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EDITORIAL

Ultrasound unveiling: Decoding venous congestion in heart failure for precision management of fluid status

Davide Ramoni, Federico Carbone, Fabrizio Montecucco

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Abstract

This editorial discusses the manuscript by Di Maria *et al*, published in the recent issue of the *World Journal of Cardiology*. We here focus on the still elusive pathophysiological mechanisms underlying cardio-renal syndrome (CRS), despite its high prevalence and the substantial worsening of both kidney function and heart failure. While the measure of right atrial pressure through right cardiac catheterization remains the most accurate albeit invasive and costly procedure, integrating bedside ultrasound into diagnostic protocols may substantially enhance the staging of venous congestion and guide therapeutic decisions. In particular, with the assessment of Doppler patterns across multiple venous districts, the Venous Excess Ultrasound (VExUS) score improves the management of fluid overload and provides insight into the underlying factors contributing to cardio-renal interactions. Integrating specific echocardiographic parameters, particularly those concerning the right heart, may thus improve the VExUS score sensitivity, offering perspective into the nuanced comprehension of cardio-renal dynamics. A multidisciplinary approach that consistently incorporates the use of ultrasound is emerging as a promising advance in the understanding and management of CRS.

Key Words: Cardio-renal syndrome; Fluid overload; Heart failure; Ultrasound assessment; Venous congestion; Venous excess ultrasound score

Core Tip: While conventional approaches of managing fluid overload in heart failure have long relied on clinical examination, there is room to incorporate patient phenotyping and predict the development of cardio-renal syndrome. We here discuss implementation of the multi-parameter Venous Excess Ultrasound scoring system, which is helpful in avoiding missteps in the assessment and therapeutic decision-making processes. Our aim is to emphasize the emerging role of these feasible, safe and low-cost tools that are easy to implement in clinical practice. Integrating echocardiographic parameters with thorough clinical assessments could provide a comprehensive approach to managing cardio-renal syndrome.

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INTRODUCTION

The article by Di Maria *et al*[1], recently published in the *World Journal of Cardiology*, emphasizes the significance of ultrasound as a diagnostic tool for assessing and managing fluid overload. Venous congestion and worsening of kidney function are common and often concomitant findings in patients with heart failure (HF). While they are traditionally approached with clinical experience, medical examination alone has been proven to be insufficient for assessing venous congestion and fluid overload status in complex scenarios. Implementing clinical practice with instrumental approaches is now becoming essential in HF and kidney disease, especially in acute-on-chronic conditions. Among these approaches, ultrasonography is emerging as the standard of practice for daily bedside evaluation and therapeutic decision-making. Advances in methodology are bringing ultrasound performance closer to that of right heart catheterization without any procedure-related risk. The intrinsic properties of ultrasonography (*e.g.* dynamism and reproducibility) may also confer the potential to reveal yet-hidden pathophysiological mechanisms linking volume overload in HF and kidney injury.

VENOUS CONGESTION AND CARDIORENAL INTERACTION

Overview and outlook

Whether HF may generate or precipitate impairment of kidney function, and *vice versa*, is undoubtedly a common finding affecting approximately 30-60% of HF patients[2,3]. The so-called cardio-renal syndrome (CRS) encompasses a broad spectrum of pathophysiologically distinct processes, where worsening renal function stands as the central tenet and ultimately drives the prognosis[4,5]. In this context, a thorough understanding of the role of venous congestion in shaping the development of CRS holds substantial promise for refining its management strategies. Recent insights are challenging the classical view of renal dysfunction in congestive HF as secondary to hypoperfusion, reduced systemic blood pressure, and/or impaired left ventricular function. As highlighted by the ESCAPE trial in 2008, the cardiac index does not account entirely for the baseline glomerular filtration rate (GFR)[6], resulting in somewhat unpredictable responses to loop diuretics among patients[7,8]. Similarly, a rise in the blood urea nitrogen/creatinine ratio in HF should not deter from treating congestion – when present – as the worsening of renal function frequently arises amid volume overloads. Both cardiac output and volume overload may indeed trigger a vicious cycle sustained by neurohormonal adaptations (*i.e.*, sympathetic nervous system and renin-angiotensin-aldosterone system) that ultimately increase cardiac work and afterload through an inotropic effect and arterial vasoconstriction, respectively. Whatever the *primum movens* is, the consequent reduction in renal perfusion exacerbates sodium retention and venous congestion[9,10]. Whether isolated or concomitant, right ventricular (RV) dysfunction poses further challenges as the rise in central venous pressure (CVP) has the potential to decrease GFR. Diuretic therapy plays a role in RV dysfunction, independently of cardiac output, with a double effect on renal venous pressure and ventricular interdependence[11,12]. However, the current extensive use of CVP for guiding fluid therapy lacks substantial evidence[13]. Finally, the decompensated HF scenario commonly involves splanchnic veins with a progressive rise in intra-abdominal pressure that further contributes to renal venous hypertension and a rise in cardiac filling pressure[14,15].

Venous excess ultrasound assessment

The use of bedside ultrasonography for fluid status assessment is established in current practice but is still limited to a one-venous region focus, mainly on the inferior vena cava (IVC). This approach limits an accurate estimation of left ventricle preload as IVC dilation diagnostic efficacy was found to be suboptimal and fails to quantify the extent of upstream venous congestion such as liver, gut, and kidneys[16]. Recognizing venous congestion – and the underlying patterns – before clinically evident is an unmet clinical need that would substantially impact a patient's prognosis and healthcare system running. The question is whether ultrasound may accomplish that without highly specialized skills. Doppler flow patterns alone may aid in grading the extent of venous congestion without insights on the underlying cause. In 2020, the Venous Excess Ultrasound (VExUS) score was introduced as a multi-parameter score able to stratify congested HF failure for severity and the risk of developing acute kidney injury (AKI)[16,17]. This scoring system

includes a 4-step protocol, ranging from grades 0 to 3. It not only assesses the IVC diameter but also evaluates the severity of venous congestion in three target organs using color Doppler and pulsed-wave Doppler in hepatic, portal, and renal veins. Hence, it has the potential to greatly contribute to a deeper comprehension of the frequently overlooked issue of venous congestion[18]. A correlation between the VExUS score and AKI in patients with acute coronary syndrome was emphasized in a prospective study[19]. Notably, an enhancement in renal function was linked to an improvement in the VExUS score grade, as demonstrated in patients admitted to the intensive care unit who experienced more days free from renal replacement therapy[20]. Once validated, the VExUS score is expected to substantially enhance clinical practice by offering valuable insights for clinical decision-making[21]. Moreover, the VExUS score might offer the opportunity to phenotype HF and the related risk of AKI, including the elusive potential of right HF. In this context, integrating the VExUS Score with a focus on right heart ultrasound patterns would be relevant, as right heart dilation and dysfunction are likely associated with CRS, especially when stemming from severe congestion[11]. The VExUS score already exhibits substantial reliability in correlating with venous congestion, right atrial pressure, assessed through right catheterization, and portal vein flow[22-24]. However, the prognostic value of the VExUS score has not yet been validated, despite some insight from the monophasic intrarenal venous pattern and high pulsatility ratio of the portal vein[25,26].

CONCLUSION

The pathophysiologic mechanisms contributing to CRS remain widely unexplained and underscore the limit of a traditional approach based on clinical experience. The VExUS score is emerging as an intriguing tool for specifically evaluating venous congestion through ultrasonography, potentially offering an approach to unravel hidden pathophysiological aspects of CRS.

FOOTNOTES

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EDITORIAL

Ultrasound based estimate of central venous pressure: Are we any closer?

Atit A Gawalkar, Akash Batta

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Abstract

Central venous pressure (CVP) serves as a direct approximation of right atrial pressure and is influenced by factors like total blood volume, venous compliance, cardiac output, and orthostasis. Normal CVP falls within 8-12 mmHg but varies with volume status and venous compliance. Monitoring and managing disturbances in CVP are vital in patients with circulatory shock or fluid disturbances. Elevated CVP can lead to fluid accumulation in the interstitial space, impairing venous return and reducing cardiac preload. While pulmonary artery catheterization and central venous catheter obtained measurements are considered to be more accurate, they carry risk of complications and their usage has not shown clinical improvement. Ultrasound-based assessment of the internal jugular vein (IJV) offers real-time, non-invasive measurement of static and dynamic parameters for estimating CVP. IJV parameters, including diameter and ratio, has demonstrated good correlation with CVP. Despite significant advancements in non-invasive CVP measurement, a reliable tool is yet to be found. Present methods can offer reasonable guidance in assessing CVP, provided their limitations are acknowledged.

Key Words: Central venous pressure; Internal jugular vein; Point of care ultrasound; Shock; Volume status; Fluid balance

Core Tip: Central venous pressure (CVP) serves as a direct approximation of right atrial pressure and is influenced by factors like total blood volume, venous compliance, cardiac output, and orthostasis. Normal CVP falls within 8-12 mmHg but varies with volume status and venous compliance. Monitoring and managing disturbances in CVP are vital in patients with circulatory shock or fluid disturbances. Despite significant advancements in non-invasive CVP measurement, a reliable tool is yet to be found. Present methods can offer reasonable guidance in assessing CVP, provided their limitations are acknowledged.

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INTRODUCTION

Central venous pressure (CVP) is crucial for assessing hemodynamic status, particularly in the intensive care unit. It is a direct approximation of the right atrial pressure and is influenced by various factors, including total blood volume, compliance of the central venous compartment, cardiac output, orthostasis, arterial dilation, and preload. CVP reflects the amount of blood returning to the heart and the ability of the heart to pump. A normal CVP reading is between 8 and 12 mmHg, but this value is altered by volume status and venous compliance. Changes in CVP can impact cardiac output, and elevated CVP is associated with impairment of microcirculatory blood flow. CVP is critical in regulating fluid distribution, cardiac output, and organ perfusion. Monitoring and managing CVP is essential in the clinical assessment and treatment of patients, particularly those with circulatory shock or fluid volume disturbances. Due to the hydrostatic pressure gradient, an increase in CVP can lead to fluid accumulation in the third space, such as the interstitial space. Conversely, decreasing CVP can result in fluid reabsorption from the third space into the vascular compartment. An elevated CVP can impede venous return to the heart, reducing cardiac preload and decreasing cardiac output. On the other hand, a low CVP can lead to an increase in venous return and cardiac preload, potentially augmenting cardiac output.

MEASURING CVP

Quantifying CVP accurately is difficult in clinical situation and disturbances are easy to miss unless obvious[1]. The state of congestion can be due to cardiac dysfunction, renal disease, liver disease, thyroid disease or drug related. Timely recognition is crucial for its management. Clinical signs, biomarkers, and invasive and non-invasive radiological measurements have been used to estimate the CVP. Classically, pulmonary artery catheter guided measurements were the gold standard for monitoring hemodynamic pressures and cardiac output. However studies have failed to demonstrate improvement in outcomes in critically ill[2]. Subsequently central venous catheters were considered as less invasive alternatives. Despite their invasive nature, they showed poor predictive value for fluid responsiveness and were affected by various conditions like right ventricular function, tricuspid regurgitation, isolated left heart diseases and variation in intrathoracic pressure with respiration[3]. They also carried risk of complications like vessel injury, infection, pneumothorax, thrombosis and arrhythmias. In the era of evidence-based medicine, measuring CVP has remained an imperfect science even with invasive modalities. In search of more noninvasive ways, ultrasound guided assessment have attracted huge attention.

The role of ultrasound-based internal jugular vein (IJV) assessment is multifaceted and provides real-time, non-invasive measurement of static and dynamic parameters. Unlike invasive methods like central venous catheterization, ultrasound-based assessment is non-invasive, reducing patient discomfort and risk of complications. The most significant advantage of IJV assessment over inferior vena cava (IVC) assessment is its superficial location, making measurements easier and more accurate. IVC, on the other hand, is deeply placed in the abdominal compartment, susceptible to influence from abdominal pathologies like ascites and mass lesions.

The shape and dimension of IJV depend on the extra venous soft tissue pressure and the intravenous expanding pressure. At a certain point distally into IJV, the intravenous expanding pressure is less than the extra venous pressure, resulting in collapse of the vein. This is the sonographic meniscus point of blood column or point of venous collapse. Ultrasound-guided detection of this level is the simplest way of estimating the CVP, which is the radiological extrapolation of the classic bedside clinical method. Additionally, the ultrasound can measure the exact right atrial depth in the same sitting, effectively augmenting the efficacy over the conventional clinical assumption of right atrium height, *i.e.* 5 cm. A more straightforward method uses the measure of circularity of the vein to infer less than 10 mmHg of pressure when the ratio of anteroposterior diameter to transverse diameter is less than 0.75. The review article by Chayapinun *et al*[4] explains the various methods of measuring CVP using ultrasound assessment of IJV. They also explain in detail different dynamic methods to predict fluid responsiveness, like collapsibility index (respiratory variation) and distensibility index (response to fluid)[5,6]. In contrast to static measurements, they do not predict exact pressure but are excellent at predicting response to fluid administration or decongestive measures.

When IJV and IVC measurements were compared with CVP, it has been found that IVC diameter, IJV ratio and IJV maximum diameter had good agreement[7]. The commonly used IVC collapsibility index did not show good correlation. Of all the measures, the IJV diameter showed excellent accuracy in predicting a low CVP[7]. Another study in spontaneously breathing patients showed that the maximal IVC diameter provided the most robust estimate of CVP when compared to IVC collapsibility and IJV measurements[8].

In a recent meta-analysis comprising of 1928 patients, the predictive value of IJV based ultrasound assessment for diagnosing hypovolemia was excellent (both sensitivity and specificity of 82%)[9]. Measurement of IJV collapsibility indices had higher diagnostic accuracy. Similarly, for the diagnoses of hypervolemic conditions and fluid overload, IJV based ultrasound assessment had an acceptable predictive power (sensitivity of 84% and specificity of 70%). Hence the role as per larger evidence is only moderate. Non-ultrasound-based techniques have also been studied in the assessment of congestion which can have practical utility in nursing and home care settings. VenCoM device uses the principle of venous occlusive plethysmograph for measuring the CVP and is currently being studied[10]. ezCVP device uses oscillometric method to reliably measure CVP[11].

Although the ultrasound guided assessment is useful, all these methods need a high level of skills for measurement and, more importantly, interpretation. The presence of downstream pathologies like tricuspid regurgitation or stenosis, venous thrombosis or external occlusion, and atrial septal defect makes the method unreliable. Specific clinical situations like ongoing surgeries requiring a fixed positioning might render the technique less reliable.

CONCLUSION

Although much advancement has been made in non-invasively measuring CVP, the journey is yet to find a reliable tool. Currently, available methods can fairly guide CVP assessment, provided the shortcomings are considered.

FOOTNOTES

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EDITORIAL

Management of a patient with an unusual trajectory of a temporary trans-venous pacing lead

Metesh Acharya, Ethan Kavanagh, Sheena Garg, Davorin Sef, Fabio De Robertis

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Abstract

Perforation of the right ventricle during placement of pacing wires is a well-documented complication and can be potentially fatal. Use of temporary pacemaker, helical screw leads and steroids use prior to implant are recognised as risk factors for development of post-permanent pacemaker effusion. We reported an unusual case of pacing wire perforating interventricular septum into the left ventricle that occurred during the implant procedure performed in another institution. After the preoperative work-up and transfer to our tertiary cardiothoracic centre, the patient underwent successful surgical management. In conclusion, early recognition and timely diagnosis using advanced multimodality imaging can guide surgical intervention and prevent unfavourable consequences of device-related complications.

Key Words: Ventricular perforation; Lead perforation; Pacing

Core Tip: Early recognition and timely diagnosis using advanced multimodality imaging can guide surgical intervention and prevent unfavourable consequences of device-related complications.

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INTRODUCTION

Perforation of the right ventricle during placement of pacing wires is a well-documented complication and can be potentially fatal[1]. Up to 9% of patients can experience a variety of complications after permanent pacemaker (PPM) implantation such as infections, battery or programming issues, lead migration, or lead fracture[2]. Pericardial effusion, consistent with cardiac perforation, can be detected in up to 1.2% of patients after the PPM implantation. Use of temporary pacemaker, helical screw leads and steroids use prior to implant are recognised as risk factors for development of post-PPM effusion[1].

We reported an unusual case of pacing wire perforating interventricular septum into the left ventricle. An 81-year-old woman presenting at a district hospital in decompensated heart failure with fast atrial fibrillation and pleural effusions underwent emergency temporary trans-jugular venous pacing using passive leads for complete heart block after beta-blockade for rate control. On the next day, a loss of PPM capture was detected on monitoring and prompted further work-up. Chest radiography (Figure 1A, arrow) and computed tomography (Figure 1B, arrow) showed that the pacing wire had traversed from the inter-ventricular septum into the left ventricle, and through the left ventricular myocardium to lie within the left pleura.

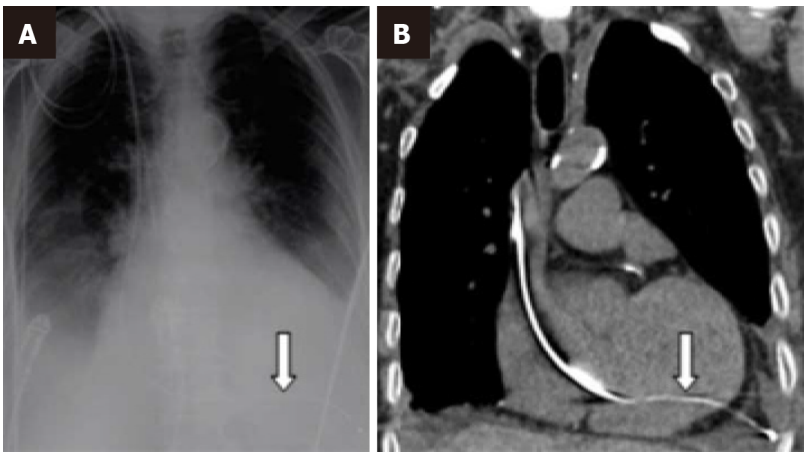

Figure 1 Chest radiography and computed tomography. A: Chest radiography (arrow); B: Computed tomography (arrow) showing that the pacing wire had traversed from the inter-ventricular septum into the left ventricle, and through the left ventricular myocardium to lie within the left pleura.

The patient was transferred to our tertiary cardiothoracic centre. Transoesophageal echocardiogram on admission demonstrated severe Carpentier IIIB mitral regurgitation from chordal entrapment by the pacing wire (Figure 2, arrow), without pericardial effusion. Multi-disciplinary team consensus was obtained for surgical pacing wire removal. Following left anterior thoracotomy in the 6th intercostal space, a Teflon-pledgeted 3-0 polypropylene purse-string suture was tied around the protruding pacing wire at the left ventricular apex (Figure 3) alongside transvenous lead withdrawal. The patient made a satisfactory recovery with only mild mitral regurgitation detected postoperatively.

Placement of temporary pacing leads has been associated with a 3-fold increased risk of cardiac perforation[1]. Therefore, in a Mayo Clinic study, which included more than 4200 patients who had PPM implantation, authors postulated that temporary pacemaker placement should be avoided unless essential[1]. In the case of symptomatic malpositioned pacing lead within the left ventricle, emergent surgical extraction is generally required[3]. Similarly, Mortensen *et al*[4] reported on a case of ventricular lead perforation late after PPM implantation with isolated haemothorax and no cardiac effusion or tamponade[4]. Definitive diagnosis was established only after fluoroscopy, and the surgical treatment included lead removal, repair suture of the right ventricle and placement of an epicardial electrode *via* thoracotomy. On the other hand, Otaal *et al*[5] reported a case of ventricular perforation in a patient who presented with mild left-sided chest pain 3 days after PPM implantation[5]. Diagnosis was confirmed with a computed tomography which detected hemopneumothorax[6]. The patient underwent successful surgical management with the placement of an epicardial pacemaker lead. For some of the above-mentioned reasons, leadless PPM is recently becoming an alternative form of transvenous pacing since it has been demonstrated that lead- and pocket-related complications can be reduced using this relatively novel approach[7]. However, the pacing position of leadless PPM can be more challenging as compared to conventional PPM, requiring careful preimplantation evaluation.

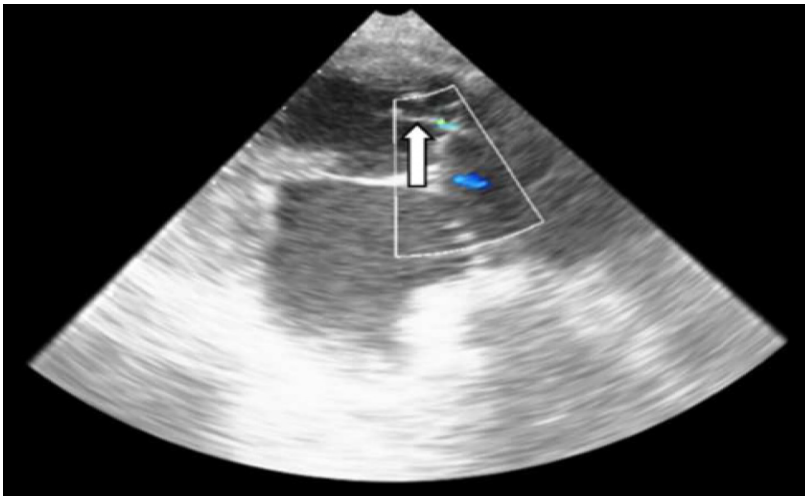

Figure 2 Transoesophageal echocardiogram on admission demonstrated severe Carpentier IIIB mitral regurgitation from chordal entrapment by the pacing wire (arrow), without pericardial effusion.

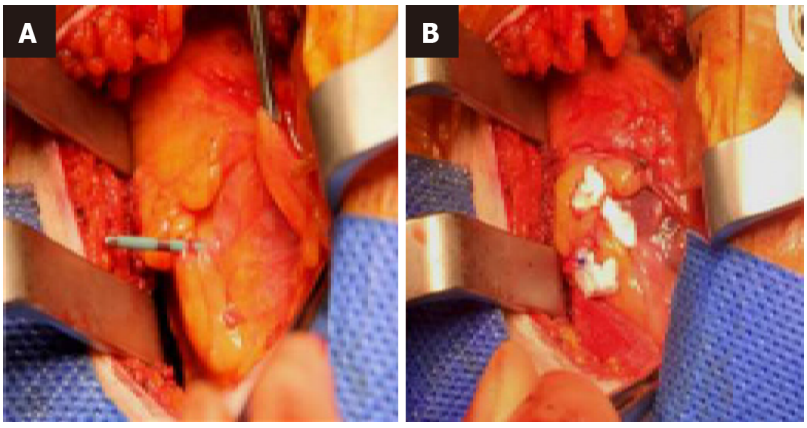

Figure 3 Following left anterior thoracotomy in the 6th intercostal space. A: A Teflon-pledgeted 3-0 polypropylene purse-string suture was tied around the protruding pacing wire at the left ventricular apex; B: Alongside transvenous lead withdrawal.

CONCLUSION

In our opinion, early recognition and timely diagnosis using advanced multimodality imaging can guide surgical intervention and prevent unfavourable consequences of device-related complications.

FOOTNOTES

Author contributions: Acharya M and Kavanagh E designed the research study; Acharya M, Kavanagh E and Garg S wrote the original draft of the manuscript; Sef D and De Robertis F analyzed the literature and edited the draft of the manuscript; All authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Echocardiographic predictors and associated outcomes of multiple vegetations in infective endocarditis: A pilot study

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Abstract

BACKGROUND

Infective endocarditis (IE) is a life-threatening infection with an annual mortality of 40%. Embolic events reported in up to 80% of patients. Vegetations of > 10 mm size are associated with increased embolic events and poor prognosis. There is a paucity of literature on the association of multiple vegetations with outcome.

AIM

To study the echocardiographic (ECHO) features and outcomes associated with the presence of multiple vegetations.

METHODS

In this retrospective, single-center, cohort study patients diagnosed with IE were recruited from June 2017 to June 2019. A total of 84 patients were diagnosed to have IE, of whom 67 with vegetation were identified. Baseline demographic, clinical, laboratory, and ECHO parameters were reviewed. Outcomes that were studied included recurrent admission, embolic phenomenon, and mortality.

RESULTS

Twenty-three (34%) patients were noted to have multiple vegetations, 13 (56.5%) were male and 10 (43.5%) were female. The mean age of these patients was 50.

Eight (35%) had a prior episode of IE. ECHO features of moderate to severe valvular regurgitation [odds ratio (OR) = 4], presence of pacemaker lead (OR = 4.8), impaired left ventricle (LV) relaxation (OR = 4), and elevated pulmonary artery systolic pressure (PASP) (OR = 2.2) are associated with higher odds of multiple vegetations. Of these moderate to severe valvular regurgitation (P = 0.028), pacemaker lead (P = 0.039) and impaired relaxation (P = 0.028) were statistically significant. These patients were noted to have an increased association of recurrent admissions (OR = 3.6), recurrent bacteremia (OR = 2.4), embolic phenomenon (OR = 2.5), intensive care unit stay (OR = 2.8), hypotension (OR = 2.1), surgical intervention (OR = 2.8) and device removal (OR = 4.8). Of this device removal (P = 0.039) and recurrent admissions (P = 0.017) were statistically significant.

CONCLUSION

This study highlights the associations of ECHO predictors and outcomes in patients with IE having multiple vegetations. ECHO features of moderate to severe regurgitation, presence of pacemaker lead, impaired LV relaxation, and elevated PASP and outcomes including recurrent admissions and device removal were found to be associated with multiple vegetations.

Key Words: Endocarditis; Echocardiography; Vegetations; Predictors; Outcome

Core Tip: Embolic events occur in up to 80% of patients with infective endocarditis (IE). Vegetations of > 10 mm in size are associated with increased embolic events and poor prognosis. In this retrospective cohort study, patients diagnosed with IE were recruited over 2 years. 34% of these had multiple vegetations. Echocardiographic features of moderate to severe regurgitation, presence of pacemaker lead, impaired left ventricle relaxation, and elevated pulmonary artery systolic pressure were associated with higher odds of multiple vegetation and outcomes including recurrent admissions and device removal were found to be associated with multiple vegetations.

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INTRODUCTION

Infective endocarditis (IE) is a life-threatening infection with an annual mortality of 40%. The complications of this disease are protean, with embolic events reported in up to 80% of patients[1]. There are several epidemiological, clinical, microbiological risk factors that contribute to adverse outcomes in patients with IE. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are the most effective diagnostic tools for IE. Even though used for diagnosis, the role of echocardiography in predicting outcome in these patients is still limited. Large vegetation size especially vegetations of > 10 mm size has been shown to be associated with increased embolic events and poor prognosis [2]. In patients with *Staphylococcus aureus* IE, ejection fraction of less than 40%, and intra-cardiac abscess has been shown to predict in-hospital mortality and perforation of valve[3-5]. Intra-cardiac abscess has been shown to independently predict 1-year mortality. There is a paucity of literature on the association of multiple vegetations with the outcome. The main objective of our study was to study the echocardiographic (ECHO) features associated with the presence of multiple vegetations and the implications of the presence of multiple vegetations on the outcome.

MATERIALS AND METHODS

In this retrospective, single center, cohort study patients diagnosed with IE were recruited from June 2017 to June 2019 from a community based tertiary care center in Massachusetts. All patients with microbiological and ECHO evidence of IE were eligible to be admitted to the study. Patients had to fulfill modified Duke's criteria to be diagnosed have IE. Once diagnosis of IE was established, patients were further subdivided as cases and controls based on presence or absence of multiple vegetations (defined as presence of 2 or more vegetations as identified in ECHO).

Instruments and protocols

For echocardiography GE (Vivid E95 model), Philips (Epic CVx3D model) machines were used. TTE for these patients were performed by skilled, American Society of Echocardiography (ASE) certified echocardiographers. During echocardiography qualitative and quantitative images of all 4 cardiac chambers, valves, vegetations, intra-cardiac complications

were obtained. Subsequently, echocardiography was analyzed by 2 independent skilled cardiologists. Initial diagnostic modality was TTE, subsequently TEE was done based on further clinical requirements.

Definitions

The following definition was used to define ECHO variables. The key papers of the ASE were used to define chamber quantifications, severity of valvular dysfunction, vegetation and diastolic dysfunction as discussed below: (1) Vegetation: 2019 American College of Cardiology/American Heart Association/ASE report defined vegetation as a mass present on a valve or its adjacent structure related to infective or collagen vascular (inflammatory) endocarditis[6]. Multiple vegetations: Defined as more than one vegetation visualized in multiple echocardiography views; (2) Valvular abnormalities: ECHO evidence of leaflet perforation, leaflet destruction, leaflet prolapse, leaflet mal coaptation, flail leaflet, valvular stenosis, and regurgitation in the presence of vegetations were defined as valvular abnormalities; (3) Valvular regurgitation: The overall interpretation of the severity of valvular regurgitation was based on the integration of all information obtained during the imaging study[6]. Acceptable degrees to describe severity of valvular regurgitation are outlined below: None - regurgitant flow is not present. Trace - minimal leakage valve is present. Mild - mild leakage of the valve is present. Mild to moderate - mild-to-moderate leakage of the valve is present. Moderate - moderate leakage of the valve is present. Moderate to severe - moderate-to-severe leakage of the valve is present. Severe - severe leakage of the valve is present; (4) Low ejection fraction: Male < 52%, female < 54% as per ASE chamber quantifications guidelines [7]; (5) Impaired left ventricle (LV) relaxation: Left ventricular diastolic function is defined by ASE as relaxation and filling during the period after aortic valve closure and before aortic valve opening. Assessment of left ventricular diastolic function includes evaluation of relaxation and compliance, using mitral inflow patterns, annular tissue Doppler velocities, tricuspid regurgitation velocity, left atrial size and pulmonary vein flow velocities[6,7]; and (6) Elevated pulmonary artery systolic pressure (PASP): As per ASE definitions, mean pressure in the pulmonary arteries ≥ 25 mmHg at rest or 30 mmHg during physical activity based on assessment of the tricuspid regurgitation jet velocity suggests probable presence of pulmonary hypertension[7].

Outcome measures

During this period a total of 84 patients were diagnosed to have IE. Sixty-seven patients with ECHO evidence of vegetation were identified. Baseline demographic, clinical, laboratory and ECHO parameters were obtained. ECHO images of these patients were reviewed for findings such as valvular abnormalities including leaflet perforation, leaflet aneurysm, flail leaflet, valvular obstruction, regurgitation, paravalvular abscess, intracardiac abscess, pseudoaneurysm, fistula, prosthetic valve dehiscence, low ejection fraction, pacemaker wire vegetation, and pericardial effusion. Outcomes that were studied included recurrent admission, recurrent bacteremia, requirement of prolonged antibiotics, embolic phenomenon, hypotension, requirement of intensive care unit (ICU) stay, mechanical ventilation, removal of device, requirement of surgical intervention and mortality. Subsequent admission for the same clinical diagnosis or its complications was defined as recurrent admissions. Repeat isolation of the prior organism with presence of bacteremia was defined as recurrent bacteremia. Requirement of longer duration of antibiotics for persistence of bacteremia was defined as prolonged antibiotics use. Definitions of outcome variables: Recurrent admission: Defined as readmission for clinical diagnosis or complications related to the prior episode of IE. Recurrent bacteremia: Subsequent isolation of the initial organism with evidence of bacteremia. Prolonged antibiotics: Longer duration of antibiotics because of persistence of bacteremia (> 8 wk) or prior discontinuation. Embolic phenomenon: Occurrence of any new embolic event or occurrence of an embolic event at a different site during the hospital stay. Hypotension: Defined as persistent low systolic blood pressure of < 90 mmHg requiring fluid or pressors. ICU stay: Is defined as upgrading of care, in a specialized unit, for the need of cardiac or respiratory support with mechanical ventilation or pressors. Mechanical ventilation: Requirement of invasive and noninvasive mechanical ventilatory support. Removal of device: Requirement of removal of temporary intravenous cannula, and cardiac implantable electronic devices.

Data analysis

TTE imaging was obtained by skilled and ASE certified echocardiographers. TTE images were reviewed and reported by two trained cardiologist blinded towards the outcome. TEE was obtained and interpreted by a trained cardiologist. Clinical data was entered in a preformed proforma by 2 independent physicians. Data obtained were entered into Microsoft Excel version 22 (Microsoft Corp.Redmond, Washington) and were analyzed using IBM SPSS version 28 (IBM Corp., Armonk, New York). Continuous data were measured as mean, median, range, and percentage. The odds ratio (OR) was used to measure the association. We used the χ^2 test to calculate the OR for categorical variables and unadjusted binary logistic regression to calculate the OR of continuous variables. A P value less than 0.05 was considered significant. Institutional review board approval was obtained before the initiation of the study.

RESULTS

Among the 67 patients 23 (34%) patients were noted to have multiple vegetations as shown in Figure 1. Among these 13 (56.5%) were male and 10 (43.5%) were female. The distribution of gender in both the subgroups were identical. Patients with multiple vegetations were older with the mean age of the patients with multiple vegetations being 50 as compared to 45 for the patients with single vegetation. Eight (35%) had a prior episode of IE. This was similar to the patients with single vegetation. Single vegetation occurred in higher percentage (84%) of patients with native valve IE. The tricuspid valve was involved in 9 (50%) patients with multiple vegetations and 21 (50%) patients in single vegetation. The mitral

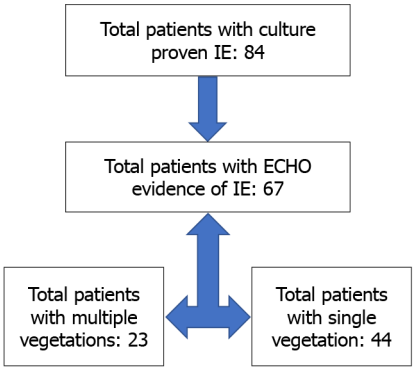

Figure 1 Strobe diagram showing the flow of the patients. IE: Infective endocarditis; ECHO: Echocardiographic.

valve was involved in 4 (22%) patients with multiple vegetations and 12 (27%) patients with single vegetation. Multiple valvular involvement was noted in 4 (22%) patients with multiple vegetation. A higher percentage of patients with multiple vegetations had transesophageal echocardiogram (78%). Heart rate and left arterial volume were almost similar in both the groups. Higher PASP was noted in patients with multiple vegetations. However, none of the differences in the baseline demographic details were statistically significant as shown in Table 1. Valvular abnormalities including leaflet perforation, leaflet destruction, flail leaflet, and regurgitation were noted in around 10% of patients. The presence of prosthetic valve (26%), pacemaker lead (26%), impaired left ventricular relaxation (83%), and elevated PASP (48%) and moderate to severe valvular regurgitation (83%) were higher in patients with multiple vegetations. The presence of an indwelling catheter, low ejection fraction (< 50%), right and left atrial enlargement were equal in both the groups. ECHO features of moderate to severe valvular regurgitation (OR = 4), presence of pacemaker lead (OR = 4.8), impaired LV relaxation (OR = 4), and elevated PASP (OR = 2.2) were associated with higher odds of multiple vegetations. Of these, moderate to severe valvular regurgitation (P = 0.028), the presence of pacemaker lead (P = 0.039) and impaired relaxation (P = 0.028) were statistically significant (Table 2).

Patients with multiple vegetation had increased percentages of requirement of prolonged antibiotics (30%), recurrent bacteremia (48%), recurrent admission (65%), embolic events (39%), requirement of ICU care (48%), hypotension (35%), requirement of mechanical ventilation (22%), removal of device (26%), and surgical intervention (35%) as shown in Table 3. Among these variables, higher odds of association (OR > 2) was present in recurrent admissions (OR = 3.6), recurrent bacteremia (OR = 2.4), embolic phenomenon (OR = 2.5), ICU stay (OR = 2.8), hypotension (OR = 2.1), surgical intervention (OR = 2.8), and device removal (OR = 4.8). However, only requirement of device removal (P = 0.039) and recurrent admissions (P = 0.017) were statistically significant. No significant difference in mortality was seen between the groups.

DISCUSSION

IE is an infectious condition that affects the cardiac endocardial surface, most commonly cardiac valves. Annual incidence of 3-7 per 100000 years have been documented in previous population surveys[1,8]. A 20-year trend analysis showed a significant decrease in annual mortality percentage change between 2004 and 2010, but age- adjusted mortality has stabilized since 2010 till 2019 at 51 deaths per 100000 person-year[9]. Demographic factors including male sex, black population, older age (> 65 years old), and rural location were associated with a higher crude and adjusted mortality rates [9,10]. Mortality ranges from 3% to 14% during index hospital admission, which increases substantially to 36%-37% at 1-year follow-up[11].

Similarly, our study had a mortality of 3% to 7%. This systematic review also showed *Staphylococcus aureus* as the most common microbe encountered in IE like in our study. Other common pathogens include *Enterococcus spp.*, *Viridians Streptococcus* and Coagulase- negative *Staphylococci*[5,11,12]. With recent developments in diagnostic investigations, including cultures and TEE, multiple organisms have been implicated in causing IE[12-14]. Based on an International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) of more than 2700 definite IE, native valve IE (72%) was most frequent followed by prosthetic valve IE (21%). Native valve endocarditis was noted in > 70% of patients in our study and > 30% patients had a remote history of IE. Vegetations were more common on the mitral valve (41%), followed by aortic (38%), and tricuspid (12%) valves[15,16].

Many risk factors including recent increase in bioprosthetic valves, use of cardiac prosthesis and grafts in adult patients with congenital heart diseases, and intravenous drug use (IVDU) with opioid epidemic are associated with increased incidence of IE. In our study 30% of patients had IVDU related IE. IVDU related increase has been seen more prominently in younger and uninsured population and associated with high health care expenditure burden[11]. A significant proportion, 6%-16%, require valvular surgery for IE thereby necessitating multidisciplinary care for this vulnerable patient population[11].

Table 1 Baseline demographic parameters of the patients with multiple vegetation as compared to single vegetation

Variable	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Gender, *n* (%)			1	0.98
Female	10 (43.5)	19 (43)		
Male	13 (56.5)	25 (57)		
Mean age (SD)	50 (20.6)	45 (18.6)	1.01	0.33
Prior IE, *n* (%)	8 (35)	14 (32)	1.1	0.8
Native valve IE, *n* (%)	18 (78)	37 (84)	0.68	0.55
TTE (*N* = 49), *n* (%)	11 (48)	20 (45)	0.91	0.8
TEE (*N* = 49), *n* (%)	18 (78)	30 (68)	1.6	0.54
HR (SD)	105 (18.5)	106 (21.8)	0.99	0.83
LAVI (SD)	32 (11.7)	30 (10.5)	1.01	0.50
PASP (SD)	38 (14.2)	32.5 (10.9)	1.03	0.10

SD: Standard deviation; IE: Infective endocarditis; TTE: Trans thoracic echocardiogram; TEE: Transesophageal echocardiogram; HR: Heart rate; LAVI: Left atrial volume index; PASP: Pulmonary artery systolic pressure; OR: Odds ratio.

Table 2 Baseline echocardiographic parameters of the patients with multiple vegetation as compared to single vegetation, *n* (%)

ECHO variable	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Valvular abnormality	2 (9)	6 (14)	0.603	0.5
Moderate to severe regurgitation	19 (83)	24 (55)	4	0.028[a]
Prosthetic valve	6 (26)	7 (16)	1.9	0.32
Pacemaker lead	6 (26)	3 (7)	4.8	0.039[a]
Indwelling catheter	3 (13)	10 (23)	0.5	0.34
Low EF (EF < 50)	2 (9)	6 (14)	0.6	0.55
RAE	8 (35)	13 (29.5)	1.3	0.66
LAE	8 (35)	15 (34)	1	0.95
Impaired LV relaxation	19 (83)	24 (55)	4	0.028[a]
Elevated PASP	11 (48)	13 (29.5)	2.2	0.1

[a]$P < 0.05$.

ECHO: Echocardiographic; OR: Odds ratio; EF: Ejection fraction; RAE: Right atrial enlargement; LAE: Left atrial enlargement; LV: Left ventricle; PASP: Pulmonary artery systolic pressure.

Predictors of poor outcomes in IE

Multiple epidemiological, clinical, microbiological, risk factors contribute to adverse outcomes in patients with IE. Embolization of vegetation is one of the feared complications of IE associated with poor prognosis, increased mortality, and increased health care utilization. Brain, spleen, lungs, coronaries, bowel, and extremities are some of the sites with highest predilection of getting affected by septic emboli. A vegetation size of 10 mm or more was associated with higher odds of systemic embolic events and all-cause mortality based on systematic review of 21 studies[3,17,18]. In our study embolic events occurred in 29% of study population, and was even higher in among patients with multiple vegetations (39%). Embolic events can complicate up to 80% of presentations. Pulmonary septic emboli are seen more commonly with right sided IE, whereas left sided IE embolizes frequently to brain and spleen. Embolic events are more prevalent with mitral vegetation of any size compared to aortic vegetation of similar size[19-21]. Anterior leaflet vegetations of mitral valve have increased propensity to detach and embolize in contrast to posterior leaflet vegetations[20]. Causative pathogens also affect embolic events incidence- more virulent microbes including *Staphylococcus aureus* and Candida are associated with higher rates[22,23]. Embolic phenomena are more common during the initial course of the disease, and decrease dramatically within 2-3 wk of appropriate antimicrobial therapy[22,24].

Table 3 Outcome of the patients with multiple vegetation as compared to single vegetation, *n* (%)

Outcomes	Multiple vegetations (*N* = 23)	Single vegetation (*N* = 44)	OR	*P* value
Prolonged antibiotics	7 (30)	9 (20.5)	1.7	0.36
Recurrent bacteremia	11 (48)	12 (27)	2.4	0.09
Recurrent admission	15 (65)	15 (34)	3.6	0.017[a]
Embolic phenomenon	9 (39)	9 (20.5)	2.5	0.1
Hypotension	8 (35)	9 (20.5)	2.1	0.2
ICU stay	11 (48)	11	2.8	0.06
MV	5 (22)	7 (16)	1.5	0.55
Removal of device	6 (26)	3 (7)	4.8	0.039[a]
Surgical intervention	8 (35)	7 (16)	2.8	0.08
Mortality	1 (4)	3 (7)	0.6	0.68

[a]$P < 0.05$.

OR: Odds ratio; ICU: Intensive care unit; MV: Mechanical ventilation.

Metastatic sources of infection can develop from septic emboli [*e.g.*, splenic abscess, mycotic aneurysms (MA)] which may require additional interventions. Extracranial and intracranial MA are life-threatening especially when they become symptomatic after rupture. They can often go undetected which underestimates their incidence. Overall mortality with intracranial MA approximates 60% based on few reports, with mortality approaching 80% when these aneurysms rupture [25-27].

In addition to embolization, local extension of infection beyond annulus of valve is dangerous. Perivalvular abscess and later fistulization or shunting between various cardiac chambers often require surgical intervention. These complications have been demonstrated to predict higher mortality, requirement of valvular surgery, pacemakers, and longer course of antibiotics[4,13,27,28]. Aortic valve vegetations are more likely to develop perivalvular abscess[5,13,29]. Among patients who survived, changes in acute physiology causing a change in APACHE-II score was seen, as compared to patients who did not. Similarly, the presence of heart failure at presentation, any stroke during disease course, diabetes mellitus, were independently associated with poor outcomes in a retrospective cohort study at a tertiary center[4]. Interestingly, cardiac surgery during admission did not affect mortality on multivariable analysis[4].

ECHO manifestations of vegetations in IE

Echocardiography remains cornerstone for diagnosis of IE. The evolution of imaging techniques in recent times that lead to an improvement of spatial image resolution have improved the sensitivity of this modality to detect vegetations. TTE is the preferred initial investigation unless device infection or prosthetic valve endocarditis is suspected[30]. TEE is the gold standard investigation. Vegetation visualization in real time for location, mobility, size, and associated local complications - valvular dehiscence, fistula, abscess makes echocardiogram a primary modality of imaging[30,31]. Multiple vegetations can be identified in TEE as it is able to differentiate smaller vegetations. In our study TEE was able to identify multiple vegetations in 78% of patients (Figure 2). Aortic valve vegetations are located on ventricular side of valve and have diastolic outflow tract prolapse. Similarly, mitral, and tricuspid valve vegetations are located on atrial side of leaflets and have tendency to prolapse into their respective atria in systolic phase. Endocardial involvement on echocardiogram is one of the major criteria in original and modified Duke's criteria[32,33]. The presence of oscillating intracardiac mass, intracardiac abscess, new dehiscence of prosthetic valve, and new valvular regurgitation are the criteria to diagnose IE on echocardiogram. Duke's criteria was modified to exclude patients with worsening or changing of pre-existing murmur as a criterion for diagnosis[32,33].

Sensitivity and specificity of TTE for native valve endocarditis ranges from 50%-90% and 90% respectively[34]. The sensitivity is poor for prosthetic valve involvement at 29% while specificity was noted to be 100% in a systematic review [35]. In contrast, TEE has higher sensitivity and specificity reaching > 90% for native valve endocarditis[34]. However, sensitivity to detect prosthetic valve endocarditis is around 80% by TEE, with no difference in specificity compared to TTE[35]. Erbel *et al*[20] elucidated improved diagnostic accuracy of TEE over TTE as smaller vegetations were hard to discern on TTE. The presence of vegetations correlated with embolic events. Embolic events appear to occur more often with larger vegetations (> 10 mm) and location on mitral valve[17,20,36]. In our study, we also identified that higher proportions of patients noted to have multiple vegetations had undergone TEE. Echocardiography is crucial in identifying vegetations on pacemakers and defibrillators. TEE is instrumental in identifying the site, number, and extent of vegetations on cardiovascular implantable device (CIED). Vegetations on CIED can become large. Echocardiography is also used to detect complications associated with vegetations. The sensitivity to diagnose paravalvular abscess with TTE and TEE is 28% and 87%, respectively, while specificity is comparable at > 95% for both TTE and TEE[22]. Valve perforation is also better detected with TEE *vs* TEE (sensitivity 95% *vs* 45%) with specificity of > 95% for both modalities [37]. Valvular and paravalvular complications in our study subgroups were similar. This is in keeping with the prior

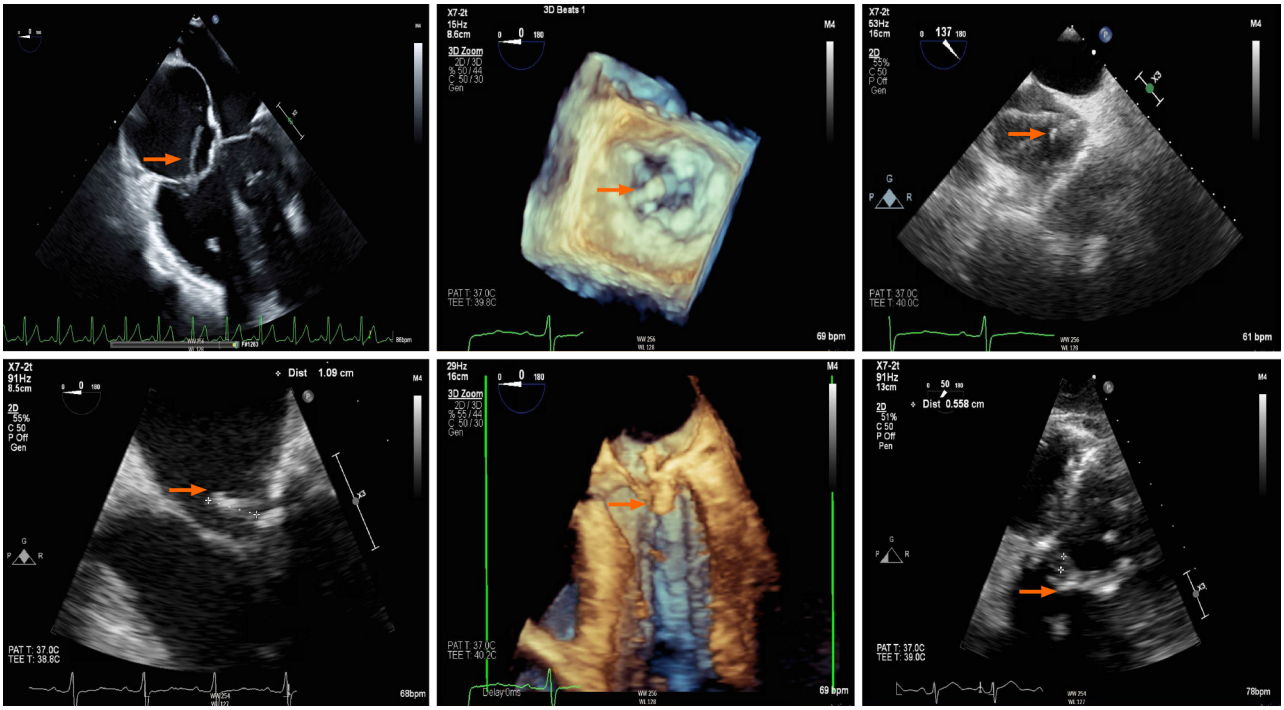

Figure 2 Echocardiographic images of vegetations.

literature showing lack of association between vegetation size and paravalvular complications[38].

ECHO features associated with outcomes of IE

Features visualized on echocardiogram can help to predict outcomes associated with IE and guide further management. As shown in Table 4 multiple ECHO parameters can predict outcome in patients with IE. A larger vegetation size (10 mm), mitral valve vegetation and anterior mitral leaflet involvement is associated with a higher odd of embolization, as described earlier. Vegetation size has been used as an independent ECHO predictor in Embolic Risk French Calculator [39]. However, caution should be maintained on discrepancy in cutoff size based on 3D *vs* 2D imaging as 3D imaging is more sensitive[40].

Vegetation mobility was noted to be an independent predictor of embolic events in an early study published in 2001 [41]. Many studies have been published since then, and cumulative evidence suggests presence of mobile vegetation was associated with double odds of embolic events in a comprehensive systematic review. Vegetation mobility with displacement angle of > 60° is further associated with higher embolic events[42]. In addition, presence of multiple vegetations was independently associated with more embolic events, however, presence of bivalvular vegetations didn't have statistical significance[43]. This was similar to our study where patients with multiple vegetations had higher odds of having embolic events.

The presence of large vegetation on CIED is known to increase hospital mortality. Similarly, CIED endocarditis is known to increase health care utilization, cost, need of intervention, surgical procedure and worsen quality of life similar to this study[44,45]. Valvular complications including leaflet perforation, flail leaflet, leaflet obstruction and acute valvular regurgitation can increase embolic events and morbidity and mortality in patients with IE. Demonstration of paravalvular complications including abscess, aneurysm, fistula and paravalvular regurgitation is associated with worst patient outcome. Presence of valvular and paravalvular complications is associated with increased odds of mortality and necessitating cardiac surgery and prolonged antibiotics[16]. In our study patients with multiple vegetations had higher odds of having severe valvular regurgitation and needing surgical intervention. There has been limited literature of implications of diastolic dysfunction in patients with endocarditis. While we found that impaired LV relaxation and elevated PASP was more among patients we are unable to conclude that elevated filling pressure and impaired LV relaxation was solely responsible for multiple vegetations.

ECHO features of IE, using modified Duke's criteria, were present in 87% of patients in ICE-PCS study[16]. Approximately 60% of these subjects had undergone TTE and TEE, and 99.2% of the study population had undergone either TTE or TEE. The most common paravalvular complication was abscess formation, noted in 14% of patients. In one-third of the patients with prosthetic valve endocarditis, their courses were complicated by dehiscence or new regurgitation lesion. Presence of mitral valve vegetations, paravalvular complications and prosthetic valve endocarditis were associated with higher odds of mortality. Interestingly in our study, patients with multiple vegetations had higher requirement of prolonged antibiotics, recurrent bacteremia, recurrent admission, embolic events, requirement of ICU care, hypotension, requirement of mechanical ventilation, removal of device, and surgical intervention. Among these variables, the requirement of device removal and recurrent admissions were statistically significant. However, there was no difference in mortality.

Table 4 Echocardiographic predictors of outcome in infective endocarditis

Finding	Embolism	Morbidity	Mortality
Vegetation size[1]	+	+	+
Mitral valve location	+	+	+
Anterior leaflet of MV	+	-	-
Vegetation mobility[2]	+	-	-
Multiple vegetation	+	+	-
Cardiac device vegetations	+	+	+
Valvular complications[3]	+	+	+
Perivalvular complications[4]	+	+	+
Prosthetic valve vegetation	+	+	+
Prosthetic valve dehiscence	+	+	+

[1]Size of 10 mm.
[2]> 60° of displacement angle.
[3]Flail leaflet, leaflet perforation, acute valvular regurgitation, valvular obstruction.
[4]Abscess, aneurysm, fistula, paravalvular regurgitation.
MV: Mechanical ventilation.

The limitations of this study are the retrospective nature, small sample size and lack of matching. While septic embolism to the lungs occurs with tricuspid valve endocarditis, systemic embolization is predominant with left sided IE. Embolic events are higher with mitral valve IE in comparison to aortic valve IE for any vegetation size. We were not able to compare the relationship between multiple vegetations on the individual valve with embolic outcomes due to identical and higher percentages of tricuspid valve involvement in both groups and a smaller number of patient involvement in the other valvular groups. We also did not have details of cost of care, patients' insurance details, lack of details on functional status at admission and at follow up which could independently affect outcome[21,44,46]. However, the strength of this study was inclusion of patients with definite IE and imaging evidence of vegetation in both the subgroups and identifying the predictors of multiple vegetations and their associated outcomes in patients with IE[47-49].

CONCLUSION

In conclusion, this study highlights the associations of ECHO features and its outcomes in patients with IE having multiple vegetations. TEE is better at identifying and characterizing multiple vegetations. ECHO evidence of moderate to severe regurgitation, presence of pacemaker lead, impaired LV relaxation, and elevated PASP were implicated with presence of multiple vegetations. IE patients with multiple vegetations can contribute to multiple comorbidities among which recurrent admissions and requirement of device removal are found to be statistically significant.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Initial decrease in the lipoprotein(a) level is a novel prognostic biomarker in patients with acute coronary syndrome

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Abstract

BACKGROUND

Lipoprotein(a) [Lp(a)] is a causal risk factor for atherosclerotic cardiovascular diseases; however, its role in acute coronary syndrome (ACS) remains unclear.

AIM

To investigate the hypothesis that the Lp(a) levels are altered by various conditions during the acute phase of ACS, resulting in subsequent cardiovascular events.

METHODS

From September 2009 to May 2016, 377 patients with ACS who underwent emergent coronary angiography, and 249 who completed ≥ 1000 d of follow-up were enrolled. Lp(a) levels were measured using an isoform-independent assay at each time point from before percutaneous coronary intervention (PCI) to 48 h after PCI. The primary endpoint was the occurrence of major adverse cardiac events (MACE; cardiac death, other vascular death, ACS, and non-cardiac vascular events).

RESULTS

The mean circulating Lp(a) level decreased significantly from pre-PCI (0 h) to 12 h after (19.0 mg/dL to 17.8 mg/dL, $P < 0.001$), and then increased significantly up to 48 h after (19.3 mg/dL, $P < 0.001$). The changes from 0 to 12 h [Lp(a)Δ0-12] significantly correlated with the basal levels of creatinine [Spearman's rank correlation coefficient (SRCC): -0.181, $P < 0.01$] and Lp(a) (SRCC: -0.306, $P < 0.05$). Among the tertiles classified according to Lp(a)Δ0-12, MACE was significantly

more frequent in the lowest Lp(a)Δ0-12 group than in the remaining two tertile groups (66.2% *vs* 53.6%, $P = 0.034$). A multivariate analysis revealed that Lp(a)Δ0-12 [hazard ratio (HR): 0.96, 95% confidence interval (95%CI): 0.92-0.99] and basal creatinine (HR: 1.13, 95%CI: 1.05-1.22) were independent determinants of subsequent MACE.

CONCLUSION
Circulating Lp(a) levels in patients with ACS decreased significantly after emergent PCI, and a greater decrease was independently associated with a worse prognosis.

Key Words: Lipoprotein (a); Acute coronary syndrome; Percutaneous coronary intervention; Major adverse cardiac events; Prognosis

Core Tip: Two hundred and forty-nine patients with acute coronary syndrome were enrolled in the study. Lipoprotein(a) [Lp(a)] levels were measured before percutaneous coronary intervention (PCI) to 48 h after using an isoform-independent assay. Lp(a) levels decreased significantly from pre-PCI (0 h) to 12 h after, and then increased up to 48 h after. The changes from 0 to 12 h [Lp(a)Δ0-12] were significantly correlated with basal creatinine and Lp(a). Among the tertiles classified according to the changes from 0 to 12 h [Lp(a)Δ0-12], major adverse cardiac events (MACE) were significantly more frequent in the lowest Lp(a)Δ0-12 group than in the other two groups. Multivariate analysis revealed that Lp(a)Δ0-12 and basal creatinine were independent determinants of subsequent MACE.

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INTRODUCTION

Lipoprotein(a) [Lp(a)] is a well-known causal risk factor for myocardial infarction, aortic valve stenosis, and other atherosclerotic diseases[1,2]. In the Lp(a) particle, apolipoprotein B (apo-B) was covalently bound to an apolipoprotein(a) [apo(a)]. The mechanism enhancing atherosclerosis by Lp(a) is considered to involve apo-B-containing lipoprotein, similar to low-density lipoprotein particles, as a carrier particle for oxidized phospholipid promoting pro-inflammatory cascade, and as its potential association with fibrinolysis owing to its structural similarity with plasminogen[2]. However, the precise mechanism underlying the Lp(a)-mediated development of atherosclerotic cardiovascular disease remains largely unknown.

Apo(a) is encoded by the *LPA* gene, and variation at the *LPA* locus is the strongest genetic determinant of circulating Lp(a) levels[3]. In contrast, within-individual variability has also been described, including an increase in autoimmune inflammatory conditions[4] and a decrease after bariatric surgery[5]. Regarding acute coronary events, Lp(a) levels during hospitalization for myocardial infarction or unstable angina have been investigated only in a small or modest sample size with various time courses[6-8]. One study reported a small decrease from days 1 to 3 in 59 patients with acute myocardial infarction[6] and an increase from days 1 to 21 in 18 patients with unstable angina pectoris[7]. Based on these discrepancies in previous study results, we hypothesized that circulating Lp(a) levels may be altered by the pathophysiological conditions of acute coronary events, which may influence the middle- or long-term prognosis through subsequent adverse cardiac events during follow-up.

In the present study, we applied the Lp(a) assay method, which has been reported to be resistant to the apo(a) isoform-dependent influence on measurement results, postulated frequently in commercially-available kits, as a potential confounder during data acquisition and interpretation.

MATERIALS AND METHODS

To evaluate Lp(a) levels in the early phase of acute coronary syndrome (ACS), we conducted a single-center observational cohort study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of our institution (I-115). Written informed consent was obtained from all patients prior to enrollment.

The inclusion criteria for the current study were patients with ACS who underwent emergent coronary angiography (CAG) between September 2009 and May 2016. The exclusion criteria were the absence of emergent CAG or admission for the treatment of conditions other than cardiac disease. Subjects presenting with myocardial damage due to concomitant

cardiac diseases other than coronary stenosis, such as myocarditis (n = 9), cardiomyopathy (takotsubo n = 5, hypertrophic n = 3), ventricular tachyarrhythmia without coronary stenosis (n = 4), and heart failure (n = 11), were also excluded. In addition, patients whose myocardial infarction occurred ≥ 72 h before arrival (n = 3) or those with prior myocardial infarction within 30 days (n = 7) were excluded. A total of 377 patients who underwent emergent CAG suggesting ACS were enrolled, and 42 and 25 patients were excluded due to causes of myocardial damage and insufficient initial data collection, respectively. As a result, 310 individuals who successfully completed the data collection were selected as the study population. While a 1000-d follow-up was initially planned, 61 individuals dropped out during the course of the study, leaving a final cohort of 249 patients eligible for the analysis (Figure 1).

Myocardial infarction was diagnosed in cases with typical chest pain continuing ≥ 20 min, electrocardiogram (ECG) with ST elevation in at least two contiguous leads (≥ 2 mm in precordial or ≥ 1 mm in limb leads) or newly-identified left bundle branch block[9,10], associated with elevation of creatine kinase-myocardial isoform (CK-MB) or troponin T.

Peripheral blood samples to measure Lp(a), high-sensitivity C-reactive protein (hs-CRP), and other laboratory tests were drawn at following time-points; before CAG and at 3 h, 6 h, 12 h, 24 h, and 48 h after percutaneous coronary intervention (PCI). In patients with no coronary occlusion nor severe stenosis responsible for myocardial ischemia, peripheral blood samples were drawn at the same time points. Serum was separated after centrifugation (2500 × g) at 4 °C for 10 min and stored at -80 °C until use. Lp(a) levels were determined using an immunoturbidemetric assay kit (Denka Seiken., Tokyo, Japan), which is a well-validated assay with good reproducibility (coefficient of variation, 1.2%-2.2%) and is generally insensitive to apo(a) size heterogeneity[11]. Other laboratory measurements were performed by using standard methods at each timepoint.

All patients underwent emergent CAG, and PCI was immediately performed for lesions considered the culprit. In cases having ≥ 2 coronary occlusions, a lesion consistent with findings of ECG and echocardiogram was identified as the target. The detail of procedures depended on the interventional cardiology staff (T-AT, MK, and YK). A loading dose of antiplatelet agents (aspirin and $P2Y_{12}$ inhibitors) was orally administered, and, before the procedure, 70 to 100 IU/kg of unfractionated heparin was given. The activated clotting time was maintained at ≥ 250 s with additional heparin administration during PCI. Primary PCI success was defined as TIMI flow grade ≥ 3 antegrade achievement with < 20% residual stenosis. Dual antiplatelet treatment was maintained during ≥ 6 months if bleeding complications requiring cessation of antiplatelet therapy did not occur, as previously described[12].

All patients were followed by an outpatient clinic at Kanazawa Medical University Hospital. Guideline-recommended medical treatments, including antiplatelet agents, statins, beta blockers, and an angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, were administered to lead the clinical and laboratory values reaching the targets for secondary prevention, if tolerable. Statins were given on hospital days 1 to 4, depending on the coronary care unit stay length, renal/liver function, and previous drug-related adverse events history; however, they were started by day 2 in most patients. Definition of major adverse cardiac events (MACE) was a composite of all-cause death, nonfatal myocardial infarction, stroke, and new angina pectoris. Newly-identified angina was defined as that in which the culprit lesion differed from the initial ACS event. Restenosis of the culprit lesion requiring revascularization was included in the MACEs category.

Continuous variables were described as the mean ± SD. Categorical variables were shown as numbers and percentages. The median with interquartile ranges was calculated for asymmetrically distributed data. Repeated measures of a one-way analysis of variance (with covariates if necessary) were applied in the assessment of serial changes in biomarker levels, and a paired t-test with Bonferroni correction for multiple tests was used to compare single time points. For variables with asymmetrical distributions, inter-group differences were compared using Kruskal-Wallis test and Scheffe's multiple comparison test. To examine between-biomarker data, Pearson's correlation coefficient (r) and Spearman's rank correlation coefficient (SRCC) were applied to data with a normal distribution and non-parametric measures, respectively. In order to analyze the between-group characteristics, the chi-square test was applied. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

The time to MACE was evaluated by means of the following two models: Model 1, variables demonstrated as risk factors for coronary heart disease in the Japanese Cohort, Suita Study[13]; age, sex, current smoking, presence of hypertension and diabetes, systolic blood pressure, pulse rate, HbA1c, low-density lipoprotein-cholesterol (LDL-C), baseline Lp(a), and the changes from 0 to 12 h [Lp(a)Δ0-12]. In model 2, well-established prognostic factors for ACS survivors (age, sex, peak CK-MB, creatinine, and Killip classification) and Lp(a)Δ0-12 were all included in the model. Outcomes were estimated by the Kaplan-Meier method and were compared with the log-rank test.

Bell Curve for Excel ver. 3.21 (Social Survey Research Information Co. Ltd., Tokyo, Japan) was used to statistical analyses, and all statistical tests were two sided. Statistical significance was set at $P < 0.05$.

RESULTS

Table 1 shows the baseline characteristics of the 249 patients with ACS included in the analysis. The majority of patients were male (79.0%), and more than half were smokers and were with a history of hypertension (52.6% and 59.8%, respectively). Statins were used in 26.9% of the patients; however, there was no significant difference in baseline Lp(a) levels between statin users and non-users. Therefore, we analyzed these patients together. The baseline LDL-C level was 122.4 mg/dL ± 36.6 mg/dL, and the creatinine level was 1.2 mg/dL ± 1.6 mg/dL.

According to the above-mentioned diagnostic criteria, the enrolled patients consisted of 169 patients with ST-elevation myocardial infarction (STEMI) patients, 47 patients with non-STEMI, and 33 patients with unstable angina pectoris. According to the Killip classification, 178 and 71 patients were classified as I + II and III + IV, respectively. Culprit lesions

Table 1 Characteristics of study subjects and baseline data

Variable	Unit	Value
Age	yr	66.6 ± 12.6
Sex (men/women)	%	196/53 (79.0/21.0)
Medical history		
Myocardial infarction	%	11 (4.4)
Unstable angina pectoris	%	5 (2.0)
Angina pectoris	%	30 (12.0)
Atrial fibrillation	%	14 (5.6)
Cerebral infarction	%	17 (6.8)
Diabetes mellitus	%	84 (33.7)
Hypertension	%	149 (59.8)
Smoking	%	131 (52.6)
Medication		
Calcium channel blocker	%	107 (43.0)
ACE-I/ARB	%	81 (32.5)
Beta blocker	%	22 (8.8)
Loop diuretics	%	20 (8.0)
Nitrates	%	37 (14.9)
Statin	%	67 (26.9)
Fibrate	%	5 (2.0)
Ezetimibe	%	1 (0.4)
Insulin	%	12 (4.8)
SGLT2 inhibitor	%	2 (0.8)
Biguanide	%	8 (3.2)
DPP4 Inhibitor	%	18 (7.2)
BMI	kg/m^2	23.8 ± 3.9
Systolic blood pressure	mmHg	134.0 ± 32.0
Heart rate	bpm	77.0 ± 22.0
Laboratory data		
Hemoglobin	mg/dL	13.4 ± 2.0
Glucose	mg/dL	190.2 ± 91.3
Hemoglobin A1c	%	6.5 ± 1.3
Total cholesterol	mg/dL	189.0 ± 41.1
Triglyceride	mg/dL	118.81 ± 76.31
LDL-cholesterol	mg/dL	122.4 ± 36.6
non-HDL cholesterol	mg/dL	146.2 ± 40.0
BNP	pg/mL	278.9 ± 1288.0
Creatinine	IU/L	1.2 ± 1.6
Alanine aminotransferase	IU/L	58.5 ± 306.5
peak CK	IU/L	2973.0 ± 3257.0
peak CK-MB	IU/L	300.0 ± 668.0

Values are the number of subjects in each category with percent proportion in parentheses [*n* (%)] or data expressed as mean ± SD. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BMI: Body mass index; BNP: Brain natriuretic peptide; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CK-MB: Creatine kinase-myocardial isoform; DPP-4: Dipeptidyl peptidase-4; SGLT2: Sodium glucose cotransporter-2.

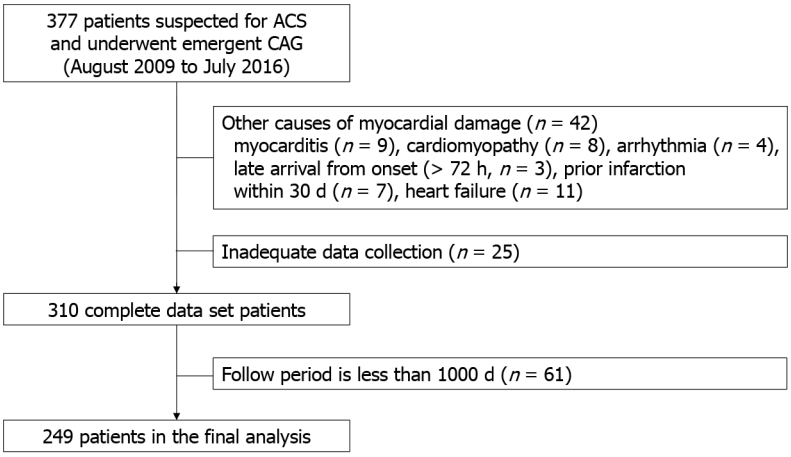

Figure 1 Flow diagram of the inclusion of study subjects. ACS: Acute coronary syndrome; CAG: Coronary angiography.

were in the left main coronary artery in five patients, left anterior descending artery in 113 patients, left circumflex artery in 31 patients, and right coronary artery in 50 patients. Immediate PCI was performed in 242 patients, including 51 with balloon dilation only and 191 with coronary stenting. Seven patients did not undergo PCI, five patients were eligible for thrombolytic therapy, and two did not undergo revascularization in the acute phase.

The changes in the levels of Lp(a), hs-CRP, CK, and CK-MB are shown in Table 2. Lp(a) initially decreased significantly to 24 h, and then increased to 48 h, which was not significantly different from that at 0 h. The mean hs-CRP levels gradually increased, and the CK and CK-MB levels both initially increased, peaked at 6 h, and then gradually decreased (these changes were both statistically significant). The change in Lp(a) from 0 h to 12 h [Lp(a)Δ0-12] was not associated with sex, age, or any associated condition. Regarding laboratory measurements, Lp(a)Δ0-12 showed significant and negative associations with basal levels of both creatinine (SRCC: -0.181, $P < 0.01$) and Lp(a) (SRCC: -0.306, $P < 0.05$). None of the remaining variables showed significant associations.

One hundred and forty-four patients developed MACE during the follow-up. Of the 17 patients who died, 13 died from heart disease, and 4 died from non-cardiac diseases (1 pneumonia, 2 cancer, and 1 unspecified cause). New angina pectoris was recorded in 111 patients, five of whom had unstable conditions. Nine patients had embolic events (seven with cerebral infarction and two with critical limb ischemia).

The prevalence of MACE was significantly greater in the tertile of Lp(a)Δ0-12; Q1 [Lp(a)Δ0-12: -31.6 to -1.8 mg/dL] than in Q2 + Q3 [Lp(a)Δ0-12: -1.8 to 8.3 mg/dL] (55 events *vs* 89 events, $P < 0.05$) (Figure 2). In univariate analysis, Lp(a)Δ0-12 and basal creatinine levels were significantly associated with the occurrence of MACE. In a multivariate analysis with the covariate as model-1, only Lp(a)Δ0-12 was identified as a significant and independent determinant [hazard ratio (HR): 0.95, $P = 0.022$]. In the analysis using model-2, Lp(a)Δ0-12 (HR: 0.96, $P = 0.019$) and basal creatinine (HR: 1.13, $P < 0.01$) were both significant and independent determinants (Table 3).

DISCUSSION

In the present study, we showed that, during the acute phase of ACS, Lp(a) initially decreased and then returned to its basal level, and that a greater decrease, expressed as Lp(a)Δ0-12, was significantly associated with the occurrence of subsequent MACE, which was independent of other well-known prognostic factors of ACS.

It has already been established that elevated Lp(a) levels are an independent causal risk factor for atherosclerotic cardiovascular diseases and aortic valve disease. In addition, recent studies have indicated its role in heart failure as well [14]. Lp(a) levels are strongly determined by genetic variants of the *LPA* gene, particularly by size polymorphism in apo(a). Therefore, previous clinical studies investigating the potential role of Lp(a) in various disease conditions were conducted using a one-point evaluation under stable conditions.

Regarding ACS, only limited data are available for small groups of patients. An initial small decrease from day 1 (mean 6.3 mg/dL) to day 3 (mean 5.8 mg/dL) in 59 AMI patients[6], a transient initial increase from day 1 (mean 327 mg/L) to day 21 (mean 376 mg/L) in 18 patients with unstable angina[7], and an initial increase from day 1 (mean 64 nmol/L) to day 30 (mean 82 nmol/L) in 35 placebo-assigned AMI patients have been reported[8]. To our knowledge, the present study is the first to examine changes in circulating Lp(a) levels in the very early phase of ACS, using the largest sample size to date. A significant increase in Lp(a) from the acute phase of AMI to the six- month follow-up has recently been reported[15] as an extension of a previous study[8]. In these studies[8,15], initial measurements were performed within 24

Table 2 Changes over time in the lipoprotein(a), high-sensitivity C-reactive protein, creatine kinase, and creatine kinase-myocardial isoform from pre-percutaneous coronary intervention to 48 h after percutaneous coronary intervention

	Baseline	3 h	6 h	12 h	24 h	48 h	ANOVA[2]
Lp(a), mg/dL	19.0 ± 21.8	18.0 ± 20.6[b]	18.0 ± 20.7[b]	17.8 ± 20.1[b]	18.2 ± 19.4[a]	19.3 ± 19.2	< 0.001
hs-CRP[1], ng/mL	9584.4 (511.0, 4745.0)	9784.1 (405.0, 5668.0)	11295.9 (631.0, 7420.0)	16680.2 (1730.0, 14700.0)[b]	34628.8 (6720.0, 47200.0)[b]	57233.6 (14400.0, 82600.0)[b]	< 0.001
CK[1], IU/L	567.1 (112.0, 594.0)	2410.3 (478.0, 3403.0)[b]	2606.7 (579.0, 3893.0)[b]	2228.0 (617.0, 3193.0)[b]	1451.6 (454.0, 1918.0)[b]	625.3 (200.0, 711.0)	< 0.001
CK-MB[1], IU/L	53.1 (10.0, 57.0)	221.1 (40.0, 309.0)[b]	234.6 (54.0, 360.0)[b]	176.8 (47.0, 261.0)[b]	81.4 (26.0, 104.0)	21.8 (10.0, 26.0)[a]	< 0.001

[a]*P* < 0.05.
[b]*P* < 0.01 *vs* baseline value.
[1]Due to skewed distribution, medians (25%, 75% tile) are shown.
[2]All *P* values remained the same when age (10-year age group) or sex was included as a covariate (ANCOVA).
CK: Creatine kinase; CK-MB: Creatine kinase MB; hs-CRP: High-sensitivity C-reactive protein; PCI: Percutaneous coronary intervention.

Table 3 Univariate and multivariate analyses to predict major adverse cardiac events

Variable	Univariate cox regression			Multivariate cox regression (model-1)			Multivariate cox regression (model-2)		
	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value
Lp(a)Δ0-12	0.96	0.93 to 0.99	0.024[a]	0.95	0.91 to 0.99	0.022[a]	0.96	0.92 to 0.99	0.019[a]
Lp(a) 0 h (baseline)	1.00	0.99 to 1.01	0.960	1.00	0.99 to 1.01	0.503	1.00	0.98 to 1.01	0.956
Age	0.99	0.98 to 1.01	0.481	1.00	0.98 to 1.01	0.833	1.00	0.98 to 1.01	0.721
Sex	1.50	0.97 to 2.33	0.068	1.46	0.89 to 2.37	0.131	1.50	0.94 to 2.40	0.091
Smoking	1.19	0.85 to 1.65	0.305	1.05	0.71 to 1.55	0.803			
Diabetes mellitus	1.28	0.91 to 1.79	0.155	1.09	0.72 to 1.65	0.676			
Systolic blood pressure	1.00	0.99 to 1.00	0.576	1.00	0.99 to 1.00	0.774			
Pulse rate	1.07	0.97 to 1.19	0.192	1.06	0.93 to 1.21	0.388			
Hemoglobin A1c	0.99	0.97 to 1.01	0.184	0.99	0.98 to 1.01	0.359			
HDL cholesterol	1.00	0.99 to 1.00	0.561	1.00	0.99 to 1.00	0.795			
LDL cholesterol	1.01	1.00 to 1.01	0.054						
Peak CK-MB	1.00	0.99 to 1.00	0.056				1.00	1.00 to 1.00	0.447
Creatinine	1.16	1.09 to 1.24	< 0.001[b]				1.13	1.05 to 1.22	< 0.01[b]
Killip classification	1.50	1.06 to 2.13	0.021[a]				1.39	0.96 to 2.02	0.078

[a]*P* < 0.05.
[b]*P* < 0.01.
Lp(a): Lipoprotein(a); CK-MB: Creatine kinase-myocardial isoform; MACE: Major adverse cardiovascular events; 95%CI: 95% confidence interval; HR: Hazard ratio.

h of the disease onset; therefore, the initial values might have been under-evaluated according to our current observations. In addition to the evaluation time point issue, the assay kits used in previous studies were highly variable, especially in terms of isoform influence. Therefore, the present study using the apo(a) isoform-resistant assay kit adds novel information to our knowledge about serial changes in circulating Lp(a) levels in patients with ACS.

The metabolism of Lp(a), synthesis, assembly, secretion, and clearance/catabolism have not yet been fully elucidated [16,17]. Similar to apolipoprotein B, apo(a) is exclusively synthesized in hepatocytes, suggesting the possibility that acute liver dysfunction may reduce apo(a) synthesis and Lp(a) assembly. None of the enrolled patients showed ALT elevation ≥ 100 IU/L or serum bilirubin elevation; therefore, the reduced production (also assembly and secretion) of Lp(a) resulting from liver dysfunction might play only a small role in the initial decrease in Lp(a) found in the present study. However, the precise mechanism underlying Lp(a) assembly remains unclear; therefore, an undetermined mechanism to reduce apo(a)-apolipoprotein B assembly may be involved.

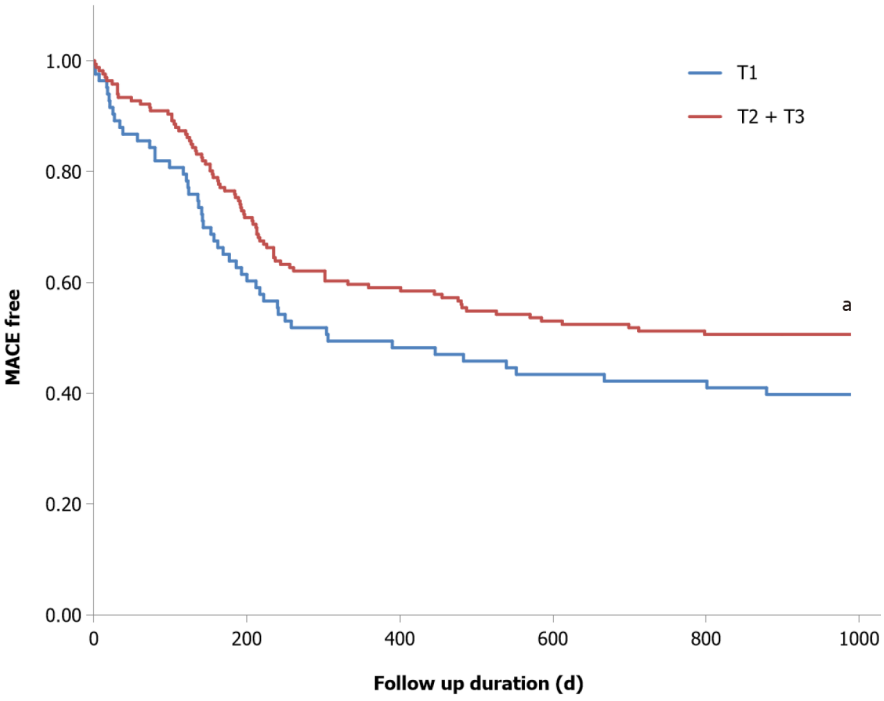

Figure 2 Cumulative freedom from the risk of major adverse cardiac events during three years of follow-up. Patients classified into the second (T2) and third (T3) tertiles of the change in lipoprotein(a) [Lp(a)] circulating levels of Lp(a) after percutaneous coronary intervention for acute coronary syndrome, The changes from 0 to 12 h [Lp(a)Δ0-12], showed significantly favorable outcomes compared to those classified into the first tertile (T1) in terms of all-cause death, nonfatal myocardial infarction and stroke, or new angina pectoris (log-rank test $\chi^2 = 4.23$, $^aP < 0.05$). MACE: Major adverse cardiac events.

The liver has also been established as the major site of Lp(a) clearance, followed to a much lesser extent by the kidneys and arterial wall[18,19]. Among the alternative pathways for Lp(a) clearance, toll-like receptor 2 (TLR2), which was proposed by a genome-wide association study[20], and the scavenger receptor BI (SR-BI), of which a rare genetic variant was reported in two human cohorts[21], are worth considering. Inflammatory processes play a pivotal role in the development of atherosclerotic vascular diseases, in which the activation of TLR2 in macrophages and other immune cells is crucial. Therefore, Lp(a) being catabolized by activated immune cells *via* TLR2 in patients with ACS after PCI, with a larger decrease indicating greater activation of this process, thereby leading to poor cardiovascular outcomes, seems to be an attractive hypothesis.

In the present study, baseline hs-CRP levels were not significantly associated with Lp(a)Δ0-12 ($r = 0.0982$, NS). This was also the case if the patient had unstable angina pectoris ($r = -0.0994$, NS), in which the influence of myocardial damage could be excluded. Further studies are needed to investigate the pathophysiology of this condition. Another potential pathway to consider is the SR-BI-mediated system, which is known to act as a high-density lipoprotein (HDL) receptor. Both human genetic studies[21] and cell biology experiments[22] have suggested that SR-BI plays a role in Lp(a) catabolism. In the present study, the fact that changes in HDL cholesterol from 0 h (44.1 mg/dL ± 10.6 mg/dL) to 12 h (41.8 mg/dL ± 9.2 mg/dL) showed a modest but significant association with Lp(a)Δ0-12 ($r = 0.1948$, $P < 0.01$) may support this possibility, which should be examined in further studies.

Our results are inconsistent with a previous report describing acute increases in both plasma Lp(a) and oxidized phospholipids after percutaneous coronary intervention in patients with stable coronary artery disease[23]. Differences in the clinical presentation of coronary artery disease (acute *vs* chronic coronary syndrome) would make it difficult to compare the study results directly; and thus, further studies are required to investigate this issue.

The present study clearly demonstrated that Lp(a) levels fluctuate during the acute phase of ACS; therefore, caution should be exercised when assessing Lp(a) levels. In addition, the determination of Lp(a) changes in the very acute phase of ACS may provide a better understanding of Lp(a) metabolism and pathophysiology in atherosclerotic vascular diseases. Another clinical implication of the present study is the modest but significant association between the initial decrease in both Lp(a) and HDL cholesterol levels. It could be hypothesized that a greater reduction in Lp(a) through the HDL-receptor might lead to worse cardiovascular effects through the atherogenic properties of Lp(a). Achieving of long-term reduction of Lp(a) levels by currently underdeveloping novel treatments could prevent this unfavorable effects in patients with high Lp(a) level.

Several limitations associated with the present study warrant mention. First, it was performed at a single center, indicating the potential for unrecognized bias. In addition, regarding the MACE criteria, we included new cases of angina pectoris because a small number of patients exhibited hard endpoints to sufficiently examine the prognostic value of Lp(a)Δ0-12. As shown in Table 4, the distribution of MACE types was compared according to the time course, but no specific trend was observed. A larger multicenter study would uncover the relationship between the Lp(a) change and the specific type of MACE. Second, this study enrolled all the type of patients diagnosed with ACS. We compared all variables derived from Lp(a) serial changes, including Lp(a)Δ0-12, but failed to find any significant differences across the

Table 4 Number of types of major adverse cardiac events during the follow-up period

Event	Total	Within 1 wk	1 wk to 1 month	1-6 months	6-12 months	After 12 months
Cardiac death	13	2	4	4	1	2
Other death	4	2	0	1	0	1
Nonfatal STEMI	2	1	0	0	0	1
Unstable angina	5	0	0	3	0	2
TLR or new PCI	102	0	5	42	36	19
New lesion with ischemia	9	0	1	2	1	5
Nonfatal stroke	7	1	0	1	1	4
EVT for PAD	2	0	0	0	2	0

EVT: Endovascular therapy; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; STEMI: ST elevation myocardial infarction; TLR: Target lesion revascularization.

ACS subgroups (data not shown). These findings suggest that the specific type of ACS manifestation did not play a major role in the current study. Theoretically, the influence of the amount of time from the ACS onset on the obtained results should be considered in the data interpretation. The time course of the Lp(a) levels found in this study can provide new ideas for future studies to investigate this issue. It is also possible that the severity of myocardial damages influences the occurrence of subsequent MACE. The lack of an association between well-known prognostic variables of ACS, such as peak CK levels or the Killip classification, suggests that Lp(a) itself or the pathophysiology responsible for Lp(a) changes might have an independent role. The introduction of a more sensitive assay for myocardial damage, such as troponin I assay, may also provide more detailed results. Third, most patients enrolled in this study were on statins the day after primary PCI without prior statin administration; thus, the possibility that statins played a role in subsequent Lp(a) changes could not be fully excluded. The beneficial effects of statin treatment after acute coronary events have been established; therefore, it is ethically difficult not to prescribe statin. Regarding the potential influence of prior medication on study results, statin are known to increase circulating Lp(a) levels[1,14,15]. In the present study, the mean baseline Lp(a) levels with prior statin treatment (22.2 mg/dL, n = 67) were slightly but statistically insignificantly higher than in those without such a history (17.8 mg/dL, n = 182). Lp(a) levels at 12 h with prior statin use (21.2 mg/dL, -4.5% from baseline) were comparable to those in patients without such a history (16.6 mg/dL, -6.5% from baseline). Further large-scale studies are needed to investigate this issue. Fourth, changes in apo-B-containing lipoprotein metabolism during the acute phase of ACS might influence circulating Lp(a) levels through altered apo-B production. However, neither baseline nor changes in lipid variables showed a significant relationship with Lp(a)Δ0-12.

CONCLUSION

The initial decrease in Lp(a) levels after PCI for ACS, as expressed by Lp(a)Δ0-12, was associated with the occurrence of MACE within three years. The pathophysiology causing this alteration in Lp(a) metabolism appears to be a novel target to improve the outcomes after successful PCI in patients with ACS.

FOOTNOTES

Author contributions: Saeki Y contributed to principal investigator (conceptualization, data curation, formal data analysis and interpretation, and drafting of the manuscript); Sawaguchi J contributed to associate investigator (conceptualization, data curation, formal data analysis, and interpretation); Takamura TA, Kitayama M, and Kawai Y contributed to coronary interventionalists (data curation and project administration regarding percutaneous coronary intervention procedures and patient management); Akita S, Fujibayashi K, Wakasa M, and Akao H contributed to staff cardiologists (data curation, preliminary data analysis, and interpretation); Kajinami K contributed to director (supervision of the overall study and manuscript editing/finalization).

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META-ANALYSIS

Establishing delivery route-dependent safety and efficacy of living biodrug mesenchymal stem cells in heart failure patients

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Abstract

BACKGROUND

Mesenchymal stem cells (MSCs) as living biopharmaceuticals with unique properties, *i.e.*, stemness, viability, phenotypes, paracrine activity, *etc.*, need to be administered such that they reach the target site, maintaining these properties unchanged and are retained at the injury site to participate in the repair process. Route of delivery (RoD) remains one of the critical determinants of safety and efficacy. This study elucidates the safety and effectiveness of different RoDs of MSC treatment in heart failure (HF) based on phase II randomized clinical trials (RCTs). We hypothesize that the RoD modulates the safety and efficacy of MSC-based therapy and determines the outcome of the intervention.

AIM

To investigate the effect of RoD of MSCs on safety and efficacy in HF patients.

METHODS

RCTs were retrieved from six databases. Safety endpoints included mortality and serious adverse events (SAEs), while efficacy outcomes encompassed changes in left ventricular ejection fraction (LVEF), 6-minute walk distance (6MWD), and pro-B-type natriuretic peptide (pro-BNP). Subgroup analyses on RoD were performed for all study endpoints.

RESULTS

Twelve RCTs were included. Overall, MSC therapy demonstrated a significant decrease in mortality [relative risk (RR): 0.55, 95% confidence interval (95%CI): 0.33-0.92, P = 0.02] compared to control, while SAE outcomes showed no significant difference (RR: 0.84, 95%CI: 0.66-1.05, P = 0.11). RoD subgroup analysis revealed a significant difference in SAE among the transendocardial (TESI) injection subgroup (RR = 0.71, 95%CI: 0.54-0.95, P = 0.04). The pooled weighted mean difference (WMD) demonstrated an overall significant improvement of LVEF by 2.44% (WMD: 2.44%, 95%CI: 0.80-4.29, P value ≤ 0.001), with only intracoronary (IC) subgroup showing significant improvement (WMD: 7.26%,

95%CI: 5.61-8.92, $P \leq 0.001$). Furthermore, the IC delivery route significantly improved 6MWD by 115 m (WMD = 114.99 m, 95%CI: 91.48-138.50), respectively. In biochemical efficacy outcomes, only the IC subgroup showed a significant reduction in pro-BNP by -860.64 pg/mL (WMD: -860.64 pg/Ml, 95%CI: -944.02 to -777.26, $P = 0.001$).

CONCLUSION

Our study concluded that all delivery methods of MSC-based therapy are safe. Despite the overall benefits in efficacy, the TESI and IC routes provided better outcomes than other methods. Larger-scale trials are warranted before implementing MSC-based therapy in routine clinical practice.

Key Words: Clinical trial; Heart failure; Mesenchymal stem cells; Living biodrug; Meta-analysis; Stem cells; Systematic review

Core Tip: Route of delivery (RoD) remains a critical determinant of safety and efficacy in cardiac stem cell therapy, particularly in heart failure (HF) patients. HF occurs when the heart's pumping ability is inadequate to meet the body's metabolic needs. Mesenchymal stem cells (MSCs) are living biopharmaceuticals with unique properties that need to be administered such that they reach the target site and are retained there to participate in the repair process. This systematic review and meta-analysis of phase II randomized clinical trials determine the RoD effect on the safety and efficacy of MSCs during HF treatment.

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INTRODUCTION

According to the updates from the American Heart Association, the prevalence of heart failure (HF) is expected to increase by 46% from 2012 to 2030, affecting approximately eight million individuals aged 18 years and older, highlighting a substantial increase in healthcare financial burden globally[1]. The contemporary treatment modalities provide only symptomatic relief without addressing the underlying issues, primarily attributed to the loss of functioning cardiomyocytes (CMs) and accentuated by the limited intrinsic repair mechanism to replace the lost CMs. This remains a challenge for the contemporary treatment options to compensate for the massive loss of functioning CMs, which enter the heart into a vicious cycle of remodeling, the hallmark of both ischemic and non-ischemic HF[2]. Hence, there is an urgent need to develop novel therapeutic strategies to address this issue that can repopulate the ischemically damaged myocardium with morphofunctionally competent CMs[3,4].

Mesenchymal stem cells (MSCs) are emerging as a promising living bio-drug for treating HF patients[5,6]. Since the reporting of the first clinical study by Hamano *et al*[7] using autologous bone marrow-derived MSCs (BM-MSCs) as an adjunct to coronary artery bypass graft surgery in five patients, several clinical trials have established the safety of MSC-based therapy in cardiac and non-cardiac diseases[8]. Current clinical trials to evaluate the efficacy of MSCs in HF patients have increased exponentially, among which are the Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1)[9], Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Heart Failure[10], Cardiopoietic stem Cell therapy in heart failure (C-CURE) study[11], and Prospective Randomized Study of MSC Therapy in Patients Undergoing Cardiac Surgery[12] besides several randomized clinical trials (RCTs) advancing to phase III as well[13,14]. Despite these advancements and some encouraging data, there is little consensus on the best cell route of delivery (RoD) for the heart, which has been shown to significantly modulate the survival and efficacy of the delivered MSCs[15].

To date, numerous studies have investigated the efficacy of MSCs using various RoD, with the most commonly employed methods being transendocardial (TESI), transepicardial injection (TEPI) under direct vision, IC infusion, and intravenous (IV) infusion[16]. Each RoD has its own set of advantages and limitations, encompassing factors such as delivery method convenience, invasiveness level, capability for site-directed cell delivery, the need for adjunct procedures, *i.e.*, left ventricular (LV) assist device (LVAD), coronary artery bypass grafting, eligibility for multiple or repeated dose administrations, and potential side-effect profiles.

This systematic review and meta-analysis primarily focus on evaluating phase II RCT data to investigate the effect of RoD of MSCs for safety and efficacy in HF patients. We hypothesize that the route of cell delivery modulates the safety and efficacy of MSC-based therapy and determines the outcome of the intervention. To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the effect of the route of administering MSCs on HF patients derived from early phase-II RCTs.

MATERIALS AND METHODS

Protocol and registration

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. Its design was comprehensively developed and prospectively registered in the PROSPERO International Prospective Register of Systematic Reviews, registration number CRD42023484749.

Literature search strategy

The identification of relevant studies was conducted from October 18 to November 19, 2023, using the following databases: PubMed/MEDLINE, Clinicaltrials.gov, ScienceDirect, Cochrane CENTRAL, EBSCOHost, and the European Union Drug Regulating Authorities Clinical Trials (EudraCT). The keyword 'heart failure' was adopted as a MeSH term. In contrast, the terms "Mesenchymal Stem Cells", "Mesenchymal Precursor Cells", "Mesenchymal Progenitor Cells", and equivalent terms were used as a text field search. We incorporated all the predefined keywords with the Boolean operators "AND" and "OR". Lastly, we thoroughly snowballed the references from retrieved articles for potentially relevant studies.

Eligibility criteria

Using our predefined eligibility criteria, the review included all studies which were: (1) Phase II RCT; (2) recruited adult patients aged over 18 years old with HF; (3) had a control arm; (4) intervention arm received MSC therapy; and (5) written in the English language. Any studies that did not fulfill the aforementioned inclusion criteria were therefore excluded. Following the literature compilation, two reviewers (MJ and IS) independently screened the retrieved studies for duplicates and compliance with eligibility criteria. Any discrepancies were solved by discussion between the reviewers and, when appropriate, the involvement of the remaining two authors (MC and KH).

Data extraction

After the initial abstract and title screening, the studies were further screened for full-text review and data extraction. The data extraction was accomplished using the predefined Excel sheet that incorporated several primary variables, including the trial registry, name of primary author, year of publication, design of the RCT, blinding status, country, sample size, mean age, type of MSC and its source, type of control arm, the RoD, MSC dose, New York Heart Association (NYHA) status at baseline, imaging modalities used for LV assessment, and time to follow up for primary outcomes and LV ejection fraction (LVEF) assessment. Furthermore, the five outcome variables were recorded, including the number of serious adverse events (SAE), number of death, LVEF (percentage), 6-minute walk distance (6MWD) (meters), and Pro-B-type natriuretic peptide (pro-BNP) (in pg/mL). The outcome variables were recorded at baseline and upon follow-up when relevant.

Quality assessment

We assessed the included RCTs using the Jadad scale to evaluate the risk of bias. In summary, the Jadad scale assesses three items: randomization (up to two points), double-blinding (up to two points), and correct reporting of withdrawals and dropouts (up to one point)[17]. Upon completion of the evaluation process, the scores ranging from zero to five were added to determine the quality score for each trial. A study with 0-2 was considered low quality, while the one scoring ≥ 3 was considered superior quality.

Outcome measures and statistical analysis

The endpoints of this study included safety and efficacy outcomes. Safety outcomes were defined as the number of deaths and SAEs on follow-up. Efficacy outcomes, on the other hand, encompassed functional, clinical, and biochemical outcomes, which were determined by changes in LVEF (percentage), 6MWD (meters), and pro-BNP (pg/mL) compared to their respective baseline values. Regenerative capacity, ideally evaluated by LV wall thickness, was not included in the efficacy outcome measure due to a lack of data almost uniformly across all the included trials. Safety outcomes were regarded as dichotomous variables and were reported in relative risk (RR). In contrast, the efficacy outcomes were regarded as continuous and reported in weighted mean difference (WMD). The random-effect model was used due to a variety of population origins. The RR was considered statistically significant if the 95% confidence interval (CI) did not contain the value of 1, *i.e.*, the null hypothesis value. On the other hand, if the WMD's 95%CI included the value of 0, the value was considered not statistically significant. Further, as our study focuses on the influence of different RoD on the outcomes, we run a subgroup analysis of the RoD in all outcome variables.

Heterogeneity analysis was evaluated with I^2 statistics and τ^2. The I^2 values of < 25% represent a low heterogeneity, with 25%-75% as moderate probability, whereas > 75% is considered high probability. The funnel plot assessed publication bias visually, using Egger's regression test for statistical assessments. Subgroup meta-analyses were implemented to identify the sources of heterogeneity. We also performed standard leave-one-out sensitivity analyses to safety and efficacy endpoints to identify studies that significantly influenced the pooled estimates. Results were considered to be statistically significant at P value ≤ 0.05. This statistical analysis used the IBM SPSS Statistics for Mac (Version 28.0. IBM Corp., Armonk, NY, United States) and Stata (Stata Statistical Software: Version 17, College Station, TX: Stata Corp LP).

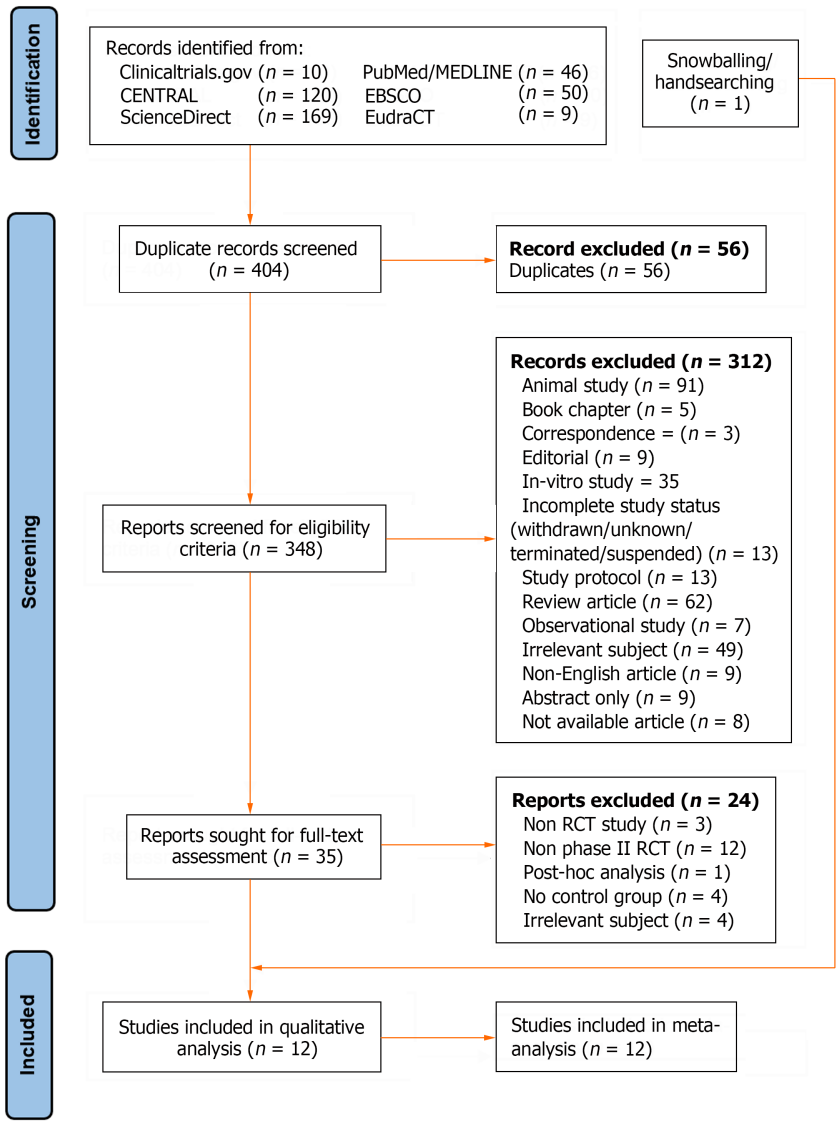

Figure 1 PRISMA flow chart. RCT: Randomized controlled trials.

RESULTS

A literature search from the databases

A total of 404 studies were identified from six databases, *i.e.*, Clinicaltrials.gov (n = 10), CENTRAL (n = 120), ScienceDirect (n = 169), PubMed/MEDLINE (n = 46), EBSCOHost (n = 50), and EudraCT (n = 9). Initial screening identified duplicates (n = 56), with further abstract/title screening excluded studies for animal studies (n = 91), book chapter (n = 5), correspondence (n = 3), editorial (n = 9), in-vitro studies (n = 35), incomplete study status (n = 13), study protocol (n = 13), review article (n = 62), observational study (n = 7), irrelevant subject (n = 49), non-English articles (n = 9), abstract only (n = 9), and not available articles (n = 8). Upon full-text assessment of the remaining 35 studies, 24 studies were excluded from the review for non-RCT study (n = 3), non-phase II RCT (n = 12), posthoc analysis (n = 1), no available control arm (n = 4), and irrelevant subject (n = 4). In addition, handpicking from the references of retrieved papers yielded one study, leaving us with twelve studies for inclusion in systematic review and meta-analysis, as depicted in the PRISMA flow diagram of the study (Figure 1).

Description of studies included in the meta-analysis

Table 1 shows the baseline characteristics of the 12 RCTs included in our study that were published between 2014 and 2023. Male participants represented most of the sample, with the mean age ranging from 40 to 70. Nine of the 12 RCTs were double-blinded. Nine studies used BM-MSC as an intervention, seven of which were allogeneic MSCs retrieved from healthy donors. On the other hand, only two and one RCTs used adipose-derived MSC (A-MSC) and umbilical cord-derived MSC, all of which were allogeneic. Ten RCTs used placebo-treated patients (*e.g.*, isotonic saline) for comparison. In contrast, Florea *et al*[18] had BM-MSC at a lower dose, *i.e.*, 20 million, as a control arm (compared to 100 million in the treatment arm). In contrast, Zhao *et al*[19] only used standard care as the control arm, *i.e.*, drug only, instead of injecting a placebo-containing solution.

Table 1 Baseline characteristics of the included trials

Ref.	Trial registry	Study design, phase, blinding	Sample size (*n*)	Size at each arm (*n*)		Sex (*n*)		Age (yr)	Intervention	Source	Cell type	RoD	Dose (million)	NYHA			
						M	F							I	II	III	IV
Ascheim *et al* [21], 2014	NCT01442129	RCT, II, double-blind	30	Exp	20	17	3	55.10 ± 15.40	BM-MSC	NA	Allo	TEPI	25	0	0	3	17
				Ctrl	10	8	12	62.20 ± 7.80	Placebo					0	1	2	7
Perin *et al*[27], 2015	NCT00721045	RCT, II, double-blind	60	Exp	45	44	1	62.20 ± 10.30	BM-MSC	Iliac crest	Allo	TESI	25, 75, 150	0	31	6	0
				Ctrl	15	11	4	62.70 ± 11.20	Placebo					0	14	9	0
Mathiasen *et al* [25], 2015	NCT00644410	RCT, II, double-blind	60	Exp	40	36	6	66.10 ± 7.70	BM-MSC	NA	Auto	TESI	NA	0	11	29	0
				Ctrl	20	14	6	64.20 ± 10.60	Placebo					0	5	15	0
Zhao *et al*[19], 2015	NA	RCT, NA, NA	59	Exp	30	24	6	52.90 ± 16.32	UC-MSC	Fetal UC	Allo	IC	NA	NA	NA	NA	NA
				Ctrl	29	19	10	53.21 ± 11.46	Standard care					NA	NA	NA	NA
Patel *et al*[23], 2016	NCT01670981	RCT, II, double-blind	109	Exp	58	55	3	65.30 ± 8.49	BM-MSC	Iliac crest	Auto	TESI	NA	0	2	52	4
				Ctrl	51	45	6	64.70 ± 9.94	Placebo					0	2	47	2
Butler *et al*[22], 2017	NCT02467387	RCT, II, single-blind	22	Exp	10	13	9	47.30 ± 12.80	BM-MSC	NA	Allo	IV	1.5/kg	0	21	1	0
				Ctrl	12				Placebo								
Xiao *et al*[29], 2017	NA	RCT, NA, double-blind	37	Exp	17	12	5	51.60 ± 12.20	BM-MSC	Iliac spine	Auto	IC	NA	NA	NA	NA	NA
				Ctrl	20	14	6	15.40 ± 11.60	Placebo					NA	NA	NA	NA
Florea *et al*[18], 2017	NCT02013674	RCT, II, double-blind	30	Exp	15	15	0	65.60 ± 9.40	BM-MSC	NA	Allo	TESI	100	6	7	1	1
				Ctrl	15	12	3	66.80 ± 12.20	BM-MSC	NA	Allo	TESI	20	4	8	3	0
Yau *et al*[20], 2019	NCT02362646	RCT, II, NA	159	Exp	106	94	12	55.50 ± 12.30	BM-MSC	NA	Allo	TEPI	150	0	0	31	75

				Ctrl	53	47	6	56.90 ± 11.70	Placebo					0	0	12	41
Bolli *et al*[26], 2021	NCT02501811	RCT, II, double-blind	94	Exp	62	58	4	61.35 ± 8.90	BM-MSC ± CPC	NA	Allo	TESI	150	2	46	14	0
				Ctrl	32	31	1	63.10 ± 8.80	Placebo					1	28	3	0
Qayyum *et al* [28], 2023	NCT03092284	RCT, II, double-blind	81	Exp	54	44	10	67.00 ± 9.00	A-MSC	Abd SC	Allo	TESI	100	NA	NA	NA	NA
				Ctrl	27	24	3	66.60 ± 8.10	Placebo					NA	NA	NA	NA
Qayyum *et al* [28], 2023	NCT02673164	RCT, II, double-blind	133	Exp	90	84	6	66.40 ± 8.10	A-MSC	Abd SC	Allo	TESI	100	0	62	28	0
				Ctrl	43	38	5	64.00 ± 8.80	Placebo					0	30	13	0

A-MSC: Adipose cell-derived mesenchymal stem cells; Abd SC: Abdominal subcutaneous fat; Allo: Allogenic; Auto: Autologous; BM-MSC: Bone marrow-derived mesenchymal stem cells; CPC: c-kit positive cardiac cells; Ctrl: Control arm; Exp: Exposure arm; IM: Intramyocardial injection; IV: Intravenous infusion; NA: Not applicable; NYHA: New York Heart Association; RCT: Randomized controlled trials; TESI: Transendocardial stem cell injection; UC-MSC: Umbilical cord-derived mesenchymal stem cells.

Regarding RoD, seven studies employed the TESI RoD, whereas both TEPI and IC routes accounted for two studies each. Only one study used IV RoD for MSC delivery. Out of the total sample of 874 participants, the TESI route contributed to the largest sample size (total n = 567, intervention arm n = 364, control arm n = 203), followed by TEPI (total n = 189, intervention arm n = 126, control arm n = 63), IC (total n = 96, intervention arm n = 47, control arm n = 49), and IV infusion (total n = 22, intervention arm n = 10, control arm n = 12). Two studies, *i.e.*, Yau *et al*[20] and Ascheim *et al* [21], included populations necessitating the placement of LVAD with the TEPI-administered MSCs or placebo during the placement of LVAD. There was a large variability in the injected dose of the MSCs, ranging from 25-150 million cells. The follow-up for primary outcomes and LVEF assessment was conducted beyond six months for all studies except Butler *et al*[22], which assessed the LVEF three months after the procedure. The measurements of LVEF, 6MWD, and pro-BNP on the baseline and during the follow-up have been summarized in Table 2.

Quality of studies

Table 3 summarizes the quality results of the twelve studies included in the meta-analysis. Using the Jadad scale risk of bias score ranging from 1-5 points, nine studies were of "high" quality (three studies scoring five points[23-25], two studies scoring four points[18,26], and four studies scoring three points each[20,21,27,28]. Three studies were considered "low" quality (one scoring two points[22], and two studies scoring one point each[19,29].

Publication bias assessment

The funnel plot (Supplementary Figure 1) depicts the visual assessment of publication bias, showing an apparent symmetric distribution across all study endpoints. Correspondingly, Egger's test for small-study effects demonstrated no publication bias for death (P = 0.64), SAE (P = 0.99), LVEF (P = 0.33), 6MWD (P = 0.73), and pro-BNP (P = 0.31). Leave-

Table 2 Outcome and follow-up characteristics of included trials

Ref.	Trial registry	Arm	FU		Imaging				SAE/death	LVEF (%)		6MWD (meter)		Pro-BNP (pg/mL)	
			For 1° outcome	For LVEF	Echo	CCT	CMR	SPECT		Baseline	FU	Baseline	FU	Baseline	FU
Ascheim *et al*[21], 2014	NCT01442129	Exp	12	12	Yes	No	No	No	19/0	17.50 ± 3.90	24.00 ± 3.90	NA	883.00 ± 233.00	NA	NA
		Ctrl							9/3	19.30 ± 5.10	22.50 ± 5.10	NA	1080.00 ± 359.50	NA	NA
Perin *et al*[27], 2015	NCT00721045	Exp	36	12	Yes	No	No	Yes	10/2	31.30 ± 8.58	32.40 ± 8.70	401.60 ± 96.40	427.30 ± 115.10	436.80 ± 563.40	347.30 ± 335.69
		Ctrl							5/3	34.60 ± 6.43	33.10 ± 9.30	319.30 ± 121.40	346.60 ± 121.80	217.70 ± 149.60	319.80 ± 193.02
Mathiasen *et al* [25], 2015	NCT00644410	Exp	6	6	Yes	Yes	Yes	No	13/1	28.20 ± 9.30	33.20 ± 3.80	401.00 ± 70.00	421.40 ± 76.60	582.69 ± 970.01	NA
		Ctrl							16/1	25.10 ± 8.50	23.80 ± 3.70	385.00 ± 81.00	414.72 ± 79.60	564.08 ± 981.86	NA
Zhao *et al*[19], 2015	NA	Exp	6	6	No	No	No	No	1/2	30.00 ± 4.50	49.00 ± 5.10	312.17 ± 89.19	466.36 ± 82.90	4376.27 ± 510.71	1648.96 ± 304.54
		Ctrl							0/7	28.00 ± 4.90	39.00 ± 3.50	295.07 ± 46.87	334.27 ± 43.80	4701.76 ± 513.53	2835.09 ± 412.03
Patel *et al*[23], 2016	NCT01670981	Exp	12	12	Yes	No	No	No	31/2	26.50 ± 5.10	28.10 ± 6.13	313.00 ± 100.00	370.62 ± 114.30	1755.00 ± 1842.00	NA
		Ctrl							41/7	24.40 ± 6.00	25.30 ± 6.10	302.00 ± 105.00	353.43 ± 128.30	2132.00 ± 2021.00	NA
Butler *et al*[22], 2017	NCT02467387	Exp	6	3	No	No	Yes	No	0/0	34.30 ± 7.91	34.10 ± 9.70	NA	NA	806.27 ± 1387.85	768.25 ± 2945.53
		Ctrl							0/0	34.50 ± 7.49	36.70 ± 5.40	NA	NA	NA	NA
Xiao *et al*[29], 2017	NA	Exp	12	12	Yes	No	No	Yes	5/0	34.10 ± 3.600	41.00 ± 6.70	309.00 ± 84.70	NA	539.20 ± 213.60	NA
		Ctrl							7/2	33.70 ± 4.00	34.30 ± 5.30	323.30 ± 89.40	NA	575.30 ± 207.60	NA
Florea *et al*[18], 2017	NCT02013674	Exp	12	12	Yes	Yes	No	No	2/1	30.10 ± 8.80	33.10 ± 7.30	434.90 ± 120.00	463.00 ± 143.10	377.70 ± NA	NA
		Ctrl							3/0	37.60 ± 13.30	37.30 ± 13.00	398.70 ± 111.60	409.70 ± 130.20	532.30 ± NA	NA

Yau *et al*[20], 2019	NCT02362646	Exp	12	6	Yes	No	No	No	88/15	17.30 ± 5.80	19.00 ± 9.40	NA	NA	NA	NA
		Ctrl							41/8	16.20 ± 6.00	17.60 ± 6.20	NA	NA	NA	NA
Bolli *et al*[26], 2021	NCT02501811	Exp	12	12	No	No	Yes	No	19/5	29.23 ± 6.30	30.50 ± 6.90	367.72 ± 83.85	398.72 ± 93.10	1026.07 ± 2702.11	640.37 ± 1512.69
		Ctrl							13/4	29.66 ± 6.18	29.40 ± 5.90	367.60 ± 85.60	384.88 ± 101.70	856.72 ± 1364.72	1072.32 ± 2161.64
Qayyum *et al*[28], 2023	NCT03092284	Exp	12	6	Yes	No	No	No	21/3	34.20 ± 7.90	34.80 ± 5.80	388.00 ± 92.00	400.00 ± 86.10	1382.71 ± 1538.32	1850.22 ± 951.24
		Ctrl							11/0	33.76 ± 2.70	33.80 ± 6.90	416.00 ± 121.00	447.87 ± 120.20	1283.77 ± 1206.81	1589.83 ± 543.70
Qayyum *et al*[28], 2023	NCT02673164	Exp	12	6	Yes	No	No	No	26/3	31.60 ± 7.20	32.80 ± 7.50	419.00 ± 12.00	432.00 ± 13.00	1495.00 ± 2242.00	1607.00 ± 274.00
		Ctrl							10/2	32.00 ± 8.90	34.70 ± 9.70	423.00 ± 18.00	451.00 ± 19	1828.00 ± 2376.00	1652.00 ± 595.00

6MWD: 6-minute walk distance; CCT: Cardiac computed tomography; CMR: Cardiac magnetic resonance imaging; Ctrl: Control arm; Echo: Echocardiography; Exp: Exposure arm; FU: Follow-up; LVEF: Left ventricular ejection fraction; Pro-BNP: Pro-B-type natriuretic peptide; SAE: Serious adverse events; SPECT: Single-photon emission computed tomography.

one-out sensitivity analyses were performed for all endpoints, as shown in Supplementary Figure 2.

Safety outcome analysis

Death: Mortality was measured in all twelve RCTs included in the meta-analysis. As illustrated in Figure 2, a significant reduction in mortality rate was evident, and the result indicated a 45% reduction in mortality among patients treated with MSCs (RR: 0.55, 95%CI: 0.33-0.92, P = 0.02). However, subgroup analyses showed no significant mortality reduction across all the delivery routes. Leave-one-out sensitivity analysis showed a non-significant decrease in the risk of death when a study by either Perin *et al*[27], Zhao *et al*[19], or Patel *et al*[23] was omitted (Supplementary Figure 2). In addition, among the TESI subgroup, the risk of death was significantly reduced when a study by Florea *et al*[18] and Qayyum *et al*[28] was omitted (Supplementary Figure 3). The studies largely showed a low overall heterogeneity (I^2 = 5.68%); within-subgroup heterogeneity between subgroups was low (I^2 = 0.00%) apart from the TEPI route (I^2 = 63.85%). The heterogeneity of the IV subgroup could not be analyzed across all study endpoints due to the availability of only one study in the subgroup.

SAEs: SAE analysis revealed no overall significant morbidity benefits (RR: 0.84, 95%CI: 0.66-1.05, P = 0.11) (Figure 3) with moderate heterogeneity (I^2 = 59.08%). Subgroup analysis revealed a significant change in the incidence of SAEs among the TESI subgroup, favoring the intervention arm (RR: 0.71, 95%CI: 0.54-0.95, P = 0.04). Other delivery routes demonstrated no difference in the risk for SAEs. Within-subgroup heterogeneity was moderate in the TESI subgroup (I^2 = 42.40%) and low in both TEPI and IC subgroups (I^2 = 0.00% in both subgroups).

Table 3 Jadad scale quality assessment of the included trials (R, randomization; B, blinding; D, dropout)

Ref.	Trial registry	Jadad scale				Quality
		R (0-2)	B (0-2)	D (0-1)	Total	
Ascheim *et al*[21], 2014	NCT01442129	1	1	1	3	High
Perin *et al*[27], 2015	NCT00721045	2	0	1	3	High
Mathiasen *et al*[25], 2015	NCT00644410	2	2	1	5	High
Zhao *et al*[19], 2015	NA	1	0	0	1	Low
Patel *et al*[23], 2016	NCT01670981	2	2	1	5	High
Butler *et al*[22], 2017	NCT02467387	1	0	1	2	Low
Xiao *et al*[29], 2017	NA	1	0	0	1	Low
Florea *et al*[18], 2017	NCT02013674	2	1	1	4	High
Yau *et al*[20], 2019	NCT02362646	2	0	1	3	High
Bolli *et al*[26], 2021	NCT02501811	1	2	1	4	High
Qayyum *et al*[28], 2023	NCT03092284	1	1	1	3	High
Qayyum *et al*[28], 2023	NCT02673164	2	2	1	5	High

Efficacy outcome analysis

Functional outcomes (LVEF): All twelve RCTs have reported changes in LVEF compared to baseline. The imaging modalities used to measure the LV systolic performance included echocardiography (n = 9), cardiac computed tomography scan (n = 2), cardiac magnetic resonance (n = 3), and single-photon emission computed tomography (SPECT) (n = 2), as shown in Table 2. Four studies evaluated the LV functional outcome with multiple imaging modalities[20,27,29,30]. As illustrated in Figure 4, there was a significant increase in LVEF compared to baseline (WMD: 2.44%, 95%CI: 0.80-4.29, $P \leq 0.001$) with significant overall heterogeneity (I^2 = 96.62%). Further subgroup analysis revealed a significant increase only in the IC subgroup (WMD: 7.26%, 95%CI: 5.61-8.92, $P \leq 0.001$). There was no significant improvement in different RoD subgroups, including TESI (WMD: 1.50%, 95%CI: -0.68-3.68), TEPI (WMD: 1.57%, 95%CI: -1.33-4.48), and IV routes (WMD: -2.40%, 95%CI: -11.49-6.69). There was a high within-subgroup heterogeneity in both TESI (I^2 = 93.89%) and TEPI subgroups (I^2 = 83.21%) and moderate heterogeneity in the IC subgroup (I^2 = 41.88%).

Clinical outcomes (6-minute walk distance): Only nine of the twelve studies assessed 6MWD as a clinical outcome parameter (Figure 5). Although Butler *et al*[22] did not report on baseline and follow-up 6MWD, they incorporated the changes in 6MWD in their study endpoints. Overall, there was no significant change in 6MWD (WMD: 19.71 m, 95%CI: -8.41-47.83, P = 0.17) with high heterogeneity across the studies (I^2 = 96.30%). Among the subgroups, IC demonstrated a significant rise in 6MWD of 114.99 m (95%CI: 91.48-138.50, $P \leq 0.001$). There was no significant increase among the IV (WMD: 38.23 m, 95%CI: -0.83-77.29, P = 0.05) and TESI subgroups (WMD: 0.56 m, 95%CI: -11.68-12.80, $P \geq 0.05$). There were no studies within TEPI RoD reporting the 6MWD outcome. Within-subgroup heterogeneity revealed moderate heterogeneity among the TEPI subgroup (I^2 = 74.24%), whereas both IC and IV subgroups were not assessed for heterogeneity because of single-study subgroups.

Biochemical outcome (pro-BNP Test): Only six studies assessed the biochemical outcome, *i.e.*, pro-BNP, as displayed in Figure 6. There was no significant overall change in the pro-BNP level (WMD: -160.35 pg/mL, 95%CI: -689.98-369.29, P = 0.54) with high heterogeneity across the studies (I^2 = 98.91%). Among subgroups, the IC delivery route significantly reduced the pro-BNP level (WMD = -860.64 pg/mL, 95%CI: -944.02 to -777.26, P value = 0.001). TESI significantly reduced the pro-BNP level among the subgroups (WMD: -860.64 pg/mL, 95%CI: -944.02 to -777.26, P value ≥ 0.05). Significant heterogeneity was found among the TESI subgroup (I^2 = 98.91%).

DISCUSSION

The emergence of MSCs as living bio-drugs has given rise to unique challenges regarding RoD, as it remains a crucial determinant of their safety and efficacy in clinical settings. MSCs are distinct from routine pharmaceuticals in molecular weight, size, shape, and above all, being with a living status; they need to be administered such that they reach the target site, *i.e.*, damaged myocardium, in large enough numbers with high viability, maintain their stemness and original phenotype and are retained at the injury site for long enough time to participate in the repair process with minimal off-target accumulation. Some commonly used RoD in the reported clinical studies encompass IM, IC, retrograde intracoronary (IC) sinus, IV, TESI, and scaffold-based delivery methods, each with advantages and limitations[16]. Our study provides a systematic review and meta-analysis of twelve published phase II RCTs to determine if different RoD affect the safety and efficacy of MSCs during HF treatment. The essential findings of the study are: (1) MSC-based

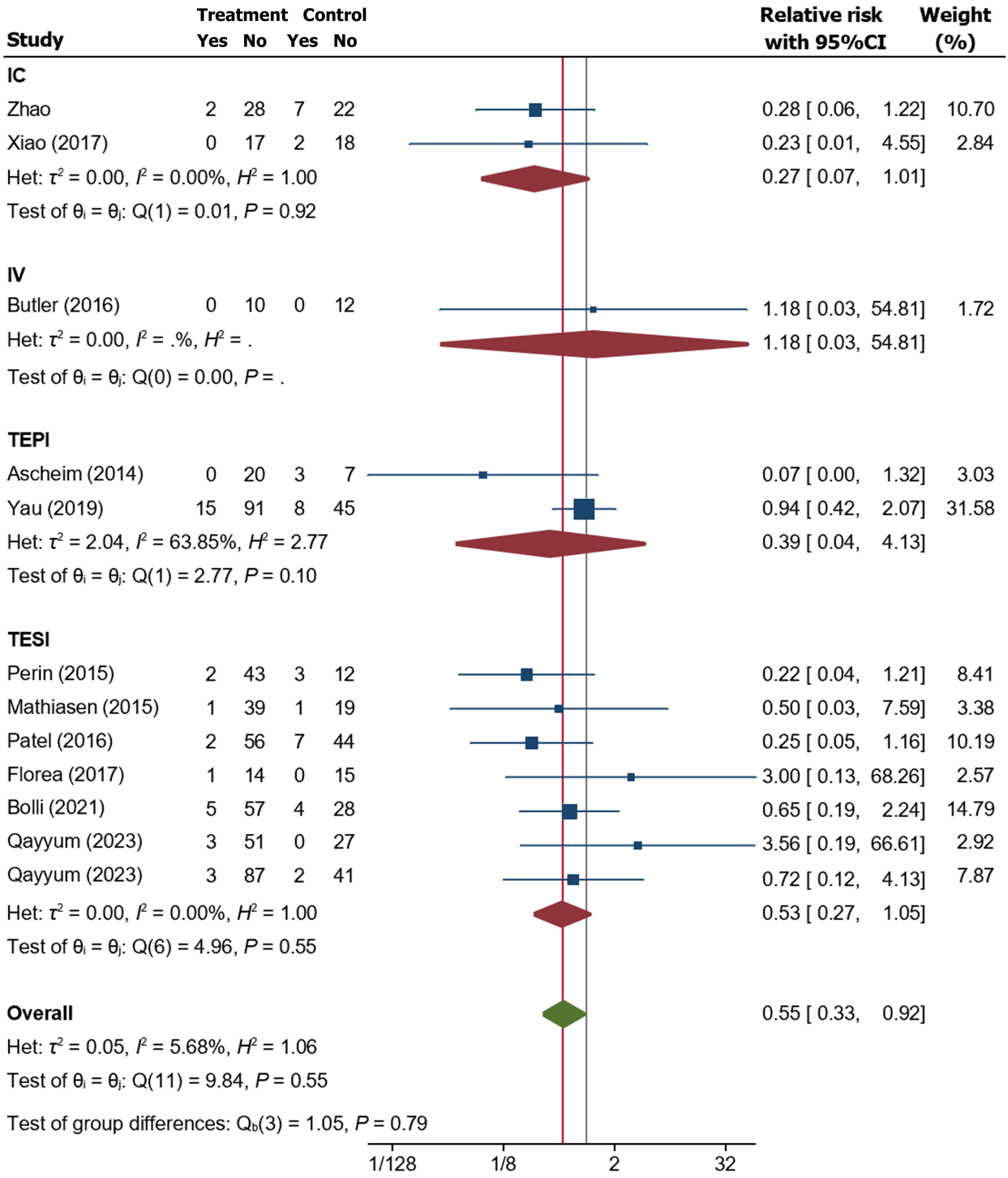

Figure 2 Relative risk of death between groups. IC: Intracoronary; IV: Intravenous injection; TEPI: Transepicardial injection; TESI: Transendocardial injection; 95%CI: 95% confidence interval.

treatment resulted in a significant reduction in all-cause mortality compared to the control; (2) there was no significant change in the incidence of SAEs depending upon the RoD; and (3) both TESI and IC injection yielded superior efficacy outcomes compared to other routes. We will discuss the effect of each RoD on MSC delivery in the following sections.

Though invasive, TEPI under direct vision as an adjunct to LVAD allows site-directed delivery of cells with a better retention rate. In our meta-analysis, however, two out of twelve studies used TEPI RoD without significantly reducing all-cause mortality and morbidity. Also, there was no significant improvement in LVEF, 6MWD, and pro-BNP levels compared to the baseline. These data contradict a meta-analysis by Soetisna *et al*[31], which reported an increase in the 6MWD in patients with ischemic heart disease treated. Nevertheless, apart from suggested efficacy limitations in our findings, one of the significant drawbacks to implementing the TEPI RoD is its invasive nature, which may also lead to perforation and arrhythmia. Therefore, this approach only offers superior advantages to other RoDs.

TESI RoD was our meta-analysis's second most utilized RoD in seven of the twelve studies. TESI is one of the minimally invasive RoDs for site-directed implantation of cells using electromagnetic mapping. Our meta-analysis did

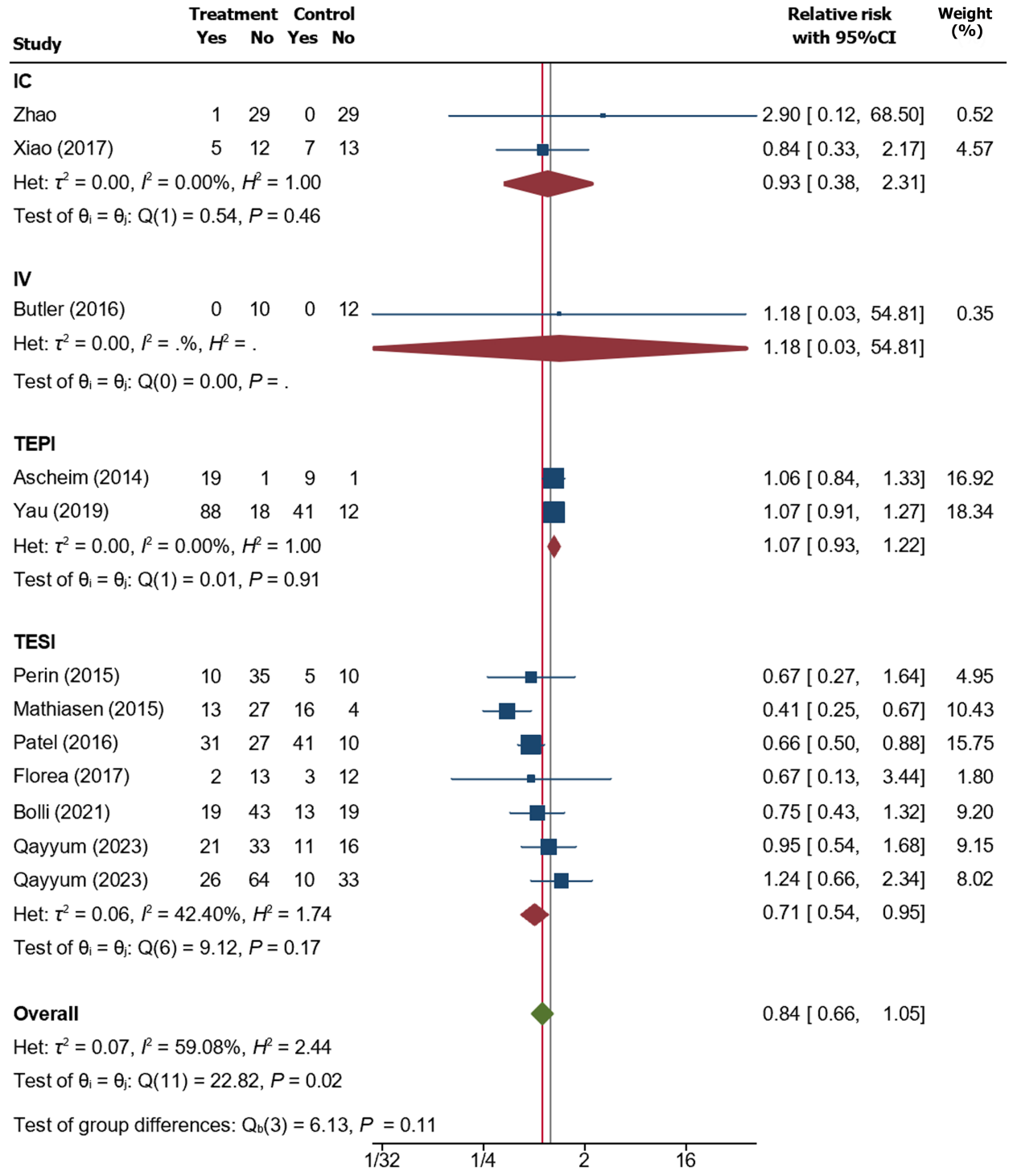

Figure 3 Relative risk of serious adverse events between groups. IC: Intracoronary; IV: Intravenous injection; TEPI: Transepicardial injection; TESI: Transendocardial injection; 95%CI: 95% confidence interval.

not reveal a significant reduction in mortality but a significant overall morbidity reduction. The finding contradicted Gyöngyösi *et al*[30], who reported a significant reduction of all-cause mortality in their pooled analysis of eighteen studies. However, it was noteworthy that the heterogeneity of the TESI RoD subgroup was substantial across all study endpoints. As such, our study found a significant reduction in mortality when excluding a Danish phase II trial by Qayyum *et al*[28] among the TESI arm subgroup. In this study, the MSC-treated arm had 3 cases of death, whereas the control arm demonstrated no mortality. Nevertheless, the leave-one-out sensitivity analysis failed to demonstrate the efficacy benefits of the TESI route, including LVEF, pro-BNP, and 6MWD. Despite the early trials demonstrating a promising efficacy performance of the TESI route, the recent SCIENCE and Danish trials (2023) did not demonstrate improvement in any of the efficacy parameters[24,28]. As such, our findings contradicted an earlier meta-analysis by Fan *et al*[32], which found an improvement in LVEF among HF patients treated with MSC therapy using the TESI delivery route.

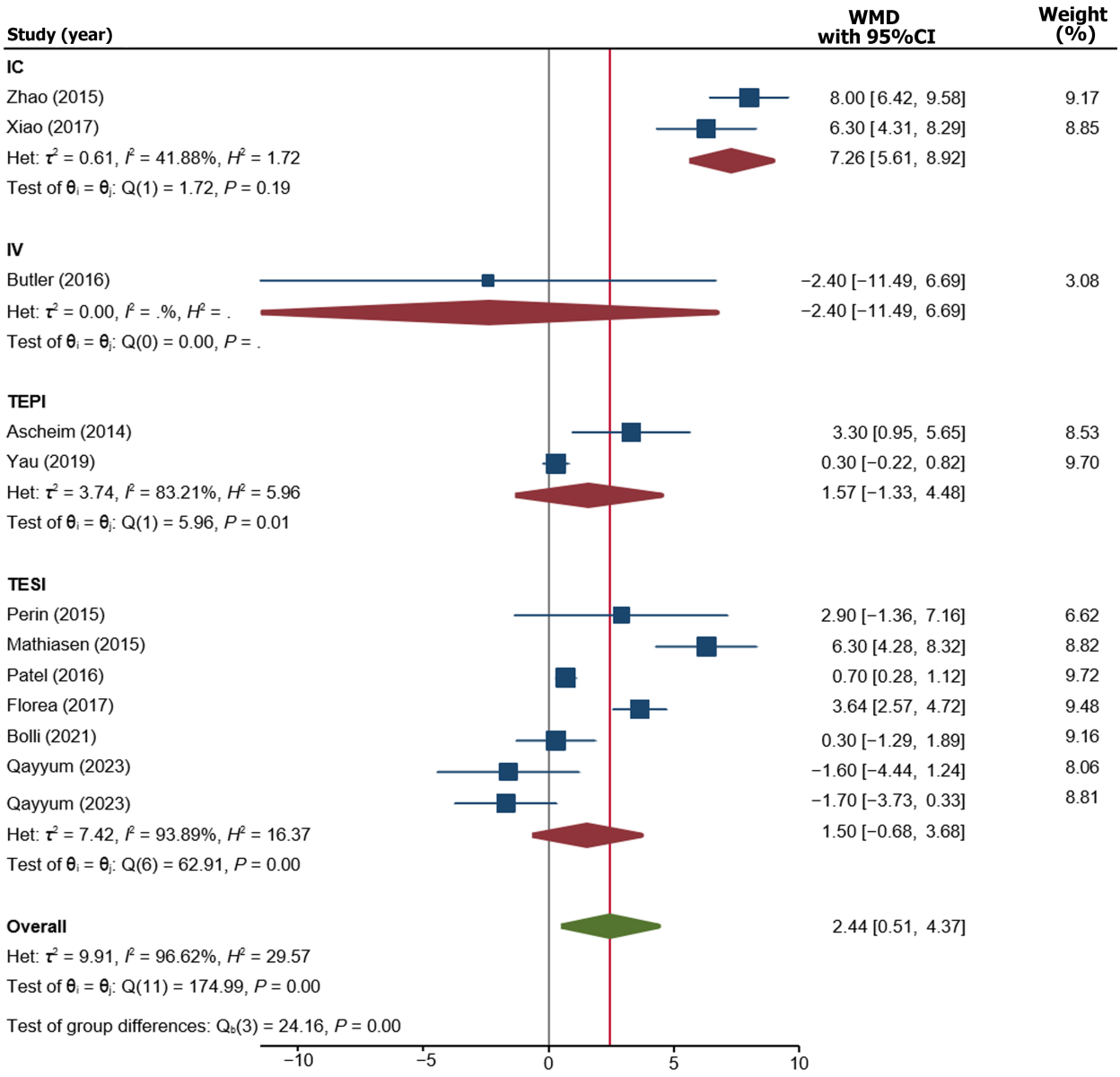

Figure 4 Changes in left ventricular ejection fraction compared to baseline between groups. IC: Intracoronary; IV: Intravenous injection; TEPI: Transepicardial injection; TESI: Transendocardial injection; WMD: Weighted-mean difference; 95%CI: 95% confidence interval.

IC RoD is technically less invasive, safe, catheter-based, and easy to manipulate in cell delivery. Still, it may not be feasible for large-size cells like MSCs and high doses of cells, especially high-consistency cell preparations. IC route demonstrated insignificant pooled safety benefits, including all-cause mortality and SAEs. However, the IC route outperformed other RoD in all efficacy endpoints, including overall superiority in improving clinical, functional, and biochemical parameters. Our data supported the use of IC routes, consistent with data reported by Fan *et al*[32] that demonstrated the superiority of MSC-based therapy *via* IC RoD in improving exercise capacity in HF patients. Nevertheless, despite the seemingly encouraging findings, the pooled data in this study was considerably low (n = 96) compared to other RoDs, such as TESI and TEPI injections (n = 567 and n = 189, respectively). The low number of analyzed samples was also compounded by the low quality of RCTs (Jadad score of 1/5 in both studies).

The assessment of the IV RoD was limited due to the inclusion of only one RCT. This study had a relatively small sample size and scored low on the Jadad scale. The IV route showed no significant reduction in both mortality and morbidity. Unfortunately, the functional and biochemical outcomes were not reported, and the clinical outcomes of 6MWD were also insignificant. At the same time, other systematic reviews have noted an increase in clinical outcomes [32]. Studies did not find significant improvements in LVEF or mortality rate for cardiac patients[32,33]. The limited effectiveness of the IV route may be attributed to the low number of cells reaching the target site and the low cell retention rate associated with systemic delivery approaches[34]. Despite the simplicity and non-invasiveness of the IV route, the current evidence needs to be more comprehensive to support its use in HF patients.

Our meta-analysis implemented strenuous efforts in study design and data analysis to evaluate the optimal RoD for MSC-based therapy. We have also included MSCs from different tissue sources, in addition to biochemical parameters, *i.e.*, pro-BNP, in efficacy outcome analysis. Most RCTs included scored high in the Jadad score (nine of the twelve

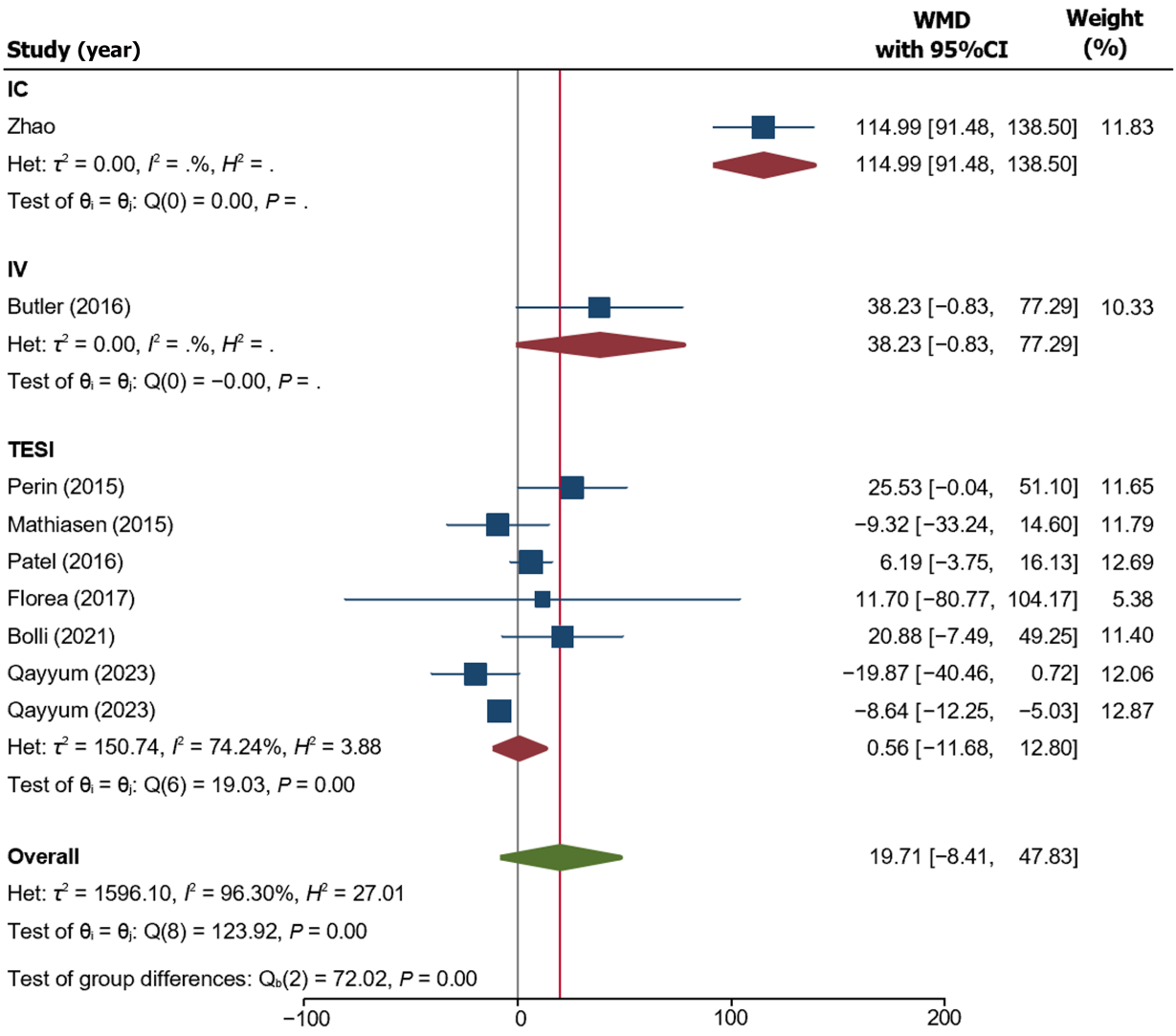

Figure 5 Changes in 6-minute walking distance compared to baseline between groups. IC: Intracoronary; IV: Intravenous injection; TEPI: Transepicardial injection; TESI: Transendocardial injection; WMD: Weighted-mean difference; 95%CI: 95% confidence interval.

studies), which reduced the risk of bias in each study and enhanced the quality of pooled evidence.

Despite our best endeavors, this study has limitations. Firstly, the analysis encompassed a small pool of RCTs, thus having a limited sample size. Also, specific relevant secondary outcomes were not analyzed, such as health-related quality of life, hospital readmission, performance status (NYHA classification), and various cardiac function indices (*e.g.*, wall motion score, LV end-systolic and diastolic volume, *etc.*) primarily due to lack of data availability. Notwithstanding these constraints, we thoroughly compared MSC-based therapy RoD for HF using the accessible evidence. From a practical standpoint, using IC routes can be an attractive choice, given the efficacy, superiority, and feasibility of a minimally invasive approach compared to TEPI[35]. Animal studies have also demonstrated an excellent cardiac retention rate using IC compared to TESI and IV RoD[36]. However, there is a potential risk of emboli, microinfarction, and inaccessibility due to the diseased coronary arteries[37,38]. Hence, the findings in this study need cautious interpretation, and we suggest analyzing phase II/III and III RCTs in the future to provide more substantial evidence to support their clinical application.

CONCLUSION

In conclusion, this study establishes the safety of IM, IC, IV, and TESI for MSC-based therapy based on pooled available data in phase II RCTs. In addition, IC and TESI routes provided superior outcomes compared to other routes in improving clinical, functional, and biochemical outcomes. These data in the early phase RCTs provide evidence that warrants investigations in phase II/III and phase III clinical trials before their implementation in clinical practice.

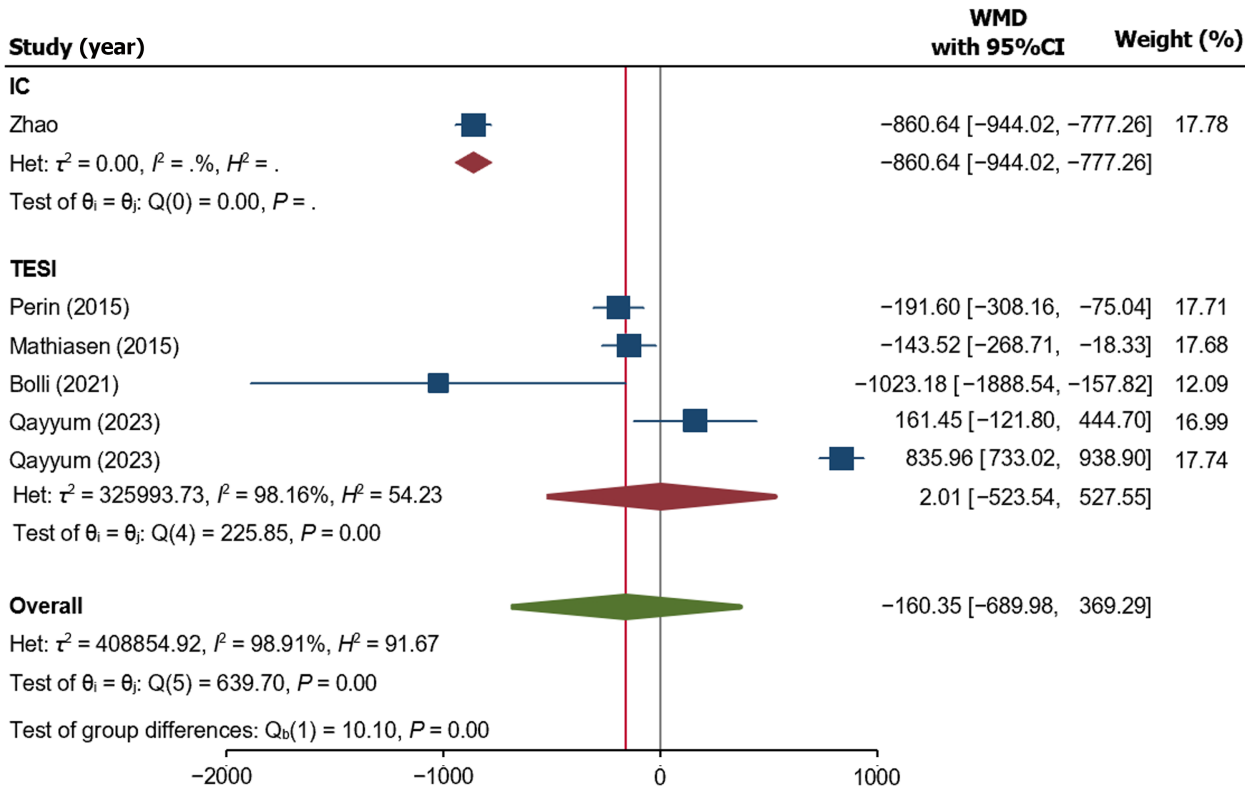

Figure 6 Forest plot of changes in the pro-B-type natriuretic peptide (pg/mL) compared to baseline between groups. IC: Intracoronary; IV: Intravenous injection; TEPI: Transepicardial injection; TESI: Transendocardial injection; WMD: Weighted-mean difference; 95%CI: 95% confidence interval.

FOOTNOTES

Author contributions: Haider KH designed and produced the study and its methodology; Jihwaprani MC and Sula I performed database research and screened the extracted records against eligibility criteria; Jihwaprani MC, Sula I, and Charbat MA performed data extraction and plotting; Sula I and Charbat MA reviewed and validated the extracted data; Jihwaprani MC, Sula I, and Charbat MA performed the quality assessment of the included trials; Jihwaprani MC, Sula I, and Charbat MA conducted the statistical analysis; Jihwaprani MC, Sula I, and Charbat MA drafted the first manuscript; Haider KH contributed to the final manuscript; Jihwaprani MC, Sula I, Charbat MA, and Haider KH reviewed the final manuscript; and all authors have read and agreed to the published version of the manuscript.

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META-ANALYSIS

Impact of D-dimer on in-hospital mortality following aortic dissection: A systematic review and meta-analysis

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Abstract

BACKGROUND

The utility of D-dimer (DD) as a biomarker for acute aortic dissection (AD) is recognized. Yet, its predictive value for in-hospital mortality remains uncertain and subject to conflicting evidence.

AIM

To conduct a meta-analysis of AD-related in-hospital mortality (ADIM) with elevated DD levels.

METHODS

We searched PubMed, Scopus, Embase, and Google Scholar for AD and ADIM literature through May 2022. Heterogeneity was assessed using I^2 statistics and effect size (hazard or odds ratio) analysis with random-effects models. Sample size, study type, and patients' mean age were used for subgroup analysis. The

significance threshold was $P < 0.05$.

RESULTS

Thirteen studies (3628 patients) were included in our study. The pooled prevalence of ADIM was 20% (95%CI: 15%-25%). Despite comparable demographic characteristics and comorbidities, elevated DD values were associated with higher ADIM risk (unadjusted effect size: 1.94, 95%CI: 1.34-2.8; adjusted effect size: 1.12, 95%CI: 1.05-1.19, $P < 0.01$). Studies involving patients with a mean age of < 60 years exhibited an increased mortality risk (effect size: 1.43, 95%CI: 1.23-1.67, $P < 0.01$), whereas no significant difference was observed in studies with a mean age > 60 years. Prospective and larger sample size studies ($n > 250$) demonstrated a heightened likelihood of ADIM associated with elevated DD levels (effect size: 2.57, 95%CI: 1.30-5.08, $P < 0.01$ *vs* effect size: 1.05, 95%CI: 1.00-1.11, $P = 0.05$, respectively).

CONCLUSION

Our meta-analysis shows elevated DD increases in-hospital mortality risk in AD patients, highlighting the need for larger, prospective studies to improve risk prediction models.

Key Words: D-dimer; Aortic dissection; Mortality; Biomarker; Systematic review; Meta-analysis

Core Tip: This study illuminates the significant prognostic value of D-dimer (DD) levels in predicting in-hospital mortality among patients with aortic dissection (AD). By systematically reviewing and meta-analyzing 13 studies encompassing 3628 patients, we found a compelling association between elevated DD levels and increased risk of in-hospital mortality in AD patients. This relationship held strong across various subgroups, notably in larger sample sizes and prospective studies. Our findings suggest that incorporating DD into risk assessment models could greatly enhance the prediction of mortality risk, offering a crucial tool for early intervention and improved patient management in AD.

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INTRODUCTION

Aortic dissection (AD) is a critical medical emergency characterized by the perforation of the aortic wall, resulting in significant morbidity and mortality. Multiple factors, including hypertension, connective tissue disorders, atherosclerosis, trauma, and genetic predisposition, contribute to the pathogenesis of AD, rendering the aortic wall susceptible to tearing. Survival in AD hinges on several factors, including the location and extent of the dissection, the presence of comorbidities, prompt diagnosis, and appropriate treatment[1].

AD has a mortality rate of 1% to 2% per hour after symptom onset if not treated promptly. Thus, early diagnosis plays a pivotal role in successful management and favorable outcomes post-AD[1]. Biomarkers may offer valuable insights into AD diagnosis and prognosis. D-dimer (DD) and other biomarkers have been investigated for their prognostic value in AD. DD is a fibrin breakdown product that is released into the circulation during fibrinolysis and holds promise as an AD biomarker. However, conflicting and limited evidence exists regarding its predictive value for in-hospital mortality in AD patients. While some studies have reported inconsistent findings, others have linked elevated DD levels and increased mortality in AD patients[2,3]. To address these discrepancies, we conducted a comprehensive systematic review and meta-analysis to evaluate the impact of DD on in-hospital mortality following AD. Our study aims to provide insights into the potential of DD as a biomarker for risk stratification and further highlight the importance of early diagnosis and timely intervention in managing AD.

MATERIALS AND METHODS

Search strategy and selection criteria

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to establish a complete search strategy and selection criteria. PubMed/Medline, Scopus, Embase, Google Scholar, and Embase were systematically searched, with articles included until May 2022. Search terms "D-dimer," "aortic dissection," and "in-hospital mortality" were utilized to retrieve relevant literature. Additionally, further publications were identified through manual

examination of the reference lists of relevant studies. The following were the study inclusion criteria: (1) Studies including patients aged 18 and greater and sample size greater than 20; (2) Studies with a confirmed diagnosis of AD; (3) DD levels were obtained; (4) The study design was two-armed, and the association was reported in terms of hazard or odds ratio for mortality with confidence intervals; and (5) In-hospital mortality reported as outcomes. Exclusion criteria included letters, comments, editorials, case reports, proceedings, personal communications, reviews, and non-English articles.

Study selection and data extraction

Two independent reviewers (Srikanth and Desai) screened identified articles based on title and abstract. Any discrepancies were resolved through consensus or consultation with a third reviewer (Subramanian). Subsequently, full-text publications from potentially relevant research were retrieved and evaluated for eligibility. Relevant data, including the first author's name, year of publication, study design, number of participants in each treatment group, participants' age and sex, type of AD, medical conditions other than AD, DD levels, and accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of DD levels for the diagnosis of acute AD were extracted from included studies.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale with modification was utilized to evaluate the quality of the included studies. This scale ranks non-randomized studies based on patient selection, research group comparability, and outcome assessment. Two reviewers (Srikanth and Desai) independently assessed the quality, with any disagreements resolved through consensus or consultation with a third reviewer (Abrishami). Each study's quality assessment score was recorded, with a minimum score of 5 considered acceptable (Supplementary Table 1).

Quantitative data synthesis and outcome measures

All statistical analyses were conducted with Open Meta-Analyst software. For each study, pooled effect sizes (hazard ratio or odds ratio) with 95% confidence intervals were determined. The Cochran Q and I^2 statistics were used to estimate study heterogeneity. Considering substantial heterogeneity (I^2 > 50%), random-effects models (DerSimonian-Laird technique) were used. The leave-one-out strategy was used for sensitivity analysis, and funnel plot asymmetry was used for publishing bias analysis by visual inspection. Subgroup analysis was also performed based on sample size, study types, and mean age of the included patient population. The statistical significance level was set at $P \leq 0.05$.

RESULTS

Thirteen studies were included in our study[2,4-15], encompassing a total of 3628 patients (Figure 1). Table 1 presents baseline characteristics, including study design, year the study was conducted, mean age of the population included in the study, diagnostic modality used to diagnose AD and its subtype, and clinical outcomes.

We discovered that the pooled prevalence of AD-related in-hospital mortality (ADIM) was 20% (95%CI: 15%-25%). In the analyzed data, higher DD values were associated with a higher risk of ADIM compared to lower DD values. This finding was supported by the statistical significance of both the unadjusted effect size (effect size: 1.94, 95%CI: 1.34-2.8, P < 0.01) and the adjusted effect size (effect size: 1.12, 95%CI: 1.05-1.19, P < 0.01) (Figure 2). However, the included studies displayed high heterogeneity and publication bias on visual inspection by funnel plot asymmetry (Supplementary Figure 1).

Subgroup analyses were conducted to delve deeper into the relationship between DD values and ADIM (Supplementary Figures 2-4). Studies with a mean age of less than 60 years demonstrated a significantly increased risk of mortality (effect size: 1.43, 95%CI: 1.23-1.67, P < 0.01), whereas those studies with a mean age of more than 60 years showed no significant difference. Furthermore, prospective studies demonstrated an increased risk of ADIM with high DD values in comparison to retrospective studies (effect size: 2.57, 95%CI: 1.30-5.08, P < 0.01 *vs* effect size: 1.05, 95%CI: 1.00-1.11, P = 0.05, respectively). Studies with a larger sample size (n > 250) revealed a higher likelihood of ADIM with high DD values, whereas those with smaller sample sizes (n = 250) indicated a lower likelihood of ADIM with high DD values (effect size: 2.90, 95%CI: 1.86-4.52, P < 0.01 *vs* effect size: 1.07, 95%CI: 1.01-1.12, P = 0.01, respectively). Sensitivity analysis was conducted, and the results of the overall and subgroup analyses remained unaffected.

DISCUSSION

AD is associated with a remarkably high mortality rate (27%)[1], yet it frequently is underdiagnosed. The findings of this systematic review and meta-analysis add to our understanding of the predictive usefulness of DD levels in AD. In-hospital mortality was found to be more likely in AD patients with elevated DD, and similar findings were observed across subgroups, *i.e.*, studies with larger sample numbers, prospective studies, and studies with mean ages under 60. DD, a degradation product of cross-linked fibrin, when elevated, indicates the activation of coagulation and fibrinolytic systems. Damage to the aortic wall in AD triggers the coagulation cascade and subsequent fibrinolysis, which raises DD levels[16]. The results of this meta-analysis lend support to the notion that higher DD levels may indicate a more severe AD pathology or more extensive dissection, thus increasing the likelihood of adverse outcomes, particularly in-hospital mortality.

Table 1 Baseline characteristics of included study population, *n* (%)

Ref.	Year	Country	Study design	Mean age/median age	Male	Total AD cases	Type of AD	Total cases with mortality in AD	Diagnostic technique
Feng *et al*[15]	2022	China	Prospective cohort	51.86 ± 10.76	396 (87.26)	470	Type A	151	CT angiography
Wang *et al*[10]	2022	China	Retrospective cohort	54	121 (75.6)	160	Type A	36	Aorta angiography with multidetector CT
Zhang *et al*[9]	2021	China	Retrospective cohort	52.76 ± 11.73	172 (76.8)	224	Type A	33	CTA, and color doppler echocardiography
Keskin *et al*[13]	2021	Turkey	Retrospective cross-sectional	61 ± 12	99 (65.6)	151	Type A	35	Contrast-enhanced CTA or MRA
Liu *et al* [5]	2021	China	Retrospective cohort	52	326 (89.8)	363	Type B	26	Multidetector contrast-enhanced CT
Xie *et al* [4]	2021	China	Retrospective cohort	Survived: 50.67 ± 11.49, died: 52.47 ± 12.52	279	345	Type A and Type B	75	CT/MRI
Zhang *et al*[11]	2020	China	Retrospective cohort	50 ± 12	149 (80)	186	Type A	40	CT
Yang *et al*[7]	2020	China	Retrospective cohort	Training set: 50.10 ± 11.58, validation set: 51.55 ± 10.62	536	703	Type A	235	CTA or MRA
Guo *et al*[14]	2019	China	Prospective cohort	Survived: 52.0 ± 13.0, died: 52.1 ± 10.2	73	109	Type A and type B	31	Contrast-enhanced CT
Itagaki *et al*[2]	2018	Japan	Retrospective cohort	64.5	143 (54.58)	262	Type A	23	Contrast-enhanced CT
Li *et al* [8]	2017	China	Retrospective	51.1 ± 13.1	262 (79.6)	329	Type A	66	CTA
Huang *et al*[6]	2015	China	Prospective cohort	48.5 ± 11.5	161 (75.9)	212	Type A	27	Multidetector CT
Wen *et al*[12]	2013	China	Prospective cohort	Survived: 48.9 ± 7.6, died: 48.6 ± 7.6	96	114	Type A and Type B	31	Chest radiography, transthoracic or transesophageal echocardiography and contrast-enhanced CT

AD: Aortic dissection; CT: X-ray micro-computed tomography; CTA: Computed tomography angiography; MRA: Magnetic resonance angiography.

Our study revealed that younger patients (< 60 years old) had higher odds of ADIM than elderly patients (> 60 years old). Younger patients may have fewer comorbidities and better overall health, thereby implying a direct association of DD levels' impact on mortality risk. DD levels increase with age, possibly due to a higher prevalence of comorbidities, and this might reduce the clinical significance of DD assay in the elderly[17]. Consequently, a higher cut-off may be more appropriate in older patients predicting mortality in AD[18]. The landscape of risk factors for AD varies between young and elderly. Younger AD patients may be at risk of worse outcomes due to the underpinning effect of connective tissue problems or hereditary factors that could cause more severe AD.

The meta-analysis showed that studies with larger sample sizes were associated with an increased risk of ADIM with elevated DD. Larger sample sizes have greater statistical power and accuracy, thereby reinforcing the predictive value of DD. As a potential key biomarker, DD can be employed in conjunction with existing recognized risk variables to enhance risk prediction in AD patients[19]. Our meta-analysis supports the idea of including DD in risk prediction models for outcomes of AD. This could assist clinicians in identifying individuals who might benefit from more aggressive management strategies, including interventions or intensive monitoring, as well as those at higher risk of unfavorable outcomes, necessitating optimal resource utilization in healthcare settings.

Comorbidities, DD levels, and AD-related outcomes can all interact in a complex, multivariate manner. The precise mechanisms and interactions between all of these factors are not fully understood and may vary depending on patient characteristics, disease severity, and other clinical factors. Cardiovascular comorbidities like hypertension, diabetes, and coronary artery disease aid in the onset and progression of AD by inducing structural changes in the aorta and promoting inflammation. Elevated DD levels may indicate the extent of aortic damage and thrombus development in AD. However, the specificity of elevated DD levels diminishes in conditions such as pregnancy, cancer, recent surgery, or trauma[20]. Cardiovascular comorbidities and higher-than-normal DD levels have both been linked to a higher risk of mortality, surgical complications, longer hospital admissions, and worse long-term survival in AD patients. The complicated and multifaceted mechanisms underlying the association between these factors and mortality in AD necessitate careful

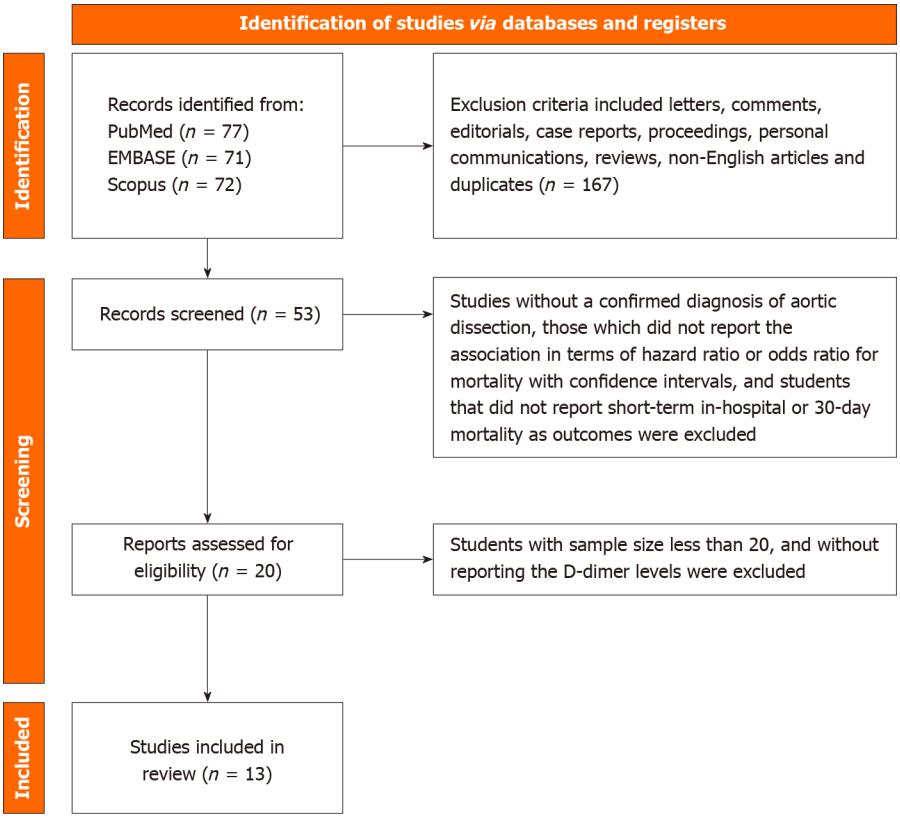

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

management and monitoring of DD levels and cardiovascular comorbidities to achieve optimal short and long-term outcomes.

DD testing is common in many clinical settings and is a popular biomarker for evaluating inflammation, coagulation, and fibrinolysis. DD is more affordable, readily available, and easier to assess than other biomarkers examined in the context of AD prognosis, such as troponins, brain natriuretic peptide, and C-reactive protein. Our study suggests that DD could be an effective biomarker for predicting in-hospital mortality in patients with AD, making it a crucial tool in clinical practice with significant implications on risk assessment, clinical judgment, and cost-effectiveness.

Limitations

Our study presents several limitations that should be taken into consideration when interpreting the findings. The inclusion of observational studies introduces the potential for selection bias, measurement bias, and confounding in the individual studies incorporated in this meta-analysis. Furthermore, the quality of the included studies could vary, which might have an impact on the robustness and generalizability of the results. Moderate to high heterogeneity among the included studies, as indicated by I^2 statistics, raises concerns about the consistency of findings. The pooled estimates may be impacted as a result of variations in study design, patient demographics, and methodology. Although heterogeneity was taken into account using random-effects models, subgroup analysis, and sensitivity analysis, caution ought to be used when interpreting the pooled results. A notable limitation is the lack of data on the etiology of AD. While this meta-analysis demonstrates an association between DD and in-hospital mortality in AD, it does not establish causation or elucidate underlying mechanisms. Future research is essential to elucidate the role of DD in AD prognosis and validate the findings of this meta-analysis, including prospective cohort studies and mechanistic investigations. Additionally, our meta-analysis focused on short-term outcomes, specifically in-hospital mortality. Long-term mortality and other important outcomes such as morbidity, quality of life, and healthcare resource utilization were not explored. Further investigation is needed to understand the relationship between DD and other clinically significant outcomes in AD.

CONCLUSION

According to this systematic review and meta-analysis, elevated DD levels are linked to a higher risk of in-hospital mortality in patients with AD. DD may be a useful prognostic biomarker for AD patients, and its incorporation into risk prediction models could enhance their accuracy and predictive capability. Despite some limitations, this review underscores the potential of DD as an advanced and cost-effective biomarker for evaluating in-hospital mortality in AD patients. However, further prospective validation studies are needed to establish the clinical utility of DD in risk stratification and management of AD patients. Subsequent investigations could explore the synergistic effects of DD with other

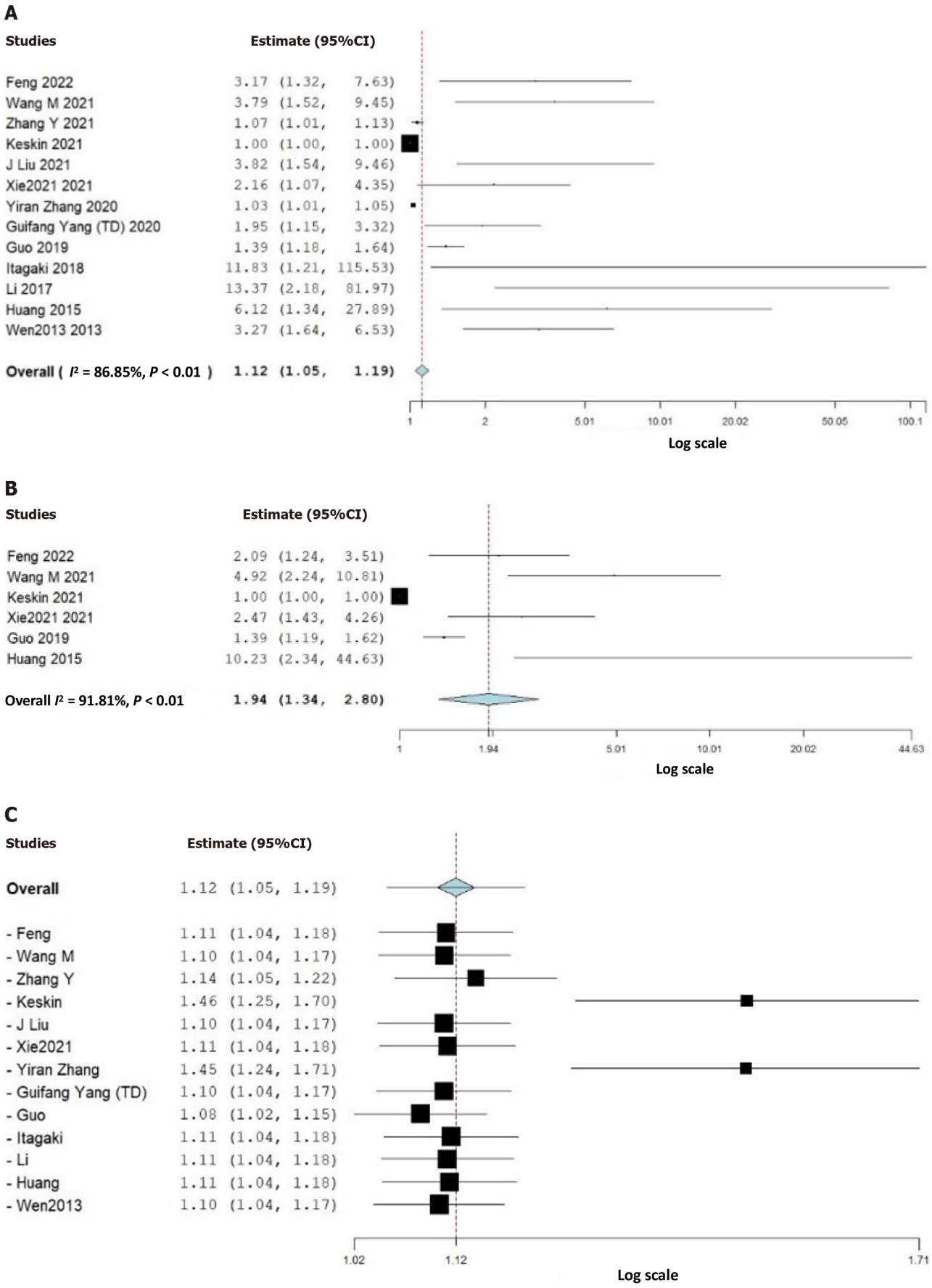

Figure 2 Association of D-dimer and in-hospital mortality following aortic dissection. A: Pooled adjusted effect size; B: Pooled unadjusted effect size; C: Leave-one-out sensitivity analysis.

biomarkers to improve risk prediction models and investigate the therapeutic implications of DD in AD management. Overall, these findings contribute to our understanding of AD prognosis and offer guidance for current and future clinical practice and research in this field.

FOOTNOTES

Author contributions: Srikanth S was responsible for conceptualization, methodology, investigation, writing-original draft, writing-review and editing, visualization; Mahadevaiah A was responsible for methodology, investigation, resources, data curation, writing-original draft, visualization; Abrishami S and Subramanian L were responsible for methodology, data curation, writing-original draft, writing-review and editing; Vyas A and Jain A were responsible for conceptualization, methodology, writing-original draft, writing-review and editing, project administration; Nathaniel S and Gnanaguruparan S were responsible for writing-review and editing; Desai R was responsible for conceptualization, methodology, software, formal analysis, resources, data curation, writing-original draft, writing-review and editing, project administration, supervision.

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CASE REPORT

Massive inferior wall aneurysm presenting with ventricular tachycardia and refractory cardiomyopathy requiring multiple interventions: A case report

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Abstract

BACKGROUND

Inferior wall left ventricular aneurysms are rare, they develop after transmural myocardial infarction (MI) and may be associated with poorer prognosis. We present a unique case of a large aneurysm of the inferior wall complicated by ventricular tachycardia (VT) and requiring surgical resection and mitral valve replacement.

CASE SUMMARY

A 59-year-old male was admitted for VT one month after he had a delayed presentation for an inferior ST-segment elevation MI and was discovered to have a large true inferior wall aneurysm on echocardiography and confirmed on coronary computed tomography (CT) angiography. Due to the sustained VT, concern for aneurysm expansion, and persistent heart failure symptoms, the patient was referred for surgical resection of the aneurysm with patch repair, mitral valve replacement, and automated implantable cardioverter defibrillator insertion with significant improvement in functional and clinical status.

CONCLUSION

Inferior wall aneurysms are rare and require close monitoring to identify electrical or contractile sequelae. Coronary CT angiography can outline anatomic details and guide surgical intervention to ameliorate life-threatening complications and improve performance status.

Key Words: Inferior wall aneurysm; True aneurysm; Ventricular tachycardia; Electrophysiology; Structural interventional cardiology; Case report

Core Tip: This case report is intended to assist clinicians anticipate and recognize complications arising from true inferior wall aneurysms in a bid to expedite timely pharmacologic and surgical interventions. It will also help outline the role of multidisciplinary care in managing inferior wall aneurysm complications to improve quality of care and help provide guidance in utilizing different imaging modalities to evaluate ventricular aneurysms and help guide therapy.

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INTRODUCTION

The prevalence of myocardial infarction (MI) in American adults aged 20 and older is 3.1 percent[1]. That equates to about 1.5 million patients in the United States and the overall incidence of left ventricular aneurysms is 30-35 percent of acute transmural MI[2]. The clinical implications of these aneurysms are profound, manifesting as wall motion abnormalities, reinfarction, ventricular tachyarrhythmias, and an increased risk of sudden cardiac death[3]. Ventricular aneurysms have two major risk factors. The first is total occlusion of the left anterior descending artery and the second is failure to obtain patency of the infarcted artery. This can lead to a true ventricular aneurysm or a ventricular pseudoaneurysm. A true aneurysm is a full-thickness outpouching of the ventricular wall. While a pseudo-aneurysm is a ventricular wall rupture that remains contained within the pericardium[2]. Differentiating between a true and pseudo-aneurysm can be difficult but is vital as pseudo-aneurysms have a propensity to rupture leading to cardiac tamponade, shock, and death. True aneurysms generally do not carry these same risk factors[4]. Nonetheless, they can lead to mural thrombus, arrhythmia, and heart failure[5]. This report details the case of a patient with a true aneurysm found after sustained ventricular tachycardia (VT) post-cardiac catheterization and placement of a drug-eluting stent (DES). The patient subsequently had surgical resection of the aneurysm, mitral valve replacement, and intracardiac cryoablation below the mitral valve to prevent future VT episodes.

CASE PRESENTATION

Chief complaints

We present a 59-year-old male with cardiovascular comorbidities. He presented to our emergency department (ED) with new onset palpitations that had lasted about 90 minutes, wide complex tachycardia tracing on his smartwatch with a heart rate of around 160/min, and concerns for VT.

History of present illness

Before presentation, the patient had no fever, nausea, vomiting, chest pain, syncope, or dyspnea. His clinical presentation was most consistent with scar-related VT arising from the aneurysm wall. Potential differentials include supraventricular tachycardia with aberrancy, pre-excited supraventricular tachycardia, and antidromic atrioventricular reciprocating tachycardia.

History of past illness

One month earlier the patient had a delayed presentation for an acute inferior wall ST segment elevation MI (STEMI) (Figure 1A) with admission high sensitivity cardiac Troponin (hs-cTn) elevated at 988 ng/L, peaked at 1225 ng/L and trended down to 954 ng/L. He underwent coronary angiography that revealed an occluded right coronary artery right coronary artery (RCA) and normal flow through the proximal, mid, and distal left anterior descending (LAD) and left circumflex artery. He then received percutaneous coronary intervention (PCI) with the placement of a DES to the occluded RCA and this hospital course was complicated by pericarditis managed with Aspirin and colchicine.

Personal and family history

He had a history of essential hypertension, dyslipidemia, and type 2 diabetes mellitus and was on Amlodipine, Metoprolol, Atorvastatin, Metformin, and dual antiplatelet with Aspirin and Ticagrelor. Past surgical history was significant for left total shoulder and total knee replacements. The family history was significant for diabetes mellitus and

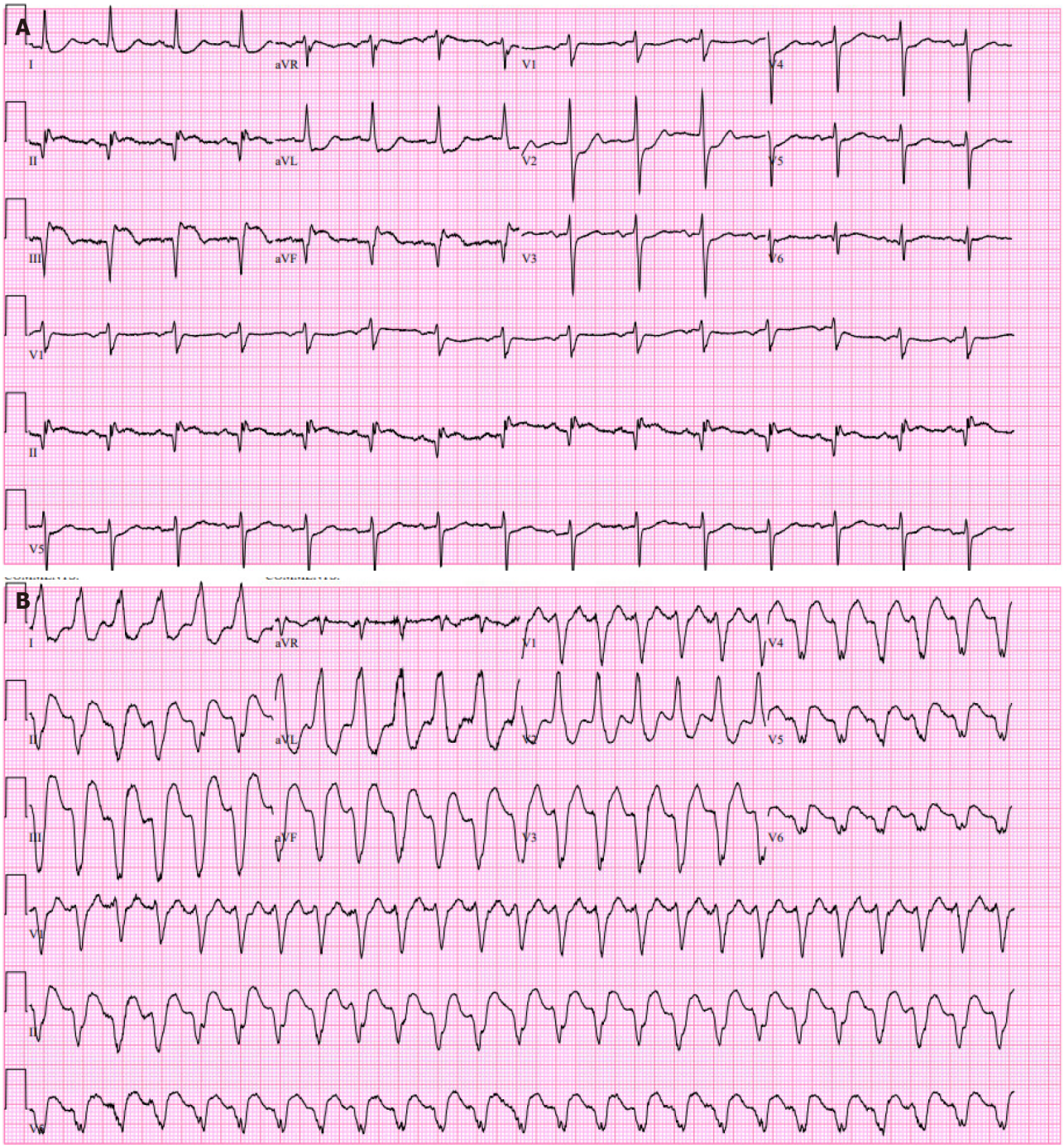

Figure 1 12-lead electrocardiograms showing an inferior ST-segment elevation myocardial infarction and ventricular tachycardia respectively. A: 12-lead electrocardiogram one month earlier showing sinus rhythm with a ventricular rate of 90 beats per minute, left axis deviation, pathologic Q waves with 2-3 mm ST-segment elevation in inferior leads (III > II) and avF, and reciprocal ST depression in I and avL; B: 12-lead electrocardiogram showing ventricular tachycardia (VT) with a left bundle branch block morphology, ventricular rate of 150 beats per minute, left superior axis, poor precordial R wave progression, V2 transition suggesting inferoseptal origin of scar-related VT.

heart disease in his father.

Physical examination

Vitals were most significant for tachycardia with a heart rate of 160/min, blood pressure of 122/98 mmHg, respiratory rate of 16/min, and SPO_2 of 97% on ambient air. He was alert, oriented, and in no painful distress. He was well hydrated, with no neck vein distension. Chest auscultation was clear bilaterally and cardiac auscultation revealed an apical pan-systolic murmur without rubs or gallops. Abdominal exam was within normal limits and he was neurologically intact with warm and well-perfused extremities, with no lower extremity edema.

Laboratory examinations

An electrocardiogram (EKG) in the ED confirmed monomorphic VT (Figure 1B). Lab testing was most significant for white blood count of 13.6 × 10^9/L and elevated hs-cTn at 117 ng/L, which increased to 140 ng/L. Other lab values were within normal limits.

Imaging examinations

The echocardiogram showed hypokinetic and dyskinetic left ventricular walls, a large basal and mid-inferior-inferoseptal aneurysm with a wide neck, reduced systolic function, and a left ventricular ejection fraction (LVEF) 44% as well as moderate mitral insufficiency from a restricted posterior mitral valve leaflet and mild aortic insufficiency with a dilated ascending aorta of 4.4 cm (Figure 2). Prior echocardiogram during the STEMI had shown a dyskinetic segment involving the inferoseptal, basal, and mid-inferior wall which subsequently became aneurysmal. To further evaluate the aneurysmal segment better, a cardiac gated computed tomography (CT) angiography was performed which showed a large true aneurysm arising from the inferobasal part of the left ventricle (LV) with a large neck (3 cm × 4 cm), dome (6.8 cm diameter) and rightward displacement of the basal septum, with no evidence of a pseudoaneurysm and without any significant stagnation of blood within the aneurysmal cavity (Figures 3 and 4). Cardiac catheterization showed patent RCA stent and 75% stenosed mid-LAD lesion. Intravascular ultrasound demonstrated a mid-LAD fibrofatty plaque with an area of plaque rupture. The lesion was dilated, and 3.5 mm × 33 mm DES was placed, with final 0% stenosis and TIMI stage 3 flow.

FINAL DIAGNOSIS

Sustained scar-related VT secondary to an inferior wall left ventricular aneurysm post inferior STEMI.

TREATMENT

He received a 150 mg Amiodarone bolus followed by an infusion at 1 mg/min and Esmolol at 50 mcg/kg/min in the ED. The esmolol dose was doubled and he received another 150 mg Amiodarone bolus for persistent VT and converted spontaneously to sinus rhythm just before anticipated electrical cardioversion. Repeat EKG showed loss of R wave progression in precordial leads and q waves with slight ST elevation in leads V3-V6. After the LAD stent placement, he was continued on dual antiplatelet therapy, high-intensity statin, guideline-directed medical therapy (GDMT) with Enalapril, Furosemide, Metoprolol succinate, Amiodarone, Dapagliflozin and a wearable cardioverter defibrillator (LifeVest).

Two months after the VT episode, due to concern for the aneurysm expansion, he was referred for LV aneurysm patch repair with polytetrafluoroethylene graft and bioprosthetic mitral valve replacement. He also received a surgical intracardiac cryoablation of the tissue between the mitral annulus and the scar of the inferior MI to prevent future recurrence of mitral annular VT. Surgery was complicated by prolonged mechanical ventilation and pneumosepsis. Due to the history of VT and persistently low pre-op LVEF of around 35%, the patient also had a dual-chamber automated implantable cardioverter defibrillator (AICD) placed and Amiodarone was discontinued due to bradycardia and prolonged QTc interval of 598 ms.

OUTCOME AND FOLLOW-UP

Three months postoperatively, he developed recurrent left-sided pleural effusions requiring two sessions of thoracentesis with drainage of 1.5 L and 0.7 L respectively. Due to postoperative persistent symptomatic LV dysfunction, GDMT was progressively optimized to include Entresto (replacing Enalapril), and Eplerenone in addition to previous medications with improvement in functional status and LVEF up to 50%.

DISCUSSION

This case outlines the complicated clinical course of a patient who developed a true inferior wall aneurysm complicated by sustained VT one month after presenting with an inferior wall STEMI despite reperfusion. It presents a unique intersection of ischemic complications combining ventricular arrhythmias post-STEMI with structural pathologies requiring combined AICD insertion and mitral valve replacement. In this case, due to unknown magnetic resonance imaging (MRI) compatibility of the patient's orthopedic implants, it was agreed to obtain a cardiac gated coronary CT angiography scan as opposed to the gold standard for LV aneurysm diagnosis, which is cardiovascular MRI[6]. Most LV aneurysms (75%-80%) arise from the apical or anterior wall and are often associated with established risk factors like absence of collateralization in the setting of LAD coronary artery total occlusion, and incomplete or delayed reperfusion [7,8]. True inferior aneurysms are rare but have similar risk factors with the culprit vessel often being the RCA and persistent inferior ST elevation on EKG is usually consistent with the development of an aneurysm[9]. Aneurysm

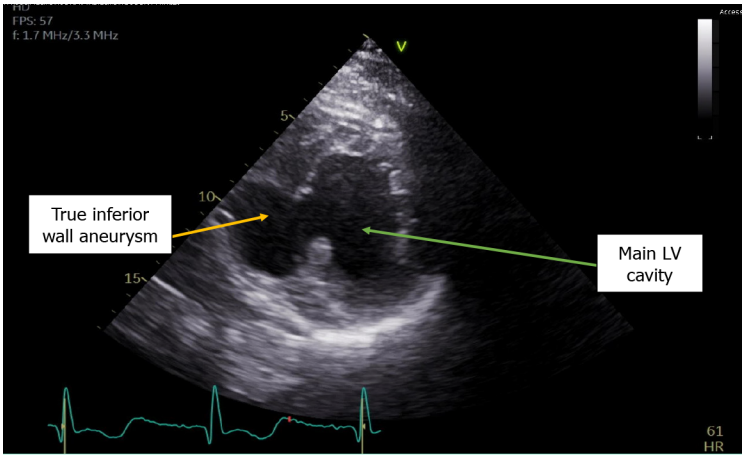

Figure 2 A large inferior wall left ventricle aneurysm shown on transthoracic echocardiography parasternal short-axis view in mid-diastole. LV: Left ventricle.

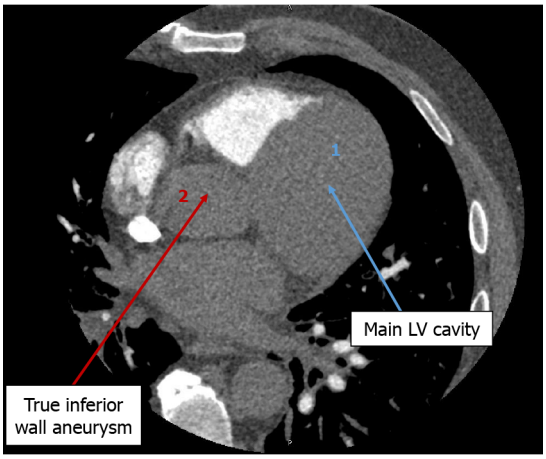

Figure 3 Coronary computed tomography angiography. Still axial coronary computed tomography images reveal an enlarged left ventricle (LV) (1) identified by the blue arrow and a true infero-basal wall LV aneurysm (2) identified by the red arrow significantly reducing aortic ejection LV stroke volume. LV: Left ventricle.

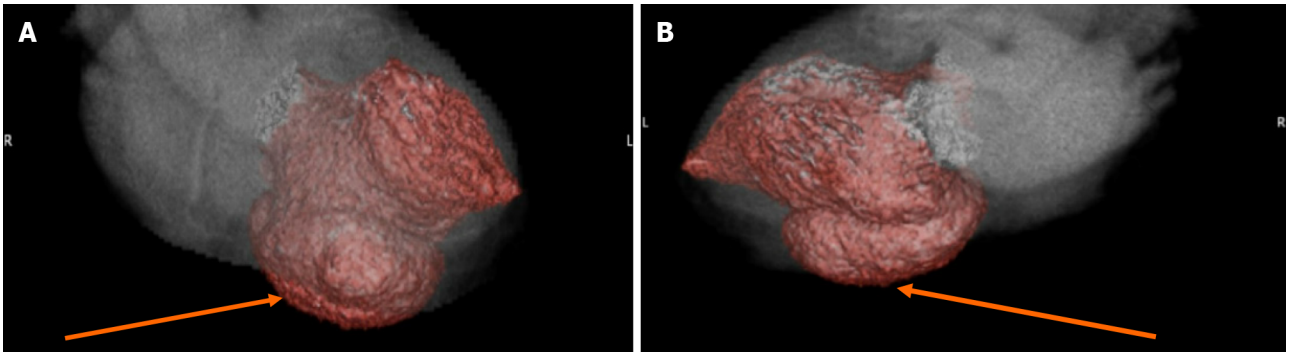

Figure 4 3-D reconstruction of the computed tomography angiography images with the anteroposterior and posteroanterior views in the systolic phase demonstrating an aneurysm (orange arrow) in the inferior wall's basal region. A: Anteroposterior; B: Posteroanterior.

development arises from infarct expansion, which occurs in about 35%-45% of anterior MI and less frequently at other locations[10].

Following the advent of thrombolysis and PCI, large ventricular aneurysms have become uncommon complications of MIs[11,12]. A true aneurysm occurring a month after a STEMI raises questions about the underlying substrate and the potential role of delayed myocardial healing and remodeling. While pseudoaneurysms are at a higher risk of rupture, true aneurysms balloon out in systole causing a loss of kinetic energy required to maintain cardiac output, thus carrying a

higher risk of heart failure, the stasis favors thrombus formation, and the scar tissue forms an arrhythmogenic substrate for ventricular arrhythmias[13,14]. Complications of aneurysm formation are responsible for a six-fold increase in the mortality of acute coronary syndrome, death is usually from sudden cardiac death[15].

This case highlights a greater need for arrhythmia risk stratification in post-infarction patients with regional myocardial dysfunction as well as the need for further exploration of potential underlying arrhythmogenic substrates, the possible role of scar-related reentry mechanisms and the impact of worsening myocardial dysfunction. Furthermore, this patient had a dual-chamber AICD placed for secondary prevention of recurrent VT managed with Amiodarone, and worsening LVEF of 35% after a trial of a LifeVest while on GDMT. Due to the patient's elevated risk of sudden cardiac death on account of depressed LVEF, history or recurrent VT, and STEMI within the past 40 d, the patient had been placed on a LifeVest. More specific indications would include LVEF ≤ 35% within 90 d of coronary artery bypass graft, newly diagnosed but potentially reversible nonischemic cardiomyopathy, or severe heart failure awaiting transplantation [16]. However, some months after VT ablation and after a device check revealed no recurrent episodes of VT, it was decided to discontinue Amiodarone due to persistent bradycardia, markedly prolonged QTc interval of 598 ms, and the increased risk of Torsades.

Inferior aneurysms could be associated with mitral regurgitation (MR) from disruption of papillary muscle anatomy due to scar formation and subsequent mitral leaflet tethering[17]. This patient had moderate MR from dyskinetic walls and a restricted posterior mitral valve leaflet further complicating his heart failure symptoms, hence mitral valve replacement was required. The coexistence of mitral valve disease emphasizes the complexity of managing concurrent structural heart disease and arrhythmias.

Uncomplicated ventricular aneurysms are usually managed pharmacologically with GDMT and anticoagulation[17]. However, in the setting of persistent ventricular arrhythmia or refractory heart failure unresponsive to GDMT (in this case), surgical intervention is strongly indicated[13]. Surgical repair significantly reduces heart failure symptoms and VT episodes[11]. Of note, the perioperative risk of mortality for aneurysmal repair is high particularly when additional coronary artery bypass or valvular surgery is required especially when the LVEF is 35% or less[9,18]. This patient had an inferoseptal/inferobasal aneurysmectomy with patch repair, concomitant bioprosthetic mitral valve replacement, and AICD implantation with significant improvement at one-year follow-up. VT Cryoablation was guided by anatomical landmarks and performed from the scar area to the posterior mitral annulus (P2/P3 area) both from the LV endocardium side and epicardium side during the MV replacement procedure. This emphasizes the challenges of managing post-infarction patients, including the potential impact of ventricular mechanics and arrhythmia substrate.

Also noteworthy was the fact that the decompensated heart failure state postoperatively was complicated by symptomatic pleural effusions requiring thoracentesis procedures with drainage of 2.2 L. In this patient, further postoperative optimization of GDMT was associated with improvements in LVEF, pleural effusion, and functional status. This case underscores the evolving landscape of collaborative care involving interventional cardiology, cardiac surgery, and electrophysiology in addressing multifaceted cardiac pathologies.

CONCLUSION

This case provides valuable insights into the management of high-risk patients with complex post-infarction complications and underscores the importance of vigilant monitoring and risk assessment in the post-STEMI period in patients with inferior wall involvement. Additionally, it reveals the significant complications, perioperative challenges, and guideline-directed interventions for a true inferior wall left ventricular aneurysm and aims to contribute to the enhancement of treatment protocols within the realm of cardiology.

FOOTNOTES

Author contributions: Anuforo A conceptualized and designed the manuscript, performed extensive literature review, wrote the first draft of the paper, critically revised the manuscript, acquired, interpreted, and analyzed data, created the final draft of the manuscript; Charlamb J wrote the first draft of the introduction, critically revised the manuscript, supported the literature review; Draytsel D critically revised the manuscript, supported the literature review; Charlamb M conceptualized and designed the manuscript, critically revised the manuscript, and approved the final version for submission.

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