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Insights in intensive care cardiovascular medicine 2022

Edited by
Marija Vavlukis and Fabio Guarracino

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Insights in intensive care cardiovascular medicine: 2022

Topic editors

Marija Vavlukis — University Clinic for Cardiology, Ss. Cyril and Methodius University in Skopje, North Macedonia

Fabio Guarracino — Azienda Ospedaliero Universitaria Pisana, Italy

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Hanne Berg Ravn,
Odense University Hospital, Denmark

*CORRESPONDENCE
Fabio Guarracino
✉ fabioguarracino@gmail.com

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Editorial: Insights in intensive care cardiovascular medicine: 2022

Fabio Guarracino[1]* and Marija Vavlukis[2,3]

[1]Department of Anaesthesia and Intensive Care Medicine, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [2]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [3]Faculty of Medicine, University Clinic for Cardiology, University Ss' Cyril and Methodius in Skopje, Skopje, North Macedonia

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shock, cardiogenic, organ dysfunction, multidisciplinary approach, pharmacological approach

Editorial on the Research Topic
Insights in intensive care cardiovascular medicine: 2022

The Research Topic "*Insights in Intensive Care Cardiovascular Medicine: 2022*" included nine manuscripts addressing four major areas in the field (Figure 1): the multidisciplinary approach to treating cardiovascular issues, the challenges of cardiogenic shock, prediction approaches to organs' acute dysfunction, and the pharmacological management of acute cardiovascular conditions.

The need for a multidisciplinary approach in the clinical management of acute cardiovascular states was explored in an interesting contribution to the Research Topic (Bouchlarhem et al.). It clearly underlined that the field of cardiac intensive care has evolved significantly since Desmond Julian's establishment of the first coronary intensive care unit (CICU) in 1961. Originally designed to improve the prognosis of myocardial infarction patients, CICUs have since expanded to address a wide range of acute cardiovascular conditions like severe arrhythmias, acute heart failure, cardiogenic shock, high-risk pulmonary embolisms, severe conduction disorders, post-implantation monitoring of percutaneous valves, and non-cardiac emergencies like septic shock, severe respiratory failure, and severe renal failure, along with managing cardiac arrest post-resuscitation. This evolution has included the incorporation of advanced therapeutic techniques such as fibrinolysis, invasive hemodynamic monitoring, and mechanical circulatory support, along with percutaneous coronary and structural interventions. Consequently, the transition to more comprehensive cardiac intensive care units was necessary to accommodate the broader spectrum of acute cardiovascular and non-cardiac conditions.

Today, the concept of a multidisciplinary approach is universally used with the aim to reduce morbidity and mortality associated with acute cardiovascular diseases and manage other critical conditions such as sepsis and respiratory failure.

Cardiogenic shock (CS) is a life-threatening condition with a poor prognosis, often requiring mechanical circulatory support. The challenges of cardiogenic shock, where again the multidisciplinary approach and teamwork is of a paramount importance, were addressed in three studies. One study investigated the still difficult phase of weaning patients off of mechanical support. Data from patients supported by Impella (Matassini et al.) were analyzed and predictors of successful weaning were searched for.

Left ventricular ejection fraction (LVEF) at the beginning of weaning and lactate variation within the first 12–24 h were the most accurate predictors of mortality during

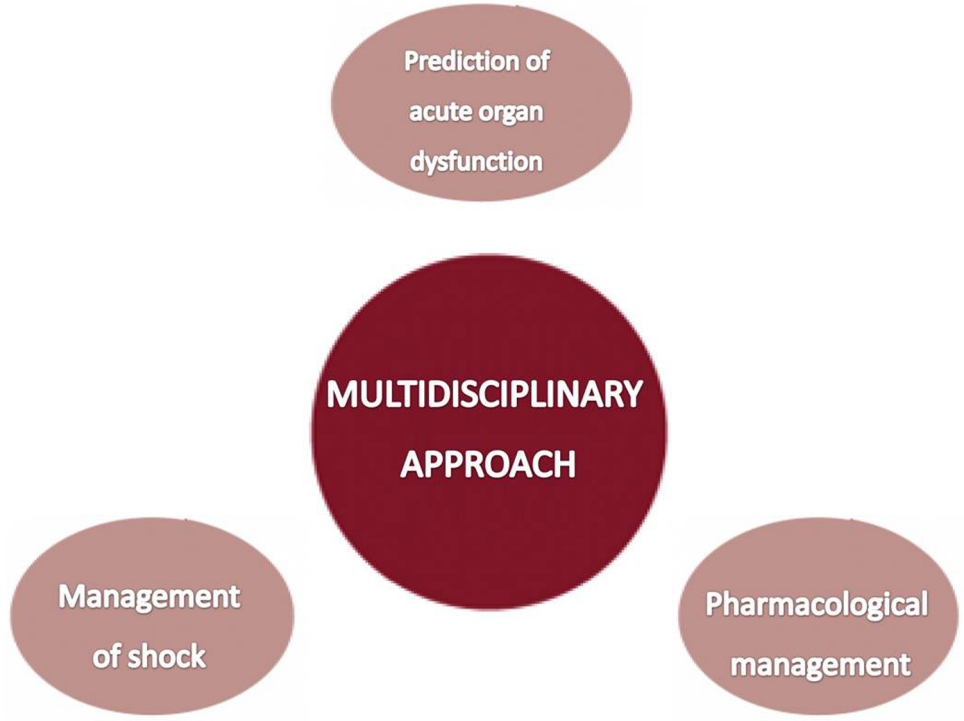

FIGURE 1
The major areas covered by the Research Topic "*Insights in Intensive Care Cardiovascular Medicine: 2022*".

the weaning process. These findings underscore the importance of these two parameters in guiding clinical decisions during Impella weaning and the importance of monitoring hemodynamic and clinical parameters together in intensive care.

Another study examined the management and outcomes of patients experiencing acute myocardial infarction complicated by cardiogenic shock (AMI-CS) in low- and lower-middle-income countries (LLMICs) using data from the Ukrainian Multicentre Cardiogenic Shock Registry (Bilchenko et al.). The study underscored the necessity of effective protocols in managing cardiogenic shock in these regions. Notably, it identified several factors independently predictive of hospital mortality: left main stem occlusion, deterioration in reperfusion, Charlson Comorbidity Index >4, and cardiac arrest.

Further research compared the effects of different P2Y12 receptor antagonists on bleeding and outcomes in patients with myocardial infarction and cardiogenic shock (Kanic and Kompara). The study found that, while the combination of P2Y12 antagonists increased bleeding risk, it did not adversely affect treatment outcomes compared to individual P2Y12 agents like ticagrelor and prasugrel. This suggests that bleeding risk should be considered when choosing P2Y12 antagonists but that it may not necessarily impact overall mortality outcomes.

Prediction of Acute Organ Dysfunction in Intensive Care represents a crucial challenge in the cardiac intensive care unit. Three studies offered insights into prediction of delirium, acute kidney injury, and hospital-acquired pneumonia in intensive care.

Postoperative delirium (POD) is a common but often undiagnosed complication in cardiac surgery patients. A study involving 232 patients (Wang et al.) identified postoperative lactate levels, maximum temperature, and cardiopulmonary bypass time as independent predictors of POD. A predictive nomogram developed from these factors demonstrated excellent discriminatory power, suggesting the potential for early interventions to prevent POD in high-risk patients.

Similarly, acute kidney injury (AKI) is a frequent and serious complication after cardiac surgery. A study of 260 patients identified the fibrinogen-to-albumin ratio (FAR) as an independent predictor of AKI (Xu et al.). Although FAR significantly improved AKI prediction, its addition to clinical prediction models did not substantially enhance the area under the receiver operating characteristic curve. This finding highlights FAR's potential role in early AKI detection and prevention.

Hospital-acquired pneumonia (HAP) is another significant risk for patients admitted with acute heart failure (AHF) in intensive care units (ICUs). In a study of 638 patients (Polovina et al.), HAP occurred in 21.5%, with higher incidence in those with *de novo* AHF, severe congestion, and a history of stroke, diabetes, and chronic kidney disease. HAP was associated with longer hospital stays, increased need for inotropes and ventilatory support, and higher in-hospital mortality. These findings emphasize the need for targeted strategies to prevent HAP and manage its complications effectively.

Pharmacological interventions play a critical role in managing various cardiac conditions, including coronary artery spasm (CAS)

and perioperative care in cardiac surgery. CAS, characterized by reversible vasoconstriction, can lead to fatal arrhythmias. Nondihydropyridine calcium channel blockers (CCBs), such as diltiazem, are recommended for treating and preventing CAS episodes. However, their use in patients with atrioventricular block (AV-B) is controversial. A case report (Zhang et al.) demonstrated the effective and safe use of diltiazem in a patient with CAS-induced complete AV-B, highlighting its potential benefits.

In cardiac surgery patients with severely reduced ventricular function, Levosimendan has been studied for its perioperative benefits. A retrospective study of 498 patients analyzed the impact of Levosimendan administration timing on outcomes (Schiefenhövel et al.). Patients who received prolonged preoperative Levosimendan treatment ("preconditioning") had significantly lower in-hospital mortality, shorter duration of mechanical ventilation, and reduced need for continuous renal replacement therapy compared to those who received it intraoperatively or postoperatively. These results support the recommendation for preconditioning with Levosimendan to improve postoperative outcomes in high-risk cardiac surgery patients.

In conclusion, advancements in cardiac intensive care, understanding and managing cardiogenic shock, predicting acute organ dysfunction, and optimizing pharmacological treatments are critical to improving patient outcomes in cardiac care.

The articles included in the Research Topic "*Insights in Intensive Care Cardiovascular Medicine: 2022*" clearly highlight that continued research and implementation of evidence-based practices are essential for addressing the complexities of cardiac and non-cardiac emergencies in modern healthcare.

Author contributions

FG: Writing – original draft, Writing – review & editing. MV: Writing – review & editing.

Conflict of interest

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

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EDITED BY
Marija Vavlukis,
Ss. Cyril and Methodius University in Skopje, North Macedonia

REVIEWED BY
Edina Cenko,
University of Bologna, Italy
Jorgo Kostov,
Saints Cyril and Methodius University of Skopje, North Macedonia
Lidija Poposka,
Saints Cyril and Methodius University of Skopje, North Macedonia

*CORRESPONDENCE
Li Liu
✉ liulibwh@163.com
Chengwei Liu
✉ whlcw60@126.com

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Diltiazem is a useful and effective medication for reversal of coronary artery spasm-induced complete atrioventricular block: A case report

Jin Zhang[1,2], Li Liu[1]*, Chengwei Liu[1]*, Min Han[1], Chengyi Xu[1] and Rujie Qiu[1]

[1]Division of Cardiac Care Unit, Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, China, [2]Department of Cardiology, Medical College of Wuhan University of Science and Technology, Wuhan, China

Coronary artery spasm (CAS) is characterized by reversible diffuse or focal vasoconstriction, a phenomenon that plays an important role in the pathogenesis of ischemic heart disease. Fatal arrhythmias, such as ventricular tachycardia/fibrillation and complete atrioventricular block (AV-B), are very common in patients with CAS. Nondihydropyridine calcium channel blockers (CCBs) such as diltiazem were recommended as first-line medications for treating and preventing CAS episodes. However, its use remains controversial in CAS patients with AV-B as this type of CCB can also cause AV-B itself. Here, we present the use of diltiazem in a patient with complete AV-B caused by CAS. The patient's chest pain was rapidly relieved, and complete AV-B was promptly restored to sinus rhythm following the administration of intravenous diltiazem without any adverse effects. In this report, we highlight the useful and effective application of diltiazem for treating and preventing complete AV-B caused by CAS.

KEYWORDS
coronary artery spasm, fatal arrhythmia, complete atrioventricular block, calcium channel blocker, diltiazem

1. Introduction

Coronary artery spasm (CAS) is defined as a severe reversible diffuse or focal vasoconstriction, a phenomenon that plays an important role in the pathogenesis of ischemic heart disease (1). Unlike classical angina, which is induced by emotional or physical stress, CAS usually occurs at rest or during regular daily activity. The clinical manifestations of CAS include variant angina, acute myocardial infarction (AMI), fatal arrhythmias [e.g., ventricular tachycardia/fibrillation (VT/VF), complete atrioventricular block (AV-B)], and even sudden cardiac death (2, 3). Vasodilators such as nitrates and calcium channel blockers (CCBs) are considered effective first-line treatment for the prevention of vasoconstriction episodes; however, the use of CCBs in patients with CAS-induced complete AV-B remains controversial as CCBs can also reduce cardiac output and cause AV-B themselves (4–6). Here, we present a case of complete AV-B with hypotension caused by CAS, where the patient's severe chest pain was relieved and complete AV-B was restored back to sinus rhythm following the administration of intravenous diltiazem without any observed adverse effects. This patient was subsequently prescribed diltiazem long-term for the prevention of CAS. In this case report, we aim to

highlight the useful and effective application of this medication for treating and preventing CAS-induced complete AV-B.

2. Case presentation

A 44-year-old female patient presented to the emergency room (ER) of our hospital with complaints of "intermittent chest pain and chest tightness for two weeks, worsening for the past 2 h." She reported that the chest pain that started 2 weeks before she attended the ER involved intermittent retrosternal pain occurring at midnight at rest, accompanied by tightness in her throat without shortness of breath, palpitations, or diaphoresis. The symptoms lasted for a few minutes and were relieved spontaneously. Her symptoms were recurring and became increasingly more frequent. Her medical history included hypertension for 7 years and noncompliance with antihypertensives (irbesartan, 150 mg/day). She also reported abnormal glucose tolerance for the past year. She denied taking any other medicines. Physical examination upon admission revealed that vitals were all within normal limits: blood pressure 105/51 mmHg (1 mm Hg = 0.133 kPa), heart rate (HR) 56 beats/min, respiratory rate 20 /min, and oxygen saturation level at 99% (room air). Cardiac and pulmonary examination revealed normal heart sounds without murmur and clear lungs to auscultation. The abdomen was soft and nontender to palpation, without rebound tenderness. There was no appreciable bilateral lower extremity edema. The electrocardiogram (ECG) performed at rest showed normal sinus rhythm with no significant ST-T changes (Figure 1A); echocardiography completed in the ER showed a mildly thickened ventricular septum and left ventricular posterior wall, mild tricuspid regurgitation, and slightly reduced left ventricular ejection fraction (LVEF 50%, normal range: 55%–75%) (Figures 1B,C). ER laboratory tests indicated normal troponin I of 0.016 ng/mL (normal range, 0–0.04 ng/mL), creatine kinase MB isoenzyme of 0.7 ng/mL (normal range, 0–5.0 ng/mL), and myoglobin of 14.1 ng/mL (normal range, 0–70.0 ng/mL) levels. Since acute coronary syndrome (ACS) cannot be excluded, a loading dose of aspirin (300 mg) + clopidogrel (300 mg) was prescribed and coronary angiography (CAG) was suggested but was refused by the patient and her family members. The patient was then admitted to the cardiac care unit (CCU) for suspicion of ACS. Twelve minutes after hospitalization, her chest pain recurred, and monitoring ECG revealed ST-segment elevation in lead II and complete AV-B with HR at 41 beats/min accompanied by hypotension (BP at 96/51 mmHg) (Figures 2A,B). According to the characteristics of the patient's chest pain, ECG (near normal when chest pain was relieved), and biomarker (normal troponin I) obtained in ER, the diagnosis of CAS was highly suspected. With a possible diagnosis of CAS, 5 mg of diltiazem was administered intravenously with prompt relief of chest pain, and complete AV-B was converted

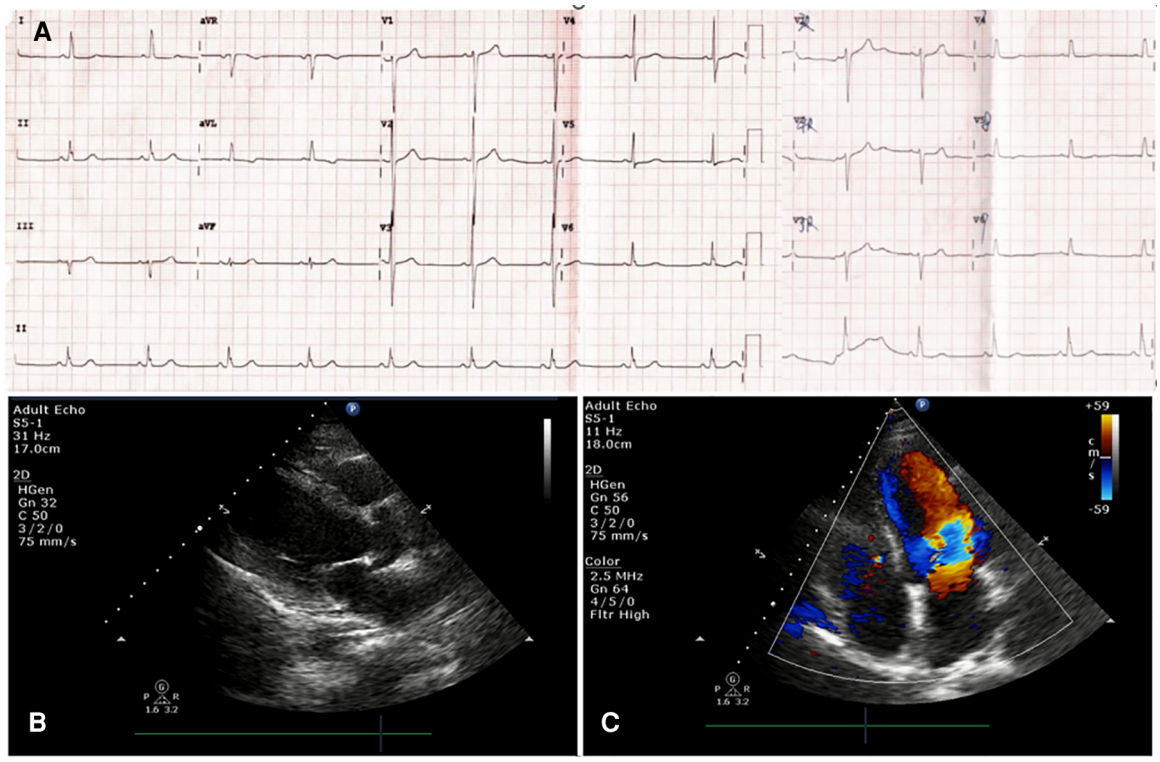

FIGURE 1
Emergency electrocardiogram (ECG) was performed at rest showed normal sinus rhythm with no significant ST-T changes in all leads (A); Echocardiography in ER indicated a mildly thickened ventricular septum and left ventricular posterior wall, mild tricuspid regurgitation and a slightly reduced left ventricular ejection fraction (LVEF 50%) (B and C).

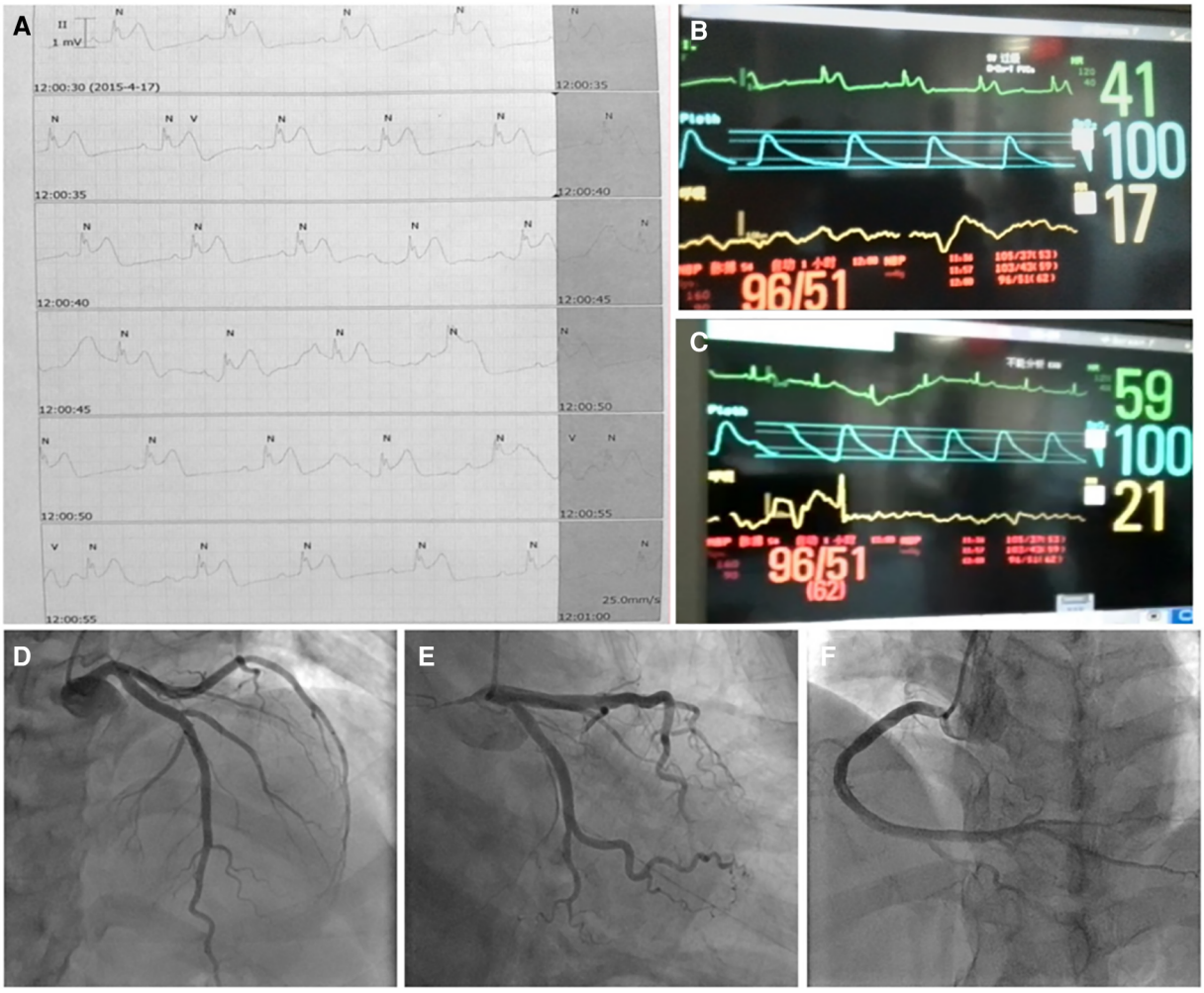

FIGURE 2
Twelve minutes after hospitalization, the chest pain recurred, and monitoring ECG revealed ST-T segments elevation in lead II and complete AV-B with HR 41 bpm accompanied by hypotension (BP 96/51 mmHg) (**A**,**B**). Five milligrams of diltiazem was administered intravenously with prompt relief of chest pain, and complete AV-B was converted back to sinus rhythm (**C**). Coronary angiography on day 2 revealed nonobstructive coronary arteries in the LAD, (**D**), LCX, or (**E**) RCA (**F**). ECG, electrocardiogram; AV-B, atrioventricular block; HR, heart rate; LAD, left anterior descending artery; LCS, left circumflex branch; RCA, right coronary artery.

back to sinus rhythm (HR at 59 beats/min) (**Figure 2C**). The patient was on 50 mg of diltiazem hydrochloride intravenously (at 5 mL/h) for maintenance. She received CAG the second day after a repeated suggestion by the physician, which revealed normal left main branch, 20%–30% stenosis at the opening and middle segment of the left anterior descending artery (LAD), 30% stenosis at the first diagonal branch (D1), 30% stenosis at the beginning of the circumflex branch (LCX), and 20% stenosis at the middle of the right coronary artery (RCA) (**Figures 2D,E,F**, **Supplementary Videos S1–S3**). Routine lab work during hospitalization revealed that white blood cell count, lipids, liver function, renal function, glycosylated hemoglobin, electrolytes, thyroid function, coagulation function, erythrocyte sedimentation rate, D-dimers, cytokines, and urinalysis were all within normal limits. Based on the patient's symptoms, ECG, and CA findings, a diagnosis of CAS was made. Repeated troponin (0.031 ng/mL) and ECG were normal (**Figure 3**). The patient was then prescribed diltiazem sustained-release capsules (90 mg, twice per day), an antiplatelet medication (aspirin, 100 mg per day), and lipid-regulating medication (atorvastatin, 20 mg per day). With other in-patient treatments and improving myocardial ischemia, the patient no longer had chest pain or discomfort during hospitalization. The patient was followed up on an outpatient basis without recurrence of chest pain or other reported symptoms. At her last follow-up appointment, she had remained symptom-free for the past 3 months and was in good clinical condition. The timeline of this case report is provided in **Table 1**.

3. Discussion

CCBs are often classified into two major categories, either nondihydropyridines such as diltiazem and verapamil or dihydropyridines such as nifedipine, amlodipine, and felodipine.

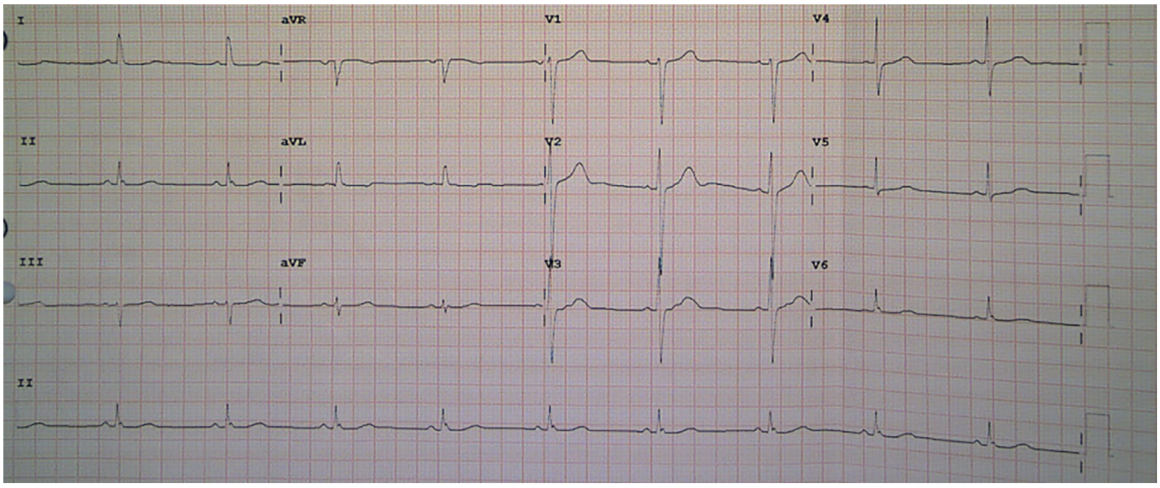

FIGURE 3
Repeated ECG revealed normal heart rate without ST-T changes after diltiazem treatment. ECG, electrocardiogram.

TABLE 1 Timeline of the case report.

Day 1, 11:33	Hospitalization
Day 1, 11:45	Chest pain recurred with complete AV-B
Day 1, 12:03	Diltiazem was intravenously
Day 1, 12:05	Chest pain revealed and complete AV-B to sinus rhythm
Day 2	CAG
Day 4	Discharge

AV-B, atrioventricular block; CAG, coronary angiography.

CCBs noncompetitively inhibit the influx of extracellular calcium ions across the myocardial and vascular smooth muscle cell membranes during depolarization by binding to the L-type voltage-gated calcium channels on the myocardium and vascular smooth muscle of the coronary arteries, weakening the contractility of the myocardium and causing coronary artery dilatation (7, 8). As a nondihydropyridine CCB, diltiazem also has inhibitory effects on atrioventricular (AV) conduction through its ability to impede slow calcium channel function, resulting in a reduced heart rate (8, 9). Diltiazem-induced AV-B was commonly seen in the clinical setting (3, 4, 9) but was thought to be reversible upon withdrawal of the medication.

CAS is one of the most common types of coronary vasomotor disorders. According to the International Study Group on Coronary Vasomotor Disorders published in 2017 (10), the diagnostic criteria for vasospastic angina include: (1) typical coronary spastic angina (e.g., resting chest pain occurring nocturnally or early morning) that is relieved by nitrates or CCB; (2) transient ischemic ECG changes, including ST-segment elevation or depression and new negative U waves; and (3) manifestations of coronary spasm, i.e., transient coronary artery spasm under acetylcholine, ergometrine, hyperventilation challenge tests or (4) spontaneous spasm with transient nonfixed stenosis of >90%, accompanied by angina pectoris and ECG ischemic changes. Based on ECG and CAG findings, CAS is classified as "definitive" or "suspected" vasospastic angina. Definitive vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changes during spontaneous episodes or coronary artery spasm criteria are fulfilled. Suspected vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes, but transient ischemic ECG changes are either equivocal or unavailable and the coronary artery spasm criteria are equivocal. Although the underlying mechanisms behind CAS remain elusive, endothelial dysfunction, autonomic nervous system disorders, and hyperreactivity of vascular smooth muscle cells were thought to contribute to the phenomenon (1, 3). Normally, endothelial cells produce nitric oxide (NO), a potent vasodilator that functions as a suppressor for vasoconstrictive metabolites (11). Endothelial dysfunction results in a deficiency of endogenous NO; therefore, circulating vasoactive substances will favor vasoconstriction and underlie a nonspecific enhancement of the response to all vasoconstrictor stimuli (12). Several clinical studies have confirmed the impaired endothelial NO bioactivity in epicardial coronary arteries of patients with CAS (13, 14). Furthermore, endothelial dysfunction in a setting of normal coronary arteries proved by selective loss of acetylcholine-induced vasodilatation has been suggested as a sign of the future development of atherosclerosis (15). Prolonged vasospasm causes cardiac ischemia and therefore easily induces acute myocardial infarction, heart failure, sudden cardiac death, and fatal arrhythmias, such as VT/VF or complete AV-B (16). CCBs are currently recommended as the first-line treatment for CAS due to their effectiveness in the remission and prevention of CAS (3, 17). However, their use in CAS patients with hypotension and bradycardia was controversial because CCBs can reduce cardiac contractility and cause AV-B (4, 5). According to the drug use instructions, nondihydropyridine CCBs (e.g., diltiazem, verapamil) are contraindicated in patients with severe hypotension, cardiogenic shock, second- or third-degree AV block, sick sinus syndrome, persistent sinus bradycardia, and sinus arrest due to the possibility of causing bradycardia and worsening cardiac output. However, studies have

shown (6, 18) that diltiazem was safe and effective in the treatment of AV-B caused by coronary spasm; therefore, it is not absolutely contraindicated in the management of malignant arrhythmia caused by CAS. In our patient, despite both complete AV-B and hypotension, 5 mg of intravenous diltiazem was administered immediately with significant improvement of symptoms after about 1 min, and ECG monitoring indicated restoration of sinus rhythm. The patient did not suffer any adverse effects from drug administration. We thought that the therapeutic effect was driven by the aggregate of several mechanisms of action of diltiazem, including a reduction in the contractile processes of the myocardial smooth muscle cells, vasodilation of the coronary and systemic arteries (including epicardial and subendocardial), and reduction in heart rate, resulting in lowering of myocardial oxygen demand. However, we must point out that an emergency CAG would have been appropriate if ACS is suspected in clinical settings. CCB is not routine management, only when CAS is highly suspected or confirmed and CA is unavailable or incompetent (e.g., unable to obtain written patient consent). CAG is still recommended even with symptom relief because coronary vasospasm may occur in the presence of fixed atherosclerotic obstructions in the epicardial coronary arteries (19).

4. Conclusion

In summary, this case report provided additional evidence that diltiazem is a useful and effective medication in managing CAS-induced angina and complete AV-B. It can achieve immediate efficacy during intravenous use; however, large studies are warranted to confirm the findings presented here.

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

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

CL, MH, CX, and RQ contributed to patient diagnosis, treatment, and follow-up. JZ drafted this manuscript. LL and CL revised the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary material

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EDITED BY
Marija Vavlukis,
University Clinic for Cardiology, Ss. Cyril and Methodius University in Skopje, North Macedonia

REVIEWED BY
Daniele Torella,
Magna Græcia University, Italy
Sergio Waxman,
Newark Beth Israel Medical Center, United States

*CORRESPONDENCE
M. V. Matassini
mariavittoria.matassini@ospedaliriuniti.marche.it

†These authors contributed equally to this work and share first authorship

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Clinical outcomes and predictors of success with Impella weaning in cardiogenic shock: a single-center experience

M. V. Matassini[1*†], M. Marini[1†], A. Angelozzi[2], L. Angelini[1], M. Shkoza[1], P. Compagnucci[3], U. Falanga[3], I. Battistoni[1], G. Pongetti[1], M. Francioni[1], T. Piva[4], A. Mucaj[4], E. Nicolini[4], A. Maolo[4], M. Di Eusanio[5], C. Munch[6], A. Dello Russo[3] and G. Perna[1]

[1]Cardiac Intensive Care Unit-Cardiology Division, Cardiovascular Department, Ospedali Riuniti di Ancona, Ancona, Italy, [2]Unit of Cardiology and Cardiac Intensive Therapy, Cardiovascular Department, G. Mazzini Hospital, Teramo, Italy, [3]Cardiology and Arrhythmology Clinic and Department of Biomedical Sciences and Public Health, University Hospital Ospedali Riuniti di Ancona and Marche Polytechnic University, Ancona, Italy, [4]Interventional Cardiology-Cardiology Division, Cardiovascular Department, Ospedali Riuniti di Ancona, Ancona, Italy, [5]Cardiac Surgery Unit, Cardiovascular Department, Ospedali Riuniti di Ancona, Ancona, Italy, [6]Anaesthesia and Cardiac Surgery Intensive Care, Ospedali Riuniti di Ancona, Ancona, Italy

Introduction: Cardiogenic shock (CS) is a severe syndrome with poor prognosis. Short-term mechanical circulatory support with Impella devices has emerged as an increasingly therapeutic option, unloading the failing left ventricle (LV) and improving hemodynamic status of affected patients. Impella devices should be used for the shortest time necessary to allow LV recovery because of time-dependent device-related adverse events. The weaning from Impella, however, is mostly performed in the absence of established guidelines, mainly based on the experience of the individual centres.

Methods: The aim of this single center study was to retrospectively evaluate whether a multiparametrical assessment before and during Impella weaning could predict successful weaning. The primary study outcome was death occurring during Impella weaning and secondary endpoints included assessment of in-hospital outcomes.

Results: Of a total of 45 patients (median age, 60 [51–66] years, 73% male) treated with an Impella device, 37 patients underwent impella weaning/removal and 9 patients (20%) died after the weaning. Non-survivors patients after impella weaning more commonly had a previous history of known heart failure ($p = 0.054$) and an implanted ICD-CRT ($p = 0.01$), and were more frequently treated with continuous renal replacement therapy ($p = 0.02$). In univariable logistic regression analysis, lactates variation (%) during the first 12–24 h of weaning, lactate value after 24 h of weaning, left ventricular ejection fraction (LVEF) at the beginning of weaning, and inotropic score after 24 h from weaning beginning were associated with death. Stepwise multivariable logistic regression identified LVEF at the beginning of weaning and lactates variation (%) in the first 12–24 h from weaning beginning as the most accurate predictors of death after weaning. The ROC analysis indicated 80% accuracy (95% confidence interval = 64%–96%) using the two variables in combination to predict death after weaning from Impella.

Conclusions: This single-center experience on Impella weaning in CS showed that two easily accessible parameters as LVEF at the beginning of weaning and lactates variation (%) in the first 12–24 h from weaning begin were the most accurate predictors of death after weaning.

KEYWORDS

heart failure, Impella, weaning, outcomes, complications, cardiogenic shock

Introduction

Cardiogenic shock (CS) is a complex and severe clinical syndrome due to a severe impairment of myocardial performance resulting in reduced cardiac output with end-organ hypoperfusion. The goal of CS treatment is to quickly restore cardiac output through a series of historical and established emergency treatments depending on the specific etiology, ranging from volume expansion to vasopressors and inotropes, from early revascularization of the infarct-related artery to intra-aortic balloon pump (IABP) counterpulsation (1–4). In the last decade, the Impella device has emerged as an increasingly therapeutic option for CS (5–12). It is a microaxial, continuous-flow pump, placed across the aortic valve to support and unload the failing left ventricle (LV), with blood flows up to 5.5 L/min. Impella directly unloads the LV, reducing total mechanical work and myocardial oxygen demand, while lowering wall stress and improving subendocardial coronary blood flow (13, 14). These actions favour LV recovery and circulatory stability.

However, mechanical unloading with the Impella device is also complicated by time-dependent device-related adverse events, such as limb ischemia, sepsis, haemolysis, stroke and bleeding. Therefore, the Impella device should be used for the shortest time necessary to allow LV recovery.

The weaning from Impella and its explant, however, are mostly performed in the absence of established algorithms and protocols, mainly based on the experience of the individual centres, and predictors of successful weaning are lacking (15–18).

The aim of this study is to retrospectively evaluate whether a multiparametrical assessment just before and during Impella weaning, including clinical, laboratory, echocardiographic, and hemodynamic data, could predict successful weaning. Furthermore, we aim to describe our experience in the complex field of weaning from Impella, in order to provide guidance in this challenging and largely unexplored critical care scenario.

Methods

Patients

The Ancona Impella Registry is a single-center retrospective registry at a high volume tertiary referral hospital with on-site cardiac surgery, including all patients older than 18 years admitted consecutively to the Cardiology Intensive Care Unit (ICU) of the University Hospital "Ospedali Riuniti", Ancona, from September 2015 to July 2021 because of Cardiogenic Shock, who were supported with an Impella pump (2,5 or CP device; Abiomed Europe GmbH, Aachen, Germany).

The diagnosis of CS was made in the presence of all of the following criteria:

- Systolic blood pressure (SBP) <90 mmHg for ≥30 min OR Support to maintain SBP ≥90 mmHg;
- End-organ hypoperfusion (urine output <30 ml/h, arterial lactate >2 mmol/L, altered mental status or cool extremities);
- Hemodynamic criteria: cardiac index (CI) ≤2.2 L min^{-1} m^{-2} and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg.

The cause of CS was classified as: ischemic (non ST elevation or ST elevation myocardial infarction), related to acute myocarditis or decompensated dilated cardiomyopathy.

Weaning from Impella

Duration of Impella support was at the discretion of the treating physician, based on the evolving conditions of affected patients, which were re-assessed four times per day or more.

The weaning process was started after hemodynamic stabilization, and in the presence of clinical/instrumental signs of improved cardiac function and end-organ perfusion (5, 8, 17, 19, 20), after a minimum of 48 h of maximal tolerated P-level support.

Weaning was performed by gradually reducing the Impella performance level from P5 to P2. The time when weaning was started was recorded as the onset of weaning.

When P2 level was tolerated for at least 120 min, the device was explanted. The completion of the weaning process usually occurred within 48 h, in absence of new events (as new ischemic clinical events, hypotension with elevate serum lactates and/or metabolic acidosis, reduction in urine output with elevation in serum creatinine, ventricular arrhythmias not related to Impella suction) or failure.

We retrieved baseline demographic variables and medical history, procedural and angiographic information (including, time to balloon, defined as the time between the arrival of a patient with acute coronary syndrome in ICU and the first balloon inflation during percutaneous coronary intervention and time to unload, defined as the time between the arrival of a patient with acute coronary syndrome in ICU and the activation of the impella pump), pharmacological therapy with special attention to inotropes and vasopressor before and during Impella weaning, echocardiographic, laboratory and hemodynamic parameters before and during Impella weaning and in-hospital complications, clinical events and deaths.

We calculated the inotropic score by the standard formula: Dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min)] + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min).

All data, which were prospectively inserted in our local electronic chart, were therefore included in a pre-specified structured database.

We measured the percent change in serum lactate levels in the first 12–24 h of weaning and named in the results section as "Δ lactate during first 12–24 h of weaning".

Left ventricular ejection fraction (LVEF) assessed at the onset of weaning was named as "baseline left ventricular ejection fraction".

All these procedures performed were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Study endpoints

The primary study outcome was death occurring during Impella weaning.

Secondary endpoints included assessment of in-hospital outcomes (weaning failure, mechanical support escalation, in-hospital deaths and complications).

We defined Impella weaning failure as the need to increase Impella support of at least 1P level because of clinical, hemodynamic and laboratory worsening during Impella support reduction.

Mechanical support escalation was represented by the need to upgrade to a higher-flow support device (veno-arterial extracorporeal membrane oxygenation, ECMO, or left ventricular assist device, LVAD).

In-hospital complications included myocardial re-infarction, arrhythmias, and stroke/transient ischemic attack, access site bleeding, acute limb ischaemia, cardiac tamponade, retroperitoneal hemorrhage or other major bleeding events, clinical significant haemolysis, Impella repositioning, systemic infections and acute kidney injury (AKI).

All bleeding events were classified according to Bleeding Academic Research Consortium (BARC) criteria (21).

Clinical significant haemolysis was defined as the presence of clinical signs (dark urine, scleral icterus, hemodynamic instability) together with laboratory signs of haemolysis (increase of LDH more than 2.5 times compared to baseline value, significant drop in haemoglobin, reduction of haptoglobin, increase of total bilirubin).

Statistical analyses

Continuous variables were checked for normality using the Shapiro–Wilk test, and are reported as mean ± standard deviation if normally distributed, or as median (1st–3rd quartile) if non-normally distributed.

The association of clinical, echocardiographic, and laboratory parameters with the primary outcome was assessed with univariable logistic regression. Variables associated with primary outcome in univariable analysis with a cut-off p value <0.10 were entered into a multivariable model, and retained in the final model according to backward stepwise selection. Performance of the final multivariable logistic regression model was assessed using area under the receiver operating characteristic curve analysis.

Comparisons between groups were performed with the Student t-test for normally distributed variables, or Wilcoxon rank sum test for non-normally distributed variables. Youden's index was used to determine the optimal cut-off of quantitative variables for predicting primary outcome events. A 2-sided $p < 0.05$ defined statistical significance. All statistical analyses were performed with the software R (R Foundation for Statistical Computing, Vien, Austria).

Results

Patient population

Between September 2015 and July 2021, 45 patients (median age, 60 [51–66] years, 73% male) were treated with an Impella device (Impella CP in 42 patients, 93%, and Impella 2.5 in 3 patients, 7%) for cardiogenic shock, which was already present at hospital admission in 30 cases (67%), or developed during hospitalization in the remaining 15 (33%).

The etiology of CS was mainly ischemic in 37 patients (82%), while acute myocarditis was responsible of 3 cases (7%), and decompensated dilated cardiomyopathy in 5 (11%).

In the setting of acute coronary syndromes, Impella was used as early support before percutaneous coronary intervention (PCI) in 30% of patients.

The main baseline characteristics of registry population are reported in **Table 1**.

The median door to unloading time was 210 min (98–1,118 min), and median time spent with Impella support was 115 (67–200) h.

At admission, the mean Charlson comorbidity index was 4 ± 3, the median LVEF was 25% (15%–60%), median TAPSE 17 mm (10–26 mm), and median RVFAC 33% (15%–40%).

TABLE 1 Baseline characteristics of patients receiving impella support for cardiogenic shock ($n = 45$).

Risk factors and previous medical history	
Age, years, median (Q1–Q3)	60 (51–66)
Male gender, *n* (%)	33 (73)
Diabetes, *n* (%)	10 (22)
Smoking, *n* (%)	23 (51)
Hypertension, *n* (%)	23 (51)
Dyslipidaemia, *n* (%)	20 (44)
Previous acute coronary syndrome, *n* (%)	9 (20)
Previous PCI, *n* (%)	8 (18)
Previous CABG, *n* (%)	1 (2)
Previous heart failure episode, *n* (%)	3 (7)
Previous atrial fibrillation, *n* (%)	4 (9)
PAD, *n* (%)	3 (7)
Previous stroke, *n* (%)	1 (2)
COPD *n* (%)	5 (11)
Clinical and instrumental characteristics on admission	
Acute coronary syndrome, *n* (%)	37 (82)
Myocarditis, *n* (%)	3 (7)
Decompensated dilative cardiomyopathy, *n* (%)	5 (11)
Time from symptoms onset to hospitalization, min, median (Q1–Q3)	300 (110–2,880)
LVEF, %, median (Q1–Q3)	25 (16–30)
TAPSE, mm, median (Q1–Q3)	17 (14–18)
RVFAC, %, median (Q1–Q3)	33 (20–37)
PAPs, mmHg, median (Q1–Q3)	35 (30–43)
Multivessel disease, *n* (%)	24 (53)
PCI as revascularization, *n* (%)	35 (78)
CABG as revascularization, *n* (%)	0 (0)
Lactate value (mmol/L), median (Q1–Q3)	3.7 (2.0–6.2)
Charlson comorbidity index, median (Q1–Q3)	3 (2–5)
Haemoglobin (mg/dl), mean (SD)	12.8 ± 2.3
Troponin (ng/ml), median (Q1–Q3)	4,668 (18–125,000)
Creatinine (mg/dl), median (Q1–Q3)	1.1 (0.9–1.4)
Orotracheal Intubation, *n* (%)	38 (84)
NIV/CPAP, *n* (%)	22 (49)
Inotropic score, median (Q1–Q3)	8 (0–15)
Impella device data	
Impella CP, *n* (%)	42 (93)
Impella 2.5, *n* (%)	3 (7)
Time "door to unloading", min, median (Q1–Q3)	210 (98–1,118)
Duration of Impella support, h, median (Q1–Q3)	112 (67–192)

At impella insertion, the mean serum lactate level amounted to 4.4 ± 2.9 mmol/L, mean ScvO2 was 64.8 ± 11.3 mmHg and median inotropic score was 9.5 (0–15).

At the time of device support initiation, the median arterial pressure was 63 (60–70) mmHg, mean heart rate was 108.7 ± 24.3, and 84.3% of patients were on mechanical ventilation.

Inotropic score and serum lactate levels significantly decreased during impella support in total population (inotropic score: 8 [0–15] at baseline, 2 [0–9] after 48 h, $p = 0.01$; serum lactate: 3.7 [2.0–6.2] at baseline, 1.2 [1.0–1.6] after 48 h, $p = 0.01$).

Weaning from Impella and outcomes

Thirty-seven patients (82%) underwent weaning from Impella or Impella removal during hospitalization.

In fact, because of clinical and/or laboratory worsening, a total of 5 patients (11%) underwent an upgrade to ECMO support, while 2 patients (4.5%) received a durable LVAD. Those cases were considered Impella removal and were not counted in the analysis of Impella weaning.

In the remaining 30 cases, the reasons for weaning were clinical improvement in 22 patients, unmanageable suction alarms in 1 patient, purge pressure alarms in 2 patients, and other complications in 5 patients (1 with major bleeding, 4 with haemolysis).

In 22 of these cases (74%) a single weaning attempt was sufficient, while the rest of patients ($n = 8$, 26%) presented at least an episode of weaning failure and underwent successive attempts, until the device could be safely explanted. The median duration of weaning from Impella was 30 h (0–48).

Seventeen patients (38%) died during hospital stay, and nine patients (20%) died after weaning from Impella.

Considering the deaths after Impella weaning, four deaths were due to refractory cardiogenic shock, one to septic shock, one to

TABLE 2 Clinical, laboratoristic and instrumental characteristics of non-survivor and survivor patients after Impella weaning.

	Survivors ($n = 28$)	Non-survivors ($n = 9$)	p
Age, years, median (Q1–Q3)	57 (44–63)	66 (53–66)	0.10
Male gender, *n* (%)	19 (68)	7 (78)	0.70
Diabetes, *n* (%)	5 (18)	1 (11)	1
Smoking, *n* (%)	15 (54)	4 (44)	0.71
Hypertension, *n* (%)	12 (43)	6 (67)	0.27
Dyslipidaemia, *n* (%)	13 (46)	4 (44)	0.93
COPD, *n* (%)	3 (11)	1 (11)	1
PAD, *n* (%)	1 (4)	0 (0)	1
Ischemic etiology of CS	21 (75)	7 (78)	0.68
ICD/CRT, *n* (%)	0 (0)	3 (33)	**0.01**
Previous HF episode, *n* (%)	0 (0)	2 (22)	**0.054**
Charlson comorbidity index, mean (SD)	2.9 (1.4)	3.0 (1.4)	0.91
Orotracheal intubation, *n* (%)	22 (79)	8 (89)	0.66
CRRT, *n* (%)	8 (29)	7 (78)	**0.02**
NIV/CPAP, *n* (%)	15 (54)	4 (44)	0.71
Pre-PCI Impella implantation	8 (29)	3 (33)	0.22
Duration of Impella support, h, median (Q1–Q3)	120 (74–192)	130 (84–219)	0.55
Positive blood culture, *n* (%)	14 (50)	5 (56)	1
Baseline Haemoglobin (mg/dl), mean (SD))	12.5 (2.2)	13.1 (2.8)	0.58
Baseline Troponin (ng/ml) median (Q1–Q3)	392 (18–103,550)	21,000 (200–200,000)	0.26
Baseline creatinine (mg/dl), mean (SD)	0.98 (0.47)	1.1 (0.7)	0.14
Lactate at impella insertion (mmol/L), mean (SD)	2.8 (2.9)	2.5 (1.3)	0.47
LVEF (%) at Impella insertion, mean (SD)	21.5 (6.3)	20 (10)	0.13
TAPSE (mm) at Impella insertion, mean (SD)	16.4 (3.5)	16.1 (3.8)	0.83
RVFAC (%) at Impella insertion, mean (SD)	34 (13)	31 (10)	0.70
Inotropic score at Impella insertion, mean (SD),	4 (14)	11 (5)	0.35
PAPs (mmHg) median (Q1–Q3)	35 (30–40)	38 (31–45)	0.71

Bold values represents statistically significant p values.

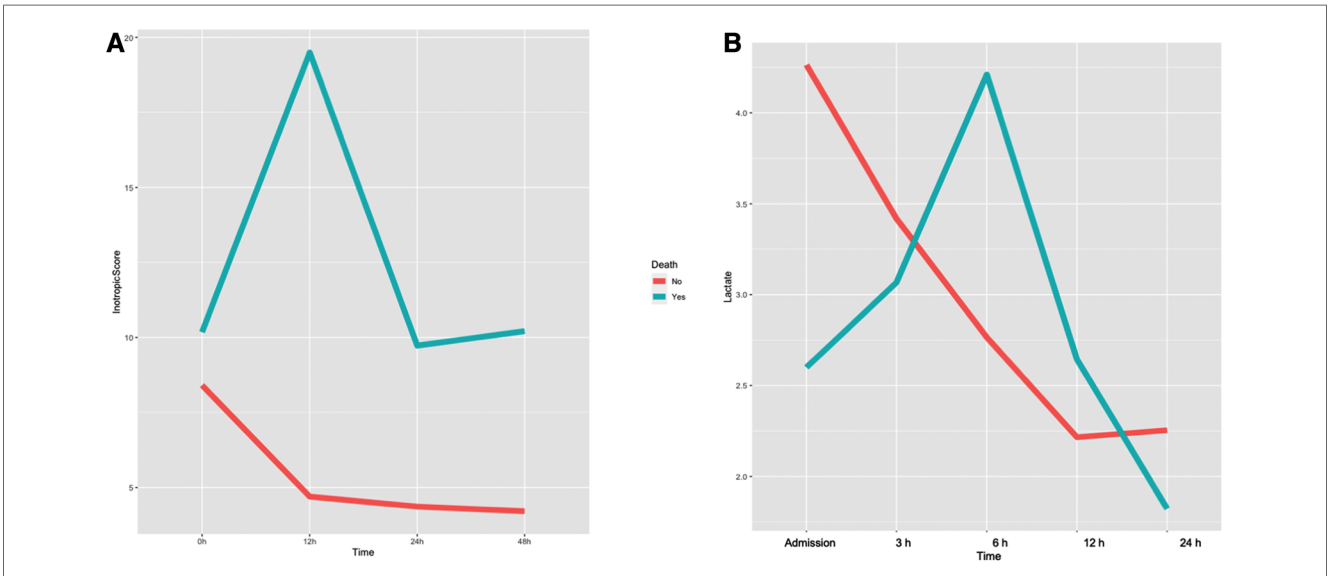

FIGURE 1
Variation of inotropic score (A) and arterial lactates (B) during impella support in survivor and non-survivor patients after Impella weaning.

TABLE 3 Univariable predictors of death after weaning, selected for having univariable $p < 0.10$.

Variable	OR	Lower CL	Upper CL	p Value
Δ lactate during first 12–24 h of weaning (per 100% variation)	10.84	1.17	100.80	0.036
Lactate after 24 h of weaning (per unit variation)	6.32	1.02	39.30	0.048
LVEF at the onset of weaning (per unit variation)	0.88	0.77	1.00	0.056
Inotropic score after 24 h of weaning (per unit variation)	1.07	0.99	1.15	0.082
Time quartile of hospital admission	0.897	0.795	1.011	0.086

TABLE 4 Multivariable predictors of death after weaning.

Variable	OR	Lower CL	Upper CL	p Value
LVEF at the onset of weaning (per unit variation)	0.87	0.76	0.99	0.039
Δ lactate during first 12–24 h of weaning (per 100% variation)	25.11	1.2	524.32	0.038

refractory ventricular fibrillation, one to acute respiratory distress syndrome and two to intracranial hemorrhage.

The etiology of CS in non-survivors patients after impella weaning was ischemic in 7 cases and decompensated dilated cardiomyopathy in the remaining 2 cases. With regard to ischemic cause, Impella support was implanted before PCI in 3 non-survivor patients.

Characteristics of non-survivor patients after Impella weaning when compared to those patients that successfully overcame Impella weaning are reported in **Table 2**. Inotropic score and serum lactate variations in survivor and non-survivor patients are represented in **Figures 1A,B**. Non-survivors more commonly had a previous history of known HF ($p = 0.054$) and an implanted ICD-CRT ($p = 0.01$), and were more frequently treated with continuous renal replacement therapy (CRRT; $p = 0.02$).

In univariable logistic regression analysis, Δ lactate during the first 12–24 h of weaning, lactate value after 24 h of weaning (per unit variation), baseline LVEF (per unit variation), and inotropic score after 24 h of weaning (per unit variation), were associated with death, as reported in **Table 3**.

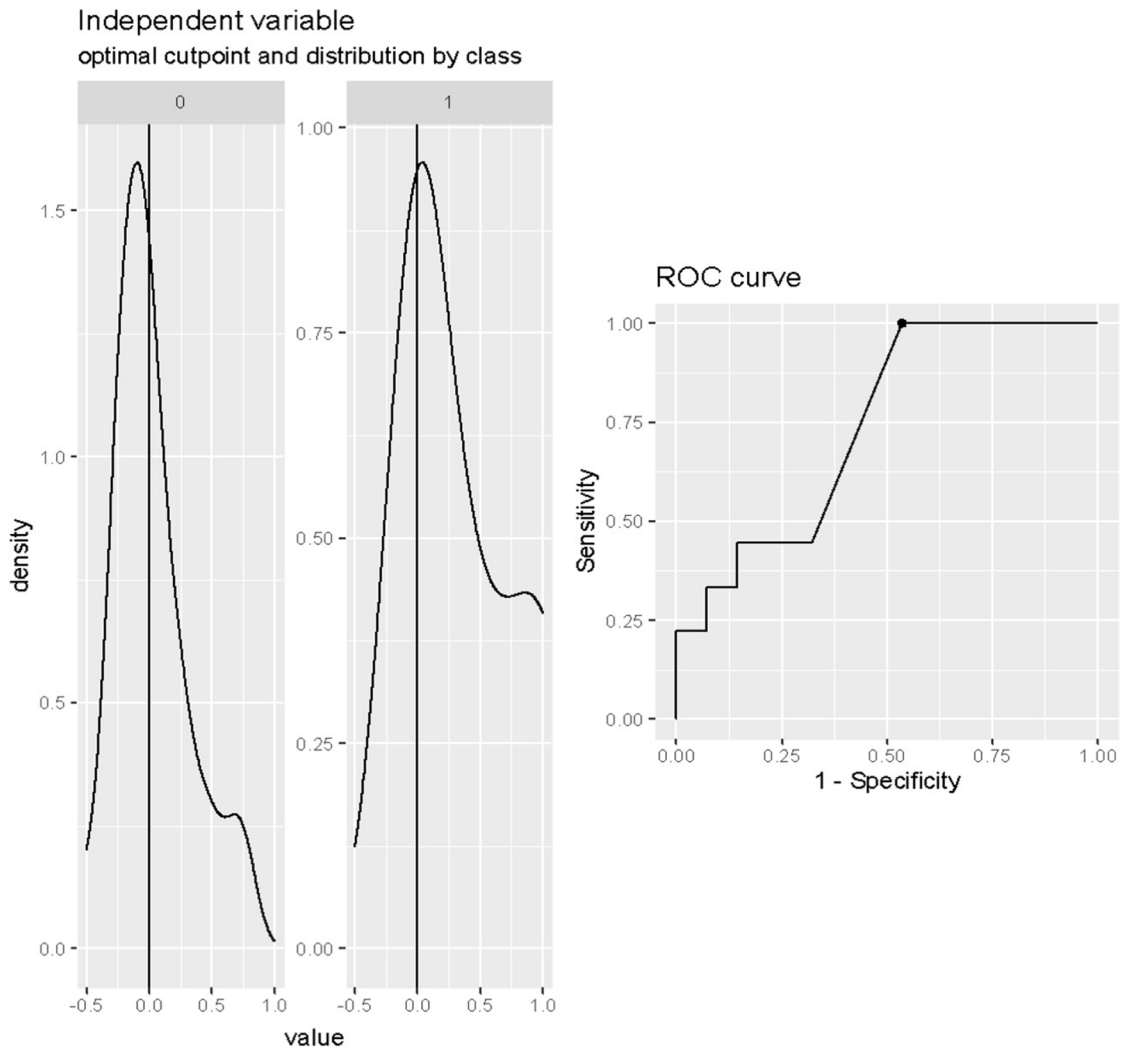

FIGURE 2
Cut-off analysis of Δ lactate (%) during first 12–24 h of weaning in predicting death after weaning. Cut-off = 0%; SE = 1; SP = 0.46; accuracy = 0.5946.

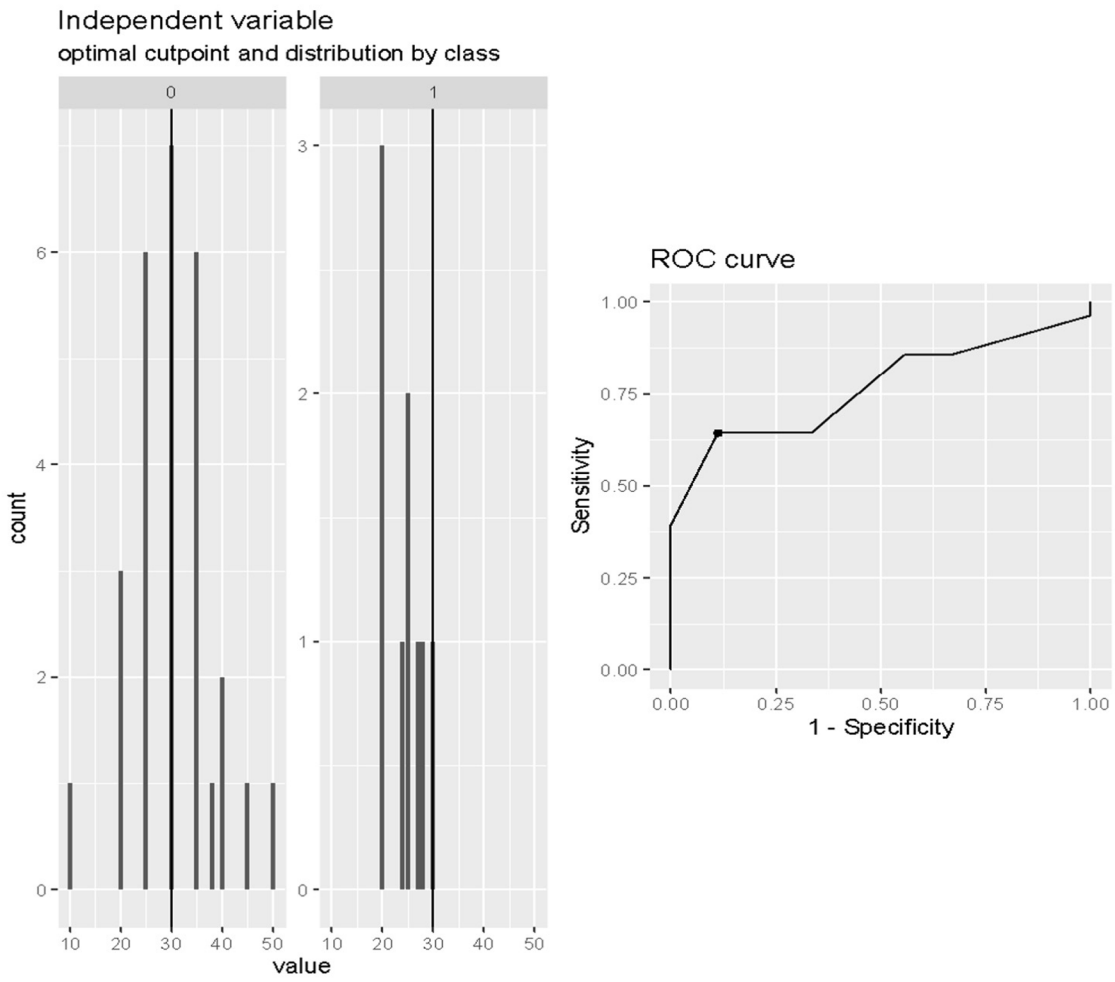

FIGURE 3
Cut-off analysis of LVEF at onset of weaning in predicting death after weaning. Cut-off = 0.30; SE = 0.64; SP = 0.89; accuracy = 0.70.

Stepwise multivariable logistic regression identified baseline LVEF and Δ lactate during the first 12–24 h of weaning as the most accurate predictors of death after weaning (Table 4).

The optimal cut-off value of the Δ lactate during the first 12–24 h of weaning for the prediction of death after weaning was any value more than 0% (Cut-off = 0%; SE = 1; SP = 0.46; accuracy = 0.5946), as shown in Figure 2.

The optimal cut-off value of the LVEF in predicting death after weaning was 30% (Cut-off = 0.30; SE = 0.64; SP = 0.89; accuracy = 0.70) as reported in Figure 3.

The ROC analysis indicated 80% accuracy (95% confidence interval = 64%–96%) using the two variables in combination to predict death after weaning from Impella (Figure 4).

Patients' characteristics with unsuccessful first attempt of Impella weaning

As reported in Table 5, patients with an unsuccessful first attempt of Impella weaning, despite similar baseline characteristics (age, gender, comorbidities) when compared to patients who positively achieved a first attempt of weaning, presented a longer total duration of Impella support ($p = 0.006$) and weaning ($p = 0.0098$), higher level of maximum creatinine ($p = 0.0167$), higher lactate at impella insertion ($p = 0.067$), and inotropic score at onset of weaning ($p = 0.047$).

In-hospital complications

No major device malfunctions were reported in the entire population. Displacement of Impella requiring repositioning procedures occurred in 23 cases.

Red blood cell transfusion was the most frequent event for the entire cohort (70%). Serial assessment of haptoglobin levels revealed an overall incidence of haemolysis in 51% of patients, although clinically significant haemolysis occurred in 4 cases (8.8%).

No retroperitoneal hemorrhage (RPH) was reported, while a patient (2.2%) developed cardiac tamponade during Impella support. Bleeding at the Impella access site was described in 14 patients (31%), and six patients (13%) experienced acute limb ischaemia.

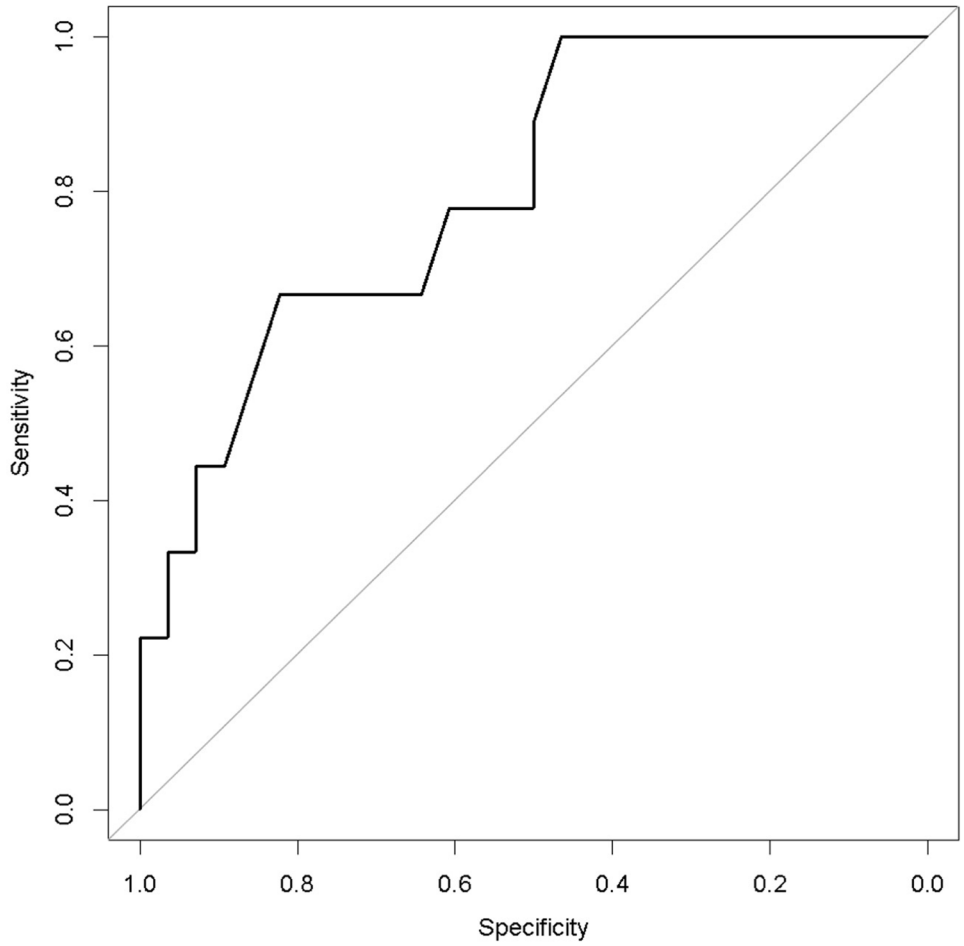

FIGURE 4
Receiver operating characteristic curve analysis of the multivariable prediction model for death after weaning from impella (accuracy = 0.80).

Two patients were diagnosed with ischemic stroke (4.4%) and other 2 with haemorrhagic stroke (4.4%).

Continuous renal replacement therapy (CRRT) was required in 16 patients (36%).

Twenty-eight patients (62%) developed fever during Impella support but only 12 of them (42%) presented positive blood cultures.

In hospital mortality trend analysis

A clear temporal trend in in-hospital mortality was evident when considering the rate along time defined as quartile (April 2014–August 2018; August 2018–October 2019; October 2019–July 2020; July 2020–July 2021), with a significant reduction in the risk of death as reported in **Figure 5** (OR = 0.523, 95%, CI = 0.275–0.992, $p < 0.05$).

Discussion

In this retrospective study we found that two easily accessible parameters could accurately predict the risk of death after weaning.

As Impella use is rapidly increasing among patients with CS, it is urgent to define the right way to perform the weaning and predict a successful process until explantation. Clinical judgment is not enough to accurately predict patient outcomes.

The weaning criteria differ widely among centres. A recent survey reported that surrogates of hemodynamic stability and end-organ perfusion are the most commonly used parameters to guide the weaning process, which is usually considered in the presence of adequate oxygenation and ventilation, followed by the lowest need of vasoactive agent (18). However, the same authors underlined the numerous knowledge gaps in this field, especially the paucity of data correlating hemodynamic estimates to imaging variables of ventricular recovery and, most importantly, to clinical outcomes.

In this scenario, our study revealed that an imaging criterion (LVEF at onset of weaning) and an organ perfusion surrogate (Δ lactate during the first 12–24 h of weaning) were the most accurate predictors of death after weaning with an accuracy of 80% when the two variables were taken together. Both parameters are easily accessible and their use could help every cardiologist dealing with cardiogenic shock and Impella support.

TABLE 5 Characteristics of patients with unsuccessful and successful first attempt of Impella weaning.

	Successful first attempt of Impella weaning ($n = 22$)	Unsuccessful first attempt of Impella weaning ($n = 8$)	p
Age, years—mean (SD)	58 (48–65)	60 (57–67)	0.76
Female gender, *n* (%)	5 (23)	3 (38)	0.64
Diabetes, *n* (%)	4 (18)	2 (25)	0.65
Smoking (past or present), *n* (%)	13 (59)	5 (63)	1
Hypertension, *n* (%)	10 (46)	5 (63)	0.68
Dyslipidaemia, *n* (%)	12 (55)	3 (38)	0.68
COPD, *n* (%)	3 (14)	1 (13)	1
PAD, *n* (%)	1 (5)	0 (0)	1
ICD/CRT, *n* (%)	1 (5)	0 (0)	1
Previous HF episode, *n* (%)	0 (0)	0 (0)	1
Charlson comorbidity index. mean (SD)	3.0 (1.9)	3.4 (1.2)	0.53
Orotracheal intubation, *n* (%)	17 (77)	7 (88)	0.92
CRRT, *n* (%)	6 (27)	4 (50)	0.38
NIV/CPAP, *n* (%)	16 (73)	6 (75)	1
Total Duration of Impella support, h, median (Q1–Q3)	94 (69–146)	201 (179–227)	**0.006**
Hours with the highest Impella P level, median (Q1–Q3)	12 (6–29)	39 (20–53)	0.15
Total duration of weaning, h, mean (SD)	34.8 (20.9)	76.4 (33.8)	**0.0098**
Positive blood culture, *n* (%)	10 (46)	4 (50)	1
Baseline Haemoglobin (mg/dl), mean (SD)	13.2 (2.3)	12.7 (2.1)	0.56
Baseline Troponin (ng/ml), median (Q1–Q3)	11,417 (82–148,250)	10,600 (50–125,000)	0.62
Troponin at onset of weaning, median (Q1–Q3)	7,254 (19–36,765)	57 (2–15,304)	0.32
Baseline creatinine (mg/dl), median (Q1–Q3)	0.98 (0.78–1.23)	1.2 (1.04–1.44)	0.17
Maximum creatinine (mg/dl), median (Q1–Q3)	1.32 (0.94–3.03)	4.13 (1.73–4.92)	**0.0167**
Baseline Lactate, Median (Q1–Q3)	2.1 (1.4–4.9)	3.3 (2.3–5.1)	0.17
Lactate at impella insertion, median (Q1–Q3)	2.4 (1.8–3.4)	4.1 (2.5–5.1)	**0.067**
Lactate at onset of weaning, median (Q1–Q3)	1.0 (0.8–1.3)	1.2 (0.9–1.2)	0.60
Heart rate at onset of weaning, mean (SD)	87 (16)	88 (18)	0.96
Mean arterial pressure at onset of weaning, median (Q1–Q3)	71 (65–75)	73 (72–75)	0.45
LVEF (%) at Impella insertion, median (Q1–Q3)	22 (20–29)	20 (15–25)	0.38
LVEF (%) at onset of weaning, median (Q1–Q3)	30 (25–35)	26 (24–30)	0.20
TAPSE (mm) at Impella insertion, mean (SD)	17 (3)	17 (3)	0.79
TAPSE (mm) at onset of weaning, median (Q1–Q3)	19 (17–19)	19 (17–19)	0.72
RV dysfunction during Impella support, *n* (%)	7 (32)	2 (25)	1
Inotropic score at Impella insertion, median (Q1–Q3)	4 (0–10)	10 (4–16)	0.25
Inotropic score at onset of weaning, median (Q1–Q3)	3 (0–10)	14 (9–18)	**0.047**
PAPs at Impella insertion (mmHg), median (Q1–Q3)	40 (33–40)	30 (30–36)	0.29

Bold values represents statistically significant p values.

Any increase in lactates should trigger a prompt answer, postponing the weaning process or modifying drugs therapy while reducing circulatory support. No studies have previously defined the entity of arterial lactate increase during weaning correlating with death: we found that any increase is associated with an unsuccessful weaning process.

In a similar manner, the LVEF cut-off value correlating with fatal outcome was 30%.

The persistence of a severe left ventricular systolic dysfunction during Impella unloading is the expression of a pronounced and serious alteration of pump function and should push cardiologists to carry out alternative strategies to prevent the failure of weaning as a inodilator infusion [for instance levosimendan, as it commonly happens in venoarterial ECMO weaning (22–24)] or, in the worst cases the upgrade to an ECMO support or consideration for long-term LV support or heart transplantation, after a case-by-case discussion.

We also found that patients with first unsuccessful attempt of Impella weaning presented a longer duration of Impella support and weaning, worst metabolic and organ characteristics and higher gravity in term of inotropic score, underscoring the greater general complexity of these patients.

Our registry also provides insight into complications of patients treated with Impella.

We describe an overall in-hospital mortality of 38%, that is lower when compared with other registry data (10, 25, 26). Moreover we found a significant reduction in the risk of death over time.

Complications rate is in agreement with previous reports (5–10) and consisted of bleeding at the Impella access site (31%), acute limb ischaemia (3%), clinical significant haemolysis (8.8%), stroke (8.8%) and cardiac tamponade (2.2%). More than half of patients (62%) developed fever during Impella support but 42% of them presented positive blood cultures.

Management and monitoring of such devices requires a level of long-term expertise in high volume tertiary centres with 24 h/7 days availability of trained intensivists and echocardiographers, together with cardiac and vascular surgeons to manage complications.

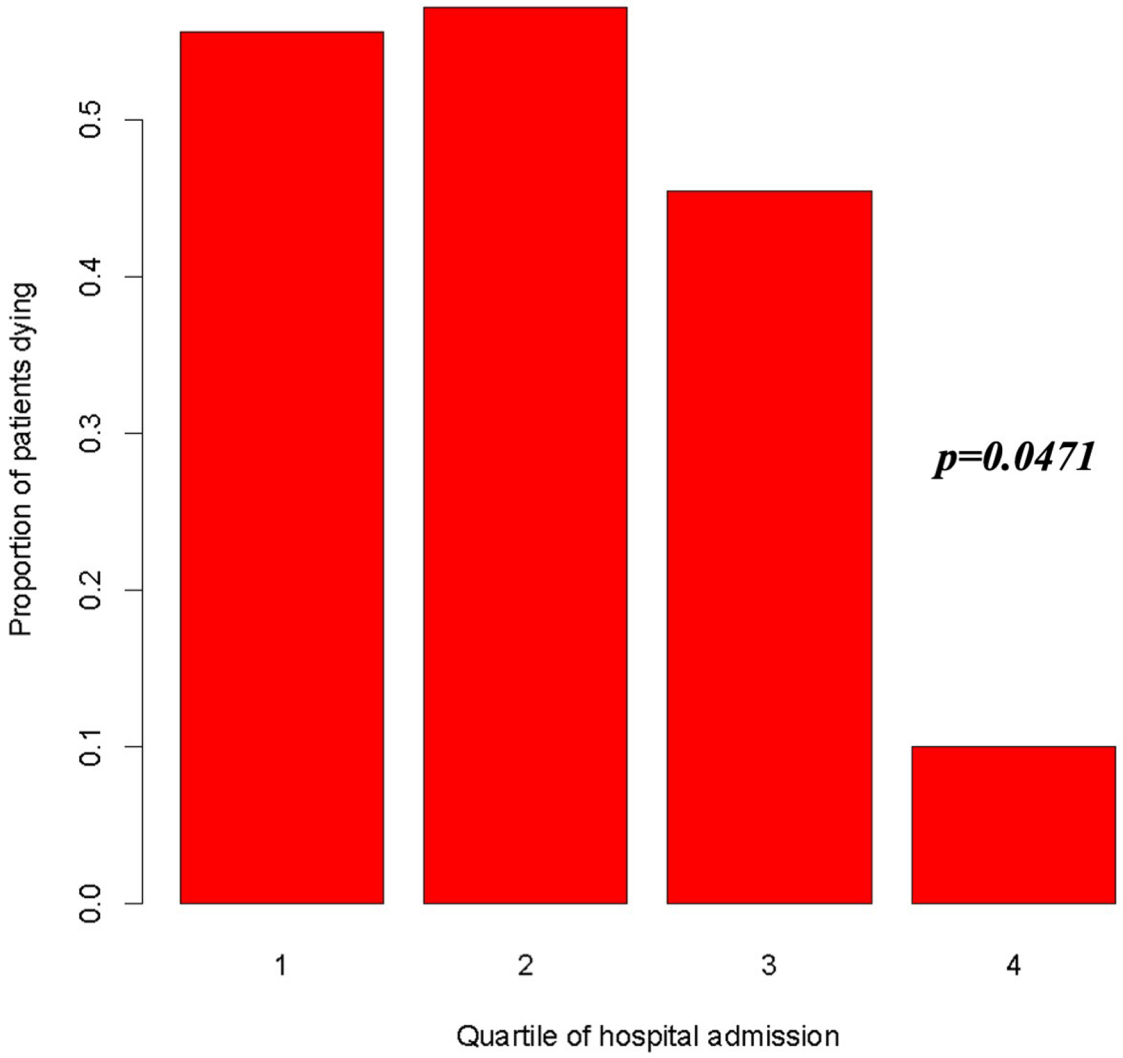

FIGURE 5
Risk of death according to quartile of admission period (1st quartile: April 28, 2014–August 20, 2018; 2nd quartile: August 20, 2018–October 14, 2019; 3rd quartile: October 14, 2019–July 12, 2020; 4th quartile: July 12, 2020–July 3, 2021). OR = 0.523, 95%, CI = 0.275–0.992, $p = 0.0471$.

Limitations

There are some important limitations to consider. First, the nature of reported data is observational from a retrospective registry, and causal relation between Impella weaning and outcomes cannot be ascertained. Moreover, our study involved a small number of patients in a single center, and all therapeutic decisions were left to the treating physicians' discretion, in the absence of a standardized protocol; all these aspects could arise the possibility of selection bias. However, patient management was in line with expert consensus recommendations, in a field in which no patient-level data is currently available. Our data may represent an important preliminary experience in the complex field of weaning from mechanical circulatory support, and stimulate further clinical research.

Conclusions

This single-center experience on Impella weaning in cardiogenic shock showed that two easily accessible parameters as LVEF at onset of weaning and a change in serum lactate levels during the first 12–24 h of weaning were the most accurate predictors of death after weaning. In the absence of a defined and universally recognized weaning protocol, the use of these two widely available parameters could help in the identification of the appropriate timing and performance of Impella weaning.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM and MM contributed to the design of the registry, to the data collection, to the analysis and interpretation of the results and to the writing of the manuscript. AA, UF, LA, MS contributed to data collection, interpretation of the results and final revision of the manuscript. PC contributed to the design of the registry and to the analysis of the results. CM contributed to the conception of the study, data interpretation, and revision of the paper. TP, AM, EN, AM, MD, AD, GP contributed to the interpretation of the results and final revision of the manuscript. 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.

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EDITED BY
Fabio Guarracino,
Azienda Ospedaliero Universitaria Pisana, Italy

REVIEWED BY
Pietro Bertini,
Azienda Ospedaliero Universitaria Pisana, Italy
Markus Velten,
University Hospital Bonn, Germany

*CORRESPONDENCE
Sascha Treskatsch
✉ sascha.treskatsch@charite.de

†These authors have contributed equally to this work

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Influence of timing of Levosimendan administration on outcomes in cardiac surgery

Fridtjof Schiefenhövel[1,2,3], Christian Berger[4], Liubov Penkova[5], Herko Grubitzsch[6], Bernhard Haller[2], Alexander Meyer[6,7], Matthias Heringlake[8], Michael Sander[9], Joachim M. Erb[10], Felix Balzer[3†] and Sascha Treskatsch[4*†]

[1]Department of Anaesthesiology and Intensive Care (AINS), Medical Center Rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany, [2]Institute for Artificial Intelligence and Informatics in Medicine (AIIM), Chair of Medical Informatics, Medical Center Rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany, [3]Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Informatics, Berlin, Germany, [4]Department of Anaesthesiology and Intensive Care Medicine, Charité Campus Benjamin Franklin, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität and Humboldt Universität zu Berlin, Berlin, Germany, [5]Department of Anaesthesiology and Intensive Care Medicine, Charité Campus Mitte and Charité Campus Virchow, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität and Humboldt Universität zu Berlin, Berlin, Germany, [6]Klinik für Kardiovaskuläre Chirurgie, Campus Virchow Klinikum, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität and Humboldt Universität zu Berlin, Berlin, Germany, [7]Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany, [8]Department of Anaesthesia, Heart and Diabetes Center, Klinikum Karlsburg, Karlsburg, Germany, [9]Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Gießen UKGM, Justus-Liebig University Gießen, Gießen, Germany, [10]Clinic for Anaesthesiology, Intermediate Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland

Purpose: Though a subgroup analysis has shown improved survival for patients suffering severely reduced ventricular function undergoing coronary artery bypass grafting, RCTs were not able to demonstrate overall beneficial effects of perioperative Levosimendan in cardiac surgery. This might be due to Levosimendan's pharmacokinetics reaching a steady-state concentration only 4–8 h after administration. Thus, this study now analysed the influence of timing of Levosimendan administration on perioperative outcome in cardiac surgery patients preoperatively presenting with severely reduced ventricular function and therefore considered at high-risk for intra- or postoperative low cardiac output syndrome. We hypothesized that prolonged preoperative Levosimendan administration ("preconditioning") would reduce mortality.

Methods: All adult patients undergoing cardiac surgery between 2006 and 2018 perioperatively receiving Levosimendan were included in this retrospective, observational cohort study ($n = 498$). Patients were stratified into 3 groups: Levosimendan started on the day prior to surgery ("preop"), Levosimendan started on the day of surgery ("intraop") or post ICU admission ("postop"). After propensity score matching (PSM) was performed, outcomes defined according to proposed standard definitions for perioperative outcome research were compared between groups.

Abbreviations

AHTN, arterial hypertension; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CRI, chronic renal insufficiency; CRRT, continuous renal replacement therapy; IABP, intra-aortic balloon pump; ICU, intensive care unit; IMCU, intermediate care unit; LCOS, low cardiac output syndrome; LVEF, left ventricular ejection fraction; NYHA, New York heart association functional classification; PAD, peripheral arterial disease; PAH, pulmonary arterial hypertension; PDMS, patient data management system; PSM, propensity score matching; RCT, randomized controlled trial; SMD, standardized mean difference; SOP, standard operating procedure; STROBE, strengthening the reporting of observational studies in epidemiology statement; VAD, ventricular assist device.

Results: After PSM, there were no significant differences in patients' characteristics, comorbidities and type/priority of surgery between groups. Compared to intraop or postop Levosimendan treatment, preop treated patients had significantly lower in-hospital-mortality (preop vs. intraop. vs. postop = 16,7% vs. 33,3% vs. 42,3%), duration of mechanical ventilation and rate of continuous renal replacement therapy.
Conclusions: Prolonged preoperative treatment with Levosimendan of cardiac surgery patients preoperatively presenting with severely reduced left ventricular function might be beneficial in terms of postoperative outcome. Our results are in line with recent experts' recommendations concerning the prolonged perioperative use of Levosimendan. We strongly recommend that future randomized trials include this "preconditioning" treatment as an experimental arm.

KEYWORDS

Levosimendan, cardiac surgery, high-risk patients, low cardiac output syndrome, mortality, outcome

Introduction

Levosimendan is a calcium-sensitising inotropic drug, which increases cardiac contractility and reduces cardiac afterload without significantly increasing myocardial oxygen consumption (1). Several trials in patients suffering from acute heart failure have shown benefits of Levosimendan treatment (2–6), although one such trial failed to show benefits (2–7). The perioperative use of Levosimendan in cardiac surgery and its effect on outcome of patients with preoperatively reduced left ventricular function has been the subject of several large randomized controlled trials (RCT) (8–10). While the results of these have not shown a clear benefit across the whole range of cardiac surgery patients, subgroup analysis has shown a significantly improved survival for patients suffering from coronary artery disease and severely reduced ventricular function undergoing coronary artery bypass grafting (CABG) (8, 11). Furthermore, another prospective study comparing an historical cohort with a prospective one (12) and one randomized trial (13) have shown benefits of prolonged preoperative treatment with Levosimendan ("preconditioning") in patients with moderate to severe left ventricular dysfunction undergoing elective coronary artery bypass surgery.

One possible reason why the abovementioned RCTs have failed to show a clear benefit of perioperative Levosimendan might be its peculiar pharmacokinetics. The steady-state concentration of Levosimendan is only reached after 4–8 h, and its active metabolite, first detectable 12 h after administration, peaks at 48–78 h after the beginning of administration (14, 15). We thus hypothesize that the optimal perioperative administration of Levosimendan might have to start well before cardiac surgery, e.g., 12–24 h prior. In a previous retrospective study, early administration of Levosimendan, i.e., start of administration following the induction of anaesthesia or start of administration intraoperatively, was associated with increased survival in contrast to a late administration postoperatively on intensive care unit (ICU) (16).

With respect to these data, the standard operating procedure (SOP) concerning the perioperative use of Levosimendan has been changed at a tertiary hospital in 2013 towards a strong recommendation to preoperatively screen all patients undergoing cardiac surgery for severely reduced ventricular function and to precondition such patients regarded as being at high-risk for developing low cardiac output syndrome (LCOS) with Levosimendan one day prior to surgery. In this retrospective single-centre cohort study, we have now analysed effects of timing of Levosimendan administration on perioperative outcome in a large cohort of cardiac surgery patients. As primary objective, we hypothesized that prolonged preoperative (12–16 h) Levosimendan treatment as a routine clinical practice in a heterogeneous cohort of cardiac surgery patients exhibiting preoperatively severely reduced left ventricular function considered high-risk reduces mortality. As secondary objective, we aimed to determine if potential outcome effects of Levosimendan differed between isolated CABG and other cardiac surgical procedures like isolated valve or combined CABG and valve surgery.

Materials and methods

Design and inclusion criteria

After approval of the Charité Ethics Committee, Berlin, Germany (study ID no.: EA4/239/19), we reviewed charts and data derived from 2 electronic patient data management systems (COPRA System GmbH, Sasbachwalden, Germany, and SAP AG, Walldorf, Germany). The requirement for informed consent from the study subjects was waived by the Ethics Committee due to the retrospective nature of the study. This observational cohort study was performed in accordance with the relevant guidelines and regulations and based on previously published approaches and in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (STROBE) (17–19). All patients admitted to our intensive care units between 2006 and 2018 scheduled for or after on-pump cardiac surgery identified by German OPS codes (5–35, 5–36; excluding 5–35A, i.e., minimally invasive valve replacement) that were treated with Levosimendan were eligible for inclusion in the study. Perioperative clinical data were extracted from the two

digital/electronic patient data management systems and inserted into an anonymized study database. Patients under the age of 18 at the time of surgery were excluded.

Perioperative management

Cardiac surgery, anaesthesia and hemodynamic management were performed in accordance with the department's SOPs displaying the most recent recommendations at that respective time (20). Normothermic cardiopulmonary bypass (CPB) was established with a flow of 2.5 L/min/m^2 and an arterial pressure ≥60 mmHg. Cardioplegic arrest was induced and maintained by intermittent administration of antegrade warm potassium-enriched blood (21) or Bretschneider's solution according to the surgeons preference.

Perioperative goal-oriented hemodynamic support was established according to institutional standards guided by the German S3 guidelines using echocardiography as the primary diagnostic/monitoring tool (20, 22). In case of difficult CPB weaning despite hemodynamic optimization, an Intra-Aortic Balloon Pump (IABP) and/or ventricular assist device (VAD) were placed intraoperatively according to the team's assessment. After chest closure, all patients were transferred intubated and mechanically ventilated to the ICU aiming at a fast-track concept (e.g., extubation within 6 h when cardiopulmonary stable). In the following patients were then transferred to the IMCU and afterwards to the normal ward before hospital discharge.

Standard operating procedure concerning Levosimendan

Before 2013, the respective SOP allowed the administration of Levosimendan based on an individualized approach. Additionally, elective cardiac patients were not actively screened preoperatively for underlying heart failure in order to routinely administer Levosimendan. Levosimendan was thus most often infused on the day of surgery or later at the discretion of the attending cardiac anaesthesiologist if severe impairment of left ventricular systolic function (LVEF ≤35%) and/or LCOS became clinically meaningful. Most importantly, Levosimendan was not administered within a prespecified pre-emptive clinical pathway.

From 2013 onwards, the revised SOP called for active preoperative screening of all cardiac surgery patients to identify those exhibiting severe impairment of left ventricular systolic function (LVEF ≤35%). Involving our colleagues from the department of cardiac surgery in a shared decision-making process, Levosimendan was then preoperatively administered in these patients. This was performed in an ICU/IMCU setting under invasive blood-pressure measurement. Typically, intravenous administration started in the early afternoon one day before surgery, resulting in 70%–80% of the loading dose of Levosimendan (12,5 mg, see below) having been administered before the induction of anaesthesia, with the remaining portion continuing to be administered afterwards. Levosimendan was always administered as a single continuous infusion (12.5 mg Levosimendan in 50 ml 5% Glucose) at a rate of 0.1 µg/kg per minute, and patients treated with Levosimendan did not receive phosphodiesterase-III inhibitors for at least 5 days.

For all other cardiac surgical patients, the recommendation concerning the administration of Levosimendan remained unchanged, i.e., allowing an individualized approach.

Definition of groups

All digital records of patients undergoing major cardiac surgery between 2006 and 2018 were filtered for the administration of Levosimendan. We then stratified patients into three groups: Patients whose Levosimendan administration started on the day prior to surgery ("preop"), i.e., having been treated prolonged preoperatively. As mentioned before, this preconditioning was performed on ICU/IMCU, depending on capacity, under invasive blood-pressure measurement. Patients whose first administration of Levosimendan started on the day of surgery, i.e., in the operating theatre during surgery or the associated anaesthesiological procedures, were labelled "intraop". Patients who received the first dose of the drug postoperatively on ICU were labelled "postop". We included only those patients who received the first administration up to 36 h before the initial cardiac surgery or up to 120 h afterwards. See Consort flowchart (**Supplementary Figure S3**) for an overview.

Outcome variables

Outcomes were defined according to proposed standard definitions for perioperative outcome research (23). ICU mortality was the study's primary outcome. In-hospital mortality, length of stay in-hospital and ICU, duration of invasive mechanical ventilation, incidence of renal dysfunction defined by KDIGO stage greater than or equal to 1 (24), and the need of continuous renal replacement therapy (CRRT) excluding cases with pre-existing chronic renal insufficiency were chosen as secondary outcomes. We calculated continuous outcomes like length of stay and mechanical ventilation twice: once an aggregated value including all patients in this group, once excluding patients who had died and reporting the aggregated value only for survivors. The reason being that we consider it valuable to report continuous outcomes that have been corrected for biases, e.g., early deaths.

Statistical analysis

Statistical analyses of the anonymized dataset were undertaken with a p value below 0.05 regarded as significant. Significance among groups was analysed by t-test or ANOVA in the case of continuous normal-distributed values, by the nonparametric Kruskal-Wallis test in the case of non-normal distributed values and by chi-squared or Fisher's exact tests for qualitative data. Results were given as median and interquartile range in non-normal distributed values, otherwise

mean ± standard deviation. Numbers with percentages characterize qualitative observations. All tests should be understood as constituting explorative analysis, as no adjustment for multiple testing has been made. Propensity score matching (PSM) was performed on the variables age, sex, type of surgery, surgical urgency, Charlson Comorbidity Index, congestive heart failure, NYHA greater or equal to 3, pulmonary hypertension, chronic obstructive pulmonary disease, arterial hypertension, peripheral arterial disease and chronic renal insufficiency. These variables were chosen because of their known impact on postoperative outcome. Matching method was "nearest neighbour", ratio was 1, and caliper was set to 0.2; matching was done in two rounds, i.e., both the group of patients that was treated with Levosimendan intraoperatively and the group that was treated with Levosimendan postoperatively was matched to the group that was preconditioned with Levosimendan. (S)MDs were depicted graphically for all matchings performed in the supplemented loveplots. Statistical analyses were performed using the R Project of Statistical Computing 4.3.0 (25); additionally we used the packages cobalt 4.5.1 (26), compareGroups 4.7.0 (27), ggpubr 0.6.0 (26), MatchIt 4.5.3 (28), tableone 0.13.2 (29) and tidyverse 2.0.0 (30).

Results

Study cohort

Out of 11,198 patients that underwent on-pump cardiac surgery during the specified period, 498 received Levosimendan during their perioperative index stay within 36 h before the start of the operation and up to 120 h after the start of the operation (see Consort flowchart, **Supplementary Figure S3**).

Timing of Levosimendan

The change in our hospital's SOP led to a drastically altered timing of Levosimendan. As can be seen in **Figure 1**: the number of Levosimendan-preconditioned patients increased strongly in the years following 2013 (graph uses matched population). Please find detailed analysis of distribution of delays between start of Levosimendan treatment and start of operation in **Supplementary Figure S1** (graph uses matched patients). See **Supplementary Figure S2** for absolute numbers of unmatched population.

Morphometry

Patients' characteristics and outcome measures for the unmatched study population are presented in **Supplementary Tables S1 and S2**. Baseline characteristics of the resulting matched groups of patients that received Levosimendan within the specified time frame are shown in **Table 1**. After PS matching, there were no significant differences in age, sex, type of intervention, priority of surgery and selected pre-existing medical conditions between the different groups. For a graphical presentation of standardized mean differences of variables used for matching, see corresponding love plots in the supplements. The majority of patients was male and received elective CABG surgery. For subgroup analyses of matched patients who received either elective CABG or valve or combined surgery see **Supplementary Tables S3–S6**. For an analysis of a subset of patients, excluding patients who received Levosimendan intra- or postoperatively after January 2013, see **Supplementary Tables S7 and S8**.

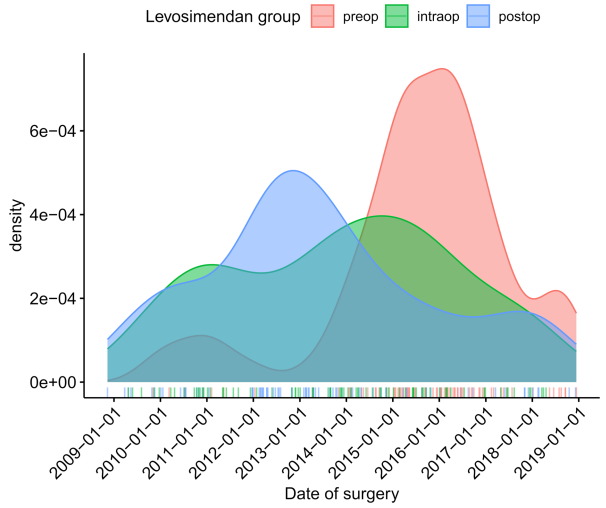

FIGURE 1
Timing of Levosimendan administration of matched population in normalized fractions (density plot).

Outcome parameters

After matching, preconditioned patients had significantly lower ICU- and in-hospital-mortality, duration of mechanical ventilation and rate of continuous renal replacement therapy (CRRT) (**Table 2**) when compared to patients who received Levosimendan on the day of the surgery or later. Length of ICU stay, length of overall hospital stay and duration of mechanical ventilation were shorter in all groups when deceased patients were excluded, since patients who died during their hospital stay died relatively early in the postoperative phase. See results of unmatched patients in **Supplementary Table S2**. The results of the unmatched subgroup of patients undergoing elective CABG surgery and the subgroup of patients undergoing elective combined surgery or valve surgery are consistent with abovementioned results and show an even lower rate of adverse outcomes in the preop group when compared to the groups that received Levosimendan later. See **Supplementary Tables S3–S6** for all morphometrical and outcome parameters of these subgroups.

Discussion

Our study has several findings of note: postoperative Levosimendan administration following cardiac surgery to

TABLE 1 Baseline characteristics.

	[ALL]	Preop	Intraop	Postop	P. overall	*N*	MD
	N = 234	*N* = 78	*N* = 78	*N* = 78			
Age*	71.0 [62.0; 76.0]	71.0 [62.0; 75.0]	71.0 [63.0; 76.0]	69.5 [61.0; 76.0]	0.716	234	0.089
Sex*					0.543	234	0.117
M	197 (84.2%)	66 (84.6%)	63 (80.8%)	68 (87.2%)			
W	37 (15.8%)	12 (15.4%)	15 (19.2%)	10 (12.8%)			
BMI	27.1 [24.4; 30.3]	27.6 [23.6; 30.1]	26.9 [24.5; 30.3]	27.2 [24.9; 30.6]	0.965	195	0.049
Type of surgery*					0.986	234	0.064
CABG	155 (66.2%)	50 (64.1%)	52 (66.7%)	53 (67.9%)			
Combined	27 (11.5%)	10 (12.8%)	9 (11.5%)	8 (10.3%)			
Valve	52 (22.2%)	18 (23.1%)	17 (21.8%)	17 (21.8%)			
Urgency*					0.876	234	0.054
Elective	154 (65.8%)	53 (67.9%)	51 (65.4%)	50 (64.1%)			
Urgent/emergent	80 (34.2%)	25 (32.1%)	27 (34.6%)	28 (35.9%)			
CCI*	6.00 [5.00; 8.00]	6.50 [5.00; 8.00]	6.00 [5.00; 8.00]	6.00 [5.00; 7.00]	0.756	234	0.053
CHF*	217 (92.7%)	73 (93.6%)	71 (91.0%)	73 (93.6%)	0.776	234	0.064
NYHA ≥3*	203 (86.8%)	69 (88.5%)	66 (84.6%)	68 (87.2%)	0.771	234	0.075
PAH*	62 (26.5%)	19 (24.4%)	23 (29.5%)	20 (25.6%)	0.752	234	0.077
CAD	203 (86.8%)	66 (84.6%)	68 (87.2%)	69 (88.5%)	0.771	234	0.075
COPD*	43 (18.4%)	14 (17.9%)	14 (17.9%)	15 (19.2%)	0.972	234	0.022
AHTN*	176 (75.2%)	58 (74.4%)	61 (78.2%)	57 (73.1%)	0.742	234	0.080
PAD*	50 (21.4%)	16 (20.5%)	17 (21.8%)	17 (21.8%)	0.975	234	0.021
Diabetes	149 (63.7%)	55 (70.5%)	46 (59.0%)	48 (61.5%)	0.290	234	0.162
CRI*	77 (32.9%)	28 (35.9%)	24 (30.8%)	25 (32.1%)	0.778	234	0.073

Baseline characteristics of matched patients that received Levosimendan within the specified time frame.
*Matched on age + sex + type of surgery + surgical urgency + Charlson Comorbidity Index (CCI) + congestive heart failure (CHF) + NYHA ≥3 + pulmonary hypertension (PAH) + chronic obstructive pulmonary disease (COPD) + arterial hypertension (AHTN) + peripheral arterial disease (PAD) and chronic renal insufficiency (CRI). Groups: preop, Levosimendan started at least one day before surgery, intraop, L. started on the day of surgery, postop, L. started one day after surgery or later. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease; CRI, chronic renal insufficiency. MD, mean differences, standardized mean differences for continuous variables (Age, BMI, CCI).

Table 2 Outcomes of matched patients.

	[ALL]	Preop	Intraop	Postop	P. overall	*N*
	N = 234	*N* = 78	*N* = 78	*N* = 78		
In-hospital mortality	72 (30.8%)	13 (16.7%)	26 (33.3%)	33 (42.3%)	0.002	234
ICU mortality	72 (30.8%)	13 (16.7%)	26 (33.3%)	33 (42.3%)	0.002	234
LOS [d]	19.0 [10.0; 35.8]	18.0 [10.0; 28.8]	18.0 [11.0; 41.8]	24.0 [10.0; 42.8]	0.345	234
LOS [d] (excl. deceased)	23.5 [13.0; 39.0]	21.0 [11.0; 30.0]	19.5 [15.5; 43.0]	31.0 [16.0; 56.0]	0.003	162
ICU duration [d]	14.0 [8.00; 29.8]	13.5 [8.00; 26.0]	14.0 [8.00; 34.8]	16.0 [7.00; 36.8]	0.659	234
ICU duration [d] (excl. deceased)	17.5 [10.0; 34.0]	14.0 [9.00; 26.0]	17.0 [9.75; 36.5]	28.0 [13.0; 46.0]	0.009	162
Duration of mech. ventilation [h]	165 [76.0; 409]	112 [56.0; 286]	200 [84.0; 443]	204 [108; 552]	0.009	233
Duration of mech. ventilation [h] (excl. deceased)	165 [77.0; 411]	108 [54.0; 251]	200 [89.5; 472]	292 [125; 670]	0.001	161
CRRT	78 (33.3%)	18 (23.1%)	24 (30.8%)	36 (46.2%)	0.008	234

Outcomes of matched patients that received Levosimendan within the specified time frame. LOS, length of stay; CRRT, continuous renal replacement therapy w/o pre-existing renal insufficiency; Groups: preop, Levosimendan started at least one day before surgery, intraop, L. started on the day of surgery, postop, L. started one day after surgery or later.

counteract already developed LCOS was associated with high mortality. Intraoperative Levosimendan treatment in patients with systolic left ventricular dysfunction, however, was associated with reduced mortality rates, compared to abovementioned postoperative administration. This finding is in line with previous studies, which analysed subgroups of large RCTs conducted in recent years (8, 11).

Most interestingly, prolonged preoperative treatment ("preconditioning") of heterogeneous cardiac surgery patients preoperatively presenting with severely reduced ventricular function with Levosimendan was associated with reduced mortality when compared to patients who receive Levosimendan intraoperatively (16,7% vs. 33,3%). Also, duration of mechanical ventilation and incidence of CRRT were significantly lower in the preconditioning group. These associations were even stronger when deceased patients were excluded, who might otherwise introduce bias. This study thus extends recent knowledge in a large cohort of patients treated

at a tertiary care hospital promoting preconditioning Levosimendan usage.

Previous research in the field has produced varying results concerning the value of perioperative Levosimendan, possibly because most RCTs have not taken full advantage of Levosimendan in their study protocols. To specify: as mentioned above, the unique pharmacokinetic profile of Levosimendan [see above and (14, 15)] recommends its administration well before the surgical/myocardial trauma occurs. In an uneventful intraoperative course, one might assume that commencing Levosimendan therapy during induction of anaesthesia and/or during weaning of CPB might be sufficient to at least "activate" cardioprotective cellular pathways. This may hold true especially if vulnerable myocardium has been verified preoperatively. Extending this hypothesis, one might expect an even more pronounced beneficial effect if most of the drug had been infused preoperatively. Such an association can be clearly seen in our data, including but not limited to elective CABG patients. This effect has been demonstrated before in a meta-analysis of two RCTs (11). Our findings are in line with the existing literature, which hints towards a positive effect of preconditioning patients with Levosimendan, but fails to find such an effect when Levosimendan is given only in the postoperative phase (8, 9, 13, 16). Additionally, a recent meta-analysis was able to demonstrate beneficial effects of Levosimendan in weaning patients from veno-arterial ECMO support (31), which is in line with our hypothesis that benefits of Levosimendan administration present themselves with a significant delay in onset.

To our knowledge, this retrospective study is the first to report a significant association of preconditioning and improved outcome not only in CABG patients, but in a cohort of patients undergoing all types of major cardiac surgery, i.e., CABG, valve surgery and combined surgery of CABG and valve (see **Supplementary Tables S3–S6**). We assume that our procedural change towards a more active screening of all cardiac surgery patients led to the abovementioned goal of reaching sufficient levels of Levosimendan or its metabolite before the surgery in high-risk patients. This is in line with the updated experts' assessment (32) on the use of Levosimendan in the perioperative setting, based on two recent studies (33, 34). This experts' assessment proposes the very early administration of Levosimendan in patients undergoing isolated CABG-surgery that exhibit severely reduced left ventricular function.

On the other hand, and not directly related to the administration of Levosimendan, the SOP change possibly increased alertness for a concomitant underlying ventricular dysfunction and pre-emptive therapeutic strategies. Previously, a patient's ventricular (dys) function was in most cases known at admission, but might have been considered unamendable by preoperative optimisation. Rather, its recognition promoted some kind of "rescue strategy" intra- and/or postoperatively, e.g., administration of high-dose adrenergic catecholamines, Levosimendan, IABP and/or VAD placement. The SOP change towards preoperative screening of all patients might have improved the perioperative treatment of high-risk patients, synergistically with the preoperative administration of Levosimendan.

Of note, the maintenance of the SOP was internally discussed since the LEVO-CTS trial in 2017 (8) did not show a clear benefit of Levosimendan and the subgroup analysis in CABG patients with severely reduced left ventricular function had not been published yet (11). Thus, the implementation of preconditioning high-risk patients with Levosimendan was somewhat abandoned. In addition, the department of cardiac surgery was internally reorganized in 2018 being transferred towards a different location with new anaesthesia responsibilities. This might explain the decrease in Levosimendan treated patients in the preop group (**Figure 1**).

Limitations

Our study is observational, and retrospective, and therefore has several important limitations.

- As mentioned before, the screening process itself in combination with heightened awareness of the treating physicians, especially the anaesthesia caregivers, might have played a significant role and introduced bias.
- We decided to include patients operated over a long time in our analysis, in order to increase the number of patients treated with Levosimendan, since after all only very few patients received this medication. While increasing the number of patients makes propensity score matching and statistical comparison in general more meaningful, it also means that (peri)procedural changes in our institution over time, other than the change of the SOP regarding Levosimendan administration, might have influenced patients' outcome.
- We also cannot rule out that patients who received Levosimendan intra-/postoperatively, especially those after the SOP change, were patients that suffered from (peri)operative complications and are therefore not comparable to the patients who presented with preoperatively severely reduced ventricular function ("ultima ratio").
- Additionally, we included operations that were classified as urgent/emergent and matched for this, but this might nevertheless introduce a bias. As group preop is defined as consisting of patients who received Levosimendan on the day before the surgery, this basically shifts all patients who have to be operated instantly, i.e., "high-grade" emergency, out of group preop. In addition, a selection towards patients who could tolerate at least 1 day of preconditioning which eventually might have leaded in postponing surgery could have taken place. See supplemental tables for subgroup analyses of patients who received elective surgeries only.
- Concerning data quality, we could not differentiate the precise origin and nature of valve dysfunctions leading to corrective surgery, e.g., mitral and/or tricuspid regurgitation.
- We did not have access to systematically recorded echocardiographic reports due to incompletely digitized patient records within the study period. Since the SOP of our institution required echocardiography by a (inter-)national certified echocardiographer before preconditioning patients

with Levosimendan, we assume that all patients who were preconditioned with Levosimendan have thus shown severely reduced left ventricular systolic function according to the recent heart failure guideline (35).
- Additionally, our digital records did not include important surgical/perioperative variables that are known to have an impact on outcome, e.g., CPB time and cross-clamp time. Therefore, we could not use these additional variables in our propensity score matching, which might introduce significant bias.

Conclusion

We have shown that establishing a screening process that aims to preoperatively identify cardiac surgical patients suffering from reduced left ventricular function and precondition these with Levosimendan is associated with significantly improved outcome when compared with patients who receive Levosimendan intra- or postoperatively. We speculate that this is predominantly caused by the pharmacodynamic properties of Levosimendan, but cannot rule out that the screening and preconditioning process, which initiates an "evaluation" period, itself in combination with experienced cardiac anaesthesia caregivers has played a part. Also, the information available to us in the form of digital records was lacking variables such as precise preoperative ejection fraction, CPB time and cross-clamp time, therefore our matching might have been suboptimal. We further speculate that this likely Levosimendan-induced effect has not widely been seen in previous randomized trials because these did not include prolonged preoperative administration of Levosimendan as an experimental stand-alone arm and/or administered the drug too broadly, i.e., previous studies did not limit its administration to patients suffering from severely reduced ventricular function strictly enough, and this might have masked its effect.

Data availability statement

The datasets presented in this article are not readily available because unaggregated data are not publicly available due to the possibility of de-anonymizing individual patients. Aggregated excerpts are available from the author FB (felix.balzer@charite.de) upon reasonable request. Requests to access the datasets should be directed to felix.balzer@charite.de.

Ethics statement

This study, involving human participants, was reviewed and approved by The Charité Ethics Committee, Berlin, Germany (study ID no.: EA4/239/19). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FS was responsible for data collection, analysis and interpretation and drafted the manuscript. FB and ST took overall responsibility for the conducted study and contributed to the development of the study design, ST helped with the final revision of the manuscript. CB, MH, MS and JE provided expert opinion from a cardiac anaesthesist's point of view. BH provided expert statistical consulting. HG and AM contributed to the discussion of findings from a cardiac surgeon's perspective, AM furthermore provided consulting concerning statistics and plotting of results. LP did important preliminary work by evaluating data completeness. All authors contributed to the article and approved the submitted version.

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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.2023.1213696/full#supplementary-material

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Henry Dunant Hospital, Greece
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Marija Zdraveska,
Saints Cyril and Methodius University of Skopje, North Macedonia

*CORRESPONDENCE
Marija Polovina
✉ marija_polovina@yahoo.com

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Predictors and prognostic implications of hospital-acquired pneumonia in patients admitted for acute heart failure

Marija Polovina[1,2]*, Milenko Tomić[1], Mihajlo Viduljević[1], Nataša Zlatić[1], Andrea Stojićević[1], Danka Civrić[1], Aleksandra Milošević[1,2], Gordana Krljanac[1,2], Ratko Lasica[1,2] and Milika Ašanin[1,2]

[1]Department of Cardiology, University Clinical Centre of Serbia, Belgrade, Serbia, [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Introduction: Data on predictors and prognosis of hospital acquired pneumonia (HAP) in patients admitted for acute heart failure (AHF) to intensive care units (ICU) are scarce. Better knowledge of these factors may inform management strategies. This study aimed to assess the incidence and predictors of HAP and its impact on management and outcomes in patients hospitalised for AHF in the ICU.
Methods: this was a retrospective single-centre observational study. Patient-level and outcome data were collected from an anonymized registry-based dataset. Primary outcome was in-hospital all-cause mortality and secondary outcomes included length of stay (LOS), requirement for inotropic/ventilatory support, and prescription patterns of heart failure (HF) drug classes at discharge.
Results: Of 638 patients with AHF (mean age, 71.6 ± 12.7 years, 61.9% male), HAP occurred in 137 (21.5%). In multivariable analysis, HAP was predicted by *de novo* AHF, higher NT proB-type natriuretic peptide levels, pleural effusion on chest x-ray, mitral regurgitation, and a history of stroke, diabetes, and chronic kidney disease. Patients with HAP had a longer LOS, and a greater likelihood of requiring inotropes (adjusted odds ratio, OR, 2.31, 95% confidence interval, CI, 2.16–2.81; $p < 0.001$) or ventilatory support (adjusted OR 2.11, 95%CI, 1.76–2.79, $p < 0.001$). After adjusting for age, sex and clinical covariates, all-cause in-hospital mortality was significantly higher in patients with HAP (hazard ratio, 2.10; 95%CI, 1.71–2.84; $p < 0.001$). Patients recovering from HAP were less likely to receive HF medications at discharge.
Discussion: HAP is frequent in AHF patients in the ICU setting and more prevalent in individuals with *de novo* AHF, mitral regurgitation, higher burden of comorbidities, and more severe congestion. HAP confers a greater risk of complications and in-hospital mortality, and a lower likelihood of receiving evidence-based HF medications at discharge.

KEYWORDS

acute heart failure, hospital acquired pneumonia, intensive care unit, mortality, heart failure treatment

1. Introduction

Acute heart failure (AHF) is one of the leading global causes of hospitalisation (1), responsible for ~2.2 million hospital admission per year in Europe alone (2). Patients hospitalised for AHF have in-hospital mortality rates ranging between ~2.5% and >50%, depending on the clinical severity, and those discharged alive suffer a long-term increased

risk of death (−20%) (3, 4). Patients with AHF admitted to the intensive care units (ICU) typically have more severe congestion and/or haemodynamic instability and represent a vulnerable category, often comprising older, frail, and multi-morbid individuals, at higher risk of complications during the hospital stay (5).

Hospital acquired pneumonia is one of the most frequent and serious complications in patients admitted to the ICU. It is defined as an inflammatory condition of the lung parenchyma caused by infectious agents, not present at least 48 h after admission, and does not include patients intubated at admission (6). It is primarily caused by bacterial pathogens (7), and its occurrence exacerbates the risk of respiratory insufficiency, haemodynamic instability and shock and confers the highest mortality among nosocomial infections (6, 8). The pathogenesis of hospital acquired pneumonia includes the aspiration of oropharyngeal pathogens, and the colonization and invasion of the lower respiratory tract, which typically occurs in the presence of compromised host defence mechanisms (9). Rarely pathogens can be directly introduced into the lower airway or spread through the bloodstream from infected intravenous catheters, leading to infection (9). In patients with AHF, congestion in the lower respiratory tract, interstitial and/or alveolar oedema, and engorgement of lymphatic vessels create an environment permissive to bacterial persistence, and impair immune-mediated defence mechanisms, making patients more susceptible to developing pneumonia. Pneumonia development, in turn, can worsen cardiac function due to an increased cardiac workload caused by factors such as tachycardia, oxygen supply-demand imbalance, reduced systemic vascular resistance, and potentially direct myocardial toxic effects of inflammatory mediators (10).

Earlier studies have reported the incidence of hospital acquired pneumonia ranging between 8% and 21% in patients admitted for AHF and its development was associated with the more severe clinical course, longer length of hospitalisation, and greater risk of in-hospital and one-year mortality (11, 12). However, most of the earlier observations were derived from retrospective analysis not specifically conducted in AHF patients admitted to the ICU. Moreover, research focus has shifted over the past few years to SARS-CoV-2 infection and there is a paucity of contemporary data on non-COVID pneumonia. Better understanding of the incidence, risk factors and clinical course of hospital acquired pneumonia in AHF patients in the ICU setting is necessary to inform future risk stratification and management strategies. Therefore, the aim of the present study is to assess the incidence and predictors of hospital acquired pneumonia and its impact on clinical outcomes and management of patients hospitalised for AHF in the ICU.

2. Materials and methods

2.1. Study design and inclusion criteria

This was a retrospective single-centre analysis of anonymised hospital registry-based dataset of patients admitted for AHF in the cardiology ICU of the Emergency Department of the University Clinical Centre of Serbia, Belgrade, Serbia, between May 2020 and July 2022. The ICU of the Department of Cardiology in the University Clinical Centre of Serbia is a tertiary level facility, which hospitalises patients with acute/critical cardiovascular disorders. AHF was defined by the presence of symptoms and signs of HF, corroborated by radiology evidence of congestion (Kerly B lines, plueral effusion) and elevated natriuretic peptide levels regardless of left ventricular (LV) ejection fraction (LVEF), in line with the European Society of Cardiology (ESC) guidelines on the management of HF (13). Patients with the first episode of AHF (*de novo* AHF) and those with a previous history of chronic HF (decompensated chronic HF) were included. Only patients with a primary diagnosis of AHF, according to the International Statistical Classification of Diseases 10th revision (ICD-10) code I50.* were included. Exclusion criteria were as follows: (1) acute coronary syndrome defined according to the ESC guidelines (14, 15); (2) other cardiovascular emergencies complicated by AHF (e.g., infective endocarditis, pulmonary embolism, high grade atrioventricular block etc); (3) patients in cardiogenic or septic shock at the time of admission; (4) patients with confirmed SARS-CoV-2 or Influenza virus infection; (5) patients with evidence of lower respiratory tract infection at admission (6) patients intubated at the time of admission or within the first 48 h. The study protocol was approved by the institutional ethics review board and informed consent was exempt on the basis of a retrospective design.

2.2. Definition of hospital acquired pneumonia

Hospital acquired pneumonia was defined according to the modified Infectious Diseases Society of America and the American Thoracic Society criteria (7, 9), including radiographic evidence of an inflammatory infiltrate that is new or progressive (on chest x-ray and/or computed tomography), along with at least two of the clinical findings suggestive of infection, namely, new onset of fever (>37.5 C), purulent expectoration, leucocytosis, elevated levels of C-reactive protein (CRP), procalcitonin, fibrinogen and decline in oxygenation. Documentation of ICD-10 codes J15.* and J18.* was also required. Only patients who developed pneumonia at least 48 h after admission and were not intubated at the time of admission were considered.

2.3. Patient-level data acquisition

Data on baseline demographic characteristics (age, sex), vital signs and HF status at admission (heart rate, systolic and diastolic blood pressure, and manifestations of congestion) were collected from the hospital registry-based dataset. HF status was evaluated in accordance with the ESC guidelines, including standard transthoracic echocardiographic examination performed

during hospitalisation to confirm structural and functional alterations (13). Based on echocardiographic exam (performed in all patients), HF was classified as HF with reduced ejection fraction, HFrEF (LVEF ≤40%), HF with mildly reduced ejection fraction, HFmrEF (LVEF >41%–49%) and HF with preserved ejection fraction, HFpEF; the latter two categories were pooled together (HFmrEF/HFpEF) (13). The diagnosis of HFpEF was based the ESC guidelines criteria (13), as follows: (1) presence of symptoms and signs of HF (all patients were admitted with symptomatic acute HF), LVEF ≥50% and " evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides". Diastolic dysfunction was diagnosed in the presence of at least 2 of the 4 criteria (16): (1) left atrial volume index >34 ml/m^2 (or >40 ml/m^2 in patients with atrial fibrillation); (2) tricuspid regurgitation jet velocity >2.8 m/s; (3) tissue doppler imaging septal e' < 7 or lateral e' < 10; and 4. E/e' > 14. In patients with only one echocardiographic criterion (due to difficulties imposed by performing exam in severely decompensated patients), HFpEF was considered present if LVEF was ≥50% and elevated admission levels of natriuretic peptides (i.e., NT-fragment of pro-B-type natriuretic peptide, NT-proBNP ≥300 pg/ml) were documented (13). Cardiovascular comorbidities, including a history of arterial hypertension (previous diagnosis of hypertension, including treatment with antihypertensive drugs), ischaemic heart disease (previous diagnosis of angina pectoris, prior myocardial infarction, and/or coronary revascularisation with percutaneous coronary intervention and/or cardiac bypass surgery), dilated cardiomyopathy (previous diagnosis of non-ischaemic dilated LV and systolic dysfunction—LVEF <45%), valvular heart disease (aortic stenosis and/or moderate/severe mitral regurgitation documented by echocardiography), atrial fibrillation (diagnosis of paroxysmal, persistent or permanent atrial fibrillation), peripheral arterial disease (previously confirmed by vascular ultrasound exam or angiography), stroke/transient ischaemic attack (as per medical documentation) were collected. Non-cardiovascular comorbidities including type 2 diabetes mellitus (T2DM—previous diagnosis of T2DM, treatment with glucose-lowering medications or newly diagnosed T2DM during hospitalisation), chronic obstructive pulmonary disease (COPD—previous diagnosis of COPD including prescribed treatment with inhaled bronchodilators/steroids/combined inhalers and/or aminophylline/theophylline), chronic kidney disease (CKD—persistent decrease in estimated glomerular filtration rate, eGFR, <60 ml/min/1.73 m^2 by Cockcroft–Gault equation) and anaemia (haemoglobin <130 g/L in men, and <120 g/L in women) were assessed from the registry-based dataset. A history of hospital admissions for any cause within the 6 months prior to current hospitalisation was collected. New York Heart Association (NYHA) functional class was defined at admission. Routine laboratory analysis along with inflammatory mediators (maximum white blood cell count, CRP, procalcitonin and fibrinogen levels) and cardiac biomarkers (admission NT-proBNP, and high-sensitivity troponin T levels, hsTnT) were collected. Assessment of congestion included clinical evaluation (dyspnoea, pulmonary rales, jugular venous congestion, lower extremity oedema), radiographic signs at admission chest x-ray (Kerley B lines, unilateral/bilateral pleural effusion), and biomarkers (elevated NT-proBNP levels). Data on the use of inotropes/vasopressors (dopamine, dobutamine, noradrenalin), non-invasive and invasive ventilatory support after the development of pneumonia, and fundamental HF medications prescribed at discharge (angiotensin converting enzyme inhibitors, ACEI; angiotensin-1 receptor blockers, ARB; angiotensin-1 receptor neprilysin inhibitor—sacubitril/valsartan, ARNI; beta-blockers; mineralocorticoid receptor antagonists, MRA; and sodium-glucose type 2 inhibitors, SGLT2I) in surviving patients were documented.

2.4. Study outcomes

The primary study outcome was in-hospital all-cause mortality. Secondary outcomes included: (i) length of hospital stay, (ii) requirement for inotropic support and/or non-invasive/invasive ventilatory support and (iii) prescription patterns of fundamental HF drug classes at discharge, depending on the presence of hospital acquired pneumonia, in patients with HFrEF and HFmrEF/HFpEF.

2.5. Statistical analysis

Expecting a hazard ratio (HR) of 2.2 for the association between hospital acquired pneumonia and all-cause mortality based on previously published data (11), we calculated a minimum sample size of 514 patients, with a power (1-β) of 0.8, and a 2-sided probability of type I error (α) of 0.05 (17). Numerical continuous variables are presented as mean and standard deviation or median and interquartile range (IQR), and categorical variables as absolute numbers and percentages. Difference between variables were compared using the parametric Student *t*-test, or non-parametric Man–Whitney *U*-test for numerical variables, and Pearson Chi-square test or Fisher exact probability test for categorical variables, as appropriate. Clinical predictors of the development of hospital acquired pneumonia were analysed in a multivariable logistic regression model, in which clinical variables from **Table 1**, achieving *p*-value < 0.05 in univariable logistic regression analysis were entered. In cases of a correlation between predictor variables (e.g., pulmonary rales and dyspnoea, *de novo* AHF and history of chronic HF, anaemia and haemoglobin, CKD, serum creatinine and eGFR), the variable with a stronger association in the univariable analysis was used in the multivariable model. Inflammatory mediators were not entered as they depicted maximum values during hospitalisation (including those observed in patients with pneumonia). Independent predictors were defined as variables with a persistent significant association with the development of pneumonia (*p*-value < 0.05) in the multivariable analysis. Cumulative survival rate during hospitalisation in patients with and without pneumonia was assessed with the Kaplan-Meier

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TABLE 1 Baseline clinical characteristics of the study population.

Variable	All patients, *n* = 638	Without pneumonia, *n* = 501	With pneumonia, *n* = 137	*p*-value
Age (years)	71.6 ± 12.7	71.0 ± 12.5	72.5 ± 14.8	0.067
Sex (male)	395 (61.9)	309 (61.7)	86 (62.7)	0.938
Heart rate (beats per min)	93.9 ± 26.1	94.1 ± 25.7	92.5 ± 27.3	0.806
Systolic blood pressure (mmHg)	118.6 ± 39.9	119.5 ± 39.0	115.7 ± 42.0	0.295
Diastolic blood pressure (mmHg)	73.5 ± 26.1	74.7 ± 18.9	69.9 ± 19.0	0.846
Dyspnoea, *n* (%)	549 (86.0)	416 (83.0)	133 (97.1)	<0.001
Lower extremity oedema, *n* (%)	364 (57.1)	286 (57.0)	78 (56.9)	0.490
Jugular vein distention, *n* (%)	173 (27.1)	135 (26.9)	38 (27.7)	0.832
Pulmonary rales, *n* (%)	462 (72.4)	339 (67.7)	123 (89.8)	<0.001
Kerley B lines, *n* (%)	555 (86.9)	420 (83.8)	135 (98.5)	<0.001
Pleural effusion, *n* (%)	461 (72.2)	344 (68.6)	117 (85.4)	<0.001
De novo AHF, *n* (%)	278 (43.8)	210 (41.9)	68 (49.6)	0.010
Decompensated chronic HF, *n* (%)	360 (56.4)	291 (58.1)	69 (50.4)	0.030
LVEF (%)	34.2 ± 15.7	33.4 ± 15.3	37.0 ± 17.0	0.050
HFrEF, *n* (%)	401 (62.8)	324 (64.7)	77 (56.2)	0.072
HFmrEF/HFpEF, *n* (%)	237 (37.1)	177 (35.3)	60 (43.8)	0.092
NYHA class III, *n* (%)[a]	346 (54.2)	275 (54.8)	71 (51.8)	0.075
NYHA class IV, *n* (%)[a]	292 (45.6)	226 (45.1)	66 (48.1)	0.061
A history of prior hospitalization, *n* (%)	154 (24.1)	113 (22.5)	41 (29.9)	0.022
Cardiovascular comorbidities				
Hypertension, *n* (%)	526 (82.4)	409 (81.6)	117 (85.4)	0.529
Coronary artery disease, *n* (%)	247 (38.7)	199 (39.7)	48 (35.0)	0.340
Dilated cardiomyopathy, *n* (%)	140 (21.9)	113 (22.5)	27 (19.7)	0.564
Aortic stenosis, *n* (%)	82 (12.8)	60 (11.9)	12 (8.7)	0.172
Mitral regurgitation, *n* (%)	198 (31.0)	131 (26.1)	68 (48.9)	<0.001
Atrial fibrillation, *n* (%)	374 (58.6)	290 (57.9)	84 (61.3)	0.525
Peripheral arterial disease, *n* (%)	113 (17.7)	84 (16.8)	29 (21.2)	0.225
Stroke/transient ischaemic attack, *n* (%)	91 (14.3)	58 (11.5)	33 (24.1)	<0.001
Non-cardiovascular comorbidities				
Type 2 diabetes, *n* (%)	252 (35.5)	180 (35.9)	72 (52.5)	<0.001
Chronic kidney disease, *n* (%)	181 (28.3)	120 (23.9)	61 (44.5)	<0.001
Chronic obstructive pulmonary disease, *n* (%)	83 (13.0)	52 (10.4)	31 (22.6)	<0.001
Anaemia, *n* (%)	303 (47.6)	220 (43.9)	83 (60.5)	<0.001
Current smokers, *n* (%)	125 (19.6)	97 (19.3)	28 (20.4)	0.966
Laboratory analysis				
White blood cell count (10^3/L)	10.6 ± 2.3	8.7 ± 2.4	14.6 ± 3.8	<0.001
CRP (mg/dl)	22.1 ± 13.2	8.9 ± 7.8	33.2 ± 12.3	<0.001
Procalcitonin (ng/ml)	0.6 (0.4–2.7)	0.1 (0.0–0.4)	1.8 (0.0–6.9)	<0.001
Fibrinogen (g/L)	2.3 (1.2–3.2)	2.0 (1.4–3.3)	4.6 (2.4–7.7)	<0.001
Na^+ (mmol/L)	138.6 ± 5.6	138.5 ± 5.5	139.0 ± 6.0	0.935
Creatinine (μmol/L)	98.1 ± 21.3	92.6 ± 17.5	101.2 ± 23.4	<0.001
Urea (mmol/L)	5.6 ± 2.8	4.9 ± 2.9	6.2 ± 3.4	0.089
eGFR (ml/min/1.73 m^2)	43.3 ± 21.1	51.4 ± 12.0	37.6 ± 18.1	<0.001
Uric acid (mmol/L)	476.4 ± 74.5	484.3 ± 81.2	472.4 ± 63.8	0.548
Haemoglobin (g/L)	125.1 ± 23.5	133.4 ± 13.8	116.5 ± 12.6	<0.001
NT-proBNP (pg/ml)	5293 (2795–11328)	4865 (998–7853)	7414 (1189–12345)	<0.001
hs-TnT (ng/ml)	78.0 (41.0–154.4)	68.4 (31.2–146.9)	78.3 (44.2–166.7)	0.089

CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsTnT, high sensitivity troponin T; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B type natriuretic peptide; Na+, serum sodium level; NYHA, New York Heart Association.

[a]There were no asymptomatic or mildly symptomatic patients (i.e., NYHA functional class I or II).

analysis and compared using the log-rank test. The association between hospital acquired pneumonia and all-cause mortality was analysed in a Cox proportional hazard model adjusted for clinically relevant covariates, including age, sex, NT-proBNP, *de novo* HF, baseline LVEF (continuous) and other variables listed in Table 1, with a p-value < 0.05 for the association with all-cause mortality in univariable analyses. If a significant correlation between explanatory variables was identified (e.g., *de novo* HF and a history of HF, systolic and diastolic blood pressure, eGFR and CKD, HFrEF vs. HFmrEF/HFpEF, etc), a variable with a stronger association in univariable analysis was used for adjustment. Time-to-event or time-to-the end of hospitalisation

was used to calculate hazard ratios (HR) with the accompanying 95% confidence intervals (CI). The likelihood of the requirement for inotropic or ventilatory support was analysed in a multivariable logistic regression model, which included hospital acquired pneumonia as predictor variable and other clinical variables (with a p-value < 0.05 in univariable logistic regression analysis) were used for adjustment. The likelihood or prescribing HF medications was analysed separately in patients with HFrEF and HFmrEF/HFpEF discharged alive, according to the same principle as described above. All analyses were performed using the IBM SPSS software version 29, and 2-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline patient characteristics and the incidence of hospital acquired pneumonia

The study included 638 patients admitted to the cardiology ICU for AHF (mean age, 71.6 ± 12.7 years, male 61.9%). Hospital acquired pneumonia was documented in 137 patients (21.5%) after a median of 5.5 days from admission (IQR, 3.0–7.8 days). Microbiological confirmation was available in a subset of patients who subsequently required intubation and mechanical ventilation, in whom positive endotracheal aspirate revealed the following pathogens: Acinetobacter spp, Klebsiella pneumonia, Pseudomonas aeruginosa or Staphylococcus aureus. Baseline clinical characteristics of the entire cohort and according to the presence of pneumonia are presented in Table 1.

Pneumonia occurred more frequently in patients with *de novo* AHF compared with those with decompensated chronic HF (49.6% vs. 41.9%, $p = 0.010$), Table 1. Patients who developed pneumonia had more severe evidence of congestion on admission in terms of dyspnoea (97.1% vs. 83.0%), pulmonary rales (89.8%. vs. 67.7%) and radiographically documented Kerley B lines (98.5% vs. 83.8%) and pleural effusions (85.4% vs. 68.6%), all p-values < 0.001, Table 1. Patients with hospital acquired pneumonia more frequently had a history of a previous hospitalisation withing the past 6 months (29.5% vs. 25.5%%, $p = 0.022$). Mitral regurgitation and a history of stroke/transient ischaemic attack were more prevalent in patients with pneumonia compared to those without pneumonia (mitral regurgitation, 48.9% vs. 26.1%; prior stroke, 24.1% vs. 11.5%, respectively both p-values < 0.001), while there was no difference in other cardiovascular comorbidities, Table 1. Mean LVEF was slightly higher in patients with pneumonia compared to the rest of the cohort ($p = 0.050$). Non-cardiovascular comorbidities, including T2DM (52.5% vs. 35.9%, p-value < 0.001), COPD (22.6% vs. 10.4%, p-value < 0.001), CKD (44.5% vs. 23.9%, p-value < 0.001) and anaemia (60.5% vs. 43.9%, p-value < 0.001) were significantly more frequent in patients with pneumonia. There was no difference in the smoking status. Patients with pneumonia had higher maximum levels of inflammatory biomarkers, and higher admission levels of serum creatinine and NT-proBNP, Table 1. Admission eGFR and haemoglobin levels were lower in patients with pneumonia, and there were no significant differences in other laboratory values, including hsTnT, Table 1.

3.2. Predictors of the development of hospital acquired pneumonia

Variables significantly associated with the development of hospital acquired pneumonia are presented in Table 2. In multivariable analysis, the development of pneumonia was independently predicted by radiographic evidence of pleural effusion at admission, *de novo* AHF, presence of mitral regurgitation, a history of stroke/transient ischaemic attack, T2DM and CKD, and increased admission levels of NT-proBNP (≥ the median value of 5,293 pg/ml), Table 2.

3.3. Association between hospital acquired pneumonia and clinical outcomes

A total of 106 (16.6%) patients died during hospitalisation. In-hospital all-cause mortality rates were significantly higher among patients with hospital acquired pneumonia (27.0%) compared with patients without pneumonia (13.8%), p-value < 0.001. Cumulative Kaplan-Meier time-to-event curves in patients with and without pneumonia are presented in Figure 1. After adjusting for age, sex and other clinically relevant covariates, the development of pneumonia was independently associated with a

TABLE 2 Univariable and multivariable predictors of the development of hospital acquired pneumonia.

Variable	Univariable analysis[a] OR (95% CI)	p-value	Multivariable analysis OR (95% CI)	p-value
Dyspnoea	1.31 (1.11–2.11)	0.007	1.20 (0.97–1.67)	0.346
Kerley B lines	1.23 (1.09–1.98)	0.001	1.19 (0.96–1.78)	0.346
Pleural effusion	2.51 (1.50–4.18)	<0.001	2.70 (1.49–4.06)	<0.001
De novo AHF	1.65 (1.12–2.41)	0.010	1.85 (1.14–3.08)	0.003
A history of prior hospitalisation	1.24 (1.13–2.41)	0.031	1.10 (0.90–1.96)	0.189
LVEF (continuous)	1.01 (1.00–1.03)	0.028	1.01 (0.89–1.04)	0.055
Mitral regurgitation	3.22 (2.81–3.84)	<0.001	2.52 (2.19–2.96)	<0.001
Stroke/transient ischaemic attack	2.28 (1.76–3.15)	<0.001	1.20 (1.07–2.13)	0.020
Type 2 diabetes	1.64 (1.24–1.95)	0.018	1.61 (1.30–2.14)	0.009
Chronic kidney disease	1.67 (1.27–2.17)	0.009	1.24 (1.12–1.79)	0.005
Chronic obstructive pulmonary disease	1.28 (1.17–2.20)	0.035	1.07 (0.87–1.82)	0.118
Anaemia	1.24 (1.04–1.83)	0.041	1.21 (0.84–1.33)	0.228
NT-proBNP (≥5293 pg/ml)[b]	3.31 (2.71–5.21)	<0.001	3.25 (3.16–4.05)	<0.001

CI, confidence interval; NT-proBNP, N-terminal pro B type natriuretic peptide; OR, Odds ratio.
[a]Only variables with a significant association with the development of pneumonia in univariable analysis are presented.
[b]median value of NT-prBNP in the study population.

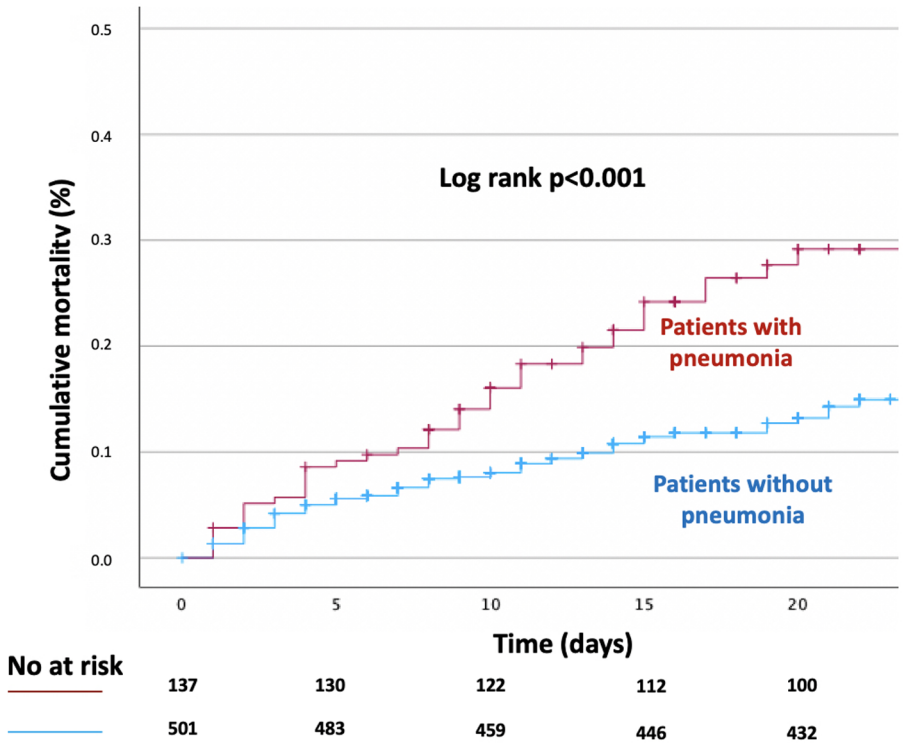

FIGURE 1
Kaplan-Meier time-to-event curve for in-hospital all-cause death according to the presence of hospital acquired pneumonia.

significantly higher risk of in-hospital all-cause mortality (adjusted HR, 2.10; 95% CI, 1.71–2.84; p-value < 0.001).

The median length of hospitalisation was significantly longer in patients with hospital-acquired pneumonia (median, 14.5 days, IQR 9.5–22 days) compared to patients without pneumonia (median, 10 days, IQR 6–16 days), $p < 0.001$, as presented in Figure 2.

During hospitalisation, inotropes/vasopressors and ventilatory support were required in 37.7% and 26.0% of the total study population; patients with hospital acquired pneumonia were significantly more likely to require either type of the support (inotropes/vasopressors, adjusted odds ratio, OR, 2.31, 95% CI, 2.16–2.81, p-value <0.001; ventilatory support, adjusted OR, 2.11, 95% CI, 1.76–2.79, p-value < 0.001), Table 3.

Prescription patterns of key evidence-based HF medications in patients discharged alive with HFrEF and HFmrEF/HFpEF are presented in Tables 4, 5, respectively. A total of 77.2% and 58.3% of HFrEF patients were prescribed at discharge with renin

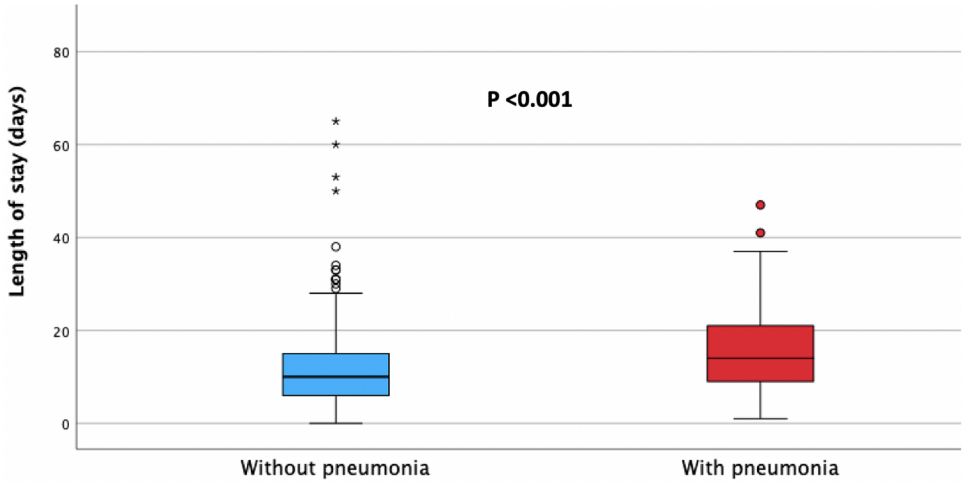

FIGURE 2
Median length of hospital stay in patients with (red) and without (blue) hospital acquired pneumonia.

TABLE 3 Association between hospital acquired pneumonia and treatment during hospitalisation.

Variable	All patients, *n* (%)	Without pneumonia, *n* (%)	With pneumonia, *n* (%)	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Inotropes/ vasopressors	241 (37.7)	170 (33.9)	71 (51.8)	2.49 (1.69–3.70)	<0.001	2.31 (2.16–2.89)	<0.001
Ventilatory support	166 (26.0)	116 (23.1)	50 (36.5)	2.37 (1.28–3.99)	<0.001	2.11 (1.76–2.78)	<0.001

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-1 receptor blocker; ARNI, angiotenin-1 receptor neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter type 2.

TABLE 4 Association between hospital acquired pneumonia and heart failure medications prescribed at discharge in patients with heart failure and reduced ejection fraction.

Heart failure medications	All patients, 317 (79)	Without pneumonia, 264 (81.5)[a]	With pneumonia, 53 (68.8)[a]	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
ACEI/ARB/ARNI	245 (77.2)	222 (84.2)	23 (43.4)	0.76 (0.47–0.97)	0.022	0.75 (0.51–0.96)	0.018
Beta-blockers	185 (58.3)	163 (61.7)	22 (41.5)	0.51 (0.30–0.87)	0.013	0.56 (0.34–0.90)	0.008
MRA	159 (50.1)	136 (51.5)	23 (43.4)	0.78 (0.45–1.30)	0.331	0.81 (0.46–1.10)	0.427
SGLT2 inhibitor	140 (44.3)	116 (43.9)	24 (45.2)	1.08 (0.67–1.18)	0.728	0.98 (0.72–1.12)	0.744

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-1 receptor blocker; ARNI, angiotenin-1 receptor neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter type 2.
[a]% of patients discharged alive in relation to all patients with HFrEF, and those with and without pneumonia.

TABLE 5 Association between hospital acquired pneumonia and heart failure medications prescribed at discharge in patients with heart failure and mildly reduced/preserved ejection fraction.

Heart failure medications	Patients, 215 (90.7)[a]	Without pneumonia, 168 (94.9)[a]	With pneumonia, 53 (68.8)[a]	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
ACEI/ARB/ARNI	174 (80.9)	134 (79.7)	36 (76.5)	0.97 (0.81–1.23)	0.854	0.99 (0.85–1.16)	0.911
Beta-blockers	97 (45.1)	83 (49.4)	14 (29.8)	0.52 (0.31–0.78)	<0.001	0.51 (0.38–0.73)	<0.001
MRA	93 (43.2)	77 (45.8)	16 (34.0)	0.78 (0.56–0.87)	<0.001	0.75 (0.52–0.84)	0.010
SGLT2 inhibitor	56 (26.0)	42 (25.0)	14 (29.8)	1.13 (0.87–1.44)	0.589	1.09 (0.89–1.28)	0.346

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-1 receptor blocker; ARNI, angiotenin-1 receptor neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter type 2.
[a]% of patients discharged alive in relation to all patients with HFmrEF/HFpEF, and those with and without pneumonia.

angiotensin system inhibitors (ACEI/ARB/ARNI) and beta-blockers, respectively, Table 4. Patients who had hospital acquired pneumonia were less likely to receive either of those drug classes compared to patients without pneumonia (ACEI/ARB/ARNI, 43.4% vs. 84.2%, adjusted OR 0.75, 95% CI, 0.51–0.96, $p = 0.018$; beta blockers, 41.5% vs. 61.7%, adjusted OR 0.56, 95% CI, 0.34–0.90, $p = 0.008$, respectively), Table 4. MRA and SGLT2I were prescribed in 50.1% and 44.3% of HFrEF patients, and there was no significant difference in the prescription rates between patients with and without pneumonia, Table 4.

Among patients with HFmrEF/HFpEF, ACEI/ARB/ARNI, beta-blockers, MRA and SGLT2I were prescribed in 80.9%, 45.1%, 43.2%, and 26.0% of patients, respectively, Table 5. Patients with hospital acquired pneumonia had a lower likelihood of being prescribed beta-blockers and MRA (beta-blockers, 29.8% vs. 49.4%, adjusted OR, 0.51, 95% CI, 0.38–0.73, $p < 0.001$; MRA, 34.0% vs. 45.8%, adjusted OR 0.75, 95% CI, 0.52–0.84; $p = 0.010$, respectively), whilst there was no difference in the prescription of ACEI/ARB/ARNI and SGLT2I, Table 5.

4. Discussion

There are three main findings of the present study in a cohort of 638 patients admitted for AHF: (i) hospital acquired pneumonia is a frequent complication of hospitalisation in the ICU, affecting 21.5% of the patients; (ii) its occurrence is more frequent in patients with *de novo* AHF and is predicted by the more severe markers of congestion (i.e., pleural effusions and higher NT-proBNP levels) and presence of mitral regurgitation and non-cardiovascular comorbidities, including a history of stroke/transient ischaemic attack, T2DM and CKD; (iii) the development of pneumonia is associated with a greater requirement for haemodynamic and ventilatory support, longer length of hospitalisation, and a significantly increased in-hospital mortality, whilst the recovered patients have a lower likelihood of receiving evidence-based treatment for HF at discharge.

Previous studies have reported variable incidence of hospital acquired pneumonia in patients admitted for AHF ranging from 8%–21%, and up to 25% in critically ill individuals (11, 12, 18).

In the present study, which included only cases of AHF in need of the cardiology ICU management, pneumonia developed in approximately one in five of the admitted patients. Of note, our analysis was restricted to non-intubated patients at the time of admission or within the first 48 h and did not account for the ventilator-associated pneumonia. The median time to the development of pneumonia was 5.5 days, consistent with the greater prevalence of the "late-onset" pneumonia (i.e., pneumonia occurring 5 days or more after admission), which is more likely to be caused by multi-drug resistant pathogens and associated with higher morbidity and mortality (9). This is consistent with culture isolates in the present study revealing gram-negative bacteria and Staphylococcus aureus, usually of the drug-resistant type.

In the present study, pneumonia developed more frequently among patients with the first episode of AHF (*de novo* AHF), compared with decompensated chronic HF, which has not been previously described. A possible explanation of this new observation is that patients with *de novo* AHF, being naïve to the diuretic treatment prior to hospitalisation, might have suffered more pronounced congestion, which had created a host environment more susceptible to nosocomial infection. Clinical course, risk of complications and outcomes of patients with *de novo* AHF as compared with decompensated chronic HF have not been consistent in previous reports (19–21). A meta-analysis of 15 studies (a total of 38,320 patients) has suggested lower mortality but a greater risk of nosocomial infections in *de novo* AHF compared with decompensated chronic HF, which is consistent with our findings (22). Moreover, our study has characterised patients at risk of acquiring pneumonia as individuals with the more pronounced congestion, documented by either radiographic evidence of pleural effusions or significantly elevated natriuretic peptide levels. It is possible that a strategy of more rapid decongestion after hospital admission (i.e., with a combination of diuretics) (23), could have a favourable impact on lowering the risk of infection and improving outcomes in those patients, which deserves future prospective evaluation. Furthermore, early initiation of antibiotic treatment in patients with suspected hospital acquired pneumonia, guided by clinical criteria alone, is strongly recommended to improve prognosis (7). The treatment may be initiated empirically, informed by the local distribution of pathogens and their antibiotic susceptibilities, and then corrected according to culture isolates (7).

The population of the present study was mostly comprised of the elderly individuals with a high prevalence of cardiovascular and non-cardiovascular comorbidities, in line with the characteristics of patients with AHF from several recent multinational registries (3, 21, 24). Similar to earlier reports, we have also observed that the presence of comorbidities increased the risk of acquiring pneumonia (11, 12). In particular, the presence of mitral regurgitation, a history of stroke/transient ischaemic attack, T2DM and CKD have emerged as significant predictors of pneumonia, independently of other clinical characteristics. Recently, mitral regurgitation has been associated with a worse clinical profile of congestion in AHF, which may have been a predisposing factor for pneumonia (25), whilst patients with a history of stroke may have had a higher risk of aspiration due to their residual neurological deficit. T2DM and CKD have been well established predictors of adverse outcomes in AHF (26, 27), however, the present study provides a new observation of their independent association with a higher risk of developing pneumonia.

Our findings confirm earlier observations that hospital acquired pneumonia is associated with significantly impaired short-term outcomes, even in the era of contemporary treatment and advanced life support provided in the cardiology ICU. Earlier studies have suggested that the development of pneumonia increased the length of hospital stay by an average of 7–9 days per patient (9) and in our study, the median length of hospital stay was prolonged by 4.5 days in patients with pneumonia. Furthermore, a significant proportion of patients with pneumonia suffered a haemodynamic (51.8%) and respiratory (36.5%) compromise with the requirement for initiation of inotropic and/or ventilatory support, which may have deteriorated their cardiovascular illness and provoked a downward spiral leading to imminent demise. It is therefore not surprising that the observed in-hospital all-cause mortality rates were doubled in the presence of pneumonia (27.0% vs. 13.8%), and the relative risk of death was over two-fold higher in patients with pneumonia compared to the rest of the cohort, even after adjustment for major clinical covariates. This is in line with previous studies reporting excess mortality in individuals with hospital acquired pneumonia reaching 30%–70% among the critically ill patients (9). A recent Japanese study has reported lower in-hospital mortality (12%) compared to our findings (11), which can be explained by inclusion of patients with the more severe HF in the present study. The Japanese study has also indicated an excess mortality in patients requiring admission to the ICU, as well as a greater risk of worsening HF and impaired long-term survival following nosocomial pneumonia (11). A British study has also demonstrated almost two-fold increased hazard ratios for in-hospital mortality in patients with pneumonia (12), which is consistent with our observations.

The present study has provided a new insight into the adverse impact on hospital acquired pneumonia on prescription patterns of evidence-based therapies for HF in patients discharged alive. In patients with HFrEF, we have observed a significantly lower prescription rates of ACEI/ARB/ARNI and beta-blockers (43.5% and 41.5%, respectively) in individuals recovering from pneumonia, compared to patients without pneumonia (84.2% and 61.7%, respectively). Following adjustment for relevant clinical variables, hospital acquired pneumonia was identified as an independent predictor of a lower likelihood of the prescription of either drug classes (odds ratio for ACEI/ARB/ARNI and betablockers, 0.75 and 0.56, respectively). There was no significant difference in the prescription of MRA and SGLT2I in patients with HFrEF with and without pneumonia. Interestingly, SGLT2I uptake has slightly exceeded that of other drug classes in HFrEF patients

recovering from pneumonia, albeit the official recommendation for their use in HFrEF has been issued in the 2021 Guidelines (approximately halfway through the study) (13). It is possible that lower prescription rates of ACEI/ARB/ARNI and beta-blockers reflect a higher incidence of haemodynamic and respiratory insufficiency occurring during hospitalisation in patients with pneumonia, which had led to a greater reluctance among the treating cardiologists to initiate these medications before discharge.

Although the ESC guidelines at the time when the study was conducted have not provided a recommendation for evidence-based therapies for HFmrEF and HFpEF, it has been a longstanding practice to prescribe renin-angiotensin-aldosterone system inhibitors and beta-blockers for the management of comorbidities (e.g., hypertension, atrial fibrillation etc.) in those patients (13, 28). This is supported by recent observational and clinical trial data indicating their broad uptake in patients discharged with HFmrEF/HFpEF (29, 30). In the present study, prescription rates of beta-blockers and MRA at discharge in patients with HFmrEF/HFpEF were lower (29.8% and 34.0%, respectively) compared with patients without pneumonia (49.4% and 45.8%, respectively) and the development of pneumonia was independently associated with a lower likelihood of providing beta-blockers and MRA at discharge in patients with HFmrEF/HFpEF. There was no difference in the prescription of ACEI/ARB/ARNI and SGLT2I. Overall prescription of SGLT2I in patients with HFmrEF/HFpEF was higher than in some of the contemporary studies (29, 30). This may reflect the high prevalence of concomitant T2DM, but also greater confidence among the treating physicians regarding the safety of SGLT2I initiation early after stabilisation in AHF. Of note, lower overall prescription of evidence-based therapies for HF at discharge in patients recovering from pneumonia may be an important contributor to their late adverse prognosis documented in earlier studies of hospital acquired pneumonia in AHF, which deserves further evaluation (11, 12).

4.1. Study limitations

Several limitations of the present study need to be acknowledged. This was a retrospective analysis of a single-centre hospital registry-based data with a limited sample size, which imposes a limitation to the generalisability of our findings. Due to the retrospective design, there is a possibility that some cases of infection other than pneumonia may have been misdiagnosed, although the diagnosis of pneumonia was based on major clinical guidelines and confirmed by documentation of specific ICD-10 codes. We did not document the reasons and circumstances leading to HF decompensation and several clinical characteristics were not systematically recorded and could not be used as covariates in the analyses, including several risk factors for pneumonia (e.g., recent hospitalisation prior to current admission, residence in the nursing home, immunosuppressive disease or therapy), pathogens isolated from microbiological samples, antibiotic regimens used, mechanical ventilation modes and duration, and reasons for not prescribing certain HF medications. Pneumonia was microbiologically confirmed in a subset of patients requiring intubation, with a positive endotracheal aspirate revealing typical gram-negative bacteria and Staphylococcus aureus, which does not rule out other causative microorganisms. Also, data on a history of previous pneumonia, or potential antibiotic use prior to hospital admission were not available, albeit this information could have improved our understanding of the risk of developing pneumonia and antimicrobial susceptibility of the causative pathogens. Furthermore, the present study has not assessed the factors contributing to the development of pneumonia or cardiovascular deterioration during pneumonia. On the basis of these limitations, observations made in the present study should be interpreted as hypothesis generating and may stimulate further prospective evaluation.

5. Conclusions

Hospital acquired pneumonia is a frequent complication in contemporary patients with AHF admitted to the ICU. Its occurrence is predicted by the more severe markers of congestion (in particular pleural effusions and higher admission lelevs of natriuretic peptides) and is more frequent in patients with *de novo* AHF, particularly in the presence of comorbidities. The development of hospital acquired pneumonia is associated with a longer and more complicated clinical course, including greater risk of haemodynamic and respiratory deterioration. Consequently, hospital acquired pneumonia is an important independent predictor of increased in-hospital all-cause mortality. Finally, patients recovering from pneumonia face a lower likelihood of being discharged with the appropriate medications for HF, which may affect their long-term outcomes. Given the clinical significance of these observations, further prospective research is required into the optimal preventive and management strategies of AHF patients suffering nosocomial pneumonia.

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 Institution review board of the Department of Cardiology of the University Clinical Centre of Serbia. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal

guardians/next of kin because of retrospective study design and analysis of anonymised data.

Author contributions

MP: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MT: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – review & editing. MV: Data curation, Investigation, Validation, Writing – review & editing. NZ: Conceptualization, Data curation, Investigation, Validation, Writing – review & editing. AS: Conceptualization, Data curation, Investigation, Validation, Writing – review & editing. DC: Conceptualization, Data curation, Investigation, Visualization, Writing – review & editing. AM: Conceptualization, Formal Analysis, Methodology, Visualization, Writing – review & editing. GK: Data curation, Formal Analysis, Methodology, Visualization, Writing – review & editing. RL: Data curation, Formal Analysis, Visualization, Writing – review & editing. MA: Formal Analysis, Methodology, Validation, Visualization, Writing – review & editing.

Conflict of interest

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

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Publisher's note

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EDITED BY
Marija Vavlukis,
University Clinic for Cardiology,
Ss. Cyril and Methodius University in Skopje,
North Macedonia

REVIEWED BY
Biljana Kuzmanovska,
Saints Cyril and Methodius University of Skopje,
North Macedonia
Mirjana Shosholcheva,
Saints Cyril and Methodius University of Skopje,
North Macedonia
Gereon Schälte,
University Hospital RWTH Aachen, Germany

*CORRESPONDENCE
Hua Jin
jhdqq2011@qq.com
Qi Liu
lq243727710@163.com
Zhe-yun Wang
wangzheyungl@163.com
Min Ge
gemin2000@outlook.com

†These authors have contributed equally to this work

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Unveiling the nexus of postoperative fever and delirium in cardiac surgery: identifying predictors for enhanced patient care

Ya-peng Wang[1†], Bei-bei Shen[2†], Cui-cui Zhu[2†], Li Li[2†], Shan Lu[2], Dong-jin Wang[1,2], Hua Jin[2*], Qi Liu[3*], Zhe-yun Wang[2*] and Min Ge[2*]

[1]Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Nanjing, China, [2]Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, The Afliated Hospital of Nanjing University Medical School, Nanjing, China, [3]Department of Critical Care Medicine, Xiangya Hospital of Central South University, Changsha, China

Background: Postoperative delirium (POD) is a significant complication observed in cardiac surgery patients, characterized by acute cognitive decline, fluctuating mental status, consciousness impairment, and confusion. Despite its impact, POD often goes undiagnosed. Postoperative fever, a common occurrence after cardiac surgery, has not been comprehensively studied in relation to delirium. This study aims to identify perioperative period factors associated with POD in patients undergoing cardiopulmonary bypass, with the potential for implementing preventive interventions.

Methods: In a prospective observational study conducted between February 2023 and April 2023 at the Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University Medical School, a total of 232 patients who underwent cardiac surgery were enrolled. POD assessment utilized the Confusion Assessment Method for the ICU (CAM-ICU), while high fever was defined as a bladder temperature exceeding 39°C. Statistical analysis included univariate and multivariate analyses, logistic regression, nomogram development, and internal validation.

Result: The overall incidence of postoperative delirium was found to be 12.1%. Multivariate analysis revealed that postoperative lactate levels [odds ratio (OR) = 1.787], maximum temperature (OR = 11.290), and cardiopulmonary bypass time (OR = 1.015) were independent predictors of POD. A predictive nomogram for POD was developed based on these three factors, demonstrating good discrimination and calibration. The prediction model exhibited a C-statistic value of 0.852 (95% CI, 0.763–0.941), demonstrating excellent discriminatory power. Sensitivity and specificity, based on the area under the receiver operating characteristic (AUROC) curve, were 91.2% and 67.9%, respectively.

Conclusion: This study underscores the high prevalence of POD in cardiac surgery patients and identifies postoperative lactate levels, cardiopulmonary bypass duration, and postoperative fever as independent predictors of delirium. The association between postoperative fever and POD warrants further investigation. These findings have implications for implementing preventive strategies in high-risk patients, aiming to mitigate postoperative complications and improve patient outcomes.

KEYWORDS

cardiac surgery, fever, CPB, postoperative delirium, prediction model

1. Introduction

Delirium is a disease characterized by acute cognitive decline, fluctuating mental status, consciousness impairment, lack of attention, or confusion (1). It is a recognized adverse prognostic marker in intensive care unit (ICU) patients, associated with increased incidence, mortality, and the development of long-term neurocognitive deficits (2). The incidence of postoperative delirium in cardiac surgery patients ranges from 16% to 73% (3–7), and is associated with early postoperative mortality, prolonged hospitalization, discharge to long-term care facilities, functional and cognitive decline, and increased healthcare costs (8, 9). While delirium is typically considered a short-term cognitive impairment, long-term consequences, such as functional and cognitive decline, are possible.

Given the high incidence of postoperative delirium in cardiac surgery patients, and its impact on functional outcomes and quality of life, it is essential to study the association between delirium and functional outcomes in this population. However, cardiac surgeons, anesthesiologists, intensivists, and nurses may fail to recognize delirium in up to 84% of patients (10, 11). Although the EuroSCORE, a cardiac surgical risk assessment system, is associated with postoperative mortality and delirium, no studies have reported on the association between postoperative fever and delirium (7, 12, 13). Postoperative fever is more common in cardiac surgery and is associated with increased cerebral embolic load after cardiopulmonary bypass and increased release of chemotactic factors (14).

Therefore, this study aims to determine the preoperative, operative, and postoperative fever-related factors associated with postoperative delirium in patients undergoing cardiopulmonary bypass. Successful identification of these factors could lead to preventative interventions in high-risk patients, with the hope of preventing subsequent complications.

2. Materials and methods

2.1. Study design

Participants between February 2023 and April 2023, we conducted a prospective observational study at the Department of Cardio-Thoracic Surgery. The study was ethically approved by the institutional review board was registered on the Chinese Clinical Trial Registry (ChiCTR2000038762).

2.2. Participants

Between February 1, 2023, and April 14, 2023, this study recruited patients who underwent cardiac surgery under general anesthesia for cardiopulmonary bypass with the inclusion criteria of being admitted to the Cardio-Thoracic Surgery ICU for more than 24 h and providing written informed consent after receiving information sheets and potential risk disclosures. Exclusion criteria included patients under the age of 18, those diagnosed with delirium and stroke during admission, those with a Glasgow Coma Scale score of ≤8 points who required intubation and mechanical ventilation, those who were deeply sedated (as determined by Richmond Agitation Sedation Scale scores of −4 and −5), and those with alcohol withdrawal reactions (15), patients with infective endocarditis and preoperative fever. A total of 232 eligible patients were enrolled (**Figure 1**), and measures were taken to ensure the validity and robustness of the research findings.

Delirium is a challenging condition to diagnose in the intensive care unit (ICU), and many patients may go unrecognized. Despite the use of many delirium assessment instruments in published studies, the most widely used instrument is the Confusion Assessment Method (CAM) (16). CAM has a sensitivity of 94% and specificity of 89% compared to the gold standard diagnosis by psychiatrists (17). CAM-ICU was developed to accurately diagnose delirium in ICU patients who are often unable to speak due to mechanical ventilation. CAM-ICU has a sensitivity of 95% and specificity of 89% (16, 18).

2.3. Definition of end-points

In surgical patients who do not have permanent neurological impairment, postoperative delirium (POD) is identified using the Confusion Assessment Method for the ICU (CAM-ICU) (18) and evaluated twice daily for seven consecutive days. This method allows for consistent monitoring and diagnosis of POD, which is a common complication after surgery and can have significant negative effects on patient outcomes (19).

We define high fever as bladder temperature greater than 39°C and continuously monitor body temperature for 24 h postoperatively. This definition of high fever allows for consistent and accurate measurement of postoperative fever, which can indicate a pathological state and may require further evaluation and treatment.

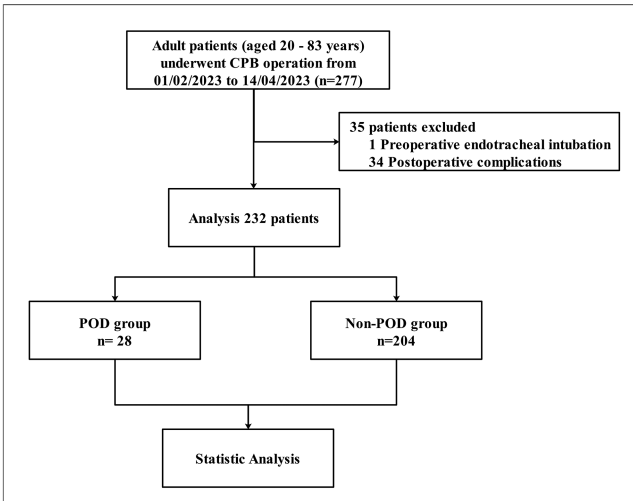

FIGURE 1
Study flowchart.

2.4. Statistical analysis

In this study, we conducted a comprehensive analysis of the data using a range of statistical methods. Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and reported either as mean ± standard deviation or median with interquartile ranges (Q1–Q3), depending on their distribution. Student's *t*-test and Mann–Whitney *U*-test were used to analyze normally and non-normally distributed continuous variables, respectively. Categorical variables were presented as frequencies and percentages and analyzed using either chi-squared test or Fisher's exact test. All statistical analyses were two-tailed, and a *P*-value less than 0.05 was considered statistically significant. Additionally, we employed single-variable binary logistic regression analysis to assess the relationship between various variables and the outcome, calculating odds ratios and 95% confidence intervals.

2.5. Model development

After conducting univariate analysis, variables that demonstrated statistical significance with a *P*-value less than 0.05 were included in a stepwise (backward: conditional) multivariate logistic regression analysis model to establish a predictive model. Furthermore, we constructed a nomogram using the variables with a *P*-value less than 0.05 in the multivariate analysis to facilitate clinical decision-making. This approach allowed us to identify the most significant predictors of the outcome of interest and develop a useful tool to aid in clinical management.

2.6. Model performance and internal validation

To assess the performance of the developed nomogram for predicting the probability of postoperative neurological complications in aortic surgery, we conducted internal validation using the bootstrap method with 1,000 resamples, evaluating both discrimination and calibration. The discrimination ability was assessed using the C-statistic, equivalent to the area under the receiver operating characteristic (ROC) curve (20). Calibration was assessed by plotting calibration curves and calculating the Brier score, which is the squared difference between observed and predicted probabilities (21). Furthermore, we conducted a decision curve analysis (DCA) to assess the clinical usefulness of the nomogram across various threshold probabilities. The statistical analysis was performed using IBM SPSS Statistics 26 and R.4.2.2, and significance was determined at $P < 0.05$. This rigorous approach enabled us to gain valuable insights into the data and identify potential predictors of the outcome of interest.

3. Results

3.1. Patients baseline characteristics

During the research period from February 1, 2023, to April 14, 2023, our analysis included a total of 232 patients, as shown in **Figure 1**.

TABLE 1 Basic characteristics in POD and Non-POD groups.

Characteristic	POD (*N* = 28)	Non-POD (*N* = 204)	*P*-value
Sex male (*N*, %)	15 (53.6)	114 (55.9)	0.817
Age (years)[a]	60.50 (50.0–64.0)	61.00 (52.0–69.0)	0.294
BMI (kg/m^2)[a]	25.0 (22.6–26.5)	23.43 (21.46–26.89)	0.421
Hypertension (*N*, %)	16 (57.1)	114 (55.9)	0.900
CAD (*N*, %)	6 (21.4)	63 (30.9)	0.305
Hepatitis (*N*, %)	2 (7.1)	8 (3.9)	0.771
Renal insufficiency (*N*, %)	1 (3.6)	7 (3.4)	1.000
Atrial fibrillation (*N*, %)	11 (39.3)	59 (28.9)	0.263
NYHK			0.301
Ⅰ (*N*, %)	3 (11.1)	22 (10.8)	
Ⅱ (*N*, %)	9 (33.3)	48 (23.6)	
Ⅲ (*N*, %)	15 (55.6)	122 (60.1)	
Ⅳ (*N*, %)	0 (0.0)	11 (5.4)	
Smoking (*N*, %)	4 (14.3)	38 (18.6)	0.576
Alcohol (*N*, %)	2 (7.1)	28 (13.7)	0.501
Surgery procedure			0.473
Valve surgery (*N*, %)	9 (32.1)	87 (42.6)	
CABG (*N*, %)	0 (0.0)	9 (4.4)	
Valve + CABG	2 (7.1)	17 (8.3)	
Valve + Maze operation	8 (28.6)	38 (18.6)	
Aortic surgery	7 (25.0)	43 (21.1)	
Congenital heart disease	2 (7.1)	10 (4.9)	
CBP time (min)[a]	168.00 (135.5–193.5)	122.00 (96.0–158.0)	0.0001
Lactate[a]	2.35 (1.53–3.60)	1.5 (1.20–2.10)	0.0001
Tmax (*N*, %)	20 (71.4)	34 (16.7)	0.0001
CCU day[a]	6.00 (4.00–8.00)	3.00 (2.00–4.00)	<0.0001
Length of stay[a]	19.50 (16.25–26.00)	18.00 (15.25–22.00)	0.151

BMI: body mass index; CAD: coronary artery disease; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass.
[a]Values are expressed as interquartile spacing [median (¼–¾ digits)].

Preoperative risk factors, such as age, gender, BMI, hypertension, NYHA class, as well as important intraoperative risk factors, including surgical category and cardiopulmonary bypass time (CPB), were identified, as presented in **Table 1**. The overall incidence of POD was found to be 12.1%, as shown in **Table 1**, and was significantly associated with CPB and postoperative lactate levels. Moreover, there were significant variations in Tmax between the POD and Non-POD groups. POD was also found to be related to ICU length of stay.

3.2. Identifying predictors

The results of multivariate analysis for POD are listed in **Table 2**, For this phase of the analysis, three variables were determined to be statistically significant. Multivariate analysis identified that lactate [Odds ratio (OR) = 1.787, 95% CI, 1.192–2.785], Tmax (OR =

TABLE 2 Multivariable logistic regression analysis of independent risk factors for POD after cardiac surgery.

Variables	β	OR	95% CI
Lactate	0.581	1.787	1.192–2.785
Tmax	2.423	11.290	4.369–32.129
CPB (min)	0.014	1.015	1.004–1.026

β: regression coefficient; OR: odds ratio; 95% CI: 95% confidence interval; CPB: cardiopulmonary bypass.

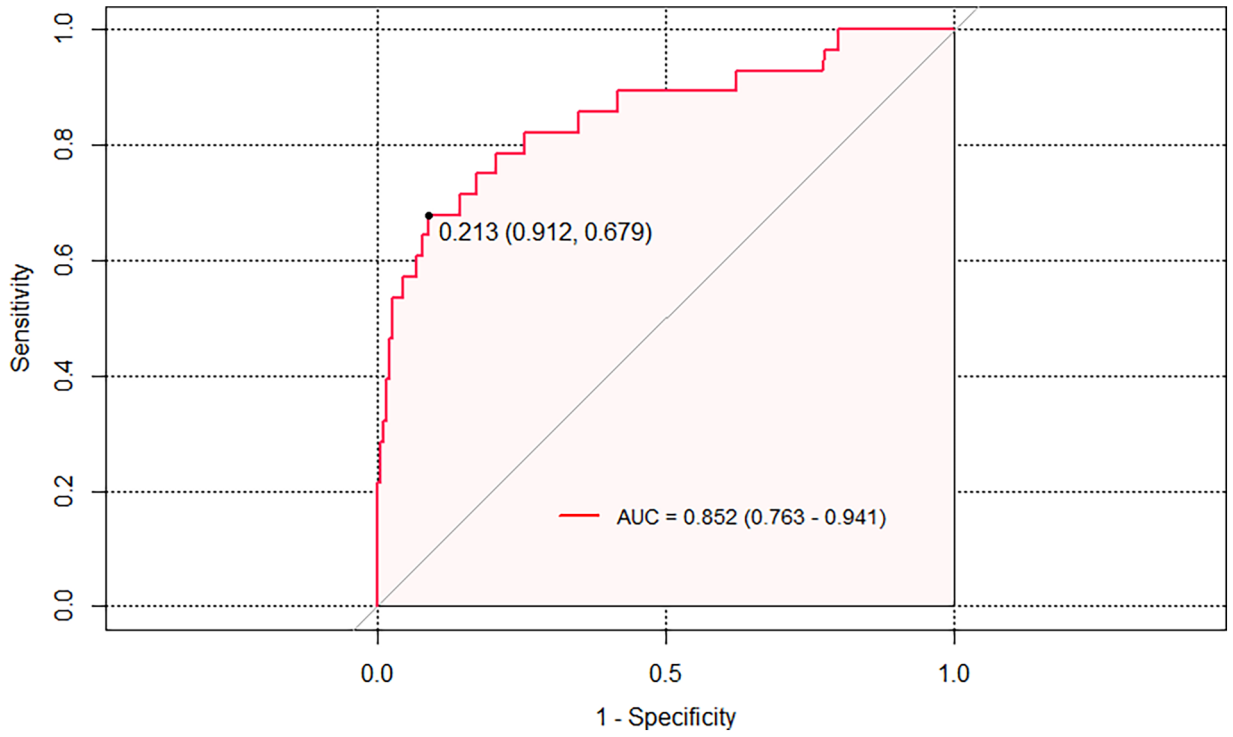

FIGURE 2
AUROC curve analysis of the model for POD; AUROC = 0.852 which is equal to a c-statistic.

11.290, 95% CI, 4.369–32.129), and CPB time (OR = 1.015, 95% CI, 1.004–1.026) were independent predictors for POD (**Table 2**).

3.3. Model performance and internal validation

The prediction model exhibited a C-statistic value of 0.852 (95% CI, 0.763–0.941), demonstrating excellent discriminatory power. Sensitivity and specificity, based on the area under the receiver operating characteristic (AUROC) curve, were 91.2% and 67.9%, respectively (**Figure 2**). The apparent calibration curve closely approximated the ideal 45° line, indicating consistent agreement between observed and predicted probabilities within the development cohort (**Figure 3**). To mitigate any potential overoptimism in the model, internal validation using the 1,000 bootstrap approach was performed, which confirmed its robust discrimination ability with a Brier score of 0.0686 (**Figure 3**). Utilizing these three candidate variables, we constructed a nomogram for predicting the probability of postoperative delirium (**Figure 4**). Furthermore, decision curve analysis demonstrated a favorable net clinical benefit (**Figure 5**).

4. Discussion

Postoperative fever after cardiac surgery is a well-known phenomenon (22, 23). It primarily arises from surgical tissue injury and the release of pro-inflammatory cytokines during CPB (22, 24, 25). Consequently, the etiology of fever in the majority of cases is non-infectious (26), particularly within the first 48 h post-surgery (27). While infections appear to be relatively rare (22, 23, 28), they represent a significant complication for patients with implanted cardiac prosthetic devices, being associated with high incidence and mortality rates (27, 29). Therefore, empirical antibiotic therapy is frequently initiated in patients experiencing postoperative fever after cardiac surgery, especially when prosthetic materials are used, potentially leading to overtreatment. Despite the recognized significance of CPB in the development of postoperative inflammation and fever following certain types of cardiac surgeries involving prosthetic materials, a comprehensive evaluation of the natural course of postoperative inflammation and fever related to CPB and implanted prosthetic materials is yet to be undertaken.

Although postoperative fever following cardiac surgery is a common occurrence (30), with an incidence as high as 38%, its etiology and significance remain incompletely understood (31). There are competing theories regarding its underlying pathophysiology. Fever may reflect an inflammatory response, which could be attributed to the surgical trauma itself or to the interaction between blood and foreign surfaces within the cardiopulmonary bypass (CPB) circuit (25, 32). Additionally, fever may serve as an indicator of altered hypothalamic thermoregulatory center function, signaling brain injury (33, 34).

Regardless of the underlying causes, fever has been demonstrated to be associated with adverse postoperative complications (25), including unfavorable cerebral outcomes (34, 35). In a recent study involving 300 patients, we described a significant relationship between postoperative hyperthermia at 6

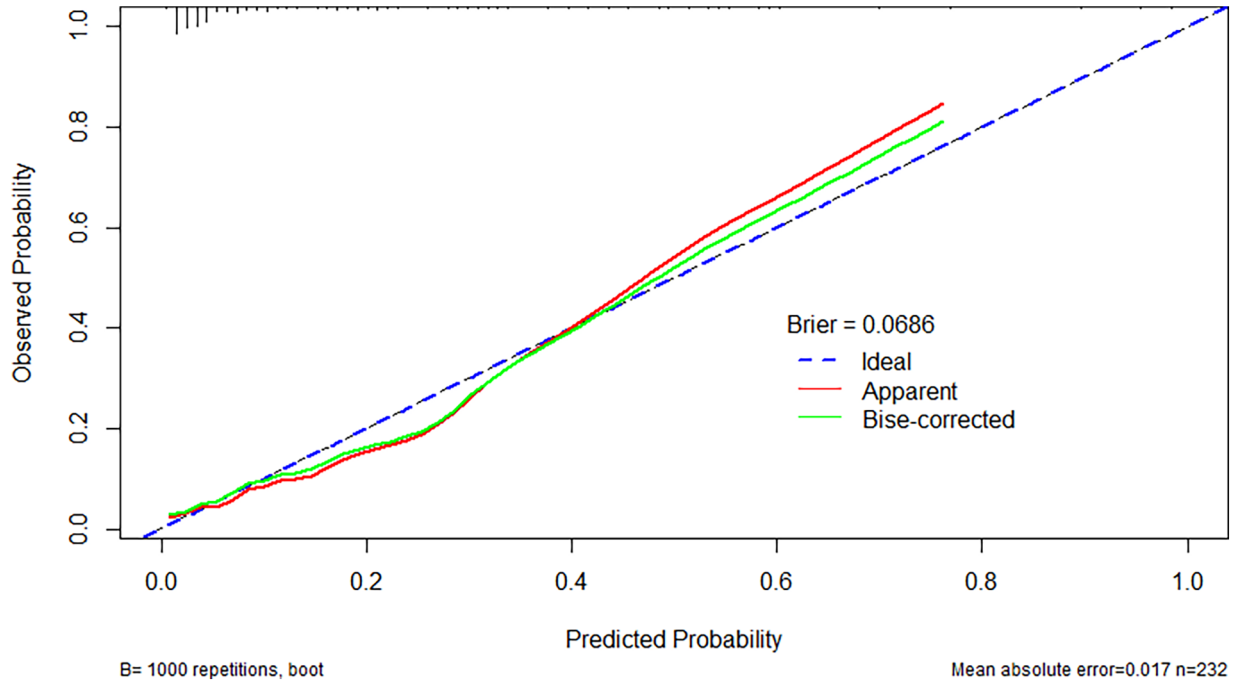

FIGURE 3
The brier score of the model was 0.0686, indicating good calibration.

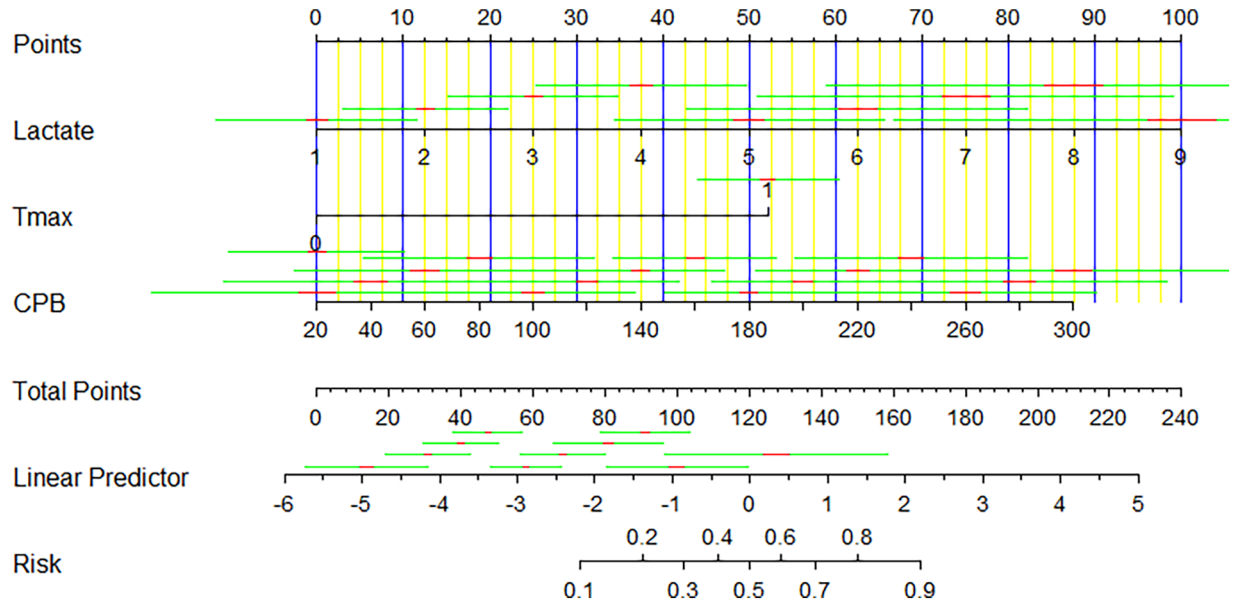

FIGURE 4
Diagnostic nomogram of model for predicting POD after cardiac surgery.

weeks following coronary artery bypass graft surgery and decline in neurocognitive function (25). The association between fever and stroke following bypass surgery remains unclear. However, even mild hyperthermia (1–2°C) in non-cardiac surgical cases has been shown to result in poorer outcomes, such as increased infarct size, deteriorating neurological function, and elevated mortality rates (25, 36).

The fluctuation in serum lactate levels serves as a reliable prognostic biomarker for mortality in critically injured patients (37). Another study demonstrates that lactate values reflect ischemia reperfusion more rapidly and reliably than novel biomarkers (38). Elevated lactate levels in cardiac surgery patients during the perioperative period are associated with adverse postoperative outcomes. Perioperative lactate levels can

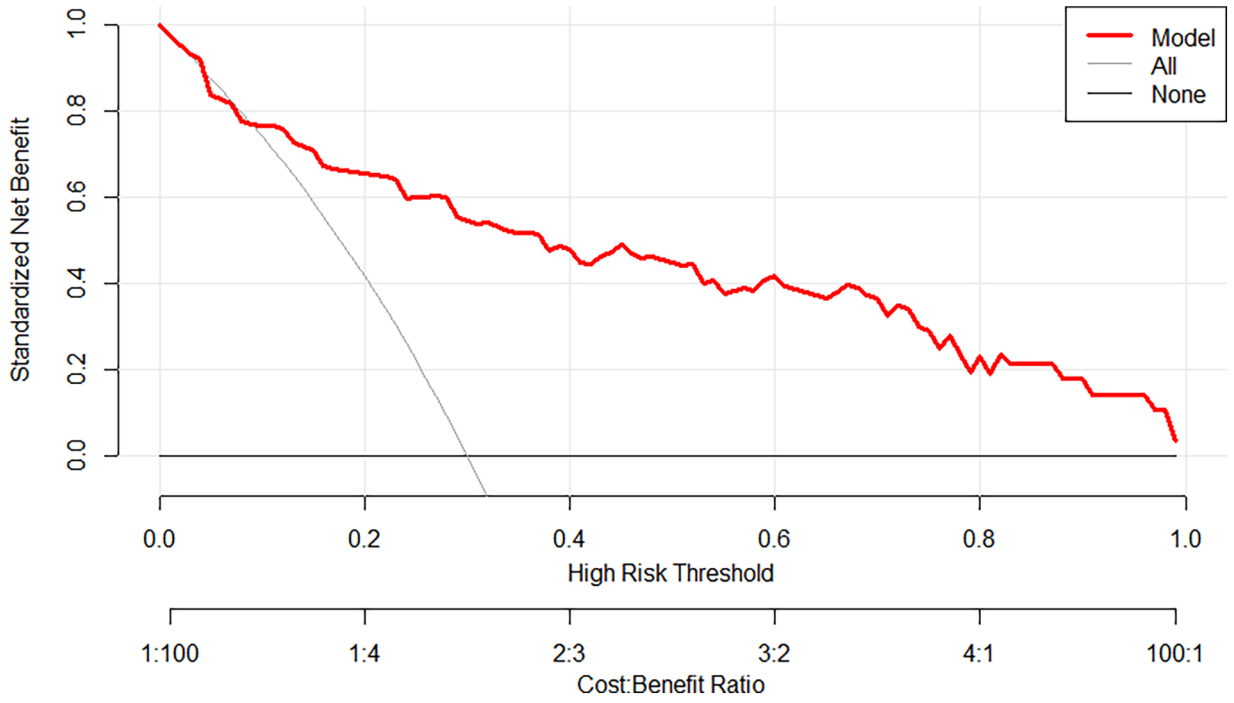

FIGURE 5
Decision curve analysis (DCA) for the study's nomogram.

serve as a predictor for the occurrence of POD in elderly trauma patients (39, 40). In our study, postoperative hyperlactatemia reflects the circulatory state during surgery and therefore correlates with the development of POD. Our research findings are consistent with these study results.

5. Conclusion

In conclusion, our study findings indicate that POD is highly prevalent among cardiac surgery patients. Postoperative lactate levels, cardiopulmonary bypass duration, and postoperative fever emerge as independent predictive factors for the development of postoperative delirium. Furthermore, the identification of postoperative fever, which is one of the intraoperative variables, may be related with the occurrence of POD.

6. Limitation

In summary, our study has some limitations that should be taken into consideration when interpreting the findings. Firstly, our study was performed at a single center, which could potentially restrict the generalizability of the findings. Secondly, the relatively small sample size could have an impact on the statistical power of the study. Additionally, the study's observational design prevents the establishment of causal relationships, and there may be additional factors not considered in the analysis. External validation of the predictive nomogram is necessary before its clinical implementation.

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 Institutional review board of The Nanjing Drum Tower Hospital of the Affiliated Hospital of Nanjing University Medical School. 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. 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

Y-pW and B-bS conducted a comprehensive literature review and performed the statistical analysis. D-jW, MG, and Z-yW were responsible for the study's conception and design. HJ, SL,

and QL carried out data collection and managed the database. Y-pW and C-cZ drafted the manuscript. Y-pW and QL made substantial contributions to manuscript revisions and finalization. All authors contributed to the article and approved the submitted version.

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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.2023.1237055/full#supplementary-material

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EDITED BY
Marija Vavlukis,
University Clinic for Cardiology,
Ss. Cyril and Methodius University in Skopje,
North Macedonia

REVIEWED BY
Marco Marini,
Azienda Ospedaliero Universitaria Ospedali Riuniti, Italy
Antoniu Petris,
Grigore T. Popa University of Medicine and Pharmacy, Romania
Daniel Lovric,
University Hospital Centre Zagreb, Croatia

*CORRESPONDENCE
Amine Bouchlarhem
✉ aminbouchlarhem63@gmail.com

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Cardiac intensive care unit: where we are in 2023

Amine Bouchlarhem[1,2]*, Zakaria Bazid[1,2], Nabila Ismaili[1,2,3] and Noha El Ouafi[1,2,3]

[1]Faculty of Medicine and Pharmacy, Mohammed First University, Oujda, Morocco, [2]Department of Cardiology, Mohammed VI University Hospital, Mohammed First University, Oujda, Morocco, [3]Faculty of Medicine and Pharmacy, LAMCESM, Mohammed First University, Oujda, Morocco

Cardiac intensive care has been a constantly evolving area of research and innovation since the beginning of the 21st century. The story began in 1961 with Desmond Julian's pioneering creation of a coronary intensive care unit to improve the prognosis of patients with myocardial infarction, considered the major cause of death in the world. These units have continued to progress over time, with the introduction of new therapeutic means such as fibrinolysis, invasive hemodynamic monitoring using the Swan-Ganz catheter, and mechanical circulatory assistance, with significant advances in percutaneous interventional coronary and structural procedures. Since acute cardiovascular disease is not limited to the management of acute coronary syndromes and includes other emergencies such as severe arrhythmias, acute heart failure, cardiogenic shock, high-risk pulmonary embolism, severe conduction disorders, and post-implantation monitoring of percutaneous valves, as well as other non-cardiac emergencies, such as septic shock, severe respiratory failure, severe renal failure and the management of cardiac arrest after resuscitation, the conversion of coronary intensive care units into cardiac intensive care units represented an important priority. Today, the cardiac intensive care units (CICU) concept is widely adopted by most healthcare systems, whatever the country's level of development. The main aim of these units remains to improve the overall morbidity and mortality of acute cardiovascular diseases, but also to manage other non-cardiac disorders, such as sepsis and respiratory failure. This diversity of tasks and responsibilities has enabled us to classify these CICUs according to several levels, depending on a variety of parameters, principally the level of care delivered, the staff assigned, the equipment and technologies available, the type of research projects carried out, and the type of connections and networking developed. The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have detailed this organization in guidelines published initially in 2005 and updated in 2018, with the aim of harmonizing the structure, organization, and care offered by the various CICUs. In this state-of-the-art report, we review the history of the CICUs from the creation of the very first unit in 1968 to the discussion of their current perspectives, with the main objective of knowing what the CICUs will have become by 2023.

KEYWORDS

acute cardiovascular care, cardiac intensive care unit, coronary care unit, acute coronary syndrome, healthcare system

1. Introduction

Cardiac critical care is an area of intense basic, translational, and clinical research (1). This began with the establishment of the first coronary intensive care units (CCUs) dedicated to the management of acute coronary syndrome (ACS) in the 1960s (2). The main objective of this period was to develop the means of myocardial revascularization, first with the arrival of thrombolytic therapy, then with the development of percutaneous coronary interventions, first with balloon, then with stenting, which revolutionized the management of acute coronary syndrome. Over time, it has been shown that acute cardiac intensive care is not only limited to ACS but to other cardiovascular emergencies, for which reason CCUs have evolved into what are now called cardiac intensive care units (CICUs) (3). This evolution has been accompanied by a change in the phenotype of patients admitted to CICUs, as ACS is no longer the leading cause of admission ahead of cardiogenic shock and acute heart failure which currently dominate the rate of admissions to modern CICUs (4). According to the World Health Organization (WHO) 2020 mortality analysis report, cardiovascular disease has remained the leading cause of death worldwide for the past 20 years. However, the number of deaths from heart disease has increased by more than 2 million since 2000, reaching nearly 9 million deaths in 2019. As a result, heart disease now accounts for 16% of total deaths from all causes, and given the high mortality rate and the complexity of managing cardiovascular emergencies, the phenotype of patients who generally have several associated comorbidities, and the translational nature of cardiovascular emergencies, the development of these units was a crucial necessity (5).

The results observed during the first half of the 20th century did not show any decrease in intra-hospital mortality in patients hospitalized for a myocardial infarction in a medical service not equipped with personnel trained in intensive care, and not equipped with telemetric monitoring despite the therapeutic means used during that period. It was not until 1961, and after the alarming mortality rates of up to 30% (6) in patients hospitalized with coronary occlusion, that Desmond Julian (2) created the very first unit dedicated specifically to the hospitalization of coronary patients and named it the "coronary intensive care unit (CCU)". Julian's vision was to decrease the mortality rate and he saw that it was necessary to have trained intensive care personnel, cardiopulmonary resuscitation (CPR) available in the hospital unit, and telemetric monitoring for all patients. Soon after, this concept was adopted by several healthcare systems, and the benefits of these units were evident from the first year of operation, with a significant decrease in the mortality rate to 15% after 1 year of activity (7) and between 3% and 6% after 2 years of activity (6).

2. The coronary care unit (CCU) concept

Desmond Julian was the first to introduce the concept of a unit dedicated only to patients with acute coronary syndrome, with the aim of early detection and treatment of ventricular arrhythmias, the main cause of death in these patients (8). According to Julian, in order to reduce mortality in patients with ACS, we need

- Continuous electrocardiographic monitoring with an alarm system that detects arrhythmias.
- Access to early and effective cardiopulmonary resuscitation with external defibrillation.
- All heart attack patients must be admitted to the same unit, where medical and paramedical staff have specialized training in cardiological care and are equipped with drugs that act on the heart.
- The ability of trained nurses to initiate cardiopulmonary resuscitation in the absence of doctors is at the origin of the concept of the Coronary Intensive Care Unit (CCU).

For these reasons, Desmond Julian founded the first coronary intensive care unit in Sydney in October 1961 (**Figure 1**) (8) and is considered the pioneer of the concept. The concept was rapidly adopted in Canada, with Kenneth Brown transforming a small four-bed room into a coronary intensive care unit at Toronto General Hospital (Canada) in March 1962, with Hughes Day adopting the concept at Bethany Hospital in Kinshasa in May 1962, and Lawrence Meltzer and Roderick Kitchell at Presbyterian Hospital in Philadelphia in November 1962 (9, 10) (**Table 1**).

In 1967, Bernard Lown published an article in the American Journal of Cardiology on the new perspectives and orientations of the CCU. Firstly, he presented the unit in which he practiced at the Peter Bent Brigham Hospital, a unit with four private single rooms, each equipped with a continuous electrocardiographic monitor, characterized by the presence of an alarm for arrhythmias and severe variations in heart rate. Adjacent to the

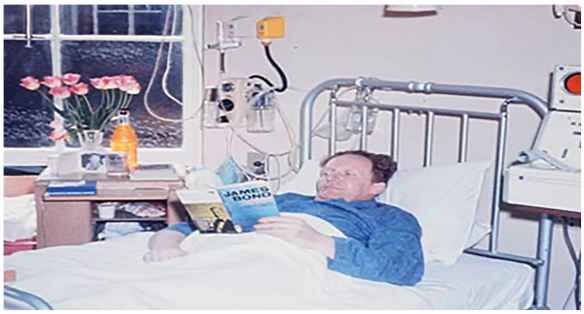

FIGURE 1
Desmond Julian simulates the experience of the first patient admitted to the coronary intensive care unit at Sydney hospital [reproduced with permission from (8)].

TABLE 1 Summarizes the chronology of the founding of the first coronary intensive care units.

Hospital structure	Founder	Date
Sydney Hospital	Desmond Julian	October 1961
Toronto General Hospital	Kenneth Brown	March 1962
Bethany Hospital in Kinshasa	Hughes Day	May 1962
Presbyterian Hospital in Philadelphia	Lawrence Meltzer et Roderick Kitchell	November 1962

rooms was a monitoring room dedicated to the nursing staff, equipped with a large oscilloscope showing all inpatient patterns (**Figure 2**) (11). According to Lown and colleagues, among the many rhythm changes in the acute phase of myocardial infarction, there are those that are benign and should be ignored and others that are more serious and should be considered prodromes of serious arrhythmias, mainly premature ventricular contraction (11, 12) bradycardia and finally atrioventricular block (AVB). The management of arrhythmias should include preventive treatment, as well as the removal of triggering factors, mainly pain, extreme bradycardia, heart failure, and psychological stress.

After the well-deserved success in preventing severe arrhythmias and decreasing the in-hospital mortality rate, the next battle was the problem of heart failure, since it was becoming the leading cause of death along with cardiogenic shock. Several studies were interested in studying the effects of myocardial infarction (MI) on the cardiorespiratory and hemodynamic systems, and despite the difference in study methods and patient phenotypes, there was a consensus on the hemodynamic and respiratory changes after MI, especially in patients with cardiogenic shock (13, 14). The most typical alteration was the association of a decrease in cardiac output associated with an increase in peripheral vascular resistance (16).

In 1970, one of the great advances in the evaluation of the cardiac pump in MI was the pulmonary artery catheterization used by Swan and Ganz, hence the name "Swan Ganz catheter" or "invasive hemodynamic monitoring by the Swan Ganz method" (17), which allowed the adaption of the medical treatment of heart failure in the acute phase of an MI according to the degree of failure by setting up a classification based on cardiac index, capillary pulmonary pressure, and clinical signs (18). This invasive hemodynamic monitoring, which has become routine in the daily practice of patients hospitalized in coronary intensive care units in North American countries, was little practiced or even neglected, in the United Kingdom, due to the limited number of centers with the expertise and resources necessary for this type of monitoring (2). Over time, invasive monitoring has become increasingly used in developed European and American countries, especially in patients with cardiogenic shock, right heart failure, or pulmonary hypertension (19), and since infarct size was considered a major prognostic factor, the limitation of myocardial size became a therapeutic pillar in the management of patients with myocardial infarction, and it was due to Chazov that thrombolytic therapy was introduced as a treatment for myocardial infarction (8).

3. Cardiac intensive care unit (CICU)

3.1. From coronary intensive care unit to cardiac intensive care unit

After validating the effectiveness of coronary intensive care units, and overcoming the main etiologies of mortality in

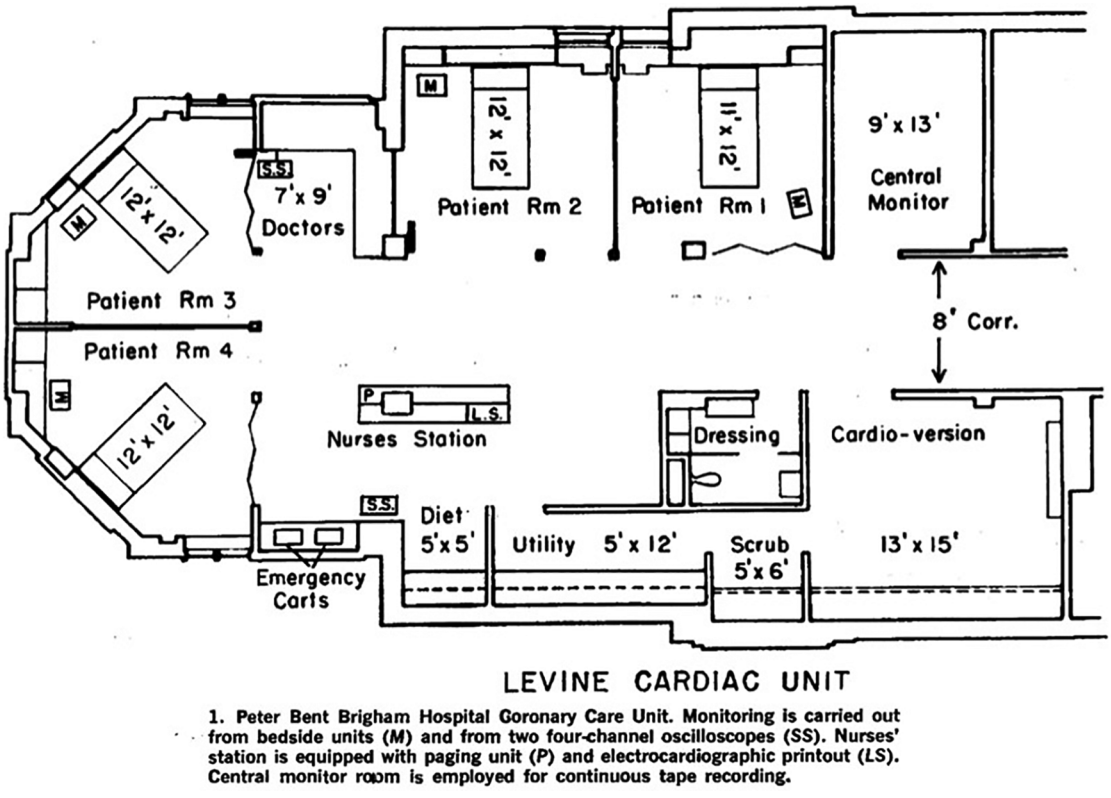

FIGURE 2
The architectural plan of the coronary intensive care unit founded by Bernard Lown at the peter bent brigham hospital (15).

patients with MI, it was observed that patients hospitalized in a CCU may require artificial ventilation, renal replacement therapy, central venous access, and cardiopulmonary arrest management, thus, cardiovascular emergencies are not only limited to the management of MI but also valvular disease, decompensated heart failure, severe pulmonary embolism, severe rhythm and conduction disorders, and postoperative cardiac surgery patients, for which coronary intensive care units evolved into what is now called cardiac intensive care units (CICUs) (20).

This concept of the CICU is quite recent (21), and it is only since the beginning of the 21st century that we started to talk about it. It is a unit that is responsible for providing increasingly complex care requiring a high level of skills to manage both cardiac and non-cardiac problems. This complexity is explained by several factors which include the age-dependent demographics of the population and associated comorbidities, the evolution of circulatory support modalities for refractory heart failure, the evolution of strategies after recovered cardiac arrest, and also the evolution of recommendations for the management of acute coronary syndromes.

It should be noted that today the ICU is no longer a cardiac rhythm monitoring unit, but rather a landing platform for patients with several associated comorbidities (27), on the one hand because of their overly charged surgical medical history, and on the other because of the complexity of the admitting pathology (22).

3.2. The definition of a CICU

The CICU is an administratively identified hospital unit, responsible for the specialized management of acute cardiovascular diseases. This unit is able to offer patients continuous telemetric monitoring and is thus characterized by the availability of medical and paramedical staff trained in the management of cardiovascular emergencies (23). This unit must have a well-defined organization in order to offer expertise 24 h a day, 7 days a week, in the management of acute cardiovascular diseases in consultation with the other specialties of the hospital.

Among the responsibilities of this unit is to provide a specialized cardiovascular environment to manage hospitalized patients in their entirety and not only on the cardiovascular level, as well as to ensure follow-up at discharge and in the long term. The CICU is responsible firstly for ensuring immediate access to care for clinically unstable patients by assisting with failing vital functions in patients with acute cardiovascular conditions, secondly for managing the admitting pathology, and then for ensuring a long-term specialized cardiovascular follow-up. For this, each ICU must have the appropriate equipment, technologies, and diagnostic means, as well as all the therapeutic means, whether medical, interventional, or surgical, in order to take care of the patient in accordance with the guidelines of the learned societies.

The medical responsibility for a ICU is assigned to a specialized cardiology team, under the supervision of a cardiology director, who decides on the care of all patients. Ideally, these medical staff should have qualified training in cardiac intensive care and ICU management (24).

3.3. Similarities and differences between an intensive care unit (ICU) and CICU

Given the current development in technology and increasingly sophisticated therapeutic means, there are now many similarities between ICUs and CICUs, but there are several important differences, mainly in the phenotype of patients admitted to ICUs compared to CICUs.

If the pathology of admission in a CICU remains an acute cardiovascular condition, then this is not the case in an ICU, since the diagnosis of admission can be a severe trauma up to septic shock. Although the pathology of admission to a CICU is acute cardiovascular disease, the patient has every right to develop hemorrhage, respiratory failure, or infection for that matter, the ICU team must first be intensivist before being cardiologic, and if this is not the case, then there will be an inescapable collaboration between the ICU and CICU care teams (**Figure 3**) (25).

In order to properly manage these patients with cardiovascular conditions, but with respiratory, neurological, and renal repercussions, management protocols must be codified and written in collaboration with the ICU medical team.

3.4. The organizational model and human resources of a CICU

The organizational structure of an intensive care unit has always been a subject of debate since all studies conducted in this sense have confirmed that this organizational model is a determining element in the quality and short- and medium-term outcome of care (26).

Cardiac intensive care units are classically divided into closed and open units. In an open unit, several physicians can admit patients and decide on the therapeutic management, thus ensuring full medical responsibility for all patients, whereas, in a closed unit, the admission of patients is under the responsibility of a single physician, who directs the therapeutic decisions. This organizational concept is not only delimited by the decision to admit patients and the therapeutic decisions but also by the staffing. In the case of an open unit, the staff is not constant, and of different disciplines, but in a closed unit, the staff is the same for all patients, and of the same discipline. Another advantage to be added for closed units is the fact that having an administrative framework allows the adjustment of the vision between the different stakeholders in the management of the patient to have well-defined protocols and objectified progress.

In 2019, a systematic review with a meta-analysis was carried out by Qian Yang et al. (27) on the mortality and clinical course of patients hospitalized in a closed intensive care unit compared to an open intensive care unit and found a higher mortality rate

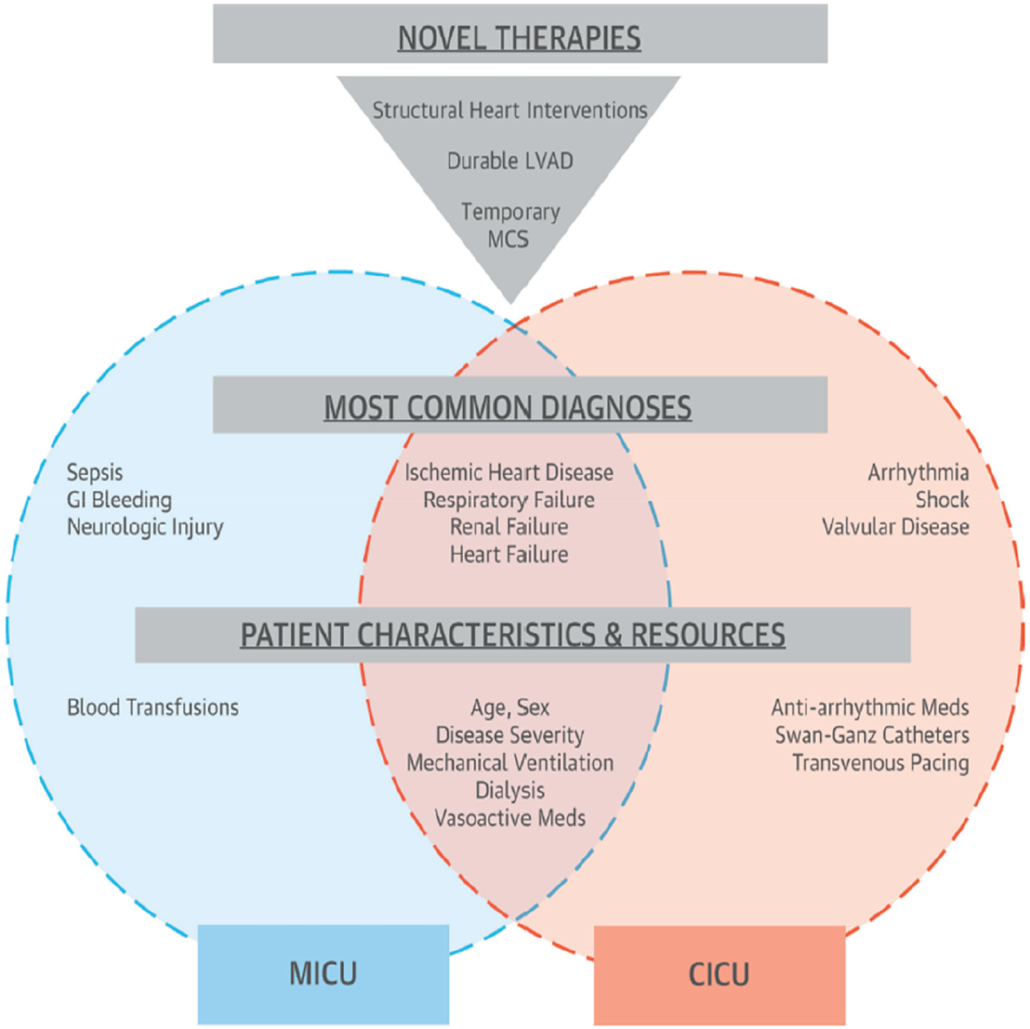

FIGURE 3
The possible differences and similarities between ICUs and CICUs (5).

in open vs. closed units with (OR: 1.31, 95% CI: 1.17–1.48; $p = .00001$). Another systematic review with meta-analysis was published in 2021 with more studies included (28). The result showed that the mortality rate in closed units was lower than in open units, but with no change in overall mortality, length of hospital stay, or severity of clinical characteristics. This difference could be explained by the constant presence of an intensivist in closed units, as well as the codification of protocols and therapeutic decisions in these closed units.

Among the reasons that explained this superiority of closed units over open ones was the satisfaction of the nursing staff in this type of unit, as well as the improvement and prioritization of responsibilities and communication among the nursing staff (29).

Regarding the difference between closed and open CICUs, few studies have been published in this sense. In 2021, a retrospective study over a period of four years was conducted in the United States to objectify the difference between demographic characteristics, clinical, management, and in-hospital mortality, at 30 days and after 1 year of a stay in a closed vs. an open CICU (26). Results for demographic parameters were similar. With regard to interventional procedures, closed ICUs performed more procedures than open ICUs. In terms of outcomes, ICU mortality rates were lower in closed units (6.9%) than in open units (7.3%) (OR, 0.70; 95% CI: 0.52–0.94; $p = 0.02$), and for median length of stay and in-hospital management costs, there was no difference between the two models. The same study was carried out by Katz et al. in Germany to compare the effectiveness of the two models on CICUs, the result did not show a significant difference in mortality but the length of hospital stay was reduced in the closed units compared to the open ones (30).

In conclusion, despite the difference that was limited to mortality for some studies, and to the length of hospitalization for other studies between the closed and open model, the superiority of the closed ICUs remains well established and clearly saw an improvement in communication, satisfaction, and thus therapeutic protocols compared to the open models.

The organizational model by itself is not enough to have optimal performance in a CICU, the human resources of a CICU represent an essential unit in the quality of care.

• The human resources of a CICU are represented as follows:

1. The medical staff

The medical staff of an ICU is the medical team in charge of taking care of the patients in consultation with the paramedical team under the direction of a unit director. This staff is usually made up of cardiology residents in training with or without the presence of a cardiologist intensivist. The presence or absence of an intensivist from a CICU is an issue that has been the subject of much controversy (31).

A study by Na et al. discussed the association between mortality in a CICU and the presence or absence of an intensivist in the unit (32) and found very high mortality in the group where the intensivist was absent by a percentage of 8.8% compared to 4.1% with a statistically significant difference ($p < 0.001$). Another study by NA et al. compared the survival of patients with cardiogenic shock between units with an intensivist and without an intensivist (33) and the result was surprising, with a mortality of 30.6% in units without intensivists with a mortality of 17.6% in units with an intensivist and a clearly significant difference ($p < 0.001$) between groups.

However, the phenotype of patients admitted to the CICU is not always stable (24) which leaves us to ask the question: when and for which patient phenotype is the presence of an intensivist in a CICU mandatory? This is the question that will be answered in the section titled "CICU classification".

2. The nursing staff

The nursing staff has represented a pillar in the care of patients admitted to the CICU since the creation of the first unit (34), and despite the considerable advances in technology currently used in the CICU, the responsibility and importance of the nursing staff are constantly increasing. In recent years, attention has been focused on the adequate level of nurse staffing, and this is secondary to several studies that have confirmed that the system adopted for nurse staffing is closely related to the evolution of patients (5). Each healthcare system has proposed an optimal level of nurse staffing but without international consensus. In North America, there is a staffing system that is standard for all intensive care units. In the United Kingdom, recommendations are proposed but not mandated by law (34).

A concept has been proposed to find the optimal staffing of nurses, named the nurse-patient ratio (NPR). In general, the ratio used in the majority of CICUs is 2:1. In 2018, a systematic review with meta-analysis was performed to study the NPR by Driscoll et al. (35) but high heterogeneity was found in the method of measuring the NPR. The most used method was the calculation of the NPR by teams (25, 34). The result of this meta-analysis revealed that a higher level of paramedic staffing was associated with improved in-hospital survival, but without being able to define an optimal level required for the NPR. Among the parameters that demonstrate the crucial role of nurses is the impact of the level of nurse staffing on hospital evolution, mortality, and length of hospitalization. Several authors have been interested in objectifying the link between these parameters. Kim et al. studied the relationship between length of stay and NPR (36) and found a significant reduction in the length of hospitalization in centers with high nurse staffing, especially in centers that took care of critically ill patients. In 2020, Chang et al. published their work on the relationship between mortality and nursing staff, and they found that the lower the NPR, the higher the mortality, especially in patients with multiple comorbidities (37).

3. Clinical pharmacists

Pharmacy has undergone a spectacular evolution in recent years, moving from a fairly passive role as a supplier of medicines to a more active role by becoming involved in the management of patients alongside other healthcare providers such as doctors and nurses (38). Clinical pharmacists are health professionals specialized in therapeutics and are qualified to indicate global management of medicines to patients, physicians, and the rest of the health care team, whose main goal is to improve the quality of life, the efficiency of care, and thus the safety of patients (39). Currently, the role of the clinical pharmacist is well demonstrated in CICUs (40). A study by Xu et al. (41) showed a 66% reduction in adverse drug events in the same CICU after the integration of pharmacists into the visit with the ICU team, with a decrease from 10.4 events to 3.5 events per 1,000 patient days ($p < 0.001$).

At present, the clinical pharmacist represents an important actor in the process of treating patients with acute cardiac disease, following the introduction of the principle of multi-disciplinary management in all consensus and guideline documents issued by scientific societies. Taking heart failure as an example, the clinical pharmacist has an essential role to play in management, from initiation of treatment, titration and adjustment of doses, monitoring and reporting of adverse effects, possible interactions with other prescribed drugs, and long-term monitoring of the efficacy of prescribed drugs in collaboration with the treating physicians (42).

4. Nutritionists and dieticians

The role of nutritionists in an ICU is well known because the majority of patients hospitalized in these units have several cardiovascular risk factors (40) or are elderly, bedridden patients with severe malnutrition, for which nutritional management is essential in an ICU. A multicenter study carried out in European ICUs has clearly demonstrated the role of the presence of a nutritionist in a unit and its impact on intra- and extra-hospital evolution (43). Today, it has been demonstrated that malnutrition has a negative impact on the prognosis of patients admitted to cardiac intensive care units, whether in the short or long term. This effect is explained by the adverse impact of malnutrition on the immune system of these patients, making it fragile, and resulting in an increase in nosocomial infections. Other hypotheses that explain the negative impact of malnutrition include sarcopenia and accelerated catabolism of the organism, which are at the root of the inflammatory mechanisms of acute

decompensation in chronic heart disease. This association of malnutrition and acute decompensation would have severe metabolic, hemodynamic, and neurological consequences (44).

Sugita et al. studied the correlation between nutritional status and delirium in 653 patients admitted to the coronary intensive care unit of Juntendo University Hospital. Nutritional status was assessed by three different scores: Geriatric Nutritional Risk Index (GNRI), Controlling Nutritional Status (CONUT) and Prognostic Nutritional Index (PNI). Results after multivariate analysis on several models showed that the PNI and CONUT were independent risk factors for the occurrence of delirium, demonstrating the seriousness of this neglected comorbidity (44).

5. Physiotherapists

The impact of chronic cardiovascular disease, mainly heart failure, on physical and musculoskeletal function has been widely demonstrated, making these patients, in addition to their multiple comorbidities and generally advanced age, more fragile, with a consequent reduction in autonomy and quality of life. For all these reasons, physical rehabilitation through physiotherapy has a significant role to play in the management of patients admitted to cardiac intensive care units (45). In a multi-center, randomized, attention-controlled trial to evaluate the value of early rehabilitation in 349 patients hospitalized for decompensated acute heart failure, the results showed a significant improvement in their quality of life at 3 months post-hospitalization, with improvements in the Short Physical Performance Battery (SPPB), 6-minute walk distance test, and the Kansas City Cardiomyopathy Questionnaire as well as a decrease in depression as assessed by the Geriatric Depression Survey-15 (46).

6. Other personnel

Other personnel are also necessary in the CICU such as medical assistants and radiology technicians.

3.5. The concept of a multi-disciplinary approach

The complexity and severe comorbidities of patients hospitalized in a CICU require intervention between the different specialists on the one hand and the different members of the integral care team in the CICU, namely, physicians, nurses, medical assistants, and clinical pharmacists, on the other. Several studies have demonstrated the effectiveness of the multidisciplinary approach in CICU patients.

Nutritionists, physical therapists, and social workers also play a major role in the management of patients with heart disease. Improved survival has been observed in units that have adopted this multidisciplinary management approach. In a Pennsylvanian CICU study, ICUs with "high-intensity" medical staffing had lower mortality than other ICUs (or 0.78, 95% CI 0.68–0.89; $p <$ 0.001), and multivariate analysis showed that multidisciplinary care was associated with significantly reduced mortality (or 0.84, 95% CI 0.76–0.93; p ¼ 0.001).

Another major determinant in the multidisciplinary approach is communication. Clear communication among the increasing number of team members responsible for the management of critically ill patients is necessary for effective, high-quality care. A study at Johns Hopkins Hospital showed that increased communication using a daily goal form during ICU visits reduced the average length of stay in the intensive care unit by 50%, from 2.2 to 1.1 days (47).

3.6. The classification of the CICU

A three-level classification was proposed by the Association for Acute Cardiovascular Care of the European Society of Cardiology for the CICU (48). This classification can be made based on the phenotype of the patients or the type of technology and equipment available, the level of care presented, and finally the staffing.

CICU level i: refers to patients with acute cardiovascular conditions whose needs cannot be met by the care provided in a general cardiology department because their condition is likely to worsen and they require special expertise, specific equipment, or higher levels of monitoring.

CICU level ii: level ii concerns patients with acute cardiovascular pathologies whose risk requires more thorough monitoring than level i.

CICU level iii: this level concerns all patients with acute cardiovascular pathology requiring acute circulatory assistance such as ECMO, invasive mechanical ventilation, or renal replacement therapy.

This classification can be made according to the following determining factors:

- Pathologies treated.
- Expertise and techniques.
- Equipment and technologies.
- Staffing and networks.

3.6.1. Classification of admission pathologies according to CICU levels

The Association for Acute Cardiovascular Care proposed the following classification of the pathologies treated according to the level of CICU (**Table 2**).

3.6.2. Classifications of equipment and technologies according to CICU levels

3.6.2.1. Classification of techniques and expertise according to CICU levels

For techniques and expertise, the Association for Acute Cardiovascular Care proposed a classification according to the techniques and expertise available in the CICU (**Tables 3**, **4**) and those available in the hospital facility to which the CICU belongs (**Table 5**).

3.6.2.2. Classification of staffing and network according to CICU levels

CICU *level i:*

- The management of these units is given to a cardiologist.
- Expertise in 24-h echocardiography is required.

TABLE 2 The classification of pathologies of admission in CICU according to the level of severity.

Level I pathology	Level II pathology	Level III pathology
Acute congestive heart failure	Acute heart failure with signs of hypoperfusion	Cardiogenic shock
Ventricular tachyarrhythmia without hemodynamic consequences	Acute heart failure with oligo-anuria	Cardiac arrest
Uncomplicated stemi after revascularization	Need for vasopressors (shock, sepsis…)	Hemodynamically poorly tolerated ventricular fibrillation or ventricular tachycardia
Uncomplicated high risk ischemic nstemi	Arrhythmia complicated by heart failure	Mechanical complications of ACS
Acute pulmonary edema	Non-revascularized stemi or nstemi at high or very high ischemic risk	Heart transplant recipient with suspected graft rejection
Atrial fibrillation complicated by heart failure	Stemi or nstemi complicated by heart failure without shock	Infectious endocarditis with heart failure
Uncomplicated myopericarditis	Complication of coronary angiography or PCI	Aortic regurgitation with heart failure
Uncomplicated pulmonary embolism	Acute mitral regurgitation with heart failure	Thrombosis of a valve prosthesis
Non fulminant myocarditis	Severe aortic stenosis with signs of heart failure	Aortic dissection type a
Peripartum cardiomyopathy	Cardiac tamponade	Uncomplicated type B aortic dissection
Complicated or uncomplicated mitral stenosis	High intermediate risk pulmonary embolism	Any level II situation in aggravation
	Uncomplicated type b aortic dissection	Massive pulmonary embolism
	Peripartum myocarditis or cardiomyopathy with reduced left ventricular ejection fraction	

TABLE 3 The equipment and technologies required according to the level of the CICU.

CICU level I	CICU level II	CICU level III
At least two ECG machines	All the equipment and technologies offered in level I	All the equipment and technologies offered in level II
Non-invasive blood pressure monitor	An extra ECG machine	Advanced invasive hemodynamic monitoring
At least one monitor for invasive blood pressure monitoring	Invasive blood pressure monitor	Right catheterization equipment
Pulse oximetry	Capnography equipment	Hemodialysis and hemofiltration equipment available in CICU
Electronic medical records archiving system with electronic prescription system	Invasive hemodynamic monitoring	Device for maintaining therapeutic hypothermia available in CICU
Telemetric monitoring of all patients	Respirator for mechanical ventilation	Circulatory assistance such as ECMO and IMPELLA
Electrical patient monitoring stations for nurses	Mobile echocardiograph with a trans-esophageal sonde	
A syringe pump	An aortic counter-pulse balloon	
Positive pressure ventilation system (CPAP)	Hemodialysis and hemofiltration equipment available in the hospital facility	
A biphasic defibrillator	Device for maintaining therapeutic hypothermia available in the hospital facility	
A ventilator for non-invasive ventilation		
Mobile echocardiography		
An electro-systolic temporary pacing probe		
Blood gas analyzer		

TABLE 4 Techniques and expertise needed in the CICUs.

CICU level I	CICU level II	CICU level III
Non-invasive monitoring of all clinical parameters	Placement of central venous accesses	Setting up and managing ECMO-type circulatory assistance
24/7 availability of an echocardiologist	The realization of pericardial drainage	The initiation and management of renal replacement therapy
Electrical cardioversion available 24/7	Performance of trans-esophageal echocardiography	The management of a mechanical ventilation
Non-invasive ventilation	Performing a pulmonary artery catheterization	
Temporary cardiac pacing available 24/7	Performance of a circulatory assistance such as aortic counterpulsation balloon	
Nutritionist team available in CICU	Thermal management of patients	
Physiotherapy and physical rehabilitation team available in CICU		

TABLE 5 Techniques and expertise required in the hospital structure to which the CICU.

CICU level I	CICU level II	CICU level III
A functional emergency department	A 24/7 functional coronary catheterization laboratory	A cardiovascular surgery team with expertise in coronary surgery, aortic surgery, valve surgery and all structural pathologies of the heart
A 24/7 functional radiology department for standard radiology, CT scan	A cardiac pacing and resynchronization program available	An interventional radiology department with expertise in the endovascular treatment of aortic diseases
The availability of an echocardiography device with trans-esophageal probe	A pacemaker and defibrillator implantation program available	An interventional radiology service available with expertise in arterial embolization
The availability of a palliative medicine service	A cardiac ablation program available	An interventional radiology department available with expertise in vascular neuro-radiology
A 24/7 functional biology laboratory for cardiac enzymes	A functional nephrology department	The availability of an interventional cardiology team with expertise in the treatment of valvulopathy by percutaneous means
A 24/7 functional biology laboratory for haemostasis tests	Magnetic resonance imaging available	Availability of a functional heart transplant program
A 24/7 functional biology laboratory for renal and hepatic assessment	A team trained in post-cardiac arrest care	
	Availability of a team trained in endo-myocardial biopsy	

- The recommended nurse-patient ratio is one nurse for four patients.
- This level of CICU must be in close contact with the different disciplines of the hospital and thus constitutes the first line of care for acute cardiovascular diseases.

CICU *level ii:*

- The management of a level ii CICU must be performed by an intensive care cardiologist.
- The nurse-patient ratio for this level is: one nurse for every two patients with a maximum of one nurse for every three patients.
- In these guidelines, ESC proposes the following formula, but it is a formula that remains to be discussed: four beds in CICU for every 100,000 inhabitants.

CICU *level iii:*

- The director of the unit must be a cardiac intensivist with proven experience and competence in acute cardiovascular care.
- The nurse-patient ratio must be one nurse for one patient and at most one nurse for two patients.
- The presence of an interventional cardiologist, a cardiac surgeon, and an anesthetist is necessary in the unit.

4. Performance indicators for a CICU

If the 21st century has seen a revolution in the development, standardization, and normalization of care in acute cardiovascular medicine, through the formalized recommendations of experts from learned societies, then there is still a wide divergence in current practice with the aim of reducing the difference between the care performed and the evidence-based care, thus to standardize and prioritize the management of the different patients in a CICU, with an objective evaluation of the effectiveness and performance of the latter, quality or performance indicators are proposed and increasingly used by the different directors of modern CICU (49).

The European Society of Cardiology has divided quality and performance indicators into three types (**Figure 4**) (50).

- **Structure indicators**: these describe the structural organization, staffing, technologies, and equipment available.
- **Process indicators**: these describe the therapeutic protocols used, as well as compliance with the guidelines of learned societies.
- **Outcome indicators**: these describe the intra- and extra-hospital evolution of patients, in terms of mortality, length of stay, readmission rates, and the patient's perception of the care provided.

In 2019, Goldfarb et al. (51) (**Figure 5**) conducted a systematic review with the main objective of determining indicators of the general performance of a CICU apart from specific indicators for a specific pathology and the results are as follows:

Among the 108 quality indicators found:

- 70 were proposed as process indicators.
- 19 were proposed as structure indicators.
- 19 were proposed as indicators of results and evolution.

To date, there are no well-established recommendations for assessing the functionality of a CICU beyond the previously cited classification proposed by the Association for Acute Cardiovascular Care, but the results of this systematic review remain applicable.

5. The training program in a CICU

In 2020, seeing the increasing demands on the practice of cardiology as well as the increased training needs, the European Society of Cardiology together with the European Union of Medical Specialists, have worked on a core curriculum for cardiologists that has been published in order to bring the visions together (52).

5.1. Objectives of intensive cardiology training

Cardiology patients remain a very special subtype of patients since they can be treated in ambulatory care, as well as

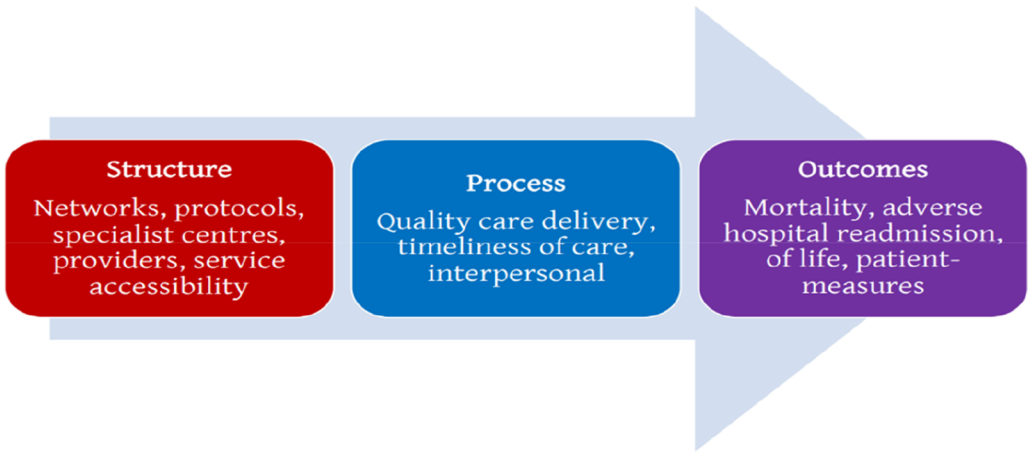

FIGURE 4
Diagram proposed by the European society of cardiology to classify the different performance indicators.

hospitalized in a cardiological intensive care unit. For this reason, a cardiologist must have both professional skills for the management of stable patients without compromised vitals and for the management of unstable patients with vital prognoses in danger.

For this purpose, five objectives have been specified by the ESC for the training program of cardiologists with regard to intensive cardiology (53):

(1) Management of a hemodynamically unstable patient.
(2) Management of a surviving cardiac arrest patient.
(3) The management of a critically ill cardiac patient.
(4) The management of a patient after an interventional cardiology procedure.
(5) Management of a cardiac patient requiring end-of-life care.

5.2. Levels of independence in intensive cardiology

The ESC classifies the levels of independence expected of a cardiology trainee into five levels (54):

- Level 1: the trainee should only observe.
- Level 2: the trainee should be able to perform an activity but under direct supervision.
- Level 3: the trainee should be able to perform an activity but under indirect supervision.
- Level 4: the trainee must be able to perform an activity but with remote supervision (the supervisor must be available in less than 20–30 min).
- Level 5: the trainee must be able to supervise other trainees.

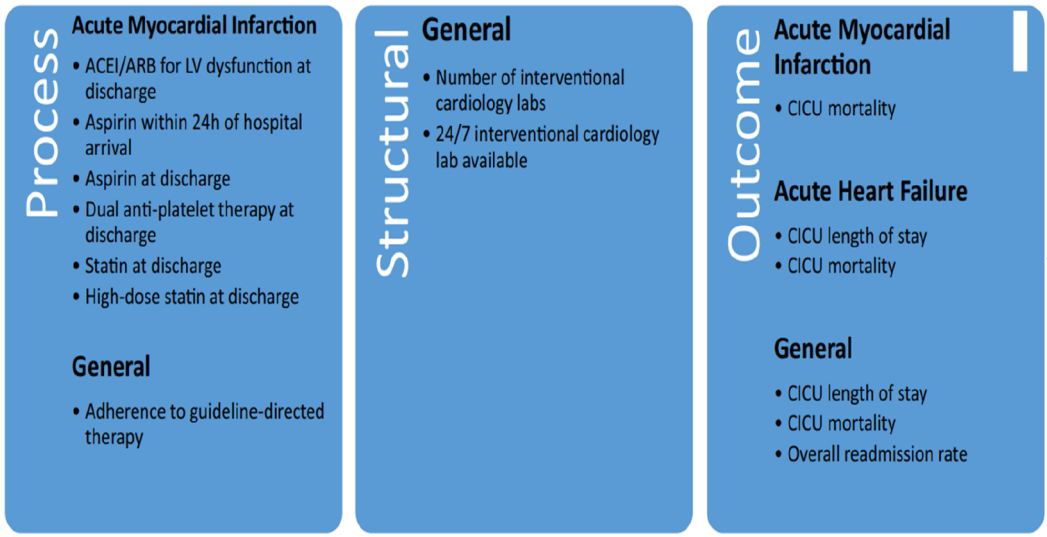

FIGURE 5
The different indicators of quality and performance of a CICU proposed by Goldfarb et al.

6. Research in CICUs

The current evolution of intensive cardiology represents a real focus for new studies and research. Given the spectacular progress of medical technology and its integration into the care of patients, especially those in the ICUs, several research topics are currently posed, especially with regard to mechanical circulatory assistance devices and thus the study of myocardial dysfunction during sepsis (55). The results of this research will undoubtedly contribute to an improvement in patient care, and thus to the standardization and creation of well-defined and more efficient functional ICU models.

The key elements to initiate and develop research topics in CICUs are:

(1) the creation of computerized databases for efficient data management.
(2) the organization of research teams.
(3) creation of multi-center and internationally focused research networks.
(4) getting support from academic organizations, government agencies, etc.
(5) ethics in a CICU.

The serious and unstable nature of CICU patients makes the ethical aspect somewhat complex, as neither the patients nor their relatives can often participate in the decision-making process regarding care. Considering that the main clinical characteristic of patients hospitalized in a CICU was a poor vital prognosis, the care team of a CICU must be well prepared and wise in the presence of a death, with all the possible ethical aspects.

Some of the ethical challenges in a CICU include writing a discontinuation of care form, negotiating with family members not to inform the patient of their diagnosis or vital prognosis, answering an interesting question, the prognosis of a patient with end-stage cardiovascular disease, and making the decision about end-of-life care.

One of the major determinants of ethical aspects in the CICU is the economic challenges and thus the limited resources, for example, in the United States, a bed in a CICU costs between 4,000 and 10,000 dollars per day (56). For this reason, prolonged care for patients with poor prognosis in the CICU is a great subject of debate, but the decision to limit care for critically ill patients for reasons of limiting economic expenses remains a real ethical challenge.

6.1. Practical guidelines for ethical decision-making

In order to make an ethical decision, the following four steps are recommended:

(i) Consider patients as major stakeholders in healthcare decision-making.
(ii) Define the person who has the authority to make the medical decision.
(iii) Communication.
(iv) Determination of patients' values.

This fourth point also remains difficult to determine and consists of the extent to which a painful experience is accepted by the patient. This question can only be answered by the patient, and may vary in terms of prognosis and how the patient advocates the definition of quality of life and thus their power to cope with the difficulties of care and the indignities of the disease, both moral and financial.

6.2. Discontinuation of care and end of life in the CICU

Discontinuation of care is the most difficult action a clinician can take. If the role of the physician is to care for patients, improving their prognosis and thus quality of life, for seriously ill patients with a therapeutic impasse, the best solution may be to propose end-of-life care for a death that is as dignified and pain-free as possible (57). In some cases, offering end-of-life care for a relatively painless and dignified death remains the best decision the healthcare team can make (58).

7. The perspectives and challenges in CICUs

Cardiovascular intensive medicine is constantly evolving, and despite all the current advances in recommendations for the organization, staffing, therapeutic management, and classification of the ICUs, as well as the magical evolution of technology and medical equipment many challenges and challenges are to be faced in the future in CICUs (59). In this section, we will try to mention the main challenges of modern CICUs:

7.1. Patient management after complex interventional procedures

Given the high frequency of complex interventional procedures in CICUs, such as percutaneous aortic valve replacement (TAVI) (60), percutaneous mitral valve repair (mitral-clip) (61), percutaneous left atrial closure (62), and percutaneous dilatation of chronic coronary occlusion (CTO) (63) as well as the high complication rate after these procedures, the CICU staff must have continuous and updated training in order to be able to decrease the morbi-mortality rate after these procedures. The main complications to be managed in these patients are as follows (**Figure 6**):

(1) vascular complications.
(2) cerebrovascular events.
(3) cardiac tamponade.
(4) arrhythmias and cardiac conductance disorders.
(5) post-interventional delirium.
(6) renal dysfunction.
(7) inflammation.

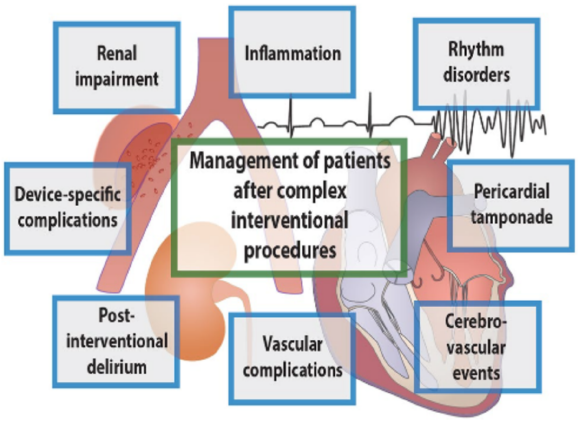

FIGURE 6
The various complications to be managed in complex post-interventional procedures [by Lüsebrink et al. (1)].

Management of cardiogenic shock and the concept of a "shock team".

Cardiogenic shock is always a subject of debate for cardiac intensivists because, on the one hand, of the problem of definition that poses it, and on the other hand, the difficulty of therapeutic management, given that the majority of guidelines mainly focus on the management of cardiogenic shock of ischemic origin as the most frequent cause of this condition (64).

Among the concepts currently adopted by several CICUs to improve the management of cardiogenic shock and its prognosis, is the shock team concept, which consists of a multidisciplinary management between interventional cardiologist, cardiologist, cardiac surgeon, and cardiologist intensivist. This approach has proven its effectiveness, especially in terms of a good individualization of the phenotypes of the patients through the more frequent use of invasive hemodynamic monitoring and catheterization of the pulmonary artery. This allows a more relevant use of circulatory support with a more adequate timing (65).

7.2. Management of post-cardiac arrest and maintenance of targeted temperature

The management of cardiac arrest and especially its post-recovery resuscitation remains a real challenge for all intensive care units (66). The CICU represents one of the basic units for the specialized management of cardiac arrest. For this, the staff of these units must be able to manage both the resuscitation of cardiac arrest and post-cardiac arrest resuscitation (67) and to achieve this result, continuous training, as well as an updating of knowledge, is necessary in order to improve the morbi-mortality of this pathology (68, 69).

7.3. Management of patients undergoing circulatory assistance and its complications

The use of circulatory assistance in CICUs has increased exponentially, especially after the modernization of the majority of ICUs in European countries (70). This use requires a heavy technical platform, with well-trained medical and paramedical personnel with the capacity to manage both the patient and the assistance, and also the complications of this circuit, which represent the principal cause of mortality in these patients (71). For all these reasons, modern ICUs must offer continuous training programs for all personnel on the management of patients on life support and thus determine well-defined protocols for the management of complications based on international guidelines.

7.4. Artificial intelligence (AI) in CICUs

The complexity as well as the severity of the patients admitted in CICUs makes this population quite special and requires personalized management based on several parameters mainly clinical, electrocardiographic, biological, and echocardiographic, in order to stratify the severity of these patients to predict the prognosis. With the evolution of artificial intelligence, it has been shown that several automated and dynamically evaluated algorithms can predict the evolution during hospitalization in CICU in a pertinent way (72).

Since 2020, several algorithms have been developed for the prediction of mortality or left systolic dysfunction in patients with atrial fibrillation or for patients hospitalized in the CICU, using ECG-based algorithms (73). The advantages include, in comparison with the scores developed in the past, the dynamic nature of the evaluation, and the fact that the gaps in the scores used are filled.

8. Conclusion

Cardiovascular diseases remain the first cause of mortality in all countries of the world whatever the level of development of the country, and the environments of cardiac intensive care units are clearly progressing with regard to their organization, management, and staffing; the introduction of the concept of indicators of the quality; and, with the objective of decreasing the rate of mortality, the cost of caring for these patients, which represents a real burden on the various healthcare systems.

Author contributions

AB: Conceptualization writing – original draft preparation and literature research, writing – review and editing. NE, NI and ZB

supervision, and final editing, 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

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EDITED BY
Marija Vavlukis,
University Clinic for Cardiology, Ss. Cyril and Methodius University in Skopje, North Macedonia

REVIEWED BY
Olivia Manfrini,
University of Bologna, Italy
Jorgo Kostov,
Saints Cyril and Methodius University of Skopje, North Macedonia

*CORRESPONDENCE
Vojko Kanic
✉ vojko.kanic@guest.arnes.si

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Clopidogrel, ticagrelor, prasugrel or an alternation of two P2Y12 in patients with acute myocardial infarction with cardiogenic shock

Vojko Kanic* and Gregor Kompara

Division of Internal Medicine, Department of Cardiology and Angiology, University Medical Center Maribor, Maribor, Slovenia

Background: Data are lacking on the effects of the alternation of P2Y12 receptor antagonists (P2Y12) on bleeding and outcome in patients with myocardial infarction (MI) with cardiogenic shock (CS). We compared the effects of different P2Y12 and alternation of P2Y12 (combination) on bleeding and outcome in patients with MI and CS.

Methods: Data from 247 patients divided into four groups: clopidogrel, ticagrelor, prasugrel, and the combination group, were analyzed. The association between P2Y12 and bleeding as well as 30-day and one-year mortality was examined.

Results: The highest bleeding rate was observed in patients in the combination group, followed by the clopidogrel, ticagrelor, and prasugrel groups [12(50%) patients, 22(28.2%), 21(18.3%) and 4(13.3%), respectively; $p = 0.003$]. Bleeding occurred with a similar frequency in the combination and clopidogrel groups ($p = 0.081$), but more frequently than in the ticagrelor and prasugrel groups ($p = 0.002$ and $p = 0.006$, respectively). Bleeding rates were similar in patients receiving P2Y12 alone ($p = 0.13$). Compared to clopidogrel, both ticagrelor and prasugrel had a lower bleeding risk (aOR: 0.40; 95% CI: 0.18–0.92; $p = 0.032$ and aOR: 0.20; 95% CI: 0.05–0.85; $p = 0.029$, respectively) and the combination had a similar bleeding risk (aOR: 2.31; 95% CI: 0.71–7.48; $p = 0.16$). The ticagrelor and prasugrel groups had more than an 80% and 90% lower bleeding risk than the combination group (aOR: 0.17; 95% CI: 0.06–0.55; $p = 0.003$ and aOR: 0.09; 95% CI: 0.02–0.44; $p = 0.003$, respectively). The unadjusted 30-day and one-year mortality were highest in the clopidogrel group, followed by the ticagrelor, prasugrel, and combination groups (44 (56.4%) and 55(70.5%) patients died in the clopidogrel group, 53(46.1%) and 56 (48.7%) in the ticagrelor group, 12(40%) and 14(46.7%) patients died in the prasugrel, and 6(25%) and 9(37.5%) patients died in the combination group; $p = 0.045$ and $p < 0.0001$. After adjustment for confounders, the P2Y12 groups were not independently associated with either 30-day ($p = 0.23$) or one-year ($p = 0.17$) mortality risk.

Conclusion: Our results suggest that the choice of P2Y12 was not associated with treatment outcome. The combination of P2Y12 increased bleeding risk compared with ticagrelor and prasugrel and was comparable to clopidogrel in patients with MI and CS. However, these higher bleeding rates did not result in worse treatment outcomes.

KEYWORDS

clopidogrel, prasugrel, ticagrelor, P2Y12 combination, cardiogenic shock, myocardial infarction, outcome, bleeding

Introduction

In patients with cardiogenic shock (CS) due to myocardial infarction (MI), percutaneous coronary intervention (PCI) is the standard recommended therapy (1). In addition, antithrombotic treatment is essential to prevent peri-PCI and later thrombotic events (2–8). In patients with CS, multiple challenges with antiplatelet action remain (9). The antiplatelet effect of orally administered drugs is delayed by gastroparesis, delayed intestinal absorption, and slower metabolism of the drugs due to compromised hemodynamics in cardiogenic shock, and after morphine administration (3, 5–7, 10). In addition, oral administration of the drugs may be problematic (9). The data on P2Y12 receptor antagonists (P2Y12) in patients with CS are sparse and still inconclusive (2, 3, 9). The combined results of two randomized trials showed that there is no difference between the P2Y12 (2) while pooled analysis of randomized and retrospective studies showed a better outcome with potent P2Y12 (3, 9). The data on bleeding are also controversial and inconclusive (9). Some have found no difference in bleeding (3, 9, 11, 12), whereas others have found a lower risk of bleeding with ticagrelor and a similar risk with prasugrel compared with clopidogrel (2). Randomized trials have numerous exclusion criteria and do not always capture the actual problems of individual patients. Some data show that almost 40% of patients with CS do not receive P2Y12 in everyday medical practice (6, 13) and even in randomized trials more than 30% do not receive P2Y12 (2). In daily practice, especially in patients with CS who are unable to communicate, patients sometimes receive a combination of P2Y12 receptor antagonists (not simultaneously). This usually occurs for two reasons-patients with STEMI received clopidogrel in pre-hospital settings (or were already on clopidogrel), which was then switched to ticagrelor or prasugrel during/after the procedure or later in hospital, or patients with MI received ticagrelor/prasugrel during initial treatment not knowing that they were previously receiving oral anticoagulant medications. Potent P2Y12 are usually later switched to clopidogrel in combination with oral anticoagulants. The combination of P2Y12 in the acute setting, when heparin/bivalirudin and GP IIb/IIIa receptor antagonists are also used, is expected to be associated with bleeding, a known predictor of worse outcome (1, 3). These patients have mostly been excluded from randomized trials or have not been evaluated separately, and there are no data on how the combination of oral P2Y12 receptor antagonists affects bleeding and outcome in patients with CS, in whom drug administration, absorption, metabolism, and efficacy differ from other patients with MI. The aim of our study was to evaluate the bleeding rate and 30-day and one-year mortality of different oral P2Y12 and their combination in patients with cardiogenic shock due to myocardial infarction.

Materials and methods

The cohort of the present single-center retrospective observational study was recruited from patients with MI who underwent PCI between 2010 and 2018 (potent P2Y12 were not previously available) at the University Medical Center Maribor, Slovenia, a tertiary referral hospital with a 24/7 PCI service. Of 6,578 consecutively screened patients with MI who underwent PCI, we identified 381(5.8%) patients with CS. Patients who did not receive P2Y12 [134 (35.2%) patients] were excluded. The final patient cohort comprised 247 eligible patients. The patients were divided into four groups according to the P2Y12 received—clopidogrel [78(31.6%) patients], ticagrelor [115(46.6%) patients], prasugrel [30(12.1%) patients] and a group with modified P2Y12 therapy [24 (9.7%) patients] who received clopidogrel and prasugrel or clopidogrel and ticagrelor or ticagrelor and prasugrel. We did not subdivide patients in the latter group according to which P2Y12 was originally administered and which was later administered because there were too few patients in each group. These four groups were compared, and in-hospital bleeding and all-cause mortality were assessed at 30 days and one year.

Group P2Y12 data were provided for all patients, and data on all other essential patient and procedural characteristics were at least 94.7% complete. Ascertainment of end points was 100% complete. Data on the dates of death were provided by the Slovenian National Cause of Death Registry. The study was approved by the local institutional ethics committee (UKC-MB-KME-59/19), and all methods were performed in accordance with the requirements of the Declaration of Helsinki.

Patients and definitions

The diagnosis of MI was made according to published guidelines, including a typical history of chest pain, diagnostic electrocardiographic changes, and serial elevations of cardiac biomarkers, and patients were treated according to published guidelines for the management of MI (1, 14, 15). Patients were eligible for analysis if they suffered MI with CS. The criteria for CS were a systolic blood pressure of ≤90 mm Hg for ≥30 min or the use of catecholamines to maintain a systolic blood pressure of >90 mm Hg, clinical signs of pulmonary congestion, and signs of end-organ hypoperfusion. Thrombolysis In Myocardial Infarction (TIMI) flow grades were used to assess coronary blood flow (16). Anemia was defined according to the World Health Organization recommendations: a serum hemoglobin level of <130 g/L in men and <120 g/L in women (17). Bleeding events were classified using the Bleeding Academic Research Consortium (BARC) definition and BARC 3,5 bleeding were used (18). For mechanical circulatory support, an intra-aortic balloon pump (IABP) was most commonly used. Extracorporeal membrane oxygenation (ECMO) was used in only two (1.4%) patients, both of whom died.

Pharmacological treatment with P2y12 receptor antagonists

The use of P2Y12 was left to the discretion of the treating physician. Administration of more potent P2Y12 in addition to

the clopidogrel loading dose given in the pre-hospital setting was not common but was left to the discretion of the operator or attending physician as was administration of clopidogrel instead of prasugrel/ticagrelor in patients who were on anticoagulation therapy or needed anticoagulation therapy.

Study end points

The end points of the study were BARC 3, 5 in-hospital bleeding and all-cause 30-day and one-year mortality.

Statistical methods

The patients were divided according to the P2Y12 received into four groups and these groups were compared. The Kolmogorov–Smirnov test was used to assess normal distribution. Differences between the groups in baseline clinical, angiographic, and procedural characteristics were compared with the two-sample *t*-test, Mann–Whitney test, or the Jonckheere–Terpstra test depending on whether the data followed the normal distribution for continuous variables and the chi-square test or Fischer's exact test for categorical variables, as appropriate. End-point events that occurred during the follow-up period were counted and their rates were compared among the groups. The cumulative incidence rates of the unadjusted one-year mortality were estimated by the Kaplan–Meier method and compared by the logrank test. Binary logistic regression models were performed using the Enter mode to determine the possible association between P2Y12 and bleeding and 30-day mortality, and Cox regression analysis was used to determine hazard ratios (HR) as estimates of one-year mortality. In addition to age and sex, the models for bleeding were adjusted for variables that had a significant univariant association ($p < 0.05$) with in-hospital bleeding [mechanical ventilation, resuscitation prior to PCI, glomerular filtration rate (GFR), anemia on admission, renal replacement therapy, and P2Y12 groups]. In addition, variables based on previous literature reports and experience that these factors are known to influence bleeding (radial access, GP IIb/IIIa receptor antagonists, bivalirudin, oral anticoagulant therapy) were added to the model. In addition to age, sex, and bleeding, the models for 30-day and one-year mortality were adjusted for variables with univariant association ($p < 0.05$) with 30-day mortality (mechanical ventilation, resuscitation prior to PCI, arterial hypertension, TIMI flow 0/1 after PCI, PCI of the right coronary artery, PCI of the circumflex artery, systolic blood pressure on admission, GFR, anemia on admission, and P2Y12 groups). Variables known to be associated with survival (diabetes and hyperlipidemia) were also included. The clopidogrel group was used as the reference group. ORs and HRs were calculated using a model stratified by P2Y12 groups. Only mechanical ventilation on admission was included as a variable in the calculations. All included variables had a variance inflation factor (VIF) < 1.8. Adjusted odds and hazard ratios (HR) for all four P2Y12 groups were calculated. Data were analyzed with SPSS 21.0 software for Windows (IBM Corp., Armonk, NY). All *p*-values were two-sided, and values less than 0.05 were considered statistically significant.

Results

The oldest patients were those on clopidogrel (70.8 ± 1.7 years) or ticagrelor (67.3 ± 12.0 years), but the P2Y12 combination group (62.2 ± 10.3 years) and especially the prasugrel group (57.9 ± 10.9 years) were younger ($p = 0.01$). Patients taking clopidogrel were not only older but also more likely to have lower GFR and to be anemic on admission compared to the prasugrel and ticagrelor patients. Clopidogrel patients were resuscitated prior to PCI more frequently than prasugrel patients ($p = 0.018$) and tended to be resuscitated more frequently than ticagrelor patients ($p = 0.056$). They were also less likely to suffer a STEMI ($p = 0.010$), but more likely to have TIMI 0/1 flow after PCI than prasugrel patients ($p = 0.034$), and they tended to receive more oral anticoagulants than prasugrel patients ($p = 0.059$) and definitely more than ticagrelor patients ($p = 0.021$). The ticagrelor group was less likely to have had a previous myocardial infarction ($p = 0.03$) and less likely to receive oral anticoagulants ($p = 0.03$) than patients receiving a combination of P2Y12. Prasugrel patients were also less likely to receive oral anticoagulants than the P2Y12 combination group ($p = 0.034$). The P2Y12 combination group was more frequently treated with PCI LCX compared to the others ($p = 0.033$, $p = 0.011$, and $p = 0.028$ for the clopidogrel, ticagrelor, and prasugrel groups, respectively) and suffered more bleeding. Patient baseline and procedural characteristics, and outcome are shown in **Table 1**.

In-hospital bleeding

Bleeding occurred in 59(23.9%) patients. The highest bleeding rate was observed in patients in the P2Y12 combination group, followed by the clopidogrel, ticagrelor, and prasugrel groups [12 (50%) patients, 22(28.2%), 21(18.3%), and 4(13.3%) patients experienced bleeding in the combination, clopidogrel, ticagrelor and prasugrel groups, respectively, $p = 0.003$) (**Figure 1**)]. Bleeding had a similar frequency in the P2Y12 combination group and the clopidogrel group ($p = 0.081$) but was more frequent than in the ticagrelor and prasugrel groups ($p = 0.002$ and $p = 0.006$, respectively) (**Figure 1**). However, when patients who received only one P2Y12 were compared, the bleeding rate was similar in the clopidogrel, ticagrelor, and prasugrel groups ($p = 0.13$). The bleeding rate was also similar when only potent P2Y12 (prasugrel, ticagrelor) were compared ($p = 0.78$). Bleeding was associated with anemia on admission (and lower hemoglobin), low GFR, age, resuscitation before PCI, mechanical ventilation, and P2Y12. In addition, stent thrombosis and renal replacement therapy during hospitalization were associated with bleeding (**Supplementary Table S1**).

After adjustment for confounders, P2Y12 were associated with bleeding ($p = 0.003$) (**Table 2**). Compared to clopidogrel, both

TABLE 1 Patient admission, procedural and outcome characteristics.

Variable	Clopidogrel	Ticagrelor	Prasugrel	P2Y12 combination	*p*
	n = 78 (31.6%)	*n* = 115 (46.6%)	*n* = 30 (12.3%)	*n* = 24 (9.7%)	
Age, years	70.8 (11.7)	67.3 (12.0)	57.9 (10.9)	62.2 (10.3)	<0.0001
Male sex	49 (62.8%)	76 (66.1%)	23 (76.7%)	17 (70.8%)	0.56
Diabetes mellitus	17 (21.8%)	27 (23.5%)	5 (16.7%)	6 (25.0%)	0.86
Hypertension	36 (46.2%)	45 (39.1%)	10 (33.3%)	7 (29.2%)	0.39
Hyperlipidemia	10 (12.8%)	21 (18.3%)	7 (23.3%)	6 (25.0%)	0.42
Chronic kidney disease	4 (5.1%)	5 (4.3%)	0 (0.0%)	0 (0.0%)	0.44
Previous MI	3 (3.8%)	4 (3.5%)	4 (13.3%)	4 (16.7%)	0.023
Previous stroke	4 (5.1%)	7 (6.1%)	0 (0.0%)	1 (4.2%)	0.58
Previous PCI/CABG	3 (3.8%)	6 (5.2%)	2 (6.7%)	1 (4.2%)	0.93
Oral AC therapy	10 (12.8%)	4 (3.5%)	0 (0.0%)	4 (16.7%)	0.009
Resuscitation before PCI	41 (52.6%)	44 (38.3%)	8 (26.7%)	9 (37.5%)	0.063
BMI, kg/m^2	26.2 (24.1, 29.4)	27.7 (24.8, 31.9)	27.7 (25.7, 31.2)	26.6 (25.3, 28.7)	0.28
Hemoglobin, g/L	123.0 (108.7, 136.5)	135.0 (119.0,143.0)	134.5 (121.7,146.0)	135.5 (110.2,146.2)	0.005
CRP, mg/L	6.0 (2.0, 39.0)	8.5 (2.0, 41.2)	6.5 (2.0, 27.0)	12.0 (2.5, 54.0)	0.86
GFR (ml/min/1.73 m^2)	52.5 (29.3, 70.1)	61.3 (47.7, 87.1)	67.0 (49.1, 94.4)	61.0 (49.6, 79.2)	0.002
Serum creatinine (mg/dl)	1.29 (1.03, 1.95)	1.12 (0.88, 1.46)	1.09 (0.87, 1.49)	1.12 (0.87, 1.49)	0.008
Anemia on admission	43 (55.1%)	35 (31.0%)	12 (40.0%)	9 (37.5%)	0.01
STEMI	63 (80.8%)	104 (90.4%)	30 (100.0%)	23 (95.8%)	0.014
RR systolic, mmHg	91.9 (17.0)	93.1 (21.8)	84.6 (16.0)	88.0 (30.0)	0.65
RR diastolic, mmHg	61.2 (10.6)	62.3 (14.7)	56.8 (12.7)	58.7 (28.0)	0.95
RR mean, mmHg	72.6 (11.3)	73.3 (15.2)	65.9 (14.9)	70.5 (22.9)	0.81
Mechanical ventilation	39 (50.0%)	53 (46.1%)	9 (30.0%)	13 (54.2%)	0.24
Radial access	11 (14.1%)	20 (17.4%)	3 (10.0%)	0 (0.0%)	0.14
PCI LMCA	9 (11.5%)	18 (15.7%)	3 (10.0%)	6 (25.0%)	0.35
PCI LAD	43 (55.1%)	56 (48.7%)	14 (46.7%)	8 (33.3%)	0.31
PCI LCX	15 (19.2%)	19 (16.5%)	4 (13.3%)	10 (41.7%)	0.03
PCI RCA	22 (28.2%)	28 (24.3%)	12 (40.0%)	8 (33.3%)	0.36
Multivessel PCI	20 (28.2%)	30 (29.1%)	6 (20.7%)	7 (41.2%)	0.53
Mechanical circulatory support	7 (9.0%)	10 (8.7%)	2 (6.7%)	45 (20.9%)	0.36
GPI	40 (51.3%)	48 (41.7%)	15 (50.0%)	12 (50.0%)	0.57
Bivalirudin	5 (6.4%)	16 (13.95%)	10 (33.3%)	2 (8.3%)	0.003
TIMI 0/1 after PCI	12 (15.4%)	18 (15.7%)	0 (0.0%)	2 (8.3%)	0.11
Troponin, µg/L	33.6 (8.2, 77.4)	32.6 (7.4, 82.9)	39.7 (16.6, 71.4)	30.3 (8.9, 90.1)	0.67
EF (%)	31.6 (5.4)	30.9 (5.1)	30.0 (0.1)	33.1 (8.8)	0.16
Renal replacement therapy	3 (3.8%)	5 (4.3%)	0 (0.0%)	4 (16.7%)	0.029
Cerebral hemorrhage	3 (3.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.29
Stent thrombosis	0 (0.0%)	5 (4.3%)	0 (0.0%)	1 (4.2%)	0.19
Bleeding	22 (28.2%)	21 (18.3%)	4 (13.3%)	12 (50.0%)	0.003
CABG during the same hospitalization	2 (2.6%)	6 (5.2%)	3 (10.0%)	3 (12.5%)	0.20
Mortality outcome					
30-day mortality	44 (56.4%)	53 (46.1%)	12 (40.0%)	6 (25.0%)	0.045
One-year mortality	55 (70.5%)	56 (48.7%)	14 (46.7%)	9 (37.5%)	0.004

BMI, body mass index; CABG, coronary artery bypass graft; CRP, C-reactive protein; GPI, GP IIb/IIIa receptor antagonist; EF, ejection fraction; GFR, glomerular filtration rate; LAD, left anterior descending artery; LCX, circumflex artery; LMCA, left main coronary artery; MI, myocardial infarction; PCI, percutaneous intervention; RCA, right coronary artery; RR, blood pressure; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.
Data are expressed as mean ± SD, a number (percentage), or the median (interquartile range).

ticagrelor, and prasugrel had a lower bleeding risk (aOR: 0.40; 95% CI: 0.18–0.92; $p = 0.032$ and aOR: 0.20; 95% CI: 0.05–0.85; $p = 0.029$, respectively), but the P2Y12 combination group had a similar bleeding risk (aOR: 2.31; 95% CI: 0.71–7.48; $p = 0.16$) (Table 2). Mechanical ventilation, age, GFR, and anemia on admission were also associated with bleeding. In contrast, GP IIb/IIIa receptor antagonists, bivalirudin, and oral anticoagulants were not associated with bleeding (Table 2). Ticagrelor and prasugrel patients had more than an 80% and 90% lower risk of bleeding compared to the P2Y12 combination group when the P2Y12 combination group was used as a reference (aOR: 0.17; 95% CI: 0.06–0.55; $p = 0.003$ and aOR: 0.09; 95% CI: 0.02–0.44; $p = 0.003$; respectively).

Mortality

After 30 days 115(46.6%) patients had died. Unadjusted 30-day all-cause mortality were highest in the clopidogrel group, followed by the ticagrelor, prasugrel, and P2Y12 combination groups [44

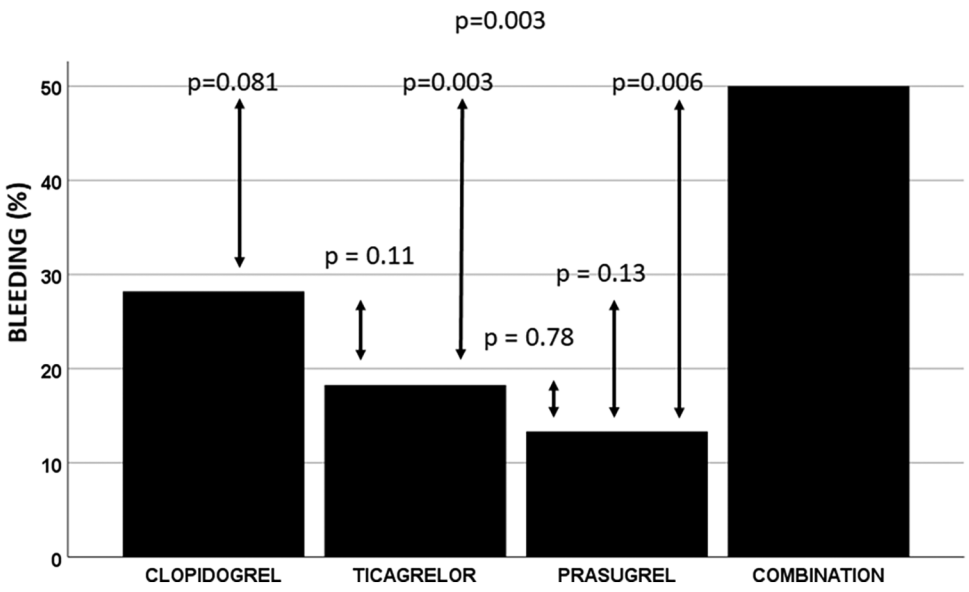

FIGURE 1
Observed in-hospital bleeding rate. Combination, P2Y12 combination. The in-hospital bleeding rate was highest in the P2Y12 combination group. It was similar to that in the clopidogrel group and more frequent than in the ticagrelor and prasugrel groups. A similar bleeding rate was observed in patients receiving only one P2Y12.

(56.4%) patients died in the clopidogrel group, 53(46.1%) died in the ticagrelor group, 12(40%) patients died in the prasugrel group, and 6(25%) patients died in the P2Y12 combination group within 30 days, respectively; $p = 0.045$] (Figure 2). Only patients in the P2Y12 combination group had lower observed 30-day mortality than the clopidogrel group ($p = 0.01$) (Figure 2). Patients who received only one P2Y12 had similar mortality ($p = 0.21$). The P2Y12 were not associated with 30-day mortality. Age, mechanical ventilation, resuscitation prior to PCI, GFR, anemia, blood pressure on admission, PCI of right or circumflex artery, TIMI 0/1 after PCI were associated with 30-day mortality (Supplementary Table S1).

TABLE 2 Association with bleeding.

Variable	Multivariable model aOR (95% CI)	p
Mechanical ventilation	2.53 (1.04–6.16)	0.042
Resuscitation prior to PCI	1.01 (0.42–2.44)	0.97
Male sex	0.90 (0.43–1.90)	0.78
Radial access	1.28 (0.47–3.51)	0.63
P2Y12[a]		0.003
Ticagrelor	0.40 (0.18–0.92)	0.032
Prasugrel	0.20 (0.05–0.85)	0.029
P2Y12 combination	2.31 (0.71–7.48)	0.16
GPI	1.002 (0.481–2.089)	0.99
Bivalirudin	2.34 (0.83–6.60)	0.11
Oral AC therapy	0.53 (0.14–2.09)	0.37
Anemia on admission	3.44 (1.55–7.67)	0.002
Age, years	0.96 (0.93–0.99)	0.015
GFR (ml/min/1.73 m^2)	0.98 (0.96–0.99)	0.003
Renal replacement therapy	1.21 (0.30–4.94)	0.80

AC, anticoagulant therapy; aOR, adjusted odd ratio; CI, confidence interval; GFR, glomerular filtration rate; GPI, GP IIb/IIIa receptor antagonist; P2Y12, P2Y12 receptor antagonist.
[a]Clopidogrel group as reference.

After one year, 134(54.3%) patients had died. The highest all-cause mortality rate was observed in patients on clopidogrel [55 (70.5%)], followed by patients on ticagrelor, prasugrel, and a P2Y12 combination (56(48.7%), 14(46.7%) and 9(37.5%) patients died, respectively; $p = 0.004$) (Figure 2). The cumulative incidence rates of unadjusted one-year mortality by the Kaplan-Meier method showed a significant difference between groups (logrank = 0.002) (Figure 3). The pairwise logrank comparison showed a significantly higher estimated mortality in the clopidogrel group compared to the other groups ($p = 0.015$ compared to ticagrelor, $p = 0.046$ compared to prasugrel, and $p = 0.004$ compared to the P2Y12 combination, respectively) (Figure 3). In addition, this pairwise comparison showed a similar estimated mortality in the ticagrelor, prasugrel, and P2Y12 combination groups ($p = 0.72$ for ticagrelor vs. prasugrel, $p = 0.20$ for ticagrelor vs. P2Y12 combination, and $p = 0.37$ for prasugrel vs. P2Y12 combination). Age, mechanical ventilation, resuscitation prior to PCI, GFR, anemia, blood pressure on admission, PCI of right coronary artery, TIMI 0/1 after PCI, hyperlipidemia, hypertension, and P2Y12 were associated with one-year mortality (Supplementary Table S1).

However, after adjustment for confounding factors, the P2Y12 groups were not independently associated with either 30-day ($p = 0.23$) or one-year mortality risk ($p = 0.36$). Resuscitation prior to PCI and systolic blood pressure were independently associated with 30-day mortality risk, while only systolic blood pressure was associated with one-year mortality risk (Table 3).

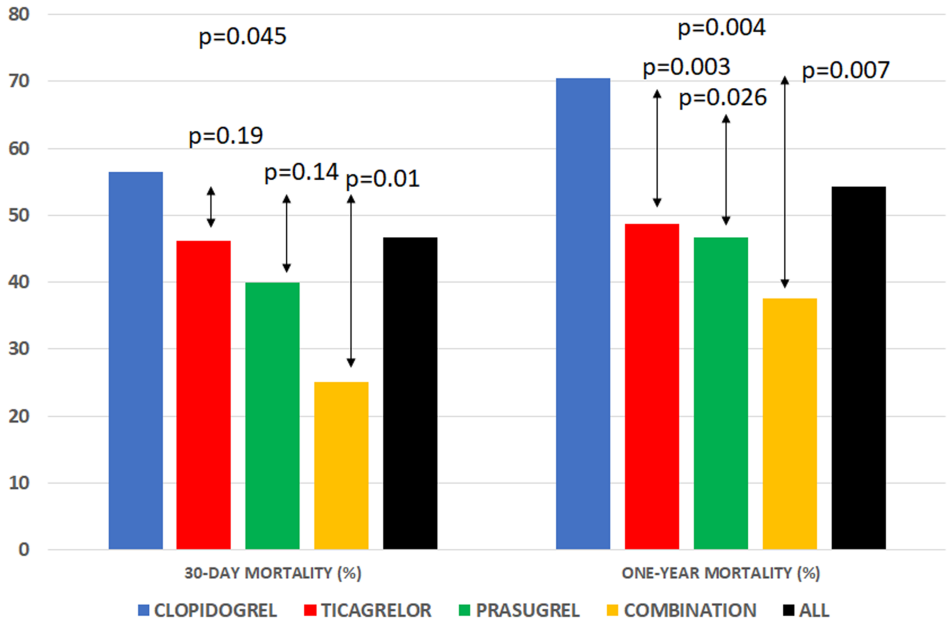

FIGURE 2
Unadjusted 30-day all-cause mortality was highest in the clopidogrel group, followed by the ticagrelor, prasugrel, and P2Y12 combination groups. Patients who received only one P2Y12 had similar mortality, and only patients in the P2Y12 combination group had lower mortality than the clopidogrel group. After one year, the highest all-cause mortality rate was observed in patients receiving clopidogrel. The groups with ticagrelor, prasugrel, and P2Y12 combinations had a lower one-year mortality rate.

Discussion

There are no data on the potential effects of the combination of more than one P2Y12 in patients with cardiogenic shock due to MI compared with a single P2Y12 (clopidogrel, ticagrelor, or prasugrel) on bleeding and outcome. We retrospectively analyzed 247 patients with MI and CS who received either clopidogrel, ticagrelor, prasugrel, or a combination of P2Y12. The main results of our analysis are as follows:

1. There was no significant difference in the multivariable-adjusted all-cause 30-day and one-year mortality risk between patients receiving clopidogrel, ticagrelor, prasugrel, and a combination of P2Y12.
2. Patients receiving a combination of P2Y12 had a significantly higher unadjusted bleeding rate than patients receiving ticagrelor or prasugrel but a similar rate to that of patients receiving clopidogrel.
3. Ticagrelor and prasugrel patients had a lower bleeding risk after adjustment for confounders than patients receiving a combination of P2Y12 or clopidogrel.

Our results suggest that the choice of P2Y12 in patients with MI and CS has no significant effect on mortality but may influence the risk of bleeding.

As previously observed, almost half of the patients were mechanically ventilated on admission (2). The percentage of patients receiving a combination of P2Y12 in our analysis (9.7%) was comparable to the pooled analysis of two randomized controlled prospective trials (13.1%) (2). Results of previous analyzes are inconclusive and sometimes contradictory (2, 3, 9, 11, 19–21). Retrospective analyzes and pooled data showed superiority of potent P2Y12 (3, 12, 9), whereas prospective and some retrospective studies showed no difference in survival between P2Y12 (2, 11, 19–21). There were substantial differences between studies in terms of the number of patients, patient selection, end points, and variables included in the multivariable analyzes. Our previous observation also showed a different result (3). However, in our previous study, we had included a smaller number of patients, including patients who were resuscitated only (and did not suffer from CS after resuscitation), we did not have data on anemia and GFR, and the definition of bleeding was different. These differences might justify a different outcome. Our results cautiously support the previous data of Orban et al, who found better observed mortality with potent P2Y12 but no independent association between P2Y12 and mortality (2).

We confirmed the previous findings in a similar group of patients that ticagrelor is associated with a lower risk of bleeding than clopidogrel (2). In addition, we showed that prasugrel was also associated with a lower bleeding risk, and both drugs had a lower bleeding risk than the P2Y12 combination, whose bleeding risk was comparable to that of clopidogrel. There was no difference in bleeding rates between ticagrelor and prasugrel, as previously observed in patients with acute coronary syndrome without cardiogenic shock (22).

When comparing the individual groups, we found that the P2Y12 combination group received oral anticoagulants more frequently than the prasugrel and ticagrelor groups ($p = 0.034$ and $p = 0.030$, respectively), and with a similar frequency to the

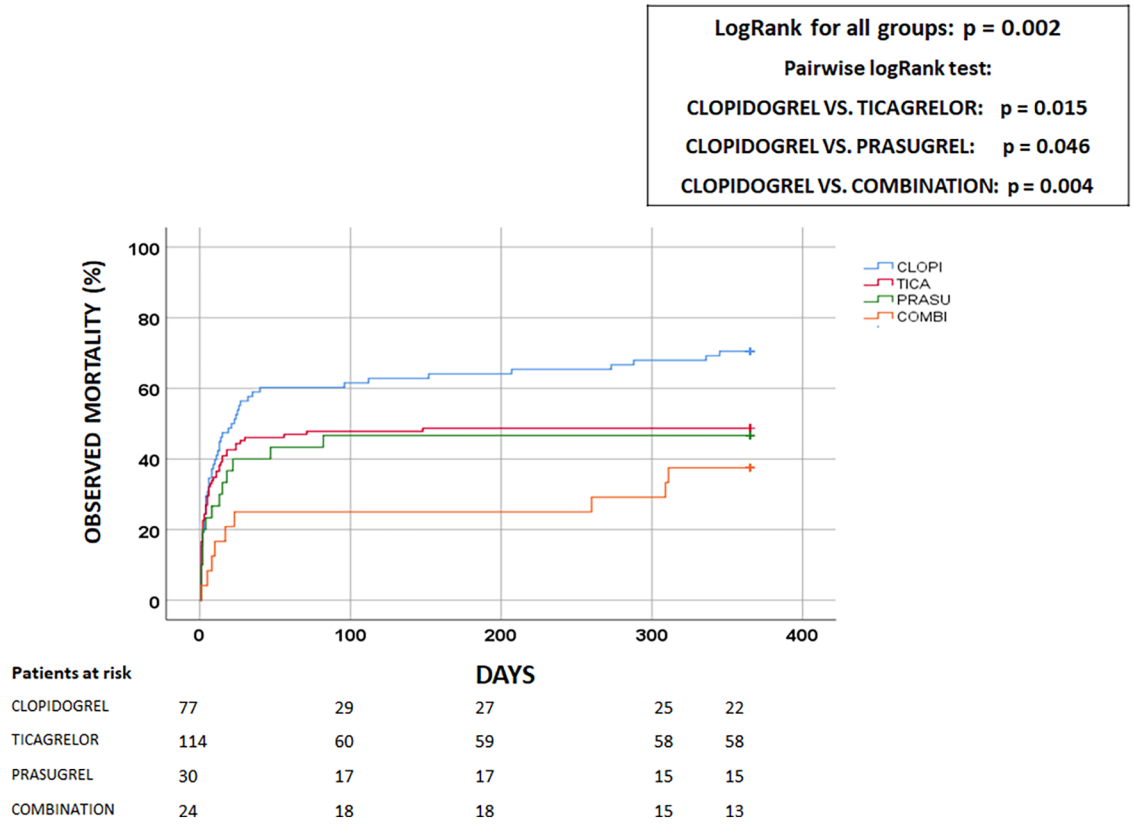

FIGURE 3
Estimated all-cause one-year mortality. Clopi, clopidogrel; Prasu, prasugrel; Tica, ticagrelor; Combination, P2Y12 receptor antagonist combination. The unadjusted one-year all-cause mortality was lowest in the P2Y12 combination group, followed by the prasugrel, ticagrelor, and clopidogrel groups. The pairwise logrank comparison showed significantly higher estimated mortality in the clopidogrel group compared with the other groups.

TABLE 3 Association with 30-day and one-year mortality.

Variable	30-day mortality[a]		One-year mortality[a]	
	aOR (95% CI)	*p*	aHR (95%CI)	*p*
Age	1.02 0.97–1.08)	0.40	1.01 (0.99–1.04)	0.26
Male sex	0.69 (0.18–2.64)	0.59	0.99 (0.54–1.84)	0.98
Diabetes mellitus	0.55 (0.11–2.80)	0.47	1.21 (0.58–2.50)	0.61
Hypertension	0.52 (0.11–2.50)	0.41	0.64 (0.32–1.32)	0.57
Hyperlipidemia	5.84 (0.55–61.57)	0.14	1.30 (0.52–3.25)	0.57
GFR	0.98 (0.96–1.01)	0.18	0.99 (0.98–1.01)	0.32
Anemia on admission	4.30 (0.90–20.65)	0.068	1.07 (0.56–2.02)	0.84
Resuscitation prior to PCI	4.45 (1.07–18.54)	0.040	1.81 (0.97–3.37)	0.063
Mechanical ventilation	0.33 (0.03–3.09)	0.33	1.01 (0.45–2.26)	0.98
RR systolic on admission	0.96 (0.0.93–0.99)	0.019	0.97 (0.96 -0.98)	<0.0001
PCI LCX	059 (0.13–2.66)	0.49	1.28 (0.63–2.61)	.0.49
PCI RCA	0.25 (0.06–1.09)	0.054	0.57 (0.29–1.15)	0.12
TIMI 0/1 after PCI	6.79 (0.93–49.54)	0.059	1.55 (0.77–3.10)	0.22
P2Y12 group[a]		0.23		0.36
Ticagrelor	4.26 (0.90–20.18)	0.068	1.42 (0.74–2.73)	0.30
Prasugrel	3.58 (0.37–34.64)	0.27	1.76 (0.61–5.10)	0.30
P2Y12 combination	0.97 (0.10–9.44)	0.98	0.66 (0.23–1.93)	0.45
Bleeding	1.51 (0.41–5.61)	0.53	1.21 (0.61–2.42)	0.58

aHR, adjusted hazard ratio; aOR, adjusted odd ratio; CI, confidence interval; GFR, glomerular filtration rate; LCX, circumflex artery; P2Y12, P2Y12 receptor antagonist; PCI, percutaneous coronary intervention; RCA, right coronary artery; RR, blood pressure; TIMI, thrombolysis in myocardial infarction.
[a]Clopidogrel as reference.

clopidogrel group ($p = 0.73$). However, oral anticoagulants were not associated with bleeding in the multivariable model (Table 2), which cannot explain the higher bleeding rate. TIMI flow after PCI was similar to the other groups and stent thrombosis was similar in all groups (Table 1). Patients in the P2Y12 combination group had significantly more PCI of the left circumflex artery, which was associated with a better 30-day outcome in univariable, but not in multivariable analysis (Table 3). In addition, peak troponin was similar in all groups, so infarct size was most probably not responsible for better survival. We also examined surgeries performed during the same hospitalization, and their frequencies were similar in all groups (Table 1). The Kaplan-Meier survival curve showed that the vast majority of patients died within the first 30 days (Figure 3). In addition, patients receiving a combination of P2Y12 were younger than those on clopidogrel and ticagrelor ($p < 0.0001$ and $p = 0.038$, respectively) and they received less bivalirudin than those on prasugrel ($p = 0.048$).

The clopidogrel patients were resuscitated more frequently prior to PCI compared to the prasugrel group ($p = 0.018$) and tended to be resuscitated more frequently than the ticagrelor group ($p = 0.056$). They had significantly lower hemoglobin and GFR values on admission, both known factors associated with bleeding and treatment outcome (15, 23, 24), and were more

likely to receive oral AC than patients receiving ticagrelor and prasugrel. In addition, they were significantly older.

The most interesting finding of our analysis was that patients with a P2Y12 combination bled significantly more often than patients with ticagrelor and prasugrel, but similarly to patients with clopidogrel. Several reasons could account for this bleeding tendency in the P2Y12 combination group. Patients with MI and CS are more prone to bleeding than other MI patients, mainly because of more aggressive treatment such as resuscitation, mechanical circulatory support, and frequent punctures of arteries and central veins (2). In patients with CS, drug absorption, biotransformation, bioavailability, and excretion are slower than in other patients with MI (3, 5–7, 10). Therefore, it can be assumed that the active ingredient of the previously administered P2Y12 remains active in the body even if the P2Y12 is changed according to the recommendations, which could explain the very high bleeding rate in the P2Y12 combination group. Unfortunately, we lack data on platelet reactivity.

Although the bleeding rate was higher in our analysis, the mortality rate was comparable to previous observations (2). As already mentioned, P2Y12 were not associated with outcome after adjustment for confounding factors. Only systolic blood pressure at admission was associated with 30-day and 1-year mortality (**Table 3**). In addition, resuscitation prior to PCI was associated with 30-day mortality. This may suggest that bleeding itself is less important in this particular patient group compared to other variables than in other patients with MI. We can only speculate that in this particular group of patients, so many vital systems are damaged that anemia and bleeding are less important to the outcome than resuscitation and systolic blood pressure on admission, which might better reflect the patient's situation.

Our finding supports previous observations in similar patients in whom the higher bleeding rate did not result in a worse outcome (2). Moreover, these patients had the lowest crude 30-day and one-year mortality rates, which were significantly lower than in the clopidogrel group and similar to those in the ticagrelor and prasugrel groups (**Figures 2**, **3**). This phenomenon remains unexplained (2).

A unique and novel finding of the present study is that the combination of P2Y12 is associated with a significantly higher risk of bleeding in the acute phase of MI with CS, which surprisingly does not lead to a worse outcome. Our data may have some clinical implications. Based on our results, it seems reasonable to wait longer than recommended before switching between P2Y12 in patients with CS. Further research is needed to determine whether platelet reactivity should be measured before switching to P2Y12 to avoid the high risk of bleeding in these patients.

Our results point to the complex relationship between treatment, bleeding, and mortality in MI patients with CS and suggest that it may be difficult to account for all possible confounding factors in these patients. The lack of association between bleeding and outcome could be due to a still unidentified specific factor related to cardiogenic shock or to unknown confounding factors that were not considered in our analysis.

Our results suggest that the combination of P2Y12 increases the risk of bleeding by 80% and 90%, respectively, compared with ticagrelor and prasugrel, but this does not translate into a worse outcome in patients with MI and CS. The possible pathomechanisms to explain the "benign" bleeding in these patients are unclear, and they were not investigated in this study, but we did propose several hypotheses. Further research is needed to determine the still unclear pathophysiological mechanisms, which are probably multifactorial.

Limitations

Our analysis has relevant limitations. It was a retrospective study at a single center and therefore provides only associative, not causal, evidence. The major limitation is the small sample size, especially when subgroups were analyzed. The number of patients might have influenced the outcome in terms of mortality. A large sample size is usually required to detect a significant difference in mortality. The population was enrolled over a long period of time, and many differences in treatment may contribute to the changes in mortality over time. However, when we included the year of admission in the multivariable analysis, it was not associated with either bleeding ($p = 0.06$) or mortality ($p = 0.33$), so it is highly unlikely that these different practices over the years had a significant impact on the outcome. Current practices were not fully accounted for in this study (nor in a previous observation), which is certainly a limitation of the study. There were fairly broad CIs in the multivariate analysis, which detracts from the power of our analysis. There were no exclusion criteria related to concomitant diseases or clinical presentation, so this population represents a real experience of high-risk patients requiring PCI.

Conclusions

Our study results suggest that the choice of P2Y12 was not associated with treatment outcome. The combination of P2Y12 increased bleeding risk compared with ticagrelor and prasugrel and was comparable to clopidogrel in patients with MI and CS. However, these higher bleeding rates did not result in worse treatment outcomes. Our results point to the complex relationship between treatment, bleeding, and mortality in MI patients with CS and suggest that it may be difficult to account for all possible confounding factors in these patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by University Medical Center Maribor Committee for Medical Ethics

(Reference: UKC-MB-KME-59/19). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because it is a retrospective analysis without any personal data.

Author contributions

VK: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Data curation, Software. GK: Investigation, Supervision, Writing – review & editing, Validation.

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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.2023.1266127/full#supplementary-material

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EDITED BY
Marija Vavlukis,
Ss. Cyril and Methodius University in Skopje, North Macedonia

REVIEWED BY
Robert Jeenchen Chen,
Stanford University, United States
Biljana Gerasimovska,
Saints Cyril and Methodius University of Skopje, North Macedonia

*CORRESPONDENCE
Chunbo Chen
✉ gghccm@163.com

†These authors have contributed equally to this work

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Prediction of acute kidney injury after cardiac surgery with fibrinogen-to-albumin ratio: a prospective observational study

Wang Xu[1†], Xin Ouyang[1†], Yingxin Lin[1,2†], Xue Lai[3†], Junjiang Zhu[1], Zeling Chen[1], Xiaolong Liu[1], Xinyi Jiang[1] and Chunbo Chen[1,4*]

[1]Department of Intensive Care Unit of Cardiac Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong Province, China, [2]Peking University Shenzhen Hospital, Shenzhen, China, [3]Day Surgery Center, Affiliated Hospital of Southwest Medical University, Luzhou, China, [4]Department of Critical Care Medicine, Shenzhen People's Hospital, Shenzhen, Guangdong Province, China

Background: The occurrence of acute kidney injury (AKI) following cardiac surgery is common and linked to unfavorable consequences while identifying it in its early stages remains a challenge. The aim of this research was to examine whether the fibrinogen-to-albumin ratio (FAR), an innovative inflammation-related risk indicator, has the ability to predict the development of AKI in individuals after cardiac surgery.
Methods: Patients who underwent cardiac surgery from February 2023 to March 2023 and were admitted to the Cardiac Surgery Intensive Care Unit of a tertiary teaching hospital were included in this prospective observational study. AKI was defined according to the KDIGO criteria. To assess the diagnostic value of the FAR in predicting AKI, calculations were performed for the area under the receiver operating characteristic curve (AUC), continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).
Results: Of the 260 enrolled patients, 85 developed AKI with an incidence of 32.7%. Based on the multivariate logistic analyses, FAR at admission [odds ratio (OR), 1.197; 95% confidence interval (CI), 1.064–1.347, $p = 0.003$] was an independent risk factor for AKI. The receiver operating characteristic (ROC) curve indicated that FAR on admission was a significant predictor of AKI [AUC, 0.685, 95% CI: 0.616–0.754]. Although the AUC-ROC of the prediction model was not substantially improved by adding FAR, continuous NRI and IDI were significantly improved.
Conclusions: FAR is independently associated with the occurrence of AKI after cardiac surgery and can significantly improve AKI prediction over the clinical prediction model.

KEYWORDS

acute kidney injury, fibrinogen-to-albumin ratio, cardiac surgery, biomarkers, cardiac surgery intensive care unit

Introduction

Cardiac surgery can lead to a serious complication known as acute kidney injury (AKI), which poses a risk of significant morbidity and mortality (1). The diagnosis and treatment of AKI have historically relied on serum creatinine (SCr) and blood urea nitrogen, as well as urine output. However, clinically significant changes often occur

within days of injury, making early treatment and nephroprotective intervention difficult (2, 3). To effectively tackle this problem, it is crucial to promptly detect individuals vulnerable to AKI. This identification will facilitate the implementation of management guidelines suggested by Kidney Disease: Improving Global Outcomes (KDIGO), which comprise adjusting hemodynamics and volume, closely monitoring renal function, and averting nephrotoxicity (4, 5).

Numerous factors have been identified as associated with the risk of postoperative AKI development, including sex, age, diabetes mellitus, surgery type, and perioperative hemodynamic goals (1, 6). Nevertheless, a limited number of investigations have endeavored to evaluate hematological biomarkers as autonomous prognosticators of AKI. Albumin, an indispensable indicator of liver function, has the potential to function as a valuable marker for assessing inflammatory and nutritional status (7). Fibrinogen, a key coagulation protein, is widely recognized as a sensitive indicator of inflammatory status (8). The innovative inflammation-based risk metric, known as the fibrinogen-to-albumin ratio (FAR), has demonstrated its value in predicting adverse outcomes in cancer (9, 10) and cardiovascular disease (11–13). Recent studies has indicated that the levels of preprocedural FAR exhibit a correlation with the incidence of AKI in individuals undergoing emergency percutaneous coronary intervention (14) and elective percutaneous coronary intervention (15) and in children following ventricular septal defect surgery (16). Nevertheless, the association linking the frequency of acute kidney injury (AKI) in individuals who have undergone cardiac surgery and the previously unexplored variable, known as FAR, remains uninvestigated.

Therefore, we undertook a prospective, observational study within the confines of the Cardiac Surgery Intensive Care Unit (CSICU) to assess the efficacy of predictive models based on FAR in the prognosis of AKI after cardiac surgery.

Materials and methods

Study design and participants

This prospective observational study was conducted at the Guangdong Provincial People's Hospital. We consecutively enrolled all patients who were admitted to the CSICU after coronary artery bypass graft (CABG), valve, and/or aortic surgery between February 2023 and March 2023. These patients all underwent cardiopulmonary bypass (CPB). Patients were excluded for the following reasons: age under 18, kidney transplantation or nephrectomy, chronic kidney disease (CKD), renal replacement therapy (RRT) prior to CSICU admission, less than 24 h in the cardiac CSICU, or missing clinical data. The primary objective was to identify the occurrence of AKI within one week from the time of admission to the CSICU. The study protocol was approved by the Ethics Committee of Guangdong Provincial People's Hospital (registered approval number: KY2020-103-01).

Data collection

Overall baseline clinical data were prospectively collected after admission, including age, sex, weight, preexisting medical conditions, smoking history, emergent surgery, American Association of Anesthesiologists (ASA)stage, type of surgery (valve surgery alone, CABG alone, aortic surgery and CABG and valve surgery), baseline SCr, baseline estimated glomerular filtration rate (eGFR), preoperative hemoglobin level, FAR, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVDD), norepinephrine use, adrenaline use, dopamine use, and diuretic use. eGFR was calculated based on the CKD Epidemiology Collaboration creatinine equation (17). SCr was measured before the operation, after the operation at CSICU admission, and thereafter at least once daily as part of routine clinical care during CSICU hospitalization. Surgical data included volume of transfused red blood cells (RBCs), plasma, and blood platelets; amount and type of intraoperative fluids administered (crystalloid and artificial colloid); duration of surgery; CPB time; aortic cross-clamping (ACC) time; and intra-aortic balloon pump (IABP) use. IABP implantation data were also collected and sorted. Hemoglobin, hematocrit, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores after surgery were recorded at CSICU admission. After recovery from anesthesia, the patient's overall condition was assessed using the APACHE II score. We calculated postoperative mean arterial pressure (MAP) as diastolic BP + (systolic BP−diastolic BP)/3.

The resulting variables included the occurrence of AKI within one week of cardiac surgery, renal replacement therapy (RRT), length of stay in the CSICU, duration of mechanical ventilation, use of extracorporeal membrane oxygenation (ECMO), length of hospital stay, and CSICU mortality.

Definitions

Based on the recent criteria for the diagnosis of acute kidney injury (AKI) associated with cardiac surgery, AKI refers to patients who have undergone cardiac surgery in the preceding seven days and meet the KDIGO standard (18). The KDIGO standard for AKI is characterized by any of the following conditions: a rise of ≥0.3 mg/dl (≥26.5 μmol/L) within 48 h, a rise of ≥1.5 times the serum creatinine (SCr) level within one week, or a urine output of less than 0.5 ml/kg/h within 6 h. The determination of baseline creatinine followed the previously described rules (19) in descending order of preference: the ICU admission considered the most recent pre-ICU value within a range of 30 to 365 days. A stable pre-ICU value >365 days before ICU admission in patients aged <40 years, (stable defined as within 15% of the lowest ICU measurement); a pre-ICU value >365 days before ICU admission and less than the initial SCr at ICU admission; a pre-ICU value (between 3 and 39 days before ICU admission) less than or equal to the initial SCr at ICU admission and not obviously in AKI; the lowest of the initial SCr

at ICU admission, the last ICU value, or the minimum value at follow-up to 365 days.

Statistical analysis

Data analysis was performed using SPSS Version 25.0 (SPSS, IL, USA) and R statistical software (version 4.2.3). To evaluate the continuous variables, we utilized the Wilcoxon rank-sum test. These variables were presented as medians, accompanied by interquartile ranges (P25, P75). For the categorical variables, we used either the chi-squared test or Fisher's exact test for analysis, and these variables were presented as frequencies (percentages). We compared baseline characteristics and hemodynamic parameters between the groups with and without AKI using the methods described above. All tests were two-sided, and a two-sided p value < 0.05 was considered statistically significant.

Clinical models were constructed by univariable and multivariable logistic regression. The clinical variables with a $P < 0.10$ in the univariate analysis were included in the multivariate analysis. Multivariate models were built using a forward variable selection method. To assess the added value of biomarkers to the prediction model for postoperative AKI, we developed two logistic regression models. Model 1 consisted of the selected clinical predictors (excluding FAR), while Model 2 incorporated these predictors in addition to the selected biomarkers. In order to assess and compare the efficacy of the mentioned prediction models, the following methodologies were utilized, as described in previous research recommendations: (1) To assess the accuracy of the prediction model, we constructed the receiver operating characteristic (ROC) curve. The accuracy of the model was measured using the area under the ROC (AUC-ROC). To compare the accuracy of different models, we conducted the Delong test (20). (2) In order to compare the prediction performance of the two models, additional measures such as net recognition improvement (NRI) and integrated discrimination improvement (IDI) were used. These measures offer a more comprehensive evaluation of the reclassification concept (21, 22). For subject categories where results were obtained, an upward movement signifies improved classification, whereas a downward movement represents worse classification. The opposite explanation is true for subjects without results. The quantification of the reclassification improvement manifests as the sum of the difference between the proportion of ascending individuals minus the proportion of descending individuals with results and the proportion of descending individuals minus the proportion of ascending individuals without results. This cumulative difference is referred to as the NRI. The central focus of the IDI is the discrepancy between the overall sensitivity and the "1 minus specificity" in the risk model, with and without incorporating novel markers. A higher IDI value indicates the superior predictive ability of the new model. The aforementioned assessment internally validates the predictive performance of Model 1 and Model 2 through the utilization of the guidance technique, replicated 1,000 times.

Results

Patient preoperative characteristics

A total of 293 patients were assessed for eligibility in the research, with 33 individuals being excluded from the study (Figure 1). Subsequently, 260 patients were selected for analysis, and their preoperative characteristics are outlined in Table 1. According to the KDIGO criteria, a total of 85 patients (32.7%) developed AKI within 7 days after cardiac surgery. The percentage of male patients among AKI patients was significantly higher than the percentage of male patients among non-AKI patients. In comparison to non-AKI individuals, patients suffering from AKI had an older age and an increased incidence of emergency surgery. The occurrence of valve surgery and aortic surgery was more prevalent in AKI patients. Additionally, individuals with AKI had elevated baseline SCr, baseline eGFR, hemoglobin levels, and FAR. A notable difference was observed in the administration of norepinephrine and dopamine before surgery in patients with acute kidney injury (AKI) compared to those without AKI. However, there were no significant differences in weight, preexisting medical conditions, smoking history, CABG alone, CABG and valve surgery, ASA classification, baseline eGFR, LVEF, LVDD, adrenaline use or diuretic use between patients with and without AKI.

Patient intraoperative characteristics

Table 2 shows the intraoperative parameters of AKI and non-AKI patients. In this cohort, it was found that AKI patients received a higher percentage of red blood cells (RBCs) and blood platelets during surgery compared to non-AKI patients. Compared to non-AKI patients, patients with AKI had a longer CPB time and duration of surgery, while there was no significant difference in IABP use. Additionally, patients with AKI received a higher volume of colloid during surgery than patients without AKI.

Patient postoperative characteristics and results

Patients with AKI were likely to have lower hemoglobin and hematocrit levels after surgery on admission to the CSICU and higher APACHE II scores than patients without AKI. The current investigation revealed that the occurrence of AKI was associated with an increased occurrence of postoperative RRT, the use of ECMO, and CSICU mortality. Additionally, patients with AKI had longer hospital and CSICU stays, along with extended periods of postoperative mechanical ventilation (Table 3).

Establishment and comparison of models

Supplementary Table S1 provides a comprehensive overview of the results obtained from univariate logistic regression analyses.

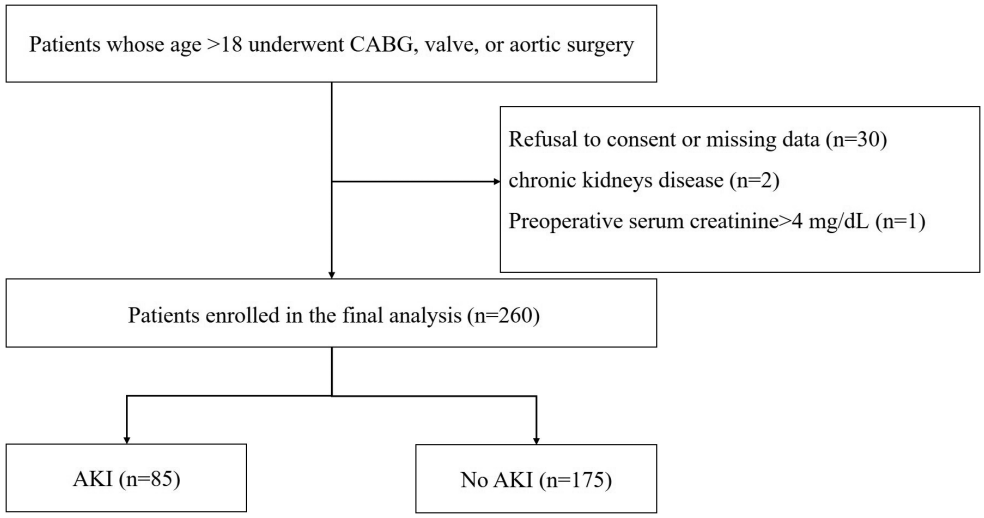

FIGURE 1
Flow chart from recruitment to outcome. CABG, indicates coronary artery bypass graft; AKI, acute kidney injury.

The predictive results are summarized in Table 4, which displays the multivariate regression analysis. The ROC curves of FAR are showcased in Figure 2. Notably, two models were considered: Model 1, which was established based on the identified clinical factors alone, and Model 2, which incorporated FAR in combination with the aforementioned factors. The ROC curve indicated that FAR at admission was a significant predictor of AKI (AUC-ROC = 0.685). Model 1 could reasonably predict postoperative AKI (AUC-ROC = 0.815). The inclusion of FAR improved the AUC-ROC of the prediction model to 0.827, as shown by the ROC curve. Furthermore, the Delong test showed that the difference was not statistically significant (Table 4, $P = 0.216$). However, to ascertain whether Model 2 could improve risk reclassification in comparison to Model 1, both the IDI and the NRI were used. (Table 5). According to the findings, the NRI yielded a value of 0.301 (0.048–0.553), meaning that Model 2 achieved a 30.1% improvement in correct classification compared to Model 1 ($P = 0.020$). Furthermore, the IDI yielded a value of 0.033 (0.009–0.057), indicating that Model 2 showed a 3.3% improvement in overall discrimination ability compared to Model 1 ($P = 0.008$).

Discussion

In this single-center prospective study, the occurrence of AKI was frequent, and it was found to be associated with adverse outcomes during hospitalization in the CSICU. The occurrence of AKI after surgery was found to be influenced by several independent risk factors, including FAR, duration of surgery, aortic surgery, and the postoperative APACHE II score. To the best of our understanding, this investigation is the first to reveal that FAR was autonomously correlated with AKI incidence following cardiac surgery and improved AKI prognosis beyond the clinical prediction model. AKI, a frequent complication arising after cardiac surgery, is observed in approximately 5%–42% of individuals worldwide who undergo this procedure annually, totaling over 2 million (1). Our study results demonstrated that in the first week following cardiac surgery, the prevalence of AKI was as high as 32.7% among individuals. Furthermore, the likelihood of developing AKI after cardiac surgery is strongly influenced by the specific type of surgery, resulting in significant differences in incidence rates (23). This conclusion is consistent with our research results. The incidence of AKI may vary between studies due to factors such as variations in patient characteristics (e.g., age groups and types of surgery), differences in sample size, and different definitions of AKI. Several investigations have consistently recognized AKI as an element in prolonged hospitalization, a complicated clinical course, and increased mortality after cardiac surgery (24). However, it is a formidable task to detect and diagnose AKI at an early stage because it presents a wide range of clinical manifestations, spanning from the absence of symptoms to oliguria and potentially even renal failure. Thus, it is crucial to identify clinical characteristics and validate biomarkers that can accurately predict patient prognosis. Achieving such breakthroughs would significantly increase the efficacy of screening and diagnostic tools (25).

During the univariate analysis of this study, it was found that AKI showed a significant correlation with various clinical variables both before and during cardiac surgery. This finding confirmed that AKI can stem from multiple clinical factors. Previous research conducted by Rosner et al. (2) showed that cardiac surgery characteristics, such as the use and duration of CPB and elevated vasopressin levels, were strongly associated with an increased risk of AKI. As per the results of one of our previous studies, patients admitted to the ICU who experienced a postoperative mean arterial pressure (MAP) below 75 mmHg for

TABLE 1 Preoperative characteristics of patients with and without postoperative AKI.

Variable	AKI ($n = 85$)	NO AKI ($n = 175$)	*P* value
Demographic variables			
Age, years	60 (50.5,67)	56 (48,61)	0.002
Sex, male, *n* (%)	56 (65.9)	92 (52.6)	0.042
Weight, kg	63 (53.5,71.25)	61 (53,71)	0.507
Preexisting medical conditions, *n* (%)			
Hypertension	30 (35.3)	44 (25.1)	0.089
Diabetes mellitus	6 (7.1)	10 (5.7)	0.672
Coronary artery disease	7 (8.2)	20 (11.4)	0.429
Stroke	8 (9.4)	11 (6.3)	0.364
Heart failure	56 (65.9)	97 (55.4)	0.108
Previous cardiac surgery	6 (7.1)	20 (11.4)	0.271
Hyperlipidemia	4 (4.7)	8 (4.6)	1.000
Smoking history, *n* (%)	22 (25.9)	31 (17.7)	0.125
Type of surgery, *n* (%)			
Valve surgery alone	37 (43.5)	119 (68)	<0.001
CABG alone	14 (16.5)	27 (15.4)	0.829
Aortic surgery	29 (34.1)	19 (10.9)	<0.001
CABG and valve surgery	5 (5.9)	10 (5.7)	1.000
Emergency surgery, *n* (%)	26 (30.6)	8 (4.6)	<0.001
ASA ≥ III grade, *n* (%)	81 (95.3)	167 (95.4)	0.961
Laboratory data			
Baseline serum creatinine, umol/L	82.75 (71.9,100.73)	76.3 (64.67,90.71)	0.011
Baseline eGFR, ml. (min.1.73 m^2)$^{-1}$	109.23 (84.24,147.2)	104 (73.98,131.42)	0.085
Hemoglobin, g/L	129 (115.5,142)	133 (123,145)	0.022
FAR(%)	9.18 (7.12,12.29)	7.42 (6.35,9.2)	<0.001
Imaging data			
LVEF (%)	64 (58,66.5)	64 (60,66)	0.564
LVDD, mm	48 (43,55)	50 (45,57)	0.155
Medication use, *n* (%)			
Norepinephrine use	20 (23.5)	23 (13.1)	0.034
Adrenaline use	62 (72.9)	130 (74.3)	0.817
Dopamine use	42 (49.4)	61 (34.9)	0.024
Diuretic use	84 (98.8)	171 (97.7)	0.541

CABG Coronary artery bypass grafting; FAR fibrinogen-to-albumin ratio; LVEF Left ventricular ejection fraction; LVDD Left ventricular end-diastolic;.

TABLE 2 Intraoperative data in patients with and without postoperative AKI.

Variable	AKI ($n = 85$)	NO AKI ($n = 175$)	*P* value
Fluid management			
Crystalloid, *n* (%)	15 (17.6)	21 (12)	0.216
Colloid, ml	500 (500,800)	500 (500,1,000)	0.004
RBC, *n* (%)	23 (27.1)	23 (13.1)	0.006
Plasma, *n* (%)	15 (17.6)	17 (9.7)	0.068
Platelets, *n* (%)	37 (43.5)	28 (16)	<0.001
IABP use, *n* (%)	4 (4.7)	7 (4)	0.791
CPB, minutes	196 (146.5,256)	146 (120,188)	<0.001
ACC, minutes	101 (74.5,134)	87 (66,119)	0.041
Duration of surgery, minutes	346 (270,443.5)	260 (218,317)	<0.001

RBC red blood cell; IABP intra-aortic balloon pump; CPB cardiopulmonary bypass time; ACC aortic cross-clamping.

TABLE 3 Postoperative characteristics and outcomes in patients with and without postoperative AKI.

Variable	AKI ($n = 85$)	NO AKI ($n = 175$)	*P* value
APACHE II score	11 (9,13)	7 (6,9)	<0.001
Laboratory data within the first 24 h of ICU admission			
Hematocrit (%)	29.7 (27,33.65)	31.6 (29.3,35.4)	0.002
Hemoglobin, g/L	100 (86,110.85)	106 (97,121)	<0.001
MAP, mmHg	87.33 (80,90)	86.67 (77.33,90)	0.689
Outcome			
RRT during ICU stay, *n* (%)	7 (8.2)	0 (0)	<0.001
Length of ICU stay, days	4 (2,8)	2 (2,3)	<0.001
Length of mechanical ventilation, hours	42 (20.5,95.5)	19 (12,16)	<0.001
ECMO use, *n* (%)	4 (4.7)	0 (0)	0.011
Hospital stay, days	18 (14,24.5)	14 (11,19)	<0.001
ICU mortality, *n* (%)	9 (10.6)	0 (0)	<0.001

MAP, mean arterial pressure; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

a duration of one hour or longer were found to have a significant independent association with the occurrence of AKI (26). The multivariate logistic regression analysis of this study also confirmed that aortic surgery and surgery time were risk factors for AKI.

In this study, aortic surgery was identified as an independent risk factor for AKI. Aortic surgery is a complex procedure that requires the use of hypothermic circulatory arrest, which can result in severe renal ischemia-reperfusion injury. While moderate hypothermic circulatory arrest has managed to shorten the duration of CPB in aortic surgery, it is still considerably longer than in other cardiac surgeries. Consequently, aortic surgery further contributes to the risk of developing AKI. Cardiac surgery with CPB is widely acknowledged for its prolonged duration and substantial trauma, frequently resulting in postoperative organ dysfunction in patients (27). Therefore, in our study, surgery time was chosen for multivariate logistic regression. In assessing the risk model, we also considered the APACHE II score, which is a physiologically based system consisting of twelve physiological parameters. Patient SCr levels and chronic kidney function status were among the parameters taken into account. The APACHE II score, a widely recognized prognostic tool, is commonly utilized to predict unfavorable outcomes in ICU patients (6). In the current study, APACHE II was selected as one of the independent predictors in the risk model.

AKI is influenced by inflammation in its pathogenic mechanisms (28). Fibrinogen and albumin are two widely reported proteins with properties related to inflammation, nutrition, and blood flow dynamics (29). Serum albumin plays a crucial role in maintaining colloid osmotic pressure, scavenging free radicals, and altering the permeability of capillary membranes (30, 31). The nutritional and inflammatory status of patients can be effectively assessed by considering the preoperative serum albumin level (32). Lower levels of serum albumin are often correlated with elevated blood viscosity and impaired endothelial cell function (33). Fibrinogen, a

TABLE 4 Multivariate logistic regression analysis variables and AUC-ROC analyses of predictive models.

Predictive model and component	OR	95% CI	*P* value	AUC-ROC	95% CI	*P* value[a]
Model1				0.815	0.755–0.875	0.216
APACHE II	1.405	1.251–1.577	<0.001			
Surgery time	1.005	1.002–1.008	0.001			
Aortic surgery	3.013	1.381–6.575	0.006			
Model2				0.827	0.768–0.885	
APACHE II	1.352	1.201–1.521	<0.001			
Surgery time	1.005	1.001–1.008	0.004			
Aortic surgery	2.935	1.303–6.612	0.009			
FAR	1.197	1.064–1.347	0.003			

AUC-ROC, area under the receiver operating characteristic curve; FAR, fibrinogen-to-albumin ratio.
[a]Versus model 1.

glycoprotein primarily synthesized by liver cells, functions as a crucial factor in blood coagulation and the regulation of coagulation pathways (34). In inflammatory situations, there is an upregulation of fibrinogen, which initiates the recruitment of cells involved in inflammation and platelets. Additionally, it activates endothelial cells, contributing to prolonged vascular inflammation, and resulting in platelet aggregation and leakage in the vasculature (35). In various diseases, both fibrinogen and albumin have been identified as important prognostic indicators, according to several studies (36, 37). FAR, an index that combines albumin and fibrinogen, shows higher sensitivity and specificity in predicting systemic inflammation, blood clot formation, and viscosity than fibrinogen and albumin alone (15). Mechanisms of AKI following cardiac surgery include renal reperfusion-induced ischemia, inflammatory response, hemolysis, oxidative damage, and exposure to nephrotoxins (38). We believe that these mechanisms could explain the predictive role of FAR in determining the likelihood of AKI occurrence.

The relationship between FAR and cardiovascular disease has received considerable attention in scientific research. For instance, FAR has shown great potential as a reliable indicator for identifying the exaggerated increase in morning blood pressure in newly diagnosed hypertensive patients who have not yet received treatment (39). Notably, recent studies have uncovered a correlation between elevated levels of FAR and the manifestation of AKI following cardiac surgery. Can Wang et al.

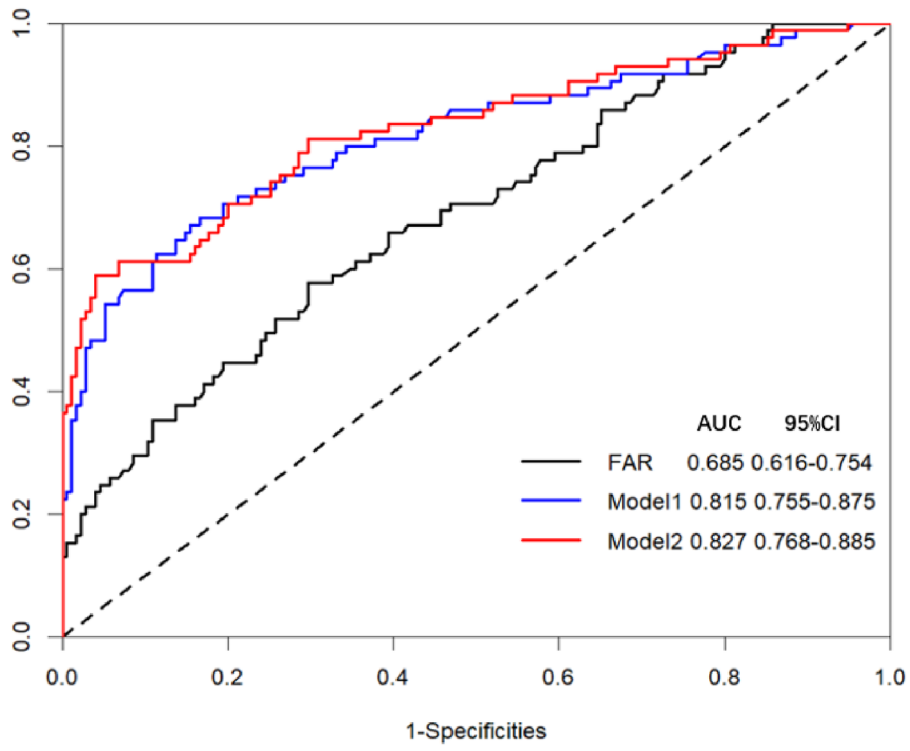

FIGURE 2
Receiver operating characteristic (ROC) curve analysis for two models and FAR in predicting AKI. Model 1 for AKI prediction is composed of APACHE II, Surgery time, and Aortic surgery; Model 2 for AKI prediction is composed of APACHE II, Surgery time, Aortic surgery, and FAR.

TABLE 5 Net reclassification improvement and integrated discrimination index of two models.

Model	cNRI (95%CI)	*P*-value[a]	IDI (95%CI)	*P*-value[b]
Model1				
Model2	0.301 (0.048–0.553)	0.020	0.033 (0.009–0.057)	0.008

cNRI, net reclassification improvement between two models; IDI, integrated discrimination index between two models; Model 1 for AKI prediction is composed of APACHE II, Surgery time, and aortic surgery; Model 2 for AKI prediction is composed of APACHE II, Surgery time, aortic surgery and FAR.
[a]cNRI model 2 versus model1.
[b]IDI model 2 versus model1.

discovered a significant independent association between the occurrence of AKI and the preoperative assessment of FAR in patients undergoing percutaneous coronary intervention (15). Fan Cao et al. demonstrated that FAR during CPB was an independent predictor of AKI in infants with ventricular septal defects who underwent cardiac surgery involving CPB (16). However, these studies were limited to children or post-contrast AKI. A difference in our study is that we explored the value of the FAR in predicting AKI after cardiac surgery in adults. Moreover, we included several types of cardiac surgery. Our findings in this study further expand the scope of the application of FAR to AKI after cardiac surgery.

By incorporating FAR into the existing risk model, the model discrimination for AKI showed an increase in AUC from 0.815 to 0.827 ($p = 0.216$), although this difference did not reach statistical significance. It is worth noting that the limited patient sample size may have influenced these findings. Nonetheless, the introduction of FAR into the prediction model yielded a significant improvement in NRI (0.301, $p = 0.020$) and IDI (0.033, $p = 0.008$). The NRI assesses how much patients improve their predicted probabilities, whereas the IDI highlights the average improvement in predicted probabilities (21). In simple terms, 30.1% of patients experienced an improvement in predictability, with an average increase of 0.033 in predicted probabilities when FAR was included in the predictive model. Hence, this study suggests that the inclusion of FAR in a model already containing established risk factors could improve the predictability of AKI. However, in recent times, there have been concerns raised by statisticians about the overestimation of the improvement in predictability of predictive models using the NRI method (40). Despite the widespread use of the NRI in discriminative prediction models in various studies, it is crucial to exercise caution when interpreting these results, and additional evaluation tools should be used to validate our findings.

This study has several limitations. First, the use of data from a single center, the inclusion of a limited number of patients, and a short selection window devalue the statistical calculations, as these calculations may vary in different institutions and patient data sets characterized by varying distributions. Second, laboratory variables were collected before and after CPB without dynamic monitoring. Third, the study cohort was probably heterogeneous in terms of cohort and surgical status, but further studies involving more homogeneous patient samples are needed to confirm our results. Finally, whether any advantage can be gained from FAR modulation (e.g., albumin infusion) in preventing AKI remains to be determined. Additional prospective multicenter studies with larger sample sizes and experimental studies are necessary to verify our results.

Conclusion

The present investigation confirms that the measurement of FAR before admission to the CSICU has emerged as a distinct risk factor for AKI in patients who have undergone cardiac surgery. This prospective study provides evidence to support the use of FAR assessment as a means of early prediction and subsequent prediction of AKI. Given its convenient accessibility as a biomarker, FAR holds promise for improving patient prognosis in clinical settings.

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 of Guangdong Provincial People's 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

WX: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. XO: Data curation, Formal Analysis, Writing – original draft. YL: Conceptualization, Methodology, Writing – review & editing. XL: Conceptualization, Writing – review & editing. JZ: Data curation, Writing – original draft. ZC: Data curation, Writing – original draft. XL: Formal Analysis, Writing – review & editing. XJ: Formal Analysis, Writing – review & editing. CC: Conceptualization, Formal Analysis, Methodology, Writing – review & editing.

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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.2024.1336269/full#supplementary-material

SUPPLEMENTARY TABLE S1
Univariate logistic analysis for prediction of AKI.

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EDITED BY
Marija Vavlukis,
Ss. Cyril and Methodius University in Skopje, North Macedonia

REVIEWED BY
Satoshi Miyashita,
Cleveland Clinic, United States
Roberto Primi,
San Matteo Hospital Foundation (IRCCS), Italy
Biljana Zafirovska Taleska,
University Clinic of Cardiology, North Macedonia

*CORRESPONDENCE
Anton O. Bilchenko
✉ bilchenko@intcardio.com

†These authors share first authorship

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Acute myocardial infarction complicated by cardiogenic shock in Ukraine: multicentre registry analysis 2021–2022

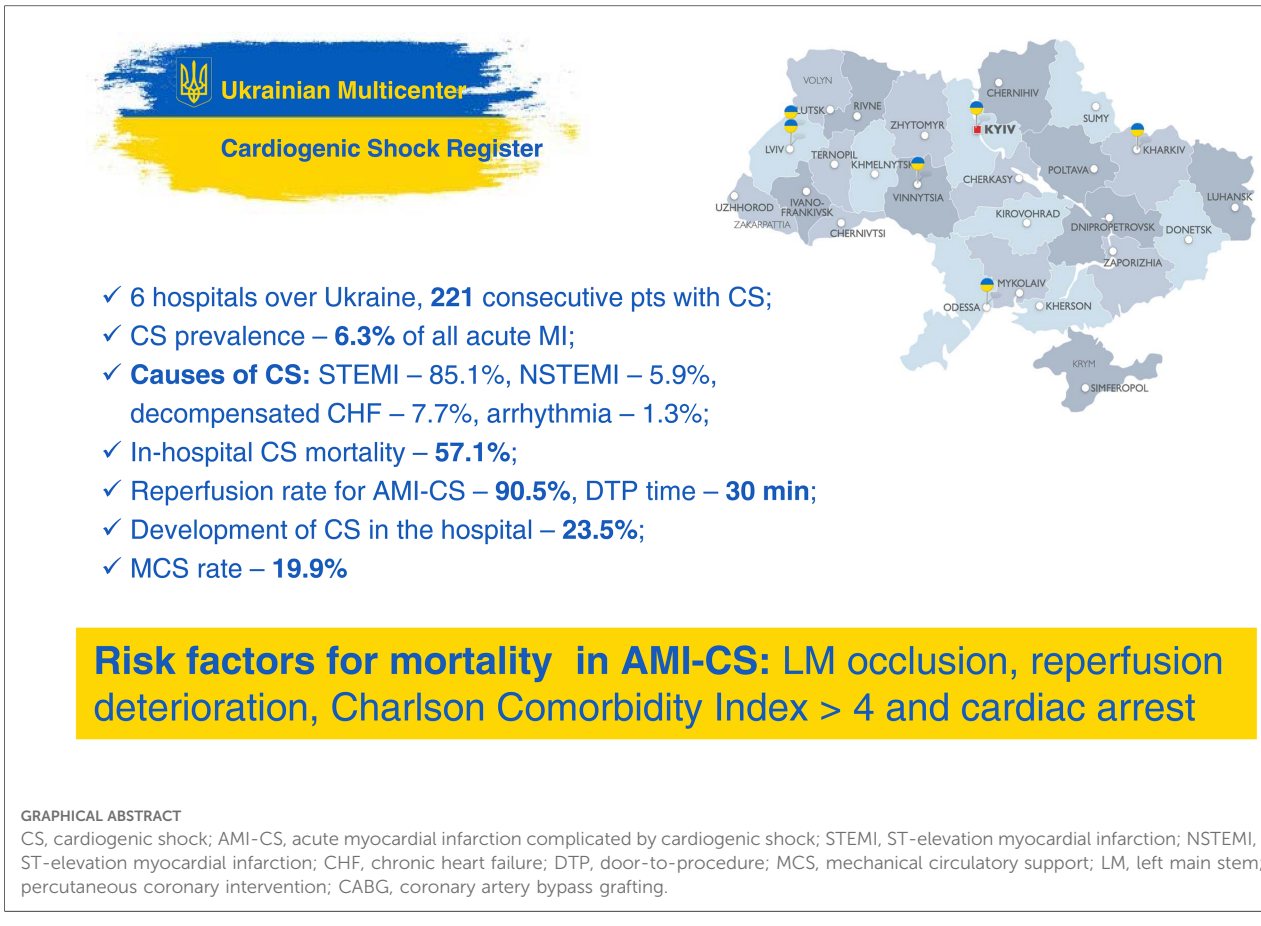
Anton O. Bilchenko[1*†], Olga V. Gritsenko[2†], Volodymyr O. Kolisnyk[3], Oleg I. Rafalyuk[4], Andrii V. Pyzhevskii[4], Yaroslav V. Myzak[5], Dmytro I. Besh[5,6], Victor M. Salo[5], Sergii O. Chaichuk[7], Mykhailo O. Lehoida[8], Ihor V. Danylchuk[8] and Ihor V. Polivenok[2,9]

[1]Department of Prevention and Treatment of Emergency Conditions, L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine, Kharkiv, Ukraine, [2]Department of Interventional Cardiology, V.T. Zaitcev Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine, Kharkiv, Ukraine, [3]Department of Interventional Cardiology, Odesa Regional Hospital, Odesa, Ukraine, [4]Department of Interventional Radiology, Lviv Regional Clinical Treatment and Diagnostic Cardiology Center, Lviv, Ukraine, [5]Department of Interventional Radiology, 1st Territorial Medical Union, Lviv, Ukraine, [6]Department of Family Medicine, Danylo Halytsky National Medical University, Lviv, Ukraine, [7]Department of Interventional Cardiology, Oleksandrivska Clinical Hospital, Kyiv, Ukraine, [8]Department of Cardiology, Vinnytsia Regional Clinical Treatment and Diagnostic Center of Cardiovascular Pathology, Vinnytsia, Ukraine, [9]Department of Therapy No 1, Kharkiv National Medical University, Kharkiv, Ukraine

Background: Data on the results and management strategies in patients with acute myocardial infarction complicated by cardiogenic shock (AMI-CS) in the Low and Lower-Middle Income Countries (LLMICs) are limited. This lack of understanding of the situation partially hinders the development of effective cardiogenic shock treatment programs in this part of the world.
Materials and methods: The Ukrainian Multicentre Cardiogenic Shock Registry was analyzed, covering patient data from 2021 to 2022 in 6 major Ukrainian reperfusion centres from different parts of the country. Analysis was focusing on outcomes, therapeutic modalities and mortality predictors in AMI-CS patients.
Results: We analyzed data from 221 consecutive patients with CS from 6 hospitals across Ukraine. The causes of CS were ST-elevated myocardial infarction (85.1%), non-ST-elevated myocardial infarction (5.9%), decompensated chronic heart failure (7.7%) and arrhythmia (1.3%), with a total in-hospital mortality rate for CS of 57.1%. The prevalence of CS was 6.3% of all AMI with reperfusion rate of 90.5% for AMI-CS. In 23.5% of cases, CS developed in the hospital after admission. Mechanical circulatory support (MCS) utilization was 19.9% using intra-aortic balloon pump alone. Left main stem occlusion, reperfusion deterioration, Charlson Comorbidity Index >4, and cardiac arrest were found to be independent predictors for hospital mortality in AMI-CS.
Conclusions: Despite the wide adoption of primary percutaneous coronary intervention as the main reperfusion strategy for AMI, CS remains a significant problem in LLMICs, associated with high in-hospital mortality. There is an unmet need for the development and implementation of a nationwide protocol for CS management and the creation of reference CS centers based on the country-wide reperfusion network, equipped with modern technologies for MCS.

KEYWORDS

cardiogenic shock, acute myocardial infarction, mortality risk factors, clinical outcomes, mechanical circulatory support



GRAPHICAL ABSTRACT
CS, cardiogenic shock; AMI-CS, acute myocardial infarction complicated by cardiogenic shock; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; CHF, chronic heart failure; DTP, door-to-procedure; MCS, mechanical circulatory support; LM, left main stem; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

1 Introduction

The widespread dissemination of reperfusion therapy for acute myocardial infarction (AMI) based on the primary percutaneous coronary intervention (pPCI) and the development of reperfusion networks has led to significant improvement in survival and decrease in complications rate in AMI (1). However, among patients with acute myocardial infarction complicated by cardiogenic shock (AMI-CS) hospital mortality has not changed significantly over the past 20 years, despite progress in reperfusion therapy and mechanical circulatory support (MCS), and remains about 30%–50% (2–4). Available data demonstrate that early and effective reperfusion is the key factor in reducing mortality in AMI-CS patients (5). However, the effectiveness of reperfusion therapy declines with the prolongation of total myocardial ischemic time (6, 7). Moreover, rapid reperfusion may cause additional myocardial damage by itself, which exacerbates the course of cardiogenic shock (CS) (8, 9).

In addition, obtaining of strong evidence for the most effective CS management, particularly for MCS, is complicated by clinical polymorphism of CS and the lack of tools for patients' stratification according to the shock severity in the majority of previous studies. The new clinical classification of CS, proposed by Society for Cardiovascular Angiography and Interventions (SCAI) in 2018, has been designed to solve this problem (10). It should also be noted that there is a clear shortage of large prospective randomized trials of CS secondary to ethical and methodological challenges in the randomization of critical patients (5), thus retrospective registries still play a significant role in CS trials. The purpose of the study is to evaluate the incidence, risk factors, therapeutic options, and outcomes among patients with AMI-CS in the programs with limited access to the MCS.

2 Materials and methods

2.1 Description of the reperfusion centers and the registry

In 2020, a Ukrainian Multicentre Cardiogenic Shock Registry was launched. By 2021, the registry included 6 major Ukrainian reperfusion centres in Kharkiv, Kyiv, Vinnytsia, Lviv and Odesa, covered different parts of the country. All of the participating reperfusion centers are the parts of the hospitals with catheterization laboratories available 24/7 for AMI and other cardiac emergencies care. All hospitals have cardiac surgery on site and dedicated cardiac ICUs. For the MCS, intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO) are available in 3 hospitals, percutaneous ventricular assist devices (pVADs) are not available in any hospital. An online registry was developed and launched by the team from Kharkiv reperfusion center. Responsible physician was

designated in each of the participating hospitals who was instructed in the SCAI shock criteria and entering data into the registry. Patients with shock were included to the registry at each center at the discretion of the designated physician, with Zoom consultations provided when necessary. The data from these centres allow to generate and systematize information on CS based on a sufficiently wide sample of at least 7 million population. The participating centres represent the healthcare infrastructure in general, and patient population across all regions of Ukraine. All previous information on CS in Ukraine was not systematic or did not focus on this issue. This study assesses detailed information on each case of CS from 1 January 2021 to 24 February 2022. Data collection ceased on the latter date due to the commencement of the Russian military invasion, which imposed significant disruptions on our research activities. After the almost 2 years break due to the destruction of our activities by the war, we were finally able to resume the maintenance of the Ukrainian Cardiogenic Shock registry.

2.2 Study design and patient selection criteria

The study is a registry-based retrospective observational analysis of CS in Ukraine. Overall, 3,892 consecutive patients with acute cardiac conditions admitted to the reperfusion centers were screened. Vast majority of them (3,596 patients) had an AMI as a cardiac emergency. After review of the sources including medical records, discharge reports and local databases, 221 patients meeting SCAI criteria of CS (10) at least stage C either on admission or during hospitalization were finally selected for the analysis (Figure 1).

2.3 Ethical declaration

All patients enrolled to the study, or their relatives signed an informed consent about personal data use according to procedure approved by Ministry of Healthcare of Ukraine. The study was performed in accordance with World Medical Association Declaration of Helsinki 1964, amended in 2013, and approved by the local ethics committee.

2.4 Diagnosis of acute myocardial infarction and reperfusion strategy

The diagnosis of AMI, as well as the choice of reperfusion strategy for all patients treated in reperfusion centers, was determined by the current recommendations of European Society of Cardiology (ESC) (11, 12).

2.5 Percutaneous coronary interventions

In cases of acute coronary syndrome invasive coronary angiography was performed immediately after hospitalization. In most cases, myocardial revascularization in acute phase was limited by stenting of culprit lesion only. Manual thrombus aspiration was performed at the discretion of the catheterization laboratory team.

2.6 Concomitant medication and mechanical circulatory support

The routine initial medication followed ESC recommendations (11, 12) and included loading doses of aspirin with ticagrelor,

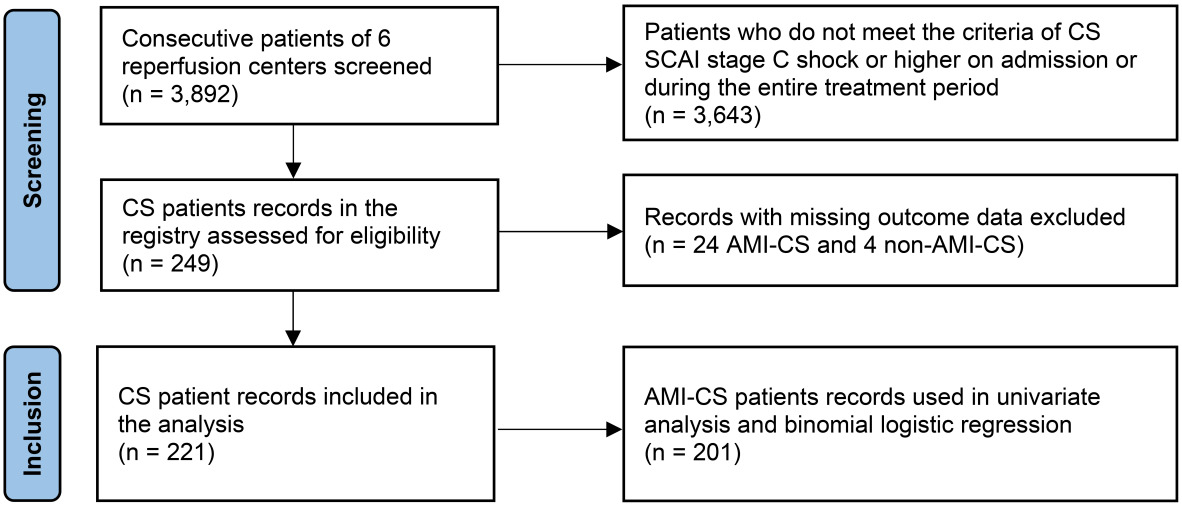


FIGURE 1
Study flowchart.

prasugrel or clopidogrel, high doses of statins and unfractionated heparin 70 IU/kg during PCI unless contraindicated. All subsequent medical therapy dependent on clinical scenario and comorbidities. Except IABP any other types of MCS are either not available in Ukraine at all (e.g., pLVAD) or very limited mostly in centers with cardiac surgery on site [Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)], which reflects the situation in a vast majority of Ukrainian reperfusion centers.

2.7 Clinical endpoints

In-hospital mortality was used as clinical endpoint.

2.8 Risk factors, concomitant and emergency conditions

Data on cardiovascular risk factors and concomitant diseases were obtained by review of primary medical records, interview of the patients or phone contact to the family physicians. Heart failure was diagnosed in accordance to the recommendations of the ESC (13, 14). The Charlson Comorbidity Index was used to assess the number and severity of comorbid conditions for each patient in a study (15). Reduced glomerular filtration rate (rGFR) was defined in our study as a GFR less than 60 milliliters per minute per 1.73 square meters (ml/min/1.73 m^2). Cardiac arrest was diagnosed in the presence of at least one of the following conditions: asystole, electromechanical dissociation, ventricular fibrillation, or pulseless ventricular tachycardia. Reperfusion deterioration was defined as an additional hemodynamic compromise longer than 30 min after the opening of infarct-related artery (IRA), required additional therapeutic interventions and clinically manifested as the recurrent arrhythmia, systemic hypotension, pulmonary edema, or an increase in SCAI stage of CS by one step or more. The blood flow in the IRA after revascularization was assessed by TIMI score (16). Concomitant chronic total occlusion (CTO) of the coronary artery was diagnosed in the case of complete non-IRA arterial occlusion with or without angiographic collateral blood flow (17). The duration of total ischemic time was verified as the total time from the onset of symptoms to the beginning of PCI. Multivessel coronary disease was defined as documented angiographic stenoses >50% of the diameter of two or more coronary arteries. The usage of IABP, inotropic support and mechanical ventilation was determined by local hospital protocols, strongly recommended to be adjusted to the currently available recommendations (11).

2.9 Data representation

Data was collected using a range of qualitative and quantitative indicators. Qualitative data was categorized into different groups and represented as percentages to allow for easy comparison. For the quantitative data, a 95% confidence interval (CI) was used.

2.10 Statistical analysis

Statistical analysis was performed using the SPSS for Mac software package, version 26 (IBM, Chicago, USA) and Jamovi Desktop 2.3.18. Categorical variables were presented as numbers and percentage, continuous ones—as the median and interquartile range (IQR). To assess the differences between subgroups, the *U* Mann–Whitney test and Fisher's exact test were used. To identify the risk factors for hospital mortality we used univariate and multivariate analysis, followed by calculating the odds ratio (OR) and 95% CI for each of the factors. Binomial logistic regression was employed to estimate the influence of various factors on a hospital mortality. Each factor was evaluated based on estimates, standard error, z-score, *p*-value, odds ratio, and a 95% confidence interval. The performance of the regression model was tested using a Receiver Operating Characteristic (ROC) curve. All statistical tests were two-sided, with *p*-values less than 0.05 considered statistically significant.

3 Results

A total of 221 patients with CS were included in the analysis. In 85.1% of cases the cause of CS was STEMI, in 5.9%—NSTEMI, in 7.7%—decompensated CHF and in 1.3% it was arrhythmia.

Baseline clinical characteristics of the patients are represented in Table 1. In general, patients with non-AMI-CS were more likely to have a history of MI and more comorbidities (high Charlson Comorbidity Index, reduced renal function, and CHF) compare with AMI-CS patients.

Among 3,596 patients with AMI, CS developed in 225 (6.3%), 24 of which were excluded from the analysis due to missed outcome data. Out of 201 analyzed AMI-CS cases, 93.6% was a result of STEMI, and 6.4% of NSTEMI. 40.3% of AMI-CS patients experienced at least one episode of circulatory arrest, which occurred before (21.5%) or after (18.8%) PCI. The dominant infarct-related artery (IRA) was the left anterior descending (LAD) one in 48.9% of the cases. Additionally, 62.7% and 34.8% of patients had multivessel disease, and CTO respectively (Tables 1, 2).

In AMI-CS patients emergent revascularization was performed in 90.5% of cases, mostly by PCI (89.5%) with few CABG (1%). After PCI was performed on the IRA, 35.8% of the patients experienced severe reperfusion disorders followed by the progression of the CS, and 18.8% experienced cardiac arrest after PCI. Failure of immediate coronary flow restoration with a post-PCI TIMI 0–1 flow was observed in 23.8% of the patients (Table 2). Median total ischemic time time for STEMI patients was 4 h (IQR, 3–9), and door-to-procedure time was 30 min (IQR, 20–45). In 23.5% of cases CS developed in the hospital after admission.

The following main therapeutic modalities—more than one inotrope/vasopressor, mechanical ventilation, and IABP—were used in 43.8%, 40.9%, and 19.9% of patients respectively (Table 2).

TABLE 1 Characteristics of the patients at baseline.

Characteristic	Total	Non-AMI-CS	AMI-CS	p*
	(n=221)	(n=20)	(n=201)	
Age—yr, Mdn (IQR)	69 (60.5–77)	73 (64–82)	68 (60–77)	ns
Male sex—no. (%)	130 (58.8)	12 (60)	118 (58.7)	ns
CS causes—no. (%)				
NSTEMI	13 (5.9)	–	13 (6.4)	
STEMI	188 (85.1)	–	188 (93.6)	
Decompensated HF	17 (7.7)	17 (85)	–	
Others	3 (1.3)	3 (15)	–	
History of MI—no. (%)	75 (33.9)	18 (90)	57 (28.3)	0.0001
History of PCI/CABG—no. (%)	16 (7.2)	3 (15)	13 (6.4)	ns
Hypertension—no. (%)	184 (83.3)	18 (90)	166 (82.5)	ns
CTO—no. (%)	74 (33.5)	4 (20)	70 (34.8)	ns
MVD—no. (%)	138 (62.4)	12 (60)	126 (62.7)	ns
Charlson comorbidity index (n=220)				
<4	50 (22.6)	1 (5)	49 (24.4)	ns
4–7	130 (58.8)	11 (55)	119 (59.2)	ns
>7	40 (18.1)	8 (40)	32 (15.9)	0.014
Comorbidities—no. (%)				
rGFR	131 (59.3)	16 (80)	115 (57.2)	0.057
DM	69 (31.2)	9 (45)	60 (29.8)	ns
CHF	87 (39.3)	18 (90)	69 (34.3)	0.0001
Total ischemic time—h, Mdn (IQR)			5 (3–9)	
DTP time—min, Mdn (IQR)			30 (20–45)	

AMI-CS, acute myocardial infarction complicated by cardiogenic shock; Mdn, median; IQR, 1 and 3 interquartile range; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CTO, chronic total occlusion; MVD, multivessel coronary disease; rGFR, reduced glomerular filtration rate; DM, diabetes mellitus; CHF, chronic heart failure; DTP, door-to-procedure.
*p—difference between Non-AMI- and AMI-CS subgroups.

TABLE 2 AMI-CS management characteristics.

Characteristic[a]	AMI-CS
	no (%)
Revascularization (n=201)	182 (90.5)
PCI	180 (89.5)
CABG	2 (1)
Infarct-related artery (n=190)	
LM	17 (8.9)
LAD	93 (48.9)
RCA	59 (31.1)
Cx	21 (11.1)
Pre-PCI TIMI flow (n=180)	
0–1	163 (90.6)
2–3	17 (9.4)
Post-PCI TIMI flow (n=181)	
0–1	43 (23.8)
2–3	138 (76.2)
Reperfusion deterioration (n=200)	129 (64.5)
Development of shock after admission (n=200)	47 (23.5)
2 or more inotropes/vasopressors (n=201)	88 (43.8)
Intra-aortic balloon pump (n=201)	40 (19.9)
Before PCI	26 (12.9)
After PCI	14 (7)
Mechanical ventilation (n=193)	79 (40.9)
Before PCI	36 (18.7)
After PCI	43 (22.2)
Cardiac arrest (n=186)	75 (40.3)
Before PCI	40 (21.5)
After PCI	35 (18.8)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LM, left main stem; LAD, left anterior descending artery; RCA, right coronary artery; Cx, circumflex artery; TIMI, thrombolysis in myocardial infarction flow grade.
[a]—data represented in numbers (%) of available records.

Overall, in-hospital mortality rate was 57.5%. There was a trend toward higher mortality in CS without AMI compared to AMI-CS —80% vs. 55.7%, without reaching a statistically significant difference ($p = 0.0552$).

The relationship between SCAI stages on admission, escalation of shock and mortality is presented in Figure 2. Most patients were admitted in stage C (42.1%). The highest mortality rate was observed in stage E—83.3%, and the lowest one in stage C—44.1%. Patients admitted without shock who developed shock in hospital (stage A) and stage B patients had a mortality rate of 56.3% and 63.3%, respectively. The progression of shock during the hospital stay was 73.3% for stage B, 38.7% for C and 56.5% for D. Obviously, all patients with stage A in our registry progressed, and stage E is the last one, so the percent of escalation in these stages (100 and 0) is irrelevant.

Results of univariant analysis of risk factors for hospital mortality in AMI-CS patients is presented in Figure 3A.

Binomial logistic regression has yielded that the four factors (LM occlusion, deterioration after reperfusion, Charlson Comorbidity Index >4 and cardiac arrest) have remained independent predictors for hospital mortality (Figure 3B). A model with independent risk factors derived from multivariate regression showed high sensitivity and specificity (Figure 3C).

We evaluated the mean scores of different groups based on the outcomes. The negative outcome group, characterized by death, had a longer total ischemic time time with median (Mdn) of 6 h compared to the positive outcome group, characterized by survival, with a median of 4 h ($U = 5{,}884.5$, $p < 0.001$). Door-to-procedure time was also longer on average in the negative outcome group (Mdn—32.5 min) compared to the positive outcome group (Mdn—30 min) ($U = 3{,}852$, $p = 0.002$). Glomerular filtration rate was significantly lower in patients with a negative outcome (Mdn—40.7 ml/min/1.73 m^2), compared to those with a positive outcome (Mdn—47.5 ml/min/1.73 m^2) ($U = 2{,}931$, $p = 0.006$).

4 Discussion

In our study the incidence of AMI-associated CS was 6.3%, which was lower compared to large registries, where the CS rate was 7.9%–8.9% amid patients with STEMI (3, 18). These findings can relate to the fact that a slightly different CS criteria are used in different registries. The introduction of the recent SCAI classification into clinical practice could contribute to the unification of approaches to CS and the use of a common language for all stakeholders (10). In addition, we observed that since the introduction of the reperfusion network in Ukraine in

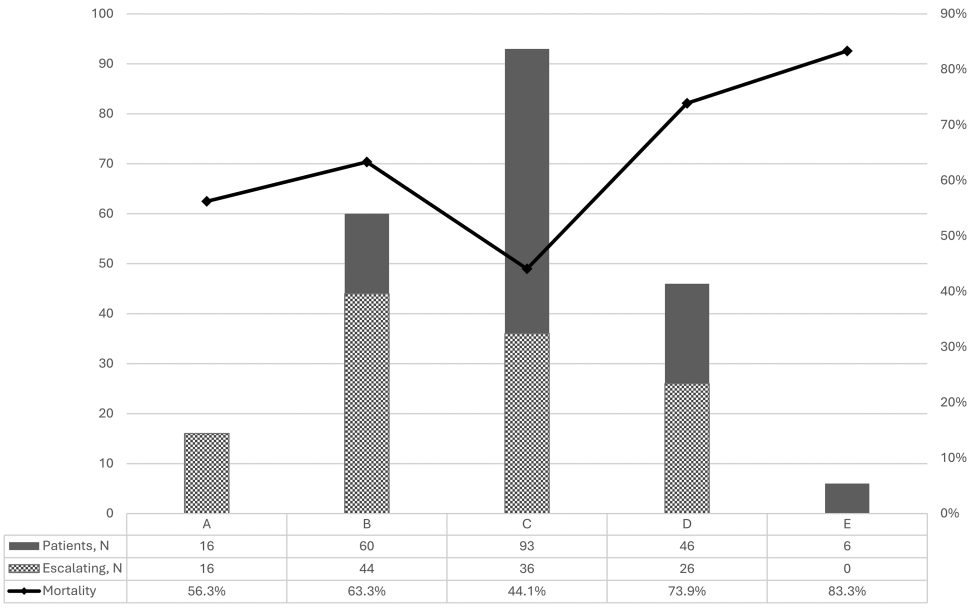


FIGURE 2
Number of patients, proportion of shock escalation and mortality according to SCAI stages of cardiogenic shock.

2016, the frequency of CS admitted to reperfusion centers continues to increase as the network improves. In the future, we should expect an increase in patients with CS in Ukraine up to the rate comparable to Western countries.

Hospital mortality for CS in our series was 57.1%, which is comparable to the data of a London registry that showed mortality rate of 45%–70% among 1,890 patients with CS with no tendency to decline over 9 years (3). In another large American registry, there was a significant decrease in hospital mortality for CS from 44.6% in 2003 to 33.8% in 2010 (18). Whether these differences are associated with different treatment strategies or are the result of the different criteria for CS remains unclear. A more recent registry series have shown an increase in survival among patients with CS up to 63%–82% when using dedicated teams, an early left ventricular unloading strategy and advanced MCS (pLVAD, MCS escalation) (19–21).

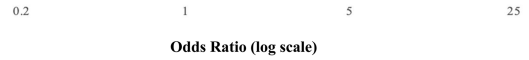
In our study, patients with non-AMI-CS tended to have higher in-hospital mortality rate compared to patients with AMI-CS (80% vs. 55.7%). This is inconsistent with previous data from the observational CardShock study (22), which showed a higher survival rate for patients with non-ACS etiology of CS. This difference can be explained by the facts that in our study (i) there were few patients with non-AMI-CS, and (ii) IABP, which is considered the most effective, especially for non-ACS-CS, was only used in 3 out of 20 patients (15%) in non-AMI-CS subgroup.

The highest mortality in our registry was among the most severe stages of shock—D and E (73.9% and 83.3% respectively), which is quite explainable by the severity of shock, and the very low level of MCS in real practice in Ukraine. However, a more interesting finding for understanding of the shock management is that a vast majority of patients with stage B (73.3%) experienced further shock escalation, and the mortality rate in this group was significantly higher than among patients who presented with stage C, where only 38.7% of patients experienced this escalation of the shock. Even patients who developed shock after hospital admission (stage A) had a higher mortality rate compared to the patients with stage C on admission. These findings are entirely consistent with those of the Cardiogenic Shock Working Group registry, which found the same trends in an analysis of 3,455 patients with CS (23). The obtained data suggest that patients in the "pre-shock" (stage B, sometimes even A) are often underestimated upon hospital admission in terms of risk assessment and do not receive adequate therapy on time. While patients with "classic" shock upon admission usually receive proper monitoring and treatment from the very first minute. Shifting the focus of shock management toward early detection, early invasive monitoring, and more aggressive management of pre-shock patients may be a reasonable strategy to improve survival.

Overall, the incidence of MCS, exclusively in the form of IABP, in our registry was 19.9%, which is significantly lower than was demonstrated in a recent large US registry, where the frequency of MCS-assisted early PCI in patients with AMI-CABG was about 50% (4). The use of IABP in our study had no impact on mortality. Data from randomized trials and meta-analysis (24–29) confirmed the lack of IABP's effect on the survival of patients with CS, leading to downgrading of the

A

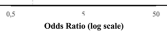
Risk factors	Odds Ratio	[95% CI]	p
Total ischemia time > 6h	2.21	[1.18-4.13]	0.014
Post-PCI TIMI flow 0-1	4.17	[1.90-9.12]	<0.001
CTO	1.94	[1.05-3.61]	0.044
Cardiac arrest	14.87	[6.68-33.08]	<0.001
History of PCI/CABG	4.71	[1.01-21.84]	0.041
Diabetes mellitus	2.22	[1.17-4.21]	0.019
Charlson Comorbidity Index > 4	4.62	[2.29-9.35]	<0.001
CHF	1.94	[1.05-3.57]	0.035
Reperfusion deterioration	7.61	[3.94-14.70]	<0.001
LM occlusion	4.51	[1.25-16.25]	0.02
rGFR	2.34	[1.14-4.83]	0.022
Hypertension	1.09	[0.48-2.50]	0.835
IABP	1.42	[0.70-2.91]	0.374
Age ≥ 75 years	1.64	[0.88-3.07]	0.16
Multivessel disease	1.82	[0.95-3.47]	0.075
Male	0.67	[0.38-1.19]	0.195
History of MI	1.08	[0.58-2.01]	0.875



Odds Ratio (log scale)

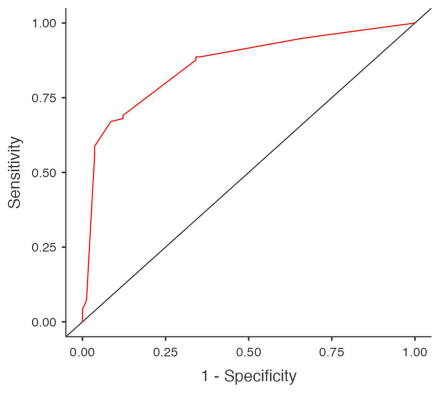
B

Risk factors	Estimate	SE	Z	Odds Ratio	[95% CI]	p
LM occlusion	1.74	0.783	2.22	5.70	[1.23-26.45]	0.026
Reperfusion deterioration	1.19	0.421	2.84	3.30	[1.45-7.54]	0.005
Charlson Comorbidity Index > 4	1.65	0.491	3.37	5.23	[2.00-13.68]	<0.001
Cardiac arrest:						
before PCI	2.52	0.614	4.11	12.47	[3.74-41.52]	<0.001
after PCI	2.05	0.568	3.62	7.80	[2.56-23.72]	<0.001



Odds Ratio (log scale)

C



Area	Specificity	Sensitivity	Asymptotic Sig.[a]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
0.859	**0.659**	**0.876**	**<0.001**	**0.804**	**0.915**

a. Null hypothesis: true area = 0.5

FIGURE 3
(**A**) Univariant analysis of risk factors for hospital mortality in AMI-CS patients. (**B**) Independent predictors for hospital mortality of CS patients by binomial logistic regression (coefficient-outcome model). (**C**) Receiver operating characteristic (ROC) curve of the logistic regression model. PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction flow grade; CABG, coronary artery bypass grafting; LM, left main stem; CTO, chronic total occlusion; rGFR, reduced glomerular filtration rate; MI, myocardial infarction; CHF, chronic heart failure; IABP, intra-aortic balloon pump.

indication for the routine use of IABP in CS to class III (11). Nevertheless, a recent registry series has shown improved outcomes with IABP (30), and IABP remains the most common MCS modality in the US (4, 31).

In addition, it remains unclear whether an early use of IABP has potential benefits in AMI patients with the risk of developing CS (e.g., SCAI stage A). As for other MCS options, such as pLVAD or VA-ECMO, these technologies are either not available in Ukraine (Impella, TandemHeart etc.), or are limited to a small number of centers with advanced cardiac surgery (VA-ECMO) and had no impact on real clinical practice.

In general, a key component of the treatment of CS is the shock team, which uses the local protocols based on early identification, advanced hemodynamic monitoring and MCS escalation/de-escalation strategies driven by such monitoring.

Management of AMI-CS poses unique challenges, particularly LLMICs. In such countries, resource constraints and limited access to advanced medical interventions often impact patient care and outcomes. Furthermore, disparities in healthcare personnel training and facility distribution can compromise the standard of care. As a LLMIC, Ukraine embodies these challenges. Thus, while the existing body of knowledge about AMI-CS risk factors and management is expanding globally, it is crucial to apply this knowledge within the specific context of Ukraine's healthcare landscape. Consequently, our study aimed to examine these variables, building upon the existing knowledge within the context of AMI-CS in Ukraine.

Previous studies, most of which, if not all, carried out in high-income countries, have identified the following risk factors for hospital mortality in CS: etiology of acute coronary syndrome, older age, history of AMI or coronary artery bypass grafting (CABG), ischemic brain damage, reduced LVEF, impaired right ventricular function, mitral regurgitation, decreased LV stroke work and cardiac power output, systolic blood pressure, the number of vasopressors to support hemodynamics, serum lactate level, systemic inflammatory response syndrome, and TIMI flow in IRA (22, 32–36).

In our study univariate analysis has revealed that TIMI 0–1 after reperfusion, chronic total occlusion, previous history of PCI/CABG, diabetes mellitus, Charlson Comorbidity Index >4, chronic heart failure, reduced GFR, LM occlusion, total ischemic time >6 h, deterioration after reperfusion and cardiac arrest were the risk factors for hospital death in patients with AMI-CS. However, LM occlusion, deterioration after reperfusion, Charlson Comorbidity Index >4 and cardiac arrest were independent predictors of hospital mortality related to AMI-CS.

5 Conclusion

Despite the wide adoption of primary PCI as a main reperfusion strategy, CS remains a significant challenge for the LLMIC healthcare system, associated with unacceptably high in-hospital mortality and a substantial burden on a resource-limited system. There is an unmet need to develop and implement a nationwide CS management protocol based on early identification, advanced hemodynamic monitoring and MCS escalation/de-escalation capability, to improve patient survival. We see a reliable solution in the creation of reference CS centers based on a reperfusion network in Ukraine, equipped with modern technologies for mechanical circulatory support.

6 Study limitations

This study has several limitations, some of which are inherent to the analysis of a web-based multicenter registry. (i) The accuracy of diagnosis and the documentation of complications may have varied among different healthcare facilities. (ii) The study may not have adequately accounted for variations in treatment protocols and healthcare provider practices across different centres. This might impact the generalizability of the results. (iii) As this is a registry analysis, the lack of randomization might lead to selection bias and confounding, potentially affecting the interpretation of the results. (iv) The study did not include long-term follow-up data that could provide important insights into the development and outcomes of patients with AMI-CS.

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 Ethics committee, V.T. Zaitcev Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine. 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

AB: Data curation, Software, Writing – original draft, Formal Analysis, Writing – review & editing. OG: Data curation, Writing – original draft, Writing – review & editing, Investigation. VK: Investigation, Writing – original draft, Writing – review & editing. OR: Investigation, Writing – original draft, Writing – review & editing. AP: Investigation, Writing – original draft, Writing – review & editing. YM: Investigation, Writing – original draft, Writing – review & editing. DB: Investigation,

Writing – original draft, Writing – review & editing. VS: Investigation, Writing – original draft, Writing – review & editing. SC: Investigation, Writing – original draft, Writing – review & editing. ML: Investigation, Writing – original draft, Writing – review & editing. ID: Investigation, Writing – original draft, Writing – review & editing. IP: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation.

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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.

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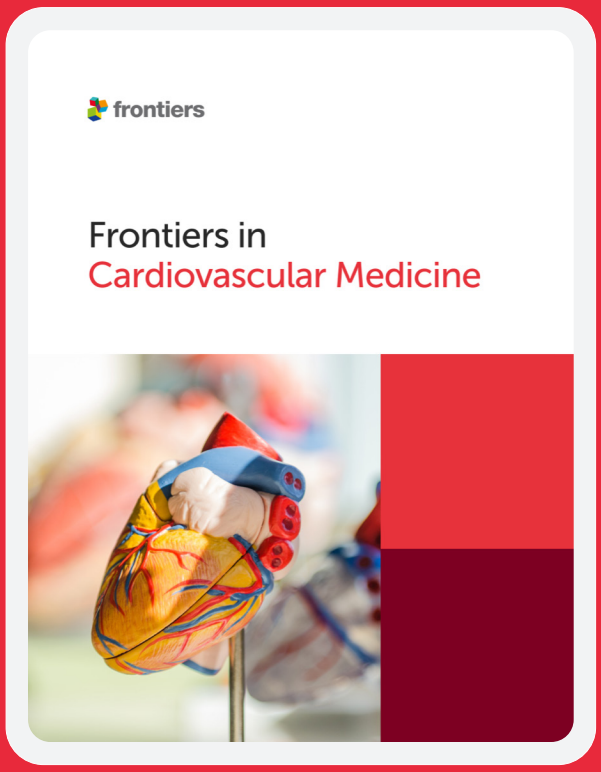

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