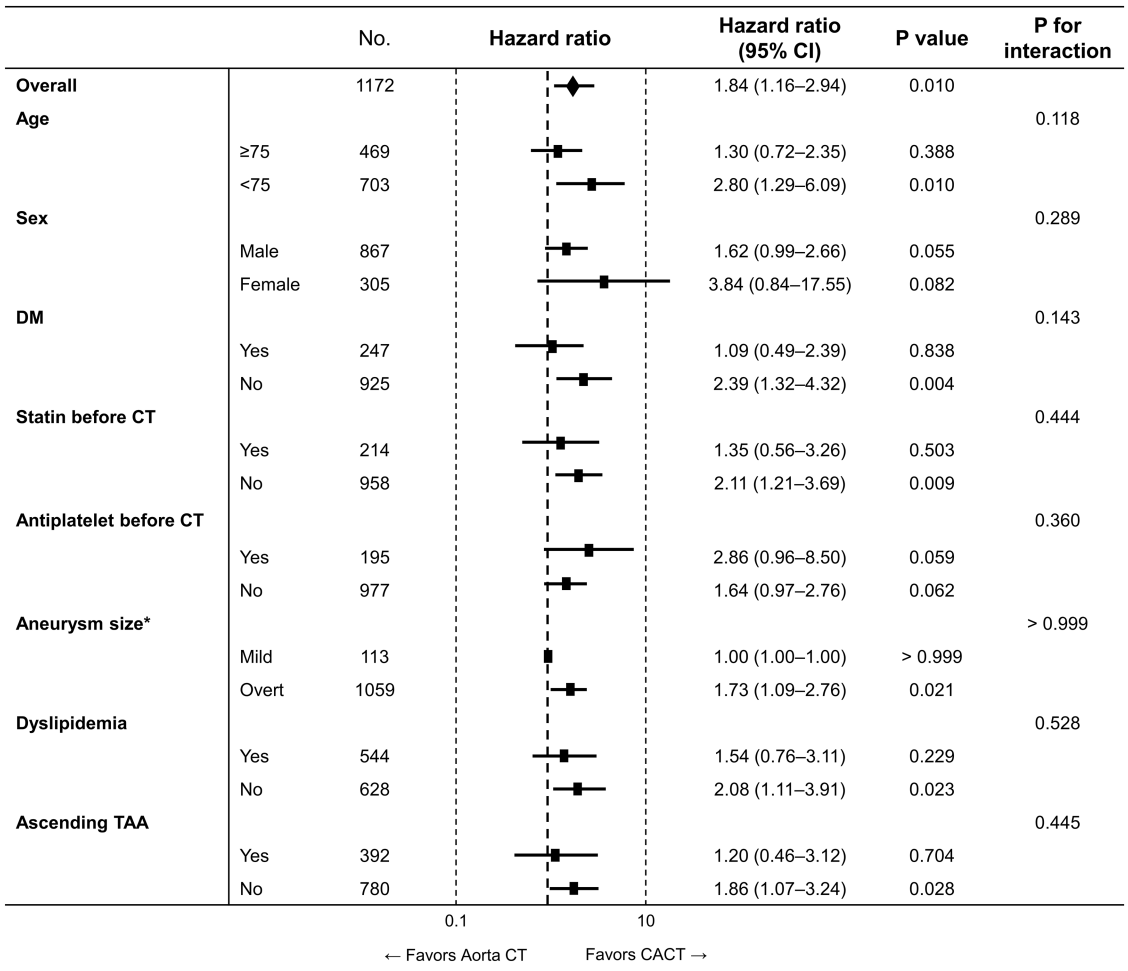


FIGURE 4
Subgroup analysis for the primary outcome. Aorta CT, thoracoabdominal aorta CT angiography protocol; CACT, coronary-aorta CT protocol; CI, confidence interval; CT, computed tomography; No., number; TAA, thoracoabdominal aortic aneurysm. * Mild form of aneurysm was defined as abdominal aorta with a size between ≥20 and <30 mm or aortic arch or descending thoracic aorta with a size between ≥30 and <35 mm, while overt aneurysm was defined as ascending aorta with a size ≥40 mm, aortic arch or descending aorta with a size ≥35 mm, and abdominal aorta with a size ≥30 mm.

3.5. Radiation exposure and CIN

The mean total DLPs were 611.6 ± 301.4 and 578.8 ± 286.8 mGy·cm in the CACT and the Aorta CT group, respectively. There were no significant differences in radiation dose (611.6 vs. 578.8 mGy·cm, $p = 0.061$) or incidence of CIN (3.6% vs. 2.6%, $p = 0.347$) between the CACT and Aorta CT groups.

3.6. Clinical outcome in patients without AA repair

Among patients who did not undergo AA repair during follow-up, the 3-year incidence of death or nonfatal MI was significantly lower in the CACT group compared with the Aorta CT group (5.7% vs. 10.6%, adjusted HR 1.72, 95% CI 1.04–2.84, $p = 0.035$) (**Supplementary Figure S4**).

4. Discussion

In the present study we compared two CT protocols, CACT and Aorta CT, to investigate the relationship between CT protocols and cardiovascular outcomes in patients with AA. The main findings were as follows. First, patients with CACT had a higher incidence of coronary revascularization and higher prescription rate of cardioprotective medications after CT than those evaluated with Aorta CT, while the probability of undergoing unnecessary CAG without revascularization was lower in those evaluated with CACT. Second, patients evaluated with CACT had a significantly lower risk of all-cause death or nonfatal MI at 3 years compared to those evaluated with Aorta CT. Third, there were no significant differences in radiation dose or CIN between the CT protocols.

Asymptomatic CAD is highly prevalent in patients with AA (4, 18). It would be clinically demanding to screen for CAD irrespective of symptoms because a significant proportion of

asymptomatic CAD, as high as 51% in a previous report by Fabio et al., meet indications for coronary revascularization (18). Previous studies showed that ECG-gated coronary CT angiography is a feasible alternative to invasive CAG for detection of CAD (19). In our study, patients evaluated with CACT underwent coronary revascularization more frequently than those evaluated with Aorta CT. Most of the coronary revascularizations in patients with CACT were performed within initial 1 month after the CT scan, which suggests that the decision to treat CAD was probably based on the CT findings. Moreover, among patients undergoing invasive CAG, the proportion of diagnostic only CAG that was not followed by revascularization was 32% in patients with CACT but 55% in those with Aorta CT. This finding may be due to the high negative predictive value of coronary CT angiography, which can prevent unnecessary CAG in asymptomatic but high-risk patients such as our study population (20). Therefore, simultaneous evaluation of coronary arteries during aortic CT scans using CACT may aid in effective screening for CAD and subsequent decisions to perform invasive CAG considering coronary revascularization in patients AA. Whether PCI can reduce mortality or MI in patients with stable CAD remains controversial (21). In patients with AA, however, several reports have suggested that appropriate management including coronary revascularization may improve clinical outcomes (4, 22). Functional tests such as stress echocardiography or single-photon emission computed tomography could be alternatives to CACT for the detection of coronary artery disease. However, CACT allows for the simultaneous screening of coronary artery disease with a single test in patients who are planned for CT evaluation for other causes, particularly in those with high-risk factors for coronary artery disease such as aortic aneurysm.

Given that CAD is the leading cause of death in patients with AA (23), coronary evaluation and subsequent management might have affected clinical outcomes in the present study. There were significant differences in medical management between the two CT protocols. After CT scans, both statins and antiplatelet agents were more frequently prescribed in patients with CACT. Underlying disease, such as hypertension and dyslipidemia, might affect the use of cardiovascular medications, but the difference in statin prescription rate between the two CT protocols increased from 5.1% before CT scan to 21.2% after the CT. Pharmacologic therapy is a key management tool for CAD as well as atherosclerotic disease to reduce adverse cardiovascular events. Hence, the guidelines for secondary prevention and risk reduction for atherosclerotic disease recommend statins and antiplatelet agents in patients with coronary artery disease (24). Coronary CT angiography-based strategies are generally associated with increased likelihood of initiation of aspirin and statin in patients with suspected CAD (25). The Scottish Computed Tomography of the Heart (SCOT-HEART) study, a randomized trial comparing coronary CT angiography with standard care alone in patients with suspected CAD, demonstrated that patients with coronary CT angiography had a lower risk of death from coronary heart disease or nonfatal MI (26). In that trial, patients with coronary CT angiography were more likely to have preventive medical therapy than those with standard care alone, which explained the difference in clinical outcomes between the two strategies. In our study, CACT would detect CAD and then guide clinicians to prescribe preventive medications even for cases of subclinical CAD not requiring further invasive CAG or revascularization. Although the relationships between antiplatelet agents and cardiovascular outcomes in patients with CAD remain controversial, a high-risk population such as those with AA are likely to benefit from antiplatelet agents (27). As antiplatelet agents are usually prescribed for patients at high risk of atherosclerotic disease (e.g., stroke) or those undergoing coronary revascularization, the beneficial effect of antiplatelet agents on cardiovascular outcomes may be diluted in our study.

Although coronary artery and aorta examinations are performed simultaneously in CACT scan, there were no significant differences in radiation dose between the CT protocols. The radiation dose of CACT was 611.6 ± 301.4 mGy·cm, which was lower than the 982.5 mGy·cm in a previous study using coronary artery scans with ECG-gated thoracoabdominal 64-detector-row CT angiography (28). Our CACT protocol used high-pitch helical mode for aorta evaluation and lower tube potential for both coronary and aorta scans to reduce radiation exposure (29). It is recommended to use smaller amounts of iodine contrast because high volumes of contrast medium increase risk of CIN (30). In our study, the amount of contrast medium could not be directly compared between CT protocols because the dose was not recorded at the time of each examination of Aorta CT. Between the two CT protocols, however, there was no significant difference in the rate of CIN, a meaningful surrogate marker of overuse of contrast medium.

There are several limitations in the present study. First, this was a retrospective observational study. The choice of CT protocol was at the clinician's discretion. Although the differences in clinical outcomes between the two protocols were significant after adjustment of baseline characteristics, there might have been selection bias. Second, because this was a single-center study, the generalizability of our findings might be limited. For example, the baseline prescription rate of statin was relatively low compared with previous studies including patients with AA (31, 32). After index CT scans, however, the prescription rate of cardiovascular medicine increased to a level similar to that of previous studies, with diagnosis of AAs by CT scans. In addition, the prevalence of obstructive CAD in the CACT group of our study (44.9%) was similar to a previous report (51%) (18). Third, AA repair surgery may have influenced the incidence of death or nonfatal MI. However, there was no death related with surgery, and all 3 cases of perioperative MI with critical coronary artery stenoses occurred in the Aorta CT group. This finding may explain the higher incidence of death or nonfatal MI in patients with Aorta CT that cannot lead to intensified treatment even in the presence of severe CAD. In addition, the higher incidence of death or nonfatal MI with Aorta CT was consistent after excluding patients undergoing AA repair. Fourth, although smoking history is one of the important factors for disease progression, there were missing values (in 29.1% of patients) in

smoking status in our study because this was a retrospective study. However, without missing values, there were no significant differences in smoking history between two groups (current or ex-smoker, 40.2% in the CACT vs. 45.8% in the Aorta CT, $p = 0.132$). Last, the sizes and progression rates of AAs, which are prognostic factors in patients with AA, were not available. However, the rate of open repair during follow-up period was not significantly different between patients evaluated with the two CT protocols.

5. Conclusion

Among patients with AA, CACT was associated with a higher rate of subsequent CAD management and a significantly lower risk of all-cause death or MI with CACT compared to Aorta CT. Therefore, when evaluating with AA using CT, simultaneous coronary and aortic evaluation using CACT would be recommended over Aorta CT.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Samsung Medical Center (IRB No. 2022-01-031-001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SK and YC conceived the study design. HK, JK, YC, and SK analyzed data and drafted the manuscript with critical revision. All authors participated in the discussion of the concept of this study. All authors contributed to the article 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1144444/full#supplementary-material.

References

1. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European society of cardiology (ESC). *Eur Heart J.* (2014) 35(41):2873–926. doi: 10.1093/eurheartj/ehu281

2. Van Kuijk JP, Flu WJ, Dunckelgrun M, Bax JJ, Poldermans D. Coronary artery disease in patients with abdominal aortic aneurysm: a review article. *J Cardiovasc Surg.* (2009) 50(1):93–107.

3. Hołda MK, Iwaszczuk P, Wszołek K, Chmiel J, Brzychczy A, Trystuła M, et al. Coexistence and management of abdominal aortic aneurysm and coronary artery disease. *Cardiol J.* (2020) 27(4):384–93. doi: 10.5603/CJ.a2018.0101

4. Takigawa M, Yokoyama N, Yoshimuta T, Takeshita S. Prevalence and prognosis of asymptomatic coronary artery disease in patients with abdominal aortic aneurysm and minor or no perioperative risks. *Circ J.* (2009) 73(7):1203–9. doi: 10.1253/circj.cj-08-1135

5. Roger VL, Ballard DJ, Hallett JW Jr, Osmundson PJ, Puetz PA, Gersh BJ. Influence of coronary artery disease on morbidity and mortality after abdominal aortic aneurysmectomy: a population-based study, 1971-1987. *J Am Coll Cardiol.* (1989) 14(5):1245–52. doi: 10.1016/0735-1097(89)90423-3

6. Watanabe K, Watanabe T, Otaki Y, Kato S, Tamura H, Nishiyama S, et al. Impact of pre-operative coronary artery disease on the clinical outcomes of patients with aortic aneurysms. *Heart Vessels.* (2021) 36(3):308–14. doi: 10.1007/s00380-020-01700-2

7. Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. *Glob J Health Sci.* (2012) 4(1):65–93. doi: 10.5539/gjhs.v4n1p65

8. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography) trial. *J Am Coll Cardiol.* (2008) 52(21):1724–32. doi: 10.1016/j.jacc.2008.07.031

9. Abdulla J, Abildstrom SZ, Gotzsche O, Christensen E, Kober L, Torp-Pedersen C. 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. *Eur Heart J.* (2007) 28(24):3042–50. doi: 10.1093/eurheartj/ehm466

10. Joshi H, Shah R, Prajapati J, Bhangdiya V, Shah J, Kandre Y, et al. Diagnostic accuracy of computed tomography angiography as compared to conventional angiography in patients undergoing noncoronary cardiac surgery. *Heart Views.* (2016) 17(3):88–91. doi: 10.4103/1995-705x.192555

11. Gorenoi V, Schönermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. *GMS Health Technol Assess.* (2012) 8:Doc02. doi: 10.3205/hta000100

12. Budde RP, Huo F, Cramer MJ, Doevendans PA, Bots ML, Moll FL, et al. Simultaneous aortic and coronary assessment in abdominal aortic aneurysm

patients by thoraco-abdominal 64-detector-row CT angiography: estimate of the impact on preoperative management: a pilot study. *Eur J Vasc Endovasc Surg*. (2010) 40(2):196–201. doi: 10.1016/j.ejvs.2010.03.032

13. Schicchi N, Fogante M, Pirani PE, Agliata G, Piva T, Tagliati C, et al. Third generation dual source CT with ultra-high pitch protocol for TAVI planning and coronary tree assessment: feasibility, image quality and diagnostic performance. *Eur J Radiol*. (2020) 122:108749. doi: 10.1016/j.ejrad.2019.108749

14. Kim H, Cho S, Sakalihasan N, Hultgren R, Joh JH. Prevalence and risk factors of abdominal aortic aneurysms detected with ultrasound in Korea and Belgium. *J Clin Med*. (2023) 12(2):484. doi: 10.3390/jcm12020484

15. Joh JH, Ahn H-J, Park H-C. Reference diameters of the abdominal aorta and iliac arteries in the Korean population. *Yonsei Med J*. (2013) 54(1):48–54. doi: 10.3349/ymj.2013.54.1.48

16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. (2009) 150 (9):604–12. doi: 10.7326/0003-4819-150-9-200905050-00006

17. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis*. (2013) 61(5):649–72. doi: 10.1053/j.ajkd.2013.02.349

18. Marsico F, Giugliano G, Ruggiero D, Parente A, Paolillo S, Guercio LD, et al. Prevalence and severity of asymptomatic coronary and carotid artery disease in patients with abdominal aortic aneurysm. *Angiology*. (2015) 66(4):360–4. doi: 10.1177/0003319714540319

19. Song YB, Arbab-Zadeh A, Matheson MB, Ostovaneh MR, Vavere AL, Dewey M, et al. Contemporary discrepancies of stenosis assessment by computed tomography and invasive coronary angiography. *Circ Cardiovasc Imaging*. (2019) 12(2):e007720. doi: 10.1161/circimaging.118.007720

20. Plank F, Friedrich G, Dichtl W, Klauser A, Jaschke W, Franz WM, et al. The diagnostic and prognostic value of coronary CT angiography in asymptomatic high-risk patients: a cohort study. *Open Heart*. (2014) 1(1):e000096. doi: 10.1136/openhrt-2014-000096

21. Chacko L Howard JP, Rajkumar C, Nowbar AN, Kane C, Mahdi D, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease: a meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes*. (2020) 13(2):e006363. doi: 10.1161/circoutcomes.119.006363

22. Mannacio VA, Mannacio L, Antignano A, Monaco M, Mileo E, Pinna GB, et al. Status of coronary disease and results from early endovascular aneurysm repair after preventive percutaneous coronary revascularization. *J Card Surg*. (2021) 36(3):834–40. doi: 10.1111/jocs.15305

23. Norman PE, Semmens JB, Lawrence-Brown MM. Long-term relative survival following surgery for abdominal aortic aneurysm: a review. *Cardiovasc Surg*. (2001) 9(3):219–24. doi: 10.1016/s0967-2109(00)00126-5

24. Smith SC J, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American heart association and American college of cardiology foundation. *Circulation*. (2011) 124(22):2458–73. doi: 10.1161/CIR.0b013e318235eb4d

25. Chang AM, Litt HI, Snyder BS, Gatsonis C, Greco EM, Miller CD, et al. Impact of coronary computed tomography angiography findings on initiation of cardioprotective medications. *Circulation*. (2017) 136(22):2195–7. doi: 10.1161/circulationaha.117.029994

26. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. (2015) 385(9985):2383–91. doi: 10.1016/s0140-6736(15)60291-4

27. Wong KH, Zlatanovic P, Bosanquet DC, Saratzis A, Kakkos SK, Aboyans V, et al. Antithrombotic therapy for aortic aneurysms: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. (2022) 64:544–56. doi: 10.1016/j.ejvs.2022.07.008

28. Willemink MJ, Meijs MF, Cramer MJ, Thijssen AS, Moll FL, de Jong PA, et al. Coronary artery assessment on electrocardiogram-gated thoracoabdominal multidetector computed tomographic angiography for aortic evaluation. *J Comput Assist Tomogr*. (2014) 38(2):185–9. doi: 10.1097/RCT.0b013e3182ab2add

29. Goetti R, Baumüller S, Feuchtner G, Stolzmann P, Karlo C, Alkadhi H, et al. High-pitch dual-source CT angiography of the thoracic and abdominal aorta: is simultaneous coronary artery assessment possible? *Am J Roentgenol*. (2010) 194 (4):938–44. doi: 10.2214/ajr.09.3482

30. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl*. (2006) 100:S11–5. doi: 10.1038/sj.ki.5000368

31. O'Donnell TFX, Deery SE, Shean KE, Mittleman MA, Darling JD, Eslami MH, et al. Statin therapy is associated with higher long-term but not perioperative survival after abdominal aortic aneurysm repair. *J Vasc Surg*. (2018) 68(2):392–9. doi: 10.1016/j.jvs.2017.11.084

32. Karrowni W, Dughman S, Hajj GP, Miller FJ Jr. Statin therapy reduces growth of abdominal aortic aneurysms. *J Investig Med*. (2011) 59(8):1239–43. doi: 10.2130/JIM.0b013e31823548e8

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 05 July 2023
DOI 10.3389/fcvm.2023.1186330

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Aoming Jin,
Capital Medical University, China
Roberto Scicali,
University of Catania, Italy
Ke-Yang Chen,
Wenzhou Medical University, China

*CORRESPONDENCE
Yujie Yang
✉ yang.yujie@imicams.ac.cn

†These authors have contributed equally to this work

RECEIVED 14 March 2023
ACCEPTED 14 June 2023
PUBLISHED 05 July 2023

CITATION
Xia Q, Chen Y, Yu Z, Huang Z, Yang Y, Mao A and Qiu W (2023) Prevalence, awareness, treatment, and control of dyslipidemia in Chinese adults: a systematic review and meta-analysis.
Front. Cardiovasc. Med. 10:1186330.
doi: 10.3389/fcvm.2023.1186330

Prevalence, awareness, treatment, and control of dyslipidemia in Chinese adults: a systematic review and meta-analysis

Qianhang Xia[1,2†], Yuquan Chen[1,2†], Zijing Yu[1,2†], Zhongyue Huang[1,2], Yujie Yang[1,2*], Ayan Mao[1,2] and Wuqi Qiu[1,2]

[1]Institute of Medical Information/Library, Chinese Academy of Medical Sciences, Beijing, China, [2]Peking Union Medical College, Beijing, China

Background: Researchers have conducted a considerable number of epidemiological studies on dyslipidemia in China over recent years. Nevertheless, a representative study to comprehensively appraise for the epidemiological status of dyslipidemia is still lacked. This meta-analysis is intended to explore the pooled prevalence, rates of awareness, treatment, and control of dyslipidemia among adults in Chinese Mainland.

Materials and methods: A systematic review was performed on relevant cross-sectional studies published since January 2012 by searching six authoritative literature databases. Meta-analyses were conducted in included studies based on a random-effect model to summarize the epidemiological status of dyslipidemia in China. A potential source of heterogeneity was detected by subgroup analysis and meta-regression. Publication bias was assessed by *Egger*'s test and funnel plots. A sensitivity analysis was conducted to examine the study quality's influence on the pooled estimate of prevalence and rates of awareness, treatment, and control.

Results: Forty-one original researches with a total of 1,310,402 Chinese participants were finally included in the meta-analysis. The prevalence, rates of awareness, treatment, and control of dyslipidemia were 42.1%, 18.2%, 11.6%, and 5.4%, respectively. With a pooled prevalence estimate at 24.5%, low HDL-C was the most prevalent among various dyslipidemia types, followed by hypertriglyceridemia (TG) (15.4%), hypercholesterolemia (TC) (8.3%), and high LDL-C (7.1%). The pooled prevalence of elevated serum lipoprotein(a) [Lp(a)] was 19.4%. By gender, the prevalence of dyslipidemia was 47.3% in males and 38.8% in females. Subgroup analyses revealed that the prevalence in southern and urban areas were higher than their counterparts. Females and population in urban areas tended to possess higher rates of awareness, treatment, and control. Meta-regression analyses suggested that the year of screening influenced prevalence estimates for dyslipidemia. The impact of the study's quality on the pooled estimates is insignificant.

Conclusion: Our study suggested a severe epidemic situation of dyslipidemia among adults in Chinese Mainland. More importantly, the awareness, treatment, and control rates were extremely low, revealing that dyslipidemia is a grave health issue. Consequently, we should attach more importance to the management of dyslipidemia, especially in economically underdeveloped areas.

Systematic review registration: PROSPERO [CRD42022366456].

KEYWORDS

dyslipidemia, prevalence, awareness rate, treatment rate, control rate, Mainland China, meta-analysis

1. Introduction

Cardiovascular disease (CVD) is one of the prior sources of global disease burden, as well as the main cause of premature death for Chinese residents (1–3). In China, cardiovascular disease is the leading cause of total deaths among residents while its prevalence and mortality are still increasing (4, 5). In 2019, cardiovascular diseases were responsible for 46.76% of the total deaths in rural areas and 44.26% in urban areas of China (6), which means that approximately two in five deaths were caused by cardiovascular diseases on average. Against the background of population aging trend and progressively prevalent metabolic risk factors such as hypertension, hyperglycemia, central adiposity, and dyslipidemia (7, 8), the disease burden caused by cardiovascular diseases kept increasing, which has developed into a critical concerning public health issue (9–12). Atherosclerotic cardiovascular disease (ASCVD) includes ischemic heart disease and ischemic stroke (13–15). Because of the same arterial pathological characteristics and risk factors, ASCVD is increasingly regarded as a special type of cardiovascular disease in Chinese and international cardiovascular disease prevention guidelines (16–20). In addition, ASCVD is the pattern that causes the most deaths among all kinds of cardiovascular diseases. In 2016, it caused about 2.4 million deaths in China, which amounts to more than 60% of all cardiovascular disease deaths as well as 25% of all causes of death (21, 22). Therefore, prevention and treatment of ASCVD are the top priorities of management for cardiovascular disease.

Characterized by hypercholesterolemia (high TC), hypertriglyceridemia (high TG), low HDL-C, or high LDL-C, dyslipidemia is a crucial risk factor for ASCVD and one of the three major risk factors that the Healthy China 2030 plan focuses on (23–27), which emphasizes the strategic role of health in China's development and outlines the major principles to achieve this. The disease burden caused by dyslipidemia in China has shown a significant growth trend in recent years (28–30). In 2017, a study showed that 862,759 deaths in China could be attributed to high LDL-C, accounting for 8.25% of all causes of death and 19.71% of cardiovascular disease deaths (31). Economist Intelligence Unit (EIU) report (2018) indicated that CVD had the economic burden of USD 21.7 billion in direct and indirect costs annually in China, of which more than 12% is due to dyslipidemia (32).

Although "co-management of hypertension, diabetes, and hyperlipidemia" was clearly proposed in the Healthy China 2030 plan, the management of dyslipidemia is far from ideal for hypertension and diabetes. The 2017 China Cardiovascular Health Index study showed the prevalence of dyslipidemia (33.7%) exceeded hypertension (26.0%), and diabetes (9.7%), while its awareness rate (14.5%), treatment rate (7.9%), and control rate (5.4%) were all below the corresponding levels of hypertension and diabetes (33). Compared with the standardized management of hypertension and hyperglycemia, that of dyslipidemia is still in a neglected position, and the public's awareness and attention to it need to be strengthened (34–38).

In recent years, researchers have carried out surveys on the epidemiological status of dyslipidemia in China, and many related data have been disclosed. Due to divergent research backgrounds and other reasons, the results varied widely between different studies (39). A comprehensive evaluation on the dyslipidemia epidemiology nationwide in China which may promote our understanding of the epidemiological status of dyslipidemia as well as benefit future research and policy formulation is needed. Consequently, we performed the meta-analyses to comprehensively synthesize the prevalence and management status of dyslipidemia among adults in Chinese Mainland.

2. Materials and methods

2.1. Search strategy

Based on and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (40) and the PRISMA statement (41), we conducted the systematic review. Studies on dyslipidemia from six databases were searched, including Web of Science, Embase, PubMed, WanFang, CNKI, and Chinese BioMedical Literature Database. The search strategy was based on a conjunction of "dyslipidemias," "hyperlipidemias," "epidemiology," "prevalence," "awareness rate," "treatment rate," "control rate," "cross-sectional study," and so on. The detailed literature retrieval strategy for each database can be found in **Supplementary Material**. Only studies published in English and Chinese between 1 January 2012 and 31 January 2023 were included.

2.2. Inclusion and exclusion criteria

The following information concerning dyslipidemia in Chinese population must be included in eligible studies: prevalence, awareness rate, treatment rate, and control rate. In addition, studies reported that the prevalence of elevated lipoprotein(a) [Lp(a)] was also included.

Eligibility criteria were set as followed: (1) research types: original cross-sectional studies; (2) study participants: Chinese adults; (3) the criteria of prevalence, awareness, treatment, and control rates of dyslipidemia were set based on the latest guideline of Prevention and Treatment for Dyslipidemia in Chinese adults (42).

The exclusion criteria we applied were the following: (1) animal research, (2) non-cross-sectional study, (3) study with a sample size lower than 500, and (4) study on specific occupational groups.

2.3. Study identification and data extraction

After combining all searched articles in EndNote *X9* and removing duplicates, two reviewers (QX and YC) independently scanned the titles and abstracts of the retrieved studies for possible eligible studies. Then, the two reviewers independently evaluated the full texts of all potential eligible studies. After discussing and determining the final list of the included studies, QX and YC extract the relevant information by a standardized

data collection form, respectively. The extracted information was cross-checked, and a third reviewer (ZY) was responsible for determining any unsettled discrepancies.

The two reviewers (QX and YC) independently extracted the data from studies including but not limited to regular information (such as title, author, and the publication year), characteristics of study (such as study area and number of participants), and characteristics of participants (such as age range, gender, and residential area). Then, the core information was extracted, i.e., the prevalence and rates of awareness, treatment, and control reported in each study. We also extracted these data stratified by age group, sex, region area, and year of screening.

According to the observational study criteria recommended by AHRQ, QX and YC independently evaluated the quality of the included studies (43). With a full score at 11 points, each study was grouped according to its own score. The grouping rules are as follows: good (above 7 points), medium (4–7 points), and poor (below 4 points). In addition, the risk of bias (ROB) of the included studies was evaluated based on the results' quality.

2.4. Statistical analysis

We calculated the pooled rates of prevalence, awareness, treatment, and control and corresponding 95% confidence intervals (95% CI) with a systematic analysis approach. Heterogeneity among studies was examined by Cochran's Q test and I^2 statistic. The I^2 statistic value at 25%, 50%, and 75% indicated a low, moderate, and high degree of heterogeneity, respectively (44, 45). The random-effect model will be used if the result suggested a high degree of heterogeneity ($I^2 > 50\%$). Otherwise, the fixed-effect model will be used (46).

To address heterogeneity between studies, subgroup analyses by age group, sex, geographic region, and the year of screening were performed. Afterward, a meta-regression was conducted, and the added variables include sex ratio (males vs. females), the year of screening, geographic area (southern vs. northern China), studies' quality score, and sample size. Finally, we performed a sensitivity analysis by evaluating the influence of the study's quality on the pooled estimates. Funnel plots and *Egger*'s test

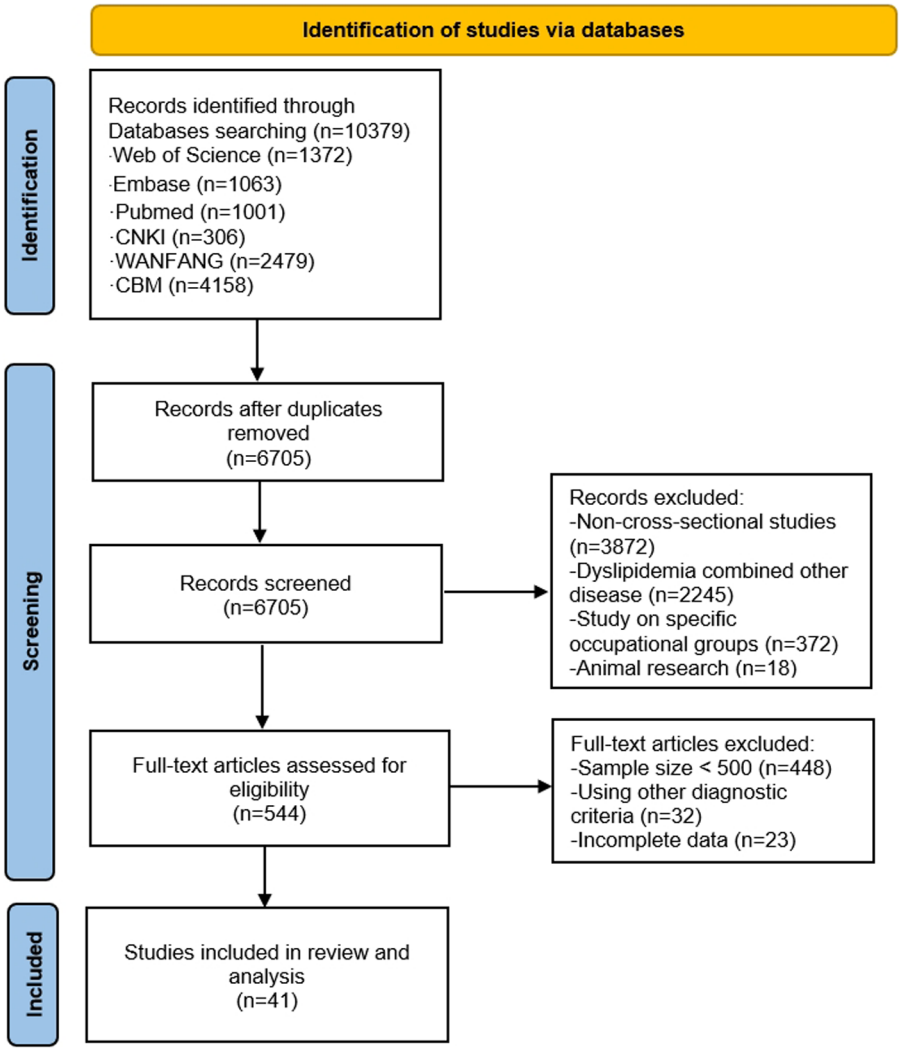


FIGURE 1
PRISMA flow chart of included studies.

were used to assess the risk of publication bias. We set the significance level at a $P < 0.05$. *Stata* and *SPSS* software were used to perform statistical analyses.

3. Results

3.1. Characteristics of included studies

3.1.1. Search results

A total of 10,379 studies from all databases were searched and gathered in EndNote *X9* software. Initially, 3,674 duplicates were removed, and then 6,161 studies were eliminated after reading the titles and abstracts, leaving 544 possibly qualified articles. Studies using other diagnostic criteria, reporting incomplete data or with a sample size of <500, were further excluded after referring to the full text. Finally, 41 studies (47–87) were included for analysis which involved a total of 1,310,402 Chinese adults. The search selection process is displayed in **Figure 1**.

3.1.2. Studies characteristics

Table 1 represented the characteristics of all included studies. Among all included 41 studies, 30 were published in Chinese (47–60, 63, 64, 68–70, 73–79, 81, 85–87), and 11 were in English (61, 62, 65–67, 71, 72, 80, 82–84). All studies were published between 2012 and 2023. As for study area, 14 studies (47, 49, 50, 58, 61, 63, 69, 70, 72, 75–77, 83, 85) were conducted on the populations of northern China, while 17 studies (48, 51–57, 59, 68, 71, 73, 74, 78, 84, 86, 87) focused

TABLE 1 Characteristic of 41 included studies of the epidemiology of dyslipidemia in Chinese adults.

No.	References	Publication year	Screening year	Region	Area	Age range	Case	Sample size
1	Liu R et al.	2021	2018	Shaanxi	Northern	≥18 years	1915	6,040
2	Luo SY et al.	2014	2010	Guangxi	Southern	≥18 years	1,907	3,599
3	Zhang R et al.	2018	2013–2014	Xinjiang	Northern	≥18 years	1,854	4,120
4	Zhang GH et al.	2017	2013	Shandong	Northern	≥18 years	3,535	11,223
5	Xu W et al.	2020	2015	Anhui	Southern	≥18 years	2,258	7,404
6	Li WY et al.	2015	2010–2011	Fujian	Southern	≥18 years	3,694	6,016
7	Mo JF et al.	2013	2010	Guangdong	Southern	≥18 years	2,171	3,577
8	Liu T et al.	2017	2011	Guizhou	Southern	≥18 years	5,392	9,280
9	Pan JJ et al.	2017	2013	Hubei	Southern	≥18 years	1,938	5,926
10	Wang YY et al.	2019	2014	Jiangsu	Southern	≥18 years	3,170	8,299
11	Chen YY et al.	2013	2010	Jiangxi	Southern	≥18 years	1,821	3,000
12	Yang XY et al.	2016	2012	Tianjin	Northern	≥18 years	2,592	8,968
13	Zhang XW et al.	2012	2010	Zhejiang	Southern	≥18 years	8,701	17,437
14	Dai Z et al.	2018	2011	–	National	≥18 years	3,459	8,669
15	Pan JH et al.	2018	2013	Shanxi	Northern	≥18 years	1,749	4,105
16	Pan L et al.	2016	2010	–	National	≥18 years	15,786	43,368
17	Lai YX et al.	2012	2007	Liaoning	Northern	≥20 years	1,542	2,989
18	Li SN et al.	2019	2012–2015	–	National	≥35 years	10,298	29,678
19	Sampson Opoku et al.	2019	2014	–	National	≥40 years	59,160	1,36,945
20	Xing LY et al.	2020	2017–2019	–	National	≥40 years	6,729	18,796
21	Song PG et al.	2019	2011	–	National	≥45 years	4,077	9,525
22	Long XT et al.	2022	2019–2020	Yunnan	Southern	≥60 years	3,282	9,709
23	Zhao Y et al.	2017	2014	Beijing	Northern	18–65 years	8220	18,809
24	Sun WF et al.	2016	2013–2014	Gansu	Northern	20–74 years	11,907	31,417
25	Huang C et al.	2021	2013–2014	Sichuan and Chongqing	Southern	35–79 years	2,801	10,221
26	Zhang J et al.	2020	2010	Zhejiang	Southern	≥18 years	–	17,437
27	Li JB et al.	2022	2018	Henan	Northern	≥18 years	–	6,809
28	Li JH et al.	2012	2010	–	National	≥18 years	–	51,818
29	Ma JJ et al.	2016	2012–2014	Xinjiang	Northern	≥35 years	–	4,314
30	Zhang M et al.	2016	2014	Guizhou	Southern	≥40 years	–	5,126
31	Sampson Opoku et al.	2021	2015	–	National	≥40 years	–	135,403
32	Xie J et al.	2017	2014	Beijing	Northern	18–65 years	–	18,809
33	He H et al.	2014	2012	Jilin	Northern	18–79 years	–	7,319
34	Zhang YF et al.	2021	2017–2020	Fujian	Southern	35–75 years	–	119,638
35	Lu Y et al.	2018	2011–2012	–	National	45–75 years	–	12,654
36	Lin LJ et al.	2023	2010–2017	–	National	≥18 years	–	411,643
37	Guo CY et al.	2021	2017	Beijing and Tianjin and Hebei	Northern	≥18 years	–	25,343
38	Xuan LP et al.	2020	2010	Shanghai	Southern	≥40 years	–	6,257
39	Niu DR et al.	2018	2015	Shandong	Northern	<100 years	–	63,882
40	Li YY et al.	2014	2012–2013	Fujian	Southern	<100 years	–	3,944
41	Chen JW et al.	2019	2018–2019	Guangzhou	Southern	≥25 years	–	886

on southern counterparts, and 10 nationwide studies (60, 62, 64–67, 79–81, 82) were conducted.

The results of quality evaluation of the included studies were displayed in **Table 2**. A total of 29 studies scored above 7 and were consequently rated as high-quality, while 12 studies were rated as medium-quality, and no studies of low-quality were observed. The studies' average quality score was 8.07, while the standard deviation was 1.09. Since no study was evaluated as low-quality, all studies were included for further analyses. **Figure 2** showed the summary plots of assessment for risk bias.

3.2. Prevalence of dyslipidemia

Twenty-five articles detailed the dyslipidemia prevalence of their population (see **Table 3**). The meta-analysis suggested that the pooled prevalence of dyslipidemia among adults in Chinese Mainland was 42.1% (95% CI: 39.2%– 44.9%), while the heterogeneity between studies was extremely high ($I^2 = 99.8\%$, $P < 0.001$). The forest plots of the pooled prevalence and rates of awareness, treatment, and control were displayed in **Figure 3**, and the corresponding funnel plots were shown in **Figure 4**. The

TABLE 2 Quality evaluation results of systematic review of epidemiology of dyslipidemia in Chinese adults.

Study ID	References	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
1	Liu R et al.	1	1	1	1	1	1	0	1	0	0	Unclear	7
2	Luo SY et al.	1	1	1	1	1	0	1	1	1	1	Unclear	9
3	Zhang R et al.	1	1	1	Unclear	1	0	1	1	1	1	Unclear	8
4	Zhang GH et al.	1	1	1	1	1	0	0	1	1	0	Unclear	7
5	Xu W et al.	1	1	1	1	1	1	1	1	0	0	Unclear	8
6	Li WY et al.	1	1	1	Unclear	1	1	0	1	0	0	Unclear	6
7	Mo JF et al.	1	1	1	1	1	1	1	1	0	1	Unclear	9
8	Liu T et al.	1	1	1	Unclear	1	0	0	1	1	1	Unclear	7
9	Pan JJ et al.	1	1	1	Unclear	1	0	0	1	1	1	Unclear	7
10	Wang YY et al.	1	1	1	1	1	0	1	1	1	1	Unclear	9
11	Chen YY et al.	1	1	1	Unclear	1	1	0	1	0	0	Unclear	6
12	Yang XY et al.	1	1	1	1	1	0	1	1	1	1	Unclear	9
13	Zhang XW et al.	1	1	1	1	1	1	1	1	1	1	Unclear	10
14	Dai Z et al.	1	1	1	1	1	1	0	1	1	0	Unclear	8
15	Pan JH et al.	1	1	1	Unclear	1	0	1	1	1	0	Unclear	7
16	Pan L et al.	1	1	1	1	1	0	0	1	1	1	Unclear	8
17	Lai YX et al.	1	1	1	1	1	0	1	1	0	0	Unclear	7
18	Li SN et al.	1	1	1	Unclear	1	1	1	1	1	0	Unclear	8
19	Sampson Opoku et al.	1	1	1	1	1	1	1	1	1	0	Unclear	9
20	Xing LY et al.	1	1	1	1	1	0	1	1	0	1	Unclear	8
21	Song PG et al.	1	1	1	1	1	0	1	1	1	1	Unclear	9
22	Long XT et al.	1	1	1	Unclear	1	1	0	1	1	0	Unclear	7
23	Zhao Y et al.	1	1	1	1	1	0	1	1	1	0	Unclear	8
24	Sun WF et al.	1	1	1	1	1	1	0	1	1	1	Unclear	9
25	Huang C et al.	1	1	1	Unclear	1	0	0	1	1	0	Unclear	6
26	Zhang J et al.	1	1	1	1	1	1	0	1	0	1	Unclear	8
27	Li JB et al.	1	1	1	1	1	1	0	1	1	1	Unclear	9
28	Li JH et al.	1	1	1	1	1	1	0	1	0	0	Unclear	7
29	Ma JJ et al.	1	1	1	1	1	1	1	1	1	0	Unclear	9
30	Zhang M et al.	1	1	1	Unclear	1	1	1	1	0	1	Unclear	8
31	Sampson Opoku et al.	1	1	1	1	1	1	1	1	1	0	Unclear	9
32	Xie J et al.	1	1	1	Unclear	1	1	1	1	1	0	Unclear	8
33	He H et al.	1	1	1	1	1	1	1	1	1	0	Unclear	9
34	Zhang YF et al.	1	1	1	Unclear	1	1	0	1	0	0	Unclear	6
35	Lu Y et al.	1	1	1	1	1	0	1	1	1	0	Unclear	8
36	Lin LJ et al.	1	1	1	1	1	1	1	1	1	1	Unclear	10
37	Guo CY et al.	1	1	1	1	1	1	1	1	1	0	Unclear	9
38	Xuan LP et al.	1	1	1	1	1	1	1	1	1	1	Unclear	10
39	Niu DR et al.	1	1	1	1	1	1	Unclear	1	Unclear	1	Unclear	8
40	Li YY et al.	1	1	1	1	1	1	1	1	Unclear	1	Unclear	9
41	Chen JW et al.	1	1	1	1	1	Unclear	1	1	Unclear	1	Unclear	8

D1: Define the source of information (survey, record review). *D2:* List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications. *D3:* Indicate time period used for identifying patients. *D4:* Indicate whether or not subjects were consecutive if not population-based. *D5:* Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants. *D6:* Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements). *D7:* Explain any patient exclusion from analysis. *D8:* Describe how confounding was assessed and/or controlled. *D9:* If applicable, explain how missing data were handled in the analysis. *D10:* Summarize patient response rates and completeness of data collection. *D11:* Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

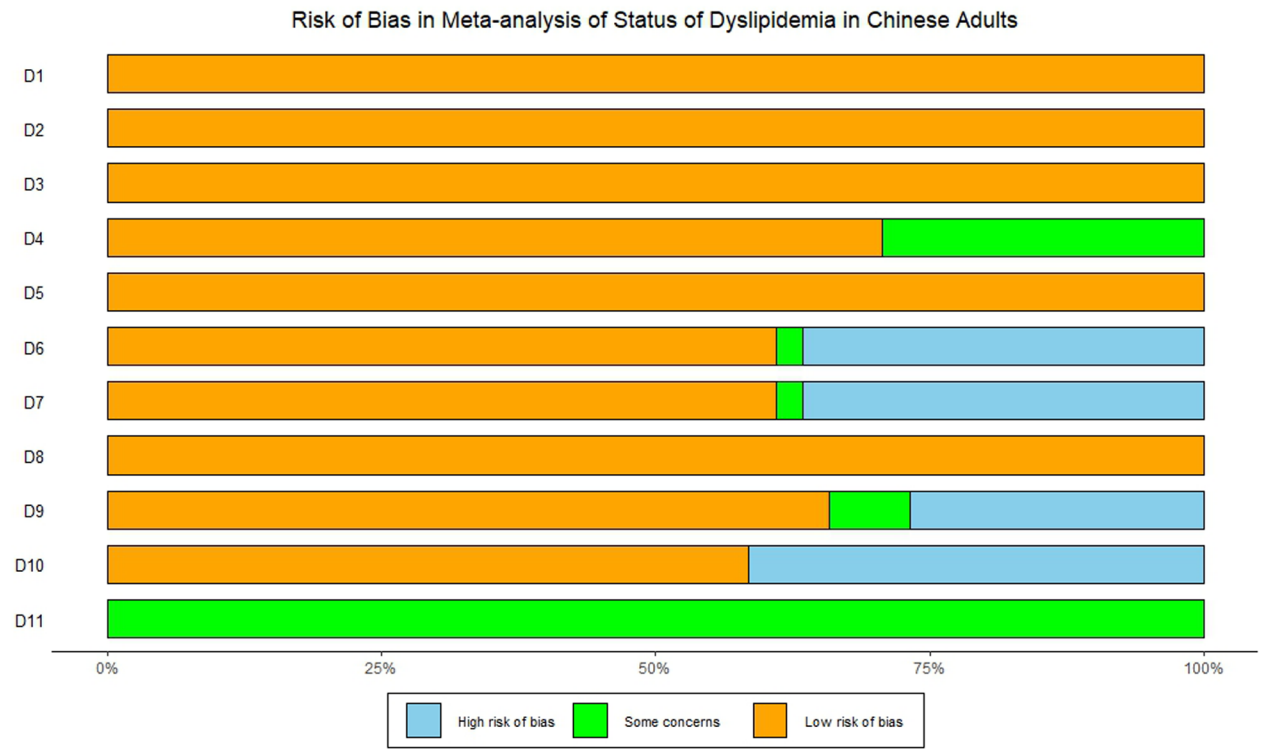


FIGURE 2
Summary plot of risk bias.

TABLE 3 Prevalence of dyslipidemia according to different categories.

Category	Subgroup	Number of studies	Prevalence (95% CI) (%)	Sample	I^2 (%)	*P*
Total		25	42.1 (39.2–44.9)	419,120	99.8	
Sex	Male	24	47.3 (44.0–50.6)	194,757	99.5	<0.001
	Female	24	38.8 (34.3–43.3)	214,121	99.8	
Age-specific group (y)	18–44	10	40.1 (33.1–47.1)	39,388	99.5	<0.001
	45–59	10	45.2 (39.7–50.7)	33,466	99.1	
	≥60	10	44.9 (38.8–50.9)	19,658	98.7	
Geographic region	Northern	8	39.1 (34.5–43.7)	87,671	99.4	<0.001
	Southern	11	46.0 (38.2–53.9)	84,468	99.8	
	Urban	21	46.3 (43.2–49.5)	167,241	99.3	<0.001
	Rural	21	41.3 (37.3–45.2)	218,097	99.7	
Screening year	2007–2010	7	53.4 (44.2–62.6)	79,986	99.8	<0.001
	2011–2013	8	38.9 (32.7–45.1)	87,374	99.7	
	2014–2020	10	36.7 (33.0–40.5)	251,760	99.7	
Types	Hypercholesterolemia (TC)	23	8.3 (6.9–9.6)	393,384	99.6	<0.001
	Hypertriglyceridemia (TG)	23	15.4 (12.5–18.3)	393,384	99.8	
	Low levels of high-density lipoprotein cholesterol (HDL-C)	23	24.5 (21.0–28.1)	393,384	99.9	
	High levels of low-density lipoprotein cholesterol (LDL-C)	23	7.1 (5.9–8.2)	393,384	99.5	
	Elevated Lp(a)	6	19.4 (16.8–22.1)	511,955	99.5	

P, *P*-value of *z*-test.

Egger's test and funnel plots (Figure 3A) demonstrated that no significant publication bias on the prevalence of dyslipidemia was found ($P = 0.996$).

Table 3 detailed the results of subgroup analysis stratified by gender, age group, geographic area, year of screening, and types of dyslipidemia. Males had higher pooled prevalence (47.3%, 95% CI: 44.0%–50.6%) of dyslipidemia than females (38.8%, 95% CI: 34.3%–43.3%), and the difference was statistically significant ($P < 0.001$). The pooled prevalence for specific age ranges was 45.2% (95% CI: 39.7%–50.7%) for subjects aged 45–59 years, which was the highest and similar to that of subjects aged ≥60 years (44.9%, 95% CI: 38.8%–50.9%), and subjects aged 18–44 years had the lowest pooled prevalence (40.1%, 95% CI: 33.1%–47.1%). Populations living in the southern area of China had

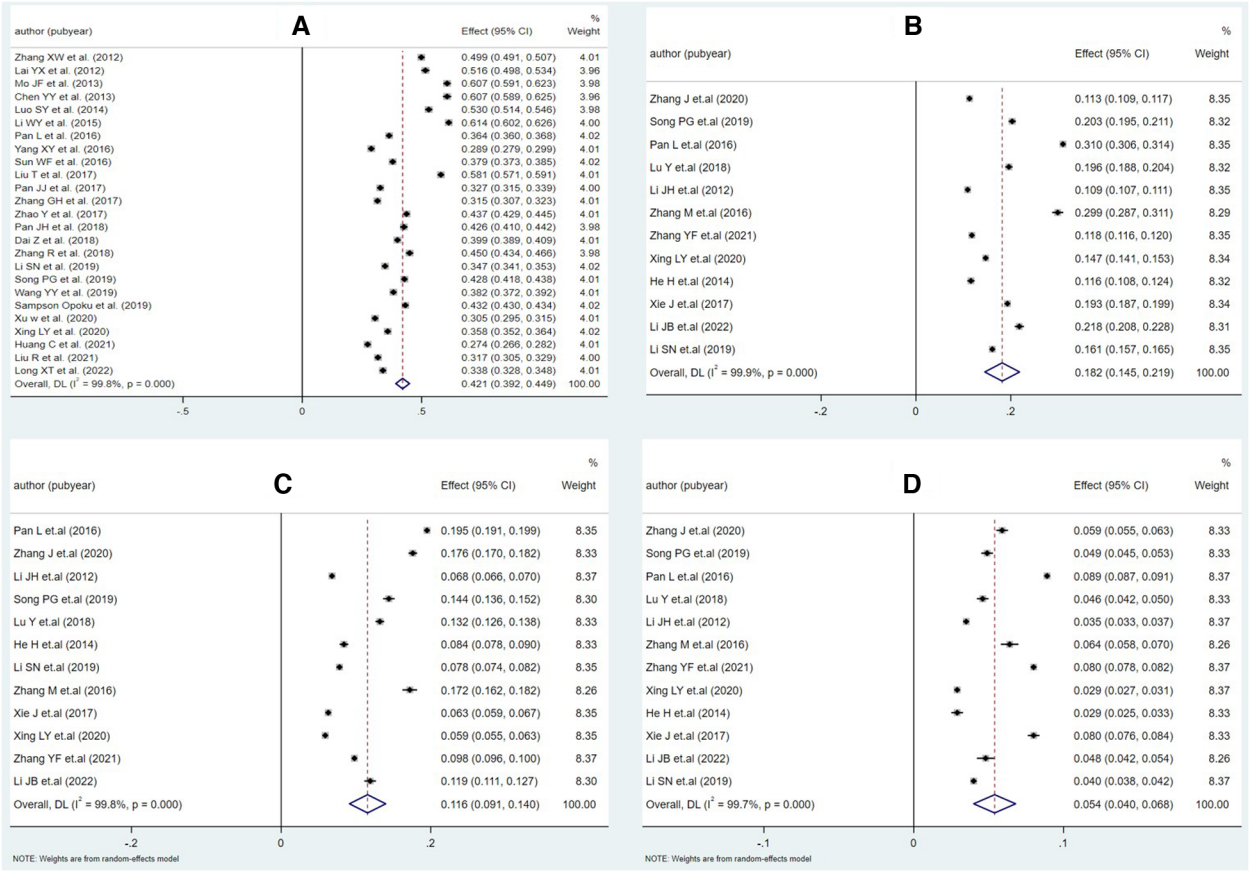


FIGURE 3
Forest plot of meta-analysis for each part of epidemiology of dyslipidemia in Chinese adults. (A) Prevalence, (B) awareness rate, (C) treatment rate, and (D) control rate.

higher pooled prevalence of dyslipidemia (46.0%, 95% CI: 38.2%–53.9%) than those living in northern China (39.1%, 95% CI: 34.5%–43.7%). In addition, the pooled prevalence of urban residents (46.3%, 95% CI: 43.2%–49.5%) was high than that of rural residents (41.3%, 95% CI: 37.3%–45.2%). In addition, the pooled prevalence of dyslipidemia decreased with time, which was 53.4% (95% CI: 44.2%–62.6%) during 2007–2010, decreasing to 38.9% (95% CI: 32.7%–45.1%) during 2011–2013, and decreasing further to 36.7% (95% CI: 33.0%–40.5%) during 2014–2020.

The pooled prevalence of different types of dyslipidemia varied widely. HDL-C was the highest at 24.5% (95% CI: 21.0%–28.1%), followed by hypertriglyceridemia at 15.4% (95% CI: 12.5%–18.3%), and the pooled prevalence of hypercholesterolemia and LDL-C were lower at 8.3% (95% CI: 6.9%–9.6%) and 7.1% (95% CI: 5.9%–8.2%), respectively. The forest plots for the pooled prevalence of different types of dyslipidemia were displayed in **Figure 5**. Corresponding funnel plots were shown in **Figure 6**. We also calculated the pooled prevalence of elevated Lp(a), which was defined as a serum Lp(a) value of >30 mg/dl according to the latest guideline of Prevention and Treatment for Dyslipidemia in Chinese adults (42). The results showed a pooled prevalence between that of HDL-C and hypertriglyceridemia at 19.4% (95% CI: 16.8%–22.1%). Forest plot and funnel plot for the prevalence of elevated Lp(a) could be searched in **Supplementary Material**.

3.3. Dyslipidemia awareness, treatment, and control

According to the related information released in 12 surveys, we arrived at pooled rates of awareness, treatment, and control of dyslipidemia at 18.2%, 11.6%, and 5.4%, respectively (see **Table 4**). The funnel plots (see **Figure 4**) and the *Egger*'s tests demonstrated that no significant publication bias on the rates was observed ($P = 0.072$, 0.110 and 0.958, respectively).

The pooled rates of awareness, treatment, and control in females (18.5%, 12.3%, and 6.4%, respectively) were higher than those in males (15.7%, 9.7%, and 4.2%, respectively). Urban residents had higher pooled rates of awareness, treatment, and control than the rural residents ($P < 0.001$). Southern residents had higher pooled rates of treatment and control (13.3% and 6.8%, respectively) than the northern populations (9.4% and 4.6%, respectively), while the difference of awareness rates was not statistically significant among them ($P = 0.055$). The pooled rates of awareness and control

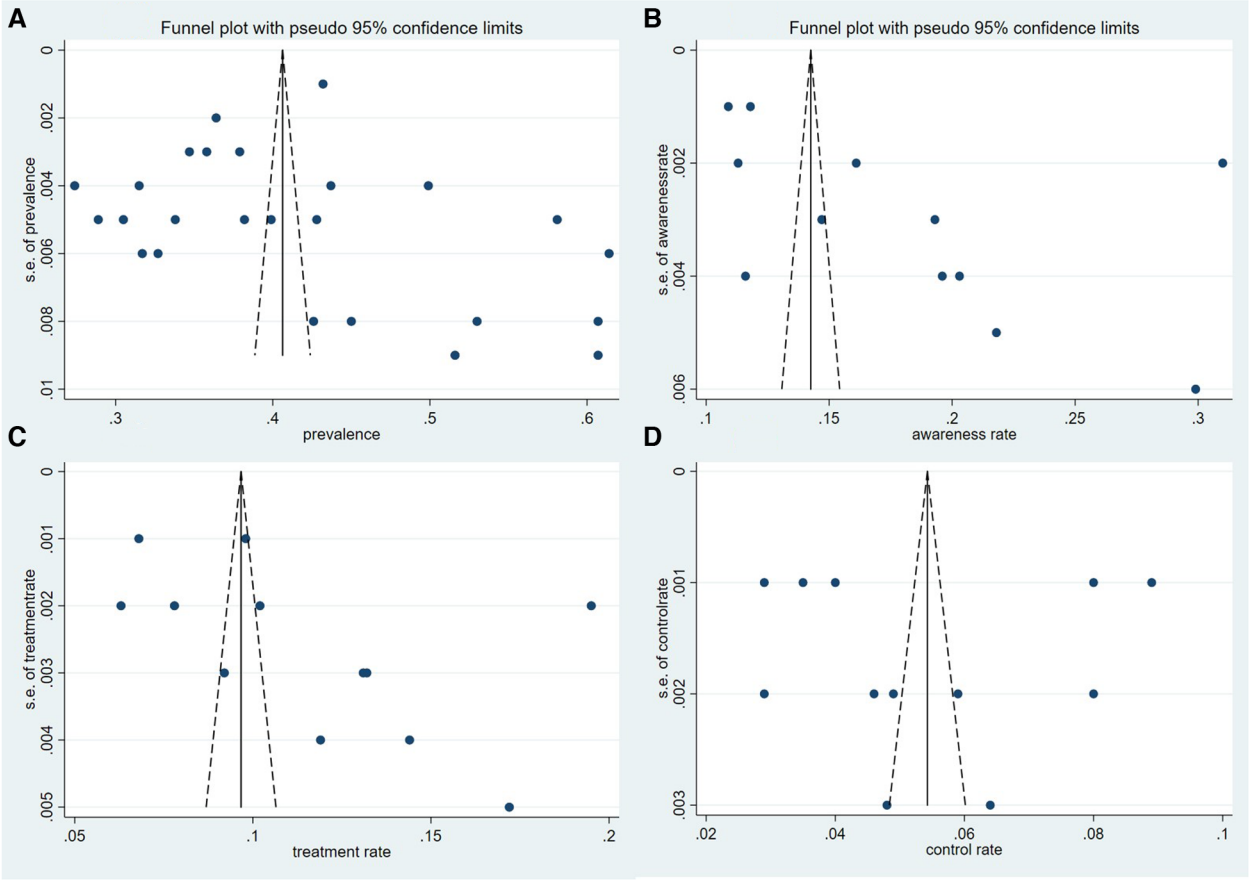


FIGURE 4
Funnel plot of each theme. (A) Prevalence, (B) awareness rate, (C) treatment rate, and (D) control rate.

increased with time. The pooled rates are 17.4% and 5.1%, respectively, during 2009–2013, increasing to 18.9% and 5.7% during 2014–2020. However, the pooled rate of treatment dropped from 12.7% to 10.5% over the same period.

3.4. Sensitivity analysis and meta-regression

In the sensitivity analysis, we excluded four citations with a quality score of 6 which was the lowest among all studies. After omitting these studies, we discovered a slight decrease in the pooled prevalence (from 42.1% to 41.0%, $P = 0.653$). Funnel plot combined with *Egger*'s test ($P = 0.639$) indicated that no significant publication bias was noted. The pooled prevalence of hypercholesterolemia, hypertriglyceridemia, HDL-C, and LDL-C changed to 8.7%, 15.9%, 23.5%, and 7.6% from 8.3%, 15.4%, 24.5%, and 7.1%, respectively. The pooled rates of awareness, treatment, and control also changed slightly (from 18.2%, 11.6%, and 5.4% to 18.8%, 11.8%, and 5.2%, respectively) after omitting these studies. The results indicated that the pooled prevalence and rates of awareness, treatment, and control had good stability.

Finally, a meta-regression was performed to address the high level of heterogeneity between studies ($I^2 = 98.7\%$–100.0%). Five variables (sex ratio, the year of screening, geographic area, studies' quality score, and sample size) were included in the analyses. The results of meta-regression demonstrated that only the year of screening variable had a significant impact on the heterogeneity ($P = 0.011$) (see Table 5).

4. Discussion

For the first time, this study comprehensively summarized and analyzed the epidemiological studies on dyslipidemia in recent years and explored its potential influencing factors. With a total number of 1,310,402 participants from different cross-sectional studies, our systematic review incorporated 41 studies conducted in multiple provinces of Chinese Mainland over the past decade. The results of the meta-analyses suggested a high-degree of prevalence of dyslipidemia in Chinese adults along with unacceptably low rates of awareness, treatment, and control. Results from this study would be a timely alarm since a comprehensive evaluation on the dyslipidemia epidemiology nationwide in China which may promote our understanding of its epidemiological status and benefit future research and policy formulation is still lacking. In 2014, the pooled prevalence of dyslipidemia among adults in Chinese Mainland is 42.1%, which is very close to the research results of Huang et al. (41.9%) (88). The deepening of aging population degree and the great changes

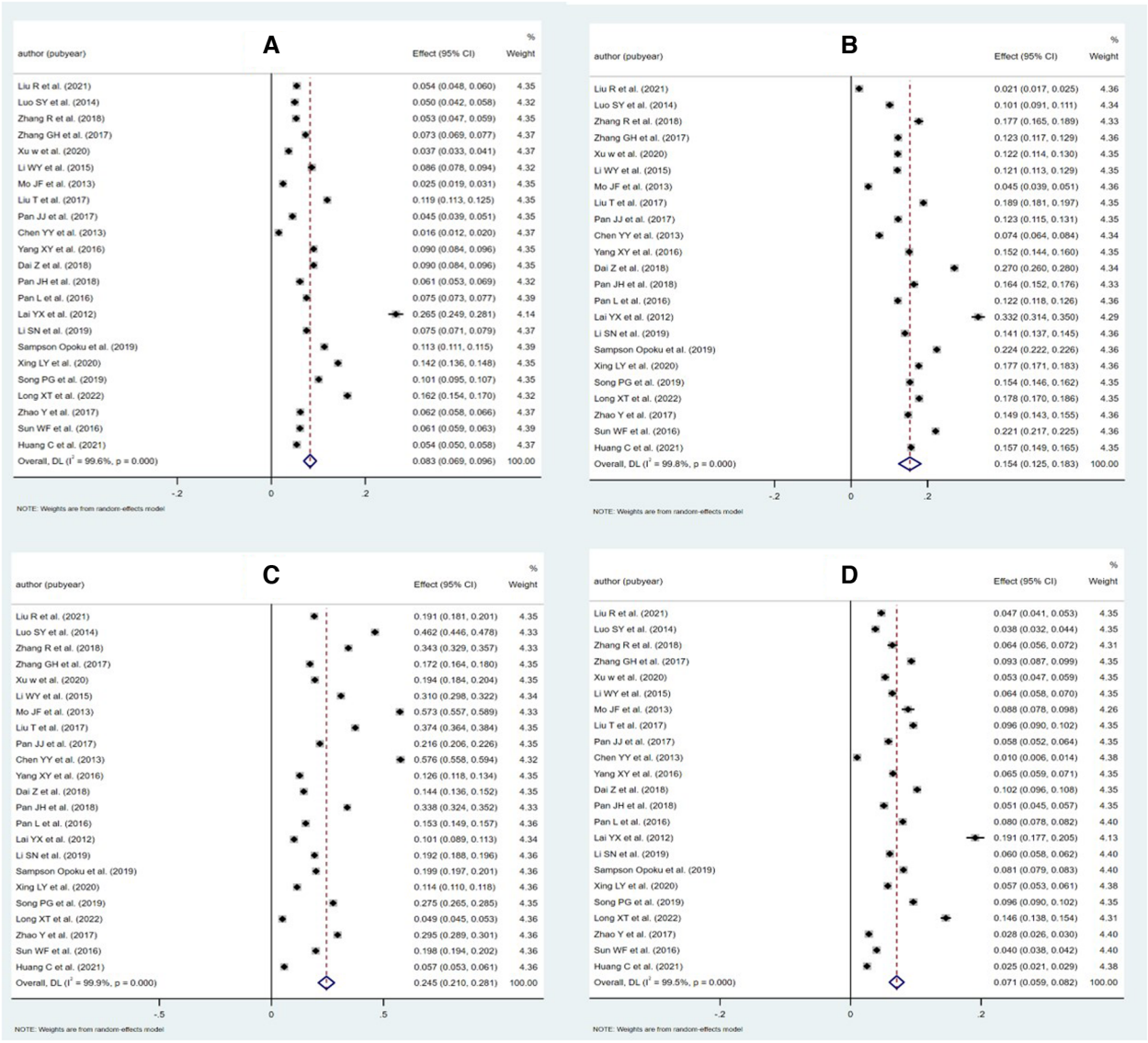


FIGURE 5
Forest plots for the pooled prevalence of different types of dyslipidemia. (**A**) Hypercholesterolemia (TC), (**B**) hypertriglyceridemia (TG), (**C**) low levels of high-density lipoprotein cholesterol (HDL-C), and (**D**) high levels of low-density lipoprotein cholesterol (LDL-C).

in residents' living habits (including but not limited to diet and physical activity) could lead to the highly prevalent dyslipidemia in recent years (89–94). By comparison with other developed countries, the dyslipidemia prevalence in Chinese adults was still lower than that reported in the United States (54.9%) (95) but much higher than that reported in Korea (16.6%) (96) and Japan (27.1%) (97). Among all types of dyslipidemia, HDL-C was the most prevalent, with a pooled estimate of 24.5%, followed by hypertriglyceridemia (15.4%), hypercholesterolemia (8.3%), and LDL-C (7.1%). In accordance with the results from surveys of Chinese Mainland in 2008–2019 (65, 98, 99), the more prevalent types of dyslipidemia in China were still HDL-C and hypertriglyceridemia. As the risk of ASCVD will be increased by all types of dyslipidemia, it is essential to treat them with applicable interventions, both clinical and non-clinical (25, 88).

The pooled estimates of dyslipidemia prevalence between different genders, age groups, and regions were calculated and analyzed. We found that males had higher pooled prevalence than females (47.3% vs. 38.8%; $P < 0.001$), which is consistent with the previous studies' results (100–103). Many factors can attribute to such difference, for instance, males are more likely to possess unhealthy behaviors than females, including but not limited to lack of vegetables and fruits in diet and fewer physical activity. Such factors could contribute to higher prevalence of many metabolic diseases in males than females, including dyslipidemia (104–108). Researches showed that estrogen changes the vascular permeability by increasing nitrous oxide production which retains a healthful lipoprotein profile (109, 110). Nonetheless, such protective mechanisms will disappear after menopause, resulting in an ascending risk for suffering

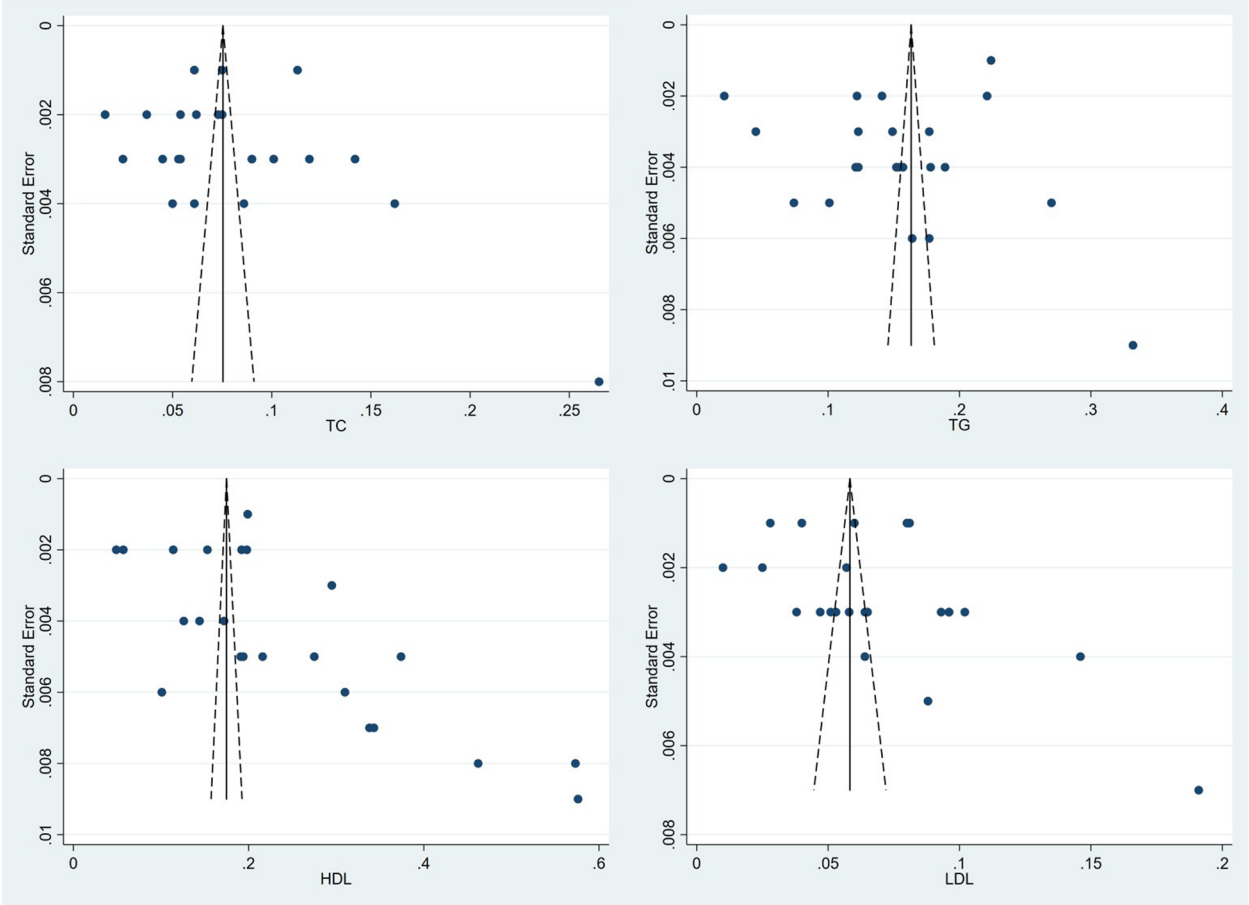


FIGURE 6
Funnel plots for the pooled prevalence of different types of dyslipidemia.

cardiovascular diseases. For example, the levels of TC, TG, LDLC, and VLDL-C aming postmenopausal women appear an upward trend, while that of HDL-C significantly decreases. Consequently, the prevalence of dyslipidemia in women often showed a dramatic increase after menopause, even surpassing that of men of the same age (60, 62, 65, 99). The systematic review revealed that southern and urban residents were more likely to suffer from dyslipidemia than their counterparts, which was a result in line with previous findings (111, 112). Another study in China suggested that economically developed areas (e.g., southeast area of China) tend to possess higher burden of dietary chronic conditions, such as dyslipidemia and obesity (113). In addition, healthcare facilities are more accessible for residents in highly urbanized and economically vibrant cities, resulting in more diagnosis and hence higher reporting rate of dyslipidemia in urban and southern areas. It is worth noting that in recent years, dyslipidemia has become more and more prevailing in Chinese youngsters. A cross-sectional study conducted in Wenzhou, Zhejiang Province, showed a prevalence at 34.11% among 7,859 young adults (114), which was much higher than the figure in Mainland China 10 years before that, as well as other Asian developing countries (115, 116). In Beijing, a study of 3,249 children aged 6–18 years showed that the prevalence of dyslipidemia was 28.9%, higher than 18.8% in 2004 (117). The younger trend of dyslipidemia may be partly attributed to the westernization of young people's lifestyle, such as dietary patterns (114). It is indisputable that corresponding risk factor intervention project should be developed based on the characteristics of young people and further screening and management programs should be strengthened.

One of the key findings of this study is a summary estimation of the pooled prevalence of elevated Lp(a) in Chinese adults, although it is not included in the definition of dyslipidemia. According to the latest guideline of Prevention and Treatment for Dyslipidemia in Chinese adults (42), we set the cutoff value at >30 mg/dl and got a pooled prevalence at 19.4%, which was much lower than that in the United States (35%) (118). As a novel lipid biomarker which could promote the formation of atherosclerosis and thrombosis, Lp(a) was considered the core pathogenesis of ASCVD and deemed as a reversible risk factor (119). Based on seven randomized controlled trials and 29,069 patients taking statin medication, one meta-analysis found that elevated Lp(a) can still increase the risk of CVD, despite a controlled LDL-C level (120). Due to the fact that the concentration level of Lp (a) in plasma is mainly caused by genetic factors, it is relatively stable throughout life (121).

TABLE 4 Awareness, treatment, and control rates of dyslipidemia according to different categories.

Category	Subgroup	Number of studies	Prevalence (95% CI) (%)	Sample	I^2 (%)	*P*
Awareness rate						
Sex	Male	10	15.7 (12.0–19.5)	149,684	99.8	<0.001
	Female	10	18.5 (14.5–22.5)	173,513	99.8	
Geographic region	Urban	8	19.1 (16.3–21.9)	94,429	99.1	<0.001
	Rural	8	11.1 (9.2–13.0)	166,591	99.1	
	Northern	4	16.8 (12.8–20.8)	51,733	99.2	0.055
	Southern	3	17.6 (12.5–22.7)	142,201	99.8	
Screening year	2009–2013	6	17.4 (10.0–24.9)	134,802	99.9	<0.001
	2014–2020	6	18.9 (15.1–22.7)	210,489	99.7	
Total		12	18.2 (14.5–21.9)	340,977	99.9	
Treatment rate						
Sex	Male	10	9.7 (7.5–12.0)	149,684	99.6	<0.001
	Female	10	12.3 (9.7–15.0)	173,513	99.9	
Geographic region	Urban	8	12.1 (6.8–17.4)	94,429	99.9	<0.001
	Rural	8	7.7 (6.4–9.1)	166,591	100.0	
	Northern	4	9.4 (7.0–11.7)	51,733	99.2	<0.001
	Southern	3	13.3 (9.6–17.1)	142,201	99.3	
Screening year	2009–2013	6	12.7 (7.8–17.6)	134,802	99.9	<0.001
	2014–2020	6	10.5 (8.7–12.3)	210,489	99.2	
Total		12	11.6 (9.1–14.0)	340,977	99.8	
Control rate						
Sex	Male	10	4.2 (3.0–5.5)	149,684	99.2	<0.001
	Female	10	6.4 (4.5–8.3)	173,513	99.7	
Geographic region	Urban	8	5.5 (3.1–8.0)	94,429	99.5	<0.001
	Rural	8	3.6 (2.5–4.7)	166,591	99.1	
	Northern	4	4.6 (2.2–7.1)	51,733	99.5	<0.001
	Southern	3	6.8 (5.3–8.3)	142,201	98.0	
Screening year	2009–2013	6	5.1 (2.9–7.4)	134,802	99.7	0.001
	2014–2020	6	5.7 (3.6–7.7)	210,489	99.7	
Total		12	5.4 (4.0–6.8)	340,977	99.7	

P, *P*-value of *z*-test.

TABLE 5 Results of meta-regression for the prevalence of dyslipidemia.

Covariate	Meta-regression coefficient	95% confidence interval	*P*
Year of screening	−0.086	−0.147 to −0.024	0.011
Sex ratio (male vs. female)	−0.110	−0.353 to 0.134	0.346
Area (southern vs. northern)	−0.034	−0.138 to 0.070	0.490
Sample size, continuous	$8.16e^{-7}$	$-6.63e^{-6}$ to $8.26e^{-6}$	0.815
Quality score	$9.56e^{-5}$	−0.056 to 0.056	0.997

P, *P*-value of meta-regression.

Chinese researchers recommended that people consider at least once measurement of Lp(a) to identify individuals who have inherited extremely increased levels of Lp(a) (≥180 mg/dl), which may bring an extremely high lifetime risk of ASCVD (119).

Publicizing the harm of dyslipidemia to the general public along with encouraging a healthier lifestyle is the basic strategy to prevent dyslipidemia and ASCVD. For patients with dyslipidemia, the focus is to control the blood lipid level to the normal range through therapeutic approaches, such as taking statins. Therefore, improving residents' awareness, treatment, and control of dyslipidemia is the key to effective management of dyslipidemia. The pooled rates of awareness, treatment, and control of dyslipidemia among Chinese adults are 18.2%, 11.6%, and 5.4%, respectively, which are slightly higher than the research results of Zhao et al. (10.9%, 6.8%, and 3.5%, respectively) in Chinese Mainland in 2010 but much lower than that reported in the United States (73.3%, 54.1%, and 35.7%) and also lower than the results from Argentina (37.3%, 36.6%, and 20.0%) and South Korea (29.4%, 17.0%, and 13.9%, respectively) (79, 122, 123). In accordance with previous studies (80, 88), our study suggested that women had higher awareness rates of dyslipidemia than men and tend to receive corresponding treatment, which further contributed to better control of their condition. Various factors can account for such phenomenon, for instance, studies demonstrated that women more frequently seek medical services than men (124). In addition, women are more likely to have a health insurance as well as an ongoing source for primary care than men (125). Therefore, we suggested strengthening the promotion and management of dyslipidemia among male residents in China. In line with the previous studies (62, 80), our results showed that urban residents had significantly higher rates of awareness, treatment, and control than rural residents. Similarly, such urban–rural difference was found in a couple of findings from other countries (119, 126, 127). The differences in rates between urban and rural areas may be partly attributed to the gap between residents' economy and education

level (128). A prior study suggested a gap in statin availability between urban and rural areas, which may support evidence that rural residents generally have difficulty accessing health care, especially in developing countries (129, 130). Therefore, it is suggested to attach more importance to the dyslipidemia management in rural areas, such as increasing the availability of drugs. The significance of this study has been highlighted by the extremely low rates of awareness, treatment, and control discovered, which may imply some disparities and deficiencies in dyslipidemia management in China. The results of a study on 99,655 patients with dyslipidemia who had prescribed statins in Tianjin showed that although high adherence to medications can reduce the risk of major adverse cardiovascular events, only 5.4% of the patients insist on taking statins for more than 50% of the days (131). Results of China Dyslipidemia Survey (DYSIS) signified that among the outpatients in China who had regularly taken lipid-lowering drugs, statin monotherapy accounted for 97.96%, while combination therapy accounted for only 2.04%. In addition, despite the steady lipid-lowering therapy, the vast majority of patients still had at least one manifestation of dyslipidemia (132). China PEACE Million Persons Project investigated the accessibility of lipid-lowering drugs in primary healthcare institutions of China. Only 49.7% of total number of 3,041 primary care institutions stocked statins, while 19.2% stored non-statin lipid-lowering drugs. The poor drug availability was particularly serious in rural medical institutions (129). The PURE study evaluated the usage of secondary prevention drugs for patients with CVD in communities of countries with different income levels (133). Results signified a positive relation between the rates of use for statins and the economic level of country. In addition, the use rate of statins in patients with coronary heart disease or stroke in China was the lowest (1.7%) among all secondary prevention drugs, which is lower than the level in North America, Europe, the Middle East, South America, Malaysia, and South Asia and only slightly higher than the level in Africa.

Consequently, at the first step, we suggested to determine a patient journey of dyslipidemia with clear process and easy understanding and operation. Second, by improving the allocation of manpower and resources in primary medical institutions, it may help in making up for their vacancy in the management of dyslipidemia and gradually play their role in patient screening, initial diagnosis, referral, and follow-up management. Finally, a comprehensive management system should be established to prevent and control various cardiovascular diseases and their risk factors.

The quality of the studies included in this systematic review is generally high; consequently, the results of sensitivity analysis revealed that when the lowest score studies were excluded, only a slight impact on the results was achieved. Data from multiple provinces in Chinese Mainland with a large sample size was incorporated in our meta-analysis. However, some limitations in this study are shown as well. Firstly, due to limitations in data availability, the relationship between the prevalence of dyslipidemia and some factors cannot be explored by subgroup analyses and meta-regression. Therefore, this study is limited in exploring the influencing factors of dyslipidemia. Secondly, only epidemiological studies were included in our systematic review and meta-analysis, and the high degree of heterogeneity between studies is inevitable (134). However, subgroup analysis and meta-regression alleviate this issue to some extent. Finally, we cannot infer causality between dyslipidemia and other factors due to the cross-sectional design in all included studies.

5. Conclusion

Nearly half of Chinese adults suffered from dyslipidemia, while the most prevalent type of dyslipidemia was low levels of high-density lipoprotein cholesterol. Males and urban residents had a higher prevalence of dyslipidemia than their counterparts. This study further suggested extremely low rates of awareness, treatment, and control for dyslipidemia in Chinese adults. The government should increase the financial and manpower support for primary medical institutions and implement effective programs to prevent and control dyslipidemia.

Data availability statement

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

Author contributions

Conceptualization, QX. Methodology, QX and YC. Material search: QX and ZY. Data extraction: QX, YC, and ZY. Data analysis: QX, ZH, WQ, and AM. Writing—original draft preparation: QX. Writing—review and editing: QX, YC, ZY, ZH, AM, WQ, and YY. Supervision: YY. Project administration: YY. Funding acquisition: YY. All authors contributed to the article and approved the submitted version.

Funding

This research was funded by the Capital health development scientific research project (2021-1g-4251). The funding bodies did not play any role in the design of the study and collection, analysis, and interpretation of data and in writing this manuscript.

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.2023.1186330/full#supplementary-material

References

1. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol*. (2019) 16:203–12. doi: 10.1038/s41569-018-0119-4

2. Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, et al. Cause-specific mortality for 240 causes in China during 1990–2013: a systematic subnational analysis for the global burden of disease study 2013. *Lancet*. (2016) 387:251–72. doi: 10.1016/s0140-6736(15)00551-6

3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study (vol 76, pg 2982, 2020). *J Am Coll Cardiol*. (2021) 77:1958–9. doi: 10.1016/j.jacc.2021.02.039

4. The writing committee of the report on cardiovascular health and diseases in China. Overview of China cardiovascular health and disease report 2021. *Chin J Cardio-Vascular Res*. (2022) 20:577–96. doi: 10.3969/j.issn.1672-5301.2022.07.001

5. China's National Health Commission. *China Health statistics yearbook*. Beijing: China Union Medical University Press (2020).

6. Interpretation of Report on Cardiovascular health and diseases in China 2021. *Chin J Cardiovasc Med*. (2022) 27:305–18. doi: 10.3969/j.issn.1007-5410.2022.04.001

7. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. (2001) 24:683–9. doi: 10.2337/diacare.24.4.683

8. Cai H, Huang J, Xu G, Yang Z, Liu M, Mi Y, et al. Prevalence and determinants of metabolic syndrome among women in Chinese rural areas. *PLoS One*. (2012) 7: e36936. doi: 10.1371/journal.pone.0036936

9. 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

10. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. (2019) 394:1145–58. doi: 10.1016/s0140-6736(19)30427-1

11. Lewington S, Lacey B, Clarke R, Guo Y, Kong XL, Yang L, et al. The burden of hypertension and associated risk for cardiovascular mortality in China. *JAMA Intern Med*. (2016) 176:524–32. doi: 10.1001/jamainternmed.2016.0190

12. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE million persons project). *Lancet*. (2017) 390:2549–58. doi: 10.1016/s0140-6736(17)32478-9

13. Wang CY, Chen YQ, Jin JY, Du R, Fan LL, Xiang R. A novel nonsense mutation of ABCA8 in a Han-Chinese family with ASCVD leads to the reduction of HDL-c levels. *Front Genet*. (2020) 11:755. doi: 10.3389/fgene.2020.00755

14. Chamberlain AM, Cohen SS, Weston SA, Fox KM, Xiang P, Killian JM, et al. Relation of cardiovascular events and deaths to low-density lipoprotein cholesterol level among statin-treated patients with atherosclerotic cardio-vascular disease. *Am J Cardiol*. (2019) 123:1739–44. doi: 10.1016/j.amjcard.2019.02.043

15. Zhou L, Mai J, Li Y, Guo M, Wu Y, Gao X, et al. Triglyceride to high-density lipoprotein cholesterol ratio and risk of atherosclerotic cardiovascular disease in a Chinese population. *Nutr Metab Cardiovasc Dis*. (2020) 30:1706–13. doi: 10.1016/j.numecd.2020.05.009

16. Okamura M, Takekawa H, Sjsum, Okabe R, Suzuki K, Hirata K. Vertebral artery Doppler waveform patterns for exclusive diagnosis of basilar artery stenosis and occlusion. *J Med Ultrason (2001)*. (2016) 43:83–9. doi: 10.1007/s10396-015-0669-6

17. Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, Krishnan AV, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American heart association. *Circulation*. (2018) 138:e1–e34. doi: 10.1161/CIR.0000000000000580

18. Nordestgaard BG. Triglyceride-Rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. (2016) 118:547–63. doi: 10.1161/CIRCRESAHA.115.306249

19. Zeng Y, Zhu S, Yu X, Wang S, Yu K, Qi H. Expert consensus on grassroots management path of adult atherosclerotic cardiovascular disease in China (draft). *Chin J Gen Pract Med*. (2017) 20:251–61.

20. Zhang M, Zhao Y, Tian S, Gao X, Yang J, Su S, et al. Risk stratification of atherosclerotic cardiovascular disease in Chinese patients with acute myocardial infarction. *Chin J Circ*. (2021) 36:852–7. doi: 10.3969/j.issn.1000-3614.2021.09.004

21. GBD results tool. GHDx http://ghdx.healthdata.org/gbd-results-tool (2018).

22. Liu S, Yuan H, Jiang C, Xu J, Qiu X, Luo J. The blood pressure control and arteriosclerotic cardiovascular risk among Chinese community hypertensive patients. *Sci Rep*. (2021) 11:19066. doi: 10.1038/s41598-021-98745-8

23. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J*. (2017) 38:2459–72. doi: 10.1093/eurheartj/ehx144

24. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, Couture P, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. (2006) 259:247–58. doi: 10.1111/j.1365-2796.2006.01616.x

25. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—executive summary. *J Clin Lipidol*. (2014) 8:473–88. doi: 10.1016/j.jacl.2014.07.007

26. Stevens W, Peneva D, Li JZ, Liu LZ, Liu G, Gao R, et al. Estimating the future burden of cardiovascular disease and the value of lipid and blood pressure control therapies in China. *BMC Health Serv Res*. (2016) 16:175. doi: 10.1186/s12913-016-1420-8

27. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) [lipoprotein(a)] concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. (2021) 41:465–74. doi: 10.1161/ATVBAHA.120.315291

28. Chen P, Zhang M, Zhang Y, Su X, Chen J, Xu B, et al. Economic burden of myocardial infarction combined with dyslipidemia. *Front Public Health*. (2021) 9:648172. doi: 10.3389/fpubh.2021.648172

29. Mendoza-Herrera K, Pedroza-Tobias A, Hernandez-Alcaraz C, Avila-Burgos L, Aguilar-Salinas CA, Barquera S. Attributable burden and expenditure of cardiovascular diseases and associated risk factors in Mexico and other selected mega-countries. *Int J Environ Res Public Health*. (2019) 16:4041. doi: 10.3390/ijerph16204041

30. Yuan KJ, Zhao CY, Yang Y, Yan DH, Zhou GQ. Analysis on the trend of disease burden attributable to high level of LDL-C in Chinese population from 1990 to 2019. *Chin J Evid Based Med*. (2022) 22:444–9. doi: 10.7507/1672-2531.202112052

31. Xu XH, Yang JJ, Wang LJ, Yin P, Liu JM, Dong WL, et al. Study on disease burden attributable to high level of LDL-C in Chinese population in 2017. *Chin J Epidemiol*. (2020) 41:839–44. doi: 10.3760/cma.j.cn112338-20191205-00861

32. EI, U. The cost of silence: Cardiovascular disease in Asia (2018).

33. Fan M, Yingying J, Yunning L, Zhenping Z, Limin W, Linhong W, et al. Status of cardiovascular disease epidemics and its risk factors prevention and control in China: an evaluation based on China cardiovascular health Index of 2017. *Chin J Prev Med*. (2021) 55:1280–6. doi: 10.3760/crna.j.cn 112150-20210822-00817

34. Peng W, Li K, Yan AF, Shi Z, Zhang J, Cheskin LJ, et al. Prevalence, management, and associated factors of obesity, hypertension, and diabetes in Tibetan population compared with China overall. *Int J Environ Res Public Health*. (2022) 19:8787. doi: 10.3390/ijerph19148787

35. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. China Hypertension survey I. Status of hypertension in China: results from the China hypertension survey, 2012-2015. *Circulation*. (2018) 137:2344–56. doi: 10.1161/CIRCULATIONAHA.117.032380

36. Li MZ, Su L, Liang BY, Tan JJ, Chen Q, Long JX, et al. Trends in prevalence, awareness, treatment, and control of diabetes mellitus in mainland China from 1979 to 2012. *Int J Endocrinol*. (2013) 2013:753150. doi: 10.1155/2013/753150

37. Mao F, Jiang YY, Liu YN, Zhao ZP, Wang LM, Wang LH, et al. Prevalence and risk factors analysis of cardiovascular and cerebrovascular diseases among Chinese residents: based on the 2017 China cardiovascular health index study. *Chin J Prev Med*. (2021) 55:1280–6. doi: 10.3760/cma.j.cn112150-20210822-00817

38. Wang X, Li X, Zhang YB, Zhang F, Sun L, Lin J, et al. Genome-Wide linkage scan of a pedigree with familial hypercholesterolemia suggests susceptibility loci on chromosomes 3q25-26 and 21q22. *Plos One*. (2011) 14:10. doi: 10.1371/journal.pone.0024838

39. Chu JR, Gao RL, Zhao SP, Lu GP, Zhao D, Li JJ. Guidelines for the prevention and treatment of dyslipidemia in Chinese adults (revised in 2016). *Chin J Circ*. (2016) 31:937–53. doi: 10.3969/j.issn.1000-3614.2016.10.001

40. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008

41. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. (2021) 372:n71. doi: 10.1136/bmj.n71

42. The writing committee of the report on cardiovascular health diseases in China. Interpretation of report on cardiovascular health and diseases in China 2021. *Chin J Cardiovasc Med*. (2022) 27:305–18.

43. Rostom A, Dubé C, Cranney A. Celiac disease. Evidence Report/Technology Assessment No. 104. AHRQ Publication No. 04-E029-2. Rockville, MD: Agency for Healthcare Research and Quality. Appendix D. Quality Assessment Forms.; 2004. (2013). Available from: https://www.ncbi.nlm.nih.gov/books/NBK35156/. [Accessed 05 March 2023].

44. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: q statistic or I2 index? *Psychol Methods*. (2006) 11:193–206. doi: 10.1037/1082-989X.11.2.193

45. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

46. Schmidt FL, Oh IS, Hayes TL. Fixed- versus random-effects models in meta-analysis: model properties and an empirical comparison of differences in results. *Br J Math Stat Psychol*. (2009) 62:97–128. doi: 10.1348/000711007X255327

47. Liu R, Wang YP, Qiu L, Sa RN, Tao YL. Cross-sectional survey on dyslipidemia among adults in Shaanxi, 2010—2018. *Mod Prev Med*. (2021) 48:3081–3087 + 3109.

48. Luo SY, Yang H, Meng XY, Huang T, Xu JJ, Huang Y. Prevalence rate and risk factors of dyslipidemia among adults in Guangxi Province. *Appl Prev Med*. (2014) 20:129–33.

49. Zhang R, Zhang WJ, Pu E, Liao PH, Zhe W, Liu LX, et al. Analysis on epidemiological characteristics and related factors of dyslipidemia am ong adult residents of Xinjiang uygur autonomous region during 2013—2014. *Chin J Prev Me*. (2018) 52:1152–7. doi: 10.3760/cma.j.issn.0253-9624.2018.11.011

50. Zhang GH, Tang JL, Chen X, Guo XL, Xu CX, Gao CC, et al. Cross-sectional survey on dyslipidemia among residents aged 18 and above in Shandong Province, 2013. *Chin J Dis Control Prev*. (2017) 21:457–60. doi: 10.16462/j.cnki.zhjbkz.2017.05.007

51. Xu W, Xing XY, He Q, Dai D, Li R, Xu JQ, et al. A cross-sectional study on the prevalence and related factors of dyslipidemia among adults in Anhui province, in 2015. *Chin J Epidemiol*. (2020) 41:195–200. doi: 10.3760/cma.j.issn.0254-6450.2020.02.011

52. L WY, Chen TH, Zhong WL, Lin SG, Lin XQ, Ye Y, et al. Epidemic characteristics and influencing factors of dyslipidemia in Fujian residents. *Strait J Prve Med*. (2015) 21:1–3.

53. Mo JF, Song XL, Xu YJ, Xu XJ, He Q, Cai QM, et al. Association study of prevalence of dyslipidemia and its risk factors among adults in Guangdong Province. *South China J Prev Med*. (2013) 39:11–7.

54. Liu T, Guo SQ, Guo M, Li L, Liu D, Zhou J, et al. Prevalence and risk factors of dyslipidemia among adult residents in Guizhou province. *Chin J Public Health*. (2017) 33:88–91. doi: 10.11847/zgggws2017-33-01-22

55. Pan JJ, He TJ, Zhang L, Tang Y, Li Q, Zhang Q. Dyslipidemia prevalence and serum lipid profiles and ratios among urban and rural residents in Hubei province, 2013: a comparison analysis. *Chin J Public Health*. (2017) 33:1439–44. doi: 10.11847/zgggws2017-33-10-06

56. Wang Y, Dai Y, Wang S, Zhang J, Zhu Q, Xie W. Prevalence and related factors of dyslipidemia among the adult residents in Jiangsu province in 2014. *J Hyg Res*. (2019) 48:945–52. doi: 10.19813/j.cnki.weishengyanjiu.2019.06.014

57. Chen Y, Zhu L, Li A, Luo W, Liu J, Yan W, et al. Epidemic characteristics of dyslipidemia among adults in Jiangxi Province. *Pract Prev Med*. (2013) 20:234–6. doi: 10.3969/j.issn.1006-3110.2013.02.039

58. Yang X, Wang T, Wang Y. Prevalence and influencing factors of dyslipidemia among adult residents in Tianjin city: a cross-sectional study. *Chin J Public Health*. (2016) 32:286–90. doi: 10.3969/j.issn.1006-3110.2013.02.039

59. Zhang X, Ye Z, Zhou D, Zhang J, Wang H, He Q, et al. Prevalence of dyslipidemia and its distribution among adults, a cross-sectional study in Zhejiang. *Dis Surveill*. (2012) 27:395–9. doi: 10.3784/j.issn.1003-9961.2012.5.019

60. Dai J, Min J, Yang Y. A study on the epidemic characteristics of dyslipidemia in adults of nine provinces of China. *Chin J Cardiol*. (2019) 27:300. doi: 10.3760/cma.j.issn.0253 –3758.2018.02.00

61. Pan J, Ren Z, Li W, Wei Z, Rao H, Ren H, et al. Prevalence of hyperlipidemia in Shanxi Province, China and application of Bayesian networks to analyse its related factors. *Sci Rep*. (2018) 8:3750. doi: 10.1038/s41598-018-22167-2

62. Pan L, Yang Z, Wu Y, Yin R-X, Liao Y, Wang J, et al. The prevalence, awareness, treatment and control of dyslipidemia among adults in China.. *Atherosclerosis*. (2016) 248:2–9. doi: 10.1016/j.atherosclerosis.2016.02.006

63. Lai Y, Li C, Teng X, Chen Y, Shan Z. The prevalence and risk factors of dyslipidemia among urban and rural adults in Liaoning province. *J China Med Univ*. (2012) 41:151–4. doi: CNKI:21-1227/R.20120117.1122.008

64. Li S, Zhang L, Wang X, Chen Z, Dong Y, Zheng C, et al. Status of dyslipidemia among adults aged 35 years and above in China. *Chin Circ J*. (2019) 34:681–97. doi: 10.3969/j.issn.1000-3614.2019.07.011

65. Opoku S, Gan Y, Fu W, Chen D, Addo-Yobo E, Trofimovitch D, et al. Prevalence and risk factors for dyslipidemia among adults in rural and urban China: findings from the China national stroke screening and prevention project (CNSSPP). *Bmc Public Health*. (2019) 19:1500. doi: 10.1186/s12889-019-7827-5

66. Xing L, Jing L, Tian Y, Yan H, Zhang B, Sun Q, et al. Epidemiology of dyslipidemia and associated cardiovascular risk factors in northeast China: a cross-sectional study. *Nutr Metab Cardio-Vascular Dis*. (2020) 30:2262–70. doi: 10.1016/j.numecd.2020.07.032

67. Song P, Zha M, Yang X, Xu Y, Wang H, Fan Z, et al. Socioeconomic and geographic variations in the prevalence, awareness, treatment and control of dyslipidemia in middle-aged and older Chinese. *Atherosclerosis*. (2019) 282:57–66. doi: 10.1016/j.atherosclerosis.2019.01.005

68. Long X, Ye A, Chen J, Mao Y, Wang X, Pu H, et al. Prevalence and influencing factors of dyslipidemia among the elderly in Anning City from 2019 to 2020. *J Prev Med Inf*. (2022) 38:965–71.

69. Zhao Y, Ma A, Fang K, Li H, Xie J, Zhou Y, et al. Study on the prevalence of dyslipidemia and its risk factors among residents aged 18-65 in Beijing in 2014. *Chin. J. Clin*. (2017) 45:25–8. doi: 10.3969/j.issn.2095-8552.2017.11.009

70. Sun W. *Epidemiological investigation of dyslipidemia in adults in Gansu province*. Lanzhou University (2016).

71. Huang C, Zhang W, Tang W, Liu Y, Liu J, Xu R, et al. Prevalence and related factors of dyslipidemia among urban adults aged 35 to 79 years in Southwestern China. *Sci Rep*. (2021) 11:17579. doi: 10.1038/s41598-021-96864-w

72. He H, Yu YQ, Li Y, Kou CG, Li B, Tao YC, et al. Dyslipidemia awareness, treatment, control and influence factors among adults in the Jilin province in China: a cross-sectional study. *Lipids Health Dis*. (2014) 3:122. doi: 10.1186/1476-511X-13-122

73. Zhang J, He Q, Wang L, Zhao M-H, Su D, Lu F, et al. Analysis of influencing factors on awareness rate, treatment rate and control rate of dyslipidemia among adults in zhejiang province. *Prev Med*. (2020) 32:1230–5. doi: 10.19485/j.cnki.issn2096-5087.2020.12.010

74. Zhang Y, Li X, Fang X, Chen T, Chen J, Yang Z, et al. Analysis of awareness, treatment and control rate of dyslipidemia in adults in Fujian Province. *Prev Med Trib*. (2021) 27:892–6. doi: 10.16406/j.pmt.issn.1672-9153.2021.12.005

75. Ma J, Gao J, Luo J, Liu F, Yang Y. The prevalence rate, awareness rate, treatment rate and control rate of dyslipidemia in Uygur people over 35 years old in Akesu area of Xinjiang. *Chin J Arterioscler*. (2016) 24:1050–4.

76. Xie J, Dong Z, Li H, Ma A, Fang K, Dong J, et al. The awareness rate, treatment rate, control rate of dyslipidemia and the influencing factors in the residents (18-65 years old) of Beijing. *Chin J Prev Contr Chron Dis*. (2017) 25:489–93. doi: 10.16386/j.cjpccd.issn.1004-6194.2017.07.003

77. Li J, Liu J, Wu E. Analysis on the status quo of awareness, treatment and control of dyslipidemia among adult residents in Zhengzhou and its influencing factors. *Chin J Prev Contr Chron Dis*. (2022) 30:525–9. doi: 10.16386/j.cjpccd.issn.1004-6194.2022.07.010

78. Zhang M, Zhang Y, Shi L, Zhang Q, Peng N, Hu Y. Awareness, treatment and control of dyslipidemia in middle-aged and older population in Guiyang: a three-year follow-up study. *J Diagn J Diagn Concepts Pract*. (2016) 15:487–91. doi: 10.16150/j.1671-2870.2016.05.011

79. Lu Y, Wang P, Zhou T, Lu J, Spatz ES, Nasir K, et al. Comparison of prevalence, awareness, treatment, and control of cardiovascular risk factors in China and the United States. *J Am Heart Sociation*. (2018) 7:e007462. doi: 10.1161/jaha.117.007462

80. Opoku S, Gan Y, Yobo EA, Tenkorang-Twum D, Yue W, Wang Z, et al. Awareness, treatment, control, and determinants of dyslipidemia among adults in China. *Sci Rep*. (2021) 11:10056. doi: 10.1038/s41598-021-89401-2

81. Li J, Wang L, Mi S, Zhang M, Li Y, Jiang Y, et al. Awareness rate, treatment rate and control rate of dyslipidemia in Chinese adults, 2010. *Chin J Prev Me*. (2012) 2012:08. doi: 10.3760/cma.j.issn.0253-9624.2012.08.004

82. Lin L, Deng KQ, Chen Z, Lei F, Qin JJ, Huang X, et al. Lipoprotein(a) distribution and its association with carotid arteriopathy in the Chinese population. *Atherosclerosis*. (2023) 372:1–9. doi: 10.1016/j.atherosclerosis.2023.03.007

83. Guo C, Cao H, Shan G, Zhao W, Zhang H, Niu K, et al. Elevated lipoprotein(a) and risk of coronary heart disease according to different lipid profiles in the general

Chinese community population: the CHCN-BTH study. *Ann Transl Med*. (2021) 9:26. doi: 10.21037/atm-20-3899

84. Xuan L, Wang T, Dai H, Wang B, Xiang J, Wang S, et al. Serum lipoprotein (a) associates with a higher risk of reduced renal function: a prospective investigation. *J Lipid Res*. (2020) 61:1320–7. doi: 10.1194/jlr.RA120000771

85. Niu DR, Liu YQ, Ju Y, Shao J, Wang ZJ, Fan WH. Investigation and analysis of serum lipoprotein (a) levels in the population of Shandong province. *Int J Lab Med*. (2018) 39:354–6. doi: 10.3969/j.issn.1673-4130.2018.03.030

86. Li YY, Li QL, Huang W. Investigation and comprehensive analysis on serum Lipoprotein (a) reference ranges in Chinese health population. *Fujian Med J*. (2014) 36:128–30.

87. Chen JW, Chen BJ, Lu CH. Investigation on Serum lipoprotein (a) levels in healthy population in Guangzhou province. *Psychologies Magazine*. (2019) 14:235–7. doi: 10.19738/j.cnki.psy.2019.24.215

88. Huang Y, Gao L, Xie X, Tan SC. Epidemiology of dyslipidemia in Chinese adults: meta-analysis of prevalence, awareness, treatment, and control. *Popul Health Metr*. (2014) 12:28. doi: 10.1186/s12963-014-0028-7

89. Fang EF, Scheibye-Knudsen M, Jahn HJ, Li J, Ling L, Guo H, et al. A re-search agenda for aging in China in the 21st century. *Ageing Res Rev*. (2015) 24:197–205. doi: 10.1016/j.arr.2015.08.003

90. Li R, Cheng X, Schwebel DC, Yang Y, Ning P, Cheng P, et al. Disability-adjusted life years associated with population ageing in China, 1990-2017. *BMC Geriatr*. (2021) 21:369. doi: 10.1186/s12877-021-02322-7

91. Liu S, Zhang M, Yang L, Li Y, Wang L, Huang Z, et al. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health*. (2017) 71:154–61. doi: 10.1136/jech-2016-207805

92. Han A, Sun T, Ming J, Chai L, Liao X. Are the Chinese moving toward a healthy diet? Evidence from macro data from 1961 to 2017. *Int J Environ Res Public Health*. (2020) 17:5294. doi: 10.3390/ijerph17155294

93. Menhas R, Dai J, Ashraf MA, Noman SM, Khurshid S, Mahmood S, et al. Physical inactivity, non-communicable diseases and national fitness plan of China for physical activity. *Risk Manag Healthc Policy*. (2021) 14:2319–31. doi: 10.2147/RMHP.S258660

94. Zhu B, Zhou J, Chen Y, Xu K, Wu Y, Wang Y, et al. Incidence rate, risk factors and behaviour changes for alcohol drinking: findings from a community-based cohort study in southwest China. *BMJ Open*. (2022) 12:e060914. doi: 10.1136/bmjopen-2022-060914

95. Ford ES, Li C, Pearson WS, Zhao G, Mokdad AH. Trends in hypercholesterolemia, treatment and control among United States adults. *Int J Cardiol*. (2010) 140:226–35. doi: 10.1016/j.ijcard.2008.11.033

96. Boo S, Yoon YJ, Oh H. Evaluating the prevalence, awareness, and control of hypertension, diabetes, and dyslipidemia in Korea using the NHIS-NSC database: a cross-sectional analysis. *Medicine (Baltimore)*. (2018) 97:e13713. doi: 10.1097/MD.0000000000013713

97. Fujiyoshi N, Arima H, Satoh A, Ojima T, Nishi N, Okuda N, et al. Associations between socioeconomic Status and the prevalence and treatment of hypercholesterolemia in a general Japanese population: nIPPON DATA2010. *J Atheroscler Thromb*. (2018) 25:606–20. doi: 10.5551/jat.42531

98. Wu Y, Huxley R, Li L, Anna V, Xie G, Yao C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from the China national nutrition and health survey 2002. *Circulation*. (2008) 118:2679–86. doi: 10.1161/CIRCULATIONAHA.108.788166

99. Yang W, Xiao J, Yang Z, Ji L, Jia W, Weng J, et al. Serum lipids and lipoproteins in Chinese men and women. *Circulation*. (2012) 125:2212–21. doi: 10.1161/circulationaha.111.065904

100. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. *Sci Rep*. (2018) 8 (1):4314. doi: 101038/s41598-018-22570-9

101. Zhao W, Zhang J, You Y, Man QQ, Li H, Wang CR, et al. Epidemiologic characteristics of dyslipidemia in people aged 18 years and over in China. *Chin J Pre Me*. (2005) 5:12–6.

102. Dai J, Min JQ, Yang YJ. Epidemic characteristics of dyslipidemia among adults in nine provinces and cities of China. *Chin J Hypertens*. (2019) 27:300. doi: 10.16439/j.cnki.1673-7245.2019.03.033

103. Li S, Zhang L, Wang X, Chen Z, Dong Y, Zheng C, et al. Status of dyslipidemia among adults aged 35 years and above in China. *Chin Circ J*. (2019) 34:681–7.

104. Liu X, Wu W, Mao Z, Huo W, Tu R, Qian X, et al. Prevalence and influencing factors of overweight and obesity in a Chinese rural population: the Henan rural cohort study. *Sci Rep*. (2018) 8: 13101. doi: 10.1038/s41598-018-31336-2

105. Chen H, Zhang X, Feng Q, Zeng Y. The effects of "diet-smoking-gender" three-way interactions on cognitive impairment among Chinese older adults. *Nutrients*. (2022) 14:2144. doi: 10.3390/nu14102144

106. Xu SH, Qiao N, Huang JJ, Sun CM, Cui Y, Tian SS, et al. Gender differences in dietary patterns and their association with the prevalence of metabolic syndrome among Chinese: a cross-sectional study. *Nutrients*. (2016) 8:180. doi: 10.3390/nu8040180

107. Li ZR, Ruan HF, Shen LP, Zhang XP, Wan LH. Gender difference in the association between stroke knowledge and health behavior before the onset of stroke among Chinese hypertensive patients. *J Neurosci Nurs*. (2021) 53:160–5. doi: 10.1097/JNN.0000000000000599

108. Mao Z, Wu B. Urban-rural, age and gender differences in health behaviours in the Chinese population: findings from a survey in Hubei, China. *Public Health*. (2007) 121:761–4. doi: 10.1016/j.puhe.2007.02.015

109. Reddy Kilim S, Chandala SR. A comparative study of lipid profile and oestradiol in pre- and post-menopausal women. *J Clin Diagn Res*. (2013) 7:1596–8. doi: 10.7860/JCDR/2013/6162.3234

110. Saha KR, Rahman MM, Paul AR, Das S, Haque S, Jafrin W, et al. Changes in lipid profile of postmenopausal women. *Mymensingh Med J*. (2013) 22:706–11.

111. Li Q, Wu H, Yue W, Dai Q, Liang H, Bian H, et al. Prevalence of stroke and vascular risk factors in China: a nationwide community-based study. *Sci Rep*. (2017) 7:6402. doi: 10.1038/s41598-017-06691-1

112. Xi Y, Niu L, Cao N, Bao H, Xu X, Zhu H, et al. Prevalence of dyslipidemia and associated risk factors among adults aged >= 35 years in northern China: a cross-sectional study. *Bmc Public Health*. (2020) 20:1068. doi: 10.1186/s12889-020-09172-9

113. C CM. Overview of obesity in mainland China. *Obes Rev*. (2008) 9(Suppl 1):14–21. doi: 10.1111/j.1467-789X.2007.00433.x

114. Zhang H, Kwapong WR, Shao MM, Yan JY, Lin XD, Chen BB, et al. Predictors of the prevalence of dyslipidemia and influencing factors for young health examination cohort: a cross-sectional survey. *Front Public Health*. (2020) 8:400. doi: 10.3389/fpubh.2020.00400

115. Islam N, Rahman MZ, Choudhury S, Afrin L, Rahman S, Aftabuddin M. Prevalence of dyslipidemia and associated factors among the sub-urban Bangladeshi population. *Univ Heart J*. (2012) 8:15–9. doi: 10.3329/uhj.v8i1.11662

116. Sharma U, Kishore J, Garg A, Garg A, Anand T, Chakraborty M, et al. Dyslipidemia and associated risk factors in a resettlement colony of Delhi. *J Clin Lipidol*. (2013) 7:653–60. doi: 10.1016/j.jacl.2013.06.003

117. Ding W, Cheng H, Yan Y, Zhao X, Chen F, Huang G, et al. 10-Year Trends in Serum lipid levels and dyslipidemia among children and adolescents from several schools in Beijing, China. *J Epidemiol*. (2016) 26(12):637–45. doi: 10.2188/jea.JE20140252

118. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated lp(a) mass levels and patient thresholds in 532 359 patients in the United States. *Arterioscler Thromb Vasc Biol*. (2016) 36(11):2239–45. doi: 10.1161/ATVBAHA.116.308011

119. Li JJ, Ma CS, Zhao D, Yan XW, Beijing Heart Society and Expert Committee. Lipoprotein(a) and cardiovascular disease in Chinese population: a Beijing heart society expert scientific statement. *JACC Asia*. (2022) 2(6):653–65. doi: 10.1016/j.jacasi.2022.08.015

120. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. (2018) 392:1311–20. doi: 10.1016/S0140-6736(18)31652-0.

121. Dubé JB, Boffa MB, Hegele RA, Koschinsky ML. Lipoprotein(a): more interesting than ever after 50 years. *Curr Opin Lipidol*. (2012 Apr) 23(2):133–40. doi: 10.1097/MOL.0b013e32835111d8

122. Lee J, Son H, Ryu OH. Management Status of cardiovascular disease risk factors for dyslipidemia among Korean adults. *Yonsei Med J*. (2017) 58:326–38. doi: 10.3349/ymj.2017.58.2.326

123. Sadler AE, Belcastro F, Yarleque CR. Hypertension and dyslipidaemia in Argentina: patient journey stages. *Int J Gen Med*. (2022) 15:7799–808. doi: 10.2147/IJGM.S358476

124. Goff DC, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, et al. Dyslipidemia prevalence, treatment, and control in the multi-ethnic study of atherosclerosis (MESA)—gender, ethnicity, and coronary artery calcium. *Circulation*. (2006) 113:647–56. doi: 10.1161/circulationaha.105.552737

125. Zhang X, Dupre ME, Qiu L, Zhou W, Zhao Y, Gu D. Age and sex differences in the association between access to medical care and health outcomes among older Chinese. *BMC Health Serv Res*. (2018) 18:1004. doi: 10.1186/s12913-018-3821-3

126. de la Sierra A, Pinto X, Guijarro C, Miranda JL, Callejo D, Cuervo J, et al. Prevalence, treatment, and control of hypercholesterolemia in high cardiovascular risk patients: evidences from a systematic literature review in Spain. *Adv Ther*. (2015) 32:944–61. doi: 10.1007/s12325-015-0252-y

127. Joshi SR, Anjana RM, Deepa M, Pradeepa R, Bhansali A, Dhandania VK, et al. Prevalence of dyslipidemia in urban and rural India: the ICMR-INDIAB study. *PLoS One*. (2014) 9:e96808. doi: 10.1371/journal.pone.0096808

128. Supiyev A, Nurgozhin T, Zhumadilov Z, Peasey A, Hubacek JA, Bobak M. Prevalence, awareness, treatment and control of dyslipidemia in older persons in urban and rural population in the Astana region, Kazakhstan. *BMC Public Health*. (2017) 17:651. doi: 10.1186/s12889-017-4629-5

129. Lu Y, Zhang H, Lu J, Ding Q, Li X, Wang X, et al. Prevalence of dyslipidemia and availability of lipid-lowering medications among primary health care settings in China. *Jama Network Open*. (2021) 4:e2127573. doi: 10.1001/jamanetworkopen.2021.27573

130. Janus ED, Tideman PA, Dunbar JA, Kilkkinen A, Bunker SJ, Philpot B, et al. Dyslipidaemia in rural Australia: prevalence, awareness, and adherence to treatment guidelines in the greater green tri-angle risk factor study. *Med J Aust*. (2010) 192:127–32. doi: 10.5694/j.1326-5377.2010.tb03449.x

131. Zhao B, He X, Wu J, Yan S. Adherence to statins and its impact on clinical outcomes: a retrospective population-based study in China. *BMC Cardiovasc Disord*. (2020) 20:282. doi: 10.1186/s12872-020-01566-2

132. Zhao S, Wang Y, Mu Y, Yu B, Ye P, Yan X, et al. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: results of the DYSlipidemia international study (DYSIS). *Atherosclerosis*. (2014) 235:463–9. doi: 10.1016/j.atherosclerosis.2014.05.916

133. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Prospective urban rural epidemiology (PURE) study investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey. *Lancet*. (2011) 378(9798):1231–43. doi: 10.1016/S0140-6736(11)61215-4

134. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol*. (2008) 37:1148–57. doi: 10.1093/ije/dyn06

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 06 September 2023
DOI 10.3389/fcvm.2023.1197427

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Andrea Sonaglioni,
IRCCS MultiMedica, Italy
Gian Luigi Nicolosi,
San Giorgio Hospital, Italy
Tetsuji Kitano,
University of Occupational and Environmental Health, Japan

*CORRESPONDENCE
Chien Van Do
✉ dovanchien108.cmh@gmail.com

RECEIVED 31 March 2023
ACCEPTED 11 August 2023
PUBLISHED 06 September 2023

CITATION
Nguyen HTT, Do CV, Dang DTV, Do LD, Doan LH and Dang HTV (2023) Progressive alterations of left atrial and ventricular volume and strain across chronic kidney disease stages: a speckle tracking echocardiography study. Front. Cardiovasc. Med. 10:1197427. doi: 10.3389/fcvm.2023.1197427

Progressive alterations of left atrial and ventricular volume and strain across chronic kidney disease stages: a speckle tracking echocardiography study

Hoai Thi Thu Nguyen[1,2], Chien Van Do[3]*, Dieu Thi Vu Dang[1], Loi Doan Do[1,4], Linh Huu Doan[1,2] and Ha Thi Viet Dang[5,6]

[1]Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam, [2]VNU University of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam, [3]Department of Cardiovascular Intensive Care Unit, 108 Military Central Hospital, Hanoi, Vietnam, [4]Department of Cardiology, Hanoi Medical University, Hanoi, Vietnam, [5]Department of Internal Medicine, Hanoi Medical University, Hanoi, Vietnam, [6]Center of Nephrology, Urology and Dialysis, Bach Mai Hospital, Hanoi, Vietnam

Background: It has been a scarcity of evidence regarding differences in left ventricular (LV) and left atrial (LA) size and strain changes across stages of chronic kidney disease (CKD) and which echocardiographic parameters could be utilized to predict the decline of glomerular filtration rate (GFR).
Objectives: This study aimed to evaluate the alterations of LV and LA strain across the reduction of renal function and potential echocardiographic parameters which could be correlated with the GFR decline among patients with CKD.
Method: A cross-sectional study was conducted on 169 CKD patients at Bach Mai General Hospital, Hanoi, Vietnam from April to November 2022. Demographic, clinical and laboratory characteristics of patients were collected. Transthoracic echocardiography was performed to measure LV and LA size and strains. Jonckheere-Terpstra test was used to measure the tendency of change. Multivariate linear regression models were performed to find associations between different echocardiographic parameters and renal function reduction.
Results: The number of patients with CKD stages 1, 2, 3, 4, and 5 was 21 (12.4%), 28 (16.6%), 27 (16.0%), 22 (13.0%) and 71 (42.0%), respectively. CKD severity was positively associated with LV diastolic and systolic diameters, LV mass, E/e' ratio, and maximal tricuspid regurgitation velocity (TR max), and negatively correlated with the LV global longitudinal strain. Higher severity of CKD stage was associated with higher LA diameter, LA strain, and volume in four and two-chamber views, and lower LA reservoir and conduit function. Left ventricular mass ($\beta = 0.068$), ejection fraction ($\beta = 0.112$) and left atrial reservoir ($\beta = -0.077$) were associated with reduced GFR.
Conclusion: Left ventricular mass, ejection fraction, and atrial longitudinal strain by STE should be done at the earlier stages of CKD patients for better follow-up of GFR decline.

KEYWORDS

chronic kidney disease, speckle tracking echocardiography, left atrial strain, left ventricular strain, cardiovascular disease

1. Introduction

Chronic kidney disease (CKD) significantly contributes to the global burden of diseases given the matter that it affected around 10% of the global population (or approximately 800 million people) (1). In literature, CKD was found to be associated with cardiovascular

diseases (CVD), particularly, the estimated glomerular filtration rate (eGFR) <60 ml/min/m^2 was associated with a higher risk of cardiovascular morbidity and mortality after adjusting to other independent factors (2). Prompt diagnosis and treatment can prevent the development of CKD to end-stage renal disease (ESRD) (3). The classic signs of cardiomyopathy in CKD are altered left ventricular (LV) mass and function. In high-risk individuals with conditions like hypertension or heart failure, the left atrium, a heart chamber that is incredibly sensitive to fluid overload and diastolic dysfunction, is a stand-alone predictor of mortality and unfavorable cardiovascular (CV) events (4).

Recently, a new class of cardiomyopathy known as uremic in CKD can be identified by imaging modalities such as echocardiography and cardiac magnetic resonance (CMR). This cardiomyopathy has distinctive phenotypes with important changes such as left ventricular (LV) enlargement, left atrial (LA) dilatation, diastolic dysfunction, and decreased myocardial deformation which could indicate myocardial fibrosis (5–7). In literature, among ESRD children undergoing hemodialysis (HD), significant abnormalities in speckle tracking analysis of systolic and diastolic LV and LA phasic function were observed, and global longitudinal strain (GLS) was found to be associated with a change in blood pressure, and this novel non-invasive indicator could be used to measure the long-term impact on the risk of cardiovascular abnormalities among children (8). However, it has been a scarcity of evidence regarding differences in LV and LA size and strain changes across stages of CKD, and which echocardiographic parameters could be utilized to predict the decline of GFR. Therefore, this study aimed to evaluate the alterations of LV and LA strain across the reduction of renal function and potential echocardiographic parameters which could be correlated with the GFR decline among patients with CKD.

2. Materials and methods

2.1. Study population

A cross-sectional study was conducted at Bach Mai General Hospital, Hanoi, Vietnam from April to November 2022. All patients who were diagnosed with CKD according to KDIGO 2012 criteria (9), and visited the hospital for cardiovascular consultation were consecutively recruited in the study. The CKD stages were defined according to GFR values (9): Stage 1 (Normal—GFR > 90 ml/min), Stage 2 (Mild CKD—GFR = 60–89 ml/min), Stage 3 (Moderate CKD—GFR = 30–59 ml/min), Stage 4 (Severe CKD—GFR = 15–29 ml/min) and Stage 5 (End stage CKD—GFR < 15 ml/min). Patients who (1) disagreed to participate in the study; (2) had significant valvular diseases; (3) had surgical valve repair or replacement, (4) had global left ventricular ejection fraction (LVEF) <50%, (5) had arrhythmias (atrial fibrillation, flutter, or pacemaker implantation), (6) heart rate >100 beats per minute, and (7) had chronic lung obstructive disease and acute renal failure were excluded. All eligible patients were asked to give signed consent forms and underwent meticulous clinical examinations before participating in the study. A total of 169 patients were included in the study. The study protocol was approved by the Institutional Review Board of Bach Mai hospital (Code CH2022/QĐBV).

2.2. Data collection and measurement

When performing transthoracic echocardiography (TTE), information about age, gender, blood pressure, heart rate, and body composition was collected. Laboratory testing results and clinical information were simultaneously obtained from a hospital's electronic database. TTE was done using a Vivid E95 ultrasound system (General electric Vingmed Ultrasound, Horten, Norway) and an M5S transducer with a frequency of 1.5–4.5 MHz. To avoid circadian effects, all ultrasound tests were carried out by qualified doctors in the late afternoon on the same day. Echocardiographic exams were performed following the scheduled hemodialysis session (10).

Based on the most recent recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, cardiac chamber measurements were performed (11). The dimensions and volumes of the left atrium were determined using the methods outlined by the European Society of Cardiology for quantifying cardiac chambers (11). The measurement of LA volume was conducted through the application of the disk summation algorithm, which bears resemblance to the methodology employed in the measurement of LV volume. The tracing of the LA endocardial borders was imperative in both the apical four- and two-chamber views. The LA anteroposterior (AP) measurement in the parasternal long-axis view was evaluated utilizing 2D echocardiography. The LA area was measured using planimetry techniques within the apical four- and two-chamber echocardiographic views (11).

The linear internal dimension parameters of the LV and its walls were measured in the parasternal long-axis view at the level of the mitral valve leaflet tips. LV mass was calculated using Devereux's formula and was indexed to body surface area (BSA). The modified Simpson's approach was used to compute LV ejection fraction (LVEF). The left atrial anteroposterior diameter (LAd) was evaluated from the parasternal long-axis view. After manual adjustment, LA volume was automatically computed and indexed to BSA. Pulmonary artery systolic pressure (PAPs) was determined by using tricuspid regurgitant (TR) jet velocity, inferior vena cava diameter, and the percentage of collapsibility into the formula:

$$\text{PAPs (mmHg)} = 4(\text{TRmax})^2 + \text{Right atrial pressure (RAP)}$$

Doppler pulsed-wave imaging was used in the apical four-chamber view to measure the velocities of the mitral inflow. Tissue Doppler Imaging (TDI) was used to determine average mitral annular velocities at the septal and lateral walls. The peak systolic velocity of the mitral annulus (s' wave), the peak early diastolic velocity of the mitral annulus (*E* wave), the peak late diastolic velocity of the mitral annulus (*e'* wave), the ratio of the two (*E*/*e'* wave), and Isovolumic relaxation time (IVRT) were all measured. Determination of LV diastolic inflow using Doppler

techniques was conducted on the apical four-chamber section by placing the sample volume at the tip level. *E* and *A* peak velocities along with their respective *E/A* ratio and *E*-wave deceleration time were computed. By using TDI, the early (*e*') diastolic velocities were evaluated at the septal and lateral insertion sites of the annulus of the mitral valve. The average value from the two measurements was then calculated (12).

Apical four-chamber and two-chamber pictures were recorded during breath hold for the speckle tracking analysis using a reliable TTE recording at a frame rate of 60–90 frames per second. In each view, three consecutive cardiac cycles were acquired for offline analysis using certain software (EchoPAC, version 204, GE Vingmed Ultrasound, Horten, Norway). Trained medical professionals measured the LV and LA speckle tracking parameters. GLS was evaluated following seven steps according to the guideline of Negishi et al. (13).

For the LV GLS and LA strain analyses, zero strain was established at the start of the *P* wave on the ECG (14). Indeed, we found no difference in the selection of *P* wave as the time reference for defining zero-baseline for both LV and LA strain curves in comparison with the use of ventricular end-diastole (15). LA phasic strains included reservoir phase (LASr), conduit phase (LAScd) and contractility (LASct).

A specific echocardiographic image was elected for analysis (**Figure 1**). LA endocardial walls were manually traced in apical four- and two-chamber views using a point-and-click method. The software automatically identified the LA epicardial boundaries, generating a region of interest (ROI) that investigators might modify in terms of width and shape. In each view, LA walls were divided into six segments. Segments with poor image quality were excluded from the examination of the tracking of speckles. The evaluation of LA speckle tracking parameters (LA volume, E/e' ratio, LVEF, LV GLS) was conducted within the uniform apical four- and two-chamber image according to the previous guidelines (16, 17).

2.3. Reproducibility

The inter-observer and intra-observer variability pertaining to LA strain and strain rate were performed. Two separate occasions using a cohort of 10 patients selected randomly were conducted. One operator and two investigators, who were blinded to the prior outcomes, were involved in this study. In the context of the study, the calculated coefficients of variation for positive train and positive strain rate in the four-chamber view were found to be 10.2% (intra-observer) and 18.8% (inter-observer), and 9.4% (intra-observer) and 13.7% (inter-observer), respectively.

2.4. Statistical analysis

Statistical Package for Social Sciences (SPSS) version 25 was used to analyze the data. For categorical variables, descriptive statistics were presented as frequencies and percentages. Continuous variables were presented as mean (SD), or median (interquartile range-IQR). The Jonckheere-Terpstra test was applied to detect trends in continuous variables across the stages of CKD. The difference of categorical among the stages of CKD was evaluated using the Chi-square test. Multivariate linear regression was performed. No multicollinearity was found in the model. A *p*-value <0.05 was considered statistically significant.

3. Results

Among 169 patients, regarding clinical characteristics, **Table 1** shows that there was no statistically significant difference in age, sex, or heart rate among the five CKD stages. Patients with higher CKD stages had a longer duration of disease (months) ($p < 0.001$), higher systolic blood pressure (mmHg) ($p < 0.001$) and higher diastolic blood pressure (mmHg) ($p < 0.001$) and different medication used (e.g., ACE-i/ARB, CCB, diuretics, SGLT2i, ARNI) ($p < 0.001$).

According to laboratory testing characteristics, **Table 2** shows that there was a statistical association between more severe stages of CKD and lower GFR ($p < 0.001$), a higher concentration of serum urea (mmol/L) ($p < 0.001$) and creatinine (mmol/L) ($p < 0.001$). In terms of hematologic findings, lower hemoglobin (g/L) and RBC results (T/L) ($p < 0.001$) were related to more severe stages. Patients at the later stages had lower cholesterol levels (mmol/L), higher plasma albumin (g/L), higher plasma

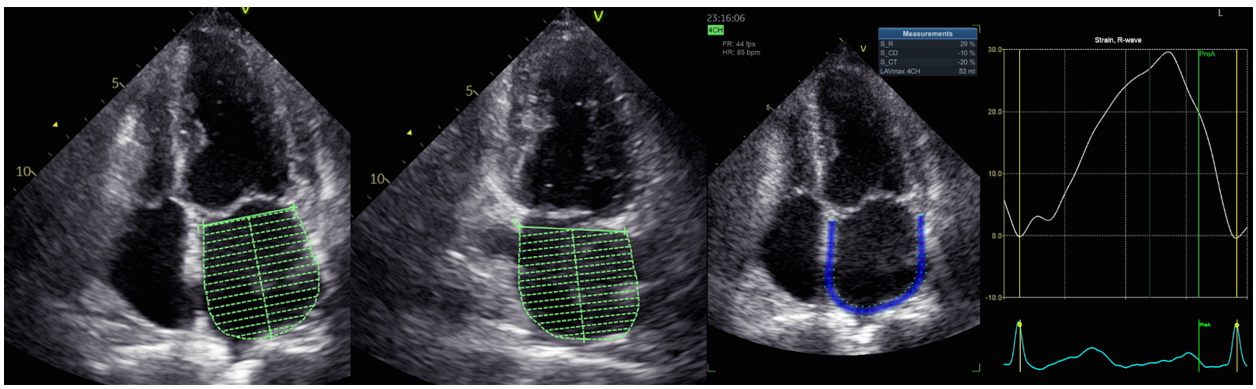


FIGURE 1
Measurement of left atrial volume (LAVI) and strain (LASr).

TABLE 1 Patients' demographic and clinical characteristics.

	Stage 1 ($n = 21$)	Stage 2 ($n = 28$)	Stage 3 ($n = 27$)	Stage 4 ($n = 22$)	Stage 5 ($n = 71$)	*p*-value
Age, years, mean (SD)	42.1 (20.7)	48.6 (18.7)	58.8 (18.3)	55.3 (10.6)	49.6 (17.5)	0.783
Male, *n* (%)	9 (42.9%)	14 (50.0%)	12 (44.4%)	12 (54.6%)	40 (56.3%)	0.747
Duration of CKD, months, median (IQR)	12 (3–24)	6 (2–12)	12 (4–24)	22 (6–60)	36 (4–84)	**<0.001**
Heart rate, beats/min, mean (SD)	85 (11)	87 (12)	83 (10)	88 (24)	86 (9)	0.9634
Systolic BP, mmHg, mean (SD)	122.1 (16.9)	130.4 (22.1)	136.1 (21.0)	142.6 (28.2)	150.5 (22.0)	**<0.001**
Diastolic BP, mmHg, mean (SD)	80.1 (12.2)	79.3 (10.2)	81.9 (11.8)	85.2 (13.8)	87.5 (13.5)	**<0.001**
History related to CKD, *n* (%)						
Nephritis	10 (47.62%)	8 (28.57%)	2 (7.41%)	5 (22.73%)	6 (8.45%)	**<0.001**
Diabetes	3 (14.29%)	8 (28.57%)	5 (18.52%)	7 (31.82%)	12 (16.90%)	0.414
Hypertension	3 (14.29%)	12 (42.86%)	15 (55.56%)	13 (59.09%)	31 (71.83%)	**<0.001**
Others	2 (9.52%)	5 (17.86%)	6 (22.22%)	5 (22.73%)	12 (16.90%)	0.781
No history reported	6 (28.57%)	4 (14.29%)	4 (14.81%)	2 (9.09%)	8 (11.27%)	0.338
Medication						
ACE-i/ARB	15 (71.4%)	16 (57.1%)	18 (66.6%)	10 (45.4%)	5 (7.0%)	<0.001
CCB	3 (14.2%)	2 (7.1%)	6 (22.2%)	6 (27.2%)	45 (63.3%)	<0.001
SGLTi	12 (57.1%)	13 (46.4%)	17 (62.9%)	10 (45.4%)	21 (29.5%)	<0.001
ARNI	4 (19.0%)	5 (17.8)	8 (29.6%)	11 (50.0%)	12 (16.9%)	<0.001
Diuretics	11 (52.3%)	12 (46.4%)	15 (55.5%)	15 (68.1%)	57 (80.2%)	<0.001

Values are mean (SD), *n* (%), or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi-square test was used to assess the difference in categorical variables across the CKD stages. A *p* value <0.05 (bold) was considered to be statistically significant.

TABLE 2 Laboratory tests results characteristics.

	Stage 1 ($n = 21$)	Stage 2 ($n = 28$)	Stage 3 ($n = 27$)	Stage 4 ($n = 22$)	Stage 5 ($n = 71$)	*p*-value
Urea, mmol/L, Median (IQR)	5.4 (4.6–6.5)	6.2 (5.2–8.25)	8.7 (6.4–14)	15.85 (12–20)	23.8 (16.6–29.8)	**<0.001**
Creatinine, mmol/L, Mean (SD)	64.9 (12.1)	97.2 (16.3)	144.7 (32.1)	277.1 (58.7)	689.9 (261.2)	**<0.001**
GFR, ml/min/1.73 m^2, mean (SD)	105.7 (15.2)	69.8 (7.3)	41.9 (8.2)	19.7 (5.0)	7.6 (3)	**<0.001**
RBC, T/L, mean (SD)	4.0 (0.9)	3.9 (0.8)	4.1 (0.6)	3.5 (0.8)	3.1 (0.6)	**<0.001**
Hemoglobin, g/L, mean (SD)	115.6 (23.4)	114.7 (23.1)	113.4 (23.4)	96.5 (18.6)	88.5 (17.6)	**<0.001**
Cholesterol, mmol/L, median (IQR)	5.1 (4.3–6.7)	5.2 (4.5–6.35)	5.1 (3.9–5.8)	4.55 (4.27–5.8)	4.6 (4–5.4)	**0.0298**
Triglyceride, mmol/L, median (IQR)	2.1 (1.6–3.0)	2.2 (1.8–3.35)	2.1 (1.8–2.8)	2.1 (1.66–2.8)	2.3 (2–2.8)	0.6151
HDL-C, mmol/L, median (IQR)	1.1 (0.9–1.3)	1 (0.9–1.3)	0.9 (0.9–1.1)	1 (0.9–1.1)	1 (0.9–1.1)	0.3869
LCL-C, mmol/L, median (IQR)	2.7 (2.3–3.6)	3.25 (2.4–3.85)	3.1 (2.8–3.2)	3.1 (2.8–3.5)	3.1 (2.6–3.4)	0.6938
Plasma albumin, g/L, mean (SD)	29.5 (9.8)	30.7 (8.6)	35.8 (5.5)	34.0 (7.4)	35.6 (5.6)	**0.0106**
Urine protein, g/L, median (IQR)	0.3 (0.15–10)	0.75 (0.3–3)	0.3 (0.15–1)	1.6 (1–3)	1 (0–3)	0.9304
Ferritin, ng/ml, median (IQR)	368 (330–510)	382.5 (300–496)	432 (340–638)	574.4 (428–851)	530.2 (304–907.9)	**0.0074**
Transferrin, ng/ml, median (IQR)	198 (160–207)	193 (162–210)	198 (170–210)	173.5 (147–190)	183 (160–200)	0.2612
Plasma protein, g/L, median (IQR)	62 (58–67)	65 (56–70)	66 (61–71)	65 (60–73.2)	68 (64–72.6)	**<0.001**

Values are mean (SD), *n* (%), or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi-square test was used to assess the difference in categorical variables across the CKD stages. A *p* value <0.05 (bold) was considered to be statistically significant.

protein (g/L) and higher ferritin (ng/ml) ($p < 0.05$). No statistical difference in serum triglyceride, HDL-C, LDL-C, transferrin, and urine protein was found among CKD stages.

Figure 2 shows the progressive reduction of LV and LA strain and increase in LA volume according to the CKD stages. The analysis of echocardiographic findings in Table 3 shows that in CKD patients, the stage of renal failure was associated with the increase in LVDs, LVDd, LV mass, E/e' ratio, TR max, LVEDV and LVESV ($p < 0.05$). The differences in GLS (%) ($p < 0.001$) among different CKD groups were also observed.

The analysis of LA volume and strain in Table 4 shows that higher severity of CKD stages was associated with higher values of LAd (mm) ($p < 0.001$), LA strain in four-chamber view (LAS 4C; %) ($p < 0.001$), LA strain in two-chamber view (LAS 2C; %) ($p < 0.001$), LA volume in four-chamber view (LAS 4C; %) ($p < 0.001$), LA volume in two-chamber view (LAV 2C; %) ($p < 0.001$), LA volume index (LAVi; ml/m^2) ($p < 0.001$), LA volume before A wave (LAV preA; ml) ($p < 0.001$). The significant reduction in the LA reservoir strain (LASr; %) ($p < 0.001$), while the remarkable increase (less negative) was observed in the LA conduit strain (LAScd; %) ($p < 0.001$) among different CKD groups. The alteration of LASct across CKD stages was not significant ($p = 0.2144$).

Table 5 shows the results of multivariate regression models. Among echocardiographic parameters, LVEF ($\beta = 0.068$; $p = 0.022$), LV mass ($\beta = 0.112$; $p = 0.001$) and LASr ($\beta = -0.077$; $p = 0.034$) were found to be significantly correlated with GFR reduction.

4. Discussion

This study contributed to the current body of literature about the progressive reduction of LV and LA strain and increase in

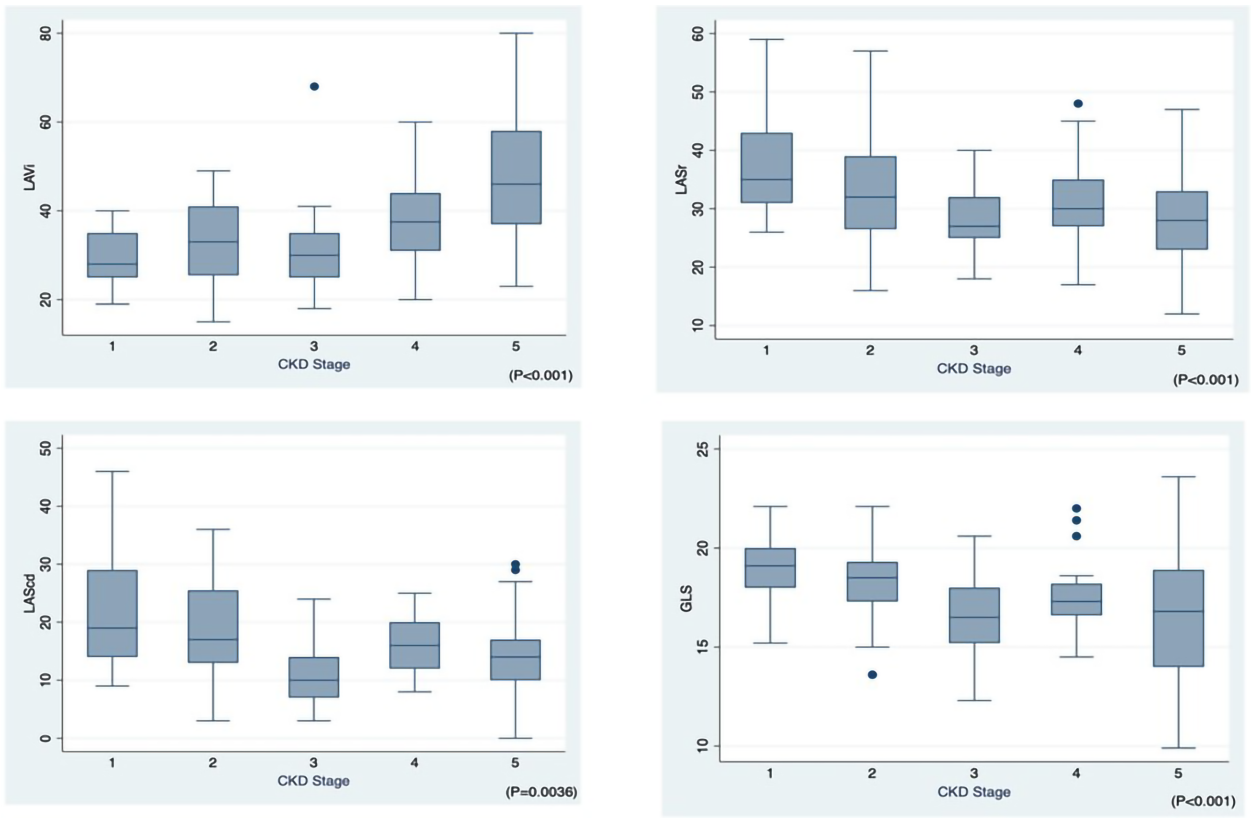


FIGURE 2
Left atrial volume index (LAVi), left atrial phasic strains reservoir phase (LASr), left atrial phasic strains conduit phase (LAScd), global longitudinal strain (GLS) across CKD stages 1–5.

TABLE 3 Left ventricular volume and function across the CKD stages.

	Stage 1 ($n = 21$)	Stage 2 ($n = 28$)	Stage 3 ($n = 27$)	Stage 4 ($n = 22$)	Stage 5 ($n = 71$)	p-value
LVDd, mm, mean (SD)	45.7 (3.2)	45.4 (3.0)	43.5 (4.9)	47.7 (3.6)	48.7 (5.1)	**<0.001**
LVDs, mm, mean (SD)	29.0 (2.8)	29.6 (2.9)	27.6 (5.1)	30.5 (2.7)	32.3 (4.9)	**<0.001**
LVEF, %, median (IQR)	64 (63–67)	65 (62.5–67)	63 (59–65)	65 (62–66)	63 (60–66)	**0.0210**
LVEDV, ml mean (SD)	66.2 (15.1)	71.4 (12.9)	62.4 (17.7)	80.7 (22.2)	91.9 (30.6)	**<0.001**
LVESV, ml mean (SD)	21.8 (6.5)	25.5 (5.8)	23.1 (8.0)	28.45 (9.6)	35.4 (14.8)	**<0.001**
LV mass, g/m^2, median (IQR)	89 (76–114)	91 (82–103.5)	93 (80–123)	107 (88–146)	154 (121–190)	**<0.001**
GLS, %, mean (SD)	−19.0 (1.7)	−18.2 (2.1)	−16.6 (1.9)	−17.7 (1.8)	−16.5 (2.9)	**<0.001**
E, cm/s, median (IQR)	78 (60–94)	72 (54–93)	60 (52–72)	71.5 (62–83)	78 (65–96)	**0.0257**
A, cm/s, median (IQR)	69 (62–83)	70.5 (58.5–95.5)	81 (74–87)	84.5 (75–104)	90 (76–113)	**<0.001**
e', cm/s, mean (SD)	11.6 (3.6)	10.2 (3.3)	8.2 (1.9)	9.1 (1.8)	8.2 (2.3)	**<0.001**
E/e', mean (SD)	6.8 (1.6)	7.3 (3.1)	7.9 (2.3)	8.2 (3.1)	10.7 (4.3)	**<0.001**
IVRT, ms, median (IQR)	110 (103–120)	111 (101–122)	119.2 (108–126)	110 (104–120)	107 (93–116)	0.0630
TR max, cm/s, mean (SD)	2.3 (0.2)	2.3 (0.2)	2.3 (0.3)	2.5 (0.3)	2.6 (0.3)	**<0.001**
s', cm/s, mean (SD)	9.1 (0.7)	9.3 (0.9)	9.3 (1.0)	9.9 (1.3)	10.4 (1.3)	**<0.001**
PAPs, mmHg, mean (SD)	29.6 (3.3)	31.0 (4.6)	31.1 (4.1)	34.6 (6.8)	36.7 (6.2)	**<0.001**

Values are mean (SD), n (%), or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi-square test was used to assess the difference in categorical variables across the CKD stages. A p value <0.05 (bold) was considered to be statistically significant.

volume according to the CKD stages. By speckle tracking echocardiography, the current study also found the associations between left atrial reservoir function assessed (LASr), left ventricular ejection fraction (LVEF) and left ventricular mass index (LV mass) and the decline of kidney filtration function (GFR).

Left ventricular hypertrophy, dilatation, and dysfunction are the most common cardiac abnormalities in CKD patients (18). Previous studies found that left ventricular hypertrophy was the first prominent cardiac impairment due to a consistently high level of plasma urea (19), which is progressively more severe across CDK stages (20), earlier than dilatation and dysfunction (6, 18). In our

TABLE 4 Left atrial volume and strain across the CKD stages.

	Stage 1 ($n = 21$)	Stage 2 ($n = 28$)	Stage 3 ($n = 27$)	Stage 4 ($n = 22$)	Stage 5 ($n = 71$)	p-value
LAd, mm, mean (SD)	33.6 (3.7)	34.6 (4.7)	33.8 (4.7)	35.7 (5.2)	39.3 (5.0)	**<0.001**
LAS 4C, %, median (IQR)	15.2 (15.2–15.2)	17.6 (16.2–18.1)	14.3 (13.7–15.2)	20.1 (19.9–20.2)	21.3 (18.0–24.2)	**<0.001**
LAS 2C, %, median (IQR)	14.0 (14.0–14.0)	15.7 (14.3–16.5)	14.2 (13.4–15.9)	17.9 (17.5–18.2)	19.9 (16.7–22.5)	**<0.001**
LAV 4C, %, mean (SD)	41.3 (6.1)	48.4 (12.4)	42.6 (17.3)	62.5 (11.3)	70.9 (23.8)	**<0.001**
LAV 2C, %, mean (SD)	41.1 (6.9)	44.9 (10.7)	40.0 (11.8)	57.3 (11.4)	63.9 (18.4)	**<0.001**
LAVi, ml/m^2, mean (SD)	29.1 (6.0)	33.25 (9.5)	30.9 (9.3)	38.3 (10.3)	48.1 (13.1)	**<0.001**
LASr, %, mean (SD)	37.4 (8.3)	33.5 (10.0)	27.6 (5.6)	31.4 (7.2)	28.1 (7.9)	**<0.001**
LAScd, %, mean (SD)	−22 (9.8)	−18.6 (8.5)	−10.9 (5.3)	−15.8 (4.8)	−13.9 (6.7)	**<0.001**
LASct, %, mean (SD)	−15.5 (6.0)	−15.1 (5.1)	−16.5 (6.6)	−15.5 (4.5)	−14.3 (5.4)	0.2144

Values are mean (SD), *n* (%), or median (interquartile range). The Jonckheere Terpstra test was used to assess for trend in continuous variables across the CKD stages. The chi-square test was used to assess the difference in categorical variables across the CKD stages. A p value <0.05 (bold) was considered to be statistically significant.

TABLE 5 Multivariate analysis to determine independent echocardiographic predictors of reduced GFR.

Predictors	Beta	p	Coefficient	Robust standard error
LVDd, mm	−0.091	0.065	−0.028	0.015
LVDs, mm	0.052	0.238	0.016	0.014
LVEF, %	0.068	**0.022**	0.020	0.008
LV mass, g/m^2	0.112	**0.001**	0.003	0.009
GLS, %	−0.007	0.804	−0.004	0.017
E, cm/s	−0.039	0.093	−0.002	0.0014
E/e'	0.035	0.071	0.107	0.059
TR max, cm/s	0.022	0.395	0.106	0.124
LAd, mm	0.084	0.129	0.0284	0.0185
LAVi, ml/m^2	−0.006	0.879	−0.007	0.004
LASr, %	−0.077	**0.034**	−0.021	0.009
LAScd, %	0.011	0.770	0.002	0.007
LASct, %	−0.009	0.825	−0.003	0.016

LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LV, left ventricle; GLS, global longitudinal strain; E, e wave velocity; TR max, tricuspid regurgitation maximal velocity, cm/s; LAd, left atrial diameter; LAVi, left atrial volume index; LASr, left atrial strain reservoir; LAScd, left atrial strain conduit; LASct, left atrial strain contraction. A p value <0.05 (bold) was considered to be statistically significant.

study, GLS increased with the severity of CKD. This phenomenon could be explained that LV strain was sensitive to the preload and fluid overload condition and uremic cardiomyopathy (21).

The LV pathological changes may cause LA function impairment as there is a close connection between the two chambers. The left atrium is a more sensitive chamber to fluid overload and increased LV filling pressure among CKD patients (4). Left atrial volume index (LAVi) is an important predictor of cardiovascular and heart failure outcomes (22, 23) and left atrial strain also plays a novel maker in CKD (24). During the cardiac cycle, the left atrium plays as a reservoir to accumulate blood from pulmonary veins. After the mitral valve opens starting the diastolic phase, it serves as a conduit to let blood from LA to LV and the remaining blood in the LA will be pushed to LV by LA contractile force (25). In our speckle tracking echocardiography study, LA reservoir (LASr) and LA conduit (LAScd) function declined in parallel with kidney function, however, the LA pump function (LASct) did not follow this trend. In addition, this study found that among left atrial speckle tracking parameters, LA reservoir conduit functions was an important indicator that was associated with the severity of CKD. Therefore, it can be implied that these echocardiographic speckle-tracking parameters might be more sensitive to fluid overload at the early stages of CKD. This finding was similar to a previous report that worsening renal function was independently related to impaired LV and LA strain in CKD patients, and eGFR was associated with GLS, LASr and LAScd (26). However, in our study, we found that LVEF, and LV mass parameters but not LV GLS were predictors of GFR decline. In literature, GLS has been widely demonstrated its superior prognostic values in projecting cardiovascular adverse events or risk of mortality among CKD patients (27), even in comparison with LVEF (28). However, its role in predicting CKD progression is debatable. A recent study by Rupal Mehta et al. (2023) on 2,134 patients found that left ventricular longitudinal strain was not an independent predictor for a 30% reduction in eGFR over 7 years (29). Meanwhile, Ramesh Sankaran et al. indicated that hemodialysis patients were more likely to have impaired LVEF and GLS in comparison with those undergoing drug therapy (30). Indeed, the issue that patients having normal LVEF but abnormal GLS had been reported elsewhere (29, 31), which could be explained by the matter that the concept of longitudinal strain pertains to the assessment of contractile functionality at the tissue level along a specific axis, whereas LVEF expressed that alterations in left ventricular volumes resulting from myocardial contraction (32). In addition, our finding could be explained by the matter of small sample size and the homogeneity of our samples. This controversial issue should be elaborated on further research with larger sample sizes and in multiple centers. Hayer et al. (33) tried to understand the myocardial abnormalities across stages of CKD using the magnetic resonance imaging technique and they found that native myocardial T1 times (a biomarker of diffuse fibrosis) increased from stage 2–5, after being adjusted to hypertension and aortic distensibility. They also demonstrated that eGFR was a significant predictor of native myocardial fibrosis (33). Collectively, findings from our study suggest that LA strain parameters should be collected by speckle tracking echocardiography together with the measurement of LV mass and LV ejection function as it might indicate earlier pathophysiological changes which could be served as a maker to prevent or slow the progression of CKD.

Our study has several limitations. This study was unable to show changes in LV and LA over time due to its cross-sectional design. Secondly, the small sample size in this study hindered the

ability to apply findings to the general population. In addition, the overwhelm of patients in CKD stage 5 might cause selection bias. Thirdly, although no difference in the selection of *P* wave as the time reference for defining zero-baseline for both LV and LA strain curves in comparison with the use of ventricular end-diastole, further research that compares both approaches should be elucidated. In addition, 2D-STE analysis has several intrinsic limitations, such as the dependency on the temporal stability of tracking patterns, the need for high-quality grey-scale images for reducing inter- and intra-observer variability of tracking data and finally a relevant intervendor variability. Finally, taking into consideration the fact that individuals with advanced stages of CKD demonstrated a higher likelihood of presenting with more severe hypertension, it is plausible that the efficacy of hypertension treatment could influence the outcomes of our study.

5. Conclusion

LV and LA volume and strain assessed by speckle tracking echocardiography were associated with advancing CKD stages. LV mass, LV ejection fraction and LA reservoir might be used to suggest the decline of kidney glomerular filtration function. They could be used at the earlier stages of CKD patients for better follow-up of GFR decline.

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 study protocol was approved by the Institutional Review Board of Bach Mai hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HN and CD: design study and analyse data; DD, LDD, LHD, and HD: data collection; All authors contributed to the article 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

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.2023.1197427/full#supplementary-material

References

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl.* (2022) 12(1):7–11. doi: 10.1016/j.kisu.2021.11.003

2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* (2010) 375(9731):2073–81. doi: 10.1016/S0140-6736(10)60674-5

3. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int.* (2011) 80(12):1258–70. doi: 10.1038/ki.2011.368

4. Paoletti E, Zoccali C. A look at the upper heart chamber: the left atrium in chronic kidney disease. *Nephrol Dial Transplant.* (2013) 29(10):1847–53. doi: 10.1093/ndt/gft482

5. Hensen LCR, Goossens K, Delgado V, Rotmans JI, Jukema JW, Bax JJ. Prognostic implications of left ventricular global longitudinal strain in predialysis and dialysis patients. *Am J Cardiol.* (2017) 120(3):500–4. doi: 10.1016/j.amjcard.2017.04.054

6. Mark PB, Johnston N, Groenning BA, Foster JE, Blyth KG, Martin TN, et al. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int.* (2006) 69(10):1839–45. doi: 10.1038/sj.ki.5000249

7. Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP. Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. *JACC Cardiovasc Imaging.* (2014) 7(7):703–14. doi: 10.1016/j.jcmg.2013.09.025

8. Doan TT, Srivaths P, Liu A, Kevin Wilkes J, Idrovo A, Akcan-Arikan A, et al. Left ventricular strain and left atrial strain are impaired during hemodialysis in children. *Int J Cardiovasc Imaging.* (2021) 37(12):3489–97. doi: 10.1007/s10554-021-02350-9

9. Levin A, Stevens P, Bilous RW, Coresh J, Francisco A, Jong PE, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* (2013) 3:1–150. doi: 10.1038/kisup.2012.73

10. Barberato SH, Pecoits-Filho R. Usefulness of left atrial volume for the differentiation of normal from pseudonormal diastolic function pattern in patients on hemodialysis. *J Am Soc Echocardiogr.* (2007) 20(4):359–65. doi: 10.1016/j.echo.2006.09.002

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. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. (2016) 29(4):277–314. doi: 10.1016/j.echo.2016.01.011

13. Negishi K, Negishi T, Kurosawa K, Hristova K, Popescu BA, Vinereanu D, et al. Practical guidance in echocardiographic assessment of global longitudinal strain. *JACC Cardiovasc Imaging*. (2015) 8(4):489–92. doi: 10.1016/j.jcmg.2014.06.013

14. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. (2016) 17(4):355–83. doi: 10.1093/ehjci/jev354

15. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. (2018) 19(6):591–600. doi: 10.1093/ehjci/jey042

16. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. *Cardiovasc Diagn Ther*. (2018) 8(1):29–46. doi: 10.21037/cdt.2017.06.08

17. Cameli M, Lisi M, Righini FM, Mondillo S. Novel echocardiographic techniques to assess left atrial size, anatomy and function. *Cardiovasc Ultrasound*. (2012) 10(1):4. doi: 10.1186/1476-7120-10-4

18. Zoccali C, Benedetto F, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, et al. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol*. (2004) 15:1029–37. doi: 10.1097/01.ASN.0000117977.14912.91

19. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int*. (1989) 36(2):286–90. doi: 10.1038/ki.1989.192

20. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*. (2012) 23(10):1725–34. doi: 10.1681/ASN.2012020145

21. Wang X, Hong J, Zhang T, Xu D. Changes in left ventricular and atrial mechanics and function after dialysis in patients with end-stage renal disease. *Quant Imaging Med Surg*. (2021) 11(5):1899–908. doi: 10.21037/qims-20-961

22. Kim SJ, Han SH, Park JT, Kim JK, Oh HJ, Yoo DE, et al. Left atrial volume is an independent predictor of mortality in CAPD patients. *Nephrol Dial Transplant*. (2011) 26(11):3732–9. doi: 10.1093/ndt/gfr118

23. Rossi A, Temporelli PL, Quintana M, Dini FL, Ghio S, Hillis GS, et al. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE heart failure). *Eur J Heart Fail*. (2009) 11(10):929–36. doi: 10.1093/eurjhf/hfp112

24. Tanasa A, Tapoi L, Ureche C, Sascau R, Statescu C, Covic A. Left atrial strain: a novel "biomarker" for chronic kidney disease patients? *Echocardiography*. (2021) 38 (12):2077–82. doi: 10.1111/echo.15259

25. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr*. (2011) 12(6):421–30. doi: 10.1093/ejechocard/jeq175

26. Iwama K, Nakanishi K, Daimon M, Yoshida Y, Sawada N, Hirose K, et al. Chronic kidney disease and subclinical abnormalities of left heart mechanics in the community. *Eur Heart J Open*. (2021) 1(3):1–5. doi: 10.1093/ehjopen/oeab037

27. Zhang T, Li J, Cao S. Prognostic value of left ventricular global longitudinal strain in chronic kidney disease patients: a systematic review and meta-analysis. *Int Urol Nephrol*. (2020) 52(9):1747–56. doi: 10.1007/s11255-020-02492-0

28. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Burrage M, Leano R, et al. Left ventricular global longitudinal strain (GLS) is a superior predictor of all-cause and cardiovascular mortality when compared to ejection fraction in advanced chronic kidney disease. *PLoS One*. (2015) 10(5):e0127044. doi: 10.1371/journal.pone.0127044

29. Mehta R, Buzkova P, Patel H, Cheng J, Kizer JR, Gottdiener JS, et al. Cardiac mechanics and kidney function decline in the cardiovascular health study. *Kidney360*. (2023) 4(5):622–30. doi: 10.34067/KID.0000000000000100

30. Sankaran R, Ramalakshmi S, Uppupetai Ganeshbabbu MB, Jayakumar M, Ramamurthy MT, Balakrishnan VK, et al. Left ventricular global longitudinal strain in patients with chronic kidney disease with and without renal replacement therapy: a cross-sectional study. *J Indian Coll Cardiol*. (2022) 12(2):60–5. doi: 10.4103/jicc.jicc_48_21

31. Hensen LCR, Goossens K, Delgado V, Abou R, Rotmans JI, Jukema JW, et al. Prevalence of left ventricular systolic dysfunction in pre-dialysis and dialysis patients with preserved left ventricular ejection fraction. *Eur J Heart Fail*. (2018) 20 (3):560–8. doi: 10.1002/ejhf.1077

32. Ikonomidis I, Andreou I, Parissis J, Iliodromitis E. Prognostic significance of global longitudinal strain in chronic kidney disease: the evidence is building. *Eur J Heart Fail*. (2018) 20(3):569–71. doi: 10.1002/ejhf.1114

33. Hayer MK, Radhakrishnan A, Price AM, Liu B, Baig S, Weston CJ, et al. Defining myocardial abnormalities across the stages of chronic kidney disease: a cardiac magnetic resonance imaging study. *JACC Cardiovasc Imaging*. (2020) 13 (11):2357–67. doi: 10.1016/j.jcmg.2020.04.021

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 22 September 2023
DOI 10.3389/fcvm.2023.1257734

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Mohammed Faisaluddin,
Rochester General Hospital, United States
Amitoj Singh,
University of Arizona, United States

*CORRESPONDENCE
Roland Kassab
✉ rolandoka@yahoo.fr

†These authors have contributed equally to this work

RECEIVED 12 July 2023
ACCEPTED 11 September 2023
PUBLISHED 22 September 2023

CITATION
Kassab J, Gebrael G, Chedid El Helou M, El Dahdah J, Haroun E, Kassab R, Abou Ali S, Khabbaz Z and Kassab R (2023) Case report: Primary cardiac lymphoma manifesting as superior vena cava syndrome.
Front. Cardiovasc. Med. 10:1257734.
doi: 10.3389/fcvm.2023.1257734

Case report: Primary cardiac lymphoma manifesting as superior vena cava syndrome

Joseph Kassab[1], Georges Gebrael[2], Michel Chedid El Helou[1†], Joseph El Dahdah[1†], Elio Haroun[1], Rebecca Kassab[2], Saad Abou Ali[3], Ziad Khabbaz[4] and Roland Kassab[4*]

[1]Cleveland Clinic Foundation, Heart Vascular and Thoracic Institute, Cleveland, OH, United States, [2]Department of Medicine, Saint Joseph University of Beirut, Achrafieh, Beirut, Lebanon, [3]Department of Cardiovascular Medicine, Sacre Coeur Hospital, Baabda, Beirut, Lebanon, [4]Department of Cardiovascular Medicine, Hotel-Dieu De France, Achrafieh, Beirut, Lebanon

A 64-year-old man presented with symptoms indicative of superior vena cava syndrome. Imaging work-up revealed an obstructing right atrial mass, which was subsequently excised and diagnosed as primary cardiac lymphoma. Post-surgery, the patient showed significant clinical improvement and was started on a chemotherapy regimen with complete remission at 1 year.

KEYWORDS

lymphoma, cardiac lymphoma, primary cardiac lymphoma, superior vena cava syndrome, diffuse large B cell lymphoma

History of presentation

A previously healthy 64-year-old man, presented to the emergency department with 2 weeks of increasing exertional dyspnea, worsening orthopnea, facial and arm swelling, and a nonproductive cough. Vital signs on admission were within normal limits. On physical examination, the patient demonstrated marked facial and upper extremity edema, as well as distended neck veins. Additionally, signs of plethora and cyanosis of the face were noted, with an increase in jugular venous pressure on cardiovascular examination.

Past medical history

The patient had no significant past medical history.

Differential diagnosis

Given the patient's symptoms suggestive of superior vena cava syndrome (SVC), a broad differential diagnosis were considered. Malignant causes included primary or secondary cardiac tumors, lung cancer, mediastinal tumors, or lymphoma, which may obstruct or compress the superior vena cava. Non-malignant etiologies encompassed SVC thrombosis, aortic aneurysm, or fibrosing mediastinitis. Cardiopulmonary conditions such as heart failure, pericardial disease, and pulmonary hypertension were also suggested, given the symptoms of dyspnea and orthopnea.

Investigations

The patient underwent a chest CT-scan, followed by a confirmatory transesophageal echocardiogram (TEE) which revealed the presence of a prominent, heterogeneous, partially non-enhancing, right atrial mass, measuring $66 \times 41 \times 37$ mm, partially disrupting inferior vena cava flow and obstructing the superior vena cava (**Figures 1**, **2**, **Supplementary Video S1**). A filling defect was also noted in the proximal right pulmonary artery, suggesting emboli origination from the tumor. A whole-body positron emission tomography/computed tomography (PET/CT) showed pronounced uptake of fluorine-18 fluorodeoxyglucose in the right atrium, with no other metabolically active lesions (**Figure 3**, **Supplementary Figure S1**).

Management

Given the high risk of deteriorating clinical condition, surgical removal of the mass was planned and successfully executed. The surgical specimen (**Supplementary Figure S2**) was then sent to the pathology lab for microscopic examination. This examination showed a diffuse proliferation of large atypical lymphocytes exhibiting mitotic activity and apoptosis along with extensive areas of necrosis. Immunohistochemistry staining tested positive for CD20 (**Figure 4**), leading to a diagnosis of right atrial diffuse large B cell lymphoma, non-germinal center (activated) type. This confirmed the diagnosis of primary cardiac lymphoma (PCL). Following surgery, the patient's clinical condition improved significantly, and he was subsequently started on a R-CHOP chemotherapy regimen (intravenous rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone).

Discussion

While secondary cardiac lymphomas are relatively frequent and can contribute to 20% of extra nodal non Hodgkin lymphomas (NHL), primary cardiac lymphoma (PCL) is extremely rare and represents only 1%–2% of all heart tumors (1), since the cardiac tissue contains little to no lymphocytes. Almost all of PCLs appear to be derived from B-cell lineage with diffuse large B cell lymphoma (DLBCL) being the most common type, whereas other types such as Burkitt lymphoma or chronic lymphocytic leukemia/small lymphocytic lymphoma are less likely to be reported (1). Although immunosuppression (e.g., transplant recipients, HIV patients, immunosuppressant drugs) could be a risk factor for developing PCL, it usually occurs in immunocompetent adults with a median age of presentation of 55–65 years and 65%–85% of all cases in males (2)—features compatible with our patient. PCL may present with a wide range of symptoms, generally depending on the site of involvement of the heart, size and growth rate. These symptoms may encompass signs of heart failure, such as shortness of breath and pedal edema, as well as chest pain, arrhythmia (particularly atrial fibrillation and AV block), constitutional symptoms (e.g., fever, chills, night sweats, weight loss), and SVC syndrome as was seen in our patient (2, 3). All heart chambers as well as the interatrial and the interventricular septum may be involved; however, the tumor tends to arise in the wall of the right heart, specifically in the right atrium, with epicardial and pericardial involvement in about 50% of cases (4).

Differential diagnoses include benign myxoma (the most common type of cardiac tumor), intracardiac thrombi (in the setting of hypokinetic dilated cardiomyopathy) and angiosarcoma, (the most common malignant heart tumor, usually found in the

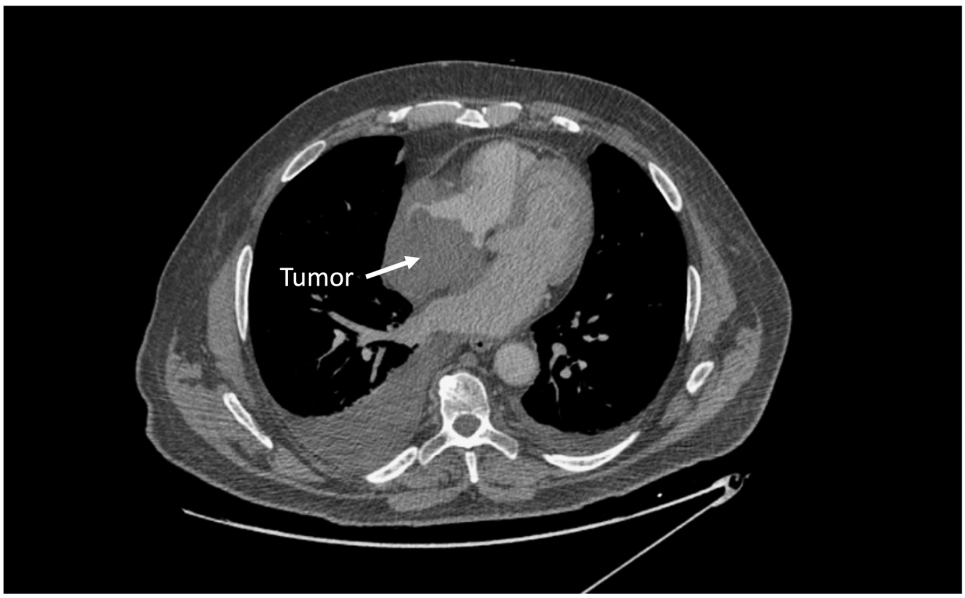


FIGURE 1
Chest CT scan demonstrating a large right atrial mass.

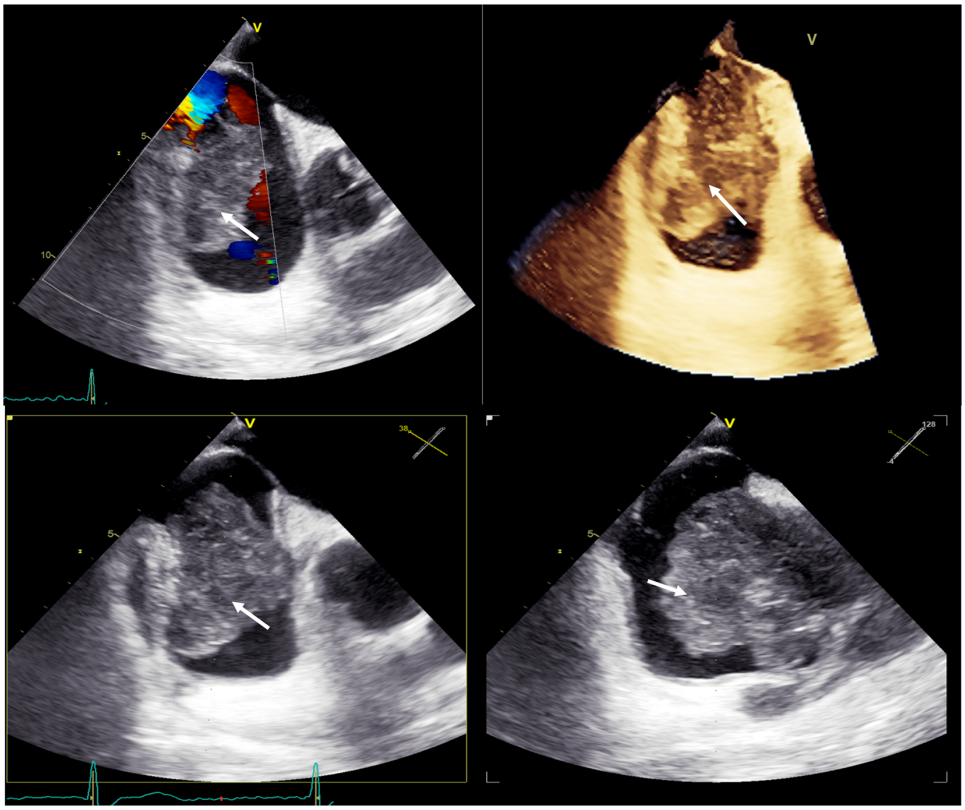


FIGURE 2
Baseline transesophageal echocardiography with 3D reconstruction, showing a large tumor arising from the lateral wall of the right atrium (white arrows).

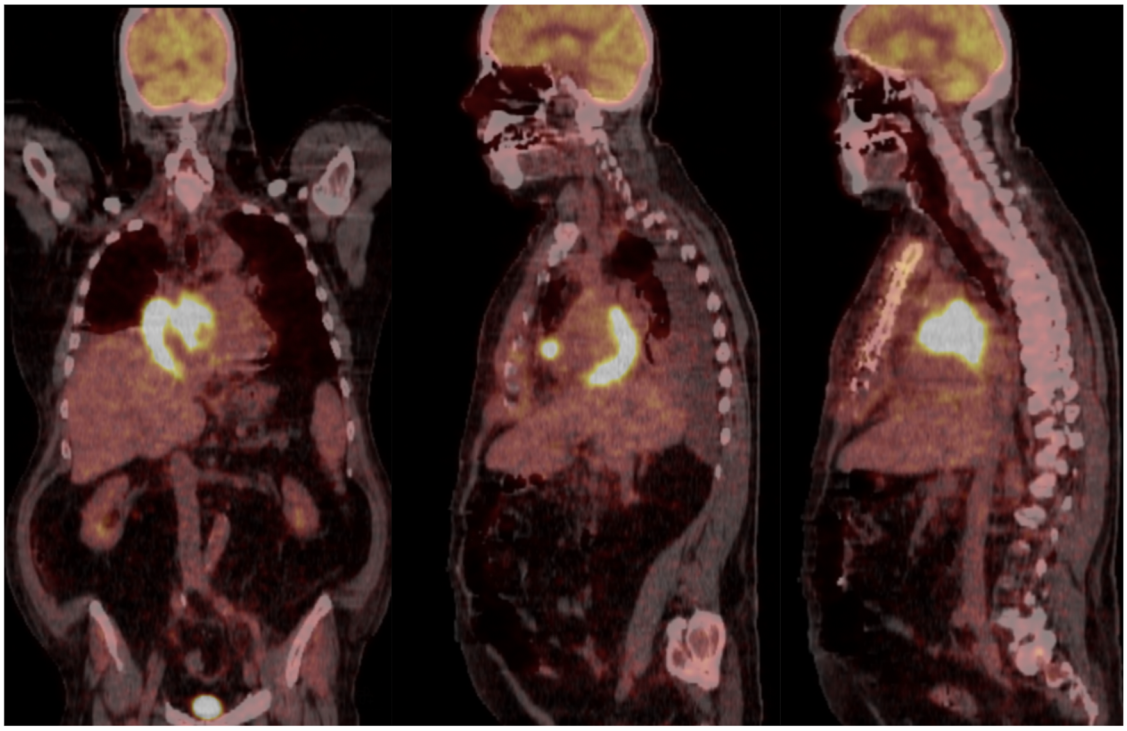


FIGURE 3
Whole-body positron emission tomography/computed tomography (PET/CT) in coronal and sagittal views showing pronounced uptake of fluorine-18 fluorodeoxyglucose in the right atrium, with no other metabolically active lesions.

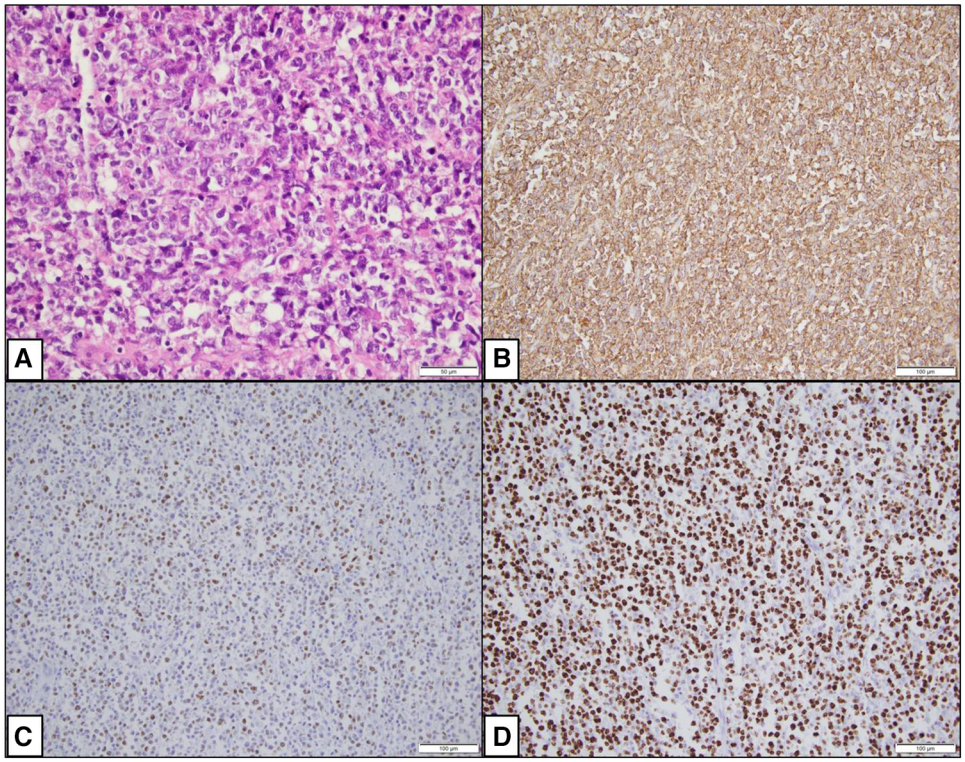


FIGURE 4
Photomicrographs showing histopathological changes. (**A**) (H&E × 400): Microscopy shows a diffuse proliferation of large atypical cells. (**B**) (IHC × 200): CD20 is positive in the large lymphocytes. (**C**) (IHC × 200): MUM1 is positive in the large lymphocytes. (**D**) (IHC × 200): Ki67 is approximately 95%.

left cavities) (5). Initial evaluation of cardiac masses often involves noninvasive multimodality imaging, including 2D or 3D echocardiography, MRI, and contrast CT scan, depending on diagnostic suspicion (6). As was done with our patient, transesophageal echocardiography is a key initial diagnostic tool for differentiating diagnosis and guiding further imaging and management. Cardiac CT scan and MRI are used to determine the extent of heart involvement and guide biopsy and/or surgical approach. PET scan may also be performed to assess for primary tumors or extracardiac involvement—which was negative in this case confirming the diagnosis of PCL. Histopathological confirmation is required for definitive diagnosis, and cytological examination is sometimes helpful in the presence of pericardial effusion.

The mainstay of PCL treatment relies on chemotherapy, using the combination of Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP regimen), which has shown a response rate of 79%–87% (5). Prompt initiation of chemotherapy often provides symptomatic relief as well as complete remission. Side effects include tumor lysis syndrome and sepsis in around 10% of cases. In addition, chemotherapy can lead to massive thromboembolism, cardiac wall perforation, ventricular septal rupture, life threatening arrhythmias and pericardial effusion. For these reasons, some reports suggest that reduced doses of chemotherapy "R-mini-CHOP" in the initial course of treatment could reduce the risk of sudden cardiac death (7). Radiation therapy may be used in combination with chemotherapy, particularly in refractory cases, and reports have shown improved survival. However, it has some limitations given the risk of radiation-induced heart disease including pericarditis, cardiomyopathy, coronary artery disease, conduction defects and diastolic dysfunction (8). While surgical management is not the mainstay of treatment, prompt surgical debulking is indicated in patients with acute and severe presentations, including SVC syndrome (as in our patient) (9) and rapidly progressive heart failure (10). The overall prognosis of PCL is generally favorable, with a remission rate of 61% following treatment with chemotherapy alone (10).

Follow up

The patient is currently in remission at 1-year follow-up.

Conclusion

PCL is an extremely rare neoplasm. While chemotherapy remains the mainstay of treatment, surgery could be considered for urgent symptomatic relief.

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.

Ethics statement

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

JK: Writing – original draft, Writing – review & editing. GG: Writing – original draft, Writing – review & editing. MC: Writing – original draft, Writing – review & editing. JE: Writing – original draft, Writing – review & editing. EH: Writing – original draft, Writing – review & editing. SA: Writing – review & editing. ZK: Writing – review & editing. RK: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.2023.1257734/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Whole-body positron emission tomography/computed tomography (PET/CT) in axial view showing pronounced uptake of fluorine-18 fluorodeoxyglucose in the right atrium, with no other metabolically active lesions.

SUPPLEMENTARY FIGURE 2
Surgical specimen of the right atrial mass (white arrow).

SUPPLEMENTARY VIDEO 1
Baseline transesophageal echocardiography, showing a large tumor arising from the lateral wall of the right atrium invading and causing significant obstruction of the superior vena cava.

References

1. Miguel CE, Bestetti RB. Primary cardiac lymphoma. *Int J Cardiol.* (2011) 149:358–63. doi: 10.1016/j.ijcard.2010.02.016

2. Csizmar CM, Sachs Z, Cayci Z, Bu L, Linden MA. Primary cardiac lymphoma: three case reports and a review of the literature. *Open J Blood Dis.* (2021) 11:120–32. doi: 10.4236/ojbd.2021.114012

3. Ikeda H, Nakamura S, Nishimaki H, Masuda K, Takeo T, Kasai K, et al. Primary lymphoma of the heart: case report and literature review. *Pathol Int.* (2004) 54:187–95. doi: 10.1111/j.1440-1827.2003.01606.x

4. Carras S, Berger F, Chalabreysse L, Callet-Bauchut E, Cordier JF, Salles G, et al. Primary cardiac lymphoma: diagnosis, treatment and outcome in a modern series. *Hematol Oncol.* (2017) 35:510–9. doi: 10.1002/hon.2301

5. Petrich A, Cho SI, Billett H. Primary cardiac lymphoma. *Cancer.* (2011) 117:581–9. doi: 10.1002/cncr.25444

6. Tyebally S, Chen D, Bhattacharyya S, Mughrabi A, Hussain Z, Manisty C, et al. Cardiac tumors. *JACC CardioOncol.* (2020) 2:293–311. doi: 10.1016/j.jaccao.2020.05.009

7. Linschoten M, Kamphuis JAM, van Rhenen A, Bosman LP, Cramer MJ, Doevendans PA, et al. Cardiovascular adverse events in patients with non-hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP): a systematic review and meta-analysis. *Lancet Haematol.* (2020) 7:e295–308. doi: 10.1016/S2352-3026(20)30031-4

8. Al Mawed M, Brockmeier J, Haertel D, Ellermeier M, Hartmann F, Gielen S. From inoperable to back to life: a case report of successfully treated obstructive right ventricular primary cardiac lymphoma. *Eur Heart J Case Rep.* (2022) 6:ytac051. doi: 10.1093/ehjcr/ytac051

9. Johri A, Baetz T, Isotalo PA, Nolan RL, Sanfilippo AJ, Ropchan G. Primary cardiac diffuse large B cell lymphoma presenting with superior vena cava syndrome. *Can J Cardiol.* (2009) 25:e210–2. doi: 10.1016/S0828-282X(09)70110-2

10. Jonavicius K, Salcius K, Meskauskas R, Valeviciene N, Tarutis V, Sirvydis V. Primary cardiac lymphoma: two cases and a review of literature. *J Cardiothorac Surg.* (2015) 10:138. doi: 10.1186/s13019-015-0348-0

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 19 October 2023
DOI 10.3389/fcvm.2023.1236144

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Hiroshi Asanuma,
Meiji University of Integrative Medicine, Japan
Jeffrey Shi Kai Chan,
Cardiovascular Analytics Group, Hong Kong SAR, China

*CORRESPONDENCE
Atsushi Tanaka
✉ tanakaa2@cc.saga-u.ac.jp
Koichi Node
✉ node@cc.saga-u.ac.jp

RECEIVED 07 June 2023
ACCEPTED 09 October 2023
PUBLISHED 19 October 2023

CITATION
Kaneta K, Tanaka A, Nakai M, Sumita Y, Kaneko H, Noguchi M and Node K (2023) Prevalence and temporal trends of prostate diseases among inpatients with cardiovascular disease: a nationwide real-world database survey in Japan.
Front. Cardiovasc. Med. 10:1236144.
doi: 10.3389/fcvm.2023.1236144

Prevalence and temporal trends of prostate diseases among inpatients with cardiovascular disease: a nationwide real-world database survey in Japan

Kohei Kaneta[1], Atsushi Tanaka[1]*, Michikazu Nakai[2], Yoko Sumita[2], Hidehiro Kaneko[3,4], Mitsuru Noguchi[5] and Koichi Node[1]*

[1]Department of Cardiovascular Medicine, Saga University, Saga, Japan, [2]Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan, [3]The Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan, [4]The Department of Advanced Cardiology, The University of Tokyo, Tokyo, Japan, [5]Department of Urology, Saga University, Saga, Japan

Introduction: Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are major prostate diseases that potentially share cardiometabolic risk factors and an elevated risk for cardiovascular disease (CVD). However, the prevalence of prostate diseases among patients with established CVD remains unclear.
Materials and methods: This nationwide retrospective study assessed the prevalence and temporal trend of prostate diseases (i.e., BPH or PCa) among patients hospitalized for CVDs in Japan. We used a claims database (the Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination), which included data on 6,078,487 male patients recorded from 1,058 hospitals between April 2012 and March 2020. We conducted the Cochran–Armitage trend test and calculated the adjusted odds ratio (aOR) with 95% confidence intervals (CIs).
Results: The prevalence of prostate diseases over the entire study period was 5.7% (BPH, 4.4%; PCa, 1.6%). When dividing the overall cohort into age categories (<65, 65–74, and ≥75 years old), the prevalence was 1.1%, 4.7%, and 9.9%, respectively (*P* for trend <0.05). In addition, the annual prevalence showed a modest increasing trend over time. Patients admitted for heart failure (HF) were significantly associated with a higher incidence of coexisting prostate diseases than those admitted for non-HF causes [aOR 1.02 (95% CI, 1.01–1.03)] or acute coronary syndrome [aOR 1.19 (95% CI, 1.17–1.22)].
Conclusions: The nationwide real-world database revealed that the prevalence of prostate diseases is increasing among patients hospitalized for CVD, particularly HF. Attention to detailed causality and continued surveillance are needed to further clarify the clinical characteristics of prostate diseases among patients with CVD.

KEYWORDS

prostate disease, benign prostate hyperplasia, prostate cancer, cardiovascular disease, acute coronary syndrome, heart failure, epidemiology, temporal trend

Introduction

Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are major prostate diseases among older men, and the global burden of these diseases continues to increase in the current aging and long-lived society (1–5). BPH is the most common cause of male lower urinary tract symptoms (LUTS) (6), adversely affecting the quality of life and cardiovascular outcomes (7). Patients with PCa also have an increased risk of developing cardiovascular diseases (CVDs) (8), which are a major cause of noncancer death among PCa survivors (9, 10).

The incidence of major CVDs, such as coronary heart disease and heart failure (HF), generally increases as age, dysregulated cardiometabolic risk factors, and inflammation increase (11–13). Furthermore, metabolic syndrome and coexisting proinflammatory status play a pivotal role in the pathogenesis of major prostate diseases, including BPH and PCa, and disrupted cardiometabolic conditions are strongly associated with an increased prevalence of these prostate diseases (14–18). Hence, prostate diseases share foundational risk factors with CVD and can represent an aspect of cardiometabolic syndrome (19). Therefore, a biological rationale for close interplay exists between such prostate diseases and CVD entities.

Numerous epidemiological and observational studies have shown an increased risk for CVD among patients with major prostate diseases (7, 8). This finding is helpful, especially for urologists (rather than cardiologists), allowing them to recognize that male patients with prostate diseases have a substantial risk for CVD and require a careful cardiovascular risk assessment in the urological care setting (20, 21). However, real-world clinical reports on the prevalence of prostate diseases among patients with entire or specific CVD are limited. Although prostate diseases are closely linked to CVD, knowledge and evidence concerning the burden of prostate diseases in the cardiovascular care setting are still insufficient.

The present study therefore assessed the burden of major prostate diseases and recent associated temporal trends among hospitalized patients with established CVD using a nationwide real-world database collected throughout Japan.

Materials and methods

Ethics

This study was approved by the Japanese Circulation Society (JCS) (No. 2020-08) and the Ethics Committee of Saga University Hospital (No. 2021-08-01 on November 01, 2021) and conducted according to the principles of the Declaration of Helsinki. The database used in this study deidentified personal information; therefore, informed consent from our study participants was not needed.

Data sources and availability

This retrospective study obtained data from the Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination (JROAD-DPC), a nationwide claims database developed by the JCS. Details in the database were previously described elsewhere (22–25). In brief, the JROAD-DPC database, which contains data from cardiovascular training facilities certified by the JCS, includes inpatients' clinical information, such as their age, sex, diagnosis, comorbidity, hospitalization duration, and discharge status. Patients' diagnoses and comorbidities were coded using the International Classification of Disease and Related Health Problems 10th version (ICD-10) codes.

Given that the JROAD-DPC dataset is owned by the JCS for the purpose of research, the data that support our findings will not be shared without JCS' permission. The dataset will be available upon reasonable request from researchers and after approval by the JCS. Inquiries are to be addressed to the JCS (contact via itdatabase@j-circ.or.jp).

Diagnoses, measurements, and definitions

In the JROAD-DPC database, each diagnosis is coded for the main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, and second-most resource-consuming diagnosis. A maximum of 10 diagnoses are coded for comorbidities encountered during admission and conditions that arise after admission.

We defined prostate diseases as BPH and PCa, coded as N40 and C61 in the ICD-10 codes, respectively, and identified them in any of the following data categories: the main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second-most resource-consuming diagnosis, comorbidities during admission, and conditions arising after admission. Complications (hypertension, diabetes, dyslipidemia, and atrial fibrillation/flutter) were identified using the Charlson comorbidity index. Furthermore, two cardiovascular causes [acute coronary syndrome (ACS) and HF] of the index hospitalization were extracted from data categories, including the main diagnosis, admission-precipitating diagnosis, and most resource-consuming diagnosis, using the ICD-10 codes I200 (unstable angina pectoris) and I21 (acute myocardial infarction) for ACS and I50 for HF. We also extracted data on the age, sex, height, weight, body mass index (BMI), and smoking status.

Study population

Of the 9,825,635 patients hospitalized for any CVDs recorded from 1,058 JCS-certified hospitals between April 2012 and March 2020 (**Figure 1**), 6,078,487 men without missing clinical data were included in the main analysis (main cohort). Next, we extracted six specific subgroups according to comorbidities (hypertension, diabetes, dyslipidemia, and atrial fibrillation/flutter) (subcohort 1) and cardiovascular causes of admission (ACS and HF) (subcohort 2). In addition, the cohorts were subdivided into 3 age groups: <65, 65–74, and ≥75 years old.

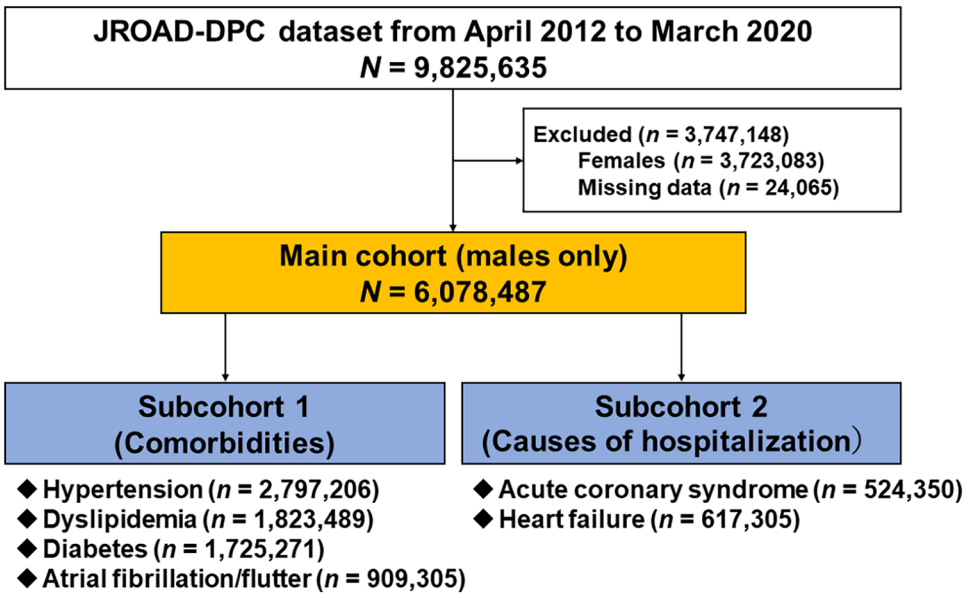


FIGURE 1
Study flowchart. JROAD-DPC, Japanese registry of all cardiac and vascular diseases–diagnosis procedure combination.

Statistical analyses

We presented categorical data as numbers (percentages) and continuous data as medians [interquartile ranges (IQRs)]. Annual frequencies of prostate diseases were calculated according to the data obtained from April of the corresponding year to March of the following year. Using the Cochran–Armitage trend test, we assessed the prevalence of prostate diseases by age group (<65, 65–74, and ≥75 years old). To determine the odds ratios and 95% confidence intervals, we constructed multilevel mixed-effects logistic regression with institution as a random intercept and adjusting for confounding factors, such as age, smoking status, hypertension, dyslipidemia, diabetes, and atrial fibrillation/flutter. In the subcohort analyses, patients with both ACS and HF were excluded in order to analyze the associations between each cardiovascular cause of admission (ACS and HF) and prostate disease individually.

All statistical data were analyzed using the STATA16 software program (College Station, TX, USA).

Results

Clinical characteristics

Of the 9,825,635 patients registered in the JROAD-DPC database between April 2012 and March 2020, 2,723,083 women and 24,065 cases with missing data were excluded (Figure 1). Ultimately, 6,078,487 male patients were analyzed as the main cohort. Overall, the median age was 71 (IQR: 63, 79) years old, and the median BMI was 23.2 (IQR: 20.8, 25.7) kg/m^2. The prevalences of current or past smoking and coexisting hypertension, dyslipidemia, diabetes, and atrial fibrillation/flutter were 56.5%, 46.0%, 30.0%, 28.4%, and 15.0%, respectively (Table 1).

Prevalence of prostate diseases

In the main cohort, 349,293 (5.7%) patients had prostate diseases (BPH: 268,778 [4.4%]; PCa: 96,131 [1.6%]), and they tended to be older and smoked less than those without such diseases. In addition, hypertension and atrial fibrillation/flutter were more common in those with prostate diseases than in those without such diseases, especially those with BPH (Table 1).

Regarding age, the prevalence of prostate diseases and individual components (BPH or PCa) significantly increased as the age increased (all *P*-values for trend <0.05) (Table 2). Figure 2 shows the annual prevalence of prostate diseases and individual components in the overall cohort and each age category from 2012 to 2019. The overall prevalence modestly increased over time in all generations, especially from 2015 to 2016 and among those who were ≥65 years old.

Subcohort analyses

Table 2 also lists the prevalence of prostate diseases by each subcohort. Similar to that in the main cohort, the prevalence increased significantly with age in each subcohort (all *P*-values for trend <0.05), and the time trend for the prevalence also showed a modest increase over time (Supplementary Figures S1–S6).

In the subcohort analysis, the lowest and highest prevalence rates of prostate diseases were observed in the subcohorts with

TABLE 1 Clinical characteristics of the main cohort.

	Overall	Without prostate disease	With prostate disease		
			BPH and/or PCa	BPH	PCa
Number of patients	6,078,487	5,729,194	349,293	268,778	96,131
Age, years	71 (63, 79)	71 (62, 79)	79 (73, 84)	79 (73, 84)	79 (73, 84)
Height, cm	164.0 (159.0, 169.0)	164.0 (159.0, 169.0)	162.0 (158.0, 167.0)	162.0 (158.0, 167.0)	162.0 (157.0, 167.0)
Weight, kg	62.0 (53.7, 70.2)	62.0 (53.8, 70.5)	60.0 (52.6, 67.1)	60.0 (52.5, 67.1)	60.0 (53.0, 67.4)
Body mass index, kg/m^2	23.2 (20.8, 25.7)	23.2 (20.8, 25.7)	22.9 (20.6, 25.1)	22.8 (20.6, 25.1)	23.0 (20.8, 25.2)
Smoking (current or past)	2,969,835 (56.5)	2,810,891 (56.8)	158,944 (51.9)	123,429 (52.4)	42,442 (50.4)
Hypertension	2,797,206 (46.0)	2,608,896 (45.5)	188,310 (53.9)	154,391 (57.4)	40,672 (42.3)
Dyslipidemia	1,823,489 (30.0)	1,726,845 (30.1)	96,644 (27.7)	79,213 (29.5)	20,630 (21.5)
Diabetes	1,725,271 (28.4)	1,629,641 (28.4)	95,630 (27.4)	75,821 (28.2)	23,311 (24.2)
Atrial fibrillation/flutter	909,305 (15.0)	847,553 (14.8)	61,752 (17.7)	49,959 (18.6)	13,965 (15.5)

Data are presented as the median (interquartile range) or numbers (percentages).
BPH, benign prostate hyperplasia; PCa, prostate cancer.

TABLE 2 Prevalence of prostate diseases according to age and subcohorts.

	Total generation	<65 years	65–74 years	≥75 years
Main cohort	(*N* = 6,078,487)	(*N* = 1,758,139)	(*N* = 1,876,056)	(*N* = 2,444,292)
Prostate disease (BPH and/or PCa)	349,293 (5.7)	18,945 (1.1)	87,481 (4.7)	242,867 (9.9)
BPH	268,778 (4.4)	15,739 (0.9)	66,903 (3.6)	186,136 (7.7)
PCa	96,131 (1.6)	3,891 (0.2)	24,817 (1.3)	67,423 (2.8)
Subcohort (Hypertension)	(*n* = 2,797,206)	(*n* = 753,246)	(*n* = 910,993)	(*n* = 107,557)
Prostate disease (BPH and/or PCa)	188,310 (6.7)	9,891 (1.3)	46,312 (5.1)	132,107 (11.7)
BPH	154,391 (5.5)	8,806 (1.2)	38,028 (4.2)	107,557 (9.5)
PCa	40,672 (1.5)	1,338 (0.2)	9,893 (1.1)	29,441 (2.6)
Subcohort (Dyslipidemia)	(*n* = 1,823,489)	(*n* = 560,581)	(*n* = 638,118)	(*n* = 624,790)
Prostate disease (BPH and/or PCa)	96,644 (5.3)	6,309 (1.1)	28,635 (4.5)	61,700 (9.9)
BPH	79,213 (4.3)	5,576 (1.0)	23,537 (3.7)	50,100 (8.0)
PCa	20,630 (1.1)	881 (0.2)	5,985 (0.9)	13,764 (2.2)
Subcohort (Diabetes)	(*n* = 1,725,271)	(*n* = 444,247)	(*n* = 617,700)	(*n* = 663,324)
Prostate disease (BPH and/or PCa)	95,630 (5.5)	5,696 (1.3)	27,157 (4.4)	62,777 (9.5)
BPH	75,821 (4.4)	4,961 (1.1)	21,646 (3.5)	49,214 (7.4)
PCa	23,311 (1.4)	879 (0.2)	6,602 (1.1)	15,830 (2.4)
Subcohort (Atrial fibrillation/flutter)	(*n* = 909,305)	(*n* = 199,451)	(*n* = 280,399)	(*n* = 429,455)
Prostate disease (BPH and/or PCa)	61,752 (6.8)	2,151 (1.1)	12,954 (4.6)	46,647 (10.9)
BPH	49,959 (5.5)	1,839 (0.9)	10,660 (3.8)	37,460 (8.7)
PCa	13,965 (1.5)	366 (0.2)	2,750 (1.0)	10,849 (2.5)
Subcohort (ACS)	(*n* = 524,350)	(*n* = 184,470)	(*n* = 167,594)	(*n* = 172,286)
Prostate disease (BPH and/or PCa)	23,413 (4.5)	1,623 (0.9)	6,820 (4.1)	14,970 (8.7)
BPH	18,834 (3.6)	1,429 (0.8)	5,529 (3.3)	11,876 (6.9)
PCa	5,263 (1.0)	220 (0.1)	1,466 (0.9)	3,577 (2.1)
Subcohort (HF)	(*n* = 617,305)	(*n* = 105,556)	(*n* = 132,524)	(*n* = 379,225)
Prostate disease (BPH and/or PCa)	53,260 (8.6)	1,190 (1.1)	6,486 (4.9)	45,584 (12.0)
BPH	41,827 (6.8)	1,042 (1.0)	5,263 (4.0)	35,522 (9.4)
PCa	13,383 (2.2)	166 (0.2)	1,413 (1.1)	11,804 (3.1)

Data are presented as numbers (percentages).
ACS, acute coronary syndrome; BPH, benign prostate hyperplasia; HF, heart failure; PCa, prostate cancer.

ACS (4.5%) and HF (8.6%) (Table 2). The closer association of prostate diseases with HF was validated through univariate and multivariate logistic regression analyses (Table 3 and Supplementary Table S1). Overall, the subcohort admitted for HF had significantly higher incidences of prostate diseases, dominated by BPH, than the subcohorts admitted for non-HF causes or ACS (Table 3). When stratifying these subcohorts into three age categories, the association of subcohorts admitted for HF with the coexistence of prostate diseases was more pronounced in the older group (≥65 years old) (Supplementary Table S1).

Discussion

This study used a nationwide claims database recorded from JCS-certified hospitals between April 2012 and March 2020. To our knowledge, this is the first study to reveal the real-world

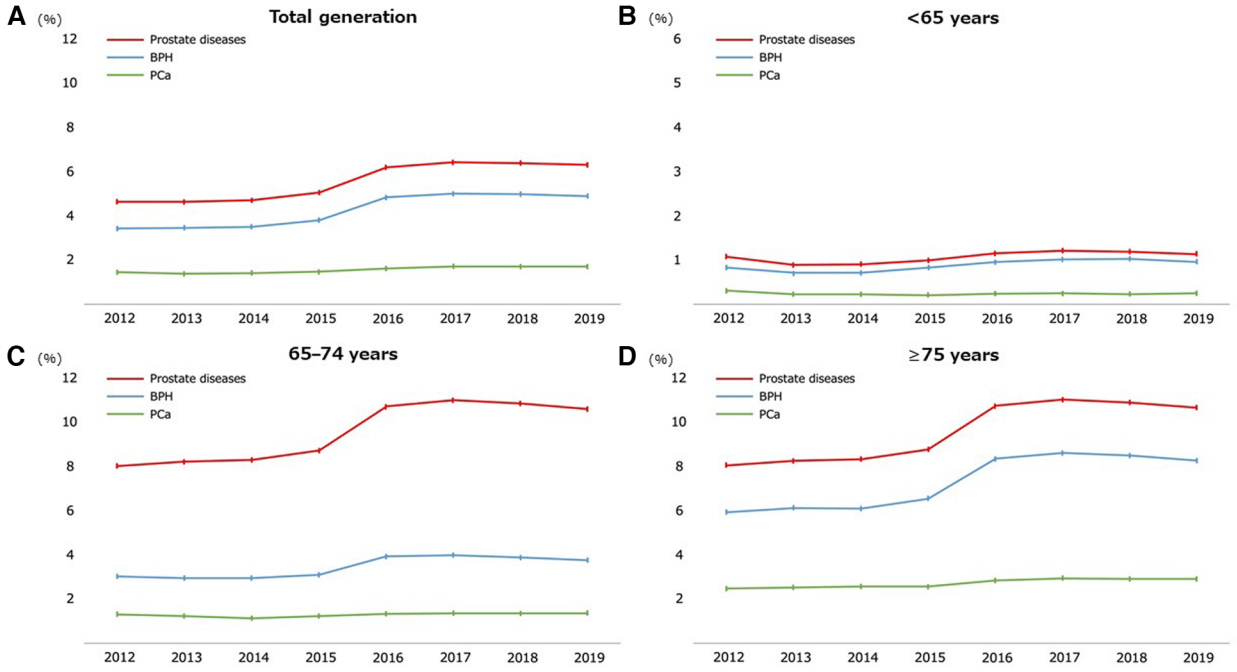


FIGURE 2
Temporal trend of the prevalence of prostate diseases from 2012 to 2019. Participants throughout the total generation (A) and stratified by age groups of <65 (B), 65–74 (C), and ≥75 years old (D). BPH, benign prostate hyperplasia; PCa, prostate cancer.

TABLE 3 Univariate and multivariate logistic regression analyses of prostate disease incidences in subcohorts according to the cause of admission.

Incidence	Causes of admission	Crude		Adjusted[a]	
		Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Prostate disease (BPH and/or PCa)	HF vs. Non-HF (reference)	1.59 (1.58–1.61)	<0.001	1.02 (1.01–1.03)	0.003
	HF vs. ACS (reference)	2.01 (1.97–2.04)	<0.001	1.19 (1.17–1.22)	<0.001
BPH	HF vs. Non-HF (reference)	1.62 (1.60–1.64)	<0.001	1.03 (1.01–1.04)	<0.001
	HF vs. ACS (reference)	1.93 (1.90–1.97)	<0.001	1.17 (1.14–1.19)	<0.001
PCa	HF vs. Non-HF (reference)	1.38 (1.35–1.41)	<0.001	0.94 (0.92–0.96)	<0.001
	HF vs. ACS (reference)	2.17 (2.10–2.24)	<0.001	1.25 (1.20–1.30)	<0.001

ACS, acute coronary syndrome; BPH, benign prostate hyperplasia; CI, confidence interval; HF, heart failure; PCa, prostate cancer.
[a]Adjusted by factors of age, smoking status, hypertension, dyslipidemia, diabetes, and atrial fibrillation/flutter.

prevalence of prostate diseases among patients hospitalized for CVDs. Prostate diseases were more prevalent in older patients than younger ones and showed a modest temporal increasing trend in the past eight years (2012–2019). Furthermore, the coexistence of prostate diseases was more common in patients hospitalized for HF than in those hospitalized for other cardiovascular causes, including ACS. Our findings highlight the potential clinical importance for cardiologists and even general physicians to recognize the potential association between CVD and the risk for prostate disease.

Metabolic syndrome and relevant cardiometabolic disorders, which are fully established as key risk factors for most CVDs, have been recently reported to play an important role in the pathogenesis of major prostate diseases (BPH and PCa) (17, 19, 26–29), highlighting an increased burden of prostate diseases coexisting with CVD in actual clinical settings. Epidemiological studies have reported that CVD is prevalent among patients with LUTS (primarily caused by BPH) or PCa (7, 30–32). Furthermore, some PCa medications, including ADT (androgen deprivation therapy), have a potency that adversely affects the cardiometabolic status and increases the risk for cardiovascular complications (33–36). Chan et al. (37) recently demonstrated temporal increasing trends of recipients of ADT therapy with cardiovascular risk factors, frequently used cardiovascular and metabolic medications, and developed cardiovascular events. CVD is the leading cause of mortality in PCa survivors (9, 10). These studies have contributed to emphasizing the clinical need for cardiovascular risk assessments and appropriate risk management in this population (20, 38, 39).

Currently, studies assessing the real-world burden of prostate diseases among patients with established CVD remain limited. In Poland, Semczuk-Kaczmarek et al. (40) reported that 62 (37.3%)

out of 166 patients hospitalized with CVD had moderate-to-severe LUTS according to the International Prostate Symptoms Score. In a nationwide survey using the National Inpatient Sample in the United States between 2004 and 2014 (41), PCa was the most prevalent in a specific population with cancer who underwent percutaneous coronary intervention. Relative to these studies, the strength of the present study was being the first to attempt to survey the burden of two major prostate diseases, namely BPH and PCa, in patients hospitalized with CVD in a real-world nationwide dataset. In addition, we found a modestly increasing temporal trend of prevalent prostate diseases in the cohort examined, consistent with the global trend of increased burden of prostate diseases in general populations (1–5). This increase may reflect aging and indicate the need to promote public and clinical awareness of prostate diseases (3, 42) and PCa screening with prostate-specific antigen tests (43–45). Collectively, continued surveillance is needed to further clarify the clinical characteristics of prostate diseases among patients with CVD. Details concerning casualties should also be further examined.

In the present study, prostate diseases, dominated by BPH, were more prevalent in inpatients with HF than in those with non-HF causes or ACS, highlighting a possible association between HF and prostate diseases. Although the reason for the difference is still uncertain, it may be at least caused by the epidemiological fact that the incidence of corresponding diseases reflects demographics with aging. Lusty et al. (46) recently revealed that the most common medications for BPH (5-alpha reductase inhibitor, α-blocker, and combination therapy) were associated with an increased risk for incident cardiac failure in older (median: 73 years old) patients with BPH. More recently, HF was proven to be the leading cause of CVD admission and an increasing cause of mortality among patients across cancer types, including PCa (47, 48). Thus, considering the increasing global burden of HF (49), clinicians need to recognize that HF is an emerging and prognostic complication in patients with prostate diseases.

Although not limited to prostate diseases, estimation of the risk and early screening of the coexistence of non-CVD in patients with established CVD may lead to better overall patient outcomes. With recent improvements in diagnostics and therapeutics in various fields, including cardiology and urology, the resultant increase in the number of survivors from individual diseases and aging will further augment the subsequent risk of developing cardiovascular and noncardiovascular complications. In particular, patients with cancer generally have an increased risk for CVD (50–52), and the development of a better healthcare system is urgently needed in order to provide multidisciplinary clinical management and appropriate cardiovascular care ("onco-cardiology") to patients with cancer.

In the present study, we showed real-world evidence concerning the burden and temporal increasing trend of major prostate diseases (BPH and PCa) among patients hospitalized for CVD. Given the close epidemiological relationship based on shared risk factors between prostate diseases and CVD entities, the prevalence of prostate diseases identified in inpatients may be merely part of a larger and more complex issue and is also common in patients with chronic CVD and even in those at risk for CVD (14–18). However, conducting clinical interviews regarding the presence of LUTS and screening tests for prostate diseases in cardiovascular care settings is currently uncommon. Our findings may be clinically useful to motivate cardiologists and even general physicians to screen patients with CVD for the presence of prostate diseases and to share clinical information with urologists. Furthermore, our study may promote clinical and research collaboration among specialists (especially urologists and cardiologists), leading to the development of a novel academic field of "uro-cardiology" in the near future.

Limitations

Our study has several limitations that need to be considered, and they were mainly based on the use of data sources obtained from medical claims. First, the present analysis was based only on the DPC data, and these data might contain certain inevitable errors, leading to the over- or underestimation of the clinical diagnosis accuracy. In particular, the JROAD-DPC data were obtained from the cardiovascular unit of several JCS-certified training facilities, and cardiologists might not be knowledgeable enough in the clinical diagnosis of prostate diseases. In addition, data were only collected from patients hospitalized for CVDs in JCS-certified hospitals; thus, selection bias is possible. We also did not compare the inpatients with CVD with healthy individuals or inpatients without CVD. Second, the DPC data system cannot share individual information among hospitals. If patients were admitted to another hospital, the previous DPC data could not be carried over, and the individuals could not be identified; thus, duplicates in the dataset are likely. Third, the DPC dataset did not include clinical information on the etiology, laboratory and imaging data, medications, or disease severity and staging of CVD and prostate diseases. Fourth, we had no information about the subsequent clinical course, rehospitalization, or mortality. Therefore, further research is needed to assess long-term outcomes in patients suffering from prostate diseases with established CVD. Finally, given that CVD and prostate diseases often vary in their prevalence by ethnicity and region (1, 3, 4), whether or not our findings from this Japanese patient population can be applied to different populations remains uncertain.

Conclusions

The nationwide real-world dataset used in this study revealed the increasing prevalence of prostate diseases among patients hospitalized for CVDs, particularly HF. Cardiologists and even general physicians must recognize that prostate diseases and CVDs often share underlying risk factors and that the frequency of their coexistence is increasing. This insight may facilitate the early screening and diagnosis of prostate diseases and help improve healthcare management.

Data availability statement

Given that the JROAD-DPC dataset is owned by the JCS for the purpose of research, the data that support our findings will not be shared without JCS' permission. The dataset will be available upon reasonable request from researchers and after approval by the JCS. Inquiries are to be addressed to the JCS (contact via itdatabase@j-circ.or.jp).

Ethics statement

This study was approved by the JCS (No. 2020-08) and the Ethics Committee of Saga University Hospital (No. 2021-08-01 on November 01, 2021) and conducted according to the principles of the Declaration of Helsinki. The database used in this study deidentified personal information; therefore, informed consent from our study participants was not needed.

Author contributions

KK, AT, and KN designed the research (project conception, development of overall research plan, and study oversight) and wrote the manuscript; KK, AT, MN, YS, and KN conducted the research (hands-on conduct of the experiments and data collection); KK, AT, MN, and YS analyzed the data or performed statistical analyses; HK, MN, and KN revised the manuscript; AT and KN had primary responsibility for the final content. All authors contributed to the article and approved the submitted version.

Funding

This work was partly supported by the Bayer Academic Support (No. BASJ20210416007) and research funding from Bristol Myers Squibb (No. 74241135).

Acknowledgments

The authors are grateful to Mikiko Kagiyama (Saga University) and Shizuka Okada (Saga University) for their dedicated assistance with the study.

Conflict of interest

KK received an academic support from Bayer. AT has received honoraria from Boehringer Ingelheim and research funding from GlaxoSmithKline, Takeda, Bristol Myers Squibb, and Novo Nordisk. HK has received research funding and scholarship funds from Medtronic Japan Co., LTD, Abbott Medical Japan Co., LTD, Boston Scientific Japan Co., LTD, and Fukuda Denshi, Central Tokyo Co., Ltd. MN has received a research funding from Pfizer. KN has received honoraria from MSD, Astellas, AstraZeneca, Novartis, Ono, Daiichi Sankyo, Mitsubishi Tanabe, Eli Lilly, Boehringer Ingelheim, and Takeda; research grants from Asahi Kasei, Astellas, Mitsubishi Tanabe, Teijin, Terumo, Boehringer Ingelheim, Eli Lilly and Company, Mochida, and Fuji; and scholarships from Daiichi Sankyo Healthcare, Teijin, Medtronic, and Bayer.

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1236144/full#supplementary-material

References

1. The global, regional, and national burden of benign prostatic hyperplasia in 204 countries and territories from 2000 to 2019: a systematic analysis for the global burden of disease study 2019. *Lancet Healthy Longev.* (2022) 3:e754–76. doi: 10.1016/S2666-7568(22)00213-6

2. Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. *Urol Clin North Am.* (2016) 43:289–97. doi: 10.1016/j.ucl.2016.04.001

3. Xu XF, Liu GX, Guo YS, Zhu HY, He DL, Qiao XM, et al. Global, regional, and national incidence and year lived with disability for benign prostatic hyperplasia from 1990 to 2019. *Am J Mens Health.* (2021) 15:15579883211036786. doi: 10.1177/15579883211036786

4. Cao Y, Zhang W, Li Y, Fu J, Li H, Li X, et al. Rates and trends in stage-specific prostate cancer incidence by age and race/ethnicity, 2000–2017. *Prostate.* (2021) 81:1071–7. doi: 10.1002/pros.24204

5. Zhang H, Huang D, Zhang Y, Wang X, Wu J, Hong D. Global burden of prostate cancer attributable to smoking among males in 204 countries and territories, 1990–2019. *BMC Cancer.* (2023) 23:92. doi: 10.1186/s12885-023-10552-8

6. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol.* (2015) 67:1099–109. doi: 10.1016/j.eururo.2014.12.038

7. Gacci M, Corona G, Sebastianelli A, Serni S, De Nunzio C, Maggi M, et al. Male lower urinary tract symptoms and cardiovascular events: a systematic review and meta-analysis. *Eur Urol.* (2016) 70:788–96. doi: 10.1016/j.eururo.2016.07.007

8. Schoormans D, Vissers PAJ, van Herk-Sukel MPP, Denollet J, Pedersen SS, Dalton SO, et al. Incidence of cardiovascular disease up to 13 year after cancer diagnosis: a matched cohort study among 32,757 cancer survivors. *Cancer Med.* (2018) 7:4952–63. doi: 10.1002/cam4.1754

9. Shikanov S, Kocherginsky M, Shalhav AL, Eggener SE. Cause-specific mortality following radical prostatectomy. *Prostate Cancer Prostatic Dis*. (2012) 15:106–10. doi: 10.1038/pcan.2011.55

10. Ng HS, Koczwara B, Roder D, Vitry A. Development of comorbidities in men with prostate cancer treated with androgen deprivation therapy: an Australian population-based cohort study. *Prostate Cancer Prostatic Dis*. (2018) 21:403–10. doi: 10.1038/s41391-018-0036-y

11. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation*. (2004) 109:II2–10. doi: 10.1161/01.CIR.0000110642.73995.BF

12. Raggi P, Genest J, Giles JT, Rayner KJ, Dwivedi G, Beanlands RS, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. *Atherosclerosis*. (2018) 276:98–108. doi: 10.1016/j.atherosclerosis.2018.07.014

13. Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. *Nat Rev Cardiol*. (2020) 17:137–44. doi: 10.1038/s41569-019-0247-5

14. Russo GI, Castelli T, Privitera S, Fragalà E, Favilla V, Reale G, et al. Increase of framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms. *BJU Int*. (2015) 116:791–6. doi: 10.1111/bju.13053

15. Yoo S, Oh S, Park J, Cho SY, Cho MC, Jeong H, et al. The impacts of metabolic syndrome and lifestyle on the prevalence of benign prostatic hyperplasia requiring treatment: historical cohort study of 130,454 men. *BJU Int*. (2019) 123:140–8. doi: 10.1111/bju.14528

16. Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, et al. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis*. (2017) 20:146–55. doi: 10.1038/pcan.2017.1

17. Hammarsten J, Damber JE, Haghsheno MA, Mellström D, Peeker R. A stage-dependent link between metabolic syndrome components and incident prostate cancer. *Nat Rev Urol*. (2018) 15:321–33. doi: 10.1038/nrurol.2018.8

18. Hernández-Pérez JG, Torres-Sánchez L, Hernández-Alcaráz C, López-Carrillo L, Rodríguez-Covarrubias F, Vázquez-Salas RA, et al. Metabolic syndrome and prostate cancer risk: a population case-control study. *Arch Med Res*. (2022) 53:594–602. doi: 10.1016/j.arcmed.2022.07.003

19. Hammarsten J, Peeker R. Urological aspects of the metabolic syndrome. *Nat Rev Urol*. (2011) 8:483–94. doi: 10.1038/nrurol.2011.112

20. Tanaka A, Node K. The emerging and promising role of care for cardiometabolic syndrome in prostate cancer. *JACC CardioOncol*. (2019) 1:307–9. doi: 10.1016/j.jaccao.2019.09.005

21. Merseburger A, Bro Falkenberg A, Kornilova OJ. New study suggests patients with advanced prostate cancer on androgen deprivation therapy need more dialogue with health care provider, especially around cardiovascular risk. *World J Urol*. (2019) 37:1085–93. doi: 10.1007/s00345-018-2495-0

22. Yasuda S, Nakao K, Nishimura K, Miyamoto Y, Sumita Y, Shishido T, et al. The current status of cardiovascular medicine in Japan—analysis of a large number of health records from a nationwide claim-based database, JROAD-DPC. *Circ J*. (2016) 80:2327–35. doi: 10.1253/circj.CJ-16-0196

23. Yasuda S, Miyamoto Y, Ogawa H. Current status of cardiovascular medicine in the aging society of Japan. *Circulation*. (2018) 138:965–7. doi: 10.1161/CIRCULATIONAHA.118.035858

24. Nakai M, Iwanaga Y, Sumita Y, Wada S, Hiramatsu H, Iihara K, et al. Associations among cardiovascular and cerebrovascular diseases: analysis of the nationwide claims-based JROAD-DPC dataset. *PLoS One*. (2022) 17:e0264390. doi: 10.1371/journal.pone.0264390

25. Ogawa M, Yoshida N, Nakai M, Kanaoka K, Sumita Y, Kanejima Y, et al. Hospital-associated disability and hospitalization costs for acute heart failure stratified by body mass index- insight from the JROAD/JROAD-DPC database. *Int J Cardiol*. (2022) 367:38–44. doi: 10.1016/j.ijcard.2022.08.044

26. Russo GI, Cimino S, Castelli T, Favilla V, Gacci M, Carini M, et al. Benign prostatic hyperplasia, metabolic syndrome and non-alcoholic fatty liver disease: is metaflammation the link? *Prostate*. (2016) 76:1528–35. doi: 10.1002/pros.23237

27. Di Francesco S, Robuffo I, Caruso M, Giambuzzi G, Ferri D, Militello A, et al. Metabolic alterations, aggressive hormone-naïve prostate cancer and cardiovascular disease: a Complex relationship. *Medicina (Kaunas)*. (2019) 55:62. doi: 10.3390/medicina55030062

28. Geng JH, Plym A, Penney KL, Pomerantz M, Mucci LA, Kibel AS. Metabolic syndrome and its pharmacologic treatment are associated with the time to castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis*. (2022) 25:320–6. doi: 10.1038/s41391-022-00494-w

29. Bhindi B, Locke J, Alibhai SMH, Kulkarni GS, Margel DS, Hamilton RJ, et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. *Eur Urol*. (2015) 67:64–70. doi: 10.1016/j.eururo.2014.01.040

30. Wollersheim BM, Boekhout AH, van der Poel HG, van de Poll-Franse LV, Schoormans D. The risk of developing cardiovascular disease is increased for patients with prostate cancer who are pharmaceutically treated for depression. *BJU Int*. (2020) 125:433–41. doi: 10.1111/bju.14961

31. Tanaka Y, Matsuyama S, Tada H, Hayashi K, Takamura M, Kawashiri MA, et al. Association of lower urinary tract symptoms based on the international prostate symptom score and cardiovascular disease. *Circ J*. (2021) 85:2092–9. doi: 10.1253/circj.CJ-21-0278

32. Wang X, Su Y, Yang C, Hu Y, Dong JY. Benign prostatic hyperplasia and cardiovascular risk: a prospective study among Chinese men. *World J Urol*. (2022) 40:177–83. doi: 10.1007/s00345-021-03817-z

33. Liu JM, Lin CC, Chen MF, Liu KL, Lin CF, Chen TH, et al. Risk of major adverse cardiovascular events among second-line hormonal therapy for metastatic castration-resistant prostate cancer: a real-world evidence study. *Prostate*. (2021) 81:194–201. doi: 10.1002/pros.24096

34. Zhang KW, Reimers MA, Calaway AC, Fradley MG, Ponsky L, Garcia JA, et al. Cardiovascular events in men with prostate cancer receiving hormone therapy: an analysis of the FDA adverse event reporting system (FAERS). *J Urol*. (2021) 206:613–22. doi: 10.1097/JU.0000000000001785

35. Lin E, Garmo H, Van Hemelrijck M, Zethelius B, Stattin P, Hagström E, et al. Association of gonadotropin-releasing hormone agonists for prostate cancer with cardiovascular disease risk and hypertension in men with diabetes. *JAMA Netw Open*. (2022) 5:e2225600. doi: 10.1001/jamanetworkopen.2022.25600

36. Schmidt C. Does prostate-cancer treatment place a strain on the heart? *Nature*. (2022) 609:S46–s47. doi: 10.1038/d41586-022-02863-w

37. Chan JSK, Satti DI, Lee YHA, Hui JMH, Dee EC, Ng K, et al. Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy: a population-based cohort study. *Br J Cancer*. (2023) 128:2253–60. doi: 10.1038/s41416-023-02271-5

38. Sun L, Parikh RB, Hubbard RA, Cashy J, Takvorian SU, Vaughn DJ, et al. Assessment and management of cardiovascular risk factors among US veterans with prostate cancer. *JAMA Netw Open*. (2021) 4:e210070. doi: 10.1001/jamanetworkopen.2021.0070

39. Katz AJ, Chen RC, Usinger DS, Danus SM, Zullig LL. Cardiovascular disease prevention and management of pre-existent cardiovascular disease in a cohort of prostate cancer survivors. *J Cancer Surviv*. (2023) 17:351–9. doi: 10.1007/s11764-022-01229-5

40. Semczuk-Kaczmarek K, Rys-Czaporowska A, Platek AE, Szymanski FM. Prevalence of lower urinary tract symptoms in patients with cardiovascular disease. *Cent European J Urol*. (2021) 74:190–5. doi: 10.5173/ceju.2021.0370.R1

41. Potts JE, Iliescu CA, Lopez Mattei JC, Martinez SC, Holmvang L, Ludman P, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. *Eur Heart J*. (2019) 40:1790–800. doi: 10.1093/eurheartj/ehy769

42. Ito K. Prostate cancer in Asian men. *Nat Rev Urol*. (2014) 11:197–212. doi: 10.1038/nrurol.2014.42

43. Okinaka Y, Kageyama S, Nishizawa K, Yoshida T, Ishitoya S, Shichiri Y, et al. Clinical, pathological, and therapeutic features of newly diagnosed prostate cancer predominantly detected by opportunistic PSA screening: a survey of shiga prefecture, Japan. *Prostate*. (2021) 81:1172–8. doi: 10.1002/pros.24212

44. Inoue T, Yoshimura K, Terada N, Tsukino H, Murota T, Kinoshita H, et al. Prostate-specific antigen density during dutasteride treatment for 1 year predicts the presence of prostate cancer in benign prostatic hyperplasia after the first negative biopsy (PREDICT study). *Int J Urol*. (2021) 28:849–54. doi: 10.1111/iju.14590

45. Lai SM, Keighley J, Garimella S, Enko M, Parker WP. Variations in age-adjusted prostate cancer incidence rates by race and ethnicity after changes in prostate-specific antigen screening recommendation. *JAMA Netw Open*. (2022) 5:e2240657. doi: 10.1001/jamanetworkopen.2022.40657

46. Lusty A, Siemens DR, Tohidi M, Whitehead M, Tranmer J, Nickel JC. Cardiac failure associated with medical therapy of benign prostatic hyperplasia: a population based study. *J Urol*. (2021) 205:1430–7. doi: 10.1097/JU.0000000000001561

47. Kobo O, Raisi-Estabragh Z, Gevaert S, Rana JS, Van Spall HGC, Roguin A, et al. Impact of cancer diagnosis on distribution and trends of cardiovascular hospitalizations in the USA between 2004 and 2017. *Eur Heart J Qual Care Clin Outcomes*. (2022) 8:787–97. doi: 10.1093/ehjqcco/qcac045

48. Raisi-Estabragh Z, Kobo O, Freeman P, Petersen SE, Kolman L, Miller RJH, et al. Temporal trends in disease-specific causes of cardiovascular mortality amongst patients with cancer in the USA between 1999 and 2019. *Eur Heart J Qual Care Clin Outcomes*. (2022) 9:54–63. doi: 10.1093/ehjqcco/qcac016

49. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. (2023) 118:3272–87. doi: 10.1093/cvr/cvac013

50. Kobo O, Khattak S, Lopez-Mattei J, Van Spall HGC, Graham M, Cheng RK, et al. Trends in cardiovascular mortality of cancer patients in the US over two decades 1999–2019. *Int J Clin Pract*. (2021) 75:e14841. doi: 10.1111/ijcp.14841

51. Battisti NML, Welch CA, Sweeting M, de Belder M, Deanfield J, Weston C, et al. Prevalence of cardiovascular disease in patients with potentially curable malignancies: a national registry dataset analysis. *JACC Cardiol Oncol*. (2022) 4:238–53. doi: 10.1016/j.jaccao.2022.03.004

52. Yeh TL, Hsu MS, Hsu HY, Tsai MC, Jhuang JR, Chiang CJ, et al. Risk of cardiovascular diseases in cancer patients: a nationwide representative cohort study in Taiwan. *BMC Cancer*. (2022) 22:1198. doi: 10.1186/s12885-022-10314-y

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 30 November 2023
DOI 10.3389/fcvm.2023.1221180

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Wilhelm Mistiaen,
University of Antwerp, Belgium
Massimo Baudo,
Spedali Civili Brescia, Italy
Maruti Haranal,
U N Mehta Institute of Cardiology and Research, India

*CORRESPONDENCE
Kentaro Akabane
✉ weaf0hh9y@yahoo.co.jp

RECEIVED 12 May 2023
ACCEPTED 17 November 2023
PUBLISHED 30 November 2023

CITATION
Akabane K, Watanabe T, Tajima Y, Toyama S, Tamate Y and Uchida T (2023) Case Report: Acute arterial occlusion of the right lower extremity due to left atrial invasion from pulmonary metastases of thyroid cancer. Front. Cardiovasc. Med. 10:1221180. doi: 10.3389/fcvm.2023.1221180

Case Report: Acute arterial occlusion of the right lower extremity due to left atrial invasion from pulmonary metastases of thyroid cancer

Kentaro Akabane[1]*, Tetsuo Watanabe[1], Yuta Tajima[1], Shuji Toyama[1], Yoshihisa Tamate[1] and Tetsuro Uchida[2]

[1]Division of Cardiovascular Surgery, Sendai City Hospital, Miyagi, Japan, [2]Second Department of Surgery, Faculty of Medicine, Yamagata University, Yamagata, Japan

Cardiac metastases of thyroid cancer are rare. The most common metastatic route is through lymphatic or hematogenous spread to the right side of the heart. Direct invasion of metastases from other adjacent organs to the left side of the heart is even rarer. In many cases, the disease progresses asymptomatically, and symptoms appear only when it is already fatal. A 68-year-old woman underwent total thyroidectomy and right-side lymph node dissection for papillary thyroid cancer and multiple lung metastases 7 years previously. The patient was referred to our hospital due to sudden pain in the right lower extremity and motor disturbance. Computed tomography revealed acute arterial occlusion of the right lower extremity due to tumor dispersal from a left atrial invasion caused by multiple pulmonary metastases of thyroid cancer, and only emergency thrombectomy was performed. Although blood flow was restored, the patient died of respiratory failure 2 months after the procedure. Radical resection is considered difficult in cases of direct invasion of metastases from other adjacent organs because multiple metastases have often already occurred. Therefore, in the terminal stage, it might be too invasive to resect a tumor only to prevent embolism recurrence. The treatment strategy should depend on the patient's prognosis and choice.

KEYWORDS

acute arterial occlusion, lower extremity, thyroid cancer, multiple pulmonary metastases, left atrial invasion

1. Introduction

Cardiac metastases of thyroid cancer are rare (1, 2). The most common metastatic route is through lymphatic or hematogenous spread to the right side of the heart (3). Direct invasion of metastases from other adjacent organs to the left side of the heart is even rarer (4). In many cases, the disease progresses asymptomatically and is already at the terminal stage when symptoms appear (5). Therefore, invasive interventions might sometimes be considered over-treatment, and it is thus necessary to consider the treatment strategy according to individual conditions. We report a case of acute arterial occlusion of the right lower extremity due to tumor dispersal from left atrial invasion by multiple pulmonary metastases of thyroid cancer for which a thrombectomy was performed. We also review the treatment strategy.

2. Case description

A 68-year-old woman underwent total thyroidectomy and right-side lymph node dissection for papillary thyroid cancer 7 years ago. The tumor, measuring approximately 2.5 cm, was located in the right lobe isthmus and had partially invaded the trachea. Additionally, two intralobular metastases, measuring approximately 8 mm, were identified in the left lobe. Because multiple lung metastases were detected preoperatively, the patient was treated with oral radioactive iodine postoperatively. Subsequent scintigraphy showed no significant accumulation in the lung lesions; hence, no additional treatment with oral radioactive iodine was administered. During follow-up, it was observed that the lung metastases were slowly spreading, leading to the initiation of oral multikinase inhibitors for the patient 2 years ago.

The patient was referred to our hospital 30 min after the onset of abrupt right lower extremity pain and motor disturbance. On arrival, the patient exhibited severe hypertension, probably due to pain, while remaining clinically stable (blood pressure, 185/117 mmHg; heart rate, 98 bpm; respiratory rate, 20 /min; SpO_2, 94%). However, the right lower extremity was cold and cyanotic, and only the common femoral artery (CFA) pulsation was faintly palpable. The electrocardiography showed normal sinus rhythm, while the bedside echocardiography revealed a mass in the left atrium. Although the images were unclear, the diameter of the mass was approximately 3 cm. The ejection fraction was approximately 60%, and no significant valvular findings were observed.

Computed tomography showed contrast deficits from the right CFA to the proximal superior femoral artery (SFA) and deep femoral artery (DFA) and at the popliteal artery behind the knee (**Figure 1A**). The pulmonary metastases were prominently enlarged compared to the condition 1 month earlier. Moreover, a contrast defect was observed from the right pulmonary vein into the left atrium, suspected to be a thrombus with direct invasion of the pulmonary metastases (**Figures 1B,C**).

Emergency surgery was planned with a diagnosis of acute ischemia of the right lower extremity (category IIb) due to suspected tumor dispersal from the left atrium. After administration of local anesthesia, the CFA, SFA, and DFA were exposed through an inguinal skin incision. The CFA was found to be filled with a yellow solid mass during the incision (**Figure 2A**), and black thrombi were removed from the SFA and DFA (**Figures 2B,C**). Blood flow resumed 5 h after onset, and apixaban was started the day after surgery. The postoperative course was uneventful. Although postoperative echocardiography showed no local wall motion abnormalities and pericardial

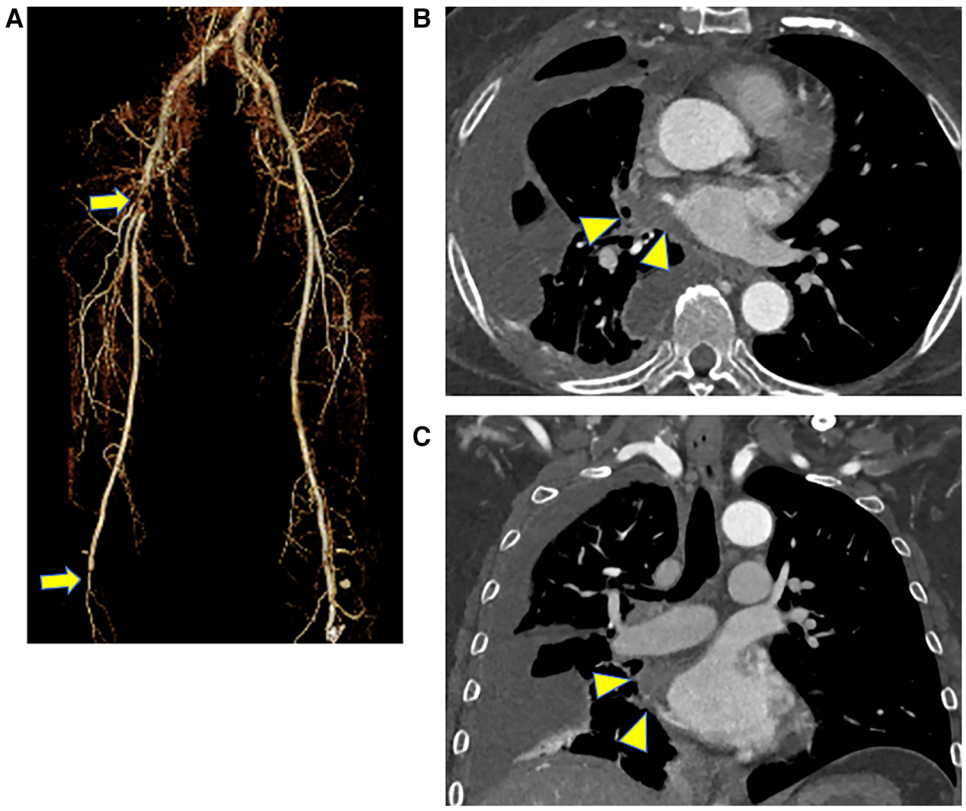


FIGURE 1
Preoperative CT scans, (**A**) three-dimensional CT of the lower extremity, and (**B**,**C**) CT of the chest level. CT showed contrast deficits from the right CFA to the proximal SFA and DFA and at the popliteal artery behind the knee (arrow). There was also a contrast defect from the right pulmonary vein into the left atrium, which might be a thrombus with a direct invasion of pulmonary metastases (arrowhead). CT, computed tomography; CFA, common femoral artery; SFA, superior femoral artery; DFA, deep femoral artery.

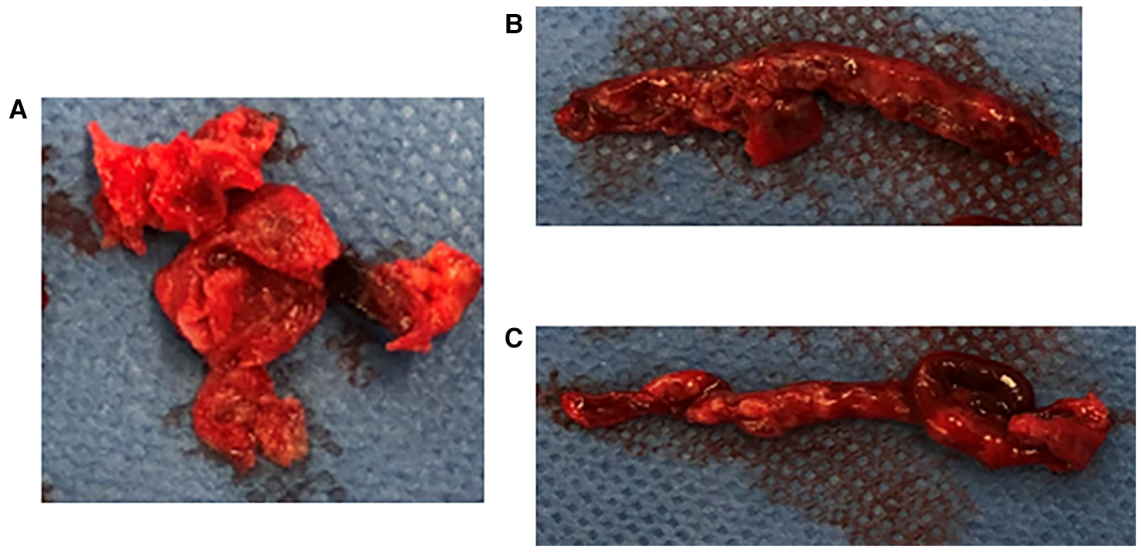


FIGURE 2
Embolus removed intraoperatively, (A) yellow solid mass removed from the CFA, (B,C) black thrombus removed from the SFA and DFA. The CFA was found to be filled with a yellow solid mass during the incision. The black thrombi were removed from the SFA and DFA. CFA, common femoral artery; SFA, superior femoral artery; DFA, deep femoral artery.

effusion, it showed a floating mass ≥3 cm extending from the left atrial orifice of the right pulmonary vein toward the atrial septum. Considering the size and location, it was the same mass observed preoperatively and thought to be a potential embolic source (Figures 3A,B). Computed tomography revealed good blood flow to the periphery, and the patient was discharged 17 days postoperatively.

The yellow embolus removed intraoperatively had atypical cells on hematoxylin and eosin staining (Figure 4A). Additional immunostaining was performed; the cells were determined to be epithelial carcinoma cells because cytokeratin AE 1/AE 3 (Figure 4B) and CAM 5.2 (Figure 4C), which are stained positive in most epithelial cells, were stained positive. Thyroid transcription factor-1 (TTF-1), normally stained positive in thyroid cancer, was stained negative (Figure 4D); however, TTF-1 is stained negative in undifferentiated carcinoma. Considering these results and the rapid clinical course, the original papillary thyroid carcinoma might have transformed into undifferentiated carcinoma, which quickly invaded the left atrium from the lung metastases, and an embolism had developed. Although myocardial enzyme levels were not elevated and obvious signs of heart failure were absent during hospitalization, shortness of breath due to the progression of pulmonary metastases gradually increased shortly after that. The patient died of respiratory failure 2 months after surgery.

3. Discussion

Cardiac metastases of malignant tumors are rare, and the most common metastases of primary tumors are carcinomas of the lung

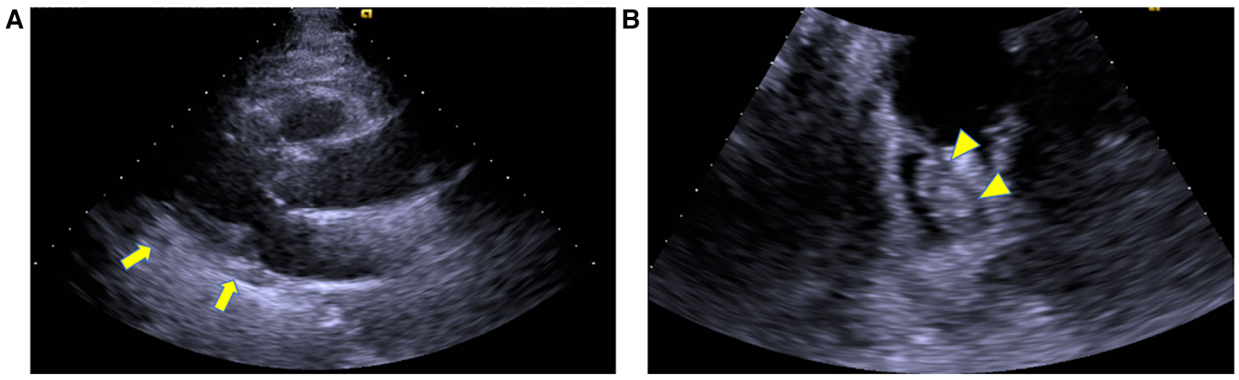


FIGURE 3
Postoperative echocardiography, (A) left ventricular long axis view, (B) 4 chamber view.echocardiography showed no pericardial effusion (arrow). It showed a floating mass extending from the left atrial orifice of the right pulmonary vein toward the atrial septum, which was considered a potential embolic source (arrowhead).

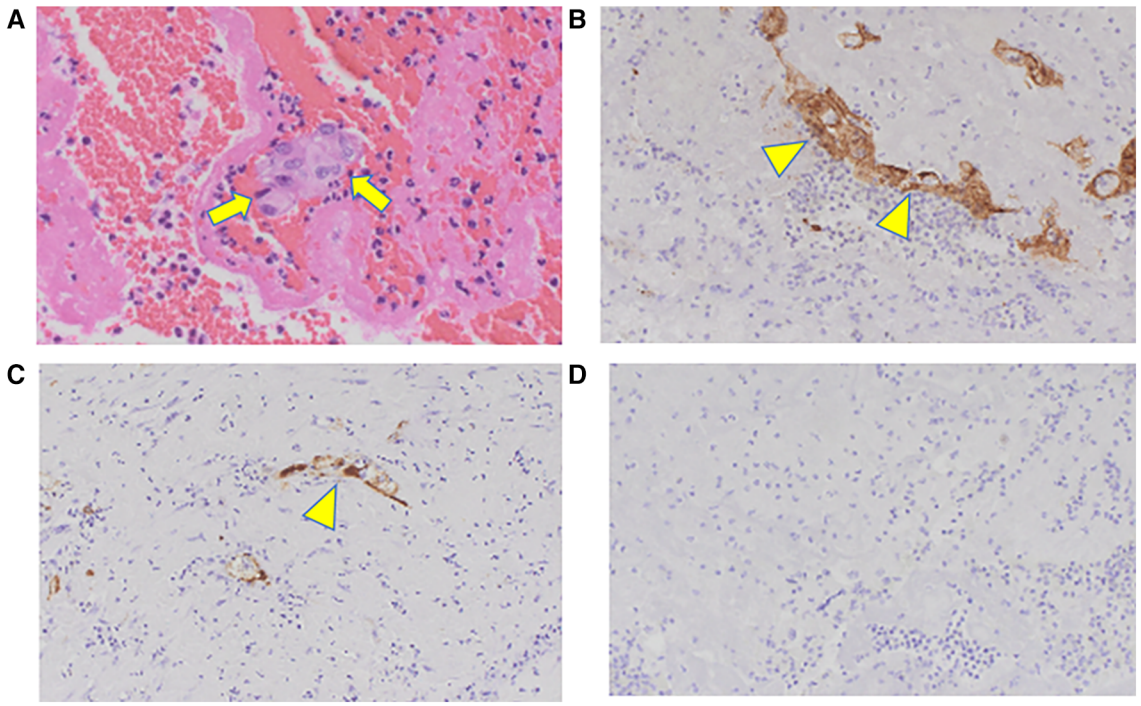


FIGURE 4
Pathological findings: (A) HE staining, (B) CK AE1/AE3, (C) CAM5.2, (D) TTF-1. The yellow embolus removed intraoperatively shows atypical cells on HE staining (arrow). The cells are typical of epithelial carcinoma cells because CK AE 1/AE 3 and CAM 5.2 are stained positive (arrowhead). TTF-1 is stained negative, indicating undifferentiated metastasized thyroid cancer. HE, Hematoxylin and eosin; CK, cytokeratin; TTF-1, thyroid transcription factor-1.

and breast (1, 2). Cardiac metastases of thyroid cancer are even less common, with only 54 cases reported in the 130 years between 1881 and 2010, most of which were diagnosed during postmortem autopsy (6). This may be attributed to the fact that most cases progress asymptomatically, and patients are at the terminal stage when symptoms appear (5). Therefore, cardiac metastases of thyroid cancer are difficult to diagnose while the patient is alive because cancerous tissues are rarely obtainable from any part of the body after symptoms manifest. The patient in the present case also had no obvious signs of cardiac failure. Hence, if acute arterial occlusion had not developed, the rapid spread of pulmonary metastases and cardiac invasion would not have been diagnosed before the patient's death. The most common routes of metastasis from the thyroid gland to the heart involve lymphatic or hematogenous spread to the right side of the heart via the vena cava (3). In contrast, metastases to the left side of the heart by direct invasion from metastases in other organs adjacent to the heart have rarely been reported (7–12).

To the best of our knowledge, this is the first reported case of acute lower extremity ischemia caused by the dispersal of a tumor invading the left atrium. Some studies have reported successful complete resection of the metastatic sites in cases of lymphatic or hematogenous spread to the right side of the heart via the vena cava (13, 14). Tumor resection should be performed if radical resection is possible and the long-term prognosis is favorable. However, in cases of direct invasion to the left side of the heart due to metastases from other organs, radical resection is regarded as challenging because multiple metastases have often already occurred (4). Considering the invasiveness of surgery and the possibility of metastatic spread due to the cardiopulmonary bypass (15), it is unclear whether tumor resection to prevent embolism is appropriate for terminal-stage prognosis, as it may sometimes be over-invasive. In our case, resection of the tumor was deemed too invasive, and only revascularization was performed. However, there was a concern that embolization might recur. Since no definitive treatment policy exists for such cases, it is necessary to consider a treatment strategy according to the patient's prognosis and choice.

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.

Ethics statement

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

KA, TW, YTaj, ST, YTam, and TU were involved in the writing and editing of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors wish to acknowledge the Division of Pathology for advice on pathology findings.

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. Abraham KP, Reddy V, Gattuso P. Neoplasms metastatic to the heart: review of 3314 consecutive autopsies. *Am J Cardiovasc Pathol.* (1990) 3:195–8.

2. Klatt EC, Heitz DR. Cardiac metastases. *Cancer.* (1990) 65:1456–9. doi: 10.1002/1097-0142(19900315)65:6<1456::AID-CNCR2820650634>3.0.CO;2-5

3. Niederle B, Hausmaninger C, Kretschmer G, Polterauer P, Neuhold N, Mirza DF, et al. Intraatrial extension of thyroid cancer: technique and results of a radical surgical approach. *Surgery.* (1990) 108:951–6.

4. Thompson NW, Brown J, Orringer M, Sisson J, Nishiyama R. Follicular carcinoma of the thyroid with massive angioinvasion: extension of tumor thrombus to the heart. *Surgery.* (1978) 83:451–7.

5. Giuffrida D, Gharib H. Cardiac metastasis from primary anaplastic thyroid carcinoma: report of three cases and a review of the literature. *Endocr Relat Cancer.* (2001) 8:71–3. doi: 10.1677/erc.0.0080071

6. Catford SR, Lee KT, Pace MD, Marasco SF, Longano A, Topliss DJ. Cardiac metastasis from thyroid carcinoma. *Thyroid.* (2011) 21:855–66. doi: 10.1089/thy.2010.0273

7. Rühli FJ, Hilfiker PR. Metastasis of thyroid cancer to the heart. *Am J Roentgenol.* (2001) 177(2):474. doi: 10.2214/ajr.177.2.1770474

8. Shai SE, Hsieh SR, Song YM, Shen GH. Resection of follicular thyroid cancer metastasized to the left lower lobe of the lung extending into the left atrium as a huge intracardiac tumor. *Thyroid.* (2005) 15:1417–8. doi: 10.1089/thy.2005.15.1417

9. Bertoldi EG, Severo MD, Scheffel RS, Foppa M, de Azevedo MJ, Maia AL. Left atrial metastases of poorly differentiated thyroid carcinoma diagnosed by echocardiography and magnetic resonance imaging—case report and review of literature. *Echocardiography.* (2012) 29:30–3. doi: 10.1111/j.1540-8175.2011.01549.x

10. Giovanella L, Treglia G, Ceriani L, Weidner S, Perriard U, Bongiovanni M. Left atrial metastasis of Hürthle-cell thyroid carcinoma mimicking myxoma. *J Nucl Cardiol.* (2014) 2:406–7. doi: 10.1007/s12350-013-9826-8

11. Sood A, Parihar AS, Sood A, Kumar R, Prakash G, Singhal M, et al. Unusual presentation of Hurthle cell carcinoma with TENIS syndrome as left atrial thrombus on 18F-FDG PET/CT. *Clin Nucl Med.* (2018) 43:352–4. doi: 10.1097/RLU.0000000000002224

12. Cassar MP, Strirrup J. Left atrial tumor thrombus in metastatic thyroid cancer. *J Cardiovasc Comput Tomogr.* (2020) 14:155–6. doi: 10.1016/j.jcct.2019.12.005

13. Kaul S, Tulchinsky M, Campbell DB, Crist HS, Manni A. Isolated cardiac metastasis from papillary thyroid cancer: prolonged survival with late diagnosis related to inadequate positron emission tomography preparation. *Thyroid.* (2012) 22:443–4. doi: 10.1089/thy.2011.0295

14. Tricard J, Chermat A, Abdelkafi E, Piccardo A. Giant intracardiac medullary thyroid cancer metastasis. *J Card Surg.* (2022) 37:5455–6. doi: 10.1111/jocs.17162

15. Hasegawa S, Otake Y, Bando T, Cho H, Inui K, Wada H. Pulmonary dissemination of tumor cells after extended resection of thyroid carcinoma with cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* (2002) 124:635–6. doi: 10.1067/mtc.2002.125060

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 05 June 2024
DOI 10.3389/fcvm.2024.1385253

OPEN ACCESS

EDITED BY
Yoshitaka Iso,
Showa University Fujigaoka Hospital, Japan

REVIEWED BY
Helmut Lieder,
University of Duisburg-Essen, Germany
Peng Zhu,
Southern Medical University, China

*CORRESPONDENCE
Jiyue Xiong
✉ xiongjiyue028@163.com

†These authors have contributed equally to this work

RECEIVED 12 February 2024
ACCEPTED 22 May 2024
PUBLISHED 05 June 2024

CITATION
Yu X, Xiong W, Zhang J, Lin J, Wang B, Huang H, Du L and Xiong J (2024) Comparison of "Huaxi-1" or "histidine-tryptophan-ketoglutarate" cardioplegia in an animal model.
Front. Cardiovasc. Med. 11:1385253.
doi: 10.3389/fcvm.2024.1385253

Comparison of "Huaxi-1" or "histidine-tryptophan-ketoglutarate" cardioplegia in an animal model

Xiang Yu[1†], Wen Xiong[1,2†], Jie Zhang[3], Jing Lin[1], Bo Wang[1], Hong Huang[4], Lei Du[1] and Jiyue Xiong[1*]

[1]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Anesthesiology, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha, Hunan, China, [3]Key Laboratory of Transplant Engineering and Immunology, West China Hospital, Sichuan University, Chengdu, China, [4]Chengdu Qingshan Likang Pharmaceutical Co. Ltd., Research and Development Department, Chengdu, Sichuan, China

Background: Using a pig model of cardiopulmonary bypass, we compared outcomes after cardioplegia either with our in-house "Huaxi-1" solution containing natural blood and crystalloid or with the entirely crystalloid, commercially available "histidine-tryptophan-ketoglutarate" solution.
Methods: Cardiopulmonary bypass was established in 13 healthy male pigs. Twelve of those animals were randomized to receive a single dose of either Huaxi-1 or entirely crystalloid cardioplegia, while the remaining animal was assigned to receive Huaxi-1 without randomization. All animals were then subjected to whole-heart ischemia for 90 min, followed by 2 h of reperfusion, after which myocardial injury was assessed in terms of cardiac function, myocardial pathology and levels of biomarkers in plasma, while levels of high-energy phosphate in myocardium were assayed using liquid chromatography.
Results: Animals given Huaxi-1 cardioplegia required significantly less time to be weaned off bypass, they received significantly lower doses of norepinephrine, and they showed significantly higher levels (mean ± SD) of adenosine triphosphate (14 ± 4 vs. 8 ± 2 μg/mg, $P = 0.005$), adenosine diphosphate (16 ± 2 vs. 13 ± 2 μg/mg, $P = 0.046$), and total adenine nucleotide (37 ± 4 vs. 30 ± 3 μg/mg, $P = 0.006$) in myocardium after 2 h of reperfusion. They also showed less severe bleeding, edema and injury to mitochondria and myofibers in myocardium. The two groups did not differ significantly in doses of inotropic drugs received, cardiac output or levels of biomarkers in plasma.
Conclusions: In this animal model of healthy hearts subjected to 90 min of ischemia, Huaxi-1 cardioplegia may be superior to entirely crystalloid cardioplegia for promoting energy generation and attenuating ischemia/reperfusion injury in myocardium.

KEYWORDS

cardiopulmonary bypass, cardioplegia, histidine-tryptophan-ketoglutarate solution, myocardial protection, animal experiment

Introduction

Stopping the heart during cardiac surgery is necessary in order to maintain a clear surgical field, but it exposes the heart to ischemia/reperfusion injury. To compensate for this, patients are routinely given cardioplegia solution composed either of a mixture of human blood and crystalloid or of only crystalloid (1–3). Cardioplegia solution is

meant to provide a high concentration of metabolic substrates in order to protect the myocardium. Adding blood to the crystalloid can also provide oxygen and potassium.

Several cardioplegia solutions have been commercialized in different countries and are widely used, but which formulations lead to better prognosis is difficult to predict in advance. Also unclear is whether, and under which conditions, blood-crystalloid cardioplegia leads to better outcomes than crystalloid-only cardioplegia. Chinese hospitals typically prepare cardioplegia solutions in-house according to internal practices, or they purchase the entirely crystalloid cardioplegia solution "histidine-tryptophan-ketoglutarate" (HTK) (4), which is the only cardioplegia formulation commercially available in the country and is widely used in other countries (5, 6). HTK cardioplegia can effectively protect the myocardium by reducing energy metabolism (1, 7). Nevertheless, our medical center, where more than 2,000 cardiac surgeries are performed each year, routinely uses an in-house formulation called "Huaxi-1" cardioplegia solution, which was developed in 2007 by mixing blood and custom-designed crystalloid. Though it has not yet been approved by the China Food and Drug Administration, Huaxi-1 cardioplegia has consistently given satisfactory results since its implementation.

We wondered how outcomes after cardiac surgery with this in-house formulation compared to outcomes after use of HTK. Therefore we compared the two cardioplegia solutions in a pig model of cardiopulmonary bypass involving healthy hearts.

Material and methods

Animal procedures were approved by the Institutional Animal Care Committee of West China Hospital, Sichuan University (2021011A) and conducted in compliance with the "Guidelines for Animal Experimentation" of Sichuan University.

Animals and cardioplegia solutions

Fourteen male pigs approximately 4 months old and weighing 53.7 ± 3.1 kg (Dashuo Laboratory Animals, Chengdu, China) were housed for one week at the Laboratory Animal Center of West China Hospital, then fasted for 12 h with *ad libitum* access to water immediately before the surgical procedures. One was exited from the study because of coronary artery injury during thoracotomy. Twelve animals were randomized 1:1 according to sealed, opaque envelopes to receive one of two cardioplegia solutions. An additional animal was assigned to the Huaxi-1 group without randomization. Female pigs were not used in the study because estrogen may exert cardioprotective effects that might have confounded our analysis (8).

Cardioplegia solutions were obtained as ready-to-use HTK crystalloid (Koehler Chemie, Alsbach-Hähnline, Germany) or prepared in-house by mixing pig blood with commercial crystalloid (Qingshan Likang, Chengdu, China) in a 4:1 (blood: crystalloid) ratio. The crystalloid contains the following components per 1,000 ml: sodium chloride (7.3 g), mannitol (13.29 g), magnesium sulfate (8.3 g), lidocaine hydrochloride (0.57 g), glucose injection (2.52 g), sodium bicarbonate (5.0 g), and insulin (12 Units). The compositions of the two solutions are shown in Table 1. The cardioplegia solutions were prepared and labelled before surgery by a researcher who was not involved in allocating animals to groups or in analyzing their tissues after surgery.

Procedures prior to cardiopulmonary bypass

Animals were administered Zoletil (100 mg; Virbac, Carros, France) and atropine (0.5 mg; Sunnyhope, Chengdu, China) intramuscularly, then midazolam (5 mg/kg; NHWA, Xuzhou, Chnia) and propofol (4 mg/kg; 1% Disoprivan, Corden Pharma, Caponago, Italy) intravenously. Animals were intubated and mechanically ventilated with a volume-controlled ventilator (Datex-Ohmeda Excel 210, Soma Technology, Cheshire, CT, USA) at an inspired oxygen fraction of 0.4 and respiratory frequency of 16–18 per minute. Throughout the procedure, tidal volume was adjusted to maintain arterial partial pressures of CO_2 at 35–45 mmHg and O_2 above 100 mmHg. Anesthesia was maintained through continuous intravenous infusion of propofol (60–120 mcg/kg per min) and midazolam (0.1 mcg/kg per h) as well as vecuronium bromide (0.2 mg/kg per h) to relax muscles. When necessary, animals received 1% isoflurane by inhalation.

Throughout the procedure, PICCO monitoring was performed (Pulsion, Feldkirchen, Germany) via a 7-F catheter (Scw Medicath, Shenzhen, China) inserted into the internal jugular vein. Cardiac output was measured continuously with the PICCO monitor, and the left ventricular ejection fraction was determined before bypass using an EPIQ Elite echocardiograph (Philips, Amsterdam, Netherlands) and the Teichholz method (9).

TABLE 1 Composition of the crystalloid components of the two cardioplegia solutions in this study.

Ion or molecule	Concentration, mmol/L	
	Huaxi-1 solution[a]	HTK solution
K^+	20.77 (4.5)	9
Mg^{2+}	6.88 (0.9)	4
Na^+	146 (140)	15
Ca^{2+}	0.25 (1.24)	0.02
HCO_3^-	31.1 (25)	0
Cl^-	120.94 (102)	100
SO_4^{2-}	7.68 (2)	0
Mannitol	13.17	29.97
Glucose	6.52 (5)	0
Lidocaine	0.35	0
Histidine	0	198
Tryptophan	0	2
Ketoglutarate	0	1

HTK, Histidine-tryptophan-ketoglutarate.
[a]Concentrations of ions or molecules in the blood component of this solution are indicated in parentheses.

Arterial blood pressure was monitored continuously via a 20-G arterial catheter (BD Bioscience, Sussex, NJ, USA) that had been inserted into the right femoral artery under ultrasound guidance.

Nasopharyngeal and venous blood temperatures were measured continuously using a thermistor integrated into the cardiopulmonary bypass circuit. Urinary output was measured regularly via a 14-F bladder catheter. Body temperature was maintained using a heating blanket. Hydration was maintained by administering Ringer's lactate solution at 10–30 ml/kg per h.

Cardiopulmonary bypass, cardioplegia, and whole-heart ischemia

Sternotomy was performed to expose the heart. A bolus of heparin (375 U/kg) was injected intravenously, which prolonged activated clotting time beyond 480 s as determined using an ACT-II system (Medtronic, Minneapolis, MN, USA). Arterial perfusion occurred via a 20-F ascending aortic cannula, while venous drainage occurred via a 28-F right atrial cannula (Medtronic).

The cardiopulmonary bypass circuit comprised a roller pump (Maquet, Rastatt, Germany), a Fusion membrane oxygenator (Medtronic) and, when necessary, a hemoconcentrator (Sorin, Mirandola, Italy). The circuit was primed with 750 ml of succinylated gelatin (B. Braun, Melsungen, Germany) and 250 ml of mannitol. Bypass was initiated with blood flow at 70 ml/kg, and the aorta was cross-clamped to allow delivery of HTK or Huaxi-1 cardioplegia solution. All animals received cardioplegia solution at 4–8°C for 5 min at a pressure of 150 mmHg in the antegrade direction from the aortic root using an XJ-40-20 delivery system (Xijing Medical Appliances, Xi'an, China).

During bypass, nasopharyngeal temperature was approximately 34°C, and mean arterial blood pressure was maintained at 60–80 mmHg. The left ventricle was decompressed during heart arrest via a venting catheter (Medtronic). During ischemia, ice was placed inside the pericardium to cool the heart. Cardioplegia was repeated for another 5 min if the electrocardiograph detected cardiac activity.

Whole-heart ischemia was performed for 90 min, which is the maximal typical duration in Chinese cardiac centers using HTK cardioplegia. Then the cross-clamp was removed to allow reperfusion for 120 min. If ventricular fibrillation occurred, lidocaine (1 mg/kg) and amiodarone (150 mg) were administered; if fibrillation persisted, electroshocks were applied. The left ventricular ejection fraction was determined at 30, 60 and 120 min after declamping.

Animals were weaned off bypass if they showed nasopharyngeal temperature of 37°C, systolic blood pressure >90 mmHg, diastolic blood pressure of 50–75 mmHg, heart rate of 70–120 beats/min, arterial partial O_2 pressure >100 mmHg, and normal electrolyte levels. Animals could receive inotropic support comprising epinephrine, norepinephrine, milrinone and vasopressin if necessary in order to maintain the mean arterial pressure above 60 mmHg and the cardiac index above 2 L/min per m^2. The decision to provide inotropic support was based on the animal's vasoactive-inotropic score (10). Weaning was considered a failure if hemodynamics did not stabilize within 2 h on cardiopulmonary bypass.

All animals received protamine in a 1:1 ratio to heparin, after which all cannulae were removed.

Analysis of blood

Blood samples were harvested from the central vein before surgery, after 85 min of ischemia, and after 30, 60, and 120 min after reperfusion. Samples were centrifuged at 4°C, and the plasma was assayed against creatine kinase isoenzyme, cardiac troponin I, cardiac troponin T, brain natriuretic peptide and lactic dehydrogenase using enzyme-linked immunosorbent assays from LSBio (Seattle, WA, USA). Investigators who sampled and analyzed blood were blinded to which type of cardioplegia solution each animal received.

Analysis of myocardial tissue

At the end of 2-h reperfusion, animals were euthanized using an overdose of potassium, then myocardial samples of the left ventricular apex were harvested and stored in liquid nitrogen for subsequent assay for levels of high-energy phosphate in myocardium, or fixed in 4% paraformaldehyde for subsequent histology, or fixed in 2.5% glutaraldehyde for subsequent electron microscopy. Investigators who prepared and analyzed these tissues were blinded to which type of cardioplegia solution each animal received.

For assay of high-energy phosphate, myocardial tissue (100 mg) was added to 1 ml of ATP buffer (catalog no. BC0304, Solarbio, Beijing, China), mechanically homogenized using a SCIENTZ-48 system (Ningbo Scientz Biotechnology, Ningbo, China), and centrifuged at 13,000 g for 10 min at 4°C. Equal amounts of protein for each sample were mixed with 5% perchloric acid, centrifuged again at 20,000 g for 15 min at 4°C, and the resulting protein-free supernatant was neutralized with 3 M K_2CO_3 (pH 6.5–6.7).

Supernatant was analyzed using a Series 1,100 HPLC System (Agilent Technologies, Santa Clara, CA, USA) with detection at 262 nm. Chromatographic separation was performed on a Chromplus C18 column (5 μm, 250 × 4.6 mm; Swell, Chengdu, China) at 25°C. The mobile phase consisted of 6 mmol/L tetrabutylammonium hydroxide in 0.05 mol/L phosphate buffer (pH 6.0) (A) and acetonitrile (B) in the A:B ratio 91:9. Supernatant (10 μl) was injected and eluted at a flow rate of 1 ml/min.

For histology, myocardial tissue was fixed overnight in 4% paraformaldehyde solution and dehydrated through an ethanol gradient. Then samples were paraffin-embedded and cut into 4-μm sections for staining with hematoxylin-eosin. Sections were examined at 40× magnification under a bright field microscope (Zeiss, Jena, Germany). Sections were graded based on the extent of bleeding, edema, damage to myocardial fibers and infiltration

by inflammatory cells. The severity of these four features was graded as not obvious (0 point), slight (1 point), moderate (2 points), extensive (3 points) or severe (4 points) (11). Scores were averaged from five tissue sections per animal in order to obtain the final score for each animal.

For electron microscopy, sections were prepared and analyzed under an HT7800 transmission electron microscope (Hitachi, Tokyo, Japan). Abnormal ultrastructure of nuclei, mitochondria and myofibers was categorized as described previously (12–14). In brief, nuclei were scored as (1) if the nuclear membrane was intact, nuclear ultrastructure was clear, and the nucleolus was obvious; (2) if the nuclear membrane was wrinkled, heterochromatin had accumulated around the perimeter of the nuclear membrane, and the nucleolus was visible; or (3) if the nuclear membrane had dissolved and the nucleolus was unclear. Mitochondria were scored as 0 if they appeared normal; (1) if their overall structure seemed normal but they lacked matrix granules; (2) if they were swollen and the matrix was clear; (3) if they were swollen, the matrix was clear, and they showed ridge fracture or matrix fusion; or (4) if they showed the same features as for 3 points as well as destruction of inner and outer membranes. Myofibers were scored as (1) if the myofibrillar cleft was ordered and the myotome clear; (2) if they showed some fusion and the myotome was unclear; or (3) if they showed swelling, disorder or fracture and the myotome was unclear. These scores were averaged for three randomly selected fields of view at 8,000× per animal.

Statistical analysis

Data were analyzed using SPSS 26 (IBM, Chicago, IL, USA), and GraphPad Prism 9 (GraphPad, Boston, MA, USA) was used to prepare data plots. Categorical data were reported as n (%), and intergroup differences were assessed for significance using Fisher's exact probability method. Continuous data were reported as mean ± standard deviation or median (interquartile range), and intergroup differences were assessed using the independent-samples t-test if the data were normally distributed, or using the Wilcoxon test otherwise. Differences associated with $P < 0.05$ were considered significant.

Results

Here we compared our in-house blood cardioplegia product Huaxi-1 to HTK cardioplegia, which lacks glucose and insulin that can promote energy generation in the myocardium (Table 1). Of the fourteen animals initially included, one was exited from the study because of coronary artery injury during thoracotomy. The remaining animals were included in the final analysis of the Huaxi-1 group ($n = 7$) and HTK group ($n = 6$). The Huaxi-1 and HTK groups did not differ significantly in terms of pig weight before the procedure (52.5 ± 3.6 kg vs. 55 ± 1.8 kg, $P = 0.16$), perfusion pressure (147 ± 11 mmHg vs. 150 ± 6 mmHg, $P = 0.58$), or use of lidocaine, amiodarone or defibrillation to restore sinus rhythm (data not shown). Two animals in the HTK group and one in the Huaxi-1 group were administered amiodarone because of defibrillation after cross-clamp removal. None of the animals showed electrocardiographic activity during the 90-min ischemia, so all animals received only one 5-min dose of their assigned cardioplegia solution. All animals were successfully weaned off cardiopulmonary bypass, which occurred within 30 min after the start of reperfusion in all but one animal in the HTK group.

The Huaxi-1 group received significantly smaller volume of cardioplegia solution [1,250 (1,250, 1,250) vs. 1,550 (1,500, 1,713) ml, $P = 0.001$], experienced cardiac arrest significantly sooner after the start of cardioplegia delivery (28 ± 7 vs. 78 ± 52 s, $P = 0.028$), and was weaned off bypass significantly sooner after the start of reperfusion (13 ± 9 vs. 29 ± 14 min, $P = 0.039$).

The two groups did not differ significantly in hemodynamics (Table 2) or requirement for inotropic drugs (Table 3), except that a significantly lower dose of norepinephrine was given to the Huaxi-1 group.

At the end of the experiment, the apical myocardium in the left ventricle of Huaxi-1 animals contained significantly higher levels of adenosine triphosphate (14 ± 4 vs. 8 ± 2 μg/mg) and adenosine diphosphate (16 ± 2 vs. 13 ± 2 μg/mg; Figure 1). As a result, the same tissue from Huaxi-1 animals also showed significantly higher levels of total adenine nucleotide (36.7 ± 3.8 vs. 29.8 ± 3.3 μg/mg) and energy charge (0.6 ± 0.07 vs. 0.5 ± 0.04). These results suggest that Huaxi-1 cardioplegia provided greater energy to the myocardium.

TABLE 2 Comparison of hemodynamic parameters in the two groups of animals.

Parameter	Minutes after reperfusion start[a]	Cardioplegia solution		P
		Huaxi-1	HTK	
Systolic blood pressure (mmHg)	0	100 ± 11	101 ± 12	0.85
	30	104 ± 6	103 ± 12[b]	0.79
	60	99 ± 15	100 ± 14	0.91
	120	105 ± 18	97 ± 13	0.38
Diastolic blood pressure (mmHg)	0	55 ± 10	57 ± 13	0.74
	30	55 ± 9	48 ± 9[b]	0.16
	60	50 ± 7	48 ± 15	0.72
	120	51 ± 11	49 ± 9	0.66
Mean arterial pressure (mmHg)	0	71 ± 9	73 ± 14	0.79
	30	74 ± 7	67 ± 9[b]	0.17
	60	69 ± 10	66 ± 14	0.63
	120	72 ± 14	68 ± 7	0.54
Ejection fraction (%)	0	61 ± 1	61 ± 1	0.97
	30	61 ± 3	59 ± 1[b]	0.15
	60	61 ± 2	60 ± 2	0.58
	120	61 ± 2	60 ± 1	0.97
Cardiac output (L/min)	0	4.08 ± 0.65	4.25 ± 0.71	0.65
	30	4.38 ± 0.92	4.02 ± 0.87[b]	0.52
	60	4.72 ± 0.76	4.21 ± 0.61	0.21
	120	4.96 ± 0.63	5.0 ± 0.88	0.91

Values are mean ± SD, unless otherwise noted. HTK, histidine-tryptophan-ketoglutarate.
[a]The "0" time point refers to before bypass.
[b]Data are from five of the six animals because one animal could not be weaned from bypass within 30 min after the start of reperfusion.

TABLE 3 Comparison of vasoactive drugs given to the two groups of animals.

Parameter	Minutes after reperfusion start	Cardioplegia solution		*P*
		Huaxi-1	HTK	
Epinephrine dose, mcg/min per kg	30	0.02 [0.00, 0.03]	0.06 [0.01,0.18]	0.15
	60	0.01 [0.00, 0.03]	0.03 [0.01,0.05]	0.15
	120	0.01 [0.00, 0.03]	0.03 [0.01,0.05]	0.24
Animals receiving epinephrine	30	4 (57.1)	6 (100)	0.19
	60	4 (57.1)	6 (100)	0.19
	120	4 (57.1)	5 (85.5)	0.56
Norepinephrine dose, mcg/min per kg	30	0.00 [0.00, 0.00]	0.00 [0.00,0.00]	0.82
	60	0.00 [0.00, 0.00]	0.01 [0.00,0.03]	0.12
	120	0.00 [0.00, 0.00]	0.04 [0.00,0.05]	0.03
Animals receiving norepinephrine	30	1 (14.3)	1 (16.7)	1.00
	60	1 (14.3)	3 (50)	0.27
	120	1 (14.3)	4 (66.7)	0.10
Maximum VIS score	30	1.86 ± 0.7	9.33 ± 3.61	0.09
	60	1.57 ± 0.61	5.33 ± 1.54	0.06
	120	1.57 ± 0.61	6.33 ± 2.32	0.09

Values are *n* (%) or median [interquartile range], unless otherwise noted. VIS, the vasoactive inotropic score.

Myocardial endocardium after 2 h of reperfusion showed petechial hemorrhaging but was intact in Huaxi-1 animals, whereas it showed numerous hemorrhagic patches in HTK animals, leading to significantly lower histopathology scores for bleeding and edema in Huaxi-1 animals (Figure 2). Tissue from the two groups showed similar levels of endocardial infiltration by inflammatory cells. Electron microscopy revealed significantly less damage to mitochondria and myofibers in the myocardium of Huaxi-1 animals (Figure 3). Neither group showed obvious damage to nuclear ultrastructure. These results suggest that Huaxi-1 cardioplegia was associated with less cellular and subcellular damage to the myocardium.

All the measured markers of myocardial injury in plasma were similar between the two groups of animals after 2 h of reperfusion, except that the Huaxi-1 group showed significantly lower levels of creatine kinase isoenzyme (Figure 4). Levels of sodium ion in plasma remained normal in Huaxi-1 animals throughout the procedure, whereas sodium levels fell significantly after HTK cardioplegia (138 ± 2 vs. 121 ± 5 mmol/L, $P < 0.01$) and remained low through the end of the procedure (Figure 5). These results suggest that Huaxi-1 cardioplegia was more effective at maintaining normal electrolyte levels in plasma.

Discussion

Our study with a pig model of cardiopulmonary bypass involving healthy hearts suggests that the combination of blood and crystalloid in Huaxi-1 cardioplegia solution leads to higher concentrations of high-energy phosphates in myocardium, faster recovery of cardiac function, less myocardial injury, and stabler concentrations of sodium and potassium ions in plasma than the entirely crystalloid HTK cardioplegia solution. Even so, a single dose of either type of

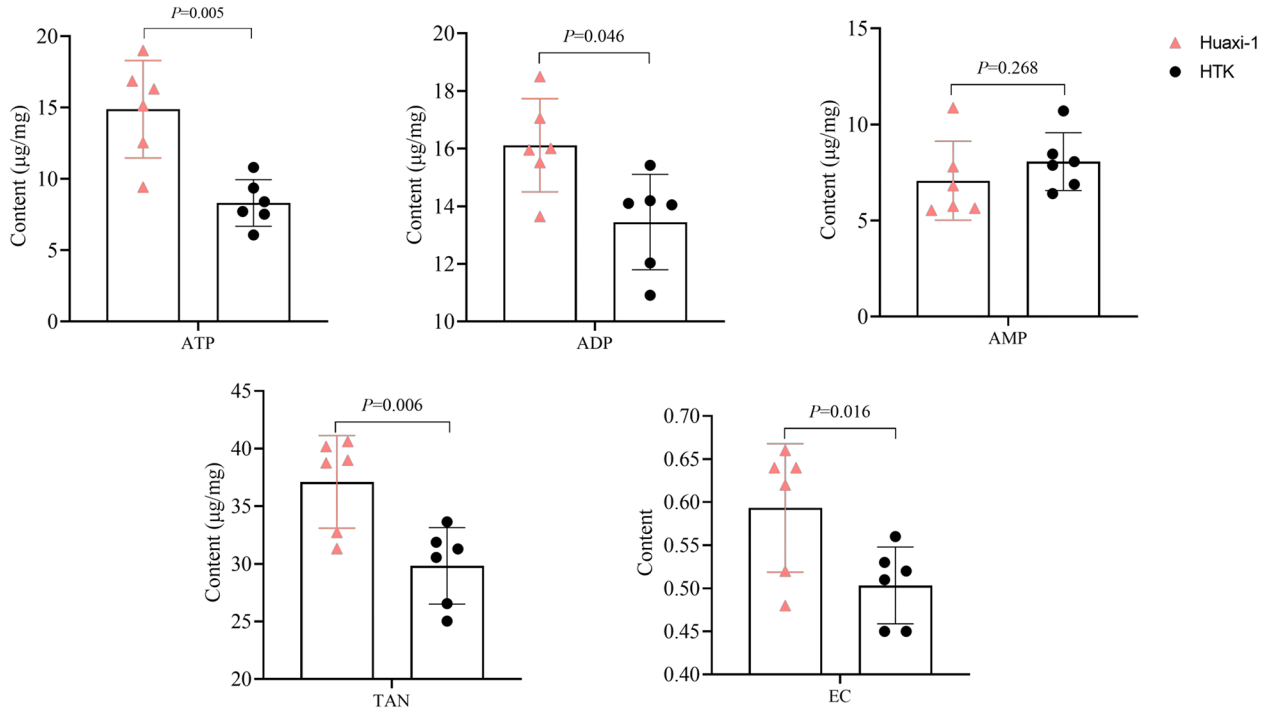


FIGURE 1
Levels of high-energy phosphate and other energy indices in left ventricular apical myocardium in each animal group after 2 h of reperfusion. ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; EC, energy charge; HTK, histidine-tryptophan-ketoglutarate; TAN, total adenine nucleotide.

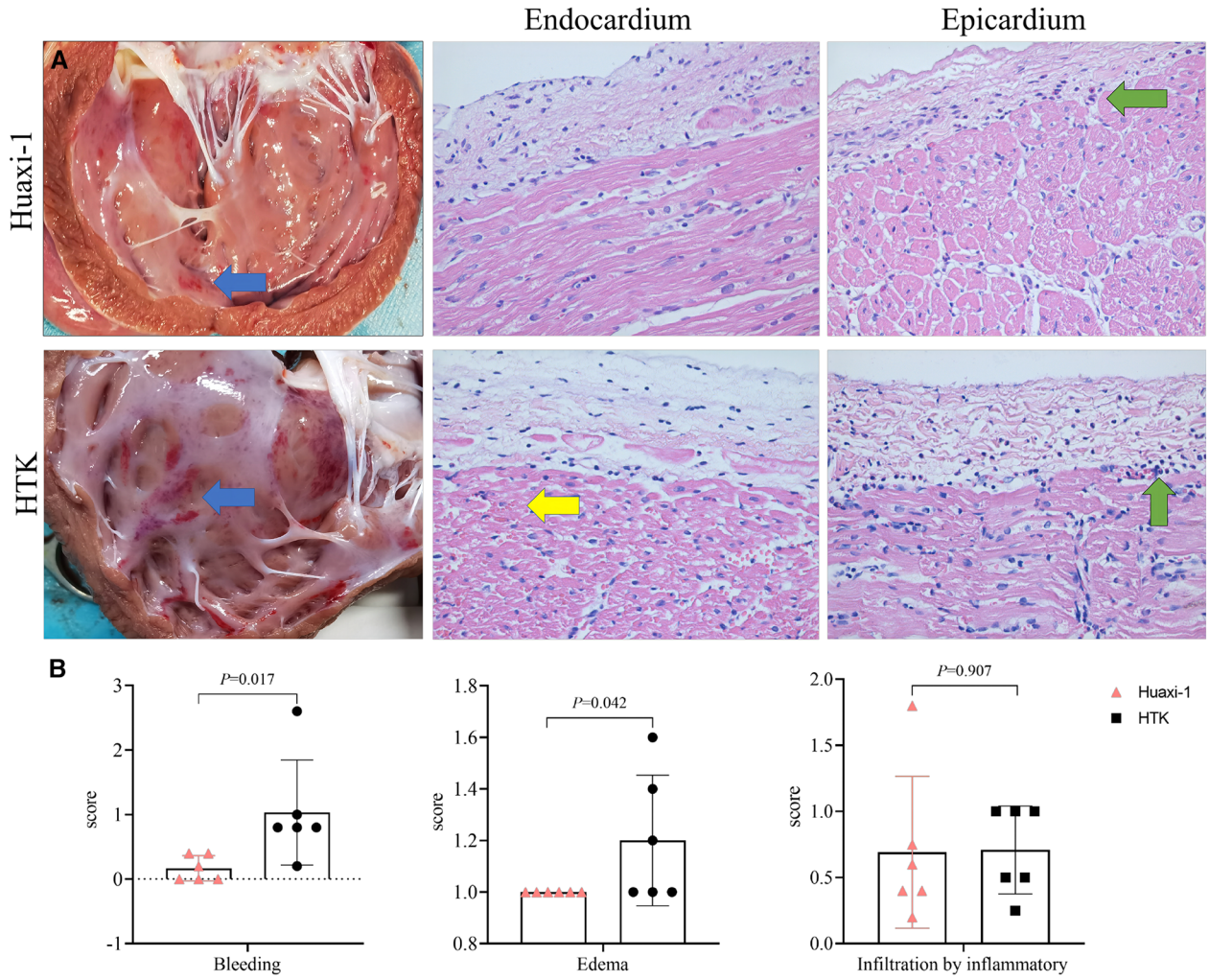


FIGURE 2
Comparison of myocardial pathology between the two groups of animals at the end of surgery. (A) Histopathology of thin sections of heart after staining with hematoxylin-eosin. The *left* column shows representative photographs of the myocardium, in which blue arrows indicate sub-endocardial bleeding. The *middle* column shows representative micrographs of endocardium, in which the yellow arrow indicates microcirculatory bleeding in the sub-endocardium. The *right* column shows representative micrographs of epicardium, in which green arrows indicate infiltration by inflammatory cells. Magnification, 40×. (B) Histopathology scores for bleeding, edema and infiltration by inflammatory cells. HTK, histidine-tryptophan-ketoglutarate.

cardioplegia led to recovery from 90-min whole-heart ischemia in all animals.

The two types of cardioplegia solution reflect different approaches to improving myocardial energy production during heart arrest. During myocardial ischemia, glucose is favored as an energy source and aerobic metabolism is favored over glycolysis, reducing the reliance on free fatty acids that normally occurs in the presence of adequate oxygen (15). In Huaxi-1 cardioplegia, the blood provides substantial oxygen, while the crystalloid provides magnesium ions, glucose and insulin to promote glucose uptake, thereby promoting glycolysis. In parallel, the natural buffers in the blood as well as the sodium bicarbonate in the crystalloid help to neutralize lactic acid and provide an adequate pH environment for glycolytic enzymes. HTK cardioplegia solution, in contrast, carries little oxygen, but it provides α-ketoglutarate and tryptophan to promote glycolysis. It also contains histidine buffer to provide a suitable pH environment (16). Our results suggest that inclusion of blood in cardioplegia solution may lead to higher levels of high-energy phosphates in myocardium.

Huaxi-1 cardioplegia was associated with less injury to mitochondria in our study. Ischemia damages mitochondria by altering the function of Na^+-K^+ and Na^+-H^+ pumps (17), by triggering Ca^{2+} overload (18), and by promoting the production of reactive oxygen species (19–21). Huaxi-1 was associated with less microcirculatory bleeding and myocardial edema, which may reflect that the much lower Na^+ concentration in HTK cardioplegia solution damages endothelial cells (22, 23); indeed, pigs treated with this solution showed hyponatremia through the end of the procedure. Myocardial edema can stiffen the

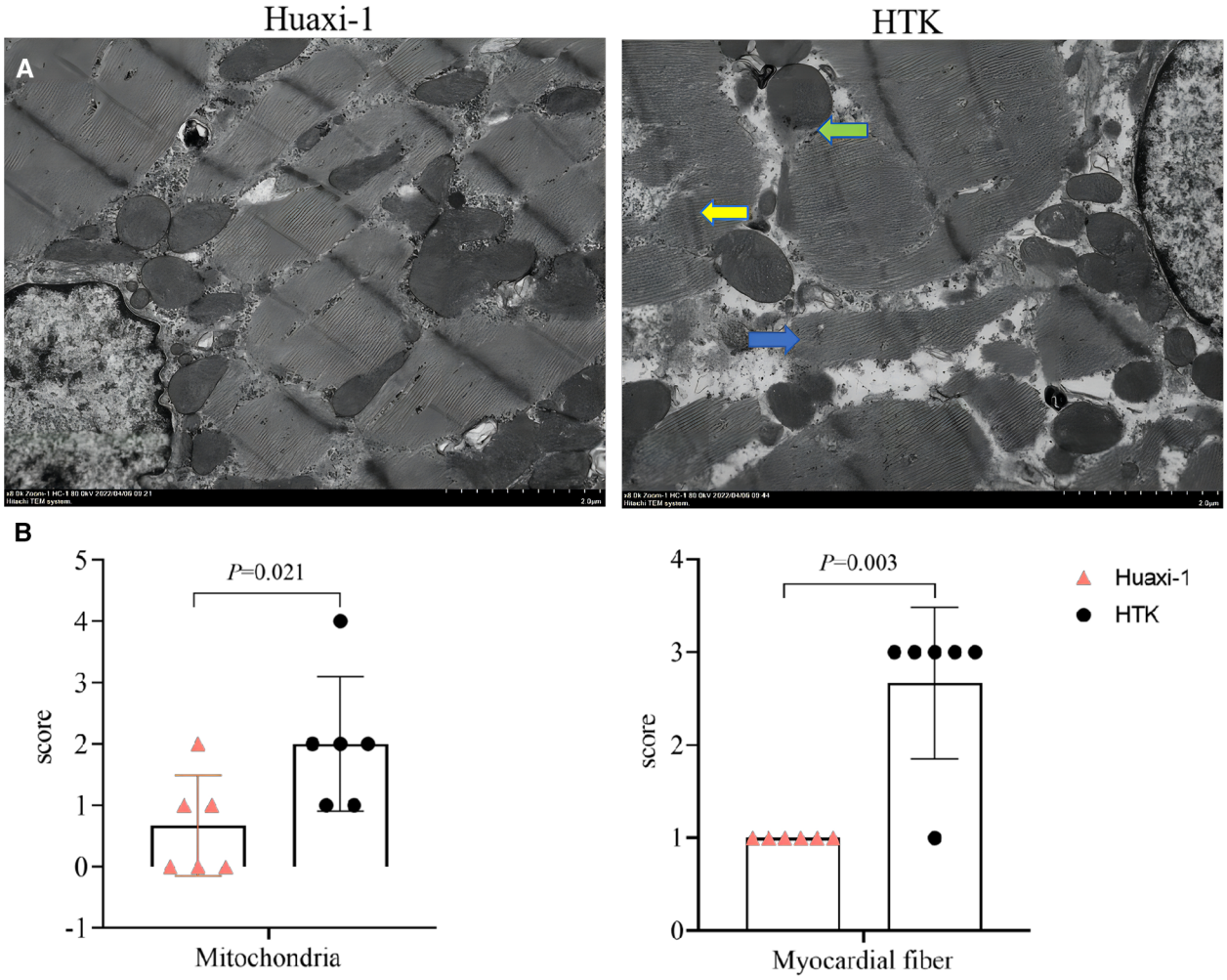


FIGURE 3
Transmission electron micrographs of myocardial tissue from the two groups of animals at the end of surgery. (A) Representative micrographs are shown. The green arrow indicates mitochondrial membrane rupture; the blue arrow, disruption of myocardial fibers; and the yellow arrow, distortion of the Z line with partial expansion of intercalated discs and sarcoplasmic reticulum. Scale bar, 2.0 μm. (B) Scores for severity of pathology observed in mitochondria and myocardial fibers. HTK, histidine-tryptophan-ketoglutarate.

ventricular wall and thereby impair cardiac function (24). Although the two types of cardioplegia solution in our study led to similar levels of cardiac function based on echocardiography, Huaxi-1 solution was associated with milder myocardial injury and faster recovery of cardiac function, as indicated by shorter weaning time, lower levels of creatine kinase isoenzyme in plasma, and lower requirement for inotropic norepinephrine.

Our finding that mixed blood-crystalloid cardioplegia led to better outcomes than entirely crystalloid cardioplegia is consistent with studies that have associated HTK cardioplegia with lower cardiac index and ventricular function soon after surgery (25) and higher incidence in spontaneous ventricular fibrillation (26) than cold blood cardioplegia. Our network meta-analysis comparing several types of cardioplegia solutions containing only crystalloid or a combination of crystalloid and blood linked HTK cardioplegia solution to the highest risk of mortality (27). This evidence base argues for including a substantial component of natural blood in cardioplegia solutions.

Our results should be interpreted with caution given that we used only male pigs with healthy hearts. While a previous comparison of cardioplegia solutions also involved only animals with healthy hearts (28), future studies may wish to use animals of both sexes with comorbidities (29, 30) in order to explore the generalizability of our findings to a broad range of patients, especially those with cardiac pathologies. Using propofol as anesthetic, which mimics routine practice with patients at our hospital, may have confounded our analysis because it may exert cardioprotective effects (31). Nevertheless, any confounding should have been balanced between the two groups because both received the same propofol dose. Similarly, amiodarone, which we gave to animals showing ventricular defibrillation, can exert cardioprotective effects (32), yet its frequency of use did not differ significantly between the two groups. We assessed levels of high-energy phosphate and histopathology in myocardial tissue at one time point, after 2 h of reperfusion. It would be important to compare outcomes at different stages of

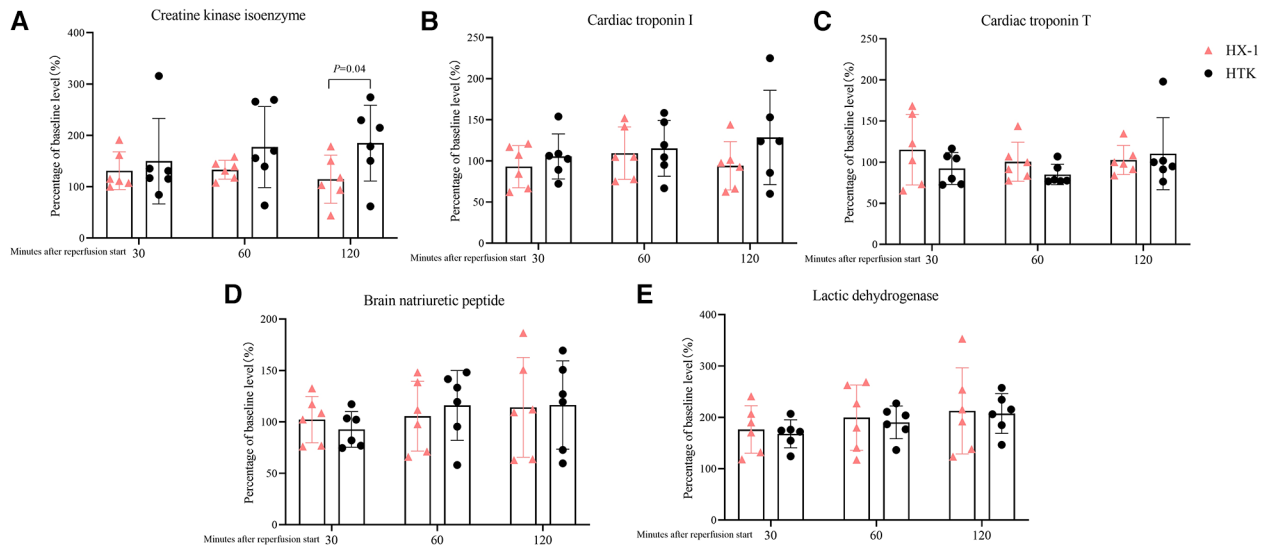


FIGURE 4
Comparison of levels of myocardial injury markers in plasma at different times after surgery between the two groups of animals. (A) Creatine kinase isoenzyme. (B) Cardiac troponin I. (C) Cardiac troponin T. (D) Brain natriuretic peptide. (E) Lactic dehydrogenase. HX-1, Huaxi-1; HTK, histidine-tryptophan-ketoglutarate.

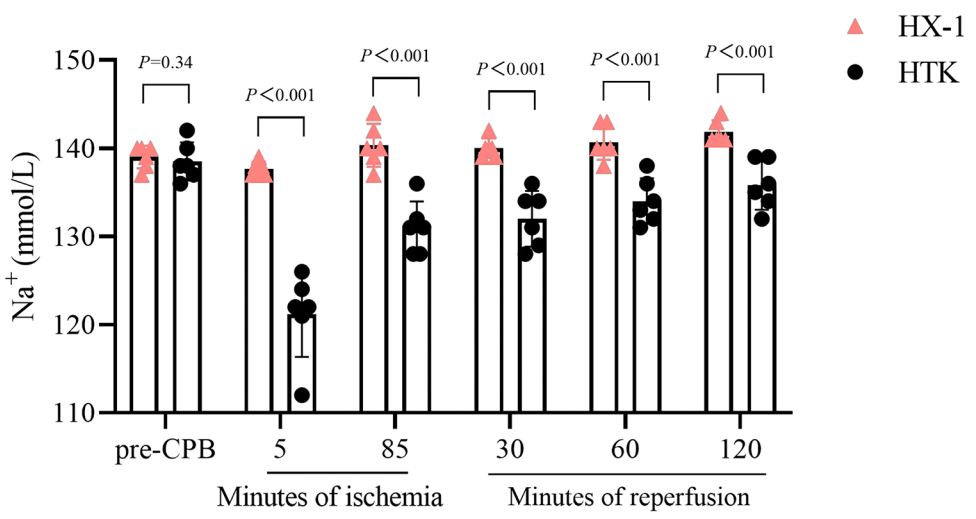


FIGURE 5
Comparison of sodium ion concentration in serum at different times during surgery between the two groups of animals. HX-1, Huaxi-1; HTK, histidine-tryptophan-ketoglutarate.

the bypass procedure, including at the end of ischemia and after longer periods of reperfusion.

Despite these limitations, our study involving healthy pig hearts suggests that combining crystalloids with natural blood may protect the myocardium from 90 min of whole-heart ischemia/reperfusion injury better than crystalloid on its own. The superiority appears to lie at least partly in the ability of blood to provide higher levels of high-energy phosphates to drive cardiac metabolism after arrest, despite the fact that HTK cardioplegia solution contains various amino acids and metabolic substrates.

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.

Ethics statement

The animal study was approved by Laboratory Animal Ethics Committee, West China Hospital, Sichuan University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

XY: Writing – original draft, Writing – review & editing, Data curation, Formal Analysis. WX: Writing – original draft, Methodology, Project administration. JZ: Writing – original draft, Conceptualization, Writing – review & editing. JL: Writing – original draft, Writing – review & editing, Supervision, Validation. BW: Writing – original draft, Writing – review & editing, Formal Analysis, Methodology. HH: Methodology, Writing – original draft, Supervision. LD: Supervision, Writing – original draft, Project administration, Software, Writing – review & editing. JX: Project administration, Supervision, Writing – original draft, Writing – review & editing, Resources.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

This study was supported by the "1•3•5 Project for Disciplines of Excellence" from West China Hospital, Sichuan University (grant 2017-120). The funders did not have any role in the design of the study; acquisition, analysis or interpretation of the data; or drafting of the manuscript.

Conflict of interest

HH was employed by the Chengdu Qingshan Likang Co. Ltd.

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1385253/full#supplementary-material

References

1. Vivacqua A, Robinson J, Abbas AE, Altshuler JM, Shannon FL, Podolsky RH, et al. Single-dose cardioplegia protects myocardium as well as traditional repetitive dosing: a noninferiority randomized study. *J Thorac Cardiovasc Surg.* (2020) 159 (5):1857–63.e1. doi: 10.1016/j.jtcvs.2019.03.125

2. Decoene C. Blood cardioplegia: advantages and disadvantages. *Ann Fr Anesth Reanim.* (2011) 30(Suppl 1):S20–2. doi: 10.1016/S0750-7658(11)70004-1

3. Zeng J, He W, Qu Z, Tang Y, Zhou Q, Zhang B. Cold blood versus crystalloid cardioplegia for myocardial protection in adult cardiac surgery: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth.* (2014) 28(3):674–81. doi: 10.1053/j.jvca.2013.06.005

4. Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: an Australian experience. *Eur J Cardiothorac Surg.* (2013) 43(3):526–31. doi: 10.1093/ejcts/ezs319

5. Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, et al. Custodiol for myocardial protection and preservation: a systematic review. *Ann Cardiothorac Surg.* (2013) 2(6):717–28. doi: 10.3978/j.issn.2225-319X.2013.11.10

6. Reynolds AC, Asopa S, Modi A, King N. HTK versus multidose cardioplegias for myocardial protection in adult cardiac surgery: a meta-analysis. *J Card Surg.* (2021) 36 (4):1334–43. doi: 10.1111/jocs.15397

7. Albadrani M. Histidine-tryptophan-ketoglutarate solution versus multidose cardioplegia for myocardial protection in cardiac surgeries: a systematic review and meta-analysis. *J Cardiothorac Surg.* (2022) 17(1):133. doi: 10.1186/s13019-022-01891-x

8. Yu X, Stallone JN, Heaps CL, Han G. The activation of G protein-coupled estrogen receptor induces relaxation via cAMP as well as potentiates contraction via EGFR transactivation in porcine coronary arteries. *PLoS One.* (2018) 13(1): e0191418. doi: 10.1371/journal.pone.0191418

9. Reeves ST, Glas KE, Eltzschig H, Mathew JP, Rubenson DS, Hartman GS, et al. Guidelines for performing a comprehensive epicardial echocardiography examination: recommendations of the American society of echocardiography and the society of cardiovascular anesthesiologists. *Anesth Analg.* (2007) 105(1):22–8. doi: 10.1213/01.ane.0000267263.40505.c0

10. Pudjiadi AH, Pramesti DL, Pardede SO, Djer MM, Rohsiswatmo R, Kaswandani N. Validation of the vasoactive-inotropic score in predicting pediatric septic shock mortality: a retrospective cohort study. *Int J Crit Illn Inj Sci.* (2021) 11(3):117–22. doi: 10.4103/IJCIIS.IJCIIS_98_20

11. Mann PC, Vahle J, Keenan CM, Baker JF, Bradley AE, Goodman DG, et al. International harmonization of toxicologic pathology nomenclature: an overview and review of basic principles. *Toxicol Pathol.* (2012) 40(4 Suppl):7s–13s. doi: 10.1177/0192623312438738

12. Flameng W, Borgers M, Daenen W, Stalpaert G. Ultrastructural and cytochemical correlates of myocardial protection by cardiac hypothermia in man. *J Thorac Cardiovasc Surg.* (1980) 79(3):413–24. doi: 10.1016/S0022-5223(19)37950-4

13. Goldstein MA. Ultrastructure of the ischemic myocardium. *Cardiovasc Res Cent Bull.* (1979) 18(1):1–33.

14. Török B, Trombitás K, Röth E. Ultrastructural consequences of reperfusion of the ischaemic myocardium. *Acta Morphol Hung.* (1983) 31(4):315–26.

15. Taha M, Lopaschuk GD. Alterations in energy metabolism in cardiomyopathies. *Ann Med.* (2007) 39(8):594–607. doi: 10.1080/07853890701618305

16. Mercan I, Dereli Y, Topcu C, Tanyeli O, Isik M, Gormus N, et al. Comparison between the effects of Bretschneider's HTK solution and cold blood cardioplegia on systemic endothelial functions in patients who undergo coronary artery bypass surgery: a prospective randomized and controlled trial. *Braz J Cardiovasc Surg.* (2020) 35(5):634–43. doi: 10.21470/1678-9741-2019-0327

17. Wang ZH, Cai XL, Wu L, Yu Z, Liu JL, Zhou ZN, et al. Mitochondrial energy metabolism plays a critical role in the cardioprotection afforded by intermittent hypobaric hypoxia. *Exp Physiol.* (2012) 97(10):1105–18. doi: 10.1113/expphysiol.2012.065102

18. Aldakkak M, Stowe DF, Lesnefsky EJ, Heisner JS, Chen Q, Camara AK. Modulation of mitochondrial bioenergetics in the isolated Guinea pig beating heart by potassium and lidocaine cardioplegia: implications for cardioprotection. *J Cardiovasc Pharmacol.* (2009) 54(4):298–309. doi: 10.1097/FJC.0b013e3181b2b842

19. Lenaz G. Mitochondria and reactive oxygen species. Which role in physiology and pathology? *Adv Exp Med Biol*. (2012) 942:93–136. doi: 10.1007/978-94-007-2869-1_5

20. Barzegar Amiri Olia M, Schiesser CH, Taylor MK. New reagents for detecting free radicals and oxidative stress. *Org Biomol Chem*. (2014) 12(35):6757–66. doi: 10.1039/C4OB01172D

21. Gupta RK, Patel AK, Shah N, Chaudhary AK, Jha UK, Yadav UC, et al. Oxidative stress and antioxidants in disease and cancer: a review. *Asian Pac J Cancer Prev*. (2014) 15(11):4405–9. doi: 10.7314/APJCP.2014.15.11.4405

22. Turner I, Ruzmetov M, Niu J, Bibevski S, Scholl FG. Scavenging right atrial Bretschneider histidine-tryptophan-ketoglutarate cardioplegia: impact on hyponatremia and seizures in pediatric cardiac surgery patients. *J Thorac Cardiovasc Surg*. (2021) 162(1):228–37. doi: 10.1016/j.jtcvs.2020.08.098

23. Van Houte J, Bindels AJ, Houterman S, Dong PV, Den Ouden M, De Bock NE, et al. Acute isotonic hyponatremia after single dose histidine-tryptophan-ketoglutarate cardioplegia: an observational study. *Perfusion*. (2021) 36(5):440–6. doi: 10.1177/0267659120946952

24. Hsu DT, Weng ZC, Nicolosi AC, Detwiler PW, Sciacca R, Spotnitz HM. Quantitative effects of myocardial edema on the left ventricular pressure-volume relation. Influence of cardioplegia osmolarity over two hours of ischemic arrest. *J Thorac Cardiovasc Surg*. (1993) 106(4):651–7. doi: 10.1016/S0022-5223(19)33707-9

25. Fannelop T, Dahle GO, Salminen PR, Moen CA, Matre K, Mongstad A, et al. Multidose cold oxygenated blood is superior to a single dose of Bretschneider HTK-cardioplegia in the pig. *Ann Thorac Surg*. (2009) 87(4):1205–13. doi: 10.1016/j.athoracsur.2009.01.041

26. Braathen B, Jeppsson A, Scherstén H, Hagen OM, Vengen Ø, Rexius H, et al. One single dose of histidine-tryptophan-ketoglutarate solution gives equally good myocardial protection in elective mitral valve surgery as repetitive cold blood cardioplegia: a prospective randomized study. *J Thorac Cardiovasc Surg*. (2011) 141(4):995–1001. doi: 10.1016/j.jtcvs.2010.07.011

27. Tan J, Bi S, Li J, Gu J, Wang Y, Xiong J, et al. Comparative effects of different types of cardioplegia in cardiac surgery: a network meta-analysis. *Front Cardiovasc Med*. (2022) 9:996744. doi: 10.3389/fcvm.2022.996744

28. Münch F, Purbojo A, Kellermann S, Janssen C, Cesnjevar RA, Rüffer A. Improved contractility with tepid modified full blood cardioplegia compared with cold crystalloid cardioplegia in a piglet model. *Eur J Cardiothorac Surg*. (2015) 48(2):236–43. doi: 10.1093/ejcts/ezu440

29. Lecour S, Andreadou I, Bøtker HE, Davidson SM, Heusch G, Ruiz-Meana M, et al. Improving preclinical assessment of cardioprotective therapies (IMPACT) criteria: guidelines of the EU-CARDIOPROTECTION COST action. *Basic Res Cardiol*. (2021) 116(1):52. doi: 10.1007/s00395-021-00893-5

30. Kleinbongard P, Lieder HR, Skyschally A, Alloosh M, Gödecke A, Rahmann S, et al. Non-responsiveness to cardioprotection by ischaemic preconditioning in ossabaw minipigs with genetic predisposition to, but without the phenotype of the metabolic syndrome. *Basic Res Cardiol*. (2022) 117(1):58. doi: 10.1007/s00395-022-00965-0

31. Kleinbongard P, Bøtker HE, Ovize M, Hausenloy DJ, Heusch G. Co-morbidities and co-medications as confounders of cardioprotection-does it matter in the clinical setting? *Br J Pharmacol*. (2020) 177(23):5252–69. doi: 10.1111/bph.14839

32. Koo EH, Park YC, Lim SH, Kim HZ. Amiodarone offsets the cardioprotective effects of ischaemic preconditioning againikst ischaemia/reperfusion injury. *J Int Med Res*. (2006) 34(2):140–51. doi: 10.1177/147323000603400203

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 02 July 2024
DOI 10.3389/fcvm.2024.1420704

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Satoru Iwashima,
Chutoen General Medical Center, Japan
Mario Carminati,
IRCCS San Donato Polyclinic, Italy

*CORRESPONDENCE
Juan Cong
congjuanmd@126.com

RECEIVED 21 April 2024
ACCEPTED 03 June 2024
PUBLISHED 02 July 2024

CITATION
Cong J, Cui C, Huang D, Wang Y, Liu S, Song S and Fan T (2024) The 3-year follow-up of a fully biodegradable implantable device closure for perimembranous ventricular septal defects in children using echocardiography. Front. Cardiovasc. Med. 11:1420704. doi: 10.3389/fcvm.2024.1420704

The 3-year follow-up of a fully biodegradable implantable device closure for perimembranous ventricular septal defects in children using echocardiography

Juan Cong[1]*, Cunying Cui[1], Danqing Huang[1], Ying Wang[1], Sifan Liu[1], Shubo Song[2] and Taibing Fan[2]

[1]Department of Ultrasound, Fuwai Central China Cardiovascular Hospital, Fuwai Central China Hospital of Zhengzhou University, Henan Provincial People's Hospital Heart Center, Zhengzhou, Henan, China, [2]Department of Children's Heart Center, Fuwai Central China Cardiovascular Hospital, Fuwai Central China Hospital of Zhengzhou University, Henan Provincial People's Hospital Heart Center, Zhengzhou, Henan, China

Objects: The aim of this study was to investigate the morphologic changes of a novel fully biodegradable implantable device after closing a perimembranous ventricular septal defect (Pm-VSD) and to evaluate the effect of the occluder on the myocardial function in patients during a 3-year follow-up period.
Methods: One-year, 2-year, and 3-year follow-ups were carried out after implantation with a total of 30 Pm-VSD patients who had successful closure by the fully biodegradable occluder. In total, 30 healthy children were enrolled as controls. At discharge and at every follow-up visit, the lengths of the left and right discs of the novel device were measured in the apical three- and four-chamber as well as short-axis views. At the end of the follow-up, using three-dimensional speckle-tracking conditions, the values of myocardial deformation, including global longitudinal strain, global circumferential strain, and global area strain, were acquired.
Results: The fully bioabsorbable double-disc occluder gradually decreased over time and was eventually invisible under echocardiographic scanning during the follow-up ($p < 0.05$). At the end of the third year, there were no significant differences in the myocardial deformation parameters between the cases implanted with the novel devices and the controls; no significant differences were found between the basal segments of the ventricle septa and that of the left ventricle (LV) free wall among the patients who completed the Pm-VSD closure using the fully biodegradable occluder ($p > 0.05$).
Conclusion: The novel fully biodegradable occluder is a safe, effective, and perfect alternative for the treatment of VSD. Echocardiography plays a crucial role in the follow-up of this new type of occluder implantation.

KEYWORDS

fully biodegradable occluder, ventricular septal defect, follow-up, echocardiography, myocardial deformation

1 Introduction

Ventricular septal defect (VSD) is one of the most common congenital heart diseases (1). In recent decades, with the improvement of interventional technology and instruments, especially since the AMPLATZER Septal Occluder was applied in clinic in 1998, transcatheter therapy has become an attractive choice of treatment for common congenital heart diseases, such as VSD, atrial septal defect, and patent ductus arteriosus (2–4).

However, clinical follow-up has found that because of the composition of the Ni-TI alloy, with a nickel content of approximately 55%, metal occluders can lead to late-onset adverse reactions, such as allergies. In addition, owing to the long-term insertion in the heart and constant pressing on the surrounding tissues, the traditional device may cause chronic inflammation, cardiac tissue abrasion, valve perforation, and other serious complications, such as high atrioventricular block (5–8).

For this reason, bioresorbable medical devices have been rapidly developed in recent years. A fully biodegradable polydioxanone occluder for VSD closure with good short- and mid-term performance was previously reported (9, 10). In this study, using echocardiography, we performed a cohort study to investigate the changes in morphology of a novel fully biodegradable implantable device after closing perimembranous VSD (Pm-VSD) in 30 children during a 3-year follow-up, and to evaluate the effect of the occluder on local myocardial function in patients at the end of the third year visit.

2 Materials and methods

2.1 Study subjects

This was a prospective cohort study approved by the ethics committee of the hospital (2019-Q009-01). All parents of the children provided signed informed consent. Between October 2019 and May 2023, a total of 34 children with Pm-VSD diagnosed using transthoracic echocardiography underwent implantation of the fully biodegradable occluder. The inclusion criteria were isolated Pm-VSD with the right-sided opening diameter ≥3 and ≤14 mm; the upper margin of VSD ≥3 mm from the aortic valve; and, in principle, age ≥1 year and weight ≥10 kg. The exclusion criteria were aortic valve prolapse, multiple VSD, no obvious edge of the defect, combined with other congenital diseases, infective endocarditis, and severe pulmonary hypertension.

Of the 34 individuals initially registered for the study, four had failed operations and were excluded. Finally, 30 patients with successful Pm-VSD closure were enrolled in the study. For the cases in this cohort, the global follow-up period was 3 years. Our outcome variables were 1-year, 2-year, and 3-year follow-ups after implantation. At every visit, all patients underwent laboratory examinations (including routinely hematologic parameters and biochemical blood indices), transthoracic echocardiogram, and electrocardiograms. To avoid radiation exposure, chest radiography was not performed unless necessary. In addition, 30 healthy children matched for sex, age, and body surface area were included as controls to compare myocardial function between the cases and controls at the end of the third year.

2.2 Occluder device and delivery system and treatment

The fully biodegradable occluder and delivery system (Shanghai Shape Memory Alloy Co. Ltd., Shanghai, China) used in this study was developed and reported initially by Chen et al. (9, 11). The occluder was a double-disc waist drum structure with a symmetrical wide edge and single riveted concave disc surface (Figure 1). The disc diameter was approximately 2–3 mm larger than the waist and the lumbar diameter matched VSD size. The skeleton frame was braided by a polydioxanone monofilament and the occlude membrane was composed of poly-L-lactic acid.

Implantation was achieved via the minimal right subaxillary incision-right atrial thoracotomy. The detailed procedure of the operation has been described previously (10). Since the novel occluder was free from x-ray radiation, the whole operation was carried out under the guidance and monitoring of transesophageal echocardiography (TEE) only. All patients received oral aspirin (5 mg/kg/day) postoperatively for 6 months.

2.3 Echocardiography

An ultrasound was performed using a system equipped with transesophageal transducers of 8–3 and 6–10 MHz (Vivid E95; GE Vingmed Ultrasound AS, Horten, Norway), depending on patient size, before, during, and after the implanting procedure with the fully biodegradable occluder for closure of the Pm-VSD.

At discharge and at every follow-up visit, according to the current recommendation (12), the participants underwent extensive transthoracic echocardiography using a 4VC transducer (1.4–5.2 MHz; GE Vingmed Ultrasound, Horten, Norway). All image recordings consisting of three consecutive cardiac cycles with a frame rate of 60–80 s^{-1} were obtained and saved in cine-loop digital format for offline analysis (EchoPAC; GE Healthcare, Horten, Norway).

The diameters of interventricular septum, posterior wall, and left ventricle (LV) diameters at end-diastole and end-systole via M-Mode were measured in the parasternal long-axis view, then LV ejection fraction and stroke volume were calculated. The lengths of left and right discs of the novel device were measured

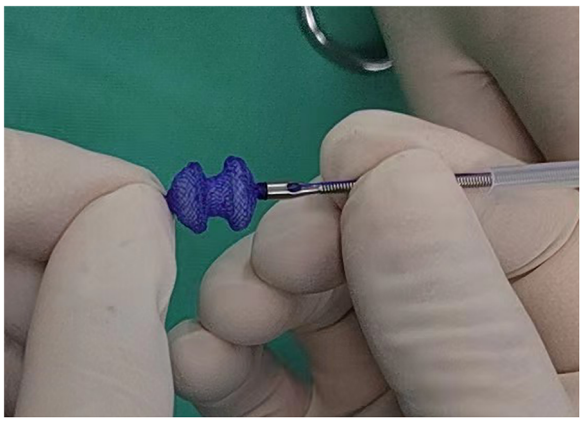


FIGURE 1
The fully biodegradable occluder and delivery system (Shanghai Shape Memory Alloy Co. Ltd.). The occluder was a double-disc waist drum structure with a symmetrical wide edge. The skeleton frame was braided by a polydioxanone monofilament and the occlude membrane was composed of poly-L-lactic acid.

in the apical three- and four-chamber as well as short-axis views, respectively. At the end of the 3-year follow-up, using three-dimensional speckle-tracking conditions, the values of regional and global strain were presented as strain curves and a color-coded 17-segment bull's eye plot. Then, global longitudinal strain (GLS), global circumferential strain (GCS), and global area strain (GAS) were calculated as previously reported (13).

2.4 Statistical analysis

The statistical analyses were performed using SPSS version 26 (SPSS Inc., Armonk, NY, USA). All data were expressed as mean ± standard deviation for continuous variables, and frequencies or percentages for nominal variables appropriately. Myocardial deformation data were presented as their absolute values. Differences between the follow-up groups were analyzed for statistical significance using paired *t*-tests with Bonferroni correction, while independent sample *t*-tests were utilized to assess the differences in myocardial function between the Pm-VSD cases with successful closure and the controls at the end of the 3-year visit. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Clinical and echocardiographic characteristics of the Pm-VSD children with successful closure

Among 34 cases suffering from Pm-VSD, 30 patients (15 boys, 15 girls) were treated successfully. Their mean age was 3.41 ± 2.29 years (range 3 months–10 years), mean height was 97.38 ± 16.99 cm (range 73–131 cm), and mean weight was 15.08 ± 5.22 kg (range 8–25.6 kg) (Table 1). The size of occluded VSDs was in the range of 3.0–6.0 mm, with a mean of 4.70 ± 1.05 mm, while the mean VSD diameter measured using echocardiography was 4.97 ± 1.67 mm. The minimum distances from the aortic valve and from the tricuspid septum were 2.80 and 1.50 mm, respectively. Meanwhile, the mean waist size of the double-disc device was 5.80 ± 1.30 mm (range 4.0–8.0 mm). With a "double-umbrella" configuration, the occluders clamped and closed the defects while it located precisely and fixed well postoperatively. Moreover, the device did not impede the opening and closing of the aortic and tricuspid valves.

TABLE 1 Clinical and echocardiographic data of the Pm-VSD cases with successful closure.

Variables	Data
Sample size (number)	30
Male (number)	17
Age (years)	3.41 ± 2.29 (1.6–10.0)
Height (cm)	97.38 ± 16.99 (70–131)
Weight (kg)	15.35 ± 5.05 (8.5–25.6)
Pm-VSD size measured by TEE (mm)	4.97 ± 1.67 (2.7–8.9)
Distance from aortic valve by TEE (mm)	4.42 ± 2.21 (2.8–12.0)
Distance from tricuspid septum by TEE (mm)	3.89 ± 2.00 (1.5–8.1)
Pm-VSD size in the operation (mm)	4.70 ± 1.05 (3.0–6.0)

Continuous data are presented as the mean ± standard deviation (range).

Because of failed operations, four individuals were excluded from the study. Among them, two cases terminated the procedure due to a mismatch between the small defects (≤3 mm) and the large sheath tube. They were treated with a Ni-TI occluder device and underwent surgical repair under extracorporeal circulation, respectively. Meanwhile, one case was characterized by multiple defects of aneurismal Pm-VSD and another patient with an unexpectedly large defect (measured at 8.4 mm preoperatively but 12 mm intraoperatively) underwent ventricular septal repair with cardiopulmonary bypass.

No serious complications occurred in those children. At every point, the quantitation of blood laboratory tests, such as white blood cells (WBCs), red blood cells (RBCs), hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase as well as creatinine, was in normal ranges (Table 2). There were no instances of left and right bundle branch block (RBBB) or atrioventricular block except for one case with incomplete RBBB at discharge but had recovered at her 1-year follow-up. During the follow-up period, a transthoracic echocardiogram was performed and the general measurements were recorded (Table 3). There were no occurrences of residual shunt, device dislocation, new or aggravated valve regurgitation, thrombosis, or infective endocarditis.

3.2 Morphological changes in the novel fully biodegradable occluder for VSD closure during the follow-up period by echocardiography

According to the time intervals between implantation and March 2024, all 30 enrolled cases completed the 1-year follow-up, 24 completed the 2-year follow-up, and 13 completed all three follow-ups. During the follow-up, the size of the left and right discs of the novel medical devices gradually decreased over time and were eventually invisible under echocardiographic scanning in the third year after implantation (Figures 2, 3). Moreover, the length of the left disc decreased slightly faster than that of the right disc, but there was no significant difference between them (Table 4).

3.3 Myocardial function characteristics in cases with the novel implantable device at the end of the 3-year follow-up period

At the end of the 3-year follow-up, the myocardial deformation measurements in the ventricular septal basal segments were almost the same as the values of the LV free wall bases among the participants implanted with the novel fully biodegradable devices ($p > 0.05$) (Table 5). In all 13 patients who completed all three follow-ups, the global values of strain along longitudinal (20.85% ± 1.79% vs. 21.04% ± 1.56%), circumferential (18.27% ± 2.06% vs.

TABLE 2 Data of blood laboratory tests at every visit point during follow-up.

Variables	Normal range	At discharge	1-year follow-up	2-year follow-up	3-year follow-up
		($n = 30$)	($n = 30$)	($n = 24$)	($n = 13$)
WBC (10^9/L)	5.10–13.20	8.12 ± 1.58	8.19 ± 1.62	8.07 ± 1.40	8.15 ± 1.49
RBC (10^{12}/L)	4.00–5.20	4.10 ± 0.50	4.33 ± 0.58	4.29 ± 0.55	4.64 ± 0.50
Hemoglobin (g/L)	107–138	108.00 ± 11.42	114.13 ± 16.16	113.68 ± 14.24	123.00 ± 16.24
Platelets (10^9/L)	180–486	322.92 ± 109.21	301.21 ± 95.60	314.26 ± 103.89	282.59 ± 80.36
ALT (U/L)	7–40	14.00 ± 3.89	16.32 ± 12.42	14.27 ± 4.04	17.57 ± 14.56
AST (U/L)	13–35	28.92 ± 7.41	29.83 ± 9.26	28.58 ± 6.49	29.82 ± 9.42
Total bilirubin (μmol/L)	0–21	4.35 ± 1.66	5.07 ± 2.02	5.31 ± 2.59	6.43 ± 2.55
Urea (mmol/L)	2.76–8.07	4.00 ± 1.05	3.98 ± 1.05	4.12 ± 1.01	4.09 ± 1.11
Creatinine (μmol/L)	14–34	27.54 ± 6.19	27.42 ± 5.73	27.95 ± 5.89	27.82 ± 5.39

Continuous data are presented as the mean ± standard deviation.

18.11% ± 2.39%), and radial (48.05% ± 5.32% vs. 48.21% ± 4.45%) dimensions in 16 segments did not have significant differences when compared to the matched controls ($p > 0.05$).

4 Discussion

In the present study, we demonstrated that the fully biodegradable double-disc occluder gradually decreased over time and was eventually absorbed during the 3-year follow-up period. Moreover, the myocardial deformation parameters were not obviously different, not only between the cases implanted with the novel devices and the normal controls, but also between the basal segments of the ventricle septa and of the LV free wall among the patients who completed the Pm-VSD closure using the fully biodegradable occluder. To the best of our knowledge, this is the first long-term follow-up of changes in the morphology of fully bioabsorbable devices over time in children with Pm-VSD and the first report evaluating myocardial deformation characteristics in the cases implanted with the novel occluder at the end of a 3-year follow-up.

Compared to the metal device, the perfect fully biodegradable occluder should meet the following conditions: (1) superior geometric adaptability—the device can fit to different morphologic defects well and clamp the site of defect effectively; (2) excellent time efficiency—the device can provide an accurate balance between the occluder absorption and the tissue regeneration, which acts as a supporting net before the defect is entirely endothelialized, which, after that, is gradually assimilated and eventually degraded completely. Meanwhile, the primary defect is covered and closed using autologous tissue without a residual shunt; and (3) good biocompatibility—it will not cause biotoxic effects to the human body, such as cytotoxicity and genotoxicity (14, 15).

TABLE 3 Routine echocardiographic measurement at every follow-up.

Variables	At discharge	1-year follow-up	2-year follow-up	3-year follow-up
	($n = 30$)	($n = 30$)	($n = 24$)	($n = 13$)
LVDd (mm)	29.15 ± 3.31	30.38 ± 3.64	31.92 ± 3.80	34.33 ± 5.21
LVDs (mm)	19.08 ± 2.66	19.23 ± 2.65	21.42 ± 1.98	21.82 ± 3.73
IVS (mm)	4.93 ± 0.45	4.62 ± 0.64	5.11 ± 0.98	5.33 ± 0.90
LVPW (mm)	4.91 ± 0.46	4.58 ± 0.60	5.09 ± 0.86	5.30 ± 0.72
LA (mm)	19.23 ± 2.01	19.58 ± 2.43	19.62 ± 2.18	21.50 ± 2.50
EF (%)	34.54 ± 3.67	35.77 ± 3.03	34.50 ± 1.88	37.58 ± 2.94
FS (%)	65.23 ± 4.71	66.62 ± 3.97	64.83 ± 2.25	68.58 ± 3.70
E (cm/s)	0.79 ± 0.10	0.78 ± 0.10	0.86 ± 0.11	0.83 ± 0.15
A (cm/s)	0.52 ± 0.13	0.51 ± 0.13	0.56 ± 0.18	0.58 ± 0.15
AO (cm/s)	1.04 ± 0.13	0.98 ± 0.14	1.00 ± 0.21	1.08 ± 0.12
E/e	7.84 ± 1.58	7.45 ± 1.31	8.30 ± 1.63	8.47 ± 1.50

LVDd, left ventricular end-diastolic diameter; IVS, interventricular septal thickness; LVPW, left ventricular posterior wall thickness; LA, left atrial anterior-posterior diameter; EF, ejection fraction; FS, fraction shortening; E, blood flow velocity through mitral valve during early diastole; A, blood flow velocity through mitral valve during late diastole; AO, blood flow velocity through aortic valve during systole; e, the average of tissue velocities on the septal and lateral sides of mitral annual during early diastole.
Continuous data are presented as the mean ± standard deviation.

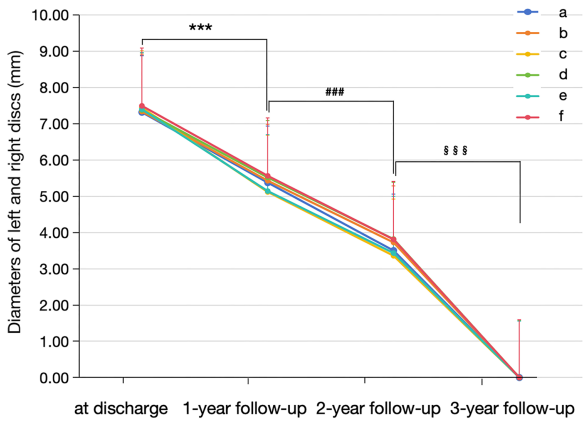


FIGURE 2
Morphological changes in the novel fully biodegradable occluder for VSD closure during the follow-up. From discharge to the third year, the diameters of the left and right discs of the novel medical devices gradually decreased over time and were eventually invisible under scanning at the end of the third year after implantation. a and b indicate the diameters of the left and right discs in the apical three-chamber view; c and d indicate the diameters of the left and right discs in the apical four-chamber view; e and f indicate the diameters of the left and right discs in the short-axis view. ***p-value < 0.001 vs. at discharge; ###p-value < 0.001 vs. 1-year follow-up; §§§p-value < 0.001 vs. 2-year follow-up.

10.3389/fcvm.2024.1420704

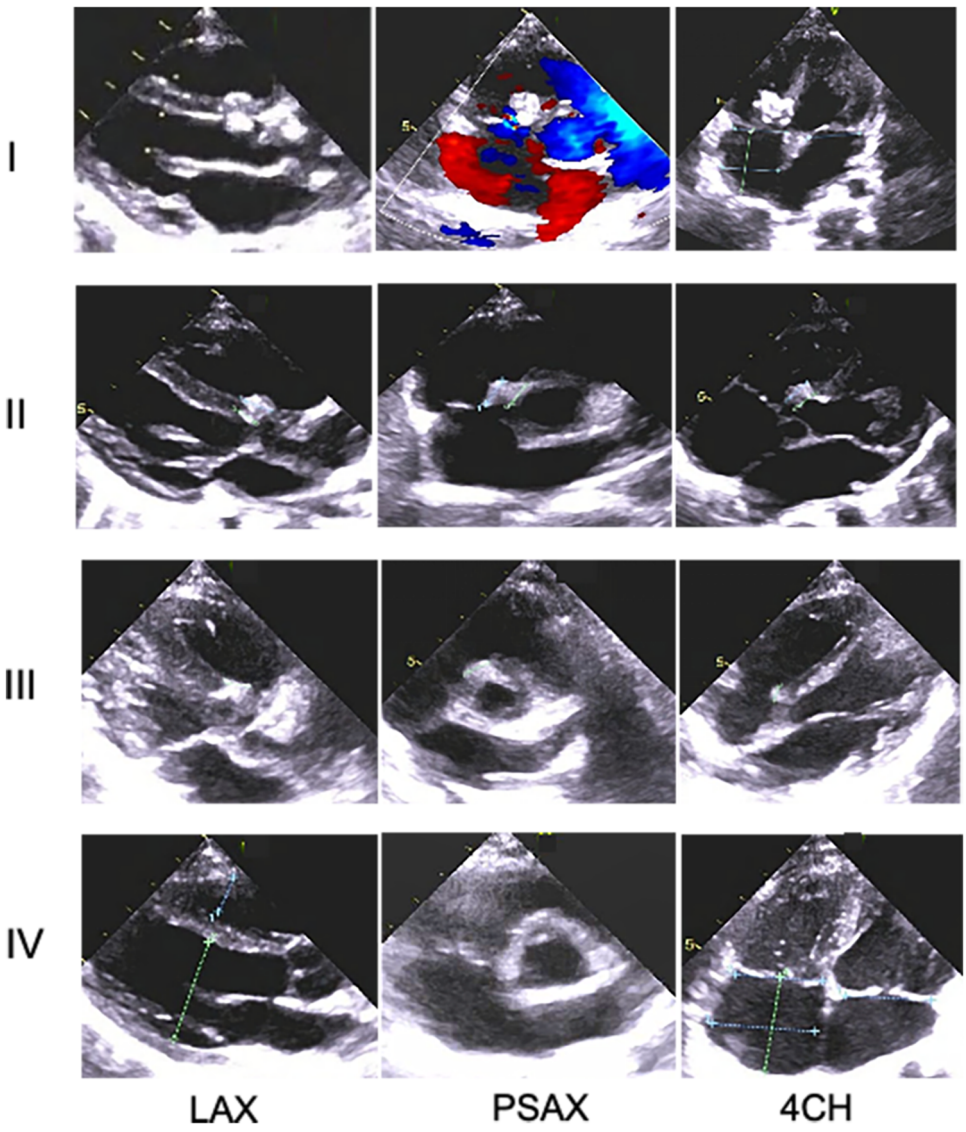


FIGURE 3
Changes in morphology of the novel device with time in one Pm-VSD patient during the follow-up period using transthoracic echocardiography. At every visit, the occluder remnants tended to gradually decline and could not be identified at the end of follow-up, indicating increasing absorption over time and eventual complete degradation of the novel device. Rows I–IV indicate at discharge and 1-year, 2-year, ,and 3-year follow-up after implantation, respectively; LAX, parasternal long-axis view of the left ventricle; PSAX, parasternal short-axis view of the aorta; 4CH, the apical four chamber.

TABLE 4 Changes in the lengths of the left and right discs of the novel fully biodegradable occluder for VSD closure during the follow-up period using echocardiography.

Variables (mm)		At discharge	1-year follow-up	2-year follow-up	3-year follow-up
		(*n* = 30)	(*n* = 30)	(*n* = 24)	(*n* = 13)
Apical 3 CH	Left	7.31 ± 0.97	5.37 ± 1.24[a]	3.50 ± 1.41[b]	0.00[c]
	Right	7.33 ± 1.04	5.43 ± 1.27[a]	3.73 ± 1.40[b]	0.00[c]
Apical 4 CH	Left	7.44 ± 1.13	5.12 ± 1.30[a]	3.36 ± 1.47[b]	0.00[c]
	Right	7.38 ± 1.09	5.52 ± 1.28[a]	3.82 ± 1.58[b]	0.00[c]
Short-axis	Left	7.40 ± 1.00	5.14 ± 1.51[a]	3.43 ± 1.73[b]	0.00[c]
	Right	7.49 ± 1.02	5.56 ± 1.46[a]	3.81 ± 1.51[b]	0.00[c]

CH, chamber.
Continuous data are presented as the mean ± standard deviation.
[a]*p*-value < 0.001 vs. at discharge.
[b]*p*-value < 0.001 vs. 1-year follow-up.
[c]*p*-value < 0.001 vs. 2-year follow-up.

In this 3-year cohort study, the novel fully bioabsorbable device demonstrated its excellent properties for VSD closure. All the Pm-VSDs were clamped successfully without serious complications, including late-onset reactions. During the postoperative follow-up, both the left and right discs of the occluder remained intact and gradually diminished in size over time. At the end of the third year, the devices were absorbed completely without any residual shunt under transthoracic echocardiography scanning. Moreover, it is interesting that the degradation and endothelialization levels of the two sides of the discs were slightly unbalanced. The left disc was absorbed slightly faster than the right, probably because of the more oxygen-rich and higher

TABLE 5 Myocardial deformation of cardiac basal segments in the cases after implanting the novel biodegradable device at the end of 3-year follow-up period.

Variables	Ante septum	Anterior	Lateral	Posterior	Inferior	Septum
Basal LS (%)	19.49 ± 1.81	19.54 ± 1.53	19.38 ± 1.61	19.92 ± 1.77	20.08 ± 2.06	19.38 ± 1.55
Basal CS (%)	16.63 ± 1.88	17.02 ± 1.72	17.11 ± 2.09	17.49 ± 1.98	17.38 ± 1.81	16.96 ± 1.76
Basal RS (%)	47.33 ± 4.63	47.35 ± 3.81	47.70 ± 5.33	48.09 ± 5.62	48.12 ± 5.77	46.82 ± 6.04

LS, longitudinal strain; CS, circumferential strain; RS, radial strain.
Myocardial deformation data are presented as the absolute value (mean ± standard deviation).

blood flow in the left ventricle. Those findings were similar to those in a previous report of an animal model and pilot clinical trial including five patients and a 3-month follow-up (11).

We also evaluated the global and segmental myocardial function of the Pm-VSD cases implanted with the bioresorbable polydioxanone device. Previous studies on animal models of VSD treated with the novel bioabsorbable occluder have shown, 36 months postoperatively, that the polydioxanone device was completely degraded accompanied by a reconstructive process of a highly fibrillar micro-structure, which was similar to the architecture of native myocardium without scar formation (9). In the present study, there were almost the same measurements of strain in the basal segments between the septa and the ventricular free wall in the patients at the end of follow-up. The values of strain along the longitudinal, circumferential, and radial dimensions were not remarkably different between the cases with the novel device implantation and the controls. Thus, the novel, fully bioabsorbable occluder for VSD showed perfect biocompatibility and had no adverse effects on the local and global myocardial deformation of the patients using the novel device.

In addition, in the present study, the procedure was undertaken through the minimal right subaxillary incision-right atrial thoracotomy, which did not require extracorporeal circulation and blood transfusion and also avoided radiation damage with a small trauma (11).

The main limitation of this study is the small sample size. In addition, although 3-year follow-up was required until the device was invisible under scanning, a more detailed longitudinal follow-up and analysis is necessary. With the future application of the novel bioresorbable implantation in the clinic, the evaluation of this occluder for VSD closure will be more comprehensive.

5 Conclusion

After the 3-year follow-up, the safety, effectiveness, and perfect biocompatibility of the novel fully bioabsorbable polydioxanone occluder for VSD treatment have been confirmed. Echocardiography plays a crucial role in the follow-up of this revolutionary procedure for Pm-VSD closure.

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.

Ethics statement

The studies involving humans were approved by the Ethics Committee Board of Central China Fuwai Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

JC: Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation. CC: Writing – original draft, Software, Methodology, Investigation, Formal Analysis, Data curation. DH: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation. YW: Writing – review & editing, Software, Methodology, Investigation, Formal Analysis, Data curation. SL: Writing – review & editing, Methodology, Investigation, Formal Analysis, Data curation. SS: Writing – review & editing, Software, Methodology, Investigation, Data curation. TF: Writing – review & editing, Supervision, Methodology, Investigation, Data curation.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article.

Science and Technology Research Project of Henan Province, China, No.242102311031.

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. Penny DJ, Vick GW 3rd. Ventricular septal defect. *Lancet*. (2011) 377 (9771):1103–12. doi: doi: 10.1016/S0140-6736(10)61339-6

2. Nassif M, Abdelghani M, Bouma BJ, Straver B, Blom NA, Koch KT, et al. Historical developments of atrial septal defect closure devices: what we learn from the past. *Expert Rev Med Devices*. (2016) 13(6):555–68. doi: doi: 10.1080/17434440.2016.1182860

3. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. (2017) 377(11):1022–32. doi: doi: 10.1056/NEJMoa1610057

4. Mijangos-Vázquez R, El-Sisi A, Sandoval Jones JP, García-Montes JA, Hernández-Reyes R, Sobhy R, et al. Transcatheter closure of perimembranous ventricular septal defects using different generations of amplatzer devices: multicenter experience. *J Interv Cardiol*. (2020) 2020:8948249. doi: doi: 10.1155/2020/8948249

5. Wongwaitaweewong K, Promphan W, Roymanee S, Prachasilchai P. Effect of transcatheter closure by Amplatzer(TM) Duct Occluder II in patients with small ventricular septal defect. *Cardiovasc Interv Ther*. (2021) 36(3):375–83. doi: doi: 10.1007/s12928-020-00677-z

6. Yildiz K, Narin N, Oksuz S, Ozdemir R, Pamukcu O, Baykan A, et al. Safety and efficacy of Amplatzer duct occluder II and konar-MF™ VSD occluder in the closure of perimembranous ventricular septal defects in children weighing less than 10 kg. *Front Cardiovasc Med*. (2023) 10:1255808 doi: doi: 10.3389/fcvm.2023.1255808

7. Huang JS, Chen Q, Chen LW, Kuo YR, Hong ZN, Cao H. Changes in the levels of inflammatory markers after transthoracic device closure of ventricular septal defects in pediatric patients. *J Cardiothorac Surg*. (2019) 14(1):70. doi: doi: 10.1186/s13019-019-0900-4

8. Yang J, Yang L, Yu S, Liu J, Zuo J, Chen W, et al. Transcatheter versus surgical closure of perimembranous ventricular septal defects in children: a randomized controlled trial. *J Am Coll Cardiol*. (2014) 63(12):1159–68. doi: doi: 10.1016/j.jacc.2014.01.008

9. Li Z, Kong P, Liu X, Feng S, Ouyang W, Wang S, et al. A fully biodegradable polydioxanone occluder for ventricle septal defect closure. *Bioact Mater*. (2023) 24:252–62. doi: doi: 10.1016/j.bioactmat.2022.12.018

10. Song S, Shao Z, Fan T, Li B, Liang W, Dong H, et al. Favorable mid-term performance of fully biodegradable implantable device for ventricular septal defect closure. *JTCVS Tech*. (2023) 17:133–7. doi: doi: 10.1016/j.xjtc.2022.11.010

11. Chen L, Hu S, Luo Z, Butera G, Cao Q, Zhang F, et al. First-in-human experience with a novel fully bioabsorbable occluder for ventricular septal defect. *JACC Cardiovasc Interv*. (2020) 13(9):1139–41. doi: doi: 10.1016/j.jcin.2019.09.057

12. 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: doi: 10.1016/j.echo.2014.10.003

13. Cong J, Fan T, Yang X, Squires JW, Cheng G, Zhang L, et al. Structural and functional changes in maternal left ventricle during pregnancy: a three-dimensional speckle-tracking echocardiography study. *Cardiovasc Ultrasound*. (2015) 13:6. doi: doi: 10.1186/1476-7120-13-6

14. Xing Quansheng WQ. Development of biodegradable occluders in device closure treatment for congenital heart defects. *Chin J Thorue Cardliovasc Surg*. (2017) 33 (6):380–4

15. Shi D, Kang Y, Zhang G, Gao C, Lu W, Zou H, et al. Biodegradable atrial septal defect occluders: a current review. *Acta Biomater*. (2019) 96:68–80. doi: doi: 10.1016/j.actbio.2019.05.073

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 02 August 2024
DOI 10.3389/fcvm.2024.1425703

OPEN ACCESS

EDITED BY
Yoshitaka Iso,
Showa University, Japan

REVIEWED BY
Yuya Yokota,
Showa University, Japan
Akhmetzhan Galimzhanov,
Semey State Medical University, Kazakhstan

*CORRESPONDENCE
Bambang Dwiputra
✉ bambangdwiputra@gmail.com

RECEIVED 30 April 2024
ACCEPTED 22 July 2024
PUBLISHED 02 August 2024

CITATION
Dwiputra B, Desandri DR, Hartopo AB, Juzar DA, Alkatiri AA, Zuhdi N, Ramadhan PA, Kenconosari BD, Phowira J and Widyantoro B (2024) Risk estimation for recurrent cardiovascular events using the SMART-REACH model and direct inpatient cost profiling in Indonesian ASCVD patients: a large-scale multicenter study.
Front. Cardiovasc. Med. 11:1425703.
doi: 10.3389/fcvm.2024.1425703

Risk estimation for recurrent cardiovascular events using the SMART-REACH model and direct inpatient cost profiling in Indonesian ASCVD patients: a large-scale multicenter study

Bambang Dwiputra[1]*, Dwita Rian Desandri[1], Anggoro Budi Hartopo[2], Dafsah Arifa Juzar[1], Amir Aziz Alkatiri[1], Naufal Zuhdi[1], Putra Andito Ramadhan[1], Bernadhet Daisy Kenconosari[2], Jason Phowira[1] and Bambang Widyantoro[1]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia—National Cardiovascular Centre Harapan Kita, Jakarta, Indonesia, [2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada—Dr. Sardjito Hospital, Yogyakarta, Indonesia

Introduction: With atherosclerotic cardiovascular disease (ASCVD) cases increasing in Indonesia, there is a growing need to identify high-risk patients for recurrent cardiovascular events. Risk stratification could guide optimal secondary preventive therapy. Understanding the ASCVD direct inpatient costs could further provide insight in reducing the economic burden that comes with Indonesia's high number ASCVD cases. However, there is a significant gap in Indonesian large-scale research on both of these valuable data. Employing the SMART-REACH model, we can profile the risk of recurrent cardiovascular events in Indonesian ASCVD patients.

Objectives: Utilize the SMART-REACH model to estimate 10-year and lifetime risk of cardiovascular events in Indonesian ASCVD patients and describe the direct inpatient cost of ASCVD.

Methods: This descriptive cross-sectional study gathered data from 3,209 ASCVD patients aged 45–80 from two major cardiovascular centers using purposive sampling. Participants were patients admitted between January 2020 and March 2023 with ST-elevated myocardial infarct (STEMI), non-ST-elevated myocardial infarct (NSTEMI), and chronic coronary syndrome (CCS) requiring elective percutaneous coronary intervention (PCI). The SMART-REACH risk estimation model required clinical data upon admission, laboratory results within the first 24 h of admission, and cardiovascular medication prescribed upon discharge. The SMART-REACH model is a Fine and Gray competing risk model incorporating cardiovascular risk factors that estimates individual 10-year and lifetime risk for recurrent cardiovascular events which includes myocardial infarction, stroke, or vascular death. Direct inpatient cost profiling totaled all medical expenses incurred from ASCVD diagnosis admission to discharge. Results were reported descriptively with subgroup analyses.

Results: The cohorts (mean age 60.15 ± 8.6 years) were predominantly male [*n* = 2,537 (79.1%)], hypertensive [*n* = 2,267 (70.6%)], and diagnosed with STEMI [*n* = 1,732 (54%)]. The SMART-REACH model calculated a mean 10-year risk of 30.2% (95% CI 29.7–30.6) and a lifetime risk of 62.5% (95% CI 62.1–62.9). The direct inpatient cost of ASCVD patients includes a median 3,033 USD, with highest median costs in the STEMI subgroup (3,270 USD).
Conclusions: A significant number of Indonesian ASCVD patients exhibited notably high 10-year and lifetime risks of experiencing a major cardiovascular event. Combined with the direct inpatient cost, therapy optimization is crucially needed to mitigate these risks and further cost burden.

KEYWORDS

coronary heart disease, atherosclerotic cardiovascular disease, risk estimation, secondary prevention, cost profiling

1 Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally and have become a major health problem across the world. The World Health Organization (WHO) has reported more than 17 million deaths globally due to CVD in 2015 (1). National Basic Health Research in Indonesia also reported that the prevalence of CVD in Indonesia has been increasing from 0.5% in 2013 to 1.5% in 2018 (2). This number might continue to rise as cases of diabetes mellitus (DM) and hypertension, both risk factors for cardiovascular disease coupled with cholesterol-related risk factors, have also increased. Cases of DM increased from 14.8% in 2013 to 21.8% in 2018, and hypertension increased from 26% in 2013 to 34% in 2018 (3).

Atherosclerotic cardiovascular disease (ASCVD) has posed an increasing burden on the healthcare system for decades. It is projected that the cost of ASCVD will increase by over 2.5-fold from 2015 to 2035 (4). This cost burden has significant consequences not only for payers but also for patients and healthcare providers. Identifying patients at high risk of ASCVD is becoming increasingly important; risk stratification could help clinicians determine which patients benefit most from innovative and often costly therapy (5). For patients, information regarding their risk is crucial for prognosis and future decisions regarding preventive treatment. One risk stratification method is the SMART-REACH model, developed in 2018, which can estimate the 10-year risk and lifetime risk for myocardial infarction, stroke, or vascular death in individual patients with clinically manifest ASCVD (6).

This study aims to assess the risk of recurrent cardiovascular events among Indonesian ASCVD patients in terms of 10-year and lifetime risk using the SMART-REACH model and to describe the direct inpatient cost burden of these patients. The results will be used as evidence to strengthen population health programs to prevent and control secondary ASCVD.

2 Materials and methods

2.1 Study design and population

This is a descriptive, non-interventional study conducted using retrospective and cross-sectional data extracted from medical records at two tertiary referral hospitals in Indonesia, which are National Cardiovascular Center Harapan Kita (NCCHK), Jakarta and Dr. Sardjito Hospital, Yogyakarta. The subjects of this study comprised patients admitted with ASCVD at these hospitals between January 2020 up to March 2023. Inclusion and exclusion criteria were applied to purposively include eligible patients in the dataset. Inclusion criteria encompassed patients aged 45–80 years admitted with a diagnosis of ST-elevated myocardial infarct (STEMI) (ICD-10: I21), non- ST-elevated myocardial infarct (NSTEMI) (ICD-10: I21), or chronic coronary syndrome (CCS) requiring elective PCI (ICD-10: I25.1) who were alive at discharge. Exclusion criteria comprised patients lacking adequate registry data necessary for risk calculation, as well as patients with terminal malignancy, end-stage renal disease, and hepatic cirrhosis. These criteria were based on those of the REACH and SMART cohorts (7, 8). Ethical clearance for the study was obtained from the local institutional review boards in both hospitals.

2.2 Data collection

Data collection involved purposive sampling from secondary sources, specifically electronic medical and billing records from both hospitals. Subjects were identified from both the One ACS Registry and the Indonesia PCI Registry (9, 10). Upon applying the inclusion and exclusion criteria, 3,209 eligible patients were selected from an initial pool of 9,494 patients for the present analysis (Figure 1). To ascertain the risk score for each patient, we examined clinical information collected upon admission, including age, gender, smoking habits, presence of diabetes mellitus (DM), previous history of vascular disease, heart failure, or atrial fibrillation. Additionally, lipid values obtained within the initial 24 h of hospitalization, baseline serum creatinine levels, baseline HbA1c levels, and medications prescribed at discharge once the patient was deemed clinically stable were taken into consideration. The medications considered in the calculation included statins, ezetimibe, PCSK9 inhibitors, antithrombotic treatments, GLP1 receptor agonists, SGLT2 inhibitors, and low-dose colchicine. The data pertaining to direct inpatient costs only encompassed the total direct medical expenses incurred during hospitalization for ASCVD diagnosis, from patient admission to discharge.

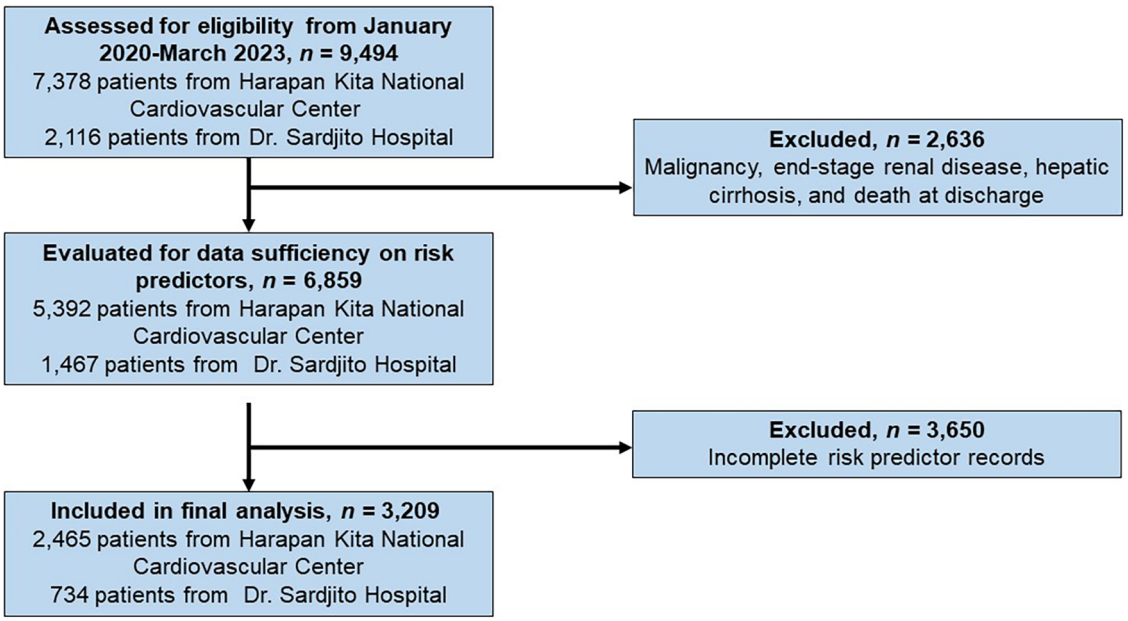


FIGURE 1
The flow diagram for patient selection and eligibility.

2.3 The SMART-REACH model

The SMART-REACH risk model is a competing-risk adjusted Fine and Gray model, designed for estimating both 10-year and lifetime risk of major cardiovascular events and non-cardiovascular mortality in patients with clinically manifest vascular disease. The underlying model formulas and methodology were detailed in the original SMART-REACH publication. Using age as the underlying timescale, life tables are constructed to calculate risks for every 1-year interval, starting from the individual's initial age and extending up to a maximum age of 90 years. The model was derived using adapted Fine and Gray models to accommodate left truncation and right censoring. It incorporates several predictors, including age, sex, current smoking status, diabetes mellitus (DM), history of heart failure, history of atrial fibrillation, systolic blood pressure (BP), serum creatinine concentration, number of locations of cardiovascular disease (cerebrovascular, coronary, and peripheral artery disease), as well as total and low-density lipoprotein cholesterol (LDL-C) levels (6).

2.4 Outcome

The outcome of this study is the 10-year and lifetime risk of recurrent cardiovascular events and associated direct inpatient cost in patients diagnosed with ASCVD. The cardiovascular events considered include myocardial infarction, stroke, and cardiovascular death. Descriptive reporting is used to present direct inpatient costs, focusing on total direct medical expenses. Additionally, further analyses of 10-year and lifetime risk are conducted within different patient subgroups. These subgroups account for various risk factors such as hypertension, diabetes mellitus (DM), and active smoking, as well as differences in lipid-lowering treatments and antiplatelet therapy usage in relation to the risk profile of recurrent cardiovascular events. Regarding direct inpatient costs, subgroup analyses examine differences between genders, diagnoses, and cardiovascular centers.

2.5 Statistical analysis

A descriptive statistical approach is utilized to outline the baseline characteristics and estimated risk within the study subgroups. Prior to analysis, the collected data underwent filtering, sorting, and cleaning procedures to ensure uniformity and data quality. Baseline characteristics of eligible patients, including age, sex, smoking status, diagnosis, past medical history, physical examination and laboratory measurements, and medication usage, are included. Frequency distributions and mean with standard deviation are used to illustrate these characteristics. Additionally, the estimated risk of recurrent cardiovascular events within the study subgroups is calculated as the mean with a 95% confidence interval (CI) derived from the SMART-REACH calculator. Direct inpatient cost data are presented in terms of overall cost, with mean, median, standard deviation, 95% CI, and percentiles provided for clarity. All statistical analysis used SPSS version 22 (IBM, USA).

3 Results

3.1 Patients baseline characteristics

Out of the total of 3,209 patients, 30.5% of patients were active smokers upon admission. Among the diagnoses, the majority of

cases were admitted with STEMI [$n = 1,732$ (54.0%)], followed by NSTEMI [$n = 904$ (28.2%)] and CCS elected for PCI [$n = 573$ (17.9%)], respectively. The subjects' medical histories encompassed various conditions including hypertension (70.6%), DM (36.7%), hypercholesterolemia (30.7%), cerebrovascular disease (4.6%), peripheral artery disease (0.9%), heart failure (13.8%), and atrial fibrillation (3.1%). HbA1c data was available for 2,345 patients, representing 73% of the total subjects in the study (Table 1). This limited data collection occurred because, according to both hospitals' standard operating procedures, HbA1c tests were only performed on patients with a known history of type 2 DM or elevated fasting blood sugar upon admission. However, the SMART-REACH model calculation only requires HbA1c for assessing the risk of diabetic patients, whereas non-diabetic patients do not require HbA1c data for the calculation of their cardiovascular risk. Consequently, complete HbA1c data is available for all diabetic patients, while all the absent HbA1c data in this study pertains to the subgroup without DM.

TABLE 1 Baseline characteristic of the study.

Total, *n* (%)	3,209 (100)
Male, *n* (%)	2,537 (79.1)
Age (years)[a]	60.15 ± 8.6
Active smoker, *n* (%)	979 (30.5)
Coronary artery disease diagnosis	
STEMI, *n* (%)	1,732 (54.0)
NSTEMI, *n* (%)	904 (28.2)
CCS, *n* (%)	573 (17.9)
Past medical history	
Hypertension, *n* (%)	2,267 (70.6)
Diabetes mellitus, *n* (%)	1,178 (36.7)
Hypercholesterolemia, *n* (%)	984 (30.7)
Cerebrovascular disease, *n* (%)	148 (4.6)
Peripheral artery disease, *n* (%)	28 (0.9)
Heart failure, *n* (%)	444 (13.8)
Atrial fibrillation, *n* (%)	100 (3.1)
Previous revascularization	
PCI	504 (15.7)
CABG	74 (2.3)
Family history of premature CVD	286 (8.9)
Physical examination and laboratory measurements	
Weight[a]	67.1 ± 12.0
BMI[a]	25.0 ± 3.7
Systolic blood pressure (mmHg)[a]	133.4 ± 26.6
Diastolic blood pressure (mmHg)[a]	77.99 ± 15.8
Heart rate[a]	81.5 ± 21.2
Total cholesterol (mg/dl)[a]	172.6 ± 43.816
LDL-C (mg/dl)[a]	115.2 ± 39.223
Creatinine (mg/dl)[a]	1.2 ± 0.5
HbA1c (mg/dl)[a] *(n = 2,345)*[b]	7.03 ± 1.96
Within DM subgroup *(n = 1,178)*	8.2 ± 2.08
Without DM subgroup *(n = 1,168)*	5.81 ± 0.62
EF[a]	45.6 ± 12.1
Medication at discharge	
Lipid lowering medication, *n* (%)	3,018 (94)
Simvastatin, *n* (%)	953 (29.8)
Atorvastatin, *n* (%)	2,024 (63.1)
Rosuvastatin, *n* (%)	41 (1.3)
Antiplatelet therapy, *n* (%)	2,900 (90.4)
Aspirin only, *n* (%)	111 (3.5)
Dual antiplatelet therapy, *n* (%)	2,789 (86.9)
Colchicine, *n* (%)	18 (0.6)

BMI, body mass index; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; LDL-C, low density lipoprotein cholesterol; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Data are displayed as mean (standard deviation).
[b]HbA1c measurement was restricted to patients with a documented history of type 2 diabetes mellitus (T2DM) or hyperglycemia on admission.

3.2 Risks of recurrent cardiovascular events

This study found an average 10-year risk of recurrent cardiovascular events of 30.2% (95% CI 29.7–30.6%), and a lifetime risk averaging 62.5% (95% CI 62.1–62.9%) (Figure 2). Subgroup analysis demonstrates differences in ASCVD risk profiles. Female patients exhibited a higher average risk than males (10-year: mean 30.5% vs. 29.6%; lifetime: mean 62.9% vs. 62.4%). Patients with diabetes mellitus (DM) had the highest average risk for both 10-year and lifetime events compared to active smokers and hypertensive subgroups (10-year: mean 36.5% vs. 30.3% vs. 30.4%; lifetime: mean 67.4% vs. 62.5% vs. 61.7%) (Figures 3A,B).

Upon discharge, nearly equal proportions of patients received simvastatin 20 mg (29.5%), atorvastatin 20 mg (30%), or atorvastatin 40 mg (32%), with a small portion (6%) not receiving a statin. Most patients receiving statins (59.9%) were prescribed moderate-intensity statins (e.g., atorvastatin 20 mg)

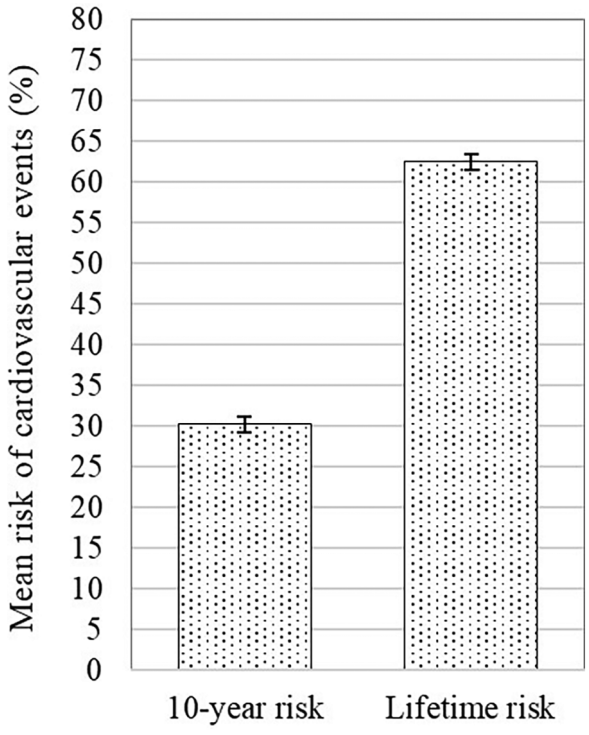


FIGURE 2
Mean 10-year risk of cardiovascular events with 95% confidence interval of the total sample.

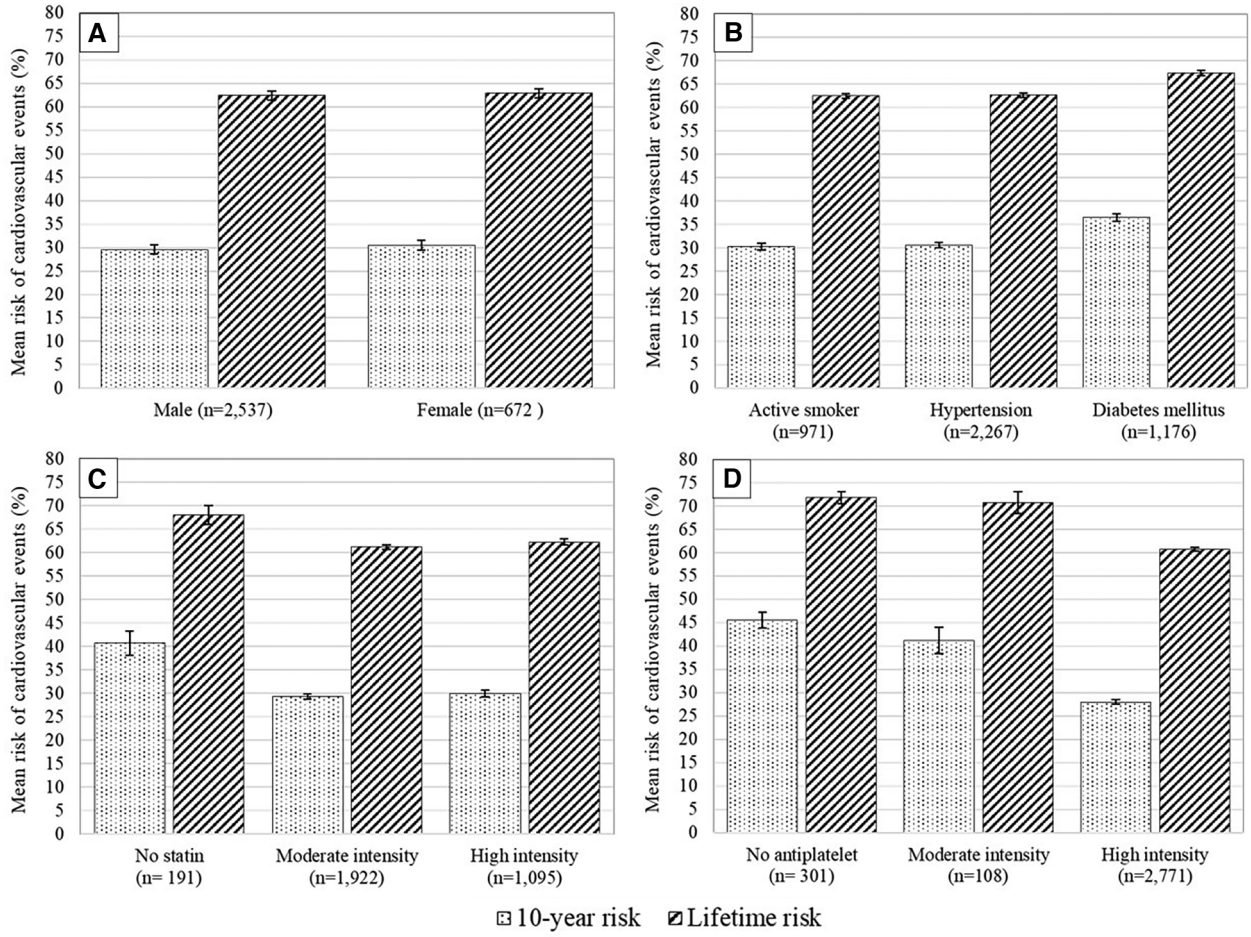


FIGURE 3
Mean 10-year risk of cardiovascular events with 95% confidence interval based on different patients' subgroups: (A) sex, (B) risk factors, (C) statin intensity given at discharge, and (D) antiplatelet therapy given at discharge.

rather than high-intensity statins (36.5%). Patients on atorvastatin 20 mg had the lowest average risk of recurrent cardiovascular events compared to those on atorvastatin 40 mg and simvastatin 20 mg, for both 10-year (28.4% vs. 29.8% vs. 30.1%) and lifetime risks (61.2% vs. 62.2% vs. 62.1%). Additionally, patients treated with moderate-intensity statins showed lower average risks compared to those on high-intensity statins (10-year: mean 29.3% vs. 29.9%; lifetime: 61.2% vs. 62.3%) (Figure 3C).

The majority of patients (86.4%) received dual antiplatelet therapy (DAPT), with others receiving aspirin only (3.4%) or no antiplatelet therapy (9.4%). Patients on DAPT had a significantly lower risk than those on aspirin only or no antiplatelet therapy (10-year: 28.0% vs. 41.2% vs. 45.6%; lifetime: 60.7% vs. 70.7% vs. 71.8%) (Figure 3D).

3.3 Direct inpatient cost of ASCVD

The median direct inpatient cost of all 3,209 patients was 3,033 USD (IQR 1,573 USD). Male and female patients showed relatively similar median expenses [3,043 USD (IQR 1,527 USD) vs. 2,956 USD (IQR 1,727 USD)]. Among the diagnosis groups, STEMI patients had the highest median direct inpatient cost compared to the NSTEMI and CCS patients (3,643 USD vs. 3,768 USD vs. 2,828 USD). Since all CCS patients in this study were elected for PCI, their length of stay and procedures were similar, resulting in a lower interquartile range (IQR 760 USD). In contrast, NSTEMI patients showed the most varied direct inpatient cost between patients (IQR 2,922 USD). Lastly, patients admitted to the National Cardiovascular Center Harapan Kita had a higher median direct inpatient cost compared to those admitted to Dr. Sardjito Hospital, [3,769 USD (IQR 1,716 USD) vs. 2,712 USD (IQR 888 USD)] (Table 2).

4 Discussion

In this study, we profiled the 10-year and lifetime recurrent ASCVD risk from two major cardiovascular centers in Indonesia. Our study highlighted the remarkably elevated 10-year and lifetime risk of experiencing major cardiovascular events among the population of Indonesian ASCVD patients. Approximately 3

TABLE 2 Total indirect inpatient cost of study subjects.

	Overall population (*n* = 3,209)	Sex		ASCVD diagnosis			CV center	
		Male (*n* = 2,537)	Female (*n* = 672)	STEMI (*n* = 1,732)	NSTEMI (*n* = 904)	CCS (*n* = 573)	NCCHK (*n* = 2,475)	Dr. Sardjito Hospital (*n* = 734)
Median	3,033	3,043	2,956	3,270	2,491	2,696	3,135	2,689
Standard deviation	3,164	3,006	3,700	2,612	4,506	1,596	3,450	1,597
25th percentile	2,285	2,333	2,100	2,698	1,140	2,307	2,281	2,301
75th percentile	3,858	3,861	3,827	4,003	4,062	3,067	3,998	3,189
Interquartile range	1,573	1,527	1,727	1,304	2,922	760	1,716	888

ASCVD, atherosclerotic cardiovascular disease; CCS, chronic coronary syndrome; CI, confidence interval; CV, cardiovascular; NCCHK, National Cardiovascular center Harapan Kita; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. Currency in USD with conversion rate of 1 USD = 15.734 IDR.

out of 10 individuals were projected to experience recurrent ASCVD within the span of 10 years, with about twice as many expected to encounter such an event over their lifetime. These risks were particularly higher among female subjects, and also among diabetic individuals compared to smoking or hypertensive patients. STEMI patients demonstrated the highest direct inpatient cost, followed by NSTEMI and CCS patients, suggesting that the acute nature of acute coronary syndrome (ACS) may result in greater associated costs during hospitalization. Given the substantial expenses associated with hospitalization in CVD patients, utilizing this model could be beneficial to help optimize therapy in patients at higher risk and to provide an estimate of future ASCVD burden.

To our knowledge, this is the first study in Asia to utilize the SMART-REACH model for estimating recurrent ASCVD risk among the secondary-prevention population. A study by van Trier et al., conducted on the European population, indicated a ten-year and lifetime risk of 26% and 55% respectively ($n = 416$, mean (SD) age 65 (9) years, and 80% men) (11). Similarly, Siniawski et al. observed a ten-year risk of 34.95% in the Argentinian population ($n = 296$, mean (SD) age 68.2 (9.4) years, and 75.7% men) (12). Discrepancies in CVD recurrent risk estimation between these studies and ours could be attributed to differences in the incidence rate of CVD and its risk factors such as hypertension, dyslipidemia, and diabetes among CVD patients.

In Indonesia, several other studies have reported their findings on ASCVD risk assessments. A study estimated CVD risk using the WHO/ISH risk charts and reported that about two-thirds of the population exhibited a CVD risk below 10%. However, the study mainly focused on primary prevention risk assessment and recruited only 3.4% of participants with a previous history of CVD (13). Another study utilizing the SMART2 algorithm to estimate the risk of recurrent coronary heart disease (CHD) demonstrated that 65% of the enrolled patients possessed a very high risk of 10-year recurrent CHD equal to or exceeding 30%. It is noteworthy that this latter study involved a more limited cohort of 395 participants (14). Moreover, the study population was localized to the eastern region of Indonesia, thus the findings may not be fully representative of the entire country.

Approximately 70% of the participants in this investigation presented with hypertension, while 36% were diagnosed with diabetes mellitus, highlighting the importance of these conditions as significant risk factors within this population. Thus, one of the important laboratory parameters assessed was HbA1c. The study observed that the average HbA1c values within the subgroup of diabetes mellitus were 8.2%, surpassing the recommended target range. This could be attributed to the inclusion of newly diagnosed diabetic patients within the subgroup. Moreover, given this study's cross-sectional nature, it is important to note that this finding cannot demonstrate a therapeutic response. A study conducted by Zhang et al., has revealed that individuals with Type 2 Diabetes Mellitus (T2DM) and moderate baseline ASCVD risk, face a significantly increased cardiovascular risk if their HbA1c levels range between 7.0% to 8.0% (15).

Our subsequent subgroup analysis revealed a varied distribution of recurrent ASCVD risks across various patient subgroups. We found higher 10-year and lifetime risks among individuals with diabetes mellitus compared to the actively smoking and hypertensive patients. An observational study among type 1 diabetes mellitus patients with a median follow-up of 29 years reported HbA1c as the strongest modifiable risk factor for the first and subsequent CVD events. Each 1% increase in mean HbA1c is associated with a 28% increased risk of developing subsequent CVD events and an 89% increased risk of encountering recurrent major adverse cardiovascular events (16). Therefore, a controlled glycemic level can significantly lower the risk of recurrent events. This information can guide more intensified treatment options for those with a higher risk of ASCVD recurrence. Given that ischemic heart disease is associated with high unit costs and financial burden, identifying and managing patients at higher risks (diabetic, hypertensive, actively smoking), especially in populations with limited access to high-quality healthcare, remains essential in lowering the CVD burden in these vulnerable populations. This also highlights the significance of devising tailored, intensive preventive strategies in ASCVD secondary prevention.

In the present study, not all patients received guideline-directed medical therapy for secondary prevention. Despite the American Heart Association/American College of Cardiology/multisociety (AHA/ACC/MS) and European Society of Cardiology (ESC) guidelines recommending the use of high-intensity statin for every patient with a history of ASCVD, only 34.1% of the included patients were prescribed high-intensity statin at discharge. This figure of high-intensity statin underutilization for very high-risk secondary prevention patients is comparable with other studies in different countries (12, 17–19). In this study, individuals receiving statins of higher intensity showed elevated ASCVD risks compared to those receiving statins of moderate intensity, albeit to a marginal extent. Similar results were found

between patients receiving 20 vs. 40 mg of atorvastatin. These findings could be attributed to a higher prevalence of risk factors among patients prescribed with the higher statin, consequently elevating the risk of recurrent ASCVD. This was confirmed by our further analysis revealing that among patients receiving high-intensity statin, not only did they demonstrate a significantly larger percentage of active smokers, but also higher total cholesterol, LDL-C, and HbA1c levels.

Some patients were not prescribed anti-thrombotic therapy and a bigger portion of the patients did not receive high-intensity statin. The use of additional drug strategies (i.e., colchicine, glucagon-like peptide-1 agonists/GLP-1a, and sodium–glucose cotransporter 2 inhibitors/SGLT2i) was not regularly prescribed in both hospitals where the study population was collected. Several studies have described the potential risk reduction of optimal guideline-directed preventive ASCVD therapy using the SMART-REACH model, which yielded a median risk reduction of 6%–10% and 9%–20% for 10-year and lifetime risk respectively (11, 20). In Indonesia, according to the Indonesian Case Base Groups (INA-CBGs), high-intensity statin is only covered by the government during hospitalization until 3 weeks post-discharge. A cost-effectiveness analysis revealed that the use of high-intensity statin post-hospitalization in ACS patients had an incremental cost-effectiveness ratio of 31.843.492.98 IDR (USD 2,024) per quality-adjusted life year compared to conventional-dose statin. This finding advocates the prescription of high-intensity over low to moderate-intensity statin as a cost-effective secondary prevention strategy to mitigate recurrent ASCVD over a prolonged time period (21).

It is of interest that our finding revealed the highest direct inpatient cost in STEMI subjects compared to patients with NSTEMI or CCS. An observational study enrolling 218 hospitals in Asia reported several significant predictors of high-cost care for ACS, including age, male sex, prior disease history, previous history of hospitalization in the last 3 months, having an invasive procedure, hospital type, and longer hospital stay (22). The higher cost observed among STEMI patients in our study could be attributed to a combination of those factors, however, this finding further confirms the high economic burden posed by CVD. When compared to other Asian countries, China was reported to incur the highest cost for hospitalized ACS patients (STEMI mean cost: USD 7,790; NSTEMI: USD 7,450), more than twice the direct inpatient cost that we presented in our study. Thailand also presented a higher cost of hospitalization averaging at USD 4,427 for STEMI and USD 3,321 for NSTEMI. The direct inpatient cost in our study was comparable to figures documented in Hong Kong and slightly surpassed those reported in Vietnam. Nonetheless, it is crucial to emphasize the distinction that in Hong Kong, the government subsidizes all emergency admissions for ACS, leading to generally low healthcare payments for patients (22).

Moreover, with an average cost of approximately Rp55 million (approximately 3,500 USD) per hospital discharge, it may be important to note that our study specifically focused on two tertiary referral hospitals in Indonesia, resulting in relatively higher costs. However, the choice of tertiary referral hospitals is justified by the superior quality of care they offer, potentially making the Rp55 million figure indicative of the optimal cost of disease care. Considering a 10-year risk of recurrent ACS at 30.2%, the significance of timely secondary preventive treatment becomes evident, especially since ischemic heart disease represents the highest expenditure (9.65% in 2016) within the Indonesian National Health Insurance (JKN) (23). In the context of secondary prevention, one study observed that even among patients categorized as having a high risk for CVD, healthcare costs were three times higher in those with a history of cardiovascular events like ACS (24). Furthermore, it is important to note that this analysis does not encompass the indirect costs of healthcare, which have been identified as significant contributors to further economic burden and productivity loss in various studies.

5 Limitations

The limitations of the ASCVD risk calculation using the SMART-REACH model have been previously discussed (6). Most existing risk prediction tools lack sufficient calibration for the Asian population, including the SMART-REACH model, which has yet to be validated for any population group other than Western European and North American. Furthermore, the SMART risk score, which the SMART-REACH model is derived from, has been updated to the SMART2 risk score in order to match the external validations done after its conception (25). This study exclusively included patients with STEMI, NSTEMI, and CCS, while omitting other coronary heart diseases, cerebrovascular disease, peripheral artery disease, and alternative forms of vascular disease. The inclusion of diverse atherosclerotic manifestations would have provided additional insights into the prevalence of recurrent CVD in Indonesia. Many diabetic ASCVD patients in this study have also been excluded since HbA1c is not regularly checked at both hospitals during admission, rendering the data unable to be calculated using the SMART-REACH model. Furthermore, due to administrative challenges in data collection, only total costs were attainable from both cardiovascular centers, excluding the breakdown of individual cost components, such as medication and procedure bills. This is a missed opportunity, as such details could have provided valuable insights, such as healthcare cost differences between patients receiving different antiplatelet medications at discharge.

6 Conclusions

By employing the SMART-REACH model, a significant number of Indonesian ASCVD patients was anticipated to exhibit considerably elevated risks of experiencing a major cardiovascular event over both a 10-year and lifetime period. Notably, patients with STEMI incurred the highest direct inpatient costs, followed by those with NSTEMI and CCS. These findings underscore the imperative of identifying those at a

heightened risk of recurrent ASCVD, as optimizing therapy and implementing tailored secondary prevention measures could lead to substantial health and financial benefit.

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 National Cardiovascular Center Harapan Kita Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. 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

BD: Conceptualization, Methodology, Writing – original draft. DD: Conceptualization, Methodology, Writing – review & editing. AH: Conceptualization, Methodology, Writing – review & editing. DJ: Data curation, Methodology, Writing – review & editing. AA: Data curation, Methodology, Writing – review & editing. NZ: Formal Analysis, Writing – original draft. PR: Formal Analysis, Writing – original draft. BK: Formal Analysis, Writing – original draft. JP: Writing – original draft. BW: Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article.

The study is funded by Novartis Indonesia through the collaborative research agreement between National Cardiovascular Center Harapan Kita, Jakarta Indonesia with Novartis Indonesia (grant no. CKJX839D1ID02R).

Acknowledgments

The authors would like to thank the National Cardiovascular Center Harapan Kita, Jakarta and Dr. Sardjito Hospital, Yogyakarta for their provision of resources and facilities to conduct this study. The authors would also like to thank Dr. Yuriawati Hendrawan, Dr. Albertus Agung Mahode, and Kadek Darmawan from Novartis Indonesia for the valuable support, intense coordination and insight, particularly on the idea creation and protocol development of this study.

Conflict of interest

The authors declare that this study received funding from Novartis Indonesia. The funder was involved in the creation of ideas and study design, but was not involved further in data collection, analysis, interpretation, and the writing of this article.

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. Lopez EO, Ballard BD, Jan A. *Cardiovascular Disease*. Treasure Island, Florida: StatPearls Publishing (2023).

2. Purnamasari D. The emergence of non-communicable disease in Indonesia. *Acta Med Indones*. (2018) 50:273–4.

3. Adisasmito W, Amir V, Atin A, Megraini A, Kusuma D. Geographic and socioeconomic disparity in cardiovascular risk factors in Indonesia: analysis of the basic health research 2018. *BMC Public Health*. (2020) 20:1004. doi: 10.1186/s12889-020-09099-1

4. Khera R, Valero-Elizondo J, Nasir K. Financial toxicity in atherosclerotic cardiovascular disease in the United States: current state and future directions. *J Am Heart Assoc*. (2020) 9:e017793. doi: 10.1161/JAHA.120.017793

5. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, Gondrie MJA, Steyerberg EW, Ridker PM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart*. (2013) 99:866–72. doi: 10.1136/heartjnl-2013-303640

6. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB Sr, Massaro JM, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. *J Am Heart Assoc*. (2018) 7:e009217. doi: 10.1161/JAHA.118.009217

7. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau C-S, et al. The REduction of atherothrombosis for continued health (REACH) registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J*. (2006) 151:786.e1–10. doi: 10.1016/j.ahj.2005.11.004

8. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol*. (1999) 15:773–81. doi: 10.1023/A:1007621514757

9. Juzar DA, Muzakkir AF, Ilhami YR, Taufiq N, Astiawati T, I Made Junior R, et al. Management of acute coronary syndrome Indonesia: insight from one ACS multicenter registry. *Indones J Cardiol*. (2022) 43:45–55. doi: 10.30701/ijc.1406

10. Alkatiri AA, Firman D, Haryono N, Yonas E, Pranata R, Fahri I, et al. Comparison between radial versus femoral percutaneous coronary intervention access in Indonesian hospitals, 2017–2018: a prospective observational study of a national registry. *Int J Cardiol Heart Vasc*. (2020) 27:100488. doi: 10.1016/j.ijcha.2020.100488

11. van Trier TJ, Snaterse M, Hageman SHJ, Ter Hoeve N, Sunamura M, Moll van Charante EP, et al. Unexploited potential of risk factor treatment in patients with atherosclerotic cardiovascular disease. *Eur J Prev Cardiol*. (2023) 30:601–10. doi: 10.1093/eurjpc/zwad038

12. Siniawski D, Masson G, Masson W, Barbagelata L, Destaville J, Lynch S, et al. Residual cardiovascular risk, use of standard care treatments, and achievement of treatment goals in patients with cardiovascular disease. *Int J Cardiol Cardiovasc Risk Prev*. (2023) 18:200198. doi: 10.1016/j.ijcrp.2023.200198

13. Maharani A, Sujarwoto, Praveen D, Oceandy D, Tampubolon G, Patel A. Cardiovascular disease risk factor prevalence and estimated 10-year cardiovascular risk scores in Indonesia: the SMARThealth extend study. *PLoS One*. (2019) 14: e0215219. doi: 10.1371/journal.pone.0215219

14. Arsyad DS, Hageman SHJ, Qalby N, Ansariadi, Wahiduddin, Qanitha A, et al. Very high risk of recurrent cardiovascular events in Indonesian patients with established coronary heart disease. *J Asian Pac Soc Cardiol*. (2023) 2. doi: 10.15420/japsc.2023.04

15. Zhang H, Qin L, Sheng C-S, Niu Y, Gu H, Lu S, et al. ASCVD risk stratification modifies the effect of HbA1c on cardiovascular events among patients with type 2 diabetes mellitus with basic to moderate risk. *BMJ Open Diabetes Res Care*. (2020) 8. doi: 10.1136/bmjdrc-2019-000810

16. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk factors for first and subsequent CVD events in type 1 diabetes: the DCCT/EDIC study. *Diabetes Care*. (2020) 43:867–74. doi: 10.2337/dc19-2292

17. Mitani H, Suzuki K, Ako J, Iekushi K, Majewska R, Touzeni S, et al. Achievement rates for low-density lipoprotein cholesterol goals in patients at high risk of atherosclerotic cardiovascular disease in a real-world setting in Japan. *J Atheroscler Thromb*. (2023) 30:1622–34. doi: 10.5551/jat.63940

18. Salem AM, Harris D, Bray JJH, Obaid DR, Stephens JW, Halcox J. Achievement of the ESC recommendations for secondary prevention of cardiovascular risk factors in high-risk patients with type 2 diabetes: a real-world national cohort analysis. *Int J Cardiol*. (2023) 377:104–11. doi: 10.1016/j.ijcard.2023.02.004

19. Authors/Task Force Members, , ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis*. (2019) 290:140–205. doi: 10.1016/j.atherosclerosis.2019.08.014

20. Gynnild MN, Hageman SHJ, Dorresteijn JAN, Spigset O, Lydersen S, Wethal T, et al. Risk stratification in patients with ischemic stroke and residual cardiovascular risk with current secondary prevention. *Clin Epidemiol*. (2021) 13:813–23. doi: 10.2147/CLEP.S322779

21. Dewi PEN, Thavorncharoensap M, Rahajeng B. Cost-utility analysis of using high-intensity statin among post-hospitalized acute coronary syndrome patients. *Egypt Heart J*. (2024) 76:47. doi: 10.1186/s43044-024-00478-2

22. Jan S, Lee SW-L, Sawhney JPS, Ong TK, Chin CT, Kim H-S, et al. Predictors of high-cost hospitalization in the treatment of acute coronary syndrome in Asia: findings from EPICOR Asia. *BMC Cardiovasc Disord*. (2018) 18:139. doi: 10.1186/s12872-018-0859-4

23. Agustina R, Dartanto T, Sitompul R, Susiloretni KA, Suparmi, Achadi EL, et al. Universal health coverage in Indonesia: concept, progress, and challenges. *Lancet*. (2019) 393:75–102. doi: 10.1016/S0140-6736(18)31647-7

24. Tran DT, Palfrey D, Welsh R. The healthcare cost burden in adults with high risk for cardiovascular disease. *Pharmacoecon Open*. (2021) 5:425–35. doi: 10.1007/s41669-021-00257-8

25. Hageman SHJ, McKay AJ, Ueda P, Gunn LH, Jernberg T, Hagström E, et al. Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm. *Eur Heart J*. (2022) 43:1715–27. doi: 10.1093/eurheartj/ehac056

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 26 September 2024
DOI 10.3389/fcvm.2024.1358378

OPEN ACCESS

EDITED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

REVIEWED BY
Łukasz Niewiara,
Jagiellonian University Medical College, Poland
Jing Hong,
Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region, China

*CORRESPONDENCE
Xuejun Deng
✉ tsysdoctor@sina.com

†These authors have contributed equally to this work

RECEIVED 19 December 2023
ACCEPTED 02 September 2024
PUBLISHED 26 September 2024

CITATION
Jiang W, Huang G, Du J, Yang H, Zhou S, Dai D, Tang K, Fang L, Wang X and Deng X (2024) White blood cell counts can predict 4-year cardiovascular disease risk in patients with stable coronary heart disease: a prospective cohort study.
Front. Cardiovasc. Med. 11:1358378.
doi: 10.3389/fcvm.2024.1358378

White blood cell counts can predict 4-year cardiovascular disease risk in patients with stable coronary heart disease: a prospective cohort study

Wencai Jiang[1†], Gang Huang[1†], Jinfeng Du[2], Hanxuan Yang[1], Shiheng Zhou[1], Dayin Dai[1], Kai Tang[1], Lingxiao Fang[1], Xiao Wang[1] and Xuejun Deng[1*]

[1]Department of Cardiology, Suining Central Hospital, Suining, Sichuan, China, [2]Department of Hematology, Chongqing Emergency Medical Center, Chongqing, China

Background: The prevalence of cardiovascular disease has increased sharply in the Asian population, and evaluation of the risk of cardiovascular events with stable coronary heart disease remains challenging. The role of white blood cell (WBC) count in assisting clinical decision-making in this setting is still unclear.
Objectives: This study sought to evaluate the prognostic meaning of WBC count among patients with stable coronary heart disease.
Methods: This study included Asian participants (n = 1,933) from the prospective STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial, which involved 15,828 patients with stable coronary heart disease with 3–5 years of follow-up on optimal secondary preventive treatment. WBC count was measured at baseline. Associations between WBC count and cardiovascular outcomes were evaluated by Cox regression analyses with multivariable adjustments. Hematologic emergencies in patients may introduce potential bias.
Results: In the lower WBC count quartiles, patients had lower-risk clinical profiles. Higher WBC counts were associated with greater event probabilities for cardiovascular death, major cardiovascular events, or all-cause death. In Cox regression models, WBC counts were an independent predictor of major adverse cardiovascular events (OR = 2.445, 95% CI 1.427–4.190, P = 0.001) for the primary outcomes. For the secondary outcomes, including the composite of all-cause death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure, WBC counts were significantly predictive of events with similar magnitude (OR = 1.716, 95% CI 1.169–2.521, P = 0.006).
Conclusions: In patients with stable coronary heart disease, higher WBC counts were associated with a heightened risk for the primary or secondary outcomes.

Registration: https://clinicaltrials.gov/; Unique identifier NCT00799903.

KEYWORDS

white blood cell (WBC) count, risk factors, cardiovascular disease, cardiovascular events, stable coronary heart disease

Introduction

Cardiovascular diseases are increasing worldwide. In Asia, the aging population has led to a particularly significant increase in the prevalence, morbidity, and mortality of cardiovascular diseases (1). This poses a huge medical burden on the families and society in this area. With the maturity and development of percutaneous coronary intervention (PCI), more and more people are surviving with these diseases (2). Increased attention to promoting ideal cardiovascular health in patients with stable coronary heart disease is necessary (3). However, evaluation of the prognosis of patients with stable coronary heart disease remains challenging. Although coronary computed tomography angiography (CTA) and coronary angiography are useful, these imaging modalities have limitations, including availability, cost, the need for specialized interpretation, and exposure to ionizing radiation (4). It is time to implement feasible and affordable strategies for the prevention and control of stable coronary heart disease and to monitor results (5).

The role of white blood cell (WBC) count in predicting the risk of coronary heart disease in a normal population has been confirmed (6–8). However, compared to other regions, there are differences in eating habits, risk factors, and gene frequencies among Asian people (9, 10). Most of the existing literature focuses on the relationship between WBC count and acute myocardial infarction (MI) but neglects the role of WBC count in managing patients with coronary heart disease. The role of WBC count in predicting the risk of recurrent cardiovascular events in patients with stable coronary heart disease remains uncertain. Our study is a *post-hoc* analysis of the prospective STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial, which is a large-scale global trial with a large amount of data on patients with stable coronary heart disease from multiple centers in Asia. The aim of the current study was to explore the associations between WBC count and clinical outcomes in patients with stable coronary heart disease, with the goal of augmenting the ability to triage patients properly with stable coronary heart disease and assist in clinical interpretation and decision-making. In addition, we aimed to better understand the potential mechanisms behind the associations.

Methods

The research data of this article can be available from https://search.vivli.org/doiLanding/studies/00000708/isLanding upon an appropriate request.

Population

Our study data were obtained from the prospective STABILITY trial, a randomized placebo-controlled study evaluating the effects of a lipoprotein-associated phospholipase A2 inhibitor, darapladib. It included 15,828 patients with stable coronary heart disease from 39 countries (11), with a follow-up of 3–5 (median, 3.7) years on optimal secondary preventive treatment. We analyzed the data on the Asian population ($n = 1933$), including China ($n = 178$, 25.9%), Japan ($n = 110$, 34.6%), the Republic of Korea ($n = 107$, 21.3%), the Philippines ($n = 20$, 9.1%), and Thailand ($n = 43$, 20.8%). The trial design, inclusion and exclusion criteria, baseline characteristics, and endpoint events have been described previously (12, 13). The trial was performed in accordance with the Declaration of Helsinki. In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations. All participants provided written informed consent for their participation. It was funded by GlaxoSmithKline and is registered at ClinicalTrials.gov (unique identifier: NCT00799903; https://clinicaltrials.gov/ct2/show/NCT00799903).

Grouping and outcomes

WBC counts were measured at baseline in the Asian population ($n = 1{,}933$). The study population was divided into four groups according to the quartiles of WBC counts: WBC < 5.3 GI/L, WBC < 6.3 GI/L, WBC < 7.5 GI/L, and WBC ≥ 7.5 GI/L. Venous blood samples from all participants were obtained in the morning after at least 8 h of fasting. The method of laboratory examination has been described in previously published studies (14, 15). Definitions of all endpoints were prespecified and distinctly represented before (12). These were adjudicated by an independent clinical events committee. The primary outcomes, defined as major adverse cardiovascular events (MACEs), included cardiovascular death, myocardial infarction, and stroke. The secondary outcomes included all-cause death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. We analyzed cardiovascular event outcomes over about 4 years in participants with different white blood cell counts. All laboratory tests were performed at central laboratories (Quest Diagnostics Clinical Laboratories) to ensure the reliability of the WBC count.

Statistical analysis

Categorical variables were represented by percentages, which will be compared using the chi-square test. Continuous variables were compared using Kruskal–Wallis non-parametric tests. A Cox proportional hazards model was used to analyze and compare the incidence of cardiovascular events of patients with chronic coronary heart disease with different WBC counts. In the multivariable model, we adjusted for the following factors: age, sex, country, BMI, waist/hip ratio, systolic blood pressure, diastolic blood pressure, hemoglobin, hematocrit, neutrophils, platelets, blood lipids, high-sensitivity C-reactive protein (hsCRP), creatinine, estimated glomerular filtration rate (eGFR), urea/blood urea nitrogen (BUN), glucose, liver function, prior MI, multivessel coronary heart disease, prior coronary artery bypass grafting (CABG), diabetes, hypertension, chronic obstructive pulmonary disease (COPD), clopidogrel bisulfate,

aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEis/ARBs), statins, β-receptor blockers, and smoking status. We used multiple imputations to deal with missing data. All statistical analyses were performed using SPSS 26.0 (IBM, New York City, NY, USA). If $P < 0.05$, the difference was statistically significant.

Results

Baseline characteristics of patients in different white blood cell count groups

The average age of the study population ($n = 1,933$) was 63.75 ± 9.40 years. Among them, 408 were women, accounting for 21.1% of the population. In total, 458 patients had a WBC count of <5.3 GI/L, 471 had a WBC count of <6.3 GI/L, 510 had a WBC count of <7.5 GI/L, and 494 had a WBC count of ≥7.5 GI/L. Among patients with stable coronary heart disease, older age was associated with lower white blood cell counts. In the WBC count <5.3 GI/L group, the proportion of females was the highest (26.2%). Patients from different countries exhibited different WBC counts. The baseline characteristics and demographics are presented in Table 1. There were statistically significant differences in sex, country, BMI, hemoglobin, hematocrit, neutrophils, platelets, high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), cholesterol, hsCRP, creatinine, glucose, alkaline phosphatase (ALP), alanine aminotransferase (ALT), prior MI, prior CABG, diabetes, clopidogrel, and smoking status among patients with different WBC counts ($P < 0.05$). To facilitate observation, except for gender and country, we created Figure 1 to highlight predictors with obvious differences and expressed their numerical values with different color scales. In the WBC count <5.3 GI/L group, BMI, hemoglobin, hematocrit, neutrophils, platelets, TGs, cholesterol, hsCRP, creatinine, glucose, ALP, ALT, prior MI, prior CABG, diabetes, and the percentage of never smokers were the lowest, while age, HDL-C, and the percentage of former smokers were the highest.

WBC count and its association with clinical outcomes

By 4 years, 133 study participants experienced the primary outcomes of MACEs, whereas 214 participants experienced the secondary outcomes that included the composite of all-cause death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. Patients who experienced secondary outcomes by 4 years had higher WBC counts at enrollment than those who did not (6.89 ± 1.75 GI/L vs. 6.50 ± 1.81 GI/L; $P = 0.003$). The associations between WBC counts and the risk of hospitalization for heart failure, stroke, MI, cardiovascular death, and all-cause death are presented in Table 2. By 4 years, the rates of all-cause death, MACEs, and cardiovascular death in patients with WBC count <5.3 GI/L were significantly lower than those with WBC count ≥5.3 GI/L, with P-values of 0.012, 0.028, and 0.033, respectively. The event probabilities for hospitalization for heart failure, stroke, or MI across WBC count quartiles were not significant.

We drew cumulative hazard curves, depicting time-to-events as a function of WBC quartiles at presentation (Figure 2). Kaplan–Meier curves suggest that the all-cause mortality in the WBC count <5.3 GI/L group was significantly lower than in the WBC count ≥5.3 GI/L groups. The log-rank test suggests that the difference in their estimated event probabilities was statistically significant ($P = 0.016$).

Results of multivariate Cox proportional hazards models

The results of multivariate Cox proportional hazards models are shown in Figure 3. In multivariate Cox proportional hazards models for predicting primary outcomes at 4 years, WBC counts were an independent predictor of events (OR = 2.445, 95% CI 1.427–4.190, $P = 0.001$). In addition, age, country, BMI, and β-receptor blockers were also independent predictors of primary outcome events. For the secondary outcomes at 4 years, in Cox proportional hazards, WBC counts were significantly predictive of events with a similar magnitude (OR = 1.716, 95% CI 1.169–2.521, $P = 0.006$). At the same time, age, country, BMI, cholesterol, urea/BUN, ALP, prior MI, β-receptor blockers, and smoking status were also independent predictors of secondary outcome events. It is worth noting that in Asia, the risk of primary and secondary outcomes in patients with stable coronary heart disease in developing countries was 1.74 and 1.84 times higher, respectively, than that in developed countries.

Discussion

With the aging population, the burden of coronary heart disease in Asia is becoming heavier than in Europe and America. On the other hand, with the development of PCI, the number of patients with stable coronary heart disease is increasing, presenting a huge challenge for its management in Asia. In a secondary analysis of this prospective cohort study of patients with stable coronary heart disease, we explored the association between WBC counts and clinical cardiovascular outcomes in the Asian population. We found that patients with stable coronary heart disease in the lowest WBC quartile had significantly lower incidences of primary and secondary outcome events than patients in other WBC quartiles. After adjusting for the effects of other factors by a multivariable Cox proportional hazards model, we found that WBC count was an independent predictor for primary and secondary outcomes. Therefore, the inclusion of WBC count in the risk assessment system of patients with coronary heart disease has important clinical and public health significance.

Among the general population, the association between WBC count and the risk of coronary heart disease has been confirmed

10.3389/fcvm.2024.1358378

TABLE 1 Baseline characteristics by WBC count quartiles.

Baseline characteristics	<5.3 GI/L *n* = 458	<6.3 GI/L *n* = 471	<7.5 GI/L *n* = 510	≥7.5 GI/L *n* = 494	*P*-value
Age (years)	65.50 ± 8.34	64.44 ± 9.23	63.85 ± 9.42	61.39 ± 10.00	<0.001
Female, *n* (%)	120 (26.2)	94 (20.0)	97 (19.0)	97 (19.6)	0.023
Country, *n* (%)					
China	178 (25.9)	170 (24.8)	172 (25.1)	166 (24.2)	<0.001
Japan	110 (34.6)	87 (27.4)	79 (24.8)	42 (13.2)	<0.001
Republic of Korea	107 (21.3)	132 (26.2)	141 (28.0)	123 (24.5)	<0.001
Philippines	20 (9.1)	40 (18.3)	66 (30.1)	93 (42.5)	<0.001
Thailand	43 (20.8)	42 (20.3)	52 (25.1)	70 (33.8)	<0.001
BMI, kg/m^2	24.86 ± 3.07	25.01 ± 3.28	25.55 ± 3.36	25.75 ± 3.6	<0.001
Waist/hip ratio	0.93 ± 0.07	0.93 ± 0.07	0.93 ± 0.08	0.93 ± 0.07	0.497
SBP, mmHg	75.96 ± 11.13	77.45 ± 10.79	77.24 ± 11.69	77.32 ± 11.03	0.254
DBP, mmHg	130.67 ± 16.91	130.19 ± 16.41	131.08 ± 17	130.12 ± 16.32	0.757
Hemoglobin, g/L	136.35 ± 15.59	139.83 ± 14.32	141.85 ± 14.57	142.87 ± 16.46	<0.001
Hematocrit	0.42 ± 0.05	0.43 ± 0.04	0.44 ± 0.04	0.44 ± 0.05	<0.001
Neutrophils, $10^9/L$	2.7 ± 0.5	3.47 ± 0.52	4.19 ± 0.62	5.7 ± 1.44	<0.001
Platelets, $10^9/L$	194.77 ± 46.66	208.69 ± 50.51	223.78 ± 53.84	246.09 ± 64.83	<0.001
HDL-C, mmol/L	1.29 ± 0.36	1.27 ± 0.34	1.24 ± 0.31	1.22 ± 0.32	0.017
LDL-C, mmol/L	2.04 ± 0.7	2.06 ± 0.74	2.15 ± 0.84	2.13 ± 0.84	0.228
TGs, mmol/L	1.56 ± 0.96	1.63 ± 0.98	1.77 ± 0.93	1.88 ± 1.61	<0.001
cholesterol, mmol/L	4.03 ± 0.88	4.06 ± 0.83	4.19 ± 0.94	4.19 ± 0.94	0.037
hsCRP, mg/L	2.18 ± 3.79	2.03 ± 2.76	2.43 ± 3.8	3.78 ± 8.76	<0.001
Creatinine, μmol/L	84.44 ± 20.74	88.25 ± 21.87	89.21 ± 21.68	92.31 ± 26.23	<0.001
eGFR (CKD-EPI)	1.34 ± 0.32	1.32 ± 0.33	1.31 ± 0.31	1.31 ± 0.36	0.230
Urea/BUN	5.76 ± 1.66	5.89 ± 1.75	5.95 ± 1.82	6.09 ± 1.97	0.129
Glucose, mmol/L	6.03 ± 2.3	6.1 ± 1.72	6.22 ± 1.92	6.38 ± 2.15	0.027
Total bilirubin, mg/dl	0.6 ± 0.22	0.61 ± 0.21	0.59 ± 0.22	0.59 ± 0.23	0.259
ALP, μmol s^{-1}/L	0.55 ± 0.15	0.56 ± 0.17	0.58 ± 0.19	0.6 ± 0.2	<0.001
ALT, nmol s^{-1}/L	0.45 ± 0.31	0.45 ± 0.25	0.49 ± 0.29	0.52 ± 0.39	<0.001
AST, nmol s^{-1}/L	0.47 ± 0.24	0.46 ± 0.25	0.47 ± 0.28	0.48 ± 0.26	0.750
Prior MI, *n* (%)	213 (46.5)	250 (53.1)	267 (52.4)	292 (59.1)	0.002
Multivessel CHD, *n* (%)	41 (9.0)	42 (8.9)	55 (10.8)	64 (13.0)	0.130
Prior CABG, *n* (%)	56 (12.2)	59 (12.5)	95 (18.6)	63 (12.8)	0.009
Diabetes, *n* (%)	158 (34.5)	201 (42.7)	217 (42.5)	242 (49.0)	<0.001
Hypertension, *n* (%)	341 (74.5)	339 (72.9)	372 (72.9)	373 (75.5)	0.606
COPD, *n* (%)	4 (0.9)	10 (2.1)	14 (2.7)	14 (2.8)	0.107
Clopidogrel, *n* (%)	243 (53.1)	248 (52.7)	236 (46.3)	230 (46.6)	0.046
Aspirin, *n* (%)	431 (94.1)	436 (92.6)	483 (94.7)	462 (93.5)	0.561
ACEi/ARB, *n* (%)	347 (75.8)	373 (79.2)	398 (78.0)	392 (79.4)	0.523
Statins, *n* (%)	441 (96.3)	460 (97.7)	499 (97.8)	474 (96.0)	0.210
β-receptor blockers, *n* (%)	198 (42.3)	195 (41.4)	229 (44.9)	221 (44.7)	0.668
Smoking status, *n* (%)					
Never smoked	42 (12.3)	71 (20.8)	88 (25.7)	141 (41.2)	<0.001
Current smoker	229 (24.2)	219 (23.2)	277 (29.3)	220 (23.3)	<0.001
Former smoker	187 (28.9)	181 (28.0)	145 (22.4)	133 (20.6)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass grafting; CDK-EPI, chronic kidney disease epidemiology collaboration; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglyceride; WBC, white blood cell.

(7, 16). Li et al. (6) conducted a follow-up study on 5,242 Japanese residents aged 40–69 years and found that WBC count was positively associated with the risk of coronary heart disease among the general Japanese population. Karino et al. (17) followed 2,879 men who were free of CHD at baseline for 8 years and found that higher total WBC counts were associated with an increased risk of incident CHD. Akinyelure et al. (8) followed 15,758 participants without a history of coronary heart disease for 11.4 years and found that WBC count was associated with an increased risk of incident CHD. Imano et al. (18) followed 4,492 Japanese men aged 40–59 for 9 years and found that WBC count is a predictor of acute myocardial infarction among Japanese middle-aged men. While all the above studies were conducted in the general population, this study focused on patients with stable coronary heart disease. Theoretically, our study can better reflect the relationship between WBC count and prognosis in patients

10.3389/fcvm.2024.1358378

WBC	Age	BMI	Hemoglobin	Hematocrit	Neutrophils	Platelet	HDL-C	TG	Cholesterol	hsCRP	Creatinine
< 5.3	65.50	24.86	136.35	0.42	2.70	194.77	1.29	1.56	4.03	2.18	84.44
< 6.3	64.44	25.01	139.83	0.43	3.47	208.69	1.27	1.63	4.06	2.03	88.25
< 7.5	63.85	25.55	141.85	0.44	4.19	223.78	1.24	1.77	4.19	2.43	89.21
≥ 7.5	61.39	25.75	142.87	0.44	5.70	246.09	1.22	1.88	4.19	3.78	92.31
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.017	< 0.001	0.037	< 0.001	< 0.001

Lowest Third Second Highest

WBC	Glucose	ALP	ALT	Prior MI	Prior CABG	Diabetes	Clopidogrel	Smoking	Never smoked	Current smoker	Former smoker
< 5.3	6.03	0.55	0.45	213.00	56.00	158.00	243.00		42.00	229.00	187.00
< 6.3	6.10	0.56	0.45	250.00	59.00	201.00	248.00		71.00	219.00	181.00
< 7.5	6.22	0.58	0.49	267.00	95.00	217.00	236.00		88.00	277.00	145.00
≥ 7.5	6.38	0.60	0.52	292.00	63.00	242.00	230.00		141.00	220.00	133.00
P value	0.027	< 0.001	< 0.001	0.002	0.009	< 0.001	0.046		< 0.001	< 0.001	< 0.001

FIGURE 1
Baseline characteristics of patients with different quartiles of WBC (predictors with $P < 0.05$, excepting gender and country). Green represents the lowest value, and yellow represents the highest value. ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CABG, coronary artery bypass grafting; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; TG, triglyceride; WBC, white blood cell.

TABLE 2 Clinical outcomes during follow-up by WBC counts.

Endpoint, *n* (%)	<5.3 GI/L *n* = 458	<6.3 GI/L *n* = 471	<7.5 GI/L *n* = 510	≥7.5 GI/L *n* = 494	*P*-value
Hospitalization for heart failure	9 (2.0)	6 (1.3)	12 (2.4)	11 (2.2)	0.628
Stroke	7 (1.5)	12 (2.5)	9 (1.8)	17 (3.4)	0.188
MI	7 (1.5)	15 (3.2)	18 (3.5)	18 (3.6)	0.199
Cardiovascular death	3 (0.7)	14 (3.0)	16 (3.1)	16 (3.2)	0.033
MACE	15 (3.3)	38 (8.1)	37 (7.3)	43 (8.7)	0.028
All-cause death	10 (2.2)	24 (5.1)	25 (4.9)	33 (6.7)	0.012

MACE, major cardiovascular event (cardiovascular death, MI, and stroke); MI, myocardial infarction.

with stable coronary heart disease. To our knowledge, this is the first multicenter study conducted in an Asian population with stable coronary heart disease that reported the association between WBC counts and cardiovascular events.

The latest research results suggested that the relationship between WBC count and the prognosis of patients with stable coronary heart disease might be related to telomere attrition, cytokines, lipid metabolism, abnormal aggregation, and so on. Recent studies have shown that WBC telomere attrition is associated with the onset of coronary heart disease (19–22), and the WBC count is, to some extent, associated with WBC telomere attrition. Higher WBC counts are associated with faster proliferation and differentiation of WBCs, leading to shorter telomeres. WBC release cytokines that further recruit macrophages and promote the proliferation of smooth muscle cells within the blood vessel walls. In addition, protease secretion leads to endothelial damage in coronary vessels, exposing thrombogenic collagen and predisposing the vessels to thrombus formation (23). The association patterns between peripheral WBC counts and serum lipid levels differ by sex, age, lipid profile, and leukocyte subset (24). They might contribute differently to atherosclerosis. For example, triglycerides and HDL cholesterol may be directly involved in leukogenesis, although the precise mechanism of this relationship and direction of causation are currently ill-defined (25). For the abnormal aggregation of WBCs, the formation of platelet–leukocyte aggregates has been reported in patients with coronary heart disease (26), suggesting that high WBC counts may be one of the possible mechanisms of disease progression.

Our study differs considerably: in analyzing patients with stable coronary heart disease—many of whom have WBC counts within the normal range—we hypothesized that WBC counts would provide useful prognostic information. In essence, this analysis addresses a commonly asked question: Can WBC counts play a role in assessing the risk of cardiovascular events in patients with stable coronary heart disease? Patients with high WBC counts represent an important group that deserves special focus, as they may be at a higher risk of cardiovascular events. Among the

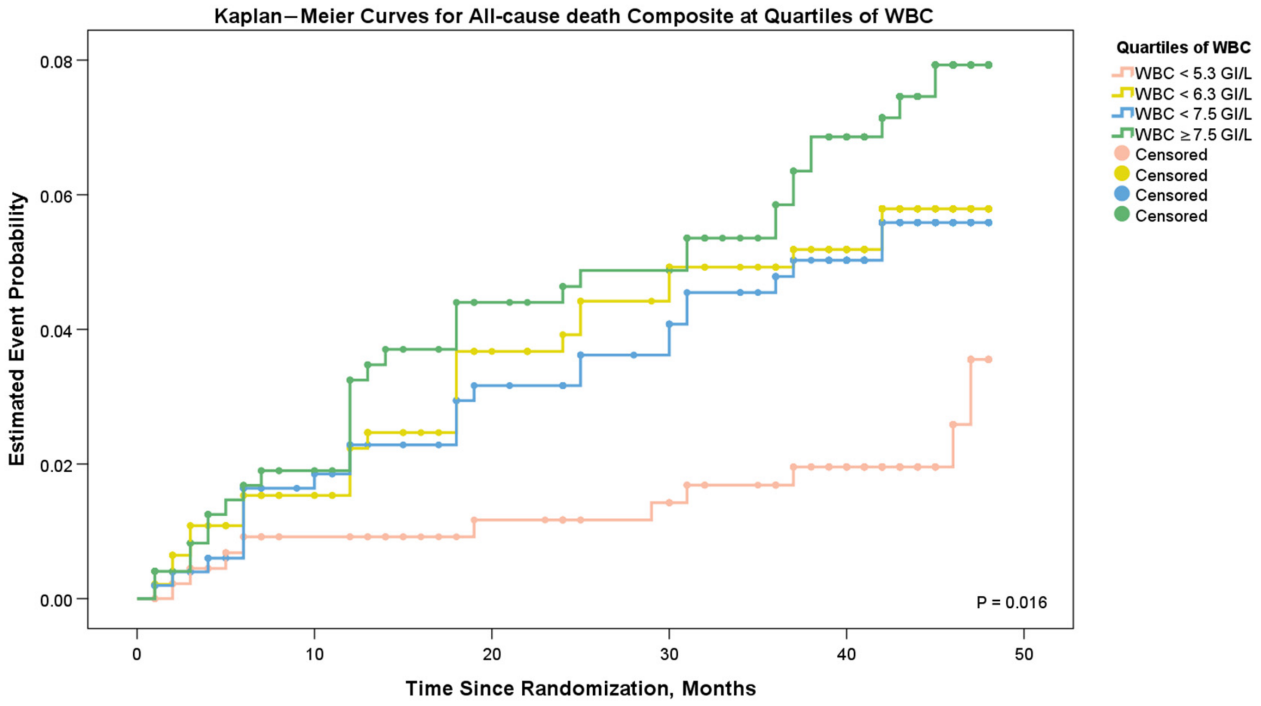


FIGURE 2
Cumulative hazard curves depicting time-to-events as a function of WBC quartiles at presentation.

1,933 study participants enrolled in the STABILITY trial with stable coronary heart disease, we found that cardiovascular events were 1.72 times more common in participants with WBC counts ≥5.3 GI/L than in participants with WBC counts <5.3 GI/L, including all-cause death, cardiovascular death, myocardial infarction, and major complications such as stroke and hospitalization for heart failure. In addition, we found that patients with stable coronary heart disease in developed countries (Korea and Japan) had a lower risk of cardiovascular events than those in developing countries (China, Thailand, and the Philippines). This was similar to previous research (27). Our data suggest that developing countries should remain a key focus for the management of patients with stable coronary heart disease in the future.

Patients with stable coronary heart disease have a high incidence of cardiovascular events, and the occurrence of cardiovascular events may be challenging to assess and manage accurately (28). In addition to standard clinical assessment, stress testing, coronary angiography, or coronary CTA are often used for risk stratification in patients with stable coronary heart disease (29–31). While useful, these methods have limitations, including cost and availability. A widely available, inexpensive, and easily interpreted tool, such as a blood test, would be an attractive option to support clinical judgment in assessing the risk of cardiovascular events in patients with stable coronary heart disease. The WBC count can be obtained in almost any medical institution, making it a convenient, fast, and low-cost tool. Although there appears to be an association between higher WBC counts and increased cardiovascular event risk, it remains unclear how individual results could be interpreted at a clinical level. Evaluating the cost-effectiveness of a WBC-leveraged clinical approach, including the development of concentration-specific counts for interpretation, is worth exploring.

Study strengths and limitations

The strengths of our study lie in the fact that the STABILITY trial was a large, prospective, randomized trial conducted across many countries. It involved not only a homogeneous cohort of patients with stable coronary heart disease but also had high-quality, long-term follow-up with centrally adjudicated endpoints. These factors made our analysis more credible. However, there are some limitations. Patients received a high standard of modern secondary prevention protocols during follow-up, including medication, smoking cessation, and advice on weight loss and regular physical activity. Although multivariate adjustments were made in the analysis, unmeasured confounding factors could not be completely excluded. For example, infection causes a temporary increase in WBC counts (32), which may have unknown effects on the results. In our study, it was unclear whether participants with higher WBC had a hematologic emergency. This also introduced a potential bias in our study. Our analysis included only Asian populations, and only 21.11% of the study population was female, so whether our results can

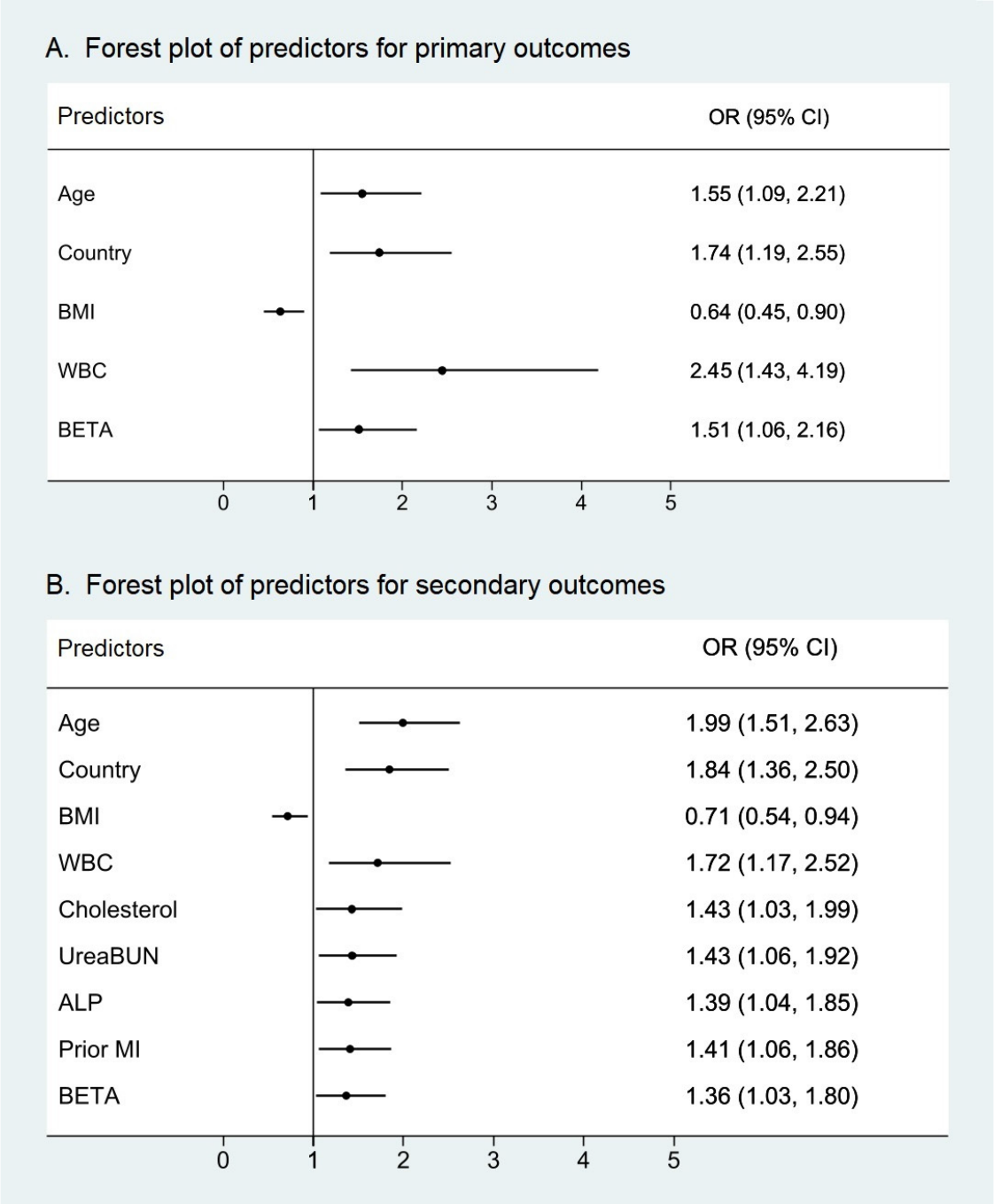


FIGURE 3
Forest plots of predictors of primary and secondary outcomes with $P < 0.05$. WBC counts were an independent predictor not only for **(A)** the primary outcomes of cardiovascular death, myocardial infarction, and stroke but also for **(B)** the secondary outcomes of all-cause death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. WBC count displayed the high variable importance measure of all predictors with $P < 0.05$. ALP, alkaline phosphatase; BETA, β-receptor blocker; BMI, body mass index; MI, myocardial infarction; WBC, white blood cell.

be extrapolated to other populations is still worthy of further study. Integrating WBC counts with other variables and performing a holistic analysis to provide a probability of cardiovascular events may be a future approach that could lead to a better assessment of patients with stable coronary heart disease. There is clearly a need for more data in this area.

Conclusions

In conclusion, we analyzed data from the Asian population in the STABILITY trial and found differences in primary and secondary outcomes among patients with stable coronary heart disease based on their different WBC counts. In the first quartile,

the probability of MACEs in patients with WBC ≥5.3 GI/L was 2.45 times higher than in those with WBC <5.3 GI/L. Analogously, the probability of the composite outcome of all-cause death, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure was 1.72 times. WBC count may be an independent predictor of cardiovascular events in patients with stable coronary heart disease. This finding may help in managing the large number of patients with stable coronary heart disease by identifying potentially high-risk groups. It is reasonable to hypothesize that patients with stable coronary heart disease with relatively higher WBC counts could benefit from more aggressive diagnostic or therapeutic management. Implementation of clinical guidelines may consider WBC count as an important reference for the management of patients with stable coronary heart disease. For higher WBC patients, the following suggestions should be considered, avoidance of tobacco use, exercise prescription, and more aggressive medical management of risk factors and so on. WBC count may provide a new idea to inform the most cost-effective management approaches for this important group of patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found from the following: Unique identifier: NCT00799903; https://clinicaltrials.gov/ct2/show/NCT00799903.

Ethics statement

The studies involving humans were approved by national regulatory authorities. The studies were conducted in accordance with local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WJ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. GH: Writing – review & editing. JD: Data curation, Writing – review & editing. HY: Formal Analysis, Writing – review & editing. SZ: Validation, Writing – review & editing. DD: Conceptualization, Writing – review & editing. KT: Visualization, Writing – review & editing. LF: Project administration, Writing – review & editing. XW: Supervision, Writing – review & editing. XD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. The STABILITY trial was supported by GlaxoSmithKline. The funder was not involved in the study design, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Acknowledgments

We thank both GSK and Vivli for providing us data and access.

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, Johnson CO, Addolorato G, Ammirati E, Baddour LM. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol.* (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010

2. Hoole SP, Bambrough P. Recent advances in percutaneous coronary intervention. *Heart.* (2020) 106:1380–6. doi: 10.1136/heartjnl-2019-315707

3. Fekete M, Szarvas Z, Fazekas-Pongor V, Feher A, Csipo T, Forrai J. Nutrition strategies promoting healthy aging: from improvement of cardiovascular and brain health to prevention of age-associated diseases. *Nutrients.* (2022) 15:1–28. doi: 10.3390/nu15010047

4. Abdelrahman KM, Chen MY, Dey AK, Virmani R, Finn AV, Khamis RY. Coronary computed tomography angiography from clinical uses to emerging technologies: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 76:1226–43. doi: 10.1016/j.jacc.2020.06.076

5. Fuster V. Global burden of cardiovascular disease: time to implement feasible strategies and to monitor results. *J Am Coll Cardiol.* (2014) 64:520–2. doi: 10.1016/j.jacc.2014.06.1151

6. Li J, Imano H, Yamagishi K, Tanaka M, Cui R, Muraki I. Leukocyte count and risks of stroke and coronary heart disease: the circulatory risk in communities study (CIRCS). *J Atheroscler Thromb.* (2022) 29:527–35. doi: 10.5551/jat.60889

7. Hoffman M, Blum A, Baruch R, Kaplan E, Benjamin M. Leukocytes and coronary heart disease. *Atherosclerosis.* (2004) 172:1–6. doi: 10.1016/S0021-9150(03)00164-3

8. Akinyelure OP, Colantonio LD, Chaudhary NS, Jaeger BC, Judd SE, Cushman M. Inflammation biomarkers and incident coronary heart disease: the reasons for

geographic and racial differences in stroke study. *Am Heart J*. (2022) 253:39–47. doi: 10.1016/j.ahj.2022.07.001

9. Kitakaze M. Trends in characteristics of CVD in Asia and Japan: the importance of epidemiological studies and beyond. *J Am Coll Cardiol*. (2015) 66:196–8. doi: 10.1016/j.jacc.2015.05.035

10. Kasim SS, Ibrahim N, Malek S, Ibrahim KS, Aziz MF, Song C. Validation of the general Framingham risk score (FRS), SCORE2, revised PCE and WHO CVD risk scores in an Asian population. *Lancet Reg Health West Pac*. (2023) 35:100742. doi: 10.1016/j.lanwpc.2023.100742

11. Held C, Hadziosmanovic N, Aylward PE, Hagström E, Hochman JS, Stewart RAH. Body mass index and association with cardiovascular outcomes in patients with stable coronary heart disease—a STABILITY substudy. *J Am Heart Assoc*. (2022) 11:e023667. doi: 10.1161/JAHA.121.023667

12. White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. (2014) 370:1702–11. doi: 10.1056/NEJMoa1315878

13. White H, Held C, Stewart R, Watson D, Harrington R, Budaj A. Study design and rationale for the clinical outcomes of the STABILITY trial (STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY) comparing darapladib versus placebo in patients with coronary heart disease. *Am Heart J*. (2010) 160:655–61. doi: 10.1016/j.ahj.2010.07.006

14. Held C, White HD, Stewart RAH, Budaj A, Cannon CP, Hochman JS. Inflammatory biomarkers interleukin-6 and C-reactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (stabilization of atherosclerotic plaque by initiation of darapladib therapy) trial. *J Am Heart Assoc*. (2017) 6:1–14. doi: 10.1161/JAHA.116.005077

15. Lindholm D, Lindbäck J, Armstrong PW, Budaj A, Cannon CP, Granger CB. Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. *J Am Coll Cardiol*. (2017) 70:813–26. doi: 10.1016/j.jacc.2017.06.030

16. Park C, Yoo K, Lee S, Kim H, Son E, Lee D. The prognostic significance of leukocyte count on all-cause and cardiovascular disease mortality: a systematic review and meta-analysis. *Am J Cardiol*. (2023) 203:226–33. doi: 10.1016/j.amjcard.2023.06.119

17. Karino S, Willcox BJ, Fong K, Lo S, Abbott R, Masaki KH. Total and differential white blood cell counts predict eight-year incident coronary heart disease in elderly Japanese-American men: the Honolulu Heart Program. *Atherosclerosis*. (2015) 238:153–8. doi: 10.1016/j.atherosclerosis.2014.12.003

18. Imano H, Sato S, Kitamura A, Kiyama M, Ohira T, Shimamoto T. Leukocyte count is an independent predictor for risk of acute myocardial infarction in middle-aged Japanese men. *Atherosclerosis*. (2007) 195:147–52. doi: 10.1016/j.atherosclerosis.2006.09.002

19. Wang XB, Cui NH, Zhang S, Liu ZJ, Ma JF, Ming L. Leukocyte telomere length, mitochondrial DNA copy number, and coronary artery disease risk and severity: a two-stage case-control study of 3064 Chinese subjects. *Atherosclerosis*. (2019) 284:165–72. doi: 10.1016/j.atherosclerosis.2019.03.010

20. Rafiq M, Liaquat A, Javed A, Ullah Shah S, Hussain R, Akram Z. Association of leukocyte telomere attrition in coronary artery disease in Pakistani population: a case-control study with meta-analysis. *Clin Chim Acta*. (2023) 547:117416. doi: 10.1016/j.cca.2023.117416

21. Opstad TB, Kalstad AA, Pettersen AA, Arnesen H, Seljeflot I. Novel biomolecules of ageing, sex differences and potential underlying mechanisms of telomere shortening in coronary artery disease. *Exp Gerontol*. (2019) 119:53–60. doi: 10.1016/j.exger.2019.01.020

22. Vecoli C, Basta G, Borghini A, Gaggini M, Del Turco S, Mercuri A. Advanced glycation end products, leukocyte telomere length, and mitochondrial DNA copy number in patients with coronary artery disease and alterations of glucose homeostasis: from the GENOCOR study. *Nutr Metab Cardiovasc Dis*. (2022) 32:1236–44. doi: 10.1016/j.numecd.2022.01.021

23. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. *Tex Heart Inst J*. (2013) 40:17–29.

24. Hu W, Zhang P, Su Q, Li D, Hang Y, Ye X. Peripheral leukocyte counts vary with lipid levels, age and sex in subjects from the healthy population. *Atherosclerosis*. (2020) 308:15–21. doi: 10.1016/j.atherosclerosis.2020.07.009

25. Sawant S, Tucker B, Senanayake P, Waters DD, Patel S, Rye KA. The association between lipid levels and leukocyte count: a cross-sectional and longitudinal analysis of three large cohorts. *Am Heart J Plus*. (2021) 4:100024. doi: 10.1016/j.ahjo.2021.100024

26. Schulte C, Pieper L, Frye M, Waldeyer C, Neumann JT, Brunner FJ. Antiplatelet drugs do not protect from platelet-leukocyte aggregation in coronary artery disease. *J Thromb Haemost*. (2024) 22:553–7. doi: 10.1016/j.jtha.2023.04.041

27. Ralapanawa U, Sivakanesan R. Epidemiology and the magnitude of coronary artery disease and acute coronary syndrome: a narrative review. *J Epidemiol Glob Health*. (2021) 11:169–77. doi: 10.2991/jegh.k.201217.001

28. Dangas G, Roumeliotis A, Giustino G. Invasive or conservative strategy for stable coronary disease. *N Engl J Med*. (2020) 383:e66. doi: 10.1056/NEJMc2024008

29. Joshi PH, de Lemos JA. Diagnosis and management of stable angina: a review. *JAMA*. (2021) 325:1765–78. doi: 10.1001/jama.2021.1527

30. Antonopoulos AS, Angelopoulos A, Tsioufis K, Antoniades C, Tousoulis D. Cardiovascular risk stratification by coronary computed tomography angiography imaging: current state-of-the-art. *Eur J Prev Cardiol*. (2022) 29:608–24. doi: 10.1093/eurjpc/zwab067

31. Corballis N, Tsampasian V, Merinopoulis I, Gunawardena T, Bhalraam U, Eccleshall S. CT angiography compared to invasive angiography for stable coronary disease as predictors of major adverse cardiovascular events—a systematic review and meta-analysis. *Heart Lung*. (2023) 57:207–13. doi: 10.1016/j.hrtlng.2022.09.018

32. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. *J Infect*. (2019) 78:339–48. doi: 10.1016/j.jinf.2019.02.006

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 27 September 2024
DOI 10.3389/fcvm.2024.1433011

OPEN ACCESS

EDITED BY
Zhonghua Sun,
Curtin University, Australia

REVIEWED BY
Ömer Faruk Çiçek,
Selcuk University, Türkiye
Vladimir M. Pisarev,
Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitation, Russia

*CORRESPONDENCE
Shu-yue Sheng
✉ shengshuyue@126.com
Shaolin Ma
✉ mslin@sohu.com
Feng Zhu
✉ alexzhujunchi@hotmail.com

†These authors have contributed equally to this work

RECEIVED 15 May 2024
ACCEPTED 11 September 2024
PUBLISHED 27 September 2024

CITATION
Zhou W, Wang H, Li C, Ma Q-m, Gu Y-h, Sheng S-y, Ma S-l and Zhu F (2024) Alterations in novel inflammatory biomarkers during perioperative cardiovascular surgeries involving cardiopulmonary bypass: a retrospective propensity score matching study.
Front. Cardiovasc. Med. 11:1433011.
doi: 10.3389/fcvm.2024.1433011

Alterations in novel inflammatory biomarkers during perioperative cardiovascular surgeries involving cardiopulmonary bypass: a retrospective propensity score matching study

Wei Zhou[1†], He Wang[1†], Chen Li[1†], Qi-min Ma[1], Yan-hui Gu[2], Shu-yue Sheng[1*], Shao-lin Ma[1*] and Feng Zhu[1*]

[1]Department of Critical Care Medicine, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China, [2]Health Department, Beijing Armed PAP Corps, Beijing, China

Background: Cardiopulmonary bypass (CPB) triggers a strong inflammatory response in cardiovascular surgery patients during the perioperative period. This article mainly focuses on the perioperative application of novel inflammatory biomarkers in cardiovascular surgeries involving CPB.
Methods: Patients were divided into a CPB group and a non-CPB group according to whether they underwent CPB during cardiovascular surgery. Novel inflammatory biomarkers and clinical results were recorded. The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet × neutrophil/lymphocyte ratio (SII), and monocyte × platelet × neutrophil/lymphocyte ratio (PIV) were calculated. The primary outcomes were perioperative prognosis between the CPB and non-CPB groups. The secondary outcomes included perioperative alterations of novel inflammatory biomarkers in the CPB group and predictive values of novel inflammatory biomarkers for postoperative infection and acute kidney injury.
Results: A total of 332 patients were initially included in the study. Before propensity score matching (PSM), there were 96 patients in the CPB group and 236 patients in the non-CPB group. After PSM, both groups included 58 patients each. Compared with the non-CPB group, the CPB group had a higher proportion of intraoperative transfusion of blood products (63.79% vs. 6.90%, $P < 0.001$), specifically for red blood cells (58.62% vs. 3.45%, $P < 0.001$) and plasma (41.38% vs. 1.72, $P < 0.001$), exhibited a higher drainage fluid volume within 24 h [380 (200–550) ml vs. 200 (24–330) ml, $P = 0.002$], and required longer durations of mechanical ventilation [14.3 (6.6–21.3) h vs. 5.75 (4.08–10.1) h, $P < 0.001$] and ICU stay [48.78 (44.92–89.38) h vs. 27.16 (21.67–46.25) h, $P < 0.001$]. After surgery, NLR [14.00 (9.93–23.08) vs. 11.55 (7.38–17.38), $P = 0.043$] was higher in the CPB group, while the PIV, PLR, and SII in the CPB group were lower than those in the non-CPB group on the first day after surgery.
Conclusions: Cardiovascular surgeries involving CPB exhibit a poorer prognosis compared to non-CPB procedures. Novel inflammatory biomarkers, including PLR, PIV, and SII, may offer valuable insights into the degree of postoperative inflammation, with NLR emerging as a potentially reliable prognostic indicator.

KEYWORDS

cardiovascular surgery, inflammation, perioperative, pan-immune inflammatory value (PIV), neutrophil/lymphocyte ratio (NLR)

Introduction

Most cardiovascular surgeries need to be assisted by cardiopulmonary bypass (CPB). Currently, relevant studies have confirmed that CPB triggers a strong inflammatory response in patients during the perioperative period, thus affecting the prognosis of patients (1). With the development of surgical counting, an increasing number of surgical operations are being performed without CPB, but the postoperative inflammatory response remains strong. Inflammation is closely related to the prognosis of patients after cardiovascular surgery. Previous studies have attempted to combine multiple biomarkers to develop more accurate indicators to improve the clinical application of biomarkers, including the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic inflammation index (SII) (2). Furthermore, in recent years, the pan-immune inflammatory value (PIV) has also emerged as a popular indicator of inflammation. First proposed in 2022 as a novel prognostic biomarker for metastatic colorectal cancer (3), its application in cardiovascular surgery is rare. This article mainly focuses on the perioperative application of novel inflammatory markers in cardiovascular surgeries involving CPB and explores the perioperative changes in these biomarkers to guide their clinical application.

Methods

Study design

Patients undergoing open cardiovascular surgery in Shanghai East Hospital from August 2022 to June 2023 were included in this study. The clinical data of these patients were retrospectively analyzed, and the patients were divided into a CPB group and a non-CPB group according to whether CPB was used during the operation. The perioperative clinical results of the two groups were compared. This study was approved by the Ethics Committee of Biomedical Research at Shanghai East Hospital, Tongji University School of Medicine (Approval No: 2024YS-043). Given the observational nature of the study, the ethics committee waived the requirement for individual patient consent.

Data collection

Preoperative data, including age, body mass index (BMI), height, underlying diseases, and laboratory test results (e.g., leukocytes, lymphocytes, monocytes, platelets, bilirubin, creatinine, etc.), were collected. We also gathered relevant intraoperative data of the patients, including intraoperative blood transfusion details. In addition, we recorded postoperative inflammatory biomarkers and clinical outcomes, such as acute kidney injury (AKI), postoperative infections, mechanical ventilation (MV) duration, ICU stay duration, and in-hospital mortality.

Definitions

In our study, the following novel inflammatory biomarkers were utilized to assess the perioperative inflammatory response:

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: platelet × neutrophil/lymphocyte ratio, and PIV: monocyte × platelet × neutrophil/lymphocyte ratio.

Furthermore, AKI is defined as any of the following: an increase in creatinine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/L) within 48 h; an increase in SCr to ≥1.5 times the baseline level, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 h (4).

Postoperative infections include pulmonary infection, bloodstream infection, and urinary system infection.

Statistical analysis

Propensity score matching (PSM) analysis is a method used to reduce selection bias between two groups of patients. We used a logistic regression model to calculate the propensity score for each patient and performed 1:1 matching between the two groups, with a caliper width of 0.2 standard deviations (SD). Baseline demographic data, preoperative data, intraoperative data, and postoperative data were compared between the two groups both before and after PSM. The results are presented as the mean ± SD or median [interquartile range (IQR)] for continuous variables, as appropriate, and as the total number (%) for categorical variables. Comparisons between groups were made using the χ^2 test or Fisher's exact test for categorical variables and the Student's *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate. The ability of NLR, PLR, SII, and PIV to predict postoperative clinical outcomes (mainly in postoperative AKI and infection) was analyzed by receiver operating characteristics (ROC) curves and the resulting area under the curve (AUC). All statistical analyses were performed with R 4.3.2 (R Foundation). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline demographic and clinical data of patients

The flowchart of patient screening is shown in Figure 1. Initially, 332 patients were included in the study. Before PSM, there were 96 patients in the CPB group and 236 patients in the non-CPB group. After PSM, both groups included 58 patients each.

The baseline data analysis is presented in Table 1. Before PSM, there were statistically significant differences in gender, age, New York Heart Association (NYHA) grade, and diabetes mellitus rate between the CPB and non-CPB groups. After PSM, there was no statistical difference between the two groups in terms of preoperative characteristics.

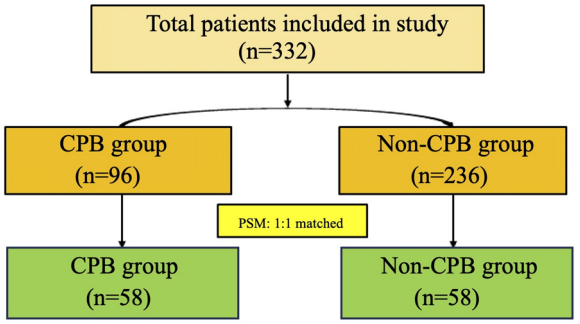


FIGURE 1
Flowchart of patient screening. PSM: propensity score matching.

Comparison of intraoperative data and postoperative clinical outcomes between the two groups

Intraoperative data and postoperative clinical outcomes for the two groups included in the final analysis were compared before and after PSM. Compared with the non-CPB group, the CPB group had a higher proportion of intraoperative transfusion of blood products (63.79% vs. 6.90%, $P < 0.001$), specifically for red blood cells (58.62% vs. 3.45%, $P < 0.001$) and plasma (41.38% vs. 1.72%, $P < 0.001$). In addition, the CPB group had a higher volume of drainage fluid within 24 h [380 (200–550) ml vs. 200 (24–330) ml, $P = 0.002$] and required longer durations of mechanical ventilation [14.3 (6.6–21.3) h vs. 5.75 (4.08–10.1) h, $P < 0.001$] and ICU stay [48.78 (44.92–89.38) h vs. 27.16 (21.67–46.25) h,

TABLE 1 Baseline demographic and clinical data between two groups.

Variable	Overall population		*P*-value	Propensity score matched population		*P*-value
	Non-CPB group (*n* = 236)	CPB group (*n* = 96)		Non-CPB group (*n* = 58)	CPB group (*n* = 58)	
Male (%)	172 (72.88)	57 (59.38)	0.023	36 (62.07)	35 (60.34)	1.000
Age (years)	67.00 [60.00, 72.25]	65.00 [54.75, 70.00]	0.012	65.00 [58.50, 70.00]	65.00 [56.50, 69.75]	0.782
BMI (kg/m^2)	24.41 [22.45, 26.53]	23.67 [21.39, 25.80]	0.101	24.46 [22.56, 26.39]	23.91 [21.89, 25.52]	0.292
NYHA grade (%)			<0.001			0.594
I	39 (16.53)	7 (7.29)		6 (10.34)	7 (12.07)	
II	123 (52.12)	55 (57.29)		36 (62.07)	30 (51.72)	
III	73 (30.93)	27 (28.12)		15 (25.86)	18 (31.03)	
IV	1 (0.42)	7 (7.29)		1 (1.72)	3 (5.17)	
Hypertension (%)	152 (64.41)	52 (54.17)	0.107	32 (55.17)	36 (62.07)	0.572
Diabetes mellitus (%)	91 (38.56)	14 (14.58)	<0.001	12 (20.69)	13 (22.41)	1
CAD (%)	171 (72.46)	24 (25.00)	<0.001	17 (29.31)	21 (36.21)	0.553
AF (%)	19 (8.05)	20 (20.83)	0.002	8 (13.79)	8 (13.79)	1
Emergency surgery (%)	3 (1.27)	3 (3.12)	0.487	0 (0.00)	1 (1.72)	1
Type of surgery (%)			0.238			0.307
CABG (%)	130 (55.08)	57 (59.38)		18 (31.03)	14 (24.14)	
Cardiac valve surgery (%)	84 (35.59)	26 (27.08)		33 (56.90)	31 (53.45)	
Others (%)	22 (9.32)	13 (13.54)		7 (12.07)	13 (22.41)	
LVEF	61.00 [50.00, 66.00]	60.00 [51.75, 65.25]	0.75	60.00 [50.25, 66.75]	60.00 [56.00, 66.00]	0.943
Leukocyte (10^9/L)	6.44 [5.03, 7.81]	5.76 [4.97, 7.28]	0.138	6.79 [5.20, 7.90]	5.76 [5.03, 7.22]	0.103
HCT	38.70 [35.68, 42.00]	39.80 [36.80, 43.23]	0.044	40.05 [36.47, 42.85]	39.90 [37.10, 43.58]	0.485
Platelets (10^9/L)	200.50 [164.75, 243.25]	197.50 [169.50, 244.75]	0.694	215.50 [167.75, 260.50]	197.00[173.50, 241.25]	0.6
Neutrophils (10^9/L)	3.70 [2.89, 5.03]	3.59 [2.73, 4.53]	0.422	3.90 [3.07, 5.72]	3.54 [2.71, 4.52]	0.323
Lymphocytes (10^9/L)	1.68 [1.31, 2.08]	1.65 [1.28, 2.00]	0.779	1.74 [1.32, 2.24]	1.69 [1.31, 2.09]	0.776
PIV	231.95 [139.85, 409.42]	219.85 [117.50, 406.20]	0.747	255.40 [150.02, 481.98]	205.00[114.10, 410.60]	0.341
NLR	2.20 [1.60, 3.30]	2.30 [1.60, 3.10]	0.773	2.30 [1.63, 3.58]	2.25 [1.60, 3.15]	0.67
PLR	119.60 [93.30, 156.95]	125.75 [92.20, 159.92]	0.596	114.35 [94.03, 170.93]	126.70 [90.22, 158.27]	0.847
SII	453.00 [292.98, 655.05]	420.30 [278.20, 684.05]	0.854	464.75 [294.32, 785.32]	398.55[301.68, 672.55]	0.556
CRP (mg/L)	1.73 [1.60, 5.54]	2.21 [1.60, 6.84]	0.519	1.60 [1.60, 4.63]	1.60 [1.60, 4.80]	0.968
Albumin (g/L)	39.80 [37.20, 42.52]	39.90 [37.18, 42.32]	0.724	40.15 [37.60, 43.95]	40.40 [37.55, 42.95]	0.609
Creatinine (μmoI/L)	80.70 [67.00, 96.25]	85.00 [68.75, 102.70]	0.279	76.00 [65.88, 93.50]	83.65 [65.65, 92.60]	0.709
TnT (μg/L)	0.01 [0.01, 0.03]	0.02 [0.01, 0.02]	0.851	0.01 [0.01, 0.03]	0.02 [0.01, 0.02]	0.695
BNP (ng/ml)	422.10 [110.60, 1,243.75]	340.35 [104.25, 970.82]	0.415	422.10 [172.80, 1,162.25]	217.10 [97.12, 978.28]	0.284

CPB: cardiopulmonary bypass; BMI, body mass index; NYHA, New York Heart Association; CAD, coronary artery disease; AF, atrial fibrillation; CABG, coronary bypass surgery; LVEF, left ventricular ejection fraction; HCT, hematocrit; PIV, pan-immune inflammatory value; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic inflammation index; CRP, C-reactive protein; TnT, Troponin T; BNP, brain natriuretic peptide.
Data are presented as median [P25, P75] or *n* (%).

$P < 0.001$]. However, there was no significant difference in mortality between the two groups (Table 2).

Comparison of postoperative clinical laboratory findings between the two groups

In terms of inflammation biomarkers, on the day after surgery, NLR was significantly higher in the CPB group [14.00 (9.93–23.08) vs. 11.55 (7.38–17.38), $P = 0.043$], whereas there were no significant differences in other indicators. On the first postoperative day, the non-CPB group exhibited higher values for several indicators: including PIV [2,220.45 (1,199.15–2,970.43) vs. 1,563.00 (738.50–2,944.78), $P = 0.039$], PLR [258.10 (178.75–363.20) vs. 202.15 (134.07–271.58), $P = 0.003$], and SII [2,434.90 (1,611.05–3,631.80) vs. 1,793.40 (1,200.65–2,829.33), $P = 0.01$]. Nevertheless, no statistical difference in NLR was found between the two groups on that day (Table 3).

Comparison of perioperative inflammatory biomarkers in the CPB group

Perioperative inflammation biomarkers in the CPB group were compared. All novel inflammatory biomarkers were significantly elevated compared to presurgery levels, peaking on the first day after surgery and then entering a downward trend (Table 4).

Predictive value of inflammatory markers for postoperative infection and AKI

The ROC curve was employed to assess the predictive ability of postoperative infection and AKI. Among the inflammatory biomarkers analyzed, namely, PIV, PLR, and SII, their predictive values were not notably high. Specifically, only preoperative NLR demonstrated moderate predictive power, with an AUC of 0.616 [95% confidence interval (CI): 0.459–0.742] for postoperative infection, using a cutoff value of 3.05. Similarly, for postoperative AKI, preoperative NLR also yielded an AUC of 0.616 (95% CI: 0.54–0.676), with a cutoff value of 2.25 (Figures 2–5).

Discussion

Currently, the majority of open cardiovascular surgeries and extensive vascular procedures still involve CPB. Most patients exhibit a systemic inflammatory response after CPB, characterized by elevated levels of circulating inflammatory cytokines and the activation of inflammatory cells (5). Clinical investigations have revealed a profound correlation between the intensity of this inflammatory response and unfavorable patient outcomes (6). Our investigation further indicates that individuals undergoing CPB surgery are at a higher risk of requiring perioperative blood transfusions and experiencing increased postoperative drainage within the first 24 h. In addition, these patients often require prolonged mechanical ventilation support and extended ICU stays due to the physiological impact of CPB. However, our study did not detect any significant increase in the likelihood of postoperative complications, such as AKI or infection, among patients who underwent CPB surgery. Moreover, there was no significant difference in the in-hospital mortality rate between the CPB and non-CPB groups.

Formerly, within the cardiovascular field, cellular inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor (TNF), C-reactive protein (CRP), and procalcitonin (PCT), have been extensively researched. Notably, an elevated IL-6 level above 421 pg/ml has been associated with a substantial increase in the risk of postoperative mortality among patients (OR = 12.6, 95% CI: 2.96–53.55) (7). In addition, IL-6 is a reliable predictor of

TABLE 2 Comparison of intraoperative data and postoperative clinical outcomes between two groups.

Variable	Overall population		*P*-value	Propensity score matched population		*P*-value
	Non-CPB Group (*n* = 236)	CPB group (*n* = 96)		Non-CPB group (*n* = 58)	CPB Group (*n* = 58)	
Intraoperative total transfusion, *n* (%)	29 (12.29)	61 (63.54)	<0.001	4 (6.90)	37 (63.79)	<0.001
RBC transfusion, *n* (%)	18 (7.63)	58 (60.42)	<0.001	2 (3.45)	34 (58.62)	<0.001
Plasma transfusion, *n* (%)	5 (2.12)	35 (36.46)	<0.001	1 (1.72)	24 (41.38)	<0.001
Platelet transfusion, *n* (%)	0 (0.00)	3 (3.12)	0.037	0 (0.00)	1 (1.72)	1.000
IABP assist, *n* (%)	0 (0.00)	2 (2.08)	0.149	0	0	N/A
AKI, *n* (%)	51 (21.61)	20 (20.83)	1.000	11 (18.91)	14 (24.14)	0.652
CRRT, *n* (%)	4 (1.69)	3 (3.12)	0.688	2 (3.45)	2 (3.45)	1.000
Postoperative infection, *n* (%)	17 (7.20)	20 (20.83)	0.001	3 (5.17)	10 (17.24)	0.077
Drainage fluid volume within 24 h (ml)	330 [166, 472]	355 [177, 555]	0.355	200 [24, 330]	380 [200, 550]	0.002
Lowest P/F within 48 h (mmHg)	213 [172, 251]	206[163, 229]	0.386	204 [156, 238]	208 [168, 246]	0.665
Mechanical ventilation duration (h)	315 [230, 551]	765[381, 1,350]	<0.001	5.75 [4.08, 10.1]	14.3 [6.6, 21.3]	<0.001
ICU stay duration (h)	32.99 [21.85, 46.33]	47.00 [43.38, 91.18]	<0.001	27.16 [21.67, 46.25]	48.78 [44.92, 89.38]	<0.001
Death *n* (%)	3 (1.27)	6 (6.25)	0.031	0 (0)	2 (3.45)	0.476

CPB, cardiopulmonary bypass; RBC, red blood cell; IABP, intra-aortic balloon pump; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; P/F, arterial partial oxygen pressure/oxygen absorption concentration; ICU, intensive care unit.
Data are presented as median [P25, P75] or *n* (%).

TABLE 3 Comparison of postoperative clinical laboratory findings between two groups.

Variable	Overall population		*P*-value	Propensity score matched population		*P*-value
	Non-CPB group (*n* = 236)	CPB group (*n* = 96)		Non-CPB group (*n* = 58)	CPB group (*n* = 58)	
Postoperative laboratory findings (day 0)						
Leukocytes (10^9/L)	9.55 [6.94, 12.13]	11.75 [8.40, 15.18]	<0.001	10.09 [6.07, 12.63]	11.16 [7.51, 13.82]	0.200
HCT (%)	31.55 [28.50, 34.60]	30.55 [28.37, 33.00]	0.026	32.65 [28.40, 34,82]	30.40 [27.55, 32.70]	0.030
Platelets (10^9/L)	164.00 [135.00, 201.00]	116.50 [97.75, 157.25]	<0.001	157.00 [132.25, 195.25]	116.50 [95.75, 158.75]	<0.001
Neutrophils (10^9/L)	8.28 [5.82, 10.82]	10.57 [7.38, 13.41]	<0.001	8.68 [4.93, 11.40]	9.88 [6.78, 11.95]	0.165
Lymphocytes (10^9/L)	0.69 [0.51, 0.93]	0.72 [0.43, 1.42]	0.563	0.69 [0.51, 1.02]	0.66 [0.37, 0.95]	0.279
PCT (ng/ml)	0.05 [0.03, 0.10]	0.06 [0.04, 0.11]	0.559	0.05 [0.03, 0.10]	0.06 [0.04, 0.12]	0.358
CRP (mg/L)	1.60 [1.60, 4.30]	2.06 [1.60, 7.29]	0.017	1.60 [1.60, 4.29]	1.72 [1.60, 4.46]	0.602
PIV	554.90 [296.88, 1,197.23]	790.80 [380.25, 1, 311.88]	0.114	560.20 [326.82, 1,633.50]	858.35 [441.52, 1,299.42]	0.397
NLR	11.40 [7.47, 17.52]	13.20 [8.40, 21.48]	0.08	11.55 [7.38, 17.38]	14.00 [9.93, 23.08]	0.043
PLR	235.10 [167.52, 336.18]	177.40 [92.17, 277.88]	<0.001	242.35 [145.25, 323.42]	196.60 [103.65, 324.35]	0.224
SII	1,796.35 [1,074.80, 2,867.17]	1,645.10 [1,010.15, 2,609.55]	0.135	1,867.05 [1,023.80, 2,719.75]	1,938.55 [1,182.43, 2,682.98]	0.963
Postoperative laboratory findings (day 1)						
Leukocytes (10^9/L)	11.92 [9.80, 14.41]	11.30 [9.11, 13.99]	0.143	11.39 [9.78, 14.49]	11.25 [8.91, 13.73]	0.481
HCT (%)	32.80 [29.30, 35.32]	30.20 [27.10, 33.42]	<0.001	33.40 [29.45, 35.62]	30.30 [26.95, 34.00]	0.009
Platelets (10^9/L)	174.00 [135.00, 210.25]	116.50 [97.75, 157.25]	0.279	157.50 [135.00, 190.50]	118.50 [92.25, 153.50]	<0.001
Neutrophils (10^9/L)	10.18 [8.37, 12.50]	9.93 [7.86, 11.53]	0.174	9.74 [7.84, 12.67]	9.88 [7.60, 11.67]	0.633
Lymphocytes (10^9/L)	0.71 [0.50, 0.97]	0.62 [0.43, 0.81]	0.029	0.62 [0.42, 0.82]	0.64 [0.44, 0.81]	0.825
PCT (ng/ml)	0.75 [0.29, 2.14]	0.59 [0.28, 2.45]	0.676	0.58 [0.33, 1.36]	0.47 [0.24, 2.67]	0.766
CRP (mg/L)	57.83 [30.49, 83.80]	55.10 [32.48, 81.74]	0.667	49.04 [30.49, 85.89]	40.99 [29.52, 63.28]	0.401
PIV	2,230.25 [1,309.98, 3,472.70]	1,605.45 [870.50, 2,714.90]	0.001	2,220.45 [1,199.15, 2,970.43]	1,563.00 [738.50, 2,944.78]	0.039
NLR	14.30 [10.47, 21.22]	15.20 [11.47, 22.52]	0.247	15.75 [10.93, 25.73]	15.05 [11.82, 19.90]	0.770
PLR	243.55 [174.45, 346.62]	202.15 [134.23, 284.10]	0.001	258.10 [178.75, 363.20]	202.15 [134.07, 271.58]	0.003
SII	2,453.90 [1,615.92, 3,666.35]	1,854.65 [1,236.30, 2,888.10]	<0.001	2,434.90 [1,611.05, 3,631.80]	1,793.40 [1,200.65, 2,829.33]	0.010

CPB, cardiopulmonary bypass; HCT, hematocrit; PCT, procalcitonin; CRP, C-reactive protein; PIV, pan-immune inflammatory value; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic inflammation index.
Data are presented as median [P25, P75] or *n* (%).

TABLE 4 Comparison of perioperative inflammation biomarkers in the CPB group.

Variable	Preoperative (*n* = 96)	Postoperative day 0 (*n* = 96)	Postoperative day 1 (*n* = 96)	Postoperative day 2 (*n* = 96)	*P*-value
Leukocytes (10^9/L)	5.76 [4.97, 7.28]	11.75 [8.40, 15.18]	11.30 [9.11, 13.99]	13.23 [10.19, 15.65]	<0.001
Neutrophils (10^9/L)	3.59 [2.73, 4.53]	10.57 [7.38, 13.41]	9.93 [7.86, 11.53]	11.18 [8.55, 13.06]	<0.001
Lymphocytes (10^9/L)	1.65 [1.28, 2.00]	0.72 [0.43, 1.42]	0.62 [0.43, 0.81]	0.87 [0.66, 1.12]	<0.001
Platelets (10^9/L)	197.50 [169.50, 244.75]	116.50 [97.75, 157.25]	118.50 [94.75, 150.50]	114.00 [82.00, 136.25]	<0.001
CRP (mg/L)	2.21 [1.60, 6.84]	2.06 [1.60, 7.29]	55.10 [32.48, 81.74]	133.22 [98.32, 164.52]	<0.001
PIV	219.85 [117.50, 406.20]	790.80 [380.25, 1,311.88]	1,605.45 [870.50, 2,714.90]	1,328 [810.95, 2,183.85]	<0.001
NLR	2.30 [1.60, 3.10]	13.20 [8.40, 21.48]	15.20 [11.47,22.52]	12.40 [9.38, 15.87]	<0.001
PLR	125.75 [92.20, 159.92]	177.40 [92.17, 277.88]	202.15 [134.23, 284.10]	129.15 [87.90, 178.57]	<0.001
SII	420.30 [278.20, 684.05]	1,645.10 [1,010.15, 2,609.55]	1,854.65 [1,236.30, 2,888.10]	1,348.45 [905.40, 1,938.62]	<0.001

CRP, C-reactive protein; PIV, pan-immune inflammatory value; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic inflammation index.
Data are presented as median [P25, P75].

postoperative delirium (8). IL-6 levels surge immediately following the commencement of CPB (9, 10), peaking at the end of surgery and gradually returning to baseline levels by the third postoperative day (11). On the other hand, CRP levels peak 48 h postoperatively, followed by a decline after 72 h, with a maximum value of 58.82 ± 42.23 mg/L, representing a 3–10-fold increase from baseline (12). Conventionally, CRP is considered more sensitive for the early diagnosis of inflammation, and a higher concentration often indicates a poorer prognosis for patients (13). However, some studies have contradicted this notion, revealing no significant correlation between elevated CRP levels and the occurrence of postoperative inflammation or clinical outcomes (14).

PCT, primarily utilized for the early diagnosis of infection, attains its peak value within 24 h postoperatively (15), averaging at 0.77 ± 0.49 ng/ml, approximately two to four times higher than the baseline level (12); however, its concentration levels are also positively associated with organ dysfunction. Studies have shown that patients with PCT >2.5 ng/L have a 4.5-fold increase in mortality at 28 days after surgery (16). When PCT concentrations exceed 0.7 ng/ml, postoperative organ failure can

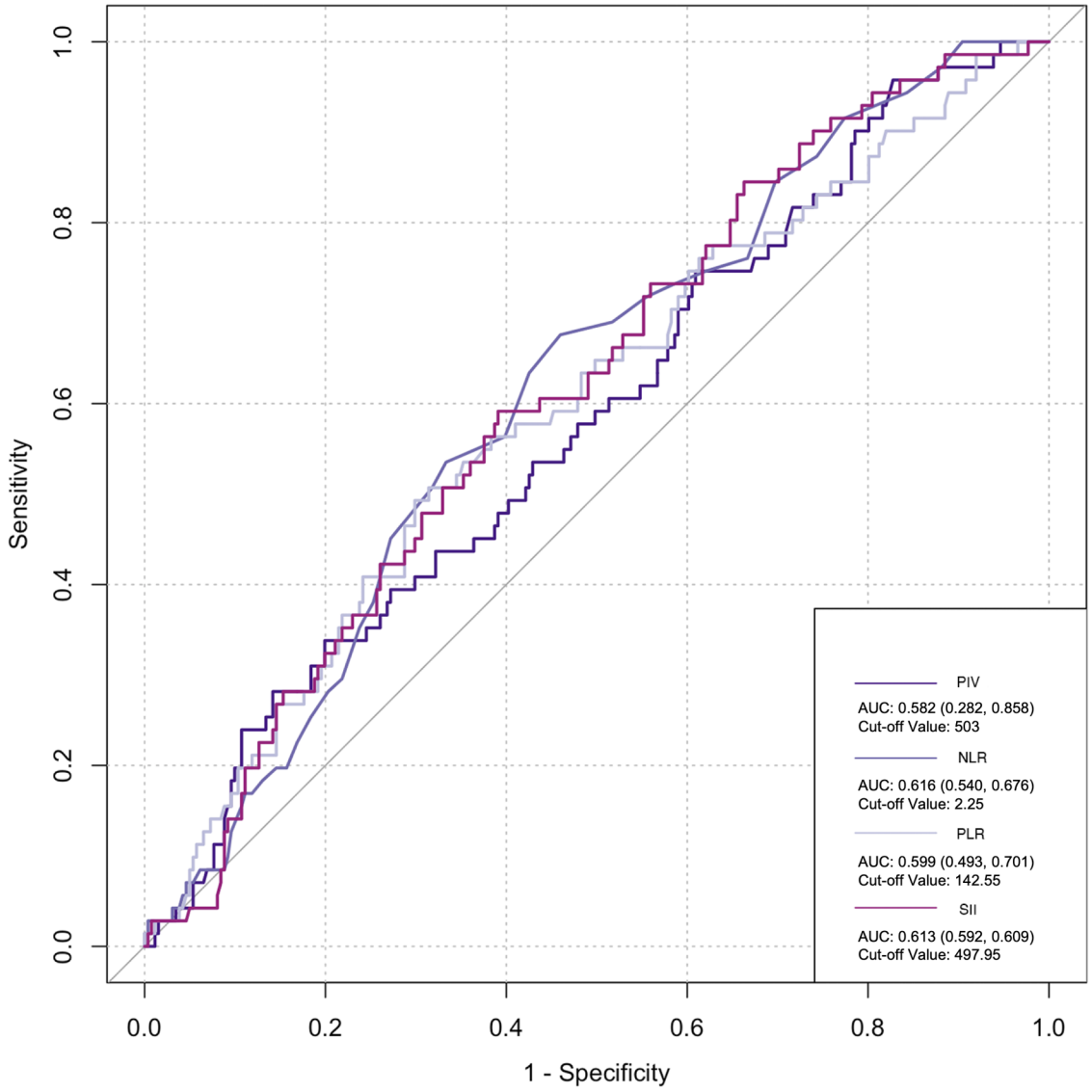


FIGURE 2
Preoperative biomarkers' predictive value for AKI.

be predicted (with a sensitivity of 85% and specificity of 58%), while when PCT concentrations exceed 7.7 ng/ml, both sensitivity and specificity reach 100% (17). Serum PCT concentrations in patients with multiple organ dysfunction can reach 20 ng/ml (18). These inflammatory markers, although informative, require careful interpretation in the context of individual patient characteristics and surgical procedures to ensure accurate prognostication and tailored treatment strategies, especially in cardiovascular surgery.

In recent years, numerous research studies have focused on developing novel inflammatory markers by integrating multiple biomarkers, including the PLR, NLR, SII, and PIV. These biomarkers have demonstrated unique roles in various studies. Many factors can affect the occurrence of AKI after cardiac surgery, such as preoperative neopterin levels, EuroSCORE II, and clamp time, all of which have been identified as independent predictors of postoperative AKI (19). Previous studies have highlighted the NLR on the first postoperative day as a robust and independent predictor of early AKI in patients undergoing isolated off-pump coronary artery bypass (OPCAB) (20). Meanwhile, PIV has garnered significant attention in the context of ST-elevation myocardial infarction (STEMI). Recently, relevant studies have expanded the application of PIV to patients with acute heart failure and STEMI, establishing its close association with patient prognosis in cardiology (21, 22). However, there is relatively little research on these indicators in the cardiovascular surgery field. Our study showed that novel inflammatory biomarkers consistently increase after cardiovascular surgeries involving CPB, peaking on the first day after surgery. However, compared to non-CPB cardiovascular surgery, our analysis of PLR, SII, and PIV revealed a paradoxical finding: a seemingly attenuated postoperative inflammatory response in the CPB group. This observation is

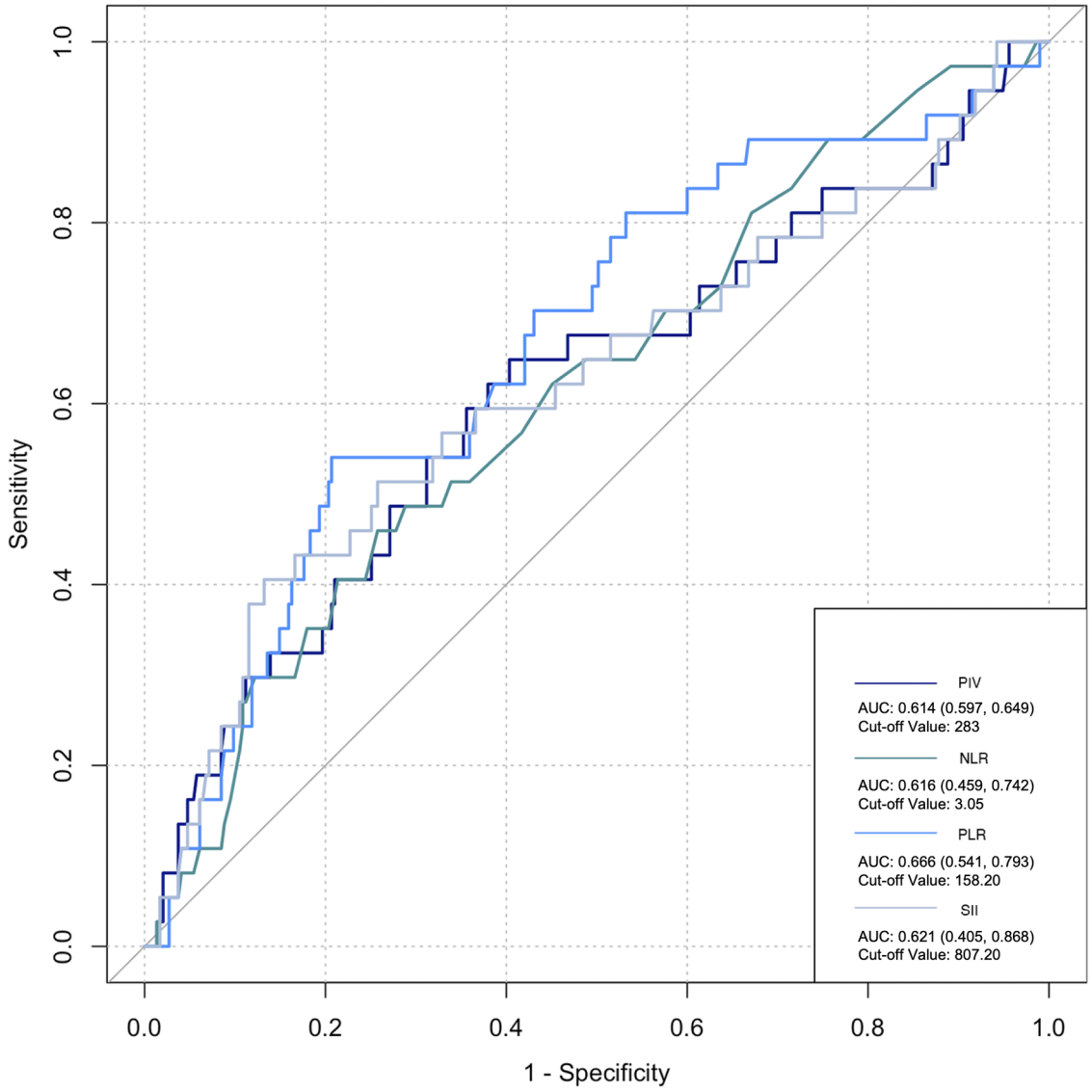


FIGURE 3
Preoperative biomarkers' predictive value for infection.

clearly in contrast with reality and is inconsistent with our impression. A careful analysis suggests that this discrepancy may be closely linked to the destruction of platelets during CPB. Current understanding suggests that platelet destruction, adhesion, and aggregation during CPB are primary factors contributing to reduced platelet counts after surgery (23). Prolonged CPB time further increases the risk of postoperative thrombocytopenia (24). Given these considerations, NLR, without the confounding influence of platelets, has emerged as a more informative metric for assessing perioperative inflammatory responses.

Previous studies have revealed that inflammatory cells contribute significantly to organ damage following CPB, primarily through two distinct mechanisms. Initially, monocytes adhere to vascular endothelial cells by upregulating CD11b expression and subsequently migrate from the blood vessels into tissues. Upon reaching the tissues, these monocytes upregulate the production of various inflammatory cytokines, including IL-6, IL-8, and TNF-α, creating a localized high-concentration zone (25). Notably, the concentration of these cytokines differs significantly from that observed intravascularly. A portion of these locally produced soluble factors enters the circulation, activating other immune effector cells, such as neutrophils. These activated neutrophils, guided by chemotactic signals from high-concentration cytokines in the tissue, migrate to the inflamed tissues through upregulated surface adhesion molecules like Mac-1 (CD11b/CD18). Upon arrival, they release oxygen free radicals, myeloperoxidase, elastase, and other agents, causing damage to surrounding tissues (26). Collectively, these observations suggest that monocytes and neutrophils are the primary immune effector cells mediating systemic inflammatory response (SIR) induced by CPB. Notably, the inclusion of more indices in research introduces more interfering factors, particularly considering the

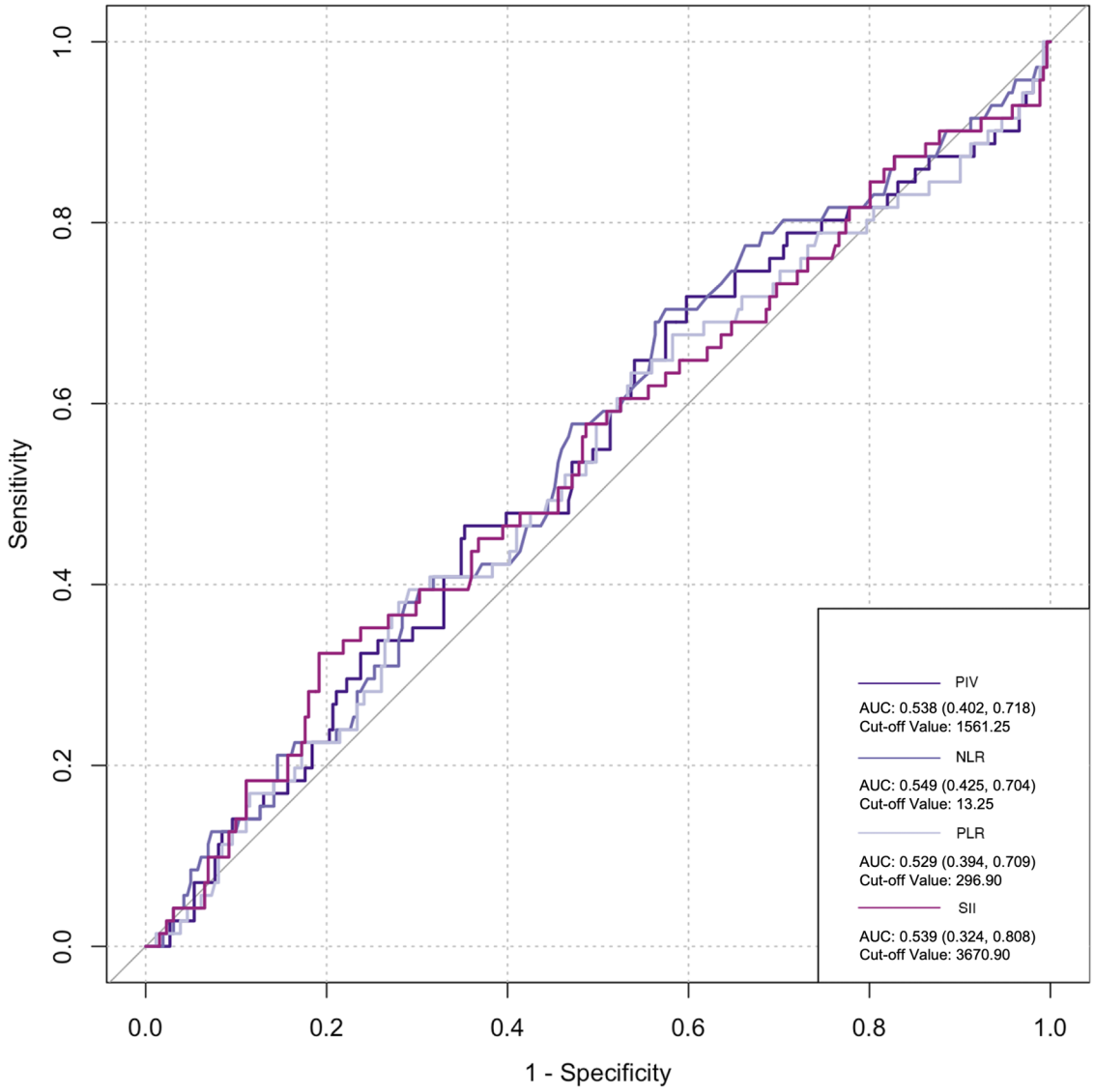


FIGURE 4
Postoperative biomarkers' predictive value for AKI.

damage to platelets and blood cells caused by CPB, thus leading to potential data deviations. However, NLR solely comprises the ratio of neutrophils to lymphocytes. Neutrophils play an important role in inflammation, while lymphocyte count reflects physiological stress and is negatively correlated with inflammation (27). Dynamic changes in NLR are attributed to systemic inflammation. High NLR significantly increases the risk of mortality, postoperative re-intubation, and atrial fibrillation after cardiovascular surgery (28, 29). A meta-analysis estimated an AUC of 0.65 for NLR in predicting AKI following cardiovascular surgery (30). Lafçi et al. emphasized the utility of NLR as a simple and effective marker for predicting outcomes in a high-risk cardiovascular cohort (31), which is consistent with our research. In the present study, ROC curve analysis yielded a similar prediction for postoperative AKI and infection with NLR (AUC: 0.616), supporting NLR as a potentially reliable prognostic indicator.

Limitations

Our study, despite its valuable contributions, has several limitations that need to be addressed. First, the clinical data collected for the study may not be comprehensive enough to provide a complete picture of the subject matter. This could be due to various reasons such as limited access to patient records, incomplete reporting of symptoms, or the absence of certain critical information. Second, the results obtained from this study may not be generalizable to other populations, given the specific characteristics of the sample population and the conditions under which the study was conducted. To overcome these limitations and further validate the findings of this study, larger, randomized controlled trials are urgently needed. Such trials would involve a more diverse and representative sample population, allowing for more robust and generalizable results. In

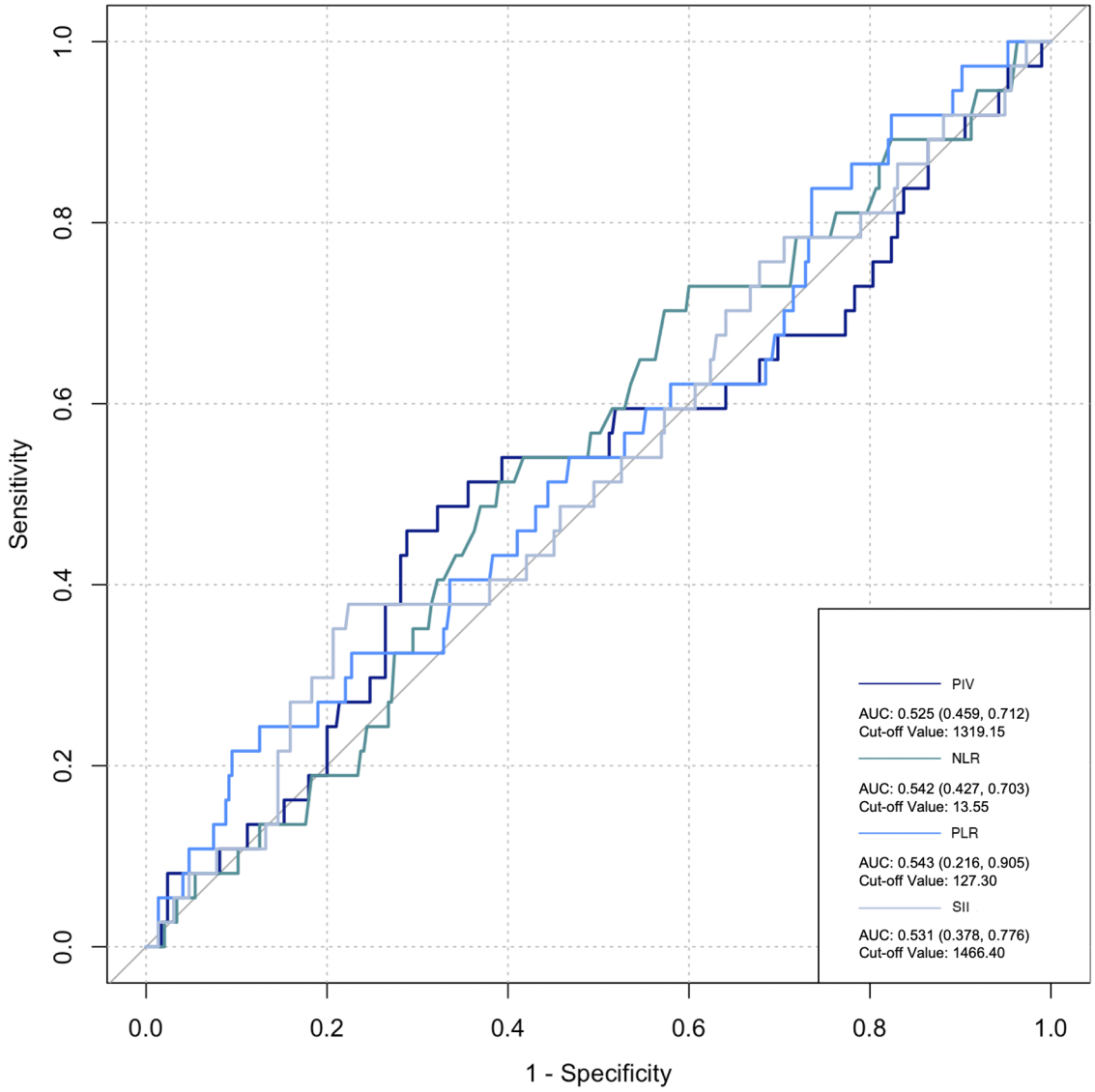


FIGURE 5
Postoperative biomarkers' predictive value for infection. PIV, pan-immune inflammatory value; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic inflammation index.

addition, the use of randomized allocation of participants to different treatment groups would help minimize potential biases and confounding factors, ensuring that the observed effects are truly attributable to the intervention being studied. By conducting such rigorous trials, we can gain a deeper understanding of the subject matter and make more informed decisions about the effectiveness of different treatment options.

Conclusions

In conclusion, patients undergoing cardiovascular surgery with CPB exhibit a poorer prognosis compared to those without CPB. Novel inflammatory biomarkers, including PLR, PIV, and SII, may offer valuable insights into the degree of postoperative inflammation, with NLR emerging as a potentially reliable prognostic indicator. Certainly, these findings necessitate further rigorous research and validation.

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 authors.

Ethics statement

The studies involving humans were approved by the Shanghai East Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional

requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WZ: Conceptualization, Writing – original draft. HW: Conceptualization, Data curation, Writing – original draft. CL: Data curation, Methodology, Writing – original draft. Q-mM: Data curation, Investigation, Writing – original draft. Y-hG: Formal Analysis, Writing – original draft. S-yS: Conceptualization, Formal Analysis, Writing – review & editing. S-lM: Project administration, Resources, Supervision, Writing – review & editing. FZ: Project administration, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by grants from the peak supporting clinical discipline of Shanghai health bureau (2023ZDFC0104 to L.T) and the National Key R&D Program "Stem Cell and Transformation Research" Key Special Project (2019YFA0110601).

Conflict of interest

Y-hG was employed by the Security Department of the Beijing Armed Police Corps.

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

References

1. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest*. (1997) 112 (3):676–92. doi: 10.1378/chest.112.3.676

2. Eltohami YI, Kao HK, Lao WW, Huang Y, Abdelrahman M, Liao CT, et al. The prediction value of the systemic inflammation score for oral cavity squamous cell carcinoma. *Otolaryngol Head Neck Surg*. (2018) 158:1042–50. doi: 10.1177/0194599817751678

3. Fucà G, Guarini V, Antoniotti C, Morano F, Moretto R, Corallo S, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. *Br J Cancer*. (2020) 123(3):403–9. doi: 10.1038/s41416-020-0894-7

4. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care*. (2013) 17(1):204. doi: 10.1186/cc11454

5. Hatami S, Hefler J, Freed DH. Inflammation and oxidative stress in the context of extracorporeal cardiac and pulmonary support. *Front Immunol*. (2022) 13:831930. doi: 10.3389/fimmu.2022.831930

6. Lindman BR, Goldstein JS, Nassif ME, Zajarias A, Novak E, Tibrewala A, et al. Systemic inflammatory response syndrome after transcatheter or surgical aortic valve replacement. *Heart*. (2015) 101(7):537–45. doi: 10.1136/heartjnl-2014-307057

7. Bauer A, Korten I, Juchem G, Kiesewetter I, Kilger E, Heyn J. EuroScore and IL-6 predict the course in ICU after cardiac surgery. *Eur J Med Res*. (2021) 26(1):29. doi: 10.1186/s40001-021-00501-1

8. Chen Y, Lu S, Wu Y, Shen Y, Zhao H, Ding S, et al. Change in serum level of interleukin 6 and delirium after coronary artery bypass graft. *Am J Crit Care*. (2019) 28(6):462–70. doi: 10.4037/ajcc2019976

9. Presta P, Bolignano D, Coppolino G, Serraino F, Mastroroberto P, Andreucci M, et al. Antecedent ACE inhibition, inflammatory response, and cardiac surgery associated acute kidney injury. *Rev Cardiovasc Med*. (2021) 22(1):207–13. doi: 10.31083/j.rcm.2021.01.288

10. Puchinger J, Ryz S, Nixdorf L, Edlinger-Stanger M, Lassnigg A, Wiedemann D, et al. Characteristics of interleukin-6 signaling in elective cardiac surgery: a prospective cohort study. *J Clin Med*. (2022) 11(3):590. doi: 10.3390/jcm11030590

11. Franke A, Lante W, Fackeldey V, Becker HP, Kurig E, Zöller LG, et al. Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? *Eur J Cardiothorac Surg*. (2005) 28(4):569–75. doi: 10.1016/j.ejcts.2005.07.007

12. Arkader R, Troster EJ, Abellan DM, Lopes MR, Júnior RR, Carcillo JA, et al. Procalcitonin and C reactive protein kinetics in postoperative pediatric cardiac surgical patients. *J Cardiothorac Vasc Anesth*. (2004) 18(2):160–5. doi: 10.1053/j.jvca.2004.01.021

13. Gutiérrez-Gutiérrez B, Morales I, Pérez-Galera S, Fernández-Riejos P, Retamar P, de Cueto M, et al. Predictive value of the kinetics of procalcitonin and C-reactive protein for early clinical stability in patients with bloodstream infections due to gram-negative bacteria. *Diagn Microbiol Infect Dis*. (2019) 93(1):63–8. doi: 10.1016/j.diagmicrobio.2018.07.019

14. Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, et al. The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. *Anesth Analg*. (2010) 111(5):1244–51. doi: 10.1213/ANE.0b013e3181f333aa

15. Amouzeshi A, Abedi F, Zardast M, Rezaeian Bilondi Y, Amouzeshi Z. Prognostic value of 16 procalcitonin for morbidity and mortality in patients after cardiac surgery. *Cardiol Res Pract*. (2021) 2021:1542551. doi: 10.1155/2021/1542551

16. Fritz HG, Brandes H, Bredle DL, Bitterlich A, Vollandt R, Specht M, et al. Postoperative hypoalbuminaemia and procalcitonin elevation for prediction of outcome in cardiopulmonary bypass surgery. *Acta Anaesthesiol Scand*. (2003) 47 (10):1276–83. doi: 10.1046/j.1399-6576.2003.00239.x

17. Celebi S, Koner O, Menda F, Balci H, Hatemi A, Korkut K, et al. Procalcitonin kinetics in pediatric patients with systemic inflammatory response after open heart surgery. *Intensive Care Med*. (2006) 32(6):881–7. doi: 10.1007/s00134-006-0180-z

18. Sablotzki A, Dehne MG, Friedrich I, Grond S, Zickmann B, Mühling J, et al. Different expression of cytokines in survivors and non-survivors from MODS following cardiovascular surgery. *Eur J Med Res*. (2003) 8(2):71–6.

19. Çiçek ÖF, Akyürek F, Akbayrak H, Orhan A, Kaya EC, Büyükateş M. Can preoperative neopterin levels predict acute kidney injury in patients undergoing on-pump cardiac surgery? *Turk J Biochem*. (2023) 48(5):531–40. doi: 10.1515/tjb-2023-0074

20. Ishikawa M, Iwasaki M, Namizato D, Yamamoto M, Morita T, Ishii Y, et al. The neutrophil to lymphocyte ratio and serum albumin as predictors of acute kidney injury after coronary artery bypass grafting. *Sci Rep*. (2022) 12(1):15438. doi: 10.1038/s41598-022-19772-7

21. Murat B, Murat S, Ozgeyik M, Bilgin M. Comparison of pan-immune-inflammation value with other inflammation markers of long-term survival after ST-segment elevation myocardial infarction. *Eur J Clin Invest*. (2023) 53(1):e13872. doi: 10.1111/eci.13872

22. Inan D, Erdogan A, Pay L, Genc D, Demırtola AI, Yıldız U, et al. The prognostic impact of inflammation in patients with decompensated acute heart failure, as assessed using the pan-immune inflammation value (PIV). *Scand J Clin Lab Invest*. (2023) 83 (6):371–8. doi: 10.1080/00365513.2023.2233890

23. Solis RT, Kennedy PS, Beall AC Jr, Noon GP, DeBakey ME. Cardiopulmonary bypass. Microembolization and platelet aggregation. *Circulation*. (1975) 52(1):103–8. doi: 10.1161/01.CIR.52.1.103

24. Hamid M, Akhtar MI, Naqvi HI, Ahsan K. Incidence and pattern of thrombocytopenia in cardiac surgery patients. *J Pak Med Assoc*. (2017) 67(7):1019–23.

25. Brix-Christensen V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. *Acta Anaesthesiol Scand*. (2001) 45 (6):671–9. doi: 10.1034/j.1399-6576.2001.045006671.x

26. Du L, Zhou J, Zhang J, Yan M, Gong L, Liu X, et al. Actin filament reorganization is a key step in lung inflammation induced by systemic inflammatory response syndrome. *Am J Respir Cell Mol Biol*. (2012) 47(5):597–603. doi: 10.1165/rcmb.2012-0094OC

27. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. *Angiology*. (2019) 70(9):802–18. doi: 10.1177/0003319719845186

28. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol*. (2010) 105 (2):186–91. doi: 10.1016/j.amjcard.2009.09.007

29. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J*. (2007) 154(5):995–1002. doi: 10.1016/j.ahj.2007.06.043

30. Chen D, Xiao D, Guo J, Chahan B, Wang Z. Neutrophil-lymphocyte count ratio as a diagnostic marker for acute kidney injury: a systematic review and meta-analysis. *Clin Exp Nephrol*. (2020) 24(2):126–35. doi: 10.1007/s10157-019-01800-y

31. Lafçi G, Çiçek ÖF, Uzun HA, Yalçinkaya A, Diken Aİ, Turak O, et al. Relationship of admission neutrophil-to-lymphocyte ratio with in-hospital mortality in patients with acute type I aortic dissection. *Turk J Med Sci*. (2014) 44(2):186–92. doi: 10.3906/sag-1301-136

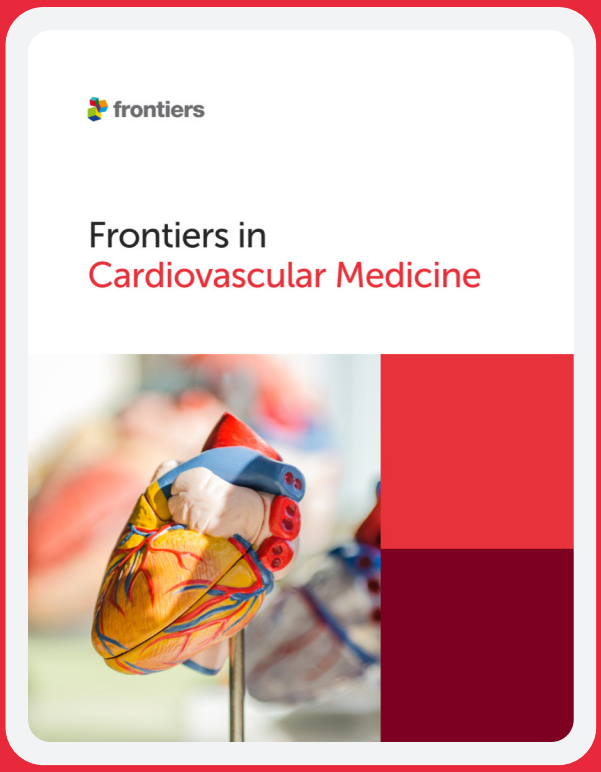
Frontiers in
Cardiovascular Medicine

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