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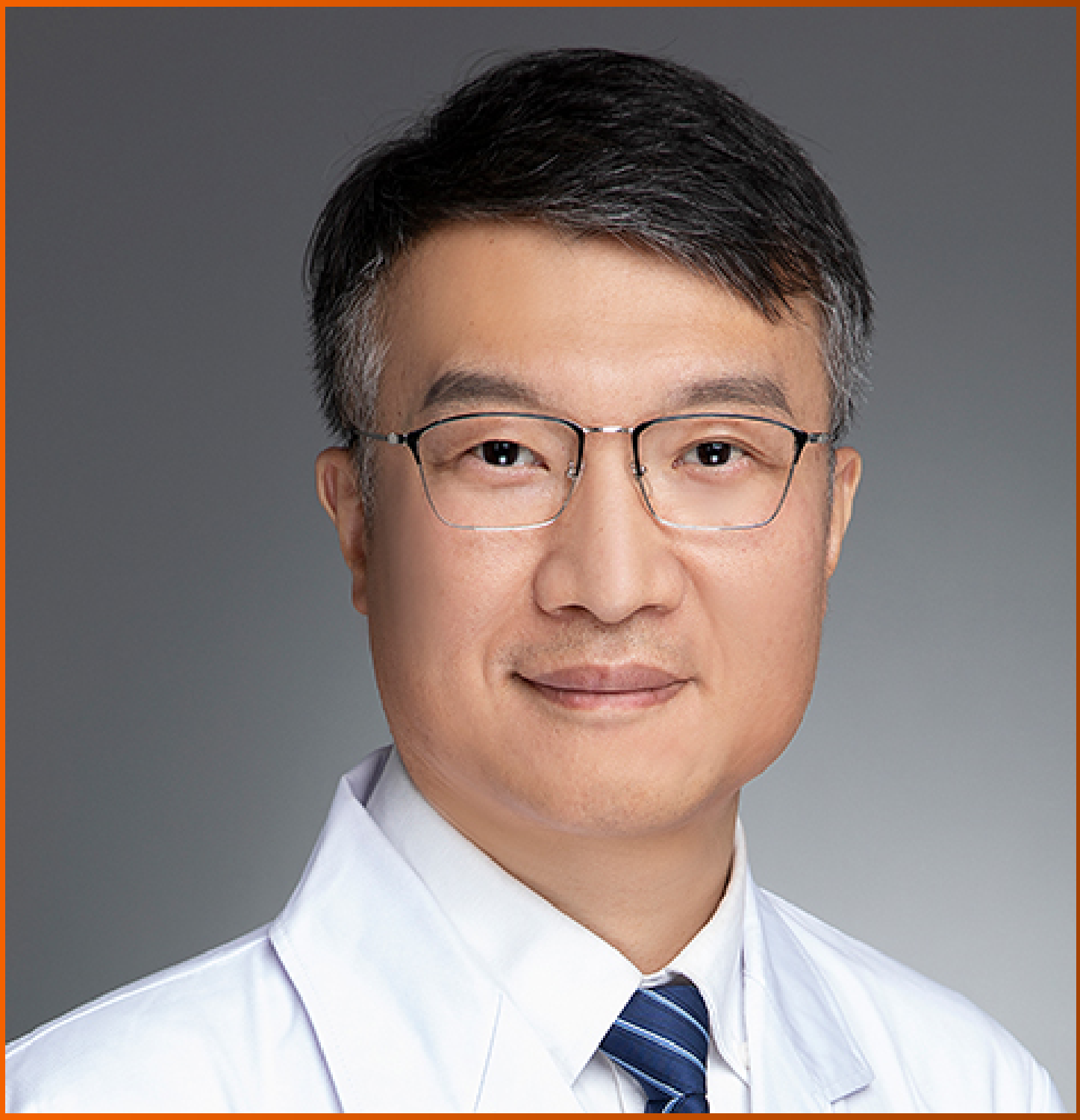

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EDITORIAL

Risk of permanent pacemaker implantation following transcatheter aortic valve replacement: Which factors are most relevant?

Akash Batta, Juniali Hatwal

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Abstract

Transcatheter aortic valve replacement (TAVR) has emerged as a formidable treatment option for severe symptomatic aortic stenosis ahead of surgical aortic valve replacement. The encouraging results from large randomized controlled trials has resulted in an exponential rise in the use of TAVR even in the low-risk patients. However, this is not without challenges. Need for permanent pacemaker (PPM) post-TAVR remains the most frequent and clinically relevant challenge. Naturally, identifying risk factors which predispose an individual to develop high grade conduction block post-TAVR is important. Various demographic factors, electrocardiographic features, anatomic factors and procedural characteristics have all been linked to the development of advanced conduction block and need for PPM following TAVR. Amongst these electrophysiological variables, most notably a prolonged QRS > 120 ms regardless of the type of conduction block seems to be one of the strongest predictors on logistic regression models. The index study by Nwaedozie *et al* highlights that patients requiring PPM post-TAVR had higher odds of having a baseline QRS > 120 ms and were more likely to be having diabetes mellitus that those who did not require PPM.

Key Words: Transcatheter aortic valve replacement; Permanent pacemaker; Diabetes mellitus; QRS duration; Electrophysiological variables

Core Tip: Transcatheter aortic valve replacement (TAVR) has emerged as a formidable treatment option for severe symptomatic aortic stenosis ahead of surgical aortic valve replacement. Despite the progress in technology, the improved valve-design and delivery systems, and the improvement in clinical skill and deployment techniques, permanent pacemaker (PPM) implantation remains a major cause of concern post-TAVR. Naturally, identifying risk factors which predispose an individual to develop high grade conduction block post-TAVR is relevant. In the index study by Nwaedozie *et al*, a baseline QRS > 120 ms and the presence of diabetes mellitus were strongest predictors of PPM need post-TAVR.

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INTRODUCTION

Over the last 2 decades, transcatheter aortic valve replacement (TAVR) has emerged as a formidable treatment option for severe symptomatic aortic stenosis ahead of surgical aortic valve replacement (SAVR). Encouraging results from large randomized controlled trials (RCTs) has resulted in expansion of its use even in the younger population with low surgical risk[1,2]. This ever-increasing volume of TAVR is expected to be coupled with complications which will have significant long-term impact. Amongst them, conduction disturbances leading to permanent pacemaker (PPM) implantation is one of the most relevant challenge. The rate of PPM implantation is around 5%-33% of all patients undergoing TAVR[3-5]. This is thought to result from a mechanical injury, ischemia, hemorrhage or associated inflammation in the conduction system which passes posterior-inferiorly to the non-coronary cusp of the aortic valve[6]. Despite the progress in technology leading to improved valve-designs and delivery systems, and improvement in clinical skill and deployment techniques, PPM implantation remains a major cause of concern post-TAVR[6]. Long-term right ventricular pacing has adverse impact on cardiac hemodynamics, chamber dimensions and ventricular functions all of which contribute to increased morbidity and mortality in the long run[7]. Although long-term impact of PPM after TAVR has been sparingly studied, emerging data points to the worse clinical outcomes in this population following PPM[8]. This association is most relevant today younger patients are who are expected to live longer are increasingly undergoing TAVR and will be most vulnerable to long-term impact of PPM. Traditionally, PPM implantation rate following SAVR is around 2-7%, which in general is lower than PPM need after TAVR. Hence, choosing between SAVR and TAVR in low-risk younger patients should take into account the risk of PPM implantation and its long-term impact[9,10]. Naturally, knowledge and awareness of preprocedural characteristics that predispose an individual to develop high-grade conduction disturbances following TAVR remains critical.

TRADITIONAL AND EMERGING PREDICTORS OF PPM FOLLOWING TAVR

As we enter the 3rd decade since the first reported use of TAVR in humans in 2002, an ever-increasing pool of data is available to clinicians and researchers to draw meaningful conclusions and ultimately improve patient outcomes. Large scale RCTs and the subsequent meta-analysis have shed light on the risk factors for PPM after TAVR. Various demographic factors, electrocardiographic features, anatomic factors and procedural characteristics have all been linked to the development of advanced conduction blocks and need for PPM following TAVR[5,11,12]. Evidence from various high-quality studies on the predictors of PPM need following TAVR has been depicted in Figure 1. Overall, the risk factors which appear to be the most closely linked to the risk of PPM following TAVR are diabetes mellitus (DM), presence of baseline RBBB or left anterior fascicular block, short membranous septum length, high volume calcium just below the non-coronary and the right coronary cusps, increased depth of valve implantation, utilization of larger valves with resultant large valve index[(valve size/LVOT diameter) × 100 > 128)] and the use of self-expanding valve in particular the Medtronic CoreValve systems (Medtronic, Inc.; Minneapolis, MN)[5,11-15].

The most recent evidence on the predictors of PPM following TAVR comes from the study by Nwaedozie *et al*[16] in which they have explored various risk factors (particularly focusing on electrophysiological variables) for PPM in patients undergoing TAVR at their centre over the last decade. In this retrospective study they conclude that the presence of DM and prolonged baseline QRS > 120 ms regardless of the type of conduction block were the strongest predictors on logistic regression model for need for PPM post-TAVR. While the results of the study are not entirely novel, the study does add to the existing pool of literature. They highlight that baseline QRS prolongation (> 120 ms) even without underlying LBBB or RBBB is an independent and a strong predictor for need for PPM. Even those with QRS 100-120 ms were found to have higher odds of needing PPM following TAVR in their study than those with a QRS < 100 ms. This is unlike previous data which suggested that it was RBBB more than other conduction disturbances that predicted PPM need. A prolonged QRS represents conduction delays from the atrioventricular node to the ventricular purkinje system. Even in general population, a prolonged QRS without typical RBBB or LBBB is associated with worse long-term outcomes and increased likelihood of sudden cardiac death[17]. It often is present as a bystander in ischemic heart disease and is believed to be a precursor to both bradyarrhythmia and tachyarrhythmia in future. Whether TAVR aggravates this ischemia process or

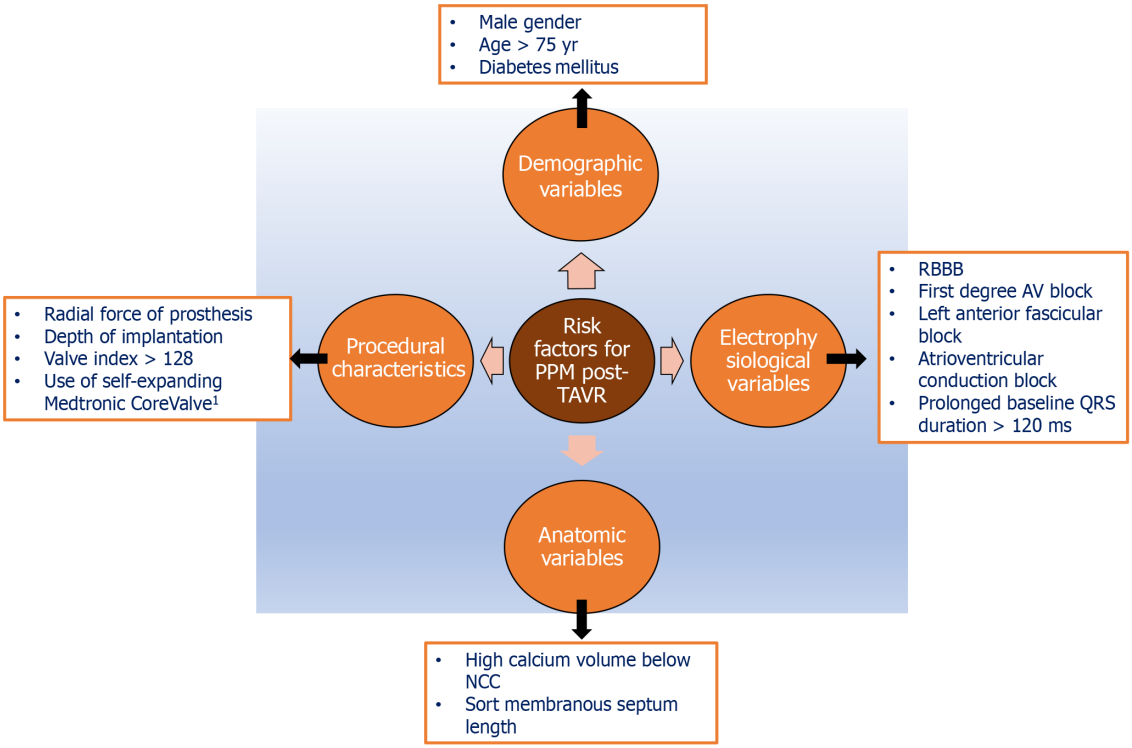

Figure 1 Various risk factors for development of high grade conduction block and need for permanent pacemaker following transcatheter aortic valve replacement. RBBB: Right bundle branch block; NCC: Non coronary cusp. [1]Medtronic CoreValve systems (Medtronic, Inc.; Minneapolis, MN, United States).

the surrounding inflammation impairs the already compromised conduction is still a matter of debate. The other major finding of the study was higher odds of DM amongst patients needing PPM. This is not surprising since DM impairs microcirculation throughout the cardiovascular system including the blood supply of the conduction tissue. Further a large recent nationwide Danish study highlighted the fact that DM patients have a higher likelihood of developing advanced conduction disease even in general population[18]. Also in the recent meta-analysis by Mahajan *et al*[5], DM was the only demographic variable on multivariable regression analysis which was independently linked to PPM following TAVR.

Another relevant area that the authors have touched upon is the clinical impact of PPM post TAVR. Unlike in general population, where the harmful effects of PPM are well established, the impact of PPM in TAVR patients is less studied and conflicting[19-22]. This study by Nwaedozie *et al*[16] is one of the few which highlights the negative impact of PPM post TAVR. They found higher odds of heart failure hospitalizations and non-fatal myocardial infarction amongst the PPM cohort at 1 year. However, the overall survival was similar in the 2 groups. Perhaps a longer follow-up would have further clarified the impact of PPM on mortality in these patients.

While the strength of the study is well apparent, one must take the results with a pinch of salt. Being a single-centre study with a retrospective study design, unaccounted biases cannot be ruled out. Hence, one cannot accept these results on their face value. Lack of validation arm is yet another limitation. Thus, generalizability of the study must be established in future studies before incorporating the evidence from the index study in our clinical practice.

CONCLUSION

The encouraging results from large RCTs has resulted in an exponential rise in the use of TAVR even in younger individuals at low-risk for surgery. Need for PPM post-TAVR remains the most frequent and clinically relevant challenge. Various risk factors have been identified and linked to PPM need following TAVR. As newer evidence emerges, our understanding of the pathophysiology improves and novel predictors are identified. Amongst them none seems to be more relevant that prolonged baseline QRS irrespective of the type of conduction block. Perhaps generating a tool or risk scoring system incorporating the current evidence seems to be the most promising approach for the future. The potential of artificial intelligence should be explored to identify and validate the emerging predictors.

FOOTNOTES

Author contributions: Batta A and Hatwal J contributed equally to this work.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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EDITORIAL

Current knowledge for the risk factors of early permanent pacemaker implantation following transcatheter aortic valve replacement and what is next for the primary prevention?

Gen-Min Lin, Wei-Chun Huang, Chih-Lu Han

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Abstract

In this editorial, we comprehensively summarized the preoperative risk factors of early permanent pacemaker implantation after transcatheter aortic valve replacement (TAVR) among patients with severe aortic stenosis from several renowned clinical studies and focused on the primary prevention of managing the modifiable factors, *e.g.*, paroxysmal atrial fibrillation before the TAVR.

Key Words: Permanent pacemaker implantation; Transcatheter aortic valve replacement; Interventricular conduction delay; Diabetes; Supraventricular arrhythmia

Core Tip: This is an invited editorial for the coming paper "novel predictors of permanent pacemaker implantation following transcatheter aortic valve replacement".

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INTRODUCTION

In this issue of the *World Journal of Cardiology*, Nwaedozie *et al*[1] explored clinical outcomes associated with early permanent pacemaker (PPM) implantation following transcatheter aortic valve replacement (TAVR) in high-risk patients with aortic stenosis. At the end of 1 year follow-up, as compared to those without PPM implantation, those with PPM implantation had a higher risk of heart failure (HF) hospitalization and nonfatal myocardial infarction (MI) [odds ratios (ORs): 2.2 and 3.9, respectively]. In contrast, in the study conducted by Fadahunsi *et al*[2], early PPM implantation after TAVR was associated with a greater risk of a composite of all-cause mortality or HF admission [hazard ratio (HR): 1.33], while not with HF admission alone. Despite the disparity in observational studies, the 1-year adverse outcomes associated with early PPM implantation after TAVR were unquestionable. Therefore, it is crucial to know the modifiable predictors of early PPM implantation in high-risk patients with severe AS before the procedure of TAVR, and a pre-procedural preventive measure may be of great interests for future trials to be taken for reducing the possibility of PPM implantation and improving the clinical outcomes.

Previous studies have shown several risk predictors of early PPM implantation after TAVR (Table 1). In this state of the art study, three novel pre-procedural predictors were added including nonspecific interventricular conduction delay (IVCD), type 2 diabetes and supraventricular arrhythmia[1] (ORs: 2.18, 2.16, and 1.82, respectively). It has been acknowledged that right bundle branch block (RBBB) is an independent electrocardiographic predictor of post-TAVR PPM implantation (ORs: 1.36-8.61)[3-5]. In this study[1], the association between RBBB and post-TAVR PPM implantation was borderline (OR: 2.15, $P = 0.081$), while the association between IVCD (QRS duration ≥ 120 ms) and post-TAVR PPM implantation was significant (OR: 2.18, $P = 0.045$). In addition, this study also demonstrated a dose-response association for each 20 ms increase in the pre-procedural QRS duration > 100 ms (ORs: 2.44, 3.25, and 6.98 for the QRS duration: 101-120 ms, 121-140 ms, and 141-160 ms, respectively). To the best of our knowledge, the development of RBBB and IVCD may be due to conduction system calcification and pressure overload in the left ventricle in severe AS[5]. The prevalence of RBBB and IVCD and the QRS duration were observed higher with increasing AS severity, and the presence of RBBB and wider QRS duration (per each 10 ms increase) was associated with greater risk of all-cause mortality (HRs: 1.59 and 1.06, respectively) in patients with AS[6]. In a large study among consecutive patients who completed 24-h Holter electrocardiography (ECG) for variety of indications[7], RBBB was an independent predictor for arrhythmia requiring further treatment which was in line with the present study findings. Obviously, the nature course in those with AS having abnormal ECG features, *i.e.*, RBBB and IVCD is consistently with poor prognosis across different groups regardless of receiving TAVR. Moreover, a prior study showed that if the QRS duration is less than 120 ms throughout the first day after TAVR, the occurrence of late atrioventricular conduction abnormalities is relatively low[8].

Diabetes mellitus has been regarded as a risk factor of cardiovascular mortality, mainly due to HF (HR: 2.61) in patients with severe AS, while not in those with mild or moderate AS[9]. The relative risk was close to the finding in this study (OR: 2.16). In addition, type 2 diabetes and insulin use were found with an association with late overall mortality (5-10 years) in patients with AS receiving surgical aortic valve replacement (HRs: 1.39 and 1.76, respectively)[10]. Furthermore, those with type 2 diabetes has been found with a 1.56-fold higher risk of PPM implantation as compared to those free of type 2 diabetes[11], and those with diabetes after PPM implantation had a greater risk of cardiovascular events[12]. Based on current evidence, the finding for diabetes mellitus as a risk factor of PPM implantation following TAVR for patients with severe AS in this study[1] was reasonable to explain the higher risk of incident HF hospitalization and nonfatal MI events.

Finally, this study also demonstrated an increased possibility of pre-procedural supraventricular arrhythmia for early PPM implantation following TAVR. As is known, the presence of atrioventricular node dysfunction in any grades were associated with a higher risk of atrial fibrillation (AF)[13]. It is notable that more than 95% of the pre-procedural supraventricular arrhythmia in patients with severe AS was AF. However, there were a discrepancy in case numbers between those with a history of AF ($n = 156$) and those with pre-procedural AF ($n = 84$), indicating that at least 47% of patients with paroxysmal or persistent AF in this study. In a meta-analysis of 981168 patients undergoing TAVR, the presence of AF was associated with a modestly increased risk of PPM implantation after TAVR (relative risk: 1.10)[14]. It would be of great interests for physicians to know if a conversion of paroxysmal or persistent AF to sinus rhythm prior to the procedure of TAVR may reduce the risk of PPM implantation in patients with severe AS or not, and a randomized clinical trial would be helpful to verify the effect. With the results of the PARTNER 3 trial for the long-term outcome (5 years) coming out[15], we can expect that in the following a few years, not only high-risk patients but also low-risk patients with severe AS will be eligible for TAVR. More observational studies to clarify the risk factors of early PPM implantation in low-risk patients undergoing TAVR are necessary in the future.

CONCLUSION

Since early PPM implantation following the TAVR is linked to poor prognosis among patients with aortic stenosis, it is crucial to clarify those potential modifiable risk factors, *e.g.*, paroxysmal AF that can be managed before the TAVR for the primary prevention of early PPM implantation.

Table 1 Established pre-procedural risk factors of early permanent pacemaker implantation following transcatheter aortic valve replacement

Pre-procedural risk factors	Age, yr	Male sex	Prior MI	DM	Risk ratio	Ref.
Prior conduction defect						[2-5,15]
RBBB	80-85	43%-52%	25%-45%	29%-37%	2.50-3.10	
Mobitz type 1 AV block					3.10	
Left anterior hemiblock					1.20-1.40	
Bifascicular block					2.40-2.60	
Peri-procedural AV block	Meta-analysis of 75 cohort studies[5]				4.17	[5]
Age ≥ 80 yr	Meta-analysis of 75 cohort studies[5]; meta-analysis of 239 cohort studies [15]				1.07-1.19	[2,5,15]
Self-expanding valve	Meta-analysis of 32 clinical trials[4]; meta-analysis of 239 cohort studies[15]				1.94-7.56	[2,4,5]
Aortic valve area < 0.75 cm^2	84	52.0%	26.4%	36.4%	1.21	[2]
≥ Moderate operative risk	84	52.0%	26.4%	36.4%	1.85	[2]
Atrial fibrillation	Meta-analysis of 75 cohort studies[5]; meta-analysis of 239 cohort studies [15]				1.05-1.10	[5,15]

AV: Atrioventricular; DM: Diabetes; MI: Myocardial infarction; RBBB: Right bundle branch block.

FOOTNOTES

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EDITORIAL

Inflammation as a cause of acute myocardial infarction in patients with myeloproliferative neoplasm

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Abstract

Myeloproliferative neoplasms (MPN) are a group of diseases characterized by the clonal proliferation of hematopoietic progenitor or stem cells. They are clinically classifiable into four main diseases: chronic myeloid leukemia, essential thrombocythemia, polycythemia vera, and primary myelofibrosis. These pathologies are closely related to cardio- and cerebrovascular diseases due to the increased risk of arterial thrombosis, the most common underlying cause of acute myocardial infarction. Recent evidence shows that the classical Virchow triad (hypercoagulability, blood stasis, endothelial injury) might offer an explanation for such association. Indeed, patients with MPN might have a higher number and more reactive circulating platelets and leukocytes, a tendency toward blood stasis because of a high number of circulating red blood cells, endothelial injury or overactivation as a consequence of sustained inflammation caused by the neoplastic clonal cell. These abnormal cancer cells, especially when associated with the JAK2V617F mutation, tend to proliferate and secrete several inflammatory cytokines. This sustains a pro-inflammatory state throughout the body. The direct consequence is the induction of a pro-thrombotic state that acts as a determinant in favoring both venous and arterial thrombus formation. Clinically, MPN patients need to be carefully evaluated to be treated not only with cytoreductive treatments but also with cardiovascular protective strategies.

Key Words: Inflammation; Myeloproliferative neoplasm; Acute coronary syndrome; Myocardial infarction; Thrombosis; Cancer

Core Tip: Myeloproliferative neoplasms (MPNs) are a group of three diseases: essential thrombocythemia, polycythemia vera, and primary myelofibrosis. MPNs have a high risk of acute coronary syndromes due to a pro-thrombotic state. This state is induced by abnormal cancer cells that tend to proliferate and secrete several inflammatory cytokines, sustaining a pro-inflammatory state throughout the body. Clinically, MPN patients need to be carefully evaluated for cytoreductive treatments and cardiovascular protective strategies.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a group of diseases characterized by the clonal proliferation of hematopoietic progenitor or stem cells. MPNs are subdivided into four main diseases: Chronic myeloid leukemia, essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis. Thrombosis is one of the most common complications of MPNs, which can occur in both arterial and venous vessels. As such, patients with MPN are at high risk of cardio- and cerebrovascular diseases such as myocardial infarction, deep venous thrombosis, and stroke[1,2]. Epidemiologically, up to 75% of patients with MPNs experience a major adverse cardiovascular event (MACE) as a complication of their clinical condition, and about a third after a first acute coronary syndrome (ACS) have another MACE[3]. Of interest, ACS might precede the development of a clinically overt MPNs[4]. Such higher cardiovascular risk is probably related to the hyperviscosity and thrombocytosis that are found in these neoplastic conditions. The main key elements that contribute to this pro-thrombotic state are the augmented number of circulating platelets and their hyperactivation, the marked leukocytosis, the Janus kinase 2 (JAK2) mutation, and the inflammatory state that especially concern the endothelium. In addition, the concomitant presence of classic cardiovascular risk factors (such as smoking, dyslipidemia, hypertension, *etc*.) further contributes to the higher risk of possible cardiovascular acute diseases in these patients. In this editorial, we comment on a recent article by Manan *et al*[5] published in the *World Journal of Cardiology* entitled "Acute myocardial infarction in myeloproliferative neoplasms". We provide the key insights of the paper, re-discussing the main topics focusing on the major mechanism underlying the relation of MPNs and ACS.

HOW INFLAMMATION IN MYELOPROLIFERATIVE NEOPLASMS CAN PREDISPOSE TO ACUTE CORONARY SYNDROMES

Inflammation plays a central role in the pathogenesis of cardiac diseases, particularly in the development of atherosclerotic disease[6]. In cases of MPN, the whole body undergoes a persistent inflammatory state, and patients typically suffer from inflammation-mediated symptoms such as fever, night sweats, weight loss, and fatigue[2]. Accordingly, in patients with ET and PV, the presence of high levels of C-reactive protein is associated with a higher risk of thrombosis [7]. Although more information is available concerning the role of inflammation in causing thrombosis, the underlying mechanisms through which MPNs contribute to the development of ACS are not completely understood. The concept is that thrombosis can affect both the arterial and venous vessels in MPN patients, and ACS are mainly caused by an arterial thrombosis of the coronary vessels[8]. The basic principle for the development of a thrombus remains the notorious Virchow triad (hypercoagulability, blood stasis, endothelial injury)[9] (Figure 1).

Hypercoagulability

MPNs, especially ET, are associated with increased platelet count as well as their functionality impairment. ET is characterized by an overproduction of platelets from megakaryocytes as these cells become excessively sensitive to thrombopoietin[10]. As such, the risk of thrombosis is particularly higher in these patients. Such cells tend to be larger and more reactive[11]. Further to their increased pro-thrombotic activity, dysfunctional platelets are less sensitive to the inhibitory effect mediated by aspirin or clopidogrel[12]. Recently, the greater reactivity of platelets in MPNs has been related to the higher number of mitochondria within their membrane[13].

Leukocytosis is known to be a non-specific marker of acute myocardial infarction (AMI)[14], where it is thought to reflect the inflammatory response toward myocardial necrosis in AMI patients. In MPNs patients, it can also be an expression of a more aggressive disease or an exaggerated inflammatory response[3]. As such, patients with AMI and marked leukocytosis are associated with a worse prognosis[15,16]. On the other hand, leukocytosis itself is a possible cause of AMI. For instance, acute leukemia patients with marked leukocytosis are known to possibly have acute myocardial infarction as a complication of their clinical condition[16]. In these patients, the presence of a pro-thrombophilic state and higher expression of adhesion molecules (*e.g*., CD56) are thought to favor the onset of ACS[17]. Similarly, patients with MPNs patients tend to have a pro-thrombotic state, and the presence of more circulating leukocytes can also reflect the presence of more reactive leukocytes with a tendency toward a dysregulated inflammatory response toward

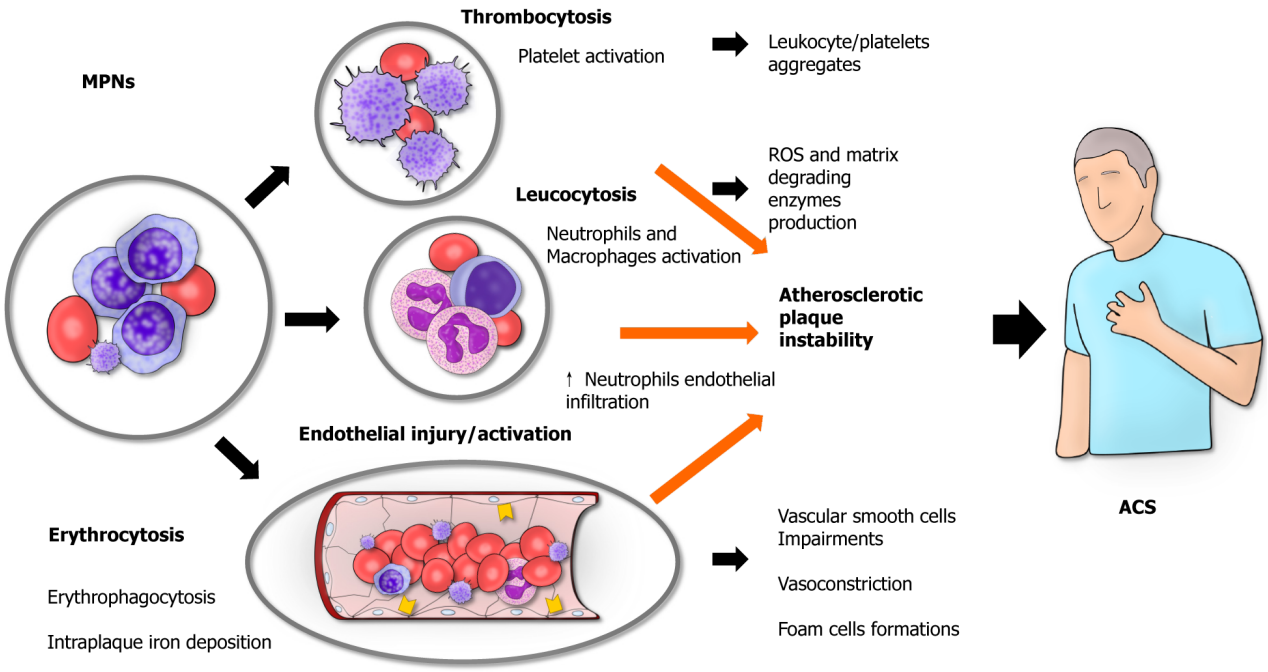

Figure 1 Myeloproliferative diseases in predisposing to acute coronary syndrome: The Virchow triad. Myeloproliferative neoplasms (MPNs) are a group of diseases characterized by the clonal proliferation of hematopoietic progenitor or stem cells. Patients with MPN are at high risk of cardiovascular events, especially those sustained by arterial thrombosis. Different causal links have been recently shown to account for increased acute myocardial infarction risk in patients with MPNs. ACS: Acute coronary syndrome; MPNs: Myeloproliferative neoplasms.

the onset of AMI. As such, leukocytosis in patients with PV can be considered as a possible hallmark of a higher cardiovascular risk[18]. Indeed, pro-inflammatory states are known to increase the expression of procoagulants such as tissue factor, fibrinogen and adhesion molecules.

JAK2 is a non-receptor tyrosine kinase in the Janus kinase family. JAK2 mutations are implicated in MPNs, including PV, ET, and myelofibrosis[19]. Furthermore, JAK2 mutation is also associated with a higher risk of ACS[3]. The most prevalent JAK2 mutation in MPNs is called JAK2V617F. This mutation consists of a substitution of a valine with phenylalanine in position 617. The resulting neoplastic clones favor the development of inflammation *via* the secretion of several inflammatory cytokines (*e.g.*, interleukin-1, interleukin-6, tumor necrosis factor-α, interferon-γ), resulting in mesenchymal and endothelial cell activation, bone marrow fibrosis, and eventually ending in acute myeloid leukemia [20]. Furthermore, JAK2V617F is associated with a higher expression of adhesion molecules, especially integrins, resulting in the favoring of thrombus formation[2]. Also, neutrophils harboring such mutations showed a higher tendency to form neutrophil extracellular traps[21-23]. Again, NETosis is known to facilitate thrombus formation working as a scaffold for fibrin and cells as well as carrying different molecules with pro-coagulant activity[24]. The result is a higher risk of thrombotic complications[25]. Other MPN-associated mutations involve genes encoding for reticulum-associated protein calreticulin and thrombopoietin receptor[26]. Of interest such mutations again result in the activation of JAK/STAT signaling and to date inhibitors of JAK2-driven signal have been approved for patients with myelofibrosis and PV[27].

Blood stasis

Blood stasis is typically found in MPNs patients. As all MPN relates with the expansion of a clone, and results in increased number of circulating cells a certain degree of blood stasis is expected in all patients with the disease[28]. The higher hematocrit found in PV patients is secondary to the higher number of circulating erythrocytes found in these patients. Such a higher number of circulating red blood cells is associated with blood stasis, blood flow disturbances, and hyper-viscosity[29], therefore favoring the development of thrombosis[30]. Similarly, in patients with ET cell count can hit high at over 1 million abnormal (see above) platelets/mL. Blood stasis together with the presence of over-reactive platelets can probably favor the development of thrombi because of platelet activation, as reported in studies on animal models that showed that platelet adhesion to the endothelium is directly related to the hematocrit levels[31]. Clinically, PV patients are more prone to have vascular complications, such ACS[18].

Endothelial damage

The endothelium is a pivotal player in the pathophysiology of arterial thrombosis. Indeed, under physiological conditions endothelial cells exert anti-thrombotic roles by producing several mediators including nitric oxide. The endothelium probably participates in the formation of thrombi as a consequence of the hyper-coagulability state rather than being the primary origin of thrombus formation[32]. However, under the pro-inflammatory pressure lead by the neoplastic clone, endothelial cells get dysfunctionally activated and secrete further pro-inflammatory cytokines propagating inflammation. Activated endothelial cells increase the expression of adhesion molecules including E-selectin on their surfaces in MPN

patients[33]. Although E-selectin is not considered a marker of unstable coronary plaque[34], the endothelial overexpression of E-selectin can trigger an excessive leukocyte response in MPN patients. As such, even the smallest plaque tear might favor an exaggerated intracoronary activation of platelets, causing the clinical manifestation of ACS.

Furthermore, endothelial cells with mutated JAK2 have been found in patients carrying the JAK2 V617F mutation[35]. Of interest, such endothelial cells express a proadhesive phenotype with increased P-selectin expression that may be a further link with the increased thrombosis risk[36]. Indeed, therapeutic approaches aiming at P-selectin blockade have shown preclinical potential to reduce thrombosis. Increased atherosclerosis may not be the only link between AMI and MPNs, as almost 20% of AMI in MPNs occurs in patients without significant atherosclerotic occlusive disease[37]. Here, coronary vasoconstriction may play a role. Indeed, JAK2 V617F mice have shown increased arterial vasoconstriction due to their lower levels of nitric oxide, increased oxidative and inflammatory stress[38]. Specifically, erythrocytes-derived microvescicles have been deemed responsible for such phenotype and proteomic analysis of particles derived from JAK2V617F erythrocytes suggested MPO as the potential mediator[38].

CONCLUSION

MPNs are associated with cardiovascular diseases, especially those sustained by a thrombotic event. MPNs arise from clonal hematopoiesis of indeterminate potential (CHIP), whose investigation in the last years provided fundamental insight into the causal link between thrombosis and MPNs. CHIP is defined as the presence of a clonal mutation in a driver gene, occurring with a variant burden of ≥ 2% but without any clinical evidence of a hematologic neoplasm. Patients with CHIP show a 10-fold increased risk of developing any hematologic malignancy, including MPNs[39]. Of interest, the magnitude of risk enrichment due to CHIP is even higher than that of classical cardiovascular risk factors [39]. Experimental and clinical observations further point at inflammation as the culprit link between CHIP and cardiovascular disease[40,41]. Indeed, CHIP is nowadays seen as another characteristic of human aging, and it accompanies with another typical features of aging which is the appearance of a chronic low-grade pro-inflammatory state (inflamm-ageing). With recent trails showing the potential for anti-inflammatory therapies in cardiology[42], targeting specific inflammatory mediators may be a way to blunt prothrombotic state of patients with MPN. The role of CHIP and inflamm-ageing in cardiovascular disease development have been recently reviewed[41,43,44].

Manan *et al*[5] reviewed the recent literature and provided insight into the pathogenesis and clinical consequences of the association between hematological and cardiovascular diseases. Further research is needed to establish cardiovascular preventive strategies for MPN patients.

FOOTNOTES

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EDITORIAL

Facing ethical concerns in the age of precise gene therapy: Outlook on inherited arrhythmias

Federico Carbone, Fabrizio Montecucco

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Abstract

This editorial, comments on the article by Spartalis *et al* published in the recent issue of the *World Journal of Cardiology*. We here provide an outlook on potential ethical concerns related to the future application of gene therapy in the field of inherited arrhythmias. As monogenic diseases with no or few therapeutic options available through standard care, inherited arrhythmias are ideal candidates to gene therapy in their treatment. Patients with inherited arrhythmias typically have a poor quality of life, especially young people engaged in agonistic sports. While genome editing for treatment of inherited arrhythmias still has theoretical application, advances in CRISPR/Cas9 technology now allows the generation of knock-in animal models of the disease. However, clinical translation is somehow expected soon and this make consistent discussing about ethical concerns related to gene editing in inherited arrhythmias. Genomic off-target activity is a known technical issue, but its relationship with ethnical and individual genetical diversity raises concerns about an equitable accessibility. Meanwhile, the cost-effectiveness may further limit an equal distribution of gene therapies. The economic burden of gene therapies on healthcare systems is is increasingly recognized as a pressing concern. A growing body of studies are reporting uncertainty in payback periods with intuitive short-term effects for insurance-based healthcare systems, but potential concerns for universal healthcare systems in the long term as well. Altogether, those aspects strongly indicate a need of regulatory entities to manage those issues.

Key Words: Ethics; Inherited arrhythmias; CRISPR/Cas9; Gene therapy; Equitable accessibility

Core Tip: As for other diseases, inherited arrhythmias may take advantage from gene editing. Even we are still far from clinical translation, ethical issues need to be considered in order to proceed in this research field avoiding any misconduct. Off-target effects, equitable accessibility of life-saving gene therapies and economic burden for healthcare systems are key issues that need to addressed by regulatory entities.

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INTRODUCTION

The manuscript "Inherited arrhythmias and gene therapy: Are there any ethical considerations to take into account?", summarizes current evidence regarding potential application of gene therapy in the context of inherited arrhythmias[1]. This class of diseases aligns well with the application field of gene therapy meeting the clinical needs of monogenic disease with no or few therapeutic options available through standard care[2,3]. The quality of life for patients with inherited arrhythmias remains an unmet clinical need[4]. Young individuals engaged in agonistic sports often find themselves compelled to cease any practice following diagnosis. Despite a general consensus from the European Society of Cardiology and American Heart Association to continue sport activities, local laws usually restrict them from any competition[5,6]. Even a life-saving device like International Classification of Diseases is burdened by the negative effects of recurrent shocks, leading to the occurrence of electrical storms triggered by the catecholamines release after each shock [7].

OVERVIEW AND OUTLOOK ON GENOME EDITING FOR INHERITED ARRHYTHMIAS

Throughout the manuscript the authors review the theoretical applications of genome editing for the treatment of inherited arrhythmias. Advances in CRISPR/Cas9 technology have broadened the potential for generating knock-in animal models[8,9]. However, current challenges lie in the development of delivery methods and ensuring editing efficiency while minimizing off-target effects[10]. In addition to technical limitations, ethical concerns are worth considering. One such concern arises from genomic off-target activity which is actively being addressed through the development of prediction assays capable of identifying unwanted editing events[11]. Furthermore, on- and off-target effects may be influenced by the individual genetical diversity, potentially limiting the equitable accessibility of life-saving gene therapies. Similarly, the cost-effectiveness may further limit the equal distribution of gene therapies. While this impact is intuitive for insurance-based healthcare systems, a similar effect is anticipated for universal healthcare systems in the long term[12-14]. In the real word, this is a poignant aspect as many patients may have to put their homes and life savings at risk[13]. This underscores the need for a regulatory entity to prevent misconduct. Leading scientists, politicians and economists are called upon to promptly update the first genome editing-specific guidance documents release by the United States Food and Drug Administration and European regulators in 2022[15,16].

CONCLUSION

In this context, the research of gene therapies for inherited arrhythmias is still in its infancy and lacks translation into a clinical setting. However, it must continue on a well-established track that adheres to defined ethical standards.

FOOTNOTES

Author contributions: Carbone F and Montecucco F performed research and wrote the paper.

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EDITORIAL

Cardiac rehabilitation after cardiac surgery: An important underutilized treatment strategy

Christos Kourek, Stavros Dimopoulos

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Abstract

Physical inactivity remains in high levels after cardiac surgery, reaching up to 50%. Patients present a significant loss of functional capacity, with prominent muscle weakness after cardiac surgery due to anesthesia, surgical incision, duration of cardiopulmonary bypass, and mechanical ventilation that affects their quality of life. These complications, along with pulmonary complications after surgery, lead to extended intensive care unit (ICU) and hospital length of stay and significant mortality rates. Despite the well-known beneficial effects of cardiac rehabilitation, this treatment strategy still remains broadly underutilized in patients after cardiac surgery. Prehabilitation and ICU early mobilization have been both showed to be valid methods to improve exercise tolerance and muscle strength. Early mobilization should be adjusted to each patient's functional capacity with progressive exercise training, from passive mobilization to more active range of motion and resistance exercises. Cardiopulmonary exercise testing remains the gold standard for exercise capacity assessment and optimal prescription of aerobic exercise intensity. During the last decade, recent advances in healthcare technology have changed cardiac rehabilitation perspectives, leading to the future of cardiac rehabilitation. By incorporating artificial intelligence, simulation, telemedicine and virtual cardiac rehabilitation, cardiac surgery patients may improve adherence and compliance, targeting to reduced hospital readmissions and decreased healthcare costs.

Key Words: Cardiac rehabilitation; Cardiac surgery; Cardiopulmonary exercise testing; Early mobilization; Treatment; Technology

Core Tip: Cardiac rehabilitation is a medically supervised program designed to maintain or improve cardiovascular health, and should be considered as an important treatment strategy in patients after cardiac surgery. It has multiple beneficial effects on functional capacity, endothelial and skeletal muscle function, and quality of life. Recent advances have been made in cardiac rehabilitation during the last decades, including the use of artificial intelligence, simulation, telemedicine and virtual cardiac rehabilitation that improve compliance. As a result, reduced hospital readmissions and decreased healthcare costs are being observed in the modern healthcare systems.

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INTRODUCTION

Cardiac surgery includes a variety of procedures with coronary artery by-pass grafting, valve replacement, aortic/mitral/tricuspid valve replacement or reconstruction, heart transplantation and Bentall surgery being the most frequent among them. Patients present a loss of cognitive and exercise capacity[1], muscle mass[2] and quality of life[3,4] after cardiac surgery due to anesthesia, surgical incision, duration of cardiopulmonary bypass, and mechanical ventilation[5]. These complications, along with pulmonary complications after surgery, lead to extended intensive care unit (ICU) and hospital length of stay and significant mortality rates[5]. Physical inactivity remains high after cardiac surgery, reaching up to 49% in these patients[6]. Moreover, physical inactivity, even late after cardiac surgery, is associated with increased long-term mortality[6].

Cardiac rehabilitation is designed to improve cardiovascular health in patients with cardiovascular diseases and is recommended by guidelines as Class IA[7,8]. In cardiac surgery, cardiac rehabilitation is associated with a lower 2-year mortality[9]. Despite the well-known beneficial effects of cardiac rehabilitation after cardiac surgery, this treatment strategy still remains underutilized due to low rates of referrals, adherence and compliance. The aim of the present editorial is to highlight the role of cardiac rehabilitation in cardiac surgery and demonstrate the most recent advances in this field.

EARLY MOBILIZATION AND PREHABILITATION

Early mobilization should be considered as an important preventive and treatment method for ICU acquired weakness in patients after cardiac surgery. Despite its safety, feasibility, beneficial effects on exercise capacity[10] and its association with reduced length of ICU stay[11], more studies are required in order to provide confirming evidence[12]. Early mobilization should be adjusted to each patient's functional capacity, initiating from passive mobilization such as stretching, splinting, passive movements and neuromuscular electrical stimulation (NMES), and increasing the functional status with simple active range of motion and resistance exercises including sitting in a chair, leg press, squats from sitting position, walking, biking on an exercise bike, walking on stairs and inspiratory muscle training[13,14]. Passive mobilization and NMES are usually implemented in intubated patients under mechanical ventilation, high-risk patients with hemodynamic instability or patients with reduced consciousness while active-assisted range-of motion exercises, inspiratory muscle training and resistance exercises are implemented in those who need mobilization after cardiac surgery, with satisfactory level of consciousness[13,14]. In general, early mobilization has been shown safe and feasible in cardiovascular diseases[15-17] and critically ill patients[18], as well as in other medical conditions such as subarachnoid hemorrhage and external ventricular drain[19], continuous renal replacement therapy[20] and sepsis[21,22]. Beyond all its beneficial effects, early mobilization of cardiac surgery patients requires close monitoring in the ICU due to possible side effects, including significant hemodynamic changes[23]. As a result, expert multidisciplinary team approach and individualized rehabilitation program, adjusted to the patient's functional status, are necessary in order to minimize adverse events[24].

Prehabilitation is another novel modality of rehabilitation defined as a process of improving functional capability of a patient prior to a surgical procedure. Recent studies have demonstrated that prehabilitation seems to improve functional capacity and enhance postoperative recovery in patients undergoing cardiothoracic surgery[25,26]. Moreover, prehabilitation contributes to better quality of life in patients with stable coronary artery disease awaiting cardiac surgery[27]. Growing evidence supports prehabilitation even in patients with advanced heart failure or extracorporeal membrane oxygenation as a bridge to left ventricle assist device or heart or lung transplantation. In these cases, prehabilitation should be performed daily for approximately 60 min including airway clearance techniques and ventilation in prone and supine position when required, and in-bed active-assisted range of motion exercises including sitting at the bedside, standing balance and tolerance, rolling, stretching, positioning in bed, strengthening and reconditioning exercises in the

supine position, bedside cycling, inspiratory muscle training, out-of-bed activities such as standing at the bedside, strength of standing force, sitting on the edge of the bed and transfer from bed to chair, exercises in the sitting position on the edge of the bed, aerobic training on a cycle ergometer or a treadmill and inspiratory muscle training according to patient's functional capacity[14].

EXERCISE PRESCRIPTION

Exercise prescription is a quite complex procedure, especially in patients after cardiac surgery. The most difficult part is to establish the beneficial "dose" of exercise in order to achieve the maximum beneficial results and avoid harmful effects. Clinical assessment and risk stratification *via* transthoracic echocardiography and cardiopulmonary exercise testing (CPET) are required prior to participation in such rehabilitation programs. CPET is the gold standard for the prescription of maximum aerobic exercise intensity[28]. Monitoring of heart rate (HR) dynamics and ventilation, as well as metabolic parameters such as oxygen uptake (VO_2) and carbon dioxide output (VCO_2), provides objective measurements of respiratory, metabolic, and cardiovascular responses to exercise and creates an individualized program for each patient[29]. Therefore, exercise training can be classified in four intensity domains, based on the percentage of peak VO_2, HR, HR reserve, and Borg scale; light to moderate, moderate to high, high to very high, and very high intensity[30]. In the first phase of rehabilitation, it is usually suggested to start with lower intensities of exercise and mostly work on both frequency and duration of each session, rather than intensity. Intensity should be maintained quite constantly, close to the lowest limit of the moderate intensity range, and then, increase to higher levels depending on the rehabilitation phase and the individualized needs[30].

RECENT ADVANCES IN CARDIAC REHABILITATION

During the last decade, recent advances have been made in cardiac rehabilitation. Rapidly-advanced technology is the cornerstone in the future of cardiac rehabilitation. Wearables such as fitness bands and smartwatches that monitor heart rhythm during exercise in order to detect arrhythmias are used by 5% to 11% of the world's adult population[31]. Intelligent computing including artificial intelligence (AI) and complex modeling are now increasingly used in biologic systems so that to create individualized rehabilitation programs[32]. Specifically, AI could estimate and quantify risk assessment of patients before and after cardiac surgery *via* special algorithms, using CPET, anaerobic threshold quantification, biomarkers and frailty parameters. Moreover, it could be a useful tool to predict mortality and morbidity[33], and detect dysrhythmias in electrocardiography during rehabilitation with promising results in accuracy and speed of interpretation[34,35], as well as in more advanced imaging such as echocardiography[36] and magnetic resonance imaging[37]. Other significant variables, including simulation and telemedicine, could be valuable for solving access problems due to disparities, disabilities, long physical distance from health care centers, and lack of expertise and specialized personnel, as well as for high-risk situations such as virulent infections and combat[32]. Virtual cardiac rehabilitation has been also shown to improve patients' adherence and compliance, reduce hospital readmissions, and decrease associated costs and cardiovascular risk[38,39]. Synchronous audiovisual technology is used to supervise patient exercise and provide education in real-time. Technological advances should translate into actual benefits for patients and health care providers, providing higher-quality of services and safety in health care systems[32].

Cardiac rehabilitation, with its traditional form, is an individualized, patient-centered program. However, the future of cardiac rehabilitation will include more options for participants with in-person visits, virtual one-on-one visits, virtual group visits, and asynchronous exercise with or without remote monitoring[40]. The choice whether the participation will include exclusively one delivery mode or a hybrid of 2 or more delivery modes depends on many variables related with the participants, such as their physical status, their opportunity of participation, the distance from the rehabilitation facilities, *etc.*

Finally, cardiac rehabilitation includes modification of previous lifestyle habits including smoking and alcohol cessation, loss of weight and medication adherence. Synchronous interventions *via* telemedicine could be used to improve access to these services, such as consultation with a registered dietitian or a behavioral therapist[40]. Core advances of a cardiac rehabilitation program are demonstrated in Figure 1.

CONCLUSION

Cardiac rehabilitation is a complex and multicomponent procedure that requires a multidisciplinary approach and includes physical activity promotion, health education, cardiovascular risk management and psychological support, personalized to the individual needs of patients after cardiac surgery. CPET remains the gold standard method for the prescription of optimal aerobic exercise intensity. Recent advances in cardiac rehabilitation have been made during the last decade, including the use of AI, simulation, telemedicine, and virtual cardiac rehabilitation that have improved adherence and compliance, and reduced hospital readmission, with decreased associated healthcare cost. However, new innovations are required in order to increase rates of patients' participation and create ideal individualized protocols for each patient.

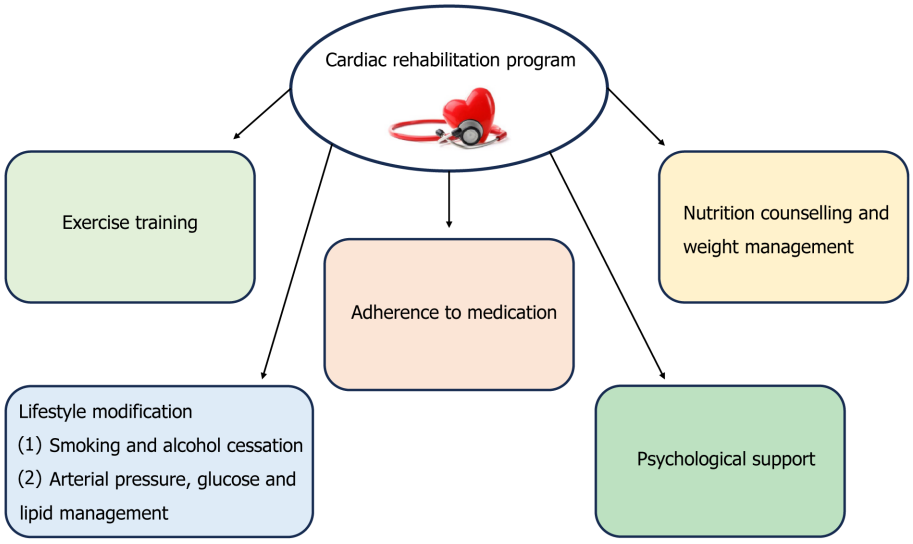

Figure 1 Components of a cardiac rehabilitation program.

FOOTNOTES

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MINIREVIEWS

Seeing beneath the surface: Harnessing point-of-care ultrasound for internal jugular vein evaluation

Vichayut Chayapinun, Abhilash Koratala, Taweevat Assavapokee

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Abstract

Point-of-care ultrasound (POCUS) of the internal jugular vein (IJV) offers a non-invasive means of estimating right atrial pressure (RAP), especially in cases where the inferior vena cava is inaccessible or unreliable due to conditions such as liver disease or abdominal surgery. While many clinicians are familiar with visually assessing jugular venous pressure through the internal jugular vein, this method lacks sensitivity. The utilization of POCUS significantly enhances the visualization of the vein, leading to a more accurate identification. It has been demonstrated that combining IJV POCUS with physical examination enhances the specificity of RAP estimation. This review aims to provide a comprehensive summary of the various sonographic techniques available for estimating RAP from the internal jugular vein, drawing upon existing data.

Key Words: Point-of-care ultrasound; Bedside ultrasound; Internal jugular vein; Right atrial pressure; Central venous pressure

Core Tip: Point of care ultrasound of the internal jugular vein serves as a non-invasive tool to evaluate right atrial pressure. This is particularly useful when neck vein inspection is challenging, or inferior vena cava sonography lacks reliability. When combined with the physical examination and other sonographic parameters, it becomes a valuable component of bedside hemodynamic evaluation.

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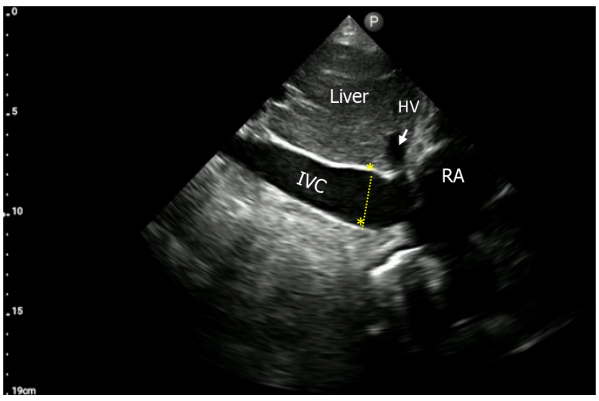
INTRODUCTION

An accurate assessment of hemodynamic status at the bedside is of utmost importance in guiding proper management through altering blood volume and cardiac output, especially in critically ill patients. Central venous pressure (CVP) is a physiologic parameter that is used to assess cardiac preload within this evaluation. CVP is identical to right atrial pressure (RAP) in the absence of vena caval obstruction, and these terms are often used interchangeably. Assessing CVP clinically by performing a neck veins examination can be challenging at times and yield low sensitivity, especially in the elderly, obese, and short-necked patients[1-4]. The gold standard for measuring CVP is *via* inserting a central venous catheter (CVC) into the superior vena cava, however, this method is invasive, time-consuming, and can cause serious complications[4-6]. With the help of point-of-care ultrasound (POCUS), RAP can be non-invasively measured through various methods including using compression ultrasound on the forearm vein[7], evaluation of the inferior vena cava (IVC), and evaluation of the internal jugular vein (IJV). The most common method is the evaluation of IVC diameter and collapsibility[8,9] (Figure 1). However, the association between IVC parameters and RAP is moderate and lacks reliability in mechanically ventilated individuals or those with abdominal compartment syndrome[10]. Moreover, imaging the IVC can be challenging in situations like morbidly obese individuals, those unable to recline, patients with cirrhosis, ascites, or those who have undergone recent abdominal surgery[11]. Owing to its location and convenient accessibility, IJV POCUS presents a viable alternative in such instances. Unlike visual inspection, where identifying the vein can be difficult in many cases, POCUS makes the IJV easily visible, saving time for physicians and improving the accuracy of the examination[12,13].



IVC diameter (cm)	% Collapse with a sniff	Estimated RAP (mmHg)
≤ 2.1	>50	3 (0-5)
>2.1	<50	15 (10-20)
≤2.1	<50	8 (5-10)
>2.1	>50	8 (5-10)

Figure 1 Estimation of right atrial pressure by inferior vena cava ultrasound in spontaneously breathing patients, based on current guidelines[8]. IVC: Inferior vena cava; RA: Right atrium; HV: Hepatic vein; RAP: Rright atrial pressure.

SONOGRAPHIC METHODS OF IJV ASSESSMENT

Multiple techniques have been described to assess CVP by IJV ultrasound. Based on available data, these methods encompass measuring the vertical height of the blood column in the IJV[13-16], utilizing the IJV height-to-width ratio (aspect ratio)[17,18], IJV collapsibility index (IJV-CI)[13,17,19-22], IJV distensibility index[23], measuring the maximal anteroposterior diameter of the IJV (AP-IJV Dmax)[18,24], calculating the difference in the percentage of the IJV cross-sectional area (IJV-CSA) or diameter before and after the Valsalva maneuver[25,26], and combining IJV vertical height with right atrial depth measured with echocardiography[27,28].

The first technique, pioneered by Lipton[14], uses POCUS to visualize the height of the blood column in the IJV above the sternal angle of Louis where a venous collapse is seen (the 'wine bottle' or 'paint brush' appearance), thereby being able to measure the height of the IJV more accurately than compared to only performing neck veins examination (Figure 2). The height is then added to the hypothesized right atrial depth below the sternum of 5 cm to calculate the RAP, abiding by the doctrine of Sir Thomas Lewis, who first proposed the use of neck veins examination in 1930. This method's accuracy is questionable, owing to the presumed right atrial depth of 5 cm, which is proven to be inaccurate[27,29]. In a study by Deol *et al*[30] ultrasound-assisted assessment of the column height underestimated CVP by 4.7 cm H_2O, whereas visual inspection underestimated it by 6.1 cm H_2O. Moreover, this approach can be time consuming as it requires two tools to assess the height of the column from the sternal angle (*e.g.*, two rulers, a pen and a ruler, or a tongue depressor and a ruler or tape, commonly employed by physicians at the bedside), further compromising measurement

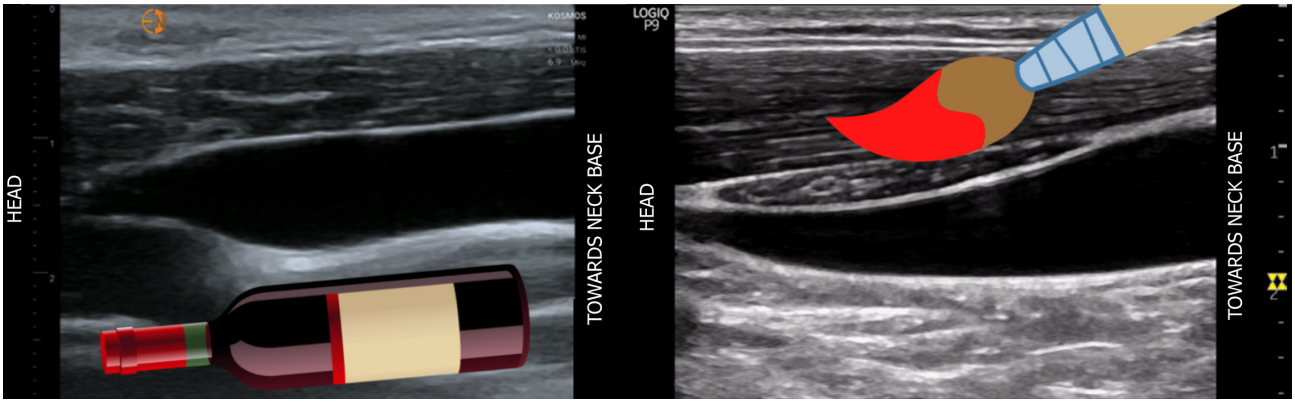


Figure 2 Internal jugular vein collapse point compared to a wine bottle and paint brush. Figures adapted from NephroPOCUS.com with permission.

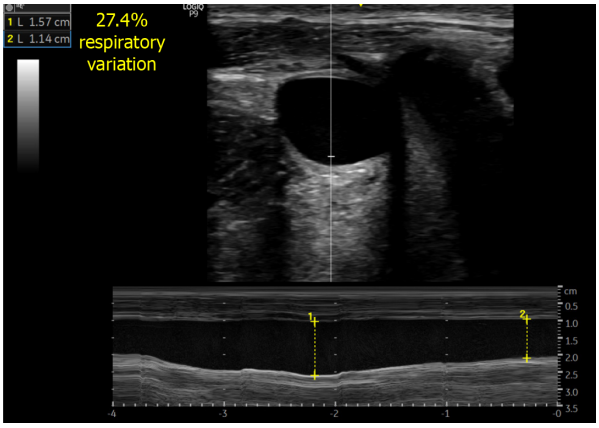


Figure 3 Anteroposterior diameter of the internal jugular vein. M-mode tracing depicts respiratory variation in the diameter.

accuracy[31].

The second technique uses the height-to-width ratio (aspect ratio) to estimate the CVP as a binary variable (*e.g.*, </> 10 mmHg), without precisely quantifying it. The transducer is positioned at the level of the cricoid cartilage in the transverse plane, then the height (anteroposterior diameter) and the width (transverse diameter) are measured to obtain the aspect ratio. A ratio of < 0.75 has shown to correlate with RAP of < 10 mmHg with a sensitivity and specificity of 62% and 67% respectively in one study[17]. This method yields mixed results, and its utility is currently not well-demonstrated[18].

The third technique uses the collapsibility index of IJV (IJV-CI) to estimate RAP. The IJV-CI is calculated by its respiratory variation, (IJVmax – IJVmin)/IJVmax expressed in percentage (Figure 3). The actual RAP cannot be quantified, but studies[13,21,22] have shown that an IJV-CI of approximately ≤ 30% signifies an elevated CVP of ≥ 8 mmHg, demonstrating good sensitivity and specificity. Worthy of particular mention, in a study by Leal-villarreal *et al* [21] in patients with cirrhosis, IJV-CI (anteroposterior diameter 2 cm above the sternoclavicular joint) ≤ 24.8% was better at predicting a CVP ≥ 8 mmHg with 100% sensitivity and 97.1% specificity outperforming IVC POCUS. In this cohort, IVC POCUS was unattainable in 18% of the cases correlating with our real-life experience in cirrhotic patients.

The fourth technique uses the IJV distensibility index to predict the fluid responsiveness in patients undergoing mechanical ventilation. IJV is imaged at the cricoid cartilage level in the transverse plane and the distensibility index is calculated by (IJVmax – IJVmin)/IJVmin, expressed in percentage. In one study, an IJV distensibility index of > 18% before volume challenge (7 mL/kg crystalloid) had an 80% sensitivity and 85% specificity to predict fluid responsiveness [23]. While this technique does not quantify the RAP, it could be a valuable adjunct to other hemodynamic parameters in assessing fluid status in mechanically ventilated patients.

The fifth technique uses the IJV maximal anteroposterior diameter (AP-IJV Dmax) to predict the RAP whether it is low (< 8 mmHg) or high. Similar to the second technique of acquiring the aspect ratio, the transducer is positioned transversely 2 cm above the clavicle, at end-expiration and the diameter is collected to correlate with RAP. It has been shown that AP-IJV Dmax has the best correlation with RAP, the best validity in predicting its values, and a very good inter-rater reliability[24] along with its accuracy in predicting low RAP of < 8 mmHg[18].

The sixth technique uses the difference in the percentage of the IJV cross-sectional area (IJV-CSA) before and after the Valsalva maneuver to assess for RAP. The Valsalva maneuver increases the IJV-CSA by about 20%-30% in patients with normal RAP, and it is assumed that in volume-overloaded patients with a decrease in venous compliance, the increase in IJV-CSA will be blunted. This technique measures the patient's IJV-CSA at the vertical column height where a venous collapse is seen and re-measures that same parameter while the patient performs the Valsalva maneuver, then calculates

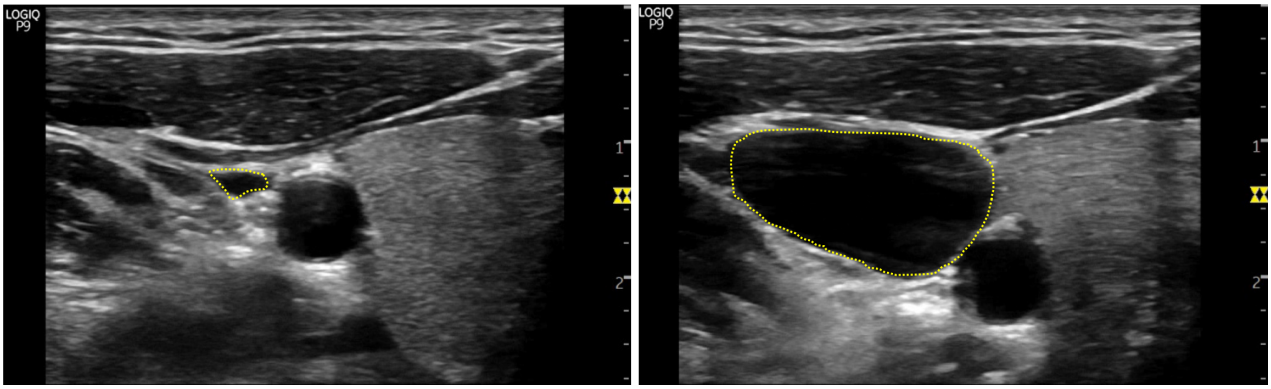


Figure 4 Increase in the size of internal jugular vein with Valsalva maneuver by several folds in a spontaneously breathing person with normal right atrial pressure.

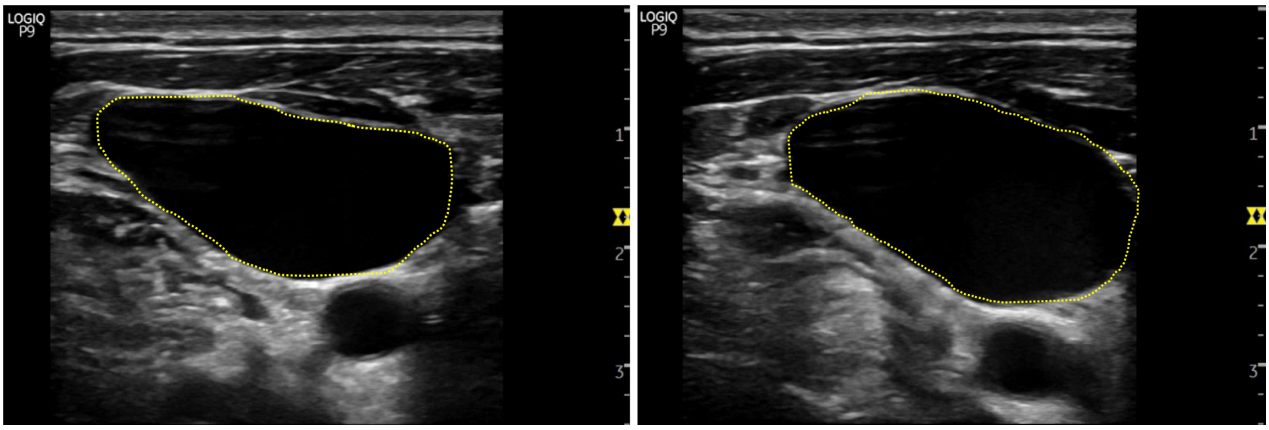


Figure 5 Minimal increase in the size of internal jugular vein with Valsalva maneuver in a spontaneously breathing heart failure patient with elevated right atrial pressure.

the difference in the percentage of the IJV-CSA (Figures 4 and 5). One study[25] found that a < 17% increase in IJV-CSA with Valsalva predicted elevated RAP (≥ 12 mmHg) with 90% sensitivity, 74% specificity, and a 94% negative predictive value. Alternatively, the ratio between maximum IJV diameter during Valsalva maneuver and diameter at rest (JVD ratio) < 4 has also shown to predict elevated RAP[26].

Another recently described technique uses the IJV vertical height combined with right atrial depth measured with echocardiography to quantify the RAP. While similar to the first technique in principle, this approach enhances accuracy by directly measuring the right atrial depth instead of relying on the assumed 5 cm. It involves marking the highest point of the venous collapse (wine bottle sign) and then performing a focused cardiac ultrasound to visualize the heart in long axis (parasternal long axis view). Right atrial depth is measured from the surface to the location of the non-coronary cusp of the aortic valve attachment to the posterior left ventricular outflow tract (Figure 6). The two parameters, the column height, and the right atrial depth, are then added together for an estimation of the RAP in cm H_2O, later converted to mmHg. This method predicted actual RAP within 3 mmHg 74% of the time when compared to cardiac catheterization-derived value[27].

In an alternative technique described by Xing *et al*[28], the initial step of measuring the height of collapse point is the same but the right atrial depth is calculated using an adjusted apical 4-chamber view with the right atrium in the center of the view, where distance between the transducer contact point and the center of the right atrium is recorded. A pencil and a ruler are then used in relation to the transducer to derive the surface projection of the center of the right atrium. The RAP is then estimated by adding the IJV column height to the right atrial depth. This technique demonstrates a substantial correlation and high accuracy, with a mean difference of 0.22 mmHg in RAP compared to CVC. Nevertheless, it lacks practicality in a clinical setting where swift assessment is essential, as it involves multiple operators and the use of various measuring instruments.

With respect to estimation of RAP using IJV POCUS in mechanically ventilated patients, there is limited data. One noteworthy study is by Hilbert *et al*[32] in a cohort of 47 patients, where they evaluated the ratio between IJV diameter in the 30° and 0° head position (30/0 ratio). A 30/0 ratio of < 0.45 indicated a low CVP, whereas a cutoff of > 0.65 predicted a CVP ≥ 10 mmHg with reasonable accuracy.

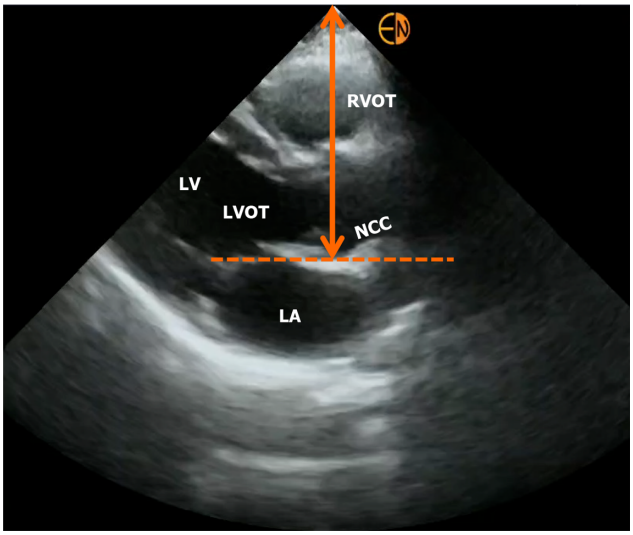


Figure 6 Measurement of right atrial depth using parasternal long axis view on focused cardiac ultrasound. RVOT: Right ventricular outflow tract; LV: Left ventricle; LVOT: LV outflow tract; LA: Left atrium; NCC: Non-coronary cusp of aortic valve.

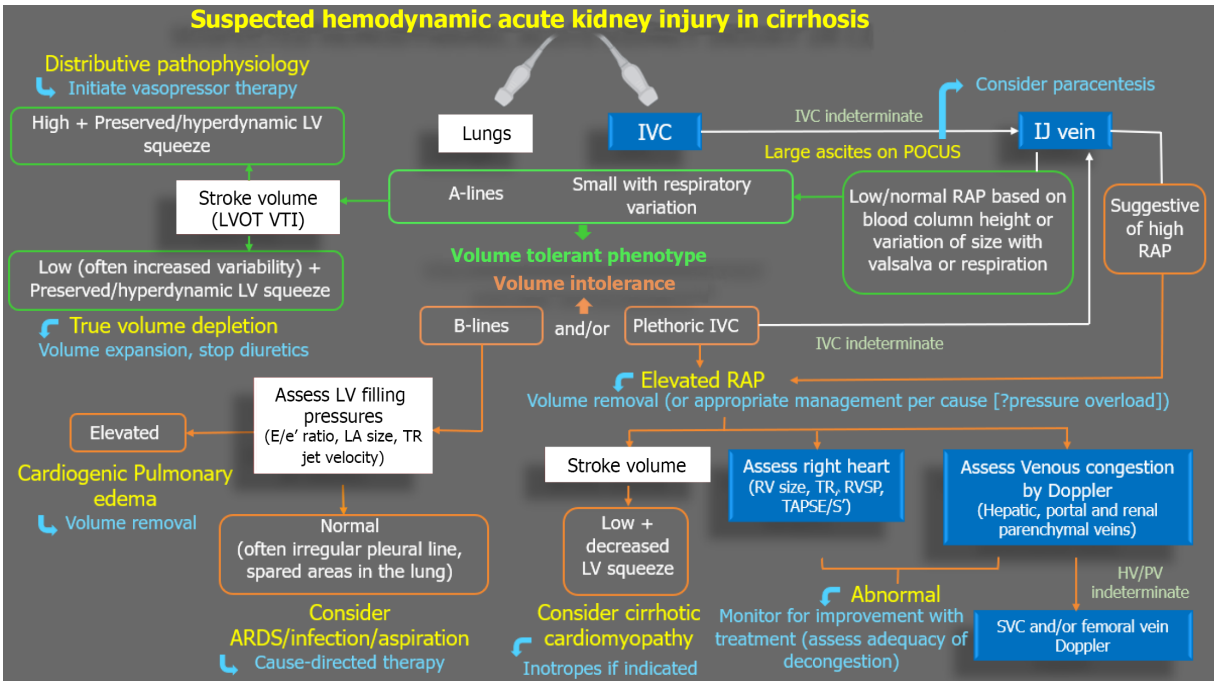


Figure 7 Diagnostic algorithm in a case of cirrhosis and suspected hemodynamic acute kidney injury. Incorrect angle of insonation is a frequent source of error when assessing LVOT VTI (surrogate for stroke volume) and other Doppler measurements listed. Adapted from Ref. 33 with kind permission of the publisher (corresponding author's prior open access publication). Blue boxes: Right heart; Red boxes: Left heart-related sonographic parameters; Green outlines: Volume tolerance phenotype; Orange outlines: Volume intolerance. POCUS: Point-of-care ultrasonography; VTI: Velocity time integral; E/e': Ratio of the early diastolic waves of the mitral inflow Doppler and mitral annular tissue Doppler; LA: Left atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TAPSE: Tricuspid annular plane systolic excursion; S': Tricuspid annular systolic velocity; SVC: Superior vena cava; ARDS: Acute respiratory distress syndrome; HV: Hepatic vein; PV: Portal vein.

CONCLUSION

In essence, IJV POCUS serves as a quick, non-invasive bedside tool for assessing RAP. However, the diversity in techniques requires cautious interpretation, avoiding overestimation of accuracy. Interpretation of IJV POCUS in the appropriate clinical context is crucial. Additionally, CVP is not a surrogate for volume status but just one component in bedside hemodynamic assessment, to be considered alongside other variables. For instance, Figure 7 presents an algorithm for hemodynamic assessment in cirrhotic patients with acute kidney injury, utilizing IJV for fluid tolerance assessment[33]. Future research should compare various techniques in different clinical settings to establish a standardized, practical method for routine use.

FOOTNOTES

Author contributions: Chayapinun V drafted the initial version of the manuscript; Assavapokee T and Koratala A have designed the manuscript; Assavapokee T and Koratala A have revised the manuscript for critical intellectual content.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Development and validation of a nomogram model for predicting the risk of pre-hospital delay in patients with acute myocardial infarction

Jiao-Yu Cao, Li-Xiang Zhang, Xiao-Juan Zhou

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Abstract

BACKGROUND

Acute myocardial infarction (AMI) is a severe cardiovascular disease caused by the blockage of coronary arteries that leads to ischemic necrosis of the myocardium. Timely medical contact is critical for successful AMI treatment, and delays increase the risk of death for patients. Pre-hospital delay time (PDT) is a significant challenge for reducing treatment times, as identifying high-risk patients with AMI remains difficult. This study aims to construct a risk prediction model to identify high-risk patients and develop targeted strategies for effective and prompt care, ultimately reducing PDT and improving treatment outcomes.

AIM

To construct a nomogram model for forecasting pre-hospital delay (PHD) likelihood in patients with AMI and to assess the precision of the nomogram model in predicting PHD risk.

METHODS

A retrospective cohort design was employed to investigate predictive factors for PHD in patients with AMI diagnosed between January 2022 and September 2022. The study included 252 patients, with 180 randomly assigned to the development group and the remaining 72 to the validation group in a 7:3 ratio. Independent risk factors influencing PHD were identified in the development group, leading to the establishment of a nomogram model for predicting PHD in patients with AMI. The model's predictive performance was evaluated using the receiver operating characteristic curve in both the development and validation groups.

RESULTS

Independent risk factors for PHD in patients with AMI included living alone, hyperlipidemia, age, diabetes mellitus, and digestive system diseases ($P < 0.05$). A

nomogram model incorporating these five predictors accurately predicted PHD occurrence. The receiver operating characteristic curve analysis indicated area under the receiver operating characteristic curve values of 0.787 (95% confidence interval: 0.716–0.858) and 0.770 (95% confidence interval: 0.660-0.879) in the development and validation groups, respectively, demonstrating the model's good discriminatory ability. The Hosmer–Lemeshow goodness-of-fit test revealed no statistically significant disparity between the anticipated and observed incidence of PHD in both development and validation cohorts ($P > 0.05$), indicating satisfactory model calibration.

CONCLUSION

The nomogram model, developed with independent risk factors, accurately forecasts PHD likelihood in AMI individuals, enabling efficient identification of PHD risk in these patients.

Key Words: Pre-hospital delay; Acute myocardial infarction; Risk prediction; Nomogram

Core Tip: The study developed a nomogram model to predict pre-hospital delay (PHD) in acute myocardial infarction (AMI) patients. Independent risk factors for PHD were identified, and a nomogram was constructed using these predictors. The model showed good discriminatory ability and satisfactory calibration. This nomogram can effectively identify PHD risk in AMI patients.

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INTRODUCTION

Acute myocardial infarction (AMI), a cardiovascular condition often stemming from coronary artery disease, arises when the abrupt blockage of the coronary artery disrupts blood circulation, leading to localized myocardial ischemic necrosis. Existing research underscores the critical impact of timely medical contact, revealing that every hour of delay increases the risk of death in patients with AMI by approximately 10%[1]. Swift restoration of blood flow in the infarct-related artery is pivotal for effective AMI treatment, with the efficacy of infarct-related artery recanalization treatment being significantly time-dependent. The shorter the duration between AMI onset and treatment, the more favorable the therapeutic outcomes[2].

The temporal aspect of AMI treatment encompasses pre-hospital delay time (PDT) and in-hospital delay time[3,4]. While measures such as optimizing hospital emergency procedures and establishing green channels have successfully reduced in-hospital delay time[5], PDT remains a challenge due to various influencing factors. Creating a universally applicable treatment protocol to minimize PDT proves challenging, given the diverse circumstances. Treating all patients with pre-hospital AMI with efficient measures poses a logistical challenge, potentially straining first aid resources and impacting the treatment of other emergency cases.

Therefore, the crux of shortening PDT lies in the identification of high-risk patients with AMI and the swift implementation of emergency measures[6]. This study aims to delve into the determinants of pre-hospital delay (PHD) in patients with AMI, with a specific focus on constructing a robust risk prediction model. The ultimate objective was to gain insights and leverage them for devising targeted and efficient strategies to mitigate PDT in patients with AMI, ensuring prompt and effective care.

MATERIALS AND METHODS

Research objects

This retrospective cohort study spanned from January 2022 to September 2022 and focused on patients with AMI admitted to a tertiary hospital in Anhui Province, China. The inclusion criteria mandated that patients were transported by ambulance and diagnosed with AMI based on clinical symptoms, electrocardiogram, and myocardial enzyme dynamic observation. The exclusion criteria comprised patients with missing data or mental disorders. The study received approval from the Institutional Review Board (IRB) of the research institution (ID: 2023-RE-124), and due to its retrospective nature, informed consent requirements were exempted by the IRB.

Data collection methods

Data encompassed diverse factors such as age, sex, coronary artery lesions, Killip classification, family monthly income, body mass index, stent count, comorbidities (hypertension, cerebral infarction, hyperlipidemia, diabetes, renal insufficiency, digestive system diseases), Timi classification, medical expenses payment method, history of AMI, onset time (daytime: 8:00–17:00, nighttime: 17:01–07:59), living arrangements, work status, heart failure, education level, marital status, alcohol consumption, smoking, atrial fibrillation—totaling 26 indicators. Predefined as the interval from myocardial infarction symptom onset to seeking medical care, PDT was set at 6 h, a threshold for thrombolytic therapy [7]. Thus, patients were categorized into two groups: PDT ≤ 6 h (non-PHD) and PDT > 6 h (PHD).

Statistical analysis

Data analysis utilized Epidata 3.1 and SPSS 23.0. Quantitative variables with normal distribution were presented as mean ± standard deviation; non-normally distributed variables were denoted as M(P25, P75), signifying the median value alongside the 25th and 75th percentiles. Counting data were expressed as case numbers and percentages. Independent risk factors influencing PHD were identified through univariate and multivariate logistic regression analysis. The nomogram model was constructed using R software (version 4.0.1), and its predictive efficacy was assessed using the receiver operating characteristic (ROC) curve. The degree of calibration of the nomogram model was evaluated through calibration curve and Hosmer–Lemeshow goodness-of-fit tests. Clinical applicability was assessed through decision curve analysis (DCA). $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of population characteristics between development and validation groups

Out of the total 252 patients with AMI, 84 (33.33%) experienced PHD. The study population was randomly divided into a development group ($n = 180$) and a validation group ($n = 72$) in a 7:3 ratio. Upon comparing demographic and clinical characteristics between the two groups, no statistically significant disparities were observed ($P > 0.05$), between both groups, indicating homogeneity (Table 1).

Univariate and multivariate analysis of PHD risk in patients with AMI

In the development group, univariate and multivariate Logistic regression methods were employed to identify risk factors associated with post-hospital discharge (PHD) in patients with AMI. Univariate analysis revealed significant associations ($P < 0.05$) with PHD for variables like living alone, nighttime onset, combined hypertension and hyperlipidemia, urban residence, age, combined diabetes, smoking, combined digestive system diseases, and female sex. Multivariate analysis identified living alone, hyperlipidemia, advancing age, diabetes, and digestive system diseases as independent risk factors for PHD in patients with AMI ($P < 0.05$), as detailed in Table 2.

Development of nomogram prediction model for PHD risk in patients with AMI

Construction of the nomogram prediction model for PHD risk in the development group involved utilizing the "rms" package in R software. Five predictors were identified through multivariate Logistic regression analysis, as depicted in Figure 1. The nomogram developed in this study is a valuable tool for assessing the risk of PHD in patients with AMI. The interpretation of the nomogram involves a systematic process. Each indicator in the nomogram corresponds to a specific vertical line that ascends from the respective score on the horizontal axis labeled "Points." Along each indicator's line, a specific score is assigned based on the patient's characteristics. Four specific scores from different indicators are added together to calculate the total score.

The total score is located on the horizontal axis labeled "Total Points." A vertical line is drawn downward from the total score to intersect with the axis labeled "Risk of Pre-hospital Delay." The value corresponding to the intersection point indicates the estimated risk of pre-hospital delay for the patient. As an example, consider a 65-year-old patient with the following scores: age (65 years): 60 points, hyperlipidemia: 27.5 points, digestive system diseases: 35 points, living with family (not living alone): 0 points. The total score for this patient would be 122.5 points. Locating 122.5 points on the "Total Points" axis and drawing a line downward intersects with the "Risk of Pre-hospital Delay" axis. The corresponding value on the "Risk of Pre-hospital Delay" axis (*e.g.*, 0.67 points) indicates the estimated risk of pre-hospital delay for this patient.

ROC curve analysis of the nomogram model

To evaluate the discrimination performance, the nomogram model's area under the ROC curve was calculated. In the development group, the area under the ROC curve was 0.787 (95% confidence interval: 0.716–0.858), and in the validation group, it was 0.770 (95% confidence interval: 0.660–0.879). These results signify favorable discrimination, as illustrated in Figure 2.

Calibration curve analysis of the nomogram model

The calibration curve and the Hosmer–Lemeshow goodness of fit test were used to assess the calibration degree of the nomogram model. The results from the Hosmer–Lemeshow goodness of fit test indicated no statistically significant deviation between the predicted probability of PHD from the nomogram model and the actual occurrence in both the development and validation groups ($P > 0.05$). This implies that the nomogram model exhibits favorable calibration, as

Table 1 Comparison of related data between development group and validation group, *n* (%)

Variable	Category	Total	Development group	Validation group	*P* value
n		252	180	72	
Sex (%)	Male	197 (78.2)	142 (78.9)	55 (76.4)	0.664
	Female	55 (21.8)	38 (21.1)	17 (23.6)	
Age, mean (SD)		61.09 (14.55)	60.94 (14.82)	61.46 (13.94)	0.798
Killip grade (%)	1	195 (77.4)	141 (78.3)	54 (75.0)	0.914
	2	42 (16.7)	29 (16.1)	13 (18.1)	
	3	10 (4.0)	7 (3.9)	3 (4.2)	
	4	5 (2.0)	3 (1.7)	2 (2.8)	
Monthly household income (%)	< 3000 yuan	125 (49.6)	82 (45.6)	43 (59.7)	0.125
	3000–5000 yuan	85 (33.7)	66 (36.7)	19 (26.4)	
	> 5000 yuan	42 (16.7)	32 (17.8)	10 (13.9)	
Number of stents placed, mean (SD)		1.47 (0.91)	1.40 (0.89)	1.64 (0.94)	0.059
Number of coronary artery lesions, mean (SD)		1.89 (0.79)	1.83 (0.79)	2.03 (0.79)	0.078
Combined with hypertension (%)	No	114 (45.2)	88 (48.9)	26 (36.1)	0.066
	Yes	138 (54.8)	92 (51.1)	46 (63.9)	
Combined with cerebral infarction (%)	No	227 (90.1)	166 (92.2)	61 (84.7)	0.072
	Yes	25 (9.9)	14 (7.8)	11 (15.3)	
Combined with hyperlipidemia (%)	No	214 (84.9)	156 (86.7)	58 (80.6)	0.221
	Yes	38 (15.1)	24 (13.3)	14 (19.4)	
Diabetes mellitus (%)	No	164 (65.1)	121 (67.2)	43 (59.7)	0.259
	Yes	88 (34.9)	59 (32.8)	29 (40.3)	
Combined with renal insufficiency (%)	No	227 (90.1)	162 (90.0)	65 (90.3)	0.947
	Yes	25 (9.9)	18 (10.0)	7 (9.7)	
Combined digestive system diseases (%)	No	217 (86.1)	155 (86.1)	62 (86.1)	1
	Yes	35 (13.9)	25 (13.9)	10 (13.9)	
Timi classification (%)	0	136 (54.0)	100 (55.6)	36 (50.0)	0.491
	1	15 (6.0)	11 (6.1)	4 (5.6)	
	2	27 (10.7)	21 (11.7)	6 (8.3)	
	3	74 (29.4)	48 (26.7)	26 (36.1)	
Payment method (%)	Self-paid	17 (6.7)	11 (6.1)	6 (8.3)	0.525
	Medical insurance reimbursement	235 (93.3)	169 (93.9)	66 (91.7)	
History of acute myocardial infarction (%)	No	242 (96.0)	175 (97.2)	67 (93.1)	0.126
	Yes	10 (4.0)	5 (2.8)	5 (6.9)	
Time of onset (%)	Daytime	110 (43.7)	73 (40.6)	37 (51.4)	0.117
	Nighttime	142 (56.3)	107 (59.4)	35 (48.6)	
Living alone (%)	No	227 (90.1)	162 (90.0)	65 (90.3)	0.947
	Yes	25 (9.9)	18 (10.0)	7 (9.7)	
Type of residence (%)	Rural	94 (37.3)	67 (37.2)	27 (37.5)	0.967
	Town	158 (62.7)	113 (62.8)	45 (62.5)	
Regular jobs (%)	No	170 (67.5)	120 (66.7)	50 (69.4)	0.671
	Yes	82 (32.5)	60 (33.3)	22 (30.6)	

History of heart failure (%)	No	227 (90.1)	165 (91.7)	62 (86.1)	0.183
	Yes	25 (9.9)	15 (8.3)	10 (13.9)	
Education level (%)	Junior high school and below	153 (60.7)	108 (60.0)	45 (62.5)	0.321
	Senior high school	45 (17.9)	36 (20.0)	9 (12.5)	
	University and above	54 (21.4)	36 (20.0)	18 (25.0)	
Marriage (%)	Married	228 (90.5)	165 (91.7)	63 (87.5)	0.114
	Divorce or widow	20 (7.9)	11 (6.1)	9 (12.5)	
	Unmarried	4 (1.6)	4 (2.2)	0 (0.0)	
Drinking (%)	No	177 (70.2)	125 (69.4)	52 (72.2)	0.663
	Yes	75 (29.8)	55 (30.6)	20 (27.8)	
Smoking (%)	No	133 (52.8)	93 (51.7)	40 (55.6)	0.576
	Yes	119 (47.2)	87 (48.3)	32 (44.4)	
Body mass index, mean (SD)		24.46 (3.35)	24.54 (3.37)	24.25 (3.33)	0.526
Combined with atrial fibrillation (%)	No	236 (93.7)	169 (93.9)	67 (93.1)	0.806
	Yes	16 (6.3)	11 (6.1)	5 (6.9)	

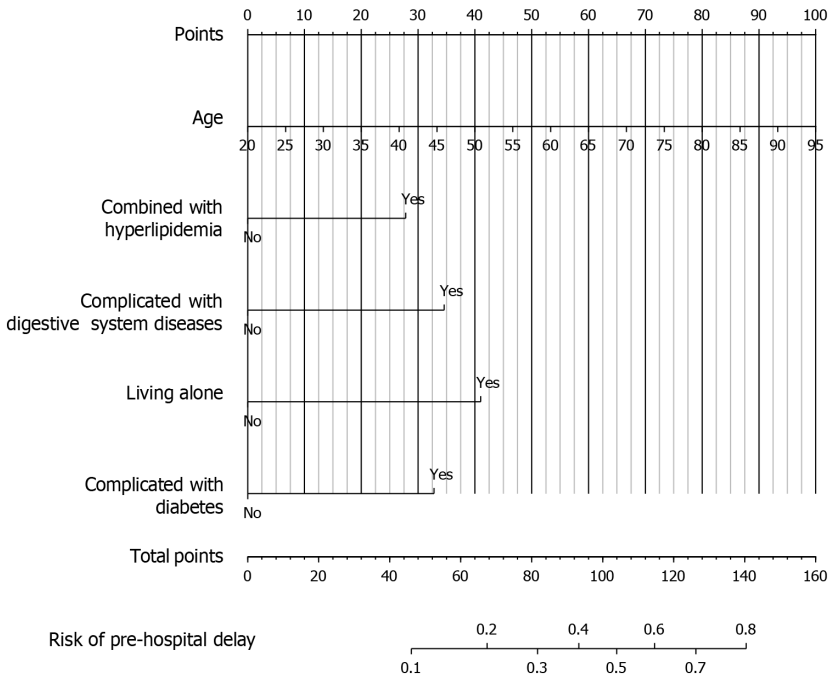

Figure 1 The nomogram prediction model for the risk of pre-hospital delay. Each indicator in the nomogram corresponds to a specific vertical line that ascends from the respective score on the horizontal axis labeled "Points." Along each indicator's line, a specific score is assigned based on the patient's characteristics. Four specific scores from different indicators are added together to calculate the total score. The total score is located on the horizontal axis labeled "Total Points." A vertical line is drawn downward from the total score to intersect with the axis labeled "Risk of Pre-hospital Delay." The value corresponding to the intersection point indicates the estimated risk of pre-hospital delay for the patient.

depicted in Figure 3.

Clinical applicability of the nomogram model

The clinical applicability of the nomogram model was assessed using the DCA curve. The DCA curve analysis indicated that the nomogram model achieved the highest clinical net rate when the threshold probability of PHD in the development group ranged from 0.09 to 0.68 and that in the validation group ranged from 0.16 to 0.59. This performance surpassed both "full intervention" and "no intervention" schemes, affirming the favorable clinical applicability of the nomogram model, as shown in Figure 4.

Table 2 Results of univariate and multivariate Logistic regression analysis on risk of pre-hospital delay in development group

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
BMI	0.956 (0.867, 1.050)	0.35		
Killip Grade 1	Reference			
Killip Grade 2	1.061 (0.429, 2.464)	0.894		
Killip Grade 3	3.143 (0.666, 16.536)	0.145		
Killip Grade 4	4.714 (0.440, 103.073)	0.211		
Timi Grade 0	Reference			
Timi Grade 1	1.855 (0.501, 6.615)	0.337		
Timi Grade 2	0.890 (0.294, 2.420)	0.826		
Timi Grade 3	1.012 (0.474, 2.109)	0.975		
Living alone	3.059 (1.138, 8.476)	0.027	4.654 (1.386, 16.957)	0.015
Daytime onset	Reference			
Nighttime onset	2.831 (1.434, 5.853)	0.004	2.200 (0.968, 5.188)	0.064
Combined with atrial fibrillation	1.875 (0.520, 6.497)	0.317		
Combined with hypertension	2.862 (1.493, 5.649)	0.002	1.990 (0.906, 4.473)	0.089
Combined with hyperlipidemia	2.467 (1.024, 5.957)	0.042	3.151 (1.095, 9.373)	0.035
Have a regular job	0.791 (0.395, 1.541)	0.497		
Number of diseased coronary artery	1.109 (0.743, 1.656)	0.61		
Marital status: married	Reference			
Marriage: Divorced or widowed	0.792 (0.168, 2.864)	0.739		
Marriage: Unmarried	0.704 (0.034, 5.648)	0.764		
Prior history of AMI	3.361 (0.542, 26.068)	0.191		
Family monthly income < 3000 yuan	Reference			
The monthly income of the family = 3000–5000 yuan	0.922 (0.449, 1.872)	0.822		
Family monthly income > 5000 yuan	1.560 (0.660, 3.636)	0.304		
Type of residence: town	0.387 (0.201, 0.737)	0.004	0.576 (0.258, 1.281)	0.175
Complicated with cerebral infarction	1.691 (0.533, 5.112)	0.353		
Age	1.043 (1.020, 1.069)	< 0.001	1.034 (1.004, 1.065)	0.027
Complicated with renal insufficiency	1.845 (0.668, 4.959)	0.225		
Complicated with diabetes	3.211 (1.662, 6.278)	0.001	3.208 (1.466, 7.228)	0.004
Education level is junior high school or below	Reference			
High school education	1.669 (0.766, 3.610)	0.193		
Education level is university or above	0.417 (0.146, 1.035)	0.076		
Smoking	0.404 (0.207, 0.771)	0.007	0.682 (0.279, 1.652)	0.395
Complicated with digestive system diseases	2.733 (1.154, 6.533)	0.022	3.937 (1.433, 11.236)	0.009
Complicated with heart failure	1.490 (0.478, 4.355)	0.471		
Female sex	2.737 (1.309, 5.753)	0.007	1.419 (0.531, 3.776)	0.482
Drinking	0.841 (0.413, 1.659)	0.622		
Payment method: medical insurance reimbursement	1.252 (0.347, 5.886)	0.747		
Number of stents placed	1.300 (0.916, 1.856)	0.142		

AMI: Acute myocardial infarction; BMI: Body mass index; OR: Odds ratio.

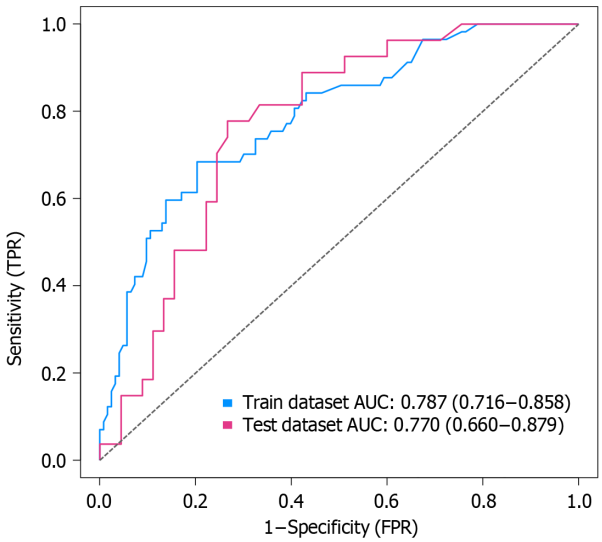

Figure 2 Receiver operating characteristic curve analysis of the nomogram model. The figure displays the receiver operating characteristic (ROC) curve analysis of the developed nomogram model. The area under the ROC curve (AUC) is used as a measure of the model's discriminatory ability. The false positive rate is plotted on the x-axis, while the true positive rate is plotted on the y-axis. The AUC values indicate the accuracy of the model in distinguishing between individuals who experienced pre-hospital delay and those who did not. A higher AUC value suggests a better predictive performance of the model. TPR: True positive rate; FPR: False positive rate.

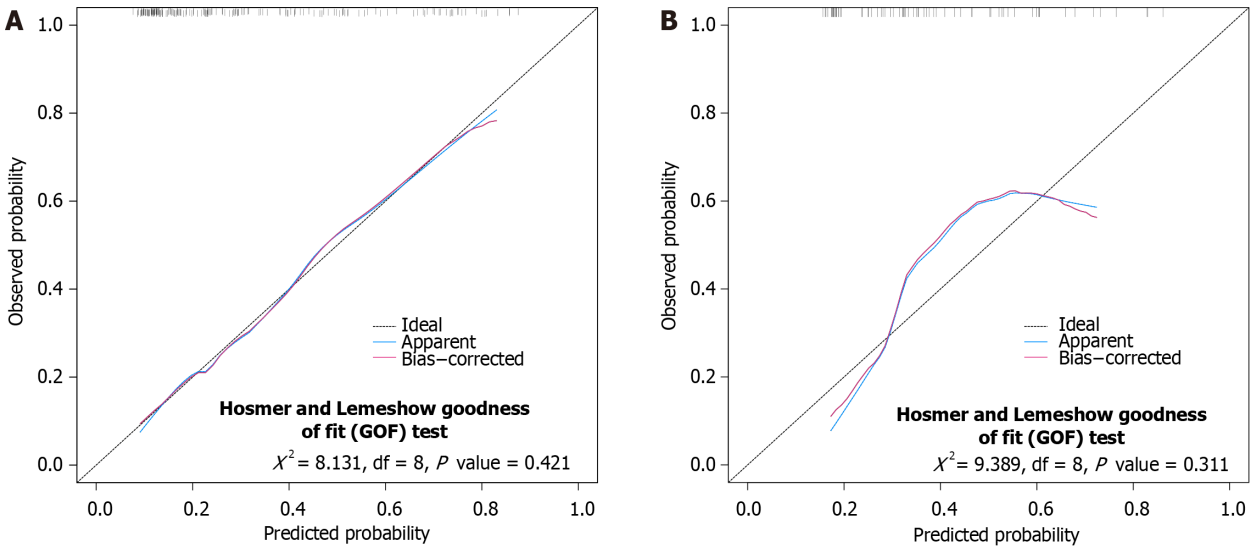

Figure 3 Calibration curve of the nomogram model. A and B: The figure illustrates the calibration curve analysis of the developed nomogram model in both the development group (A) and the validation group (B). The calibration curve assesses the agreement between the predicted and observed probabilities of pre-hospital delay likelihood. The x-axis represents the predicted probabilities, while the y-axis represents the observed probabilities. The goodness-of-fit is evaluated to determine the accuracy of the model. A well-calibrated model would show a close alignment of the predicted probabilities with the observed probabilities along the 45-degree diagonal line. GOF: Goodness-of-fit.

DISCUSSION

AMI represents a common emergency with high morbidity and mortality, particularly affecting a younger demographic, posing a substantial threat to patients' lives[8]. Studies have underscored the significance of recanalization in restoring cardiovascular supply, enhancing cardiac oxygen delivery, and improving patient prognosis[9]. However, the success of reperfusion therapy is contingent upon its timeliness; the earlier the patient reaches the hospital, the better the treatment outcomes[10]. Despite the recognized importance of prompt intervention, delays in treatment time, including PHD and in-hospital delay, contribute to a significant proportion of cases where myocardial infarction patients fail to receive timely treatment[11]. Currently, 30%-40% of patients with AMI experience PHD, presenting a challenge due to numerous

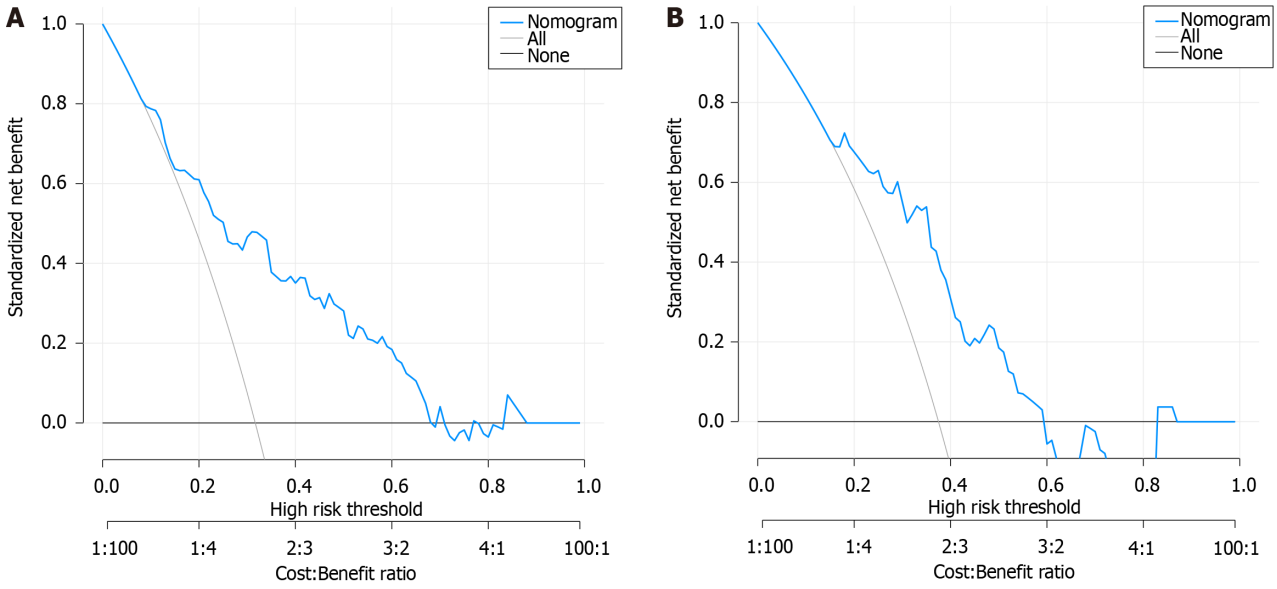

Figure 4 Decision curve analysis curve of the nomogram model. A and B: The figure presents the decision curve analysis (DCA) curve of the developed nomogram model in both the development group (A) and the validation group (B). The DCA curve measures the net benefit of the model by plotting the threshold probability on the x-axis against the net benefit on the y-axis. The net benefit is calculated by weighting the true-positive and false-positive classifications based on the clinical consequence of each classification. The DCA curve assesses the clinical usefulness of the nomogram model by comparing it to the strategies of treating all or no patients with the condition of interest. A higher net benefit value indicates a better clinical utility of the model.

interference factors that impede the development of a unified and efficient treatment process[12,13]. To address this challenge and reduce the time interval from symptom onset to percutaneous coronary intervention, it is imperative to identify individuals at high risk before discharge and administer specific interventions to enhance the efficacy of treatment for myocardial infarction. In the present study, potential risk factors influencing the occurrence of post-hospital discharge were identified through univariate analysis and subsequently adjusted using multivariate logistic regression analysis. Consequently, five distinct risk factors were identified as independent predictors of PHD in patients with AMI: advanced age, living alone, comorbidity with digestive system diseases, comorbidity with hyperlipidemia, and comorbidity with diabetes.

This study has provided evidence supporting the role of age as an independent determinant of PHD in patients with AMI, aligning with findings reported by Ouellet *et al*[14]. Atypical symptoms in the elderly were identified as a significant cause of PHD[15]. Older patients, often burdened with comorbidities such as hypertension, diabetes, and cerebrovascular disease, may present with atypical symptoms and symptoms of pre-infarction angina pectoris, contributing to a misperception of a general mild disease. Additionally, traditional ideas influencing the elderly's choice to be sent to the hospital by their children can lead to delays in medical treatment. This hesitation, especially prevalent in cases where children are not around to assist, may result in the use of self-administered oral drugs or waiting for symptoms to naturally disappear, further increasing the risk of PHD with serious consequences[16]. The study substantiates the association between living alone and an elevated risk of PHD, establishing it as an independent risk factor.

The challenges posed by China's burgeoning aging population, marked by a rising number of elderly individuals residing alone and empty nesters, necessitate innovative approaches to address healthcare concerns, particularly in cases of acute and severe illnesses[17,18]. For patients living alone, the potential delay in medical treatment due to the inability to take necessary self-help measures, especially in cases affecting their activities, poses a serious risk, with potential life-threatening consequences. In this context, the study highlights the potential utility of remote monitoring systems, such as smart watches and bracelets, to control the health of elderly individuals living alone in real-time. This technological intervention holds promise in effectively reducing the risk of PHD in patients living alone, thereby enhancing timely medical intervention and improving outcomes.

The study also brings attention to the significant impact of co-occurring digestive system diseases as an autonomous risk factor for PHD in patients with AMI. Diseases like chronic gastritis and gastrointestinal ulcers are identified for their potential to cause pain and mask symptoms of myocardial infarction[19], leading to missed treatment opportunities. To address this, the study advocates for tailored AMI health education for patients with digestive system diseases, particularly ulcer diseases. Concrete measures proposed include the preparation of a basic knowledge manual about heart disease, emphasizing causes, symptoms, and preventive measures. Additionally, the involvement of medical staff for in-home health talks, encouraging participation in mutual support groups, and imparting knowledge on developing good daily habits are suggested strategies to empower the elderly living alone with digestive system diseases to better understand and cope with heart disease.

Furthermore, the study substantiates a positive association between hyperlipidemia and the susceptibility to PHD among patients with AMI. This finding aligns with a cross-sectional investigation on PHD in patients with AMI in Saudi Arabia, as reported by Alahmadi *et al*[20]. Hyperlipidemia, a common cause of AMI, is elucidated as a contributor to atherosclerosis, leading to the formation of lipid plaques on arterial walls. The instability of these plaques can result in

rupture and thrombus formation, culminating in the occurrence of AMI. The study underscores the multifaceted impact of hyperlipidemia on vascular function, inducing endothelial cell injury and inflammatory reactions, ultimately affecting the occurrence and prognosis of AMI and increasing the risk of PHD. Previous studies[21-23] have highlighted prolonged PDT in patients with AMI with diabetes, aligning with the current study's findings indicating that diabetes can increase the risk of PHD in patients with AMI. The study by Ängerud *et al*[24] emphasized a significantly longer median PDT in diabetic patients compared to non-diabetic patients (75 min), suggesting the need for targeted strategies to address the unique challenges faced by this subgroup. Additionally, the study in China proposed that the atypical presentation of chest pain symptoms in diabetic patients, with a higher proportion of NSTEMI patients, contributes to the PHD risk in this population[25].

The cumulative evidence from this study highlights the necessity for comprehensive strategies addressing the diverse risk factors influencing PHD in patients with AMI, including technological interventions, tailored education programs, and targeted management approaches for specific comorbidities. The integration of clinical prediction models into medical practice, particularly nomograms, has become pivotal in risk and benefit assessments, providing a more objective and precise means of information acquisition[26,27]. Within cardiovascular research, nomograms have proven effective in predicting various outcomes, ranging from in-hospital mortality to the risk of specific complications post-diagnosis[28-31]. Despite these advancements, there exists a notable gap in literature pertaining to nomogram studies specifically examining the risk of post-hospital discharge in patients with AMI. Addressing this void, our study utilized univariate and multivariate Logistic regression to identify independent risk factors for PHD in patients with AMI, culminating in the development of a nomogram model tailored to predict this risk. Notably, our findings underscore the nomogram model's favorable calibration, discrimination, and clinical applicability, as evidenced by the Hosmer-Lemeshow goodness of fit test, ROC curve analysis, and DCA curve.

The nomogram model developed in this study fills a crucial gap in predicting the risk of PHD in patients with AMI, providing a valuable tool for rapid risk assessment and more targeted treatment strategies. By identifying high-risk patients, the nomogram facilitates swift and effective intervention, ultimately enhancing patient prognosis.

However, it is imperative to acknowledge certain limitations inherent in this study. The retrospective nature of the research introduces potential issues such as incomplete data, low data quality, and case selection bias, which may impact result accuracy. Additionally, the study's reliance on data from a single medical institution raises concerns about its representativeness for broader populations. The limited sample size and consideration of only a subset of predictors further necessitate caution in generalizing the results. Future endeavors should prioritize large-scale, multi-center, and multi-regional studies to enhance result representativeness and generalizability.

CONCLUSION

In conclusion, this study, despite its limitations, successfully identified five independent risk factors associated with PHD in patients with AMI. The subsequent construction of a nomogram model exhibited robust predictive value, offering valuable insights for pre-hospital treatment strategies in patients with AMI and mitigating the risk of PHD. The results emphasize the significance of incorporating nomograms into clinical practice for enhanced risk assessment and tailored interventions in the context of AMI.

ARTICLE HIGHLIGHTS

Research background

Acute myocardial infarction (AMI), a lethal heart condition, results from coronary artery blockages that cause myocardial ischemia and necrosis. Treatment delays heighten death risks, making prompt medical response critical. This study focuses on reducing pre-hospital delays by identifying high-risk AMI patients, developing a risk prediction model, and implementing tailored strategies for timely care.

Research motivation

The timely management of AMI is crucial for improving patient outcomes, yet pre-hospital delay time (PDT) poses a significant challenge, leading to increased morbidity and mortality rates. This research is motivated by the need to understand the determinants of PDT in AMI patients and develop a robust risk prediction model. By identifying high-risk individuals and implementing targeted strategies to reduce PDT, this study aims to enhance the delivery of prompt and effective care. Its significance lies in addressing a critical knowledge gap in cardiovascular medicine and offering practical solutions to optimize AMI treatment outcomes for future research in this field.

Research objectives

The main objective is to investigate determinants of pre-hospital delay (PHD) in AMI patients and construct a risk prediction model. Realizing these objectives has significant implications for future research in this field, allowing refinement of models, development of evidence-based guidelines, and optimization of AMI treatment strategies for improved patient outcomes.

Research methods

This retrospective cohort study investigated determinants of PHD in AMI patients and developed a risk prediction model. Data on 26 indicators were collected from AMI patients admitted to a tertiary hospital in Anhui Province, China. Statistical analysis involved logistic regression, nomogram modeling, receiver operating characteristic curve analysis, calibration tests, and decision curve analysis. The study contributes to advancing AMI management research.

Research results

This study identified risk factors for post-hospital discharge in acute myocardial infarction patients. Living alone, hyperlipidemia, age, diabetes, and digestive system diseases were significant predictors. A nomogram model accurately predicted the risk of post-hospital discharge. This model can help healthcare professionals identify high-risk patients and provide targeted interventions, but further validation is needed in larger populations.

Research conclusions

This study concludes that the newly developed nomogram model, incorporating independent risk factors, accurately predicts the likelihood of post-hospital discharge in acute myocardial infarction patients. This model offers a valuable tool for efficiently identifying individuals at risk of post-hospital discharge, providing potential benefits for targeted interventions and improved patient outcomes in clinical practice.

Research perspectives

Future research should address limitations of the retrospective design, limited sample size, and subset of predictors. Large-scale, multi-center studies with comprehensive data are needed to enhance generalizability. Exploring additional risk factors and refining predictive models can improve accuracy for forecasting post-hospital discharge outcomes in acute myocardial infarction patients, benefiting clinical decision-making.

FOOTNOTES

Co-first authors: Jiao-Yu Cao and Li-Xiang Zhang.

Author contributions: Cao JY and Zhang LX contributed equally to this work; Cao JY and Zhou XJ designed the research study; Cao JY and Zhang LX performed the research; Zhang LX contributed analytic tools; Cao JY and Zhang LX analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study obtained ethical approval from the Medical Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China, under the approval ID: 2023-RE-124.

Informed consent statement: Due to the retrospective nature of the study, the necessity for informed consent from the study participants was exempted by the Medical Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

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CASE REPORT

Spontaneous coronary artery rupture after lung cancer surgery: A case report and review of literature

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Abstract

BACKGROUND

Spontaneous coronary artery rupture (SCAR) is a rare and life-threatening complication after lung cancer surgery. We present a case of SCAR following left upper lobectomy, successfully managed through emergency thoracotomy and coronary artery ligation.

CASE SUMMARY

A 61-year-old male patient underwent left upper lobectomy and mediastinal lymph node dissection for lung cancer. The surgery was performed using single-port video-assisted thoracoscopic surgery, and there were no observed complications during the procedure. However, 19 h after surgery, the patient experienced chest discomfort and subsequently developed severe symptoms, including nausea, vomiting, and a drop in blood pressure. Urgent measures were taken, leading to the diagnosis of SCAR. The patient underwent emergency thoracotomy and coronary artery ligation, successfully stopping the bleeding and stabilizing the condition. Despite postoperative complications, the patient made a successful recovery and was discharged from the hospital.

CONCLUSION

SCAR is a rare but life-threatening complication following lung cancer surgery. Immediate thoracotomy has been shown to be a life-saving measure, while stenting is not the preferred initial approach.

Key Words: Spontaneous coronary artery rupture; Lung cancer; Surgery; Case report

Core Tip: Spontaneous coronary artery rupture (SCAR) is a rare but life-threatening complication that may arise following lung cancer surgery. Close monitoring of patients for acute chest pain after resection is paramount. Rapid evaluation, timely intervention, and thorough examinations are critical in attaining favorable treatment outcomes. In cases where SCAR is suspected, immediate thoracotomy should be considered as an emergency life-saving procedure, while stent implantation is not the preferred initial approach. Maintaining awareness of SCAR as a potential complication and taking prompt action by thoracic surgeons can significantly enhance patient survival and facilitate recovery.

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INTRODUCTION

Coronary artery rupture (CAR) has various causes, including atherosclerosis, aneurysm, trauma, infection, and vascular anomalies[1-11]. Spontaneous CAR (SCAR) denotes unexplained CAR, with unclear etiology and pathology[12]. Consequently, SCAR has limited literature coverage[8,13-22]. Only two reports discuss coronary bleeding after pulmonary surgery[18,22]. One case involved a 68-year-old man with left circumflex coronary artery bleeding on postoperative day 4, managed successfully through left thoracotomy[22]. The other concerned a 58-year-old man experiencing SCAR 3 mo after surgery; emergency thoracotomy revealed a ruptured left coronary artery ramus branch, and the patient succumbed to it[18].

No reports have documented survival after SCAR within 24 h of lung cancer surgery. This study presents the first such case: A patient with significant pericardial effusion and cardiogenic shock who underwent emergent left thoracotomy, proximal left anterior descending branch ligation, and suturing. As a result, the patient successfully recovered and was discharged without complications.

CASE PRESENTATION

Chief complaints

A 61-year-old Chinese man presented to the thoracic surgery clinic with left-sided chest pain lasting 1 mo.

History of present illness

The patient has had intermittent left-sided chest pain for 1 mo. A nodule was found in the upper lobe of the left lung during the thoracic surgery clinic evaluation, suggesting a possible tumor.

History of past illness

The patient denied any surgeries or comorbidities.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.4°C; blood pressure, 135/94 mmHg; heart rate, 79 beats/min; respiratory rate, 20 breaths/min. The patient has no palpable lymph nodes in the neck and supraclavicular region. The chest wall appeared normal, without tenderness. The breath sounds in both lungs were clear, and the heartbeat was regular without any audible murmurs. The patient had normal limb mobility. Digital anal examination was not performed.

Laboratory examinations

Blood chemistry, cardiac enzymes, tumor markers were normal.

Imaging examinations

Computed tomography (CT) revealed a 25.4 mm × 19 mm solid nodule in the left lung apex. Electrocardiography (ECG) and 24-h Holter monitoring were normal. Echocardiography found 69.7% left ventricular ejection fraction and no other issues (Figure 1).

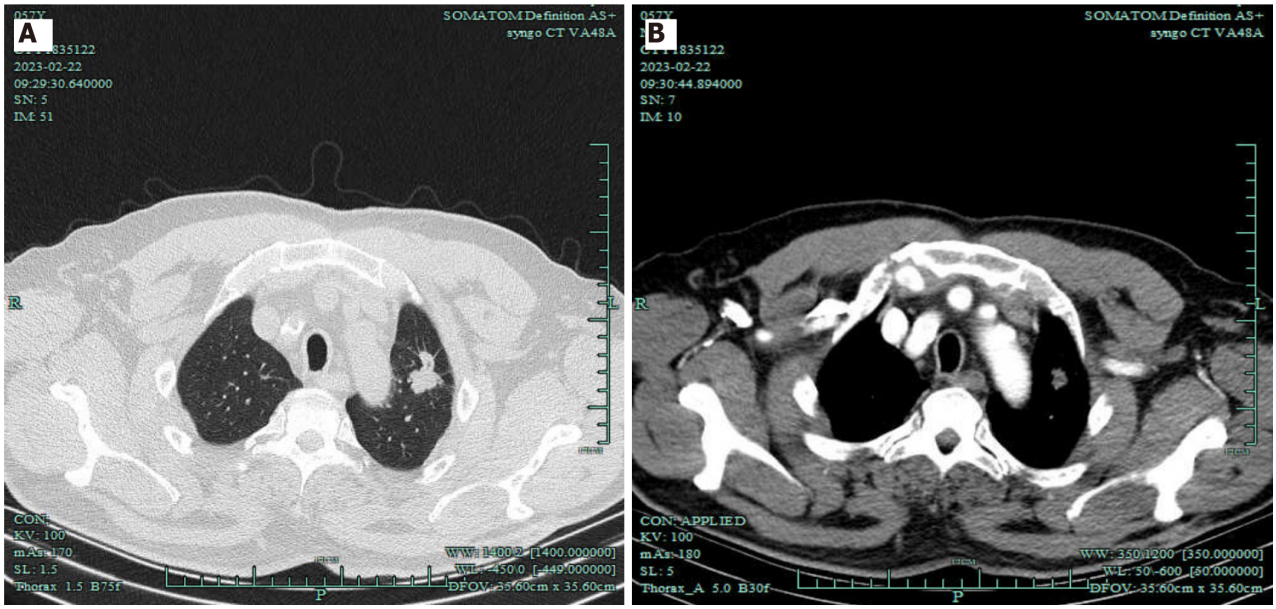

Figure 1 Imaging of pulmonary masses. A: Chest computed tomography (CT); B: Chest CT angiography revealed 50 HU.

FINAL DIAGNOSIS

Based on the patient's medical history, the primary diagnosis was malignant lung tumor (adenocarcinoma, sT1bN0M0/IA2). Additionally, the patient was diagnosed with SCAR.

TREATMENT

On postoperative day 2, bedside echocardiography indicated no pericardial bleeding or myocardial ischemia, and coronary angiography displayed no issues (Figure 2). The patient experienced postoperative complications, including pulmonary infection, acute renal failure, and gastrointestinal infection. However, with active treatment, the patient successfully recovered and was discharged from the hospital after 10 d.

OUTCOME AND FOLLOW-UP

The patient is still alive and in good health.

DISCUSSION

SCAR is a rare life-threatening condition that involves rupture of a normal coronary artery[13]. Symptoms vary based on rupture site; some patients quickly deteriorate due to cardiac tamponade and shock, leading to sudden death[1,13-14]. SCAR occurring within 24 h of video-assisted thoracoscopic left upper lobectomy, followed by successful rescue, is rarer. Our patient recovered and resumed a normal life (Figure 3 and Video).

Cardiac tamponade after lung resection has been documented. Causes include: (1) Residual pulmonary veins retracting into pericardial space, causing intrapericardial hemorrhage[23]; (2) division of aberrant bronchial arteries during surgery, retracting proximal ends into pericardium, causing tamponade[24]; and (3) injury to the ascending aorta during right upper mediastinal lymph node dissection, possibly causing pericardial bleeding[25]. Based on the clinical presentation and relevant examination results, we primarily attributed it to SCAR for the following reasons. Firstly, there was no evidence of coronary heart disease or a family history of the condition in the preoperative examination and medical history. During surgery, we observed no pericardial defects caused by sharp instruments, electrocautery burns, erosion, or local infection. Additionally, postoperative coronary angiography revealed no abnormalities, ruling out the possibility of hemorrhage caused by ruptured atherosclerotic coronary arteries. Since no underlying causes were identified, we consider the CAR to be spontaneous.

Prior research on coronary artery bleeding shows that pressure between the sternum and spine can rapidly raise coronary artery wall pressure. Excessive pressure beyond arterial compliance might trigger rupture[26]. In this case, symptoms like nausea, vomiting, chest discomfort, and hypotension arose 19 h after surgery. Hence, we theorize that the abrupt intrathoracic pressure surge from nausea and vomiting possibly caused SCAR.

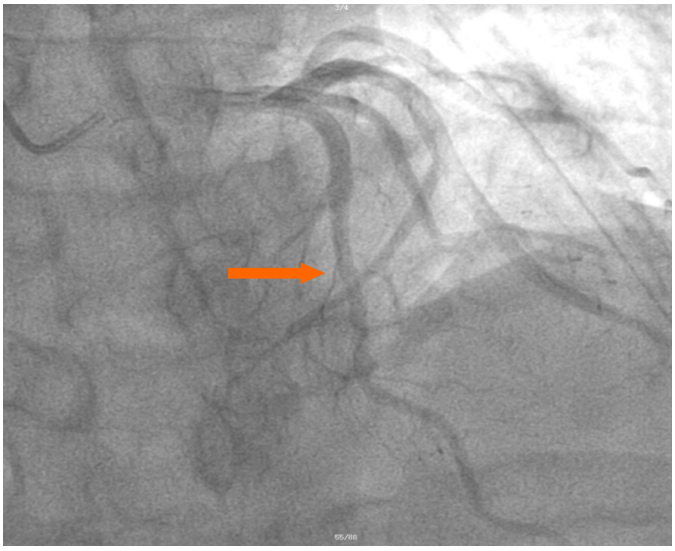

Figure 2 Partial views of coronary angiography were performed after hemostasis completion, and no abnormalities were observed in the coronary arteries (arrow).

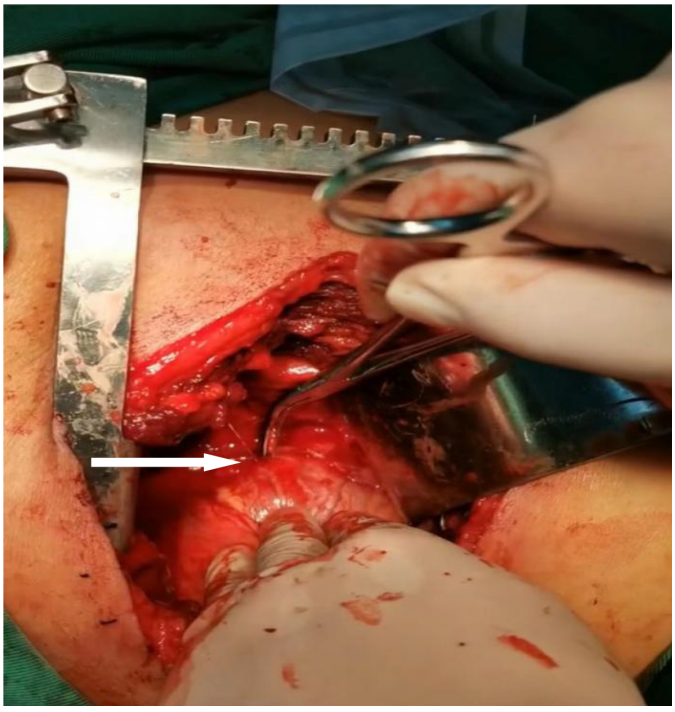

Figure 3 View of the operative field. After opening, we revealed a bleeding point in the left anterior descending coronary artery (arrow).

Typical SCAR clinical features mimic acute coronary syndrome, aortic dissection, or cardiac tamponade[15,27]. Symptoms vary by rupture site. Left or distal right CAR leads to intrapericardial bleeding, causing tamponade and shock with hypotension, tachycardia, anxiety, altered consciousness, or sudden death. Proximal right CAR often results in subepicardial hematoma but not pericardial bleeding[15,28].

In this case, the patient primarily experienced acute chest pain and hypotension, which align with the acute clinical presentation of SCAR. Therefore, SCAR should be considered as a differential diagnosis for post-pulmonary resection pericardial tamponade.

Common diagnostic methods for CAR include chest X-ray, ECG, echocardiography, and cardiac enzyme profiles. Some cases exhibit abnormal ECG and positive cardiac biomarkers, but most have significant pericardial effusion[19]. Transthoracic echocardiography (TTE) and CT angiography (CTA) are key in diagnosing SCAR. TTE confirms pericardial tamponade post-pericardiocentesis, while CTA excludes aortic dissection and other cardiovascular ruptures[3,15,18]. Rapid SCAR progression and similarity to acute coronary syndrome can lead to overlooked or delayed diagnosis. Selective coronary angiography provides definitive diagnosis, but unstable patients cannot undergo the procedure. Thus, SCAR is often diagnosed during surgery.

Treating SCAR involves factors like bleeding site, severity, patient age and condition, and medical response plan. If angiography pinpoints rupture, stent implantation or coil embolization can manage bleeding[1,3,17,29]. However, as most SCAR patients have tamponade and shock, angiography might not work. Timely identification *via* TTE and chest CTA is crucial for rapid surgical intervention.

For emergency surgery, selecting the right incision matters. Urgent thoracotomy needs a left anterolateral approach; stable cases use midline sternotomy. Treatments include ligation, suturing, patch repair, and revascularization. Distal artery ruptures can be ligated, causing minor heart damage. Proximal ruptures may lead to extensive infarction and heart failure, so distal revascularization is vital[30].

If the bleeding artery is not found, pericardium or patches can cover, reinforced by medical glue[2,3,19]. Despite the grave outlook of SCAR, many recover well *via* emergency surgery or intervention[3]. Based on Ellis' classification[31], this SCAR could be type III, linked to 63% tamponade incidence, requiring thoracotomy, with 19% mortality. Limited data exists on coronary bleeding treatment; some cases used cardiopulmonary bypass (CPB) and cardiac arrest[1,15,19]. Successful surgery removing hematoma, resolving symptoms, absence of severe plaques or artery stenosis permits safe on-beating-heart repair, avoiding the drawbacks of CPB.

Our patient had bedside echocardiography, confirming rising pericardial effusion. Emergency left anterolateral thoracotomy within 2 h revealed the bleeding site, preventing tamponade, and saving the patient's life.

Although the patient was discharged safely and recovered his health, to date, there is a lack of large-scale research data regarding the treatment of SCAR. Therefore, it is important to determine the most appropriate medical intervention measures definitively.

CONCLUSION

Although SCRA is rare, it is vital for thoracic surgeons to watch for acute chest pain after lung resection. Monitoring vital signs, timely observation, and comprehensive examination aid rapid, accurate decisions. SCAR should be among post-resection differential diagnosis. If SCAR arises after surgery, immediate thoracotomy boosts survival, and stenting is not preferred initially.

FOOTNOTES

Author contributions: Ruan YD contributed to manuscript writing and editing, and data collection and analysis; Han JW contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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