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Peer Reviewer of *World Journal of Cardiology*, Hean Ong, FACC, Lecturer, Gleneagles Medical Centre, Island Hospital, Penang 10350, Malaysia. ongheanteik@gmail.com

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REVIEW

Cardiovascular implications of inflammatory bowel disease: An updated review

Arshia Bhardwaj, Arshdeep Singh, Vandana Midha, Ajit Sood, Gurpreet Singh Wander, Bishav Mohan, Akash Batta

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Arshia Bhardwaj, Arshdeep Singh, Ajit Sood, Department of Gastroenterology, Dayanand Medical College and Hospital, Punjab, Ludhiana 141001, India

Vandana Midha, Department of Internal Medicine, Dayanand Medical College and Hospital, Punjab, Ludhiana 141001, India

Gurpreet Singh Wander, Bishav Mohan, Akash Batta, Department of Cardiology, Dayanand Medical College and Hospital, Punjab, Ludhiana 141001, India

Corresponding author: Akash Batta, Doctor, FACC, MBBS, MD, Assistant Professor, Department of Cardiology, Dayanand Medical College and Hospital, Tagore Nagar, Civil Lines, Punjab, Ludhiana 141001, India. akashbatta02@gmail.com

Abstract

Emerging data highlights the heightened risk of atherosclerotic cardiovascular diseases (ASCVD) in patients with chronic inflammatory disorders, particularly those afflicted with inflammatory bowel disease (IBD). This review delves into the epidemiological connections between IBD and ASCVD, elucidating potential underlying mechanisms. Furthermore, it discusses the impact of current IBD treatments on cardiovascular risk. Additionally, the cardiovascular adverse effects of novel small molecule drugs used in moderate-to-severe IBD are investigated, drawing parallels with observations in patients with rheumatoid arthritis. This article aims to comprehensively evaluate the existing evidence supporting these associations.

To achieve this, we conducted a meticulous search of PubMed, spanning from inception to August 2023, using a carefully selected set of keywords. The search encompassed topics related to IBD, such as Crohn's disease and ulcerative colitis, as well as ASCVD, including coronary artery disease, cardiovascular disease, atrial fibrillation, heart failure, conduction abnormalities, heart blocks, and premature coronary artery disease. This review encompasses various types of literature, including retrospective and prospective cohort studies, clinical trials, meta-analyses, and relevant guidelines, with the objective of providing a comprehensive overview of this critical intersection of inflammatory bowel disease and cardiovascular health.

Key Words: Inflammatory bowel diseases; Cardiovascular disorders; Pericarditis;

myocarditis; Thromboembolism; Chronic inflammation; Oxidative stress; Endothelial dysfunction

Core Tip: A substantial association has been established between cardiovascular disorders (CVD) and inflammatory bowel diseases (IBD), with a notably higher prevalence of CVD in IBD patients compared to the general population. Potential mechanisms underlying CVD in IBD involve chronic inflammation, oxidative stress, altered platelet function, endothelial dysfunction, hypercoagulability, gut dysbiosis, and drug-related side effects. This review comprehensively synthesizes the latest evidence on the epidemiology, pathophysiological mechanisms, and cardiovascular manifestations in IBD.

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INTRODUCTION

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions affecting the gastrointestinal tract, characterized by a relapsing-remitting disease course. Extraintestinal symptoms may occur either concomitantly with or independently of luminal symptoms[1-4]. An association has been established between cardiovascular disorders (CVD) and IBD, with a notably higher prevalence of CVD in IBD patients compared to the general population. The cardiovascular manifestations in IBD patients encompass pericarditis, myocarditis, venous and arterial thromboembolism, atherosclerotic CVD, heart failure, arrhythmias and conduction disorders, infective endocarditis, valvulopathy, and rarely, Takayasu arteritis[5-7]. Potential mechanisms underlying CVD in IBD involve chronic inflammation, oxidative stress, altered platelet function, endothelial dysfunction, hypercoagulability, gut dysbiosis, and drug-related side effects[8]. This review comprehensively synthesizes the latest evidence on the epidemiology, pathophysiological mechanisms, and cardiovascular manifestations in IBD.

PATHOPHYSIOLOGY OF CVD IN IBD

The intricate pathogenesis linking IBD and CVD remains an enigma, characterized by a complex interplay of diverse factors. Dysregulated immune responses, endothelial dysfunction, a pro-thrombotic state, accelerated atherosclerosis, and genetic polymorphisms collectively contribute to this intricate web connecting IBD with CVD.

Chronic low-grade inflammation, marked by alterations in both innate and adaptive immunity, plays a pivotal role in the pathogenesis of atherosclerotic CVD[9]. In IBD, the stimulation of inflammatory T cell pathways, mediated by T helper (Th) 17 and Th1 responses fosters a pro-inflammatory milieu, leading to increased production of cytokines, including interleukin (IL)-1b, IL-6, IL-23, tumor necrosis factor (TNF), and interferon-gamma. Elevated expression of Toll-like receptors (TLR)-2 and TLR-4 further contributes to the pro-inflammatory state by amplifying IL-6 and IL-12 production[10,11]. These pro-inflammatory cytokines, *via* oxidative stress, provoke inflammation, tissue damage, and proliferation of endothelial and mesenchymal cells, synergistically contributing to the pathogenesis of CVD[12]. Furthermore, TNF, IL-1, IL-6, vascular endothelial growth factor (VEGF), and reactive oxidative species promote endothelial dysfunction by increasing the expression of cell adhesion molecules like ICAM-1, MCP-1, E selectin and intensify endothelial cell apoptosis, micro- and macrovascular dysfunction, tissue remodelling, angiogenesis, lymphangiogenesis, and fibrosis[13-15]. C-reactive protein (CRP), a marker of inflammation, is elevated in IBD and contributes to atherogenesis, correlating with increased CVD risk. Elevated CRP levels, especially exceeding 5 mg/L, serve as predictors of cardiovascular events. Notably, CRP levels rise with IBD disease activity, heightening cardiovascular risk during active disease[16,17].

Gut microbial dysbiosis, an important risk factor for IBD development, is also associated with CVD and increased thromboembolic event risk, particularly in younger age groups[12,18,19]. Alterations in the *Firmicutes/Bacteroidetes* ratio are linked to hypertension, while enrichment in Enterobacteriaceae, including *Escherichia coli*, is observed in patients with IBD and CVD[20-23]. *Streptococcus spp.* increase CVD risk, and opportunistic bacteria like *Enterobacter* and *Oscillibacter* are associated with ischemic stroke and transient ischemic attacks[24-26].

Gut dysbiosis can also increase gut permeability, leading to elevated absorption of lipopolysaccharide (LPS) from the intestines. The LPS, in turn, heightens pro-inflammatory cytokine secretion, exacerbating atherosclerosis, inducing macrophage activation, vascular endothelitis, and increasing CRP[27]. Gut bacterial metabolites, such as indole and phenyl derivatives, also exacerbate atherosclerosis and lead to hypertension[26]. Additionally, the gut bacteria-derived metabolite, Trimethylamine-N-oxide (TMAO), contributes to atherogenesis and hypertension, serving as a predictor of coronary artery disease. TMAO promotes platelet responsiveness, thrombosis, and cardiovascular risk through the

expression of pro-inflammatory cytokines, ox-low density lipoprotein (LDL) deposition, and cardiac mitochondrial dysfunction[25,28,29]. The drugs used for treatment in IBD, through various mechanisms, are also associated with cardiovascular side effects and are discussed in the subsequent sections[30]. The pathogenesis of CVD in IBD is outlined in Figure 1.

CARDIOVASCULAR MANIFESTATIONS AND ITS MANAGEMENT IN IBD

Cardiovascular manifestations in IBD may be infrequent, yet they carry significant clinical implications when left unaddressed. We discuss the common CVD seen in patients with IBD.

Pericarditis and myocarditis

Pericarditis and myocarditis account for 70% and 10% of cardiac extra-intestinal manifestations (EIMs) respectively. Patients with IBD are at a greater risk of developing myopericarditis as compared to the general population[31,32]. Notably, pericarditis displays a higher incidence in males with UC[30-32]. On the other hand, myocarditis, constituting around 10% of cardiovascular EIMs in IBD, is more prevalent in patients diagnosed with CD[33].

Pathogenesis

It is difficult to determine whether the complications are secondary to the systemic disease or therapy related adverse events. Two possible mechanisms that are responsible for pericarditis and myocarditis in patients with IBD include immune mediated, secondary to the exposure of autoantigens, and cardiotoxicity associated with aminosalicylates and its derivatives[34-36].

Experimental models suggest that exposure to autoantigens produced during an acute flare of IBD, *via* inflammatory cytokines and an activated immune response, can lead to direct cytotoxicity of the cardiac myocytes[37]. This process may involve both the myocardium and pericardium and lead to myopericarditis. Continued inflammation and remodeling may result in chronic myocarditis which may cause valvular abnormalities (*via* papillary muscle fibroses and dysfunction), chamber dilation resulting in systolic dysfunction and decreased ejection fraction or arrhythmias[38,39].

Pericarditis almost exclusively occurs as a drug induced adverse event, in particular with 5-amino salicylic acid (ASA) derivatives such as sulfasalazine, mesalamine, and balsalazide[40-42]. The underlying mechanisms responsible for pericarditis associated with mesalamine include IgE-mediated allergic reactions, direct cardiac toxicity, cell-mediated hypersensitivity, or a humoral antibody response against 5-ASA derivatives[43].

Clinical features and diagnosis

Patients with 5-ASA induced pericarditis usually develop symptoms within two weeks of initiation of therapy[44]. Myopericarditis may present as acute coronary syndrome, new onset or decompensated heart failure, arrhythmias, cardiogenic shock or sudden death[45]. The electrocardiogram may show ST segment and T wave changes or conduction disorders. Leucocytosis, elevated levels of erythrocyte sedimentation rate, CRP and cardiac biomarkers such as troponin, creatine kinase-MB, B-type natriuretic peptide and N-terminal pro-brain natriuretic peptide may be present[30,46]. Echocardiographic features of myocarditis such as left ventricular dysfunction, anomalies of parietal kinetics, low ejection fraction, or pericardial effusion may be present. The cardiovascular magnetic resonance (CMR) imaging in a patient with myocarditis may reveal myocardial (regional or global) oedema, myocardial hyperaemia, and focal fibrosis or necrosis with non-coronary artery distribution[46]. The endomyocardial biopsy is the gold standard but is seldom performed in view of its invasive nature and availability of non-invasive CMR. The endomyocardial biopsy is however indicated in patients where CMR is not feasible or in life threatening conditions to establish the diagnosis and aetiology of myocarditis [39]. Histologically, two forms of IBD-associated myocarditis are known: The acute/chronic lymphocytic myocarditis and the giant cell myocarditis. Giant cell myocarditis is associated with a poor prognosis[47].

Management

The two major goals of treatment are optimal care of heart failure and arrhythmias, regardless of etiology and disease-specific therapy. Patients with fulminant myocarditis and hemodynamic instability should be shifted to intensive care units (ICU) with facilities of advanced cardiopulmonary support such as mechanical ventilation and extracorporeal membrane oxygenation[36,48].

Discontinuation of the causative drug remains the mainstay of treatment for pericarditis and resolution occurs within 2 wk. For inflammatory myocarditis associated with IBD, immune-suppressive treatment should always be considered especially in the presence of ventricular systolic dysfunction and severe arrhythmias[49-52]. The commonly used immune suppressive agents for treatment of inflammatory myocarditis are corticosteroids, azathioprine, cyclosporine, or immunoglobulins[53]. Interestingly, these agents are also used for treatment of IBD and therefore no specific alteration in therapy may be required in majority of the patients. The current guidelines also discourage patients with myocarditis from participating in competitive and leisure sports[54].

If pericarditis arises as an EIM, steroids are indicated after ruling out sepsis[55-57]. Alternatively, indomethacin, aspirin and colchicine can be used. However, their use can exacerbate underlying IBD and caution is recommended. Pericardial effusion and tamponade can complicate pericarditis which can be managed with pericardiocentesis or pericardiectomy[30,58].

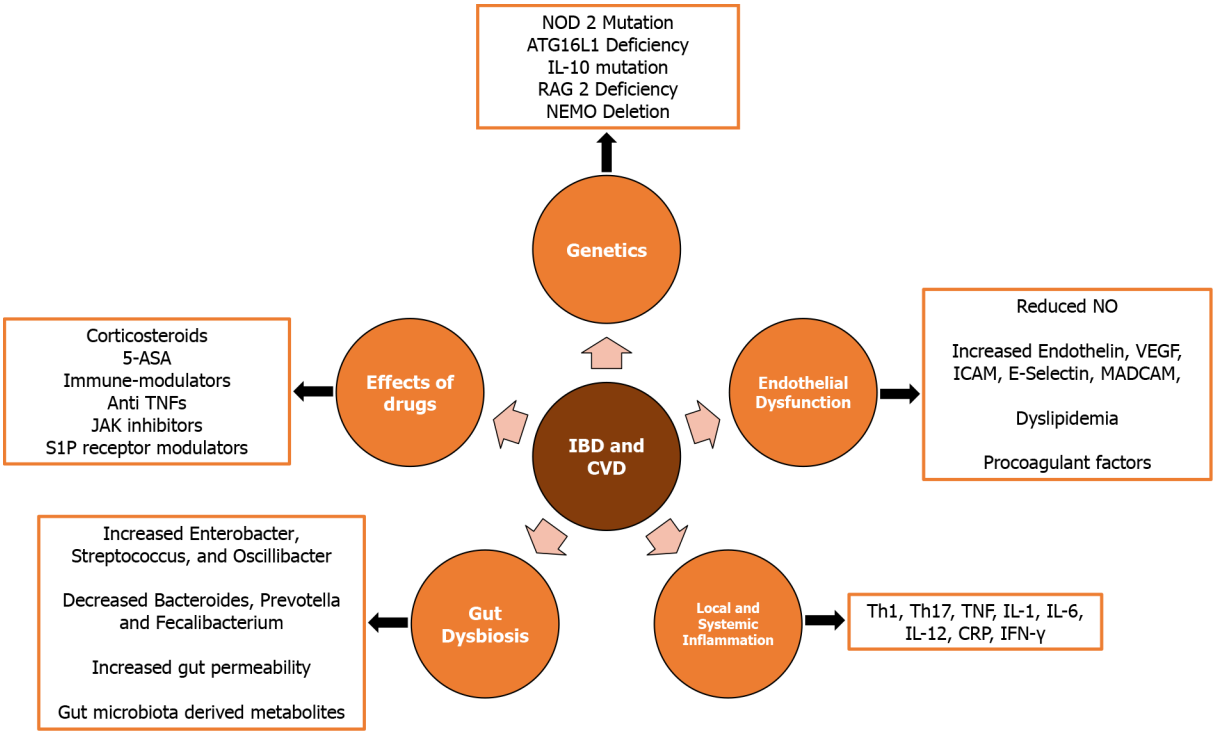

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Figure 1 Factors implicated in development of cardiovascular disease in patients with inflammatory bowel disease. JAK: Janus kinase; ASA: Amino salicylic acid; TNF: Tumor necrosis factor; CVD: Cardiovascular diseases; IBD: Inflammatory bowel disease; VEGF: Vascular endothelial growth factor; IFN-γ: Interferon-gamma; CRP: C-reactive protein; S1P: Sphingosine-1-phosphate; IL: Interleukin.

VENOUS THROMBOEMBOLISM (VTE)

IBD patients are at an increased risk for VTE. Systematic reviews and meta-analyses report that patients with IBD are at a two-fold increased risk for VTE as compared to general population (RR = 2.20; 95%CI: 1.83-2.65)[59,60]. The most common reported VTE events include deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The involvement of portal, the superior mesenteric, the splenic, the internal jugular, and the cerebral veins has also been reported[61]. The reported frequency is higher in patients with active IBD and directly proportional to the extent and severity of the disease in the absence of provoking factors[62]. In a retrospective study, VTE was more common in patients with UC (pancolitis more than left sided colitis or proctitis). In CD, VTE is more frequent in patients with ileocolonic or colonic involvement than with ileal disease alone[62].

The risk of in-hospital and post-hospitalisation VTE in patients with IBD is increased with intestinal or non-intestinal surgery when compared to non-IBD patients (OR = 2.03; 95%CI: 1.52-2.70 and OR = 4.45; 95%CI: 1.72-11.49, respectively). The risk factors for VTE include emergency surgery, open procedure, longer operative time, ileostomy formation, anastomotic leak, ileus, diagnosis of UC (higher risk as compared with CD), age > 65 years, and obesity[59,63,64]. Patients with IBD are also at a significantly high risk of recurrent VTE (HR = 2.5; 95%CI: 1.4-4.2; P = 0.001)[65].

Pregnant females with IBD (UC > CD, active disease) are also at two to three times increased risk of VTE during pregnancy and postpartum period (RR = 2.13; 95%CI: 1.66-2.73 and RR = 2.61; 95%CI: 1.84-3.69, respectively)[66,67].

Pathogenesis

The pathogenesis of VTE in IBD patients is multifactorial. The various mechanisms that contribute to thrombosis in IBD include genetic predisposition, inflammation, gut dysbiosis, spontaneous platelet aggregation, vascular thrombotic events secondary to flares, surgery, drug therapy and compounding risk factors such as pregnancy. Altered intestinal microbiota reduces mucus secretion and fibre fermentation that promotes inflammation *via* endothelial damage[68]. Genetic mutations in NOD2, ATG16L1, recombination activating gene 2, IL-10 receptor deficiency, and nuclear factor kappa beta essential modulator also lead to a pro-inflammatory state[36,69-71]. Inflammatory cytokines such as TNF and IL-1 result in a prothrombotic state due to increased levels of thrombin (which initiates the coagulation cascade through tissue factor) and simultaneous suppression of antithrombotic factors (such as endothelial thrombin and protein C)[72,73]. Another contributory mechanism is hyperhomocysteinemia secondary to inflammation induced malabsorption, and vitamin B and folate deficiency. Increased factor V thromboxane A2, arachidonic acid peroxidation product 8-iso-prostaglandin F2, tissue factor and mRNA synthesis further promote platelet activation and inhibit thromboregulation [74,75]. Estrogen based oral contraceptives and hormone replacement therapy promote production of coagulant factors leading to increased risk of VTE[76,77]. There is increased production of fibrinogen and decreased production of protein S during pregnancy which increases the risk of VTE[78].

IBD drugs and impact on VTE

5-ASA: No VTE or related complications have been reported with 5-ASA. In vitro studies have shown that 5-ASA inhibits platelet activation by thrombin, and therefore could have a role in preventing VTE. However further studies are required to evaluate the beneficial effect of 5-ASA in reducing the VTE risk[79-81].

Corticosteroids: Corticosteroids are potent anti-inflammatory drugs that also exert an independent thrombogenic effect (*via* increase in the serum levels of the clotting factors and fibrinogen)[82]. Systemic glucocorticoids and endogenous production of cortisol are associated with an increased risk of VTE. The risk of VTE is increased patients who are treated with corticosteroids, more so with higher doses [incidence risk ratio (IRR) = 2.31, 95%CI: 2.18-2.45][83,84].

Immunemodulators: There has been no reported risk of VTE with immunomodulatory drugs[85-87]. Although, it has been hypothesized that thiopurines reduce VTE risk by decreasing platelet aggregation and inhibiting platelet-leucocyte aggregation in vitro, more studies are required to confirm this hypothesis[88].

Biologics: TNF-α directly promotes endothelial dysfunction resulting in increased thrombus formation[89]. Patients treated with anti-TNF-α agents are therefore likely to have a decreased risk of VTE (OR = 0.267; 95%CI: 0.106-0.674, P = 0.005)[83]. It has been demonstrated that clot lysis profile normalises and there is a reversal of clotting abnormalities in patients receiving infliximab, suggesting benefit to reduce the VTE risk[63,72,82,90].

The overall risk of VTE with vedolizumab is low[91,92]. Pooled safety analysis from Phase 2/3 studies on ustekinumab reported no significant difference in VTE risk in patients treated with ustekinumab compared to placebo (0.75/100 person years *vs* 0.34/100 person years, respectively)[93-95].

Janus kinase (JAK) inhibitors: A safety study done in patients older than 50 year with rheumatoid arthritis and more than one cardiovascular risk factor showed that VTE, DVT and PE was higher for tofacitinib when used in the dose of 10 mg twice daily[95]. Similar to these observations, in the OCTAVE open study, with a follow-up of 7 years, 10 mg tofacitinib group had 0.1% and 0.7% prevalence of DVT and PE, respectively [IR = 0.06 (95%CI: 0.00-0.31) and 0.28 (95%CI: 0.09-0.65)]. There were no cases of DVT or PE in 5 mg tofacitinib group. Overall IR for tofacitinib was 0.06 (95%CI: 0.00-0.31) and 0.28 (95%CI: 0.09-0.65), for DVT and PE, respectively. Majority of the patients with thromboembolic complications had one or more underlying risk factors for DVT, except one patient with no pre-existing risk factors [96]. In IBD, therefore, tofacitinib appears to have an acceptable safety profile from VTE point of view, though The United States Food and Drug Administration has issued a black box warning recommending avoidance of JAK inhibitors in patients at risk of DVT, VTE and PE[97]. These risk factors include history of recent surgery, trauma, stroke or myocardial infarction (MI) in previous 3 mo, age > 50 years, morbid obesity, use of oral contraceptive pills, long flights and previous history of DVT, PE or acute thromboembolic event[98]. In case, when no therapeutic alternatives are available, a close coordination with cardiologist is required. The 10 mg twice daily dose is restricted to a maximum of 3 mo (for induction of remission) with de-escalation to 5 mg twice daily as soon as possible[99]. The randomized controlled trials (RCTs) of upadacitinib and filgotinib did not report a higher rate of VTE[100,101].

Management

All patients with IBD hospitalised for any cause, should receive a prophylactic dose of low-molecular-weight heparin (LMWH) or fondaparinux. LMWH is recommended over unfractionated heparin in critically ill patients[102]. Thromboprophylaxis during hospitalisation reduces the risk of VTE in IBD after discharge by 54% and should be maintained during the inpatient period[103]. Older age, *Clostridioides difficile* infection in index admission, longer hospital stay (> 7 d), ICU admission, previous VTE, and coronavirus disease are indications of extended prophylaxis (at least 2 mo after discharge) as these conditions are associated with increased the risk of post-discharge VTE[104]. IBD patients treated in the outpatient settings with moderate to severe flare and a high risk profile for VTE may benefit from thromboprophylaxis until resolution[105].

Guidelines recommend that the treatment of VTE should follow the general antithrombotic therapy guidelines. Direct oral anticoagulants are first line drugs and should be used at a therapeutic dose in IBD, LMWH is an alternative. In case of unprovoked VTE, the duration of treatment is indefinite. For provoked VTE secondary to an identifiable risk factor, anticoagulation is continued for 3 mo beyond the resolution of the risk factor. It is essential to know that thromboprophylaxis does not increase the risk of further IBD-related gastrointestinal bleeding in patients with active disease. It is important to remember that controlling the disease activity is most critical to prevent the recurrence of VTE[102,105,106]. The duration of anticoagulation is summarized in Figure 2.

ATHEROSCLEROTIC AND ATHEROTHROMBOTIC CARDIOVASCULAR DISEASE (ASCVD)

In addition to VTE, there is a moderate increase in the risk of arterial thrombotic events, such as acute myocardial infarction (MI), mesenteric ischemia, and stroke, in IBD, albeit lower than the VTE risk. Interestingly, this risk is comparable between UC and CD patients[14]. The risk of ischemic heart disease (IHD) is slightly elevated in younger age groups and women, peaking within the first year of IBD diagnosis[12,13,107,108].

Pathogenesis

The pathogenesis involves a multifaceted interplay between inflammatory cytokines, endothelial dysfunction, smooth muscle proliferation mediated by VEGF, ICAM-1, MADCAM-1, E-selectin, reduced vasodilator nitric oxide, and NOD2

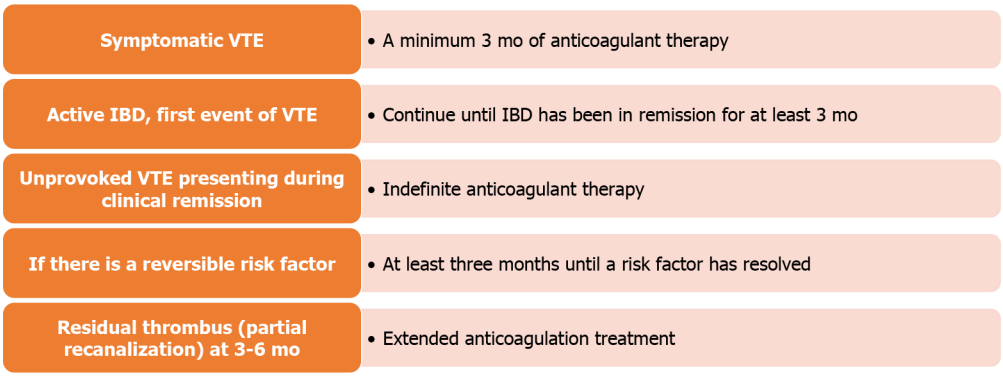

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Figure 2 Duration of anticoagulation in inflammatory bowel disease patients with venous thromboembolism. IBD: Inflammatory bowel disease; VTE: Venous thromboembolism.

polymorphisms[106].

The incidence of CVD and cerebrovascular accidents is higher in females with IBD, and could be due to inherent differences in distribution of risk factors in males and females, including greater immune response and higher levels of CRP in females[109,110]. The role of sex hormones in the development of ASCVD in IBD patients remains inconclusive. Moreover, younger IBD patients exhibit an increased relative risk of ASCVD, possibly stemming from earlier disease onset and a more severe disease course that results in prolonged exposure to chronic inflammation. Notably patients with IBD have similar prevalence traditional risk factors for coronary artery disease such as hypertension, diabetes, smoking, and obesity[111] (Figure 3).

Despite the lack of conventional risk factors for coronary artery disease, both UC and CD are independently associated with an increased risk of acute MI[112]. The IBD patients with CVD have been reported to have a higher level of high sensitive-CRP and fibrinogen, and greater prevalence of NOD-2 mutations[113]. Paradoxically, IBD patients tend to have lower levels of total cholesterol and LDL-cholesterol, with unaffected high density lipoprotein (HDL)-cholesterol and triglyceride concentrations. In CD patients, ileal resection and ileoanal anastomosis are inversely correlated with plasma total cholesterol and LDL-cholesterol levels[114,115].

The overall level of serum lipids in IBD patients is negatively associated with disease severity[113,116]. On the contrary, disease activity has been reported to be an independent risk factor for development of CVD[117-119]. This quandary is explained on the basis of presence of a more pro-atherogenic lipid profile characterized by small dense LDL-cholesterol particles and dysfunctional HDL-cholesterol in chronic inflammation associated with IBD[120]. The extent and location of inflammation is also associated with CVD risk. Patients with colonic involvement, in both UC and CD, have a threefold higher risk of developing MI[112].

Subclinical atherosclerosis

The occurrence of subclinical atherosclerosis is more frequent in individuals with IBD. To identify subclinical atherosclerosis, various diagnostic measures are employed, including assessing arterial stiffness through pulse-wave velocity between the carotid and femoral arteries (carotid-femoral pulse wave velocity, calculated as $^{\Delta}$distance/$^{\Delta}$time), measuring carotid intima-media thickness, evaluating flow-mediated dilation of arteries, and determining the coronary artery calcium score[106].

IBD drugs and impact on ASCVD

5-ASA: As with nonsteroid anti-inflmmatory drugs such as aspirin, 5-ASA shares anti-inflammatory, anti-platelet and antioxidant properties. Thus 5-ASAs may be associated with a decreased risk of IHD in patients with IBD[121,122]. IBD patients using 5-ASA were reported to have a lower risk of IHD than non-users (IRR = 1.16; 95%CI: 1.06-1.26 and IRR = 1.36; 95%CI: 1.22-1.51 P = 0.02, respectively). In long-term users of 5-ASA, the risk of IHD was even lower (IRR = 1.08; 95%CI: 0.98-1.19)[103,123].

Corticosteroids: Corticosteroid users are at a higher risk of developing IHD compared to non-users[123-125]. Corticosteroids predispose to risk factors such as hypertension, obesity, dyslipidemia and insulin resistance which may exacerbate IHD in IBD[126]. However, a direct causal association cannot be established.

Thiopurines: Thiopurines are not associated with acute arterial events in IBD and the effect of methotrexate on IHD in IBD is unknown. However in a beneficial effect on arterial stiffness has been demonstrated in various other chronic inflammatory disorders[127,128]. Thiopurines also decrease the production of transforming growth factor-beta and IL-10, which are responsible for endothelial dysfunction, and hence may have some protective role, though there is very limited data to make any conclusive recommendations at the moment[129,130].

Biologics: *In vitro* studies on infliximab have suggested an atheroprotective effect in monocytes by increasing both ABCA1 and LXR gene expression and removing excess cholesterol and preventing foam cell formation[127,129,131].

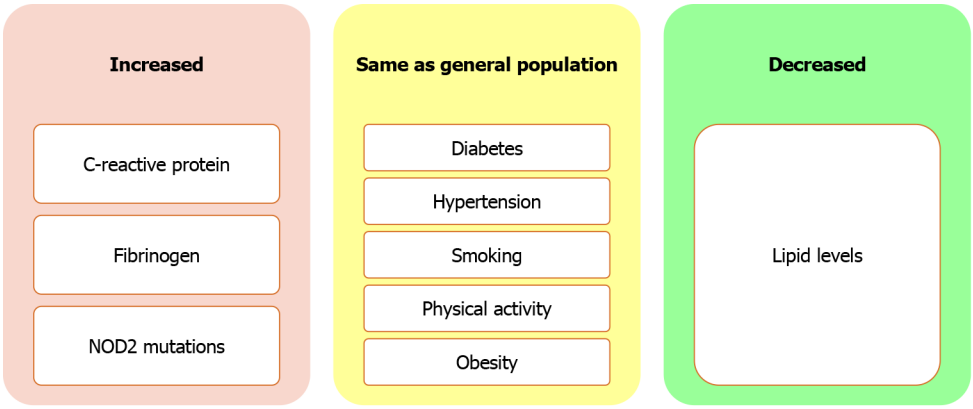

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Figure 3 Prevalence of risk factors for atherosclerotic cardiovascular disease in patients with inflammatory bowel disease.

However, the *in vivo* biological mechanisms are very complex. TNF-α is proatherogenic. Contradictory results have been reported with regards to the effect of anti TNF-α agents on the lipid profile. While some studies report an increase the levels of HDL-cholesterol and apoprotein-A1, others report an increase in the small dense LDL-cholesterol and total cholesterol. Also, TNF-α inhibition increases abdominal fat, leading to increased risk of ASCVD. On the contrary, the anti TNF-α agents exert beneficial effect by improving insulin sensitivity, endothelial function, arterial stiffness and fibrinolysis[89,132,133]. The anti-TNF-α agents may be associated with reduced risk of new-onset acute arterial events and prevent recurrence when used in patients with previous history of acute arterial events. Vedolizumab and ustekinumab have not reported any augmented risk of ASCVD[134,135].

JAK inhibitors: Small molecules tend to increase the risk of cardiovascular diseases by causing dyslipidaemia. Tofacitinib is associated with reversible changes in the lipid profile specifically total cholesterol, HDL-cholesterol and LDL-cholesterol[136,137]. Clinical trials in rheumatoid arthritis showed that tofacitinib is associated with higher rates of major adverse cardiovascular events (MACE). Older patients aged > 50 years with at least one cardiovascular risk factor had higher risk of MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) as compared with anti TNF agents (HR = 1.33; 95%CI: 0.91-1.94)[138]. However, the same has not been shown in the clinical trials in IBD. In the OCTAVE trials, one patient with several risk factors had acute coronary syndrome, one died of dissecting aortic aneurysm and one patient with a history of cardiovascular disease had congestive heart failure. During the maintenance phase, one subject with several risk factors receiving tofacitinib 5 mg twice daily had an adjudicated MACE (myocardial ischaemia/ myocardial infarction), and one patient, also with multiple risk factors, receiving tofacitinib 10 mg twice daily had an adjudicated MACE (haemorrhagic stroke). The overall incidence rate for MACE in the OCTAVE trials was 0.16 (95%CI: 0.04-0.42). Multiple real life studies of tofacitinib also did not demonstrate increase in the risk for MACE compared to anti TNF agents[96,139,140].

In a meta-analysis assessing safety of JAK inhibitors in IBD and other immune-mediated inflammatory diseases evaluated MACE in 32765 patients on JAK inhibitors (17 tofacitinib; 6 upadacitinib; 4 baricitinib; 3 filgotinib), the incidence rate of MACE was 0.67 per 100 patient-years[141]. Real life safety data on upadacitinib and filgotinib are lacking, however in the registry trials, MACE were infrequent and no difference was reported compared to placebo[142, 143]. Though the risk of MACE appears low, JAK inhibitors should be used cautiously in patients over the age of 50 years with concomitant risk factors for CVD.

Management of ASCVD

Current risk assessment tools for predicting CVD, such as the Framingham risk score and the ASCVD risk calculator, lack validation for individuals with chronic inflammatory conditions, potentially leading to an underestimation of their CVD risk. European guidelines suggest incorporating a 1.5-fold multiplier when assessing the 10-year CVD risk in patients with rheumatoid arthritis. However, there remains an information void regarding whether a similar adjustment is warranted for patients with IBD.

Controlling inflammation in IBD is the key to reduce the risk of CVD[105]. Adequate treatment of underlying IBD with the aim to achieve and maintain remission is important. Additionally, the patients should be screened for atherosclerotic risk factors such as obesity, smoking, hypertension, diabetes, dyslipidaemia and positive family history[144]. Definitive role of statins in IBD is controversial, but statins in addition to the lipid lowering function have pleiotropic effects, including modulation of the immune system[145,146]. IBD is not a contraindication to low-dose aspirin for primary and/ or secondary prevention.

HEART FAILURE

The risk of heart failure is twice as higher in IBD than non IBD subjects when adjusted for traditional cardiovascular risk factors with the highest risk reported in females with UC[112].

Heart failure in individuals with IBD may manifest as either new-onset (de novo) or as a consequence of deteriorating health in those with pre-existing conditions. These underlying conditions, which predispose individuals to heart failure, encompass IHD, hypertension, dyslipidemia, diabetes, smoking, valvular heart disease, congenital heart disease, *etc.* The frequent triggers for decompensation leading to heart failure involve infections or inadequate adherence to prescribed treatment regimens.

Pathogenesis

Heart failure in IBD could be a consequence of the chronic inflammation or the drug therapy used. The compromised integrity of the intestinal barrier and ongoing intestinal inflammation are contributing factors to the development of heart failure. This can be attributed to the translocation of bacterial LPS, which triggers the production of TNF-α. Both LPS and TNF-α are implicated in inducing structural changes in the heart that progress to heart failure[147,148]. Additionally, several other proposed mechanisms may contribute to the development of heart failure in these patients. These mechanisms include myocardial fibrosis due to altered collagen metabolism, impaired nitric oxide-mediated vasodilation, deficiencies in essential vitamins and trace elements, heart muscle atrophy resulting from prolonged corticosteroid use, total parenteral nutrition, myocarditis, endocarditis, and valvulopathy[30,149-151].

Anti-TNFs and heart failure

There have been case reports and studies of anti TNF induced heart failure[152,153]. The biological effects of TNF-α are mediated *via* two distinct cell surface receptors. TNFFR-1 is cardiotoxic and antagonising its action attenuates ventricular dysfunction and improves post MI survival whereas TNFR2 is cardioprotective and its inhibition upregulates TNFR1 and increases ventricular dysfunction and remodelling[154,155]. The effects of TNF-α are concentration dependent and involve two pathways. In lower concentrations, survivor activating factor enhancement pathway is activated, while higher concentration leads to stimulation of death-promoting pathway functions[156,157]. Chung *et al*[158] evaluated the effect of infliximab in patients with New York heart association (NYHA) Class III or IV heart failure with ejection fraction ≤ 35% and found that patients in the 10 mg/kg infliximab group were more likely to die or be hospitalized for heart failure than patients in the placebo group or 5 mg/kg infliximab group (HR = 2.84, 95%CI: 1.01-7.97; P = 0.043).

Prevention

Routine screening tests for cardiovascular diseases prior to the administration of biologics is not recommended. However, employment of an echocardiogram prior to initiation of anti TNF therapy to evaluate baseline cardiac function is vital [105,157]. Although there are no specific guidelines for the use of anti TNF in heart failure, it is suggested to avoid anti TNF agents in patients with NYHA class III or IV disease and switching to an alternative non-TNF inhibitor in patients with patients who develop acute heart failure on anti TNFs[105,157,159,160].

ARRHYTHMIAS AND CONDUCTION DISORDERS

As with other chronic inflammatory disorders, IBD carries a risk of major cardiac arrhythmias, which include atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation. The risk of arrhythmias correlates with the disease activity[43,161]. A large population-based cohort study found that risk of atrial fibrillation was increased in patients with IBD with a higher risk in CD and was particularly increased in younger patients with age < 45 years[21].

Pathogenesis

Although the pathogenesis of arrhythmias is incompletely understood, chronic inflammation is hypothesized to predisposes to rhythm disorders and conduction abnormalities in patients with IBD[30,162]. Also, patients on systemic steroids, immunomodulators or biologics had a higher risk, highlighting the role of moderate-to-severe active disease. Atrial electromechanical conduction delay, a predictor of atrial fibrillation, has been shown to be significantly prolonged in patients with IBD, especially those with active disease and longer disease duration.

IBD drugs and arrhythmias

Sphingosine-1-phosphate (S1P) receptor modulators (ozanimod) have been implicated in cardiac arrhythmias. S1PRMs have 5 G protein coupled receptor subtypes S1PR1 to S1PR5. The S1PR1, which is extensively expressed on cardiomyocytes and vascular endothelial cells, is the target of S1P modulators. In phase 3 RCT of ozanimod in UC, five cases of bradycardia were reported during the induction period and none during the maintenance period[163-165]. In the TOUCHSTONE open label long term extension study of ozanimod 1 mg per day in patients with UC, no bradycardia nor evidence of atrioventricular (AV) block was reported at 44 wk[163,166]. In the OASIS trial, a phase 2 induction trial of etrasimod which selectively target S1P1, S1P4, and S1P5, no such cardiac events were reported[167,168]. In the ELEVATE UC study, 5 patients receiving etrasimod reported bradycardia and 1 patient had first degree AV block that resolved without interventional treatment. The real-world studies, though scarce, did not report cardiac conduction abnormalities after 26 wk of treatment exposure of ozanimod.

Recommendations for patients with IBD to mitigate cardiovascular risk

The probability of experiencing cardiovascular events is inherently intertwined with the presence of systemic inflammation and the level of disease activity in individuals with IBD. It is imperative to adopt a proactive approach by conducting regular screenings and monitoring of cardiovascular risk factors for all IBD patients. Those identified as being at risk should adhere to established recommendations applicable to the general population. Collaborative efforts with cardiologists are vital in managing these risks effectively. Considering that these risk factors may evolve over time, especially with advancing age, routine screening and monitoring are indispensable for sustaining optimal cardiovascular well-being. It is of paramount importance to provide counseling and education to patients regarding their specific cardiovascular risks. Encouraging the adoption of healthy lifestyle modifications is crucial in this regard[169]. A concise summary of practical guidance for managing CVD in individuals with IBD is presented in Table 1.

Table 1 Practical guide to management of cardiovascular diseases in inflammatory bowel disease

Cardiovascular disease	Risk factors	Suggested testing	Therapeutic considerations
Pericarditis and myocarditis	**Disease related**	Onset of symptoms within 2-4 wk of starting 5-ASA	Discontinuation of therapy
	Disease activity		
	Drugs	ECG: ST-T changes	Immunesuppressives for inflammation associated myocarditis
	5-ASA		
		2D Echocardiography: LV dysfunction, pericardial effusion	Pericardiocentesis or pericardial window, if cardiac tamponade
		Cardiac MRI	Control IBD disease activity
		Endo-myocardial biopsy, if cardiac MRI contraindicated or life threatening disease	
		Elevated cardiac biomarkers	
Venous Thromboembolism	**Patient related**	Screening for genetic risk factors in patients with recurrent venous thromboembolic events	**Thromboprophylaxis**
	Elderly age		All IBD patients during hospitalization of any cause
	Females		Ambulatory patient with active IBD and known risk factors for VTE
	Obesity		Prophylaxis should be maintained during the inpatient period
	Malnutrition		
	Disease related		**Treatment**
	Disease activity		LMWH
	Colonic disease location		Direct oral anticoagulants
	UC > CD		Cautious use of JAK inhibitors
	Hospitalization		Aim the lowest effective dose to maintain remission
	Emergency surgery		
	Longer operative time		
	Open surgery		
	Drugs		
	JAK inhibitors		
	Corticosteroids		
Atherosclerotic cardiovascular disease	**Patient related**	Lipid profile at baseline, end of induction and every 6 mo	Treatment of ASCVD is similar to non IBD patients and should be done in close collaboration with an expert cardiologist
	Younger age		
	Females		
	Disease related	**Test for subclinical atherosclerosis**	Control IBD disease activity
	Disease activity	Carotid intima media thickness	

	Colonic disease location	Pulse-wave velocity between the carotid and femoral arteries	
	Increased hs CRP	Coronary artery calcium	
	Increased fibrinogen		
	Drugs	2D echocardiography/stress echocardiography/TMT	Cautious use of JAK inhibitors
	Corticosteroids		
	JAK inhibitors		
		Coronary angiography	Treat JAK inhibitor induced dyslipidemia/hyerlipidemia with statins
Heart failure	**Patient related**	**2D Echocardiography**	Avoid anti TNF in NYHA Class III or IV heart failure, especially with ejection fraction ≤ 35%
	Females	Ventricular dysfunction	
	Underlying cardiac structural diseases	Structural abnormalities	
	Diabetes		
	Hypertensive heart disease		
	Chagas disease		
	Deposit diseases		
	Valvular heart disease		
	Disease related		
	UC > CD		
	Drugs		
	Anti TNF agents in high dose		
Arrhythmias and conduction abnormalities	**Patient related**	**ECG**	Control disease activity
	Age > 65 yr	Increased P-wave dispersion	Caution with S1P receptor modulators
	Previous arrhythmias or cardiac conduction abnormalities	Increased QTc dispersion	Caution in patients with risk factors
	Ischemic heart disease	Prolonged QTc interval	
	Cardiomyopathy with septal involvement		
	Drugs (*e.g*: beta-blockers, calciumchannel inhibitors, antiarrhythmics)		
	Uncontrolled hypertension		
	Previous cardiac surgery		
	Surgical/percutaneous treatment of valvular disease		
	Disease related		
	Disease activity		
	Drugs		
	S1P receptor modulators		

ASA: Amino salicylic acid; ECG: Electrocardiogram; LV: Left ventricular; MRI: Magnetic resonance imaging; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; VTE: Venous thromboembolism; LMWH: Low-molecular-weight heparin; JAK: Janus kinase; ASCVD: Atherosclerotic cardiovascular diseases; CRP: C-reactive protein; TMT: Treadmill test; TNF: Tumor necrosis factor; NYHA: New York heart association; S1P: Sphingosine-1-phosphate.

Future directions

The pathophysiology of CVD in IBD needs further elaboration. The current knowledge gaps include the following: Immunological mechanisms at play in both the development of IBD and the formation of atherosclerosis, prevalence of cardiometabolic risk factors, risk stratification and identification of IBD patients at the highest risk for cardiovascular

complications, allowing for more targeted preventive measures, role of pre-emptive screening for subclinical atherosclerosis and its cost effectiveness, long term outcomes in patients with CVD and IBD, and effective strategies for monitoring cardiovascular risk factors in IBD patients, and how often should such monitoring occur.

CONCLUSION

The prevalence of cardiovascular manifestations in patients with IBD, though rare, is higher when compared to the general population. The CVD in IBD represent a complex and multifaceted relationship between chronic gastrointestinal inflammation and cardiovascular health. The inflammatory cytokines, immune responses and chronic systemic inflammation associated with disease activity contributes to the development and progression of CVD. Individual patient factors, such as age, gender, pre-existing cardiovascular conditions, and genetics, also play a significant role in determining the cardiovascular impact. The spectrum of CVD in IBD is wide. Additionally, the cardiovascular effects of drugs used in IBD are multifaceted and depend on various factors, including the specific medicines involved and individual patient characteristics.

In individuals with IBD who are at an elevated risk of cardiovascular issues, there is a need to shift the focus of care from a reactive approach to a proactive one, emphasizing preventive measures for cardiovascular management. To minimize cardiovascular risk a multidisciplinary approach involving gastroenterologists and cardiologists is often necessary. This will ensure that IBD treatment is optimized while minimizing cardiovascular risk.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Arshia Bhardwaj 0000-0001-5820-7758; Arshdeep Singh 0000-0001-7163-0454; Vandana Midha 0000-0003-0192-3969; Ajit Sood 0000-0001-6961-6389; Gurpreet Singh Wander 0000-0002-4596-4247; Bishav Mohan 0000-0002-4337-3603; Akash Batta 0000-0002-7606-5826.

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MINIREVIEWS

Acute myocardial infarction in myeloproliferative neoplasms

Muhammad Romail Manan, Vincent Kipkorir, Iqra Nawaz, Maryann Wanjiku Waithaka, Bahadar Singh Srichawla, Amelia Maria Găman, Camelia Cristina Diaconu, Mihnea-Alexandru Găman

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Muhammad Romail Manan, Services Institute of Medical Sciences, Lahore 54000, Pakistan

Vincent Kipkorir, Maryann Wanjiku Waithaka, Department of Human Anatomy and Physiology, University of Nairobi, Nairobi 00100, Kenya

Iqra Nawaz, Quaid-e-Azam Medical College, Bahawalpur 63100, Pakistan

Bahadar Singh Srichawla, Department of Neurology, University of Massachusetts Chan Medical School, Worcester, MA 01655, United States

Amelia Maria Găman, Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Craiova 200143, Romania

Amelia Maria Găman, Clinic of Hematology, Filantropia City Hospital, Craiova 200143, Romania

Camelia Cristina Diaconu, Department of Internal Medicine, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Camelia Cristina Diaconu, Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest 105402, Romania

Mihnea-Alexandru Găman, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Mihnea-Alexandru Găman, Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest 022328, Romania

Mihnea-Alexandru Găman, Department of Cellular and Molecular Pathology, Stefan S. Nicolau Institute of Virology, Romanian Academy, Bucharest 030304, Romania

Corresponding author: Mihnea-Alexandru Găman, Doctor, MD, PhD, Doctor, Research Fellow, Researcher, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, 8 Eroii Sanitari Boulevard, Bucharest 050474, Romania. mihneagaman@yahoo.com

Abstract

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematologic malignancies characterized by an abnormal proliferation of cells of the myeloid lineage. Affected individuals are at increased risk for cardiovascular and thrombotic events. Myocardial infarction (MI) may be one of the earliest clinical manifestations of MPNs or may be a thrombotic complication that develops

during the natural course of the disease. In the present review, we examine the epidemiology, pathogenesis, clinical presentation, and management of MI in MPNs based on the available literature. Moreover, we review potential biomarkers that could mediate the MI-MPNs crosstalk, from classical biochemical tests, *e.g.*, lactate dehydrogenase, creatine kinase and troponins, to pro-inflammatory cytokines, oxidative stress markers, and clonal hematopoiesis.

Key Words: Myeloproliferative neoplasms; Polycythemia vera; Essential thrombocythemia; Myelofibrosis; Myocardial infarction; Acute coronary syndrome; Biomarker; Clonal hematopoiesis

Core Tip: Patients diagnosed with myeloproliferative neoplasms (MPNs) are at risk of developing thrombotic complications, among which acute coronary syndromes are of relevance. Myocardial infarction (MI) can emerge as the initial event in the diagnosis of MPNs or occurs during the evolution of the disease. Here, we examine the interplay between MI and MPN, with a focus on the epidemiology, presentation, risk factors, diagnosis, and management of MI in MPNs, as well as discuss potential biomarkers of MI in MPNs, as well as the role of inflammation and clonal hematopoiesis.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a heterogeneous class of blood disorders characterized by an abnormal proliferation of cells of the myeloid lineage[1]. They comprise a group of chronic myeloid malignancies with various phenotypes, marked by the clonal proliferation of hematopoietic stem cells and excessive proliferation of terminally differentiated myeloid blood cells[2]. The four classic types of MPNs include chronic myeloid leukemia, essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)[1]. Furthermore, chronic neutrophilic leukemia, chronic eosinophilic leukemia, and unclassified MPN are also included in the classification presented by the World Health Organization (WHO)[1]. Among these, PV (characterized by an absolute increase in erythrocytes due to the proliferation of the erythroid lineage[3]), ET (marked by the excessive proliferation of hyperlobulated mature megakaryocytes in the bone marrow along with persistent peripheral blood thrombocytosis[4]) and PMF (characterized by abnormal differentiation of the megakaryocytic clone, ultimately resulting in excessive proliferation of reactive fibroblasts and fibrosis[5]) are BCR-ABL1 negative and will remain the focus of this review. The major cause of morbidity and mortality in MPNs are thrombo-hemorrhagic complications. This review aims to describe the complex pathogenesis, risk stratification, diagnostic criteria, and management of acute coronary syndrome (ACS) in MPNs.

Patients with MPNs have a higher risk of cardiovascular events[6]. It is important to note that ACS can be one of the first clinical manifestations of MPN[7], or it can be a thrombotic complication of ET and PV. PV typically affects the large arteries of the cardiovascular and cerebrovascular system, while ET tends to involve the microcirculatory system[7]. Previously published literature suggests that the reported incidence of cardiovascular complications related to MPNs ranges from 4% to 21%[7]. In patients diagnosed with ET, the incidence of thrombosis was reported to be 25%, with arterial thrombosis occurring more frequently than venous thrombosis[8]. During the follow-up of patients with PV, over a 10-year period, coronary events were frequently observed, with a reported rate of 11.4%[3]. Among a total of 1213 PV patients, thrombosis was identified in 19% of cases over a 20-year period, with 21.7% thrombotic events resulting in myocardial infarction (MI)[9]. In patients diagnosed with ET and PV, the mortality rate attributed to cardiovascular disease was 26% and 25%, respectively, higher than the mortality rate caused directly by the disorder itself[10]. Cerebral venous thrombosis, although a rare complication of PV, has been reported to cause the death of 8.3% of patients[11]. Furthermore, complications of MI may develop in 12 mo after the diagnosis of ET or PV[12].

Pathogenesis

The mechanisms responsible for the increased tendency for thrombosis in MPNs are not yet fully understood. ACS in myeloproliferative diseases is mostly attributed to coronary thrombosis due to hyperviscosity and thrombocytosis. The etiology of MPN-related hemostatic conditions is complex and multifactorial, involving a combination of quantitative and qualitative changes[12]. Pathophysiological mechanisms likely involve complex interactions between blood components and vascular cells, together with hemodynamic changes[13]. These, coupled with risk factors such as advanced age, a history of thrombotic events, leukocytosis, and cardiovascular risk factors such as hypertension, smoking, diabetes mellitus, have been observed to increase the risk associated with developing thrombosis in the context of myeloproliferative diseases. Factors that contribute to the thrombophilic state in MPNs include: Increased cell mass resulting from

the clonal expansion of hematopoietic stem cells[11]; prothrombotic state induced by increased platelet accumulation, along with the release of activation products and increased expression of surface activation markers[5]; elevated leukocyte count, which has been documented to be a stronger predictor of thrombogenesis than platelet count or hematocrit/hemoglobin levels[13]; elevated blood viscosity that pushes platelets centrifugally, causing them to adhere to the vessel wall, consequently initiating the process of thrombus formation; increased tendency of erythrocytes to attach to the endothelium; inflammatory response resulting from increased cytokine expression; and an elevated level of microparticles exhibiting procoagulant activity[14].

Furthermore, in most patients with MPN, driver mutations are observed in the pro-inflammatory JAK-STAT signaling pathway, with *JAK2* mutations the most prevalent. MPN patients carrying *JAK2* mutations are at higher risk of developing arterial thrombosis[6], which is evident in reports that around > 95% PV and approximately 50% of patients with ET and PMF have a mutation of the *JAK2* gene, *i.e.*, *JAK2V617F*[2,11]. In addition to mutations in exon 14 of the *JAK2* gene, deletions, and mutations in exon 12 of the *JAK2* gene have been observed. Furthermore, mutations in *MPL*, the thrombopoietin receptor gene, as well as in *CALR*, the calreticulin gene, have been identified along with several mutations in non-driver genes, for example, the ten-eleven translocation 2 gene[2,14]. Although a susceptibility haplotype to *JAK2* mutations, 46/1, haplotype, has been reported, the presence of a *JAK2* mutation is not strictly associated with the initialization of MPN[2].

RISK FACTORS FOR ACS/MI IN MPNS

Patients with MPNs have an overall increased risk of developing cardiovascular disease, especially under the spectrum of ACS[15,16]. The incidence of ACS in these patients has been attributed to significant morbidity and mortality, with up to 76% of deaths due to cardiovascular events and approximately 32% having major adverse cardiovascular events up to 1 year post-ACS[6]. As discussed above, the basis for ACS and MPNs comorbidity is largely due to the prothrombotic, pro-inflammatory, and profibrotic states seen in patients with MPNs secondary to gain of function mutations in the *JAK* signaling pathway[14,16].

Risk factors for ACS in MPNs are chiefly based on the level of ischemic risk, classified as either; high, intermediate or low, based on a set of established criteria[17-19]. Increasing age, previous thrombosis, and diabetes have been identified as consistent and independent predictors of cardiovascular events in MPNs and therefore have been classified as the main risk factors for ischemic events in MPNs[17]. Minor risk factors in this criterion include smoking, hypertension, and hypercholesterolemia. Therefore, a high-risk patient is often < 60 years of age, has a history of thrombosis, or diabetes. Intermediate-level risk patients have ages between 40 and 60 years along with one of the minor risk factors or an age < 40 years with two minor risk factors. Patients with a low-risk level do not have any identifiable risk factors[4]. A schematic representation of the risk factors that contribute to the development of ACS in MPNs is depicted in Figure 1.

The European Collaboration on Low-Dose Aspirin in Polycythemia (ECLAP) study reported higher incidences of cardiovascular complications in patients with PV > 65 years (5% patient-years) and in those with a history of thrombosis (4.93% patient-years) compared to younger patients without a history of thrombosis (2.5% patient-years)[20]. Similarly, Barbui *et al*[21] based on the results of an epidemiological study of 1638 patients with PV, observed an 8:6 hazard ratio in patients > 60 years compared to younger patients. Carobbio *et al*[22] observed a similar trend in an international study of 891 patients with emergency department (ED) where individuals over 60 years of age and with a thrombotic history had risk ratios (RR) of 1.5 and 1.93, respectively, to develop major thrombosis when followed for about 6.2 years.

Another risk factor for the thrombosis and MI in MPN patients is leukocytosis[17]. A study using data from the ECLAP database assessed the association between hematological variables and risk of MI[23]. They observed a 70% increased risk of thrombosis in patients with PV with a white blood cell (WBC) count > 15 × 10^9/L. The proposed mechanism of thrombosis is believed to involve endothelial inflammation from activated WBCs. Consequently, the consensus recommends that as part of the cytoreduction in PV and ET, the WBC count should remain within the normal range[24]. It is noteworthy, however, that this association has not yet been proven in randomized clinical trials. Interestingly, while elevated platelet levels can be assumed to be the leading risk factor for MI in these patients, the findings of the ECLAP study showed that neither the proposed therapeutic target (400 × 10^9/L) nor other platelet count thresholds served as a predictor of increased risk of the aforementioned complication[25].

Most minor risk factors for the occurrence of MI in MPNs constitute conventional atherosclerosis risk factors and serve as accentuators in the background of the aforementioned major risk factors leading to the transition from low to intermediate or high-risk levels[26,27]. The International Prognostic Score for Thrombosis categorizes cardiovascular risk factors as part of the variables that are significantly and independently associated with increased rates of thrombosis in patients with ED[26]. Genetic interplay in the causality of MI in MPNs is also to be considered as key risk factors. A study evaluating PV patients observed a higher risk of cardiovascular events (RR = 7.1; P = 0.003) in patients harboring > 75% of the mutant allele JAK2V617F[28]. Similarly, a systematic review showed a twice as high odds (odds ratio = 1.92; 95% confidence interval: 1.45-2.53) in patients with similar mutations in ET, although heterogeneity between included studies [29]. The coexistence of this mutation with leukocytosis results in the highest levels of fatal and non-fatal thrombosis[30].

CLINICAL PRESENTATION

Approximately 0.27% and 0.1% of MI-related hospitalizations due to thrombosis are attributed to ET and PV, respectively [31]. Thus, despite the relatively high incidence of this vascular complication in MPNs, it contributes very little to the

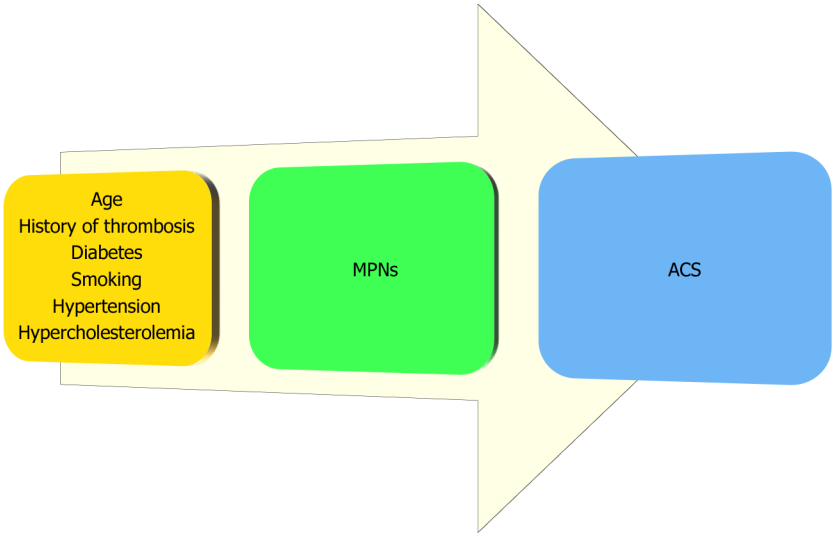

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Figure 1 Schematic representation of the risk factors that contribute to the development of acute coronary syndromes in myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes.

etiology of MIs. ACS has been reported as the initial presentation in some patients with MPN; however, most incidences of MI develop within one year after diagnosis of ET and PV[12]. This usually occurs despite the initiation of MPN treatment. Patients usually present with the typical symptoms associated with MI, that is, severe retrosternal chest pain radiating to the shoulder that is squeezing in character, exertional chest pain, dyspnea combined with profuse sweating. These patients often lack a history of risk factors associated with ACS, *e.g.*, hypertension, diabetes, or hyperlipidemia; however, one or more may be present[32]. They may or may not have a family history of coronary artery disease or a history of smoking with varied pack-years. Other associated symptoms include headache prior to acute condition, nausea, general malaise, and diaphoresis[32].

Examination and lab findings often vary from patient to patient. Vital signs including heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation often remain stable within the reference ranges. Lung auscultation is often clear throughout both lungs, however, cardiac examination at times reveals an S4 gallop[33] and splenomegaly may at times be palpable on abdominal examination[34]. The peripheries do not show edema, but erythromelalgia of the hands is positive in some cases[33]. Lab tests reveal elevated platelets, troponins, D-dimers, triglycerides and hematocrit with low potassium levels and normal urea, electrolytes, and creatinine[35,36].

On radiological investigation, the thrombus in ET is often located within the left anterior descending artery; however, right coronary involvement has also been reported in the literature[36,37]. Electrocardiography usually shows a regular sinus rhythm with elevation of the ST or non-ST segment[33,34]. Notably, as part of treatment, an oral imidazoquinazoline drug, anagrelide, has been observed to cause ACS in some (1%-5%) patients with ED by directly inducing coronary artery vasospasm[4]. The incidence of ACS increases with increasing age; therefore, most of the presenting patients are over 60 years of age and those with a history of thrombosis or in the background of mutations in the *JAK2* or *MPL* genes[35].

DIAGNOSIS

For ACS, risk factors such as age, family history of coronary artery disease, hypertension, diabetes, dyslipidemia, or smoking should be considered[7]. An electrocardiogram should be performed to assess the type of MI to guide emergency management. Cardiac markers may be elevated[38]. Coronary angiogram may reveal the coronary artery involved, of which the most reported in MPNs is the left anterior descending artery[7]. Echocardiography may be performed to assess ventricular ejection fraction[7].

The complete blood cell count becomes an important baseline investigation, particularly in this case. Lab tests may reveal an increase in platelet count, an increase in hematocrit, and/or leukocytosis. However, reactive thrombocytosis and leukocytosis can be observed due to an inflammatory response in the case of acute MI, resulting in a delayed or missed diagnosis of MPN[7]. The international normalized ratio and prothrombin time may be normal[39]. In addition, giant platelets and megakaryocyte fragments can be seen in the peripheral blood smear[39].

Diagnosis of ET according to the criteria issued by the WHO is given by a persistent elevation of the platelet count of ≥ 450×10^9 platelets/L, presence of typical mutations associated with ET, a negative translocation of BCR-ABL1 and bone marrow biopsy for histopathological confirmation. Molecular biology studies for *JAK2* mutations confirm the diagnosis, as evidence of the *JAK2V617F* mutation has been observed in 60% of patients with ET[7]. In the analysis of the *CALR* or *MPL* mutations, mutations of the *CALR* exon 9 and *MPL* exon 10 have been reported in 30% of patients who are *JAK2V617F* negative[7]. Cellular bone marrow with maturing trilineage hematopoiesis and large atypical hypolobulated

megakaryocytes may be seen in bone marrow biopsy, as reported in previously published literature[39].

Furthermore, the abdomen should be examined for hepatosplenomegaly, which may be indicative of thrombocytosis, leukocytosis, or polycythemia, followed by abdominal ultrasound if indicated[7]. The following three 'red flags' have been reported in previous literature that should raise suspicion of ET in ACS and should therefore inform relevant investigations, including bone marrow biopsy and genetic testing for driver mutations[40]: (1) There are few or no coronary artery disease-related risk factors present in ACS patients; (2) Platelet count > 450 × 10^9/L. A mild increase above this level should also warrant investigation; and (3) In coronary angiography, severe atherosclerotic narrowing is not reported. However, thrombotic occlusion may sometimes be observed.

PV is diagnosed when the three main criteria are met, or when the patients meet the first two main criteria and the minor criterion defined by the WHO[3]. The main criteria for PV issued by the WHO include: (1) Hemoglobin level > 16.5 g/dL in males, and > 16.0 g/dL in women or a hematocrit > 49% in males and > 48% in women or increased red cell mass; (2) Hypercellularity for age with trilinear growth observed on bone marrow biopsy; (3) Detection of *JAK2* mutations (V617F or exon 12 mutations). The minor criterion includes a decreased serum erythropoietin level[3]. In patients with PMF, circulating platelets exhibit an activated state and demonstrate notably elevated levels of protein kinase Cepsilon (PKCepsilon)[41]. Furthermore, in patients with MF, PKCepsilon levels in platelets were found to be associated with high-risk disease and a history of major cardiovascular events[41].

MANAGEMENT

For patients with ACS, emergency management should begin depending on the specific type of MI. ACS management in ET involves initiating cytoreductive therapy, administration of antithrombotic drugs, and revascularization based on risk-oriented recommendations. Thus, risk stratification of thrombosis becomes important to guide management. Patients are classified as 'high risk' when any of the three specified criteria is met: (1) Age ≥ 60 years; (2) A previous history of thrombosis or major bleeding; and (3) A blood platelet count of ≥ 1500 × 10^9/L[40]. Patients are labeled low risk if their age is less than 60 years and there is no history of previous thrombotic event[12].

As all patients with ACS with ET are classified as 'high risk'[40], their management involves monitoring the associated risk factors and initiating cytoreductive therapy. The first-line drug is hydroxyurea and the objective of the therapy is to maintain a platelet target of less than 400 × 10^9/L[42]. Platelet target count of 400 × 10^9/L is generally considered acceptable by most hematologists; however, a target count of 600 × 10^9/L may be appropriate to avoid anemia and leukocytopenia, and in particularly younger patients, malignant transformation possibly related to intensive cytoreductive therapy can be prevented[40]. With long-term administration of hydroxyurea, irreversible gonadal toxicity has been reported[42]. Therefore, in younger patients with reproductive intentions, interferon alpha is preferred[42]. In addition, limited information is available on the safety of cytoreductive therapy in very elderly patients[12].

Given the risk of thrombosis with the *JAK2V617F* mutation and cardiovascular risk factors, cytoreductive therapy may be combined with antiplatelet therapy with low-dose acetylsalicylic acid. The combination of cytoreductive therapy with antiplatelet agents or oral anticoagulants has also been reported to be more effective than the administration of single drugs[43]. Furthermore, the JAK1/2 inhibitor ruxolitinib has also been used in the management of ET[44]. Platelet reducing agents such as anagrelide can also be prescribed[43]. Anagrelide (imidazoquinazoline) selectively affects megakaryocytes by inhibiting cyclic-AMP phosphodiesterase III activity, resulting in inhibition of platelet aggregation. Although it is recommended for patients resistant to or intolerant to hydroxyurea, it can induce spasm of the coronary arteries, leading to cardiovascular events such as ACS, heart failure, and/or arrhythmias[4].

The estimate of the rate of recurrence of thrombosis after cytoreductive therapy was halved in the overall cohort of 494 patients with PV and ET[43]. In addition, the use of tirofiban, a glycoprotein IIb/IIIa receptor blocker, has also been highlighted in the treatment of acute MI in an ET patient[45]. Thrombotic complications in PV are substantially reduced by cytoreductive management of blood hyperviscosity either by phlebotomy or chemotherapy along with antiplatelet therapy using low-dose aspirin to achieve target hematocrit levels below 45%[44].

Other treatment options for ED include aspiration thrombectomy and distal protection revascularization to prevent distal embolization. Percutaneous coronary intervention has been described as an effective approach to revascularization in patients with ER, however, an increased incidence of complications such as stent thrombosis and restenosis has been reported[8]. However, cytoreduction is advised before revascularization to prevent platelet activation and future thrombotic events[39]. The management of ACS in MPNs is therefore a combination of aggressive pharmacotherapy and an appropriate revascularization approach.

PROGNOSIS

Thrombosis remains the most common complication of MPNs. There is an increased risk of in-hospital mortality due to MI associated with ET and PV. It has been reported that around 4% of patients with MPNs die from MI[46]. The incidence of recurrence of thrombosis after previous arterial or venous thrombosis is high, with studies reporting a rate of 33%[47]. Furthermore, in patients with ACS due to this pathological hypercoagulable state, a diagnosis may be missed in the absence of marked thrombocythemia as clinicians focus on the restoration of normal cardiac function and coronary vessel revascularization and thus may overlook this rare etiology[46]. Thus, recurrence can further worsen the prognosis for this condition. The prognosis also worsens with increasing age, the presence of atherosclerotic risk factors, the presence of a previous thrombotic event, and comorbid conditions[32]. Treatment must therefore involve a multidisciplinary team in

order to treat the underlying etiology, prevent recurrence, and decrease the risk of additional thrombotic complications.

FUTURE PERSPECTIVES: CAN WE QUEST FOR BIOMARKERS?

In the era of genomic and precision medicine, it is warranted to identify biomarkers that could predict the onset of thrombotic complications or link ACS and MPN. Lactate dehydrogenase is of poor utility in the ACS-MPNs interaction, as it is not an ideal biomarker for the heart and is also frequently detected in elevated concentrations in MPN[48]. Furthermore, creatine kinase, a potential marker of myocardial damage useful for its low execution costs as opposed to other more heart-specific biochemical panels, has been shown to exhibit a low mean creatinine kinase activity compared to ACS, healthy individuals and subjects diagnosed with a wide range of chronic disorders. However, Pan *et al*[49] have highlighted that creatinine kinase activity was the best biomarker for MPNs among 36 disorders, including ACS, stroke, diabetes, leukemia, lymphoma, multiple myeloma, and several solid cancers. Increased troponin concentrations have rarely been reported in MPNs. Tortorella *et al*[50] investigated cardiovascular risk factors and events in ET subjects prescribed anagrelide, discovering that only 2 of 55 analyzed patients had elevated troponin values. However, therapy with this platelet-lowering agent did not influence troponin concentrations nor the risk of MI, and the two individuals diagnosed with ET who also developed MI did not require discontinuation of anagrelide.

Oxidative stress could be a mediator of MPN-ACS crosstalk. Ischemia-modified albumin has been detected at elevated concentrations in both MI[48] and MPN[51-53]. Regardless of the disease subtype, MPN subjects showed increased albumin values modified by ischemia compared to healthy controls, with notable elevations exhibited by individuals with PMF and *ASXL1*-mutated MPN[51]. Similarly, Karahan *et al*[52] have highlighted that subjects living with PV show elevated levels of ischemia-modified albumin compared to healthy counterparts and that ischemia-modified albumin is an excellent predictor of tissue ischemia in PV. Additionally, prescription of ruxolitinib has been reported to decrease levels of oxidative stress in PMF. After one month of therapy, ischemia-modified albumin values decreased in PMF patients regardless of their mutational landscape. Subjects with PMF mutated with *ASXL1, JAK2V617F,* and *CALR*-mutated PMF (P = 0.001 for all), followed by *MPL*-mutated (P = 0.005) and triple negative PMF (P = 0.028)[53].

S100A, a myeloid-related protein, has also been reported in elevated values in ACS[48] and MPN. S100A is inhibited by pro-inflammatory cytokines and may emerge as a potentially relevant biomarker of inflammation in the diagnosis of MPN[54]. Furthermore, S100A proteins interact with cell signaling pathways in MPNs *via* Toll-like receptor 4 and RAGE in a burden-dependent manner of the *JAK2V617F* and *CALR* alleles, respectively[55]. Choline-related metabolites have been detected at high levels in ACS[48], however, Gómez-Cebrián *et al*[56] noted that there are low concentrations of these biomarkers in MPN.

Inflammation markers remain elevated in both ACS[48] and MPNs[57,58]. MPN inflammation is dependent and independent of the mutational landscape of the disease and is influenced not only by genetics, but also by the immune system, diet, metabolism, and comorbidities[59]. Furthermore, researchers have pointed out that both MPN patients[58] and MI subjects have elevated concentrations of ferritin[60,61], C-reactive protein[62,63], and fibrinogen[64]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin (IL)-6 and IL-1, and the NACHT, LRR, and PYD domains-containing protein 3 inflammasome have been reported to contribute to the pathogenesis of both MI[65-67] and MPN[58,59,68-70].

Dyslipidemia is recognized as a contributor to the development of MI[48]. In addition, several assessments have also delineated the role of lipid alterations in MPN. Furuya *et al*[71] have revealed that elevated levels of triglycerides and low-density lipoprotein-cholesterol are associated with thrombotic complications and survival in ET. Apolipoprotein A1 levels were also associated with the burden of the *JAK2V617F* allele in people with PV[72].

Clonal hematopoiesis of indeterminate potential has also emerged as a contributing factor to the onset of MI[73-75]. Moreover, inflammation has depicted as a possible link between the hematologic malignancies, thrombosis, and ACS in particular[76]. A schematic representation of potential biomarkers linking ACS and MPNs is depicted in Figure 2.

As new instruments are continuously being developed to evaluate cardiovascular risk, we may experience the beginning of an improved prognostication of thrombotic events in MPNs. For example, Mehta *et al*[77] have assessed the QRISK3 score in a cohort of 438 individuals diagnosed with MPNs, revealing that subjects with a history of arterial thrombosis have an elevated burden of cardiovascular risk factors and thus an increased cardiovascular risk warranting for a more aggressive management of associated comorbidities. The QRISK3 tool takes into consideration age (25-84 years), sex, ethnicity, smoking status, presence of comorbidities (diabetes, atrial fibrillation, chronic kidney disease stage 3-5, migraines, lupus, rheumatoid arthritis, severe mental illness, erectile dysfunction), family history of angina or AMI in a 1st degree relative aged < 60 years, use of several medications (antihypertensive agents, antipsychotics, oral corticosteroids, treatment for erectile dysfunction) and several other variables (body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, systemic blood pressure values and the standard deviation of at least two most recent systolic blood pressure readings)[77]. Moreover, Skov *et al*[78] have highlighted that in MPNs there is a dysregulation of the genes involved in the onset of premature/accelerated atherosclerosis, depicting an aberrant expression of 45-56 out of 84 investigated genes. Thus, their findings might explain the crosstalk between inflammation and thrombosis in MPNs and the contribution of this axis to the onset of atherosclerosis and ACS in these blood cancers.

Nevertheless, Leiva *et al*[79] reported that 76% MPN patients are likely to experience another major cardiovascular event or even death following an episode of ACS. The researchers examined 41 individuals with MPNs and a history of ACS who were followed-up for 80 mo, demonstrating that the presence of leukocytosis [leukocyte count ≥ 20000 leukocytes/μL; hazard ratio (HR) = 9.10], the occurrence of ACS in the first year after the established diagnosis of MPN (HR = 3.84), the presence of JAK2 gene mutations (HR = 3.71) and history of cardiovascular disease (HR = 2.60) were risk

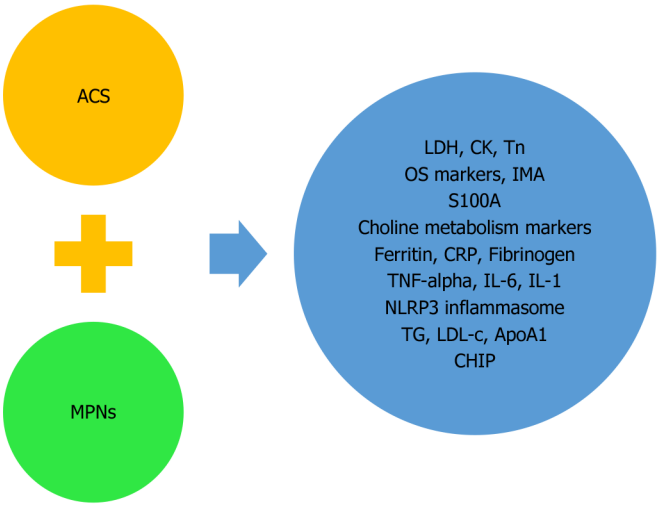

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Figure 2 Potential biomarkers linking acute coronary syndromes and myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes; LDH: Lactate dehydrogenase; CK: Creatine kinase; Tn: Troponin; OS: Oxidative stress; IMA: Ischemia-modified albumin; CRP: C-reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin-6; IL-1: Interleukin-1; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; CHIP: Clonal hematopoiesis of indeterminate potential.

factors for another major cardiovascular event or death in this MPN subpopulation[79]. These results are particularly interesting as the same group of scientists have previously reported that according to their propensity score analysis MPN patients who suffer an episode of AMI are less likely to experience in-hospital death and cardiac arrest but elevated rates of hemorrhages *vs* individuals who experienced an AMI but do not associate MPNs[80]. Therefore, based on these findings, we suggest a close monitorization and follow-up of individuals diagnosed with MPNs and who experience an episode of AMI.

CONCLUSION

MI remains a potentially fatal complication of MPNs and may be the presenting event in MPN diagnosis or develop during the natural course of the disease. Patients who develop MI and have persistent hematological abnormalities warrant screening for MPN. Driver mutations, inflammation, and clonal hematopoiesis may to contribute to the pathogenesis of MI in MPN. Future investigations should focus on the discovery of biomarkers that could predict the development of MI in MPN subjects, as well as indicate which MI patients could also suffer from blood cancers.

FOOTNOTES

Co-corresponding authors: Camelia Cristina Diaconu and Mihnea-Alexandru Găman.

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Country/Territory of origin: Romania

ORCID number: Muhammad Romail Manan 0000-0002-3436-5206; Vincent Kipkorir 0000-0001-6946-8857; Maryann Wanjiku Waithaka 0000-0002-4694-3173; Bahadar Singh Srichawla 0000-0002-5301-4102; Amelia Maria Găman 0000-0001-6974-2772; Camelia Cristina Diaconu 0000-0001-6837-260X; Mihnea-Alexandru Găman 0000-0001-7133-8875.

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Novel predictors of permanent pacemaker implantation following transcatheter aortic valve replacement

Somto Nwaedozie, Haibin Zhang, Javad Najjar Mojarrab, Param Sharma, Paul Yeung, Peter Umukoro, Deepa Soodi, Rachel Gabor, Kelley Anderson, Romel Garcia-Montilla

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Somto Nwaedozie, Param Sharma, Deepa Soodi, Kelley Anderson, Department of Cardiovascular Disease, Marshfield Clinic, Marshfield, WI 54449, United States

Haibin Zhang, Hospitalist Medicine, Marshfield Clinic, Marshfield, WI 54449, United States

Javad Najjar Mojarrab, Department of Nephrology, Henry Ford Health System, Detroit, MI 48202, United States

Paul Yeung, Department of Hospital Medicine, Marshfield Clinic, Marshfield, WI 54449, United States

Peter Umukoro, Department of Nephrology, Hendricks Regional Health, Danville, IN 46122, United States

Rachel Gabor, Clinical Research Center, Marshfield Clinic, Marshfield, WI 54449, United States

Romel Garcia-Montilla, Department of Trauma Surgery and Surgical Critical Care, Marshfield Clinic, Marshfield, WI 54449, United States

Corresponding author: Somto Nwaedozie, MD, Research Fellow, Department of Cardiovascular Disease, Marshfield Clinic, 621 W Upham, Marshfield, WI 54449, United States.
nwaedozie.somto@marshfieldclinic.org

Abstract

BACKGROUND

Conduction and rhythm abnormalities requiring permanent pacemakers (PPM) are short-term complications following transcatheter aortic valve replacement (TAVR), and their clinical outcomes remain conflicting. Potential novel predictors of post-TAVR PPM, like QRS duration, QTc prolongation, and supraventricular arrhythmias, have been poorly studied.

AIM

To evaluate the effects of baseline nonspecific interventricular conduction delay and supraventricular arrhythmia on post-TAVR PPM requirement and determine the impact of PPM implantation on clinical outcomes.

METHODS

A retrospective cohort study that identified patients with TAVR between January 1, 2012 to December 31, 2019. The group was dichotomized into those with post-TAVR PPM and those without PPM. Both groups were followed for one year.

RESULTS

Out of the 357 patients that met inclusion criteria, the mean age was 80 years, 188 (52.7%) were male, and 57 (16%) had a PPM implantation. Baseline demographics, valve type, and cardiovascular risk factors were similar except for type II diabetes mellitus (DM), which was more prevalent in the PPM cohort (59.6% *vs* 40.7%; $P = 0.009$). The PPM cohort had a significantly higher rate of pre-procedure right bundle branch block, prolonged QRS > 120 ms, prolonged QTc > 470 ms, and supraventricular arrhythmias. There was a consistently significant increase in the odds ratio (OR) of PPM implantation for every 20 ms increase in the QRS duration above 100 ms: QRS 101-120 [OR: 2.44; confidence intervals (CI): 1.14-5.25; $P = 0.022$], QRS 121-140 (OR: 3.25; CI: 1.32-7.98; $P = 0.010$), QRS 141-160 (OR: 6.98; CI: 3.10-15.61; $P < 0.001$). After model adjustment for baseline risk factors, the OR remained significant for type II DM (aOR: 2.16; CI: 1.18-3.94; $P = 0.012$), QRS > 120 (aOR: 2.18; CI: 1.02-4.66; $P = 0.045$) and marginally significant for supraventricular arrhythmias (aOR: 1.82; CI: 0.97-3.42; $P = 0.062$). The PPM cohort had a higher adjusted OR of heart failure (HF) hospitalization (aOR: 2.2; CI: 1.1-4.3; $P = 0.022$) and nonfatal myocardial infarction (MI) (aOR: 3.9; CI: 1.1-14; $P = 0.031$) without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; $P = 0.796$) at one year.

CONCLUSION

Pre-TAVR type II DM and QRS duration > 120, regardless of the presence of bundle branch blocks, are predictors of post-TAVR PPM. At 1-year post-TAVR, patients with PPM have higher odds of HF hospitalization and MI.

Key Words: Transcatheter aortic valve replacement; Balloon-expandable valve; Self-expandable valve; Myocardial infarction; Left bundle-branch block; Nonspecific inter-ventricular defect; Coronary artery bypass graft; Coronary artery disease

Core Tip: This study found that patients with pre-transcatheter aortic valve replacement (TAVR) type 2 diabetes mellitus and QRS duration > 120 ms regardless of the presence of right or left bundle branch block, are at increased risk of permanent pacemaker implantation post-TAVR. The study also demonstrated a linear association between post-TAVR permanent pacemakers (PPM) incidence for every 20 ms prolongation in QRS duration > 100 ms. The study also showed post-TAVR PPM is associated with greater risks of heart failure hospitalization and non-fatal myocardial infarction in our study cohort. In light of the expanded indication of TAVR and the clinical and economic impact of PPM implantation, multidisciplinary heart teams should meticulously risk stratify pre-TAVR patients regarding PPM requirements using novel evidence.

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INTRODUCTION

Patients with untreated symptomatic severe aortic valve stenosis within the first two years have 50% mortality[1]. Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive therapeutic option with proven survival benefits for the management of these patients regardless of their surgical risks after evaluation by a multidisciplinary heart valve team[2,3]. Since the TAVR idea was conceptualized in 1989 and the first-in-human procedure successfully performed thirteen years later by Alain Cribier in France, TAVR procedure has caused a therapeutic paradigm shift, is a safer, non-inferior alternative to surgical aortic valve replacement which is contraindicated in about a third of patients due to prohibitive surgical risks[4-8].

Despite improvement in TAVR procedure techniques over the last two decades to optimize patient safety, cardiac conduction abnormalities requiring permanent pacemakers (PPM) implantation are some post-TAVR complications observed in about 5%-20% of patients[7,9-11]. These conduction abnormalities have been shown to be dependent on patient and periprocedural factors[6,8,9-12]. The atrioventricular (AV) conduction system courses posterior-inferiorly to the non-coronary cusp of the aortic valve annulus as it passes through the membranous septum and the central fibrous body as the bundle of HIS before bifurcation as it enters the interventricular septum[12,13]. This anatomic proximity of the conduction system to the aortic annulus and subarticular region poses a risk of a procedural, mechanical injury during TAVR through direct trauma during catheter insertion, balloon pre-dilation, valve deployment, or peri-implantation swelling[10,14-16]. The resultant post-procedural electrical conduction abnormalities, though may be

transient and self-resolving, sometimes may require permanent pacemaker implantation[15,17]. The prevalence of these conduction abnormalities can vary depending on the valve type implanted and have been shown to be more common with the self-expandable Medtronic CoreValve revealing system (MRCS) with a 24%-33% PPM implantation rate compared to the balloon-expandable Edwards Sapien valve (ESV) (5%-12%)[6,8,16]. The flaring, self-expanding nature coupled with the greater radial force generated when deploying the MRCS has been thought to contribute to a higher rate of conduction abnormalities and pacemaker placement than balloon-expandable valves (BEV)[8,17].

In order to reliably risk-stratify patients with respect to post-TAVR pacemaker requirements, several studies have identified several pre-procedural, electrocardiographic (EKG), anatomic, and procedural factors that could predict pacemaker implantation. Although pre-existing conduction abnormalities like AV block, right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior fascicular hem-block, potential risk factors like baseline QRS duration without RBBB or LBBB (nonspecific interventricular conduction delay), supraventricular arrhythmia or type 2 diabetes mellitus (DM) have not been well studied[6,8,12,16,18,19]. Also, although studies in non-TAVR patients have shown an association of isolated right ventricular pacemakers with adverse outcomes like increased heart failure (HF) hospitalization and mortality due to electro-mechanical dyssynchrony, studies on whether post-TAVR PPM patients is associated with adverse clinical outcomes have remained controversial[6,16,20-24].

Therefore, in this study, we intend to retrospectively evaluate the effects of baseline type 2 DM, nonspecific interventricular conduction delay, and supraventricular arrhythmia on post-TAVR PPM requirement and determine the impact of PPM implantation clinical outcomes in a tertiary referral center in Central Wisconsin, United States.

MATERIALS AND METHODS

Study population

This retrospective cohort study included all patients who underwent TAVR for symptomatic aortic stenosis from January 1, 2012 to December 31, 2019. TAVR was offered to patients after evaluation by a comprehensive multidisciplinary heart team according to guideline requirements[25].

Preoperative risks were determined after a thorough review by interventional cardiologists and cardiothoracic surgeons, and patients were classified based on the Society of Thoracic Surgeons risk score for prediction of mortality [26]. Preoperative risk was classified into low risk (< 4%), intermediate-risk (4%-7%), and high risk (> 8%) or inoperable if the multidisciplinary heart team considered the patient inoperable for other clinical reasons. Only the first TAVR procedure during index hospitalization was considered. Patients with a prior history of PPM placement, international classification of disease (ICD) placement, unsuccessful procedures, who died during the procedure, and who had a conversion to open procedures were excluded from the study (Figure 1). The study population was then dichotomized into two cohorts: (1) Patients who required PPM post-TAVR within one year post-TAVR; and (2) Patients who did not require PPM. All the patients were followed up for one year.

Data collection

The patients' data were extracted both electronically and manually from the Marshfield Clinic health system (MCHS), electronic health records obtained by mapping with ICD versions 9 and 10 billing codes for TAVR. Baseline EKG and transthoracic echocardiographic data done within 1 mo prior to the TAVR procedure were manually abstracted by trained physicians after reviewing EKGs and transthoracic echocardiogram reports interpreted and approved by board-certified cardiologists. Similarly, postoperative EKG and echocardiographic data were abstracted from the first postoperative EKGs and complete transthoracic echocardiography, which was performed within one month post-TAVR. All other data were electronically abstracted. 15% of the manually and electronically abstracted data were re-verified by three independent physician reviewers and were found to be over 99% accurate. The MCHS IRB committee granted Institutional Review Board approval prior to patients' electronic medical record review in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Study variables

Baseline demographics, comorbid conditions, pre-procedural, intraprocedural, and post-procedural EKG and echocardiographic data were collected. Demographic data obtained included patient sex, age, and race. Some of the pre-procedure clinical characteristics obtained include body mass index (BMI), society of thoracic surgeons (STS) preoperative risk score, comorbidities like a history of atrial fibrillation, coronary artery disease (CAD), history of myocardial infarction (MI), HF, New York Heart Association (NYHA) class, coronary artery bypass graft, preoperative balloon valvuloplasty (BV), hypertension, diabetes, chronic obstructive pulmonary disease, cancer and others outlined in Table 1. Preprocedural and post-procedural EKG data collected include supraventricular arrhythmias (atrial fibrillation, atrial flutter, and junctional rhythm), conduction abnormalities like RBBB, LBBB, AV blocks, left anterior fascicular block, left posterior fascicular block, bifascicular or trifascicular blocks, intervals including P-R, QRS, QTc. Nonspecific interventricular conduction defect was defined at QRS > 120 ms without RBBB or LBBB morphology. Baseline and postprocedural transthoracic Echocardiographic variables obtained include aortic valve area, peak velocity, mean gradient, peak gradient, aortic valve mitral and tricuspid valve regurgitation, aortic annulus area, and sinus diameter, left ventricular ejection fraction (LVEF), pulmonary artery pressure, left ventricular diastolic diameter, and left ventricular outflow tract (LVOT). Preoperative computed tomography (CT) annulus diameter was also obtained.

Table 1 Demographics and clinical characteristics of the patient population

Characteristics	No PPM	PPM	*P* value
	n = 300 (%)	*n* = 57 (%)	
Age	81.0 (8.2)	80.3 (7.6)	0.530
Male	158 (52.7)	30 (52.6)	1.00
BMI	30.5 (6.6)	31.4 (6.6)	0.380
STS risk score			0.168
High (≥ 8%)	194 (64.7)	41 (73.2)	
Intermediate (4%-7%)	72 (24)	12 (21.4)	
Low (< 4%)	34 (11.3)	3 (5.4)	
Cardiovascular history			
AF	128 (42.7)	28 (49.1)	0.385
CAD	260 (86.7)	51 (89.5)	0.670
MI	62 (20.7)	16 (28.1)	0.223
HF	280 (93.3)	54 (94.7)	1.00
NYHA HF class			0.495
1	4 (1.5)	1 (1.9)	
2	101 (38.1)	18 (34)	
3	148 (55.8)	30 (56.6)	
4	12 (4.5)	4 (7.5)	
PCI or stent	134 (44.7)	29 (50.9)	0.469
CABG	47 (15.7)	13 (22.8)	0.182
Previous AV replacement	24 (8.0)	1 (1.8)	0.151
Hypertension	284 (94.7)	56 (98.2)	0.493
Dyslipidemia	271 (90.3)	51 (89.5)	0.810
Diabetes	122 (40.7)	34 (59.6)	0.009
PVD	73 (24.3)	20 (35.1)	0.101
Stroke/TIA	32 (10.7)	8 (14)	0.491
Balloon valvuloplasty	149 (50)	35 (62.5)	0.108
Other comorbidities			
COPD	89 (29.7)	11 (19.3)	0.147
Liver disease	4 (1.3)	1 (1.8)	0.583
Cancer	142 (47.3)	26 (45.6)	0.885
Anemia	259 (86.3)	51 (89.5)	0.670
Dialysis	15 (5)	4 (7)	0.521

P values and mean ± SD from a 2-sample *t*-test were reported for continuous variables. Counts (%) and *P* values from Fisher's exact test were reported for categorical variables. Kruskal-Wallis test was used for ordinal variables (STS and NYHA HF class). BMI: Body mass index; PPM: Permanent pacemaker; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack; PVD: Peripheral vessel disease; PCI: Percutaneous coronary intervention; HF: Heart failure; MI: Myocardial infarction; AF: Atrial fibrillation; STS: Society of thoracic surgeons; PPM: Permanent pacemakers; NYHA: New York Heart Association; CABG: Coronary artery bypass graft.

The valve index, which is a relation of the valve size in relation to the aortic annulus, was calculated as valve size/LVOT diameter × 100[27,28]. Other periprocedural variables obtained include procedure urgency, valve type (BEV and SEV), valve size, access site, and post procedure complications.

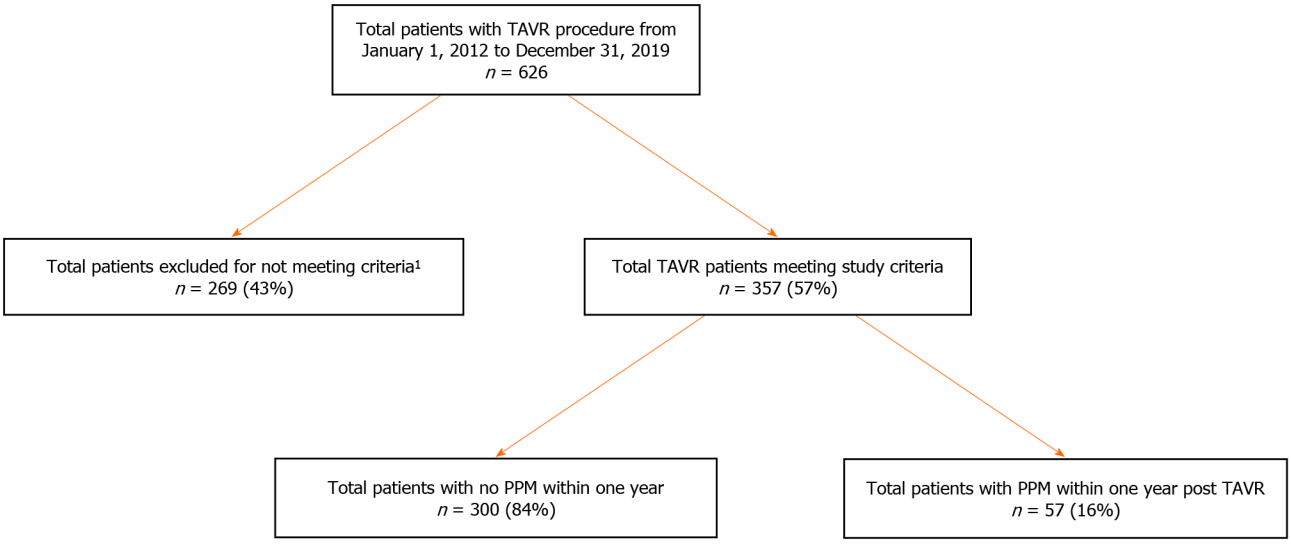

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Figure 1 Study cohort distribution. [1]Patients with prior history of permanent pacemakers placement, international classification of disease placement, unsuccessful procedures, died during the procedure, had a conversion to open procedures were excluded from the study. PPM: Permanent pacemakers; TAVR: Transcatheter aortic valve replacement.

Follow-up and clinical outcomes

The patients were followed up one year postprocedure and clinical outcome data were evaluated at in-hospital, 30-d, and at 1-year post-TAVR. In-hospital outcomes data included length of hospital stay. 30-d and 1-year outcomes studied will include all-cause mortality, HF admission, and hospitalization for MI or stroke as defined by the Valve Academic Research Consortium two endpoint criteria[29-34]. The causes of mortality were also evaluated to determine whether they were cardiovascular or non-cardiovascular.

Statistical analysis

Patient characteristics were described using mean ± SD for normal continuous variables, medians and interquartile range (IQR) for non-normal continuous variables, and counts and percentages for categorical and ordinal variables. Characteristics of patients who received PPM implantation within one year and those who did not receive PPM implantation within one year were compared using a *t*-test, Wilcoxon-rank sum test, Fisher's exact test, or the Kruskal-Wallis test as appropriate.

Incidence of PPM implantation was reported by age group, sex, preoperative risk, valve type, prior BV, procedure time, preoperative EKG findings, QRS intervals, QTc intervals, and prior conduction defects. *P* values reported were derived from Fisher's exact test or the Kruskal-Wallis test. Unadjusted odds ratios (OR) for PPM implantation were calculated for variables selected a priori, which were thought to be independently associated with pacemaker placement. Variables selected a priori with significant unadjusted OR and variables with $P < 0.10$ in a univariate comparison were considered for a multivariable logistic regression model to predict PPM implantation.

The collinearity between prior RBBB, QRS intervals, and QTc intervals was examined. Abnormal QRS intervals were strongly associated with PPM implantation among patients with RBBB but also among patients without RBBB. As such, we kept both terms in the model. Prolonged QTc interval also appeared to be a strong predictor of PPM implantation. However, there was not a significant association between QTc interval and PPM implantation after stratifying by abnormal QRS interval. Adjusted ORs, 95% confidence intervals (CI), and *P* values were reported. The significant *P* value was set to < 0.05.

Clinical outcomes at 30 d and one year were reported among patients with PPM implantation within one year and those without. The median length of stay was compared using a Wilcoxon rank-sum test. All other clinical outcomes were regressed on PPM and adjusted for patient characteristics that were significantly different at baseline (diabetes). Adjusted ORs, 95%CI, and *P* values were reported. Differences in survival in the year following TAVR by cohort (no PPM, PPM) were compared using Kaplan-Meier curves and a log-rank test.

RESULTS

Study population clinical characteristics

The baseline demographic and clinical characteristics of the study cohort are presented in Table 1. The mean age of the population was 80.8 years, comparable for both cohorts (81.0 years for no PPM and 80.3 years for the PPM). 52.7% of the population were male, and the average BMI was 30.7 kg/m^2. 66% of the population had a high operative risk (STS > 8%), which was comparable between the 2 populations. Over four-fifths had CAD (87.1%) and HF (93.6%), and two-thirds of

the patients had at least NYHA class III HF. Besides type 2 DM, which was more common in the PPM cohort than the non-PPM cohort (59.6% *vs* 40.7%; $P = 0.009$), there were no differences in the comorbidities or cardiovascular risk factors, as shown in Table 1.

Baseline EKG and echocardiographic characteristics

Baseline EKG and echocardiographic findings as shown in Table 2. Compared to patients without PPM, patients with PPM were found to be more likely to have a supraventricular arrhythmia (atrial fibrillation, atrial flutter, or junctional rhythm) (No PPM: 23.7%; *vs* PPM: 36.9%. $P = 0.054$). Baseline RBBB was found to be significantly higher in the PPM patients (No PPM: 11% *vs* PPM: 32%; $P < 0.001$). Prolonged QRS ≥ 120 ms and prolonged QTC (≥ 470 ms) were found to be higher in the PPM cohorts: (No PPM: 21% *vs* PPM: 47%, $P < 0.001$ and No PPM: 23% *vs* PPM: 47%, $P < 0.001$ respectively). There were no significant differences noted in the other conduction abnormalities noted. As shown in Table 2, there was no echocardiographic difference in baseline LVEF or other parameters.

Procedure characteristics and periprocedural complications

The procedure characteristics shown in Table 3 demonstrated that 96.6% of the procedures where elective femoral access was used in 95.2% of the patients, 53.8% of the valve were balloon-expandable with no differences in the two cohorts. Although the PPM patients received a mildly larger mean valve size (27.3 mm *vs* 26.8 mm), this was not statistically significant ($P = 0.266$). The mean valve index was 129.4 and was not different in the two cohorts. However, a marginally significant higher procedure time of 1.6 h in the PPM cohort when compared to the no PPM cohort (1.4 h) ($P = 0.056$).

There was no difference in perioperative complications of stroke (0.3%), atrial fibrillation/flutter (0.6%), bleeding (2.2%), and blood transfusion (0.3%) between the two cohorts. Also, although we observed no difference in the occurrence of type I AV block, perioperative complete heart block occurred at a significantly higher rate in the PPM cohort (40.4%), in comparison with no PPM cohort (0.3%); $P < 0.001$.

PPM implantation timing, indications, and incidence

The study found that 57 out of 357 patients (16%) required PPM placement within one year following TAVR. The median time to implantation was two days. One-fourth of the patients received PPM within one day following TAVR, half received it within two days following TAVR, and three-quarters received it within nine days post-TAVR. A dual-chamber pacemaker was implanted in 56.2% of patients, a single-chamber in 24.6%, and a biventricular pacemaker type were placed in 8.8% of patients. Complete AV block was the predominant indication for PPM placement (66.7%), followed by CHF with LV dysfunction (10.5%), symptomatic bradycardia (8.8%), and symptomatic second-degree AV block (1.8%).

As presented in Table 4, the incidence of PPM was significantly higher in patients with baseline RBBB (35% *vs* 13%, $P < 0.001$), prolonged QRS ≥ 120 (30% *vs* 11%, $P < 0.001$), and prolonged QTc (29% *vs* 12%, $P < 0.001$) in comparison with the no PPM cohort. Further analysis showed that when compared to patients with normal QRS interval (< 100), patients with QRS > 100 ms interval had a higher PPM incidence for every 20ms above the normal QRS interval (Table 5). Also, the occurrence of preoperative supraventricular arrhythmia (A. fib, a flutter, junctional rhythm), was associated with a higher incidence of PPM when compared to sinus rhythm with marginal significance (22.8% *vs* 13.6%; $P = 0.055$).

Although the self-expanding valve (SEV) had a higher pacemaker incidence of 17.6% compared to the balloon-expandable valve (14.6%), this did not achieve statistical significance ($P = 0.471$). A higher procedure time of 1.5 h or more had a marginally significant higher PPM incidence of 20.6% compared to the procedure time of < 1.5 h ($P = 0.071$). There was also no significant association between age, sex, preoperative risk, or prior BV and a higher incidence of PPM placement in our cohort.

Predictors of PPM implantation

Positive predictors of PPM implantation in the cohort after multivariate analysis is shown in Table 6. As shown in Table 6, age, sex, prior AV replacement, self-expandable valve, valve index, operative risk, and aortic valve area were not significantly predictive of PPM Placement in our cohort. The odds of PPM implantation in patients with prior RBBB was 3.73 times that in patients without prior RBBB (95%CI: 1.92-7.26; $P < 0.001$). QRS interval ≥ 120 ms has 3.45 odds of PPM implantation (95%CI: 1.91-6.23, $P < 0.001$) compared to patients with normal QRS intervals. Although we observed that compared to patients with normal QTc interval, those with prolonged QTC interval had a 2.94 OR of PPM placement (95%CI: 1.64-5.28, $P < 0.001$); due to collinearity between QRS and QTc intervals, after stratification by abnormal QRS interval, there was no significant association between QTc intervals and PPM implantation. Further analysis showed an incremental impact of baseline prolonged QRS duration with reference to the normal value of < 100 ms. There was a consistently significant increase in the OR for every 20 ms increase in the QRS duration above 100 ms as shown in Figure 2.

After further multivariate analysis and adjusting the OR using a logistic regression model of PPM implantation regressed on baseline differences, diabetes, prior RBBB, QRS interval, and preoperative supraventricular arrhythmias, baseline type 2 DM, and abnormal QRS (≥ 120 ms), remained a significant predictor of PPM implantation (aOR: 2.16; CI: 1.18-3.94; $P = 0.012$), (aOR: 2.18; CI: 1.02-4.66; $P = 0.045$) respectively (Table 7). Baseline supraventricular arrhythmia had marginally significantly higher odds of PPM implantation when compared to sinus rhythm after multivariate-adjusted analysis (aOR: 1.82; CI: 0.97-3.42; $P = 0.062$) (Table 7).

Follow-up and clinical outcomes

All the patients we have followed up for one year from TAVR or until death using MCHS electronic medical records. For deceased patients, we obtained the primary and secondary causes of death from the hospital records. For those not

Table 2 Baseline electrocardiographic and echocardiogram findings

	All	No PPM	PPM	*P* value
	n = 357	*n* = 300	*n* = 57	
EKG rhythm abnormalities				0.054
Sinus	265 (74.2)	229 (76.3)	36 (63.2)	
Atrial fibrillation	84 (23.5)	66 (22.0)	18 (31.6)	
Atrial flutter	4 (1.1)	2 (0.7)	2 (3.5)	
Junctional rhythm	2 (0.6)	1 (0.3)	1 (1.8)	
Other	2 (0.6)	2 (0.7)	0 (0)	
Sinus bradycardia	38 (10.6)	35 (11.7)	3 (5.3)	0.229
Sinus tachycardia	3 (0.8)	3 (1)	0 (0)	1.00
Conduction abnormalities				
RBBB	51 (14.3)	33 (11)	18 (31.6)	< 0.001
LBBB	29 (8.1)	24 (8)	5 (8.8)	0.794
AV block I	55 (15.4)	46 (15.3)	9 (15.8)	1.00
AV block IIa	0	0	0	-
AV block IIb	0	0	0	-
AV block III	0	0	0	-
Bifascicular block	5 (1.4)	5 (1.7)	0 (0)	1.00
Left anterior fascicular block	16 (4.5)	12 (4)	4 (7)	0.299
Left posterior fascicular block	1 (0.3)	0 (0)	1 (1.8)	0.16
Abnormal QRS (≥ 120 ms)	89 (25)	62 (20.7)	27 (47.4)	< 0.001
Prolonged QTc (≥ 470 ms)	97 (27.2)	70 (23.4)	27 (47.4)	< 0.001
Echocardiogram findings				
Left ventricular EF	58.1 (12.7)	58.5 (11.9)	56 (16.1)	0.272
AV peak velocity	4.1 (0.7)	4.1 (0.7)	4.1 (0.7)	0.957
AV mean gradient	42 (14.7)	42.1 (14.7)	41.3 (14.8)	0.707
AV peak gradient	68.4 (21.9)	68.4 (21.7)	68.1 (23.2)	0.933
AV regurgitation				0.247
None	147 (43.9)	116 (41.6)	31 (55.4)	
Mild	162 (48.4)	141 (50.5)	21 (37.5)	
Moderate	23 (6.9)	19 (6.8)	4 (7.1)	
Severe	3 (0.9)	3 (1.1)	0 (0)	
MV regurgitation				0.242
None	28 (8.2)	24 (8.4)	4 (7.1)	
Mild	255 (74.8)	208 (73.0)	47 (83.9)	
Moderate	52 (15.2)	48 (16.8)	4 (7.1)	
Severe	6 (1.8)	5 (1.8)	1 (1.8)	
TV regurgitation				0.129
None	19 (5.6)	19 (6.6)	0 (0)	
Mild	272 (79.8)	226 (79.0)	46 (83.6)	
Moderate	43 (12.6)	36 (12.6)	7 (12.7)	
Severe	7 (2.1)	5 (1.7)	2 (3.6)	

Pulmonary artery pressure	46.9 (14.1)	45.9 (13.1)	51.6 (17.7)	0.073
Annulus area	0.8 (0.2)	0.8 (0.2)	0.8 (0.3)	0.968
Aortic sinus diameter	3.2 (0.5)	3.2 (0.5)	3.3 (0.5)	0.074
CT annulus diameter 1	25.1 (4.4)	25 (4.3)	25.2 (4.8)	0.849
CT annulus diameter 2	24.2 (4.2)	24.1 (4.2)	24.8 (4.3)	0.273
LV diastolic diameter	4.7 (0.8)	4.7 (0.8)	4.8 (0.8)	0.290
LVOT	20.9 (1.9)	20.8 (1.9)	21.1 (1.9)	0.354

P values and mean ± SD from a 2-sample *t*-test reported for continuous variables. Counts (%) and *P* values from Fisher's exact test were reported for categorical variables. RBBB: Right Bundle Branch Block; LBBB: Left Bundle branch block; CT: Computed tomography; AV: Aortic valve; MV: Mitral valve; TV: Tricuspid valve; PPM: Permanent pacemakers; LVOT: Left ventricular outflow tract.

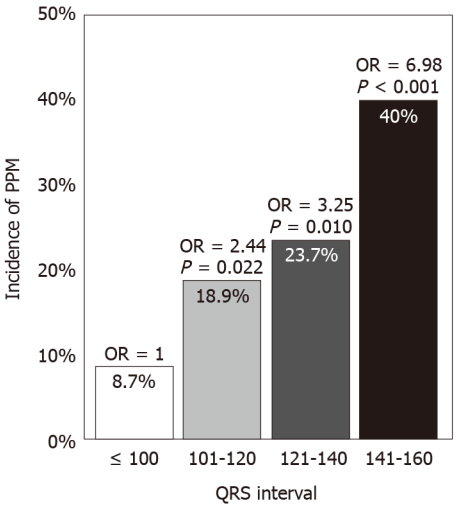

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Figure 2 Incidence and odds ratios for permanent pacemakers implantation by QRS interval. PPM: Permanent pacemakers; OR: Odds ratios.

available within the MCHS, a death certificate was obtained from the state vital statistics record office. Compared to those without a PPM placement, patients with a PPM placement had a significantly longer median length of hospital stay (5 d *vs* 2 d; $P < 0.001$).

30-day and 1-year outcome

Clinical outcomes of any hospitalization, HF hospitalization, nonfatal MI, stroke, and mortality are presented in Figure 3. There was no difference in the clinical outcomes within 30 d. However, at one year, patients with PPM placement had a significantly higher incidence of hospitalization for HF (28% *vs* 14% $P = 0.022$) and nonfatal MI (9% *vs* 2%; $P = 0.031$). There was no significant difference in the incidence of stroke or all-cause mortality, as in Figure 3. Multivariate adjustments adjusted OR for the clinical outcome at one year revealed that compared to the no PPM cohort, the PPM implantation cohorts had a higher adjusted OR of HF hospitalization (aOR: 2.2; CI: 1.1-4.3; $P = 0.022$), and nonfatal MI (aOR: 3.9; CI: 1.1-14; $P = 0.031$) without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; $P = 0.796$) at one year.

DISCUSSION

Incidence, indicators, and dependency of pacemaker

Our study found that 16% of the patients required PPM placement within one year following TAVR with a median time to implantation of 2 days and 75% of the patients receiving the pacemakers within nine days. The balloon-expandable ESV was used in 54% of the procedures, which resulted in a PPM implantation rate of 14.6%. In comparison, the auto-expanding MCRS was implanted in 46%, resulting in a 17.6% PPM implantation rate ($P = 0.471$). This PPM implantation rate was roughly at the median rate observed in a recent systematic review involving 17139 patients that showed a PPM implantation rate between 2.3% and 36.1%[35]. Also, in this study, MCRS resulted in higher PPM implantation rates (16.3%-37.7%), whereas ESV valves resulted in a lower pacemaker rate (4%-24%), which was also comparable to our study[35]. Similarly, Ullah *et al*[6], in a recent large-scale meta-analysis involving 31261 patients with a mean age of 81± 8 years, similar to our population, reported a mean PPM rate of 19.8% and a net rate ranging from 0.16% to 51.1%[6].

Table 3 Procedural characteristics and peri-procedural complications

	All	No PPM	PPM	*P* value
	n = 357	*n* = 300	*n* = 57	
Urgency				0.699
Elective	344 (96.6)	288 (96.3)	56 (98.2)	
Emergency	12 (3.4)	11 (3.7)	1 (1.8)	
Valve				0.471
Balloon expandable	192 (53.8)	164 (54.7)	28 (49.1)	
Self-expandable	165 (46.2)	136 (45.3)	29 (50.9)	
Valve size	26.9 (3)	26.8 (2.9)	27.3 (3)	0.266
Valve index	129.4 (14.9)	129.3 (15.1)	129.9 (13.5)	0.792
Valve sheath access site				0.270
Right femoral	241 (68.5)	206 (69.8)	35 (61.4)	
Left femoral	94 (26.7)	72 (24.4)	22 (38.6)	
Right subclavian	2 (0.6)	2 (0.7)	0 (0)	
Left subclavian	4 (1.1)	4 (1.4)	0 (0)	
Right radial	2 (0.6)	2 (0.7)	0 (0)	
Transaortic	9 (2.6)	9 (3.1)	0 (0)	
Procedure time	1.5 (0.8)	1.4 (0.8)	1.6 (0.9)	0.056
Perioperative complications				
Atrial fibrillation	1 (0.3)	1 (0.3)	0 (0)	1.00
Atrial flutter	1 (0.3)	1 (0.3)	0 (0)	1.00
AV block I	6 (1.7)	6 (2)	0 (0)	0.595
AV block II	0	0	0	-
Complete AV block	24 (6.7)	1 (0.3)	23 (40.4)	< 0.001
Ventricular tachycardia	0	0	0	-
Ventricular fibrillation	0	0	0	-
Bleeding	8 (2.2)	8 (2.7)	0 (0)	0.365
Stroke	1 (0.3)	1 (0.3)	0 (0)	1.00
Transfusion	3 (0.8)	3 (1)	0 (0)	1.00
Site bleeding	0	0	0	-
Left axis deviation	3 (0.8)	2 (0.7)	1 (1.8)	0.408
LBBB	0	0	0	-
RBBB	0	0	0	-
Left anterior fascicular block	0	0	0	-
Left posterior fascicular block	0	0	0	-
MI	1 (0.3)	1 (0.3)	0 (0)	1.00
Other	31 (8.7)	24 (8)	7 (12.3)	0.305

P values and mean ± SD from a 2-sample *t*-test reported for continuous variables except for procedure time which was heavily right skewed. Median (IQR) and *P* value from a Wilcoxon rank sum test reported for procedure time. Counts (%) and *P* values from Fisher's exact test reported for categorical variables. The following tests excluded patients due to missing values: Procedure urgency (1), valve index (2), valve sheath access site (5), procedure time (37). RBBB: Right Bundle Branch Block; LBBB: Left Bundle branch block; AV: Aortic valve; MI: Myocardial infarction; PPM: Permanent pacemakers.

Table 4 Incidence of permanent pacemakers implantation

Variable	Group	*n*	Incidence (%)	*P* value
Age	< 65 yr	10	0 (0)	0.284
	65-85 yr	235	41 (17.4)	
	> 85 yr	112	16 (14.3)	
Sex	Male	169	27 (16.0)	1.00
	Female	188	30 (16.0)	
Pre-operative risk	Low	37	3 (8.1)	0.168
	Intermediate	84	12 (14.3)	
	High	235	41 (17.4)	
Valve type	Balloon expanding	192	28 (14.6)	0.471
	Self-expanding	165	29 (17.6)	
Prior BAV	Yes	184	35 (19.0)	0.116
	No	170	21 (12.4)	
Procedure time	< 1.5 h	160	20 (12.5)	0.071
	≥ 1.5 h	160	33 (20.6)	
Pre-op EKG rhythm abnormalities	Sinus	265	36 (13.6)	0.054
	Atrial fibrillation	83	18 (21.4)	
	Atrial flutter	4	2 (50.0)	
	Junctional rhythm	2	1 (50.0)	
	Other	2	0 (0)	
RBBB	Yes	51	18 (35.3)	< 0.001
	No	306	39 (12.7)	
LBBB	Yes	29	5 (17.2)	0.794
	No	328	52 (15.9)	
AV block I	Yes	55	9 (16.4)	1.000
	No	302	48 (15.9)	
Bifascicular block	Yes	5	0 (0)	1.000
	No	352	57 (16.2)	
Left anterior fascicular block	Yes	16	4 (25.0)	0.299
	No	341	53 (15.5)	
Left posterior fascicular block	Yes	1	1 (100)	0.160
	No	356	56 (15.7)	
QRS interval	Abnormal (≥ 120 ms)	89	27 (30.3)	< 0.001
	Normal	267	30 (11.2)	
QTc interval	Prolonged (≥ 470 ms)	97	27 (27.8)	< 0.001
	Normal	259	30 (11.6)	

EKG: Electrocardiographic; BAV: Balloon aortic valvuloplasty; RBBB: Right bundle branch block; LBBB: Left Bundle branch block; AV: Aortic valve.

Fadahunsi *et al*[8], in the recent retrospective analysis of 9785 patients from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, reported a median time of 3 d (IQR: 1 d-6 d) from TAVR to PPM implantation which also correlated with our study[8].

The most common indications for post-TAVR PPM implantation reported in several studies are high-grade AV block, new-onset or worsening LBBB, symptomatic bradycardia, unstable nodal conduction, and progressively worsening first-degree AV block with LBBB[16,36,37]. Similarly, in our study, complete AV block was the predominant indication for

Table 5 Incidence of permanent pacemakers implantation by QRS duration

Variable	Group	*n*	Incidence	*P* value
QRS interval	≤ 100	194	17 (8.8)	< 0.001
	101-120	74	14 (18.9)	
	121-140	38	9 (23.7)	
	141-160	40	16 (40.0)	
	161-180	10	1 (10.0)	
Pre-op EKG supraventricular arrhythmia	Supraventricular arrhythmia[1]	91	21 (22.8)	0.05
	Sinus rhythm	265	36 (13.6)	

[1]Supraventricular arrhythmia includes-atrial fibrillation, atrial flutter and junctional rhythms.
EKG: Electrocardiographic.

Table 6 Odds ratios for permanent pacemakers implantation

	OR	95%CI	*P* value
Age (per 5 yr)	0.95	0.8-1.12	0.549
Male	1.00	0.57-1.76	0.996
Prior AV replacement	0.21	0.03-1.55	0.125
CAD	1.31	0.53-3.25	0.563
HF	1.29	0.37-4.48	0.693
Self-expanding (Reference: balloon)	1.25	0.71-2.20	0.442
Prior conduction defect-RBBB	3.73	1.92-7.26	< 0.001
Prior conduction defect-LBBB	1.11	0.40-3.03	0.845
Prior conduction defect-LFAB	1.81	0.56-5.83	0.319
Valve index	1.00	0.98-1.02	0.806
Abnormal QRS (≥ 120 ms)	3.45	1.91-6.23	< 0.001
Prolonged QTc (≥ 470 ms)	2.94	1.64-5.28	< 0.001
Aortic valve area > 0.75	1.31	0.73-2.36	0.364
High preoperative risk (Reference: Low)	2.40	0.70-8.17	0.163
Intermediate preoperative risk (Reference: Low)	1.89	0.50-7.14	0.348
Supraventricular Arrhythmia on pre-op EKG (Reference: Sinus)	1.88	1.03-3.43	0.039

EKG: Electrocardiographic; RBBB: Right bundle branch block; LBBB: Left Bundle branch block; AV: Aortic valve; LFAB: Left anterior fascicular block; CAD: Coronary artery disease; HF: Heart failure; OR: Odds ratios.

PPM placement (66.7%), followed by CHF with LV dysfunction (10.5%), symptomatic bradycardia (8.8%), and symptomatic second-degree AV block (1.8%).

Unlike most other studies, our study went further to evaluate the rate of pacemaker dependency following pacemaker interrogation at 1 mo and found that 78.9% of PPM patients were found to be pacemaker dependent one month after TAVR. This finding is supported by a previous observation that about half of the patients developing conduction abnormalities after TAVR improve over time without PPM implantation due to the resolution of reversible procedural per-aortic edema and inflammation caused during the procedure[16,38]. Although the exact proportion of patients and timing of resolution of this conduction abnormality remains unclear, from our study, it can be inferred that one-fifth of post-TAVR PPM patients may not be dependent on their pacemakers by one month, possibly due to the resolution of their transient abnormalities.

As presented in Table 3, the incidence of PPM was significantly higher in patients with RBBB (35% *vs* 13%, $P < 0.001$), prolonged QRS ≥ 120 without left or right bundle branch morphology, (30% *vs* 11%, $P < 0.001$), and prolonged QTc (29% *vs* 12%, $P < 0.001$). Further analysis showed that when compared to patients with normal QRS interval (≤ 100), patients with prolonged QRS interval had a higher PPM incidence for every 20 ms above the normal QRS interval (Figure 2).

Table 7 Adjusted odds ratios for permanent pacemakers implantation

	aOR	95%CI	*P* value
Diabetes	2.16	1.18-3.94	0.012
Prior RBBB	2.15	0.91-5.09	0.081
Abnormal QRS (≥ 120 ms)	2.18	1.02-4.66	0.045
Supraventricular arrhythmia on pre-op EKG (Reference: Sinus rhythm)	1.82	0.97-3.42	0.062

Adjusted odds ratios generated from logistic regression model of permanent pacemakers implantation regressed on diabetes, prior right bundle branch block, QRS interval, and pre-operative electrocardiographic Supraventricular arrhythmias. EKG: Electrocardiographic; RBBB: Right bundle branch block; aOR: Adjusted odds ratios.

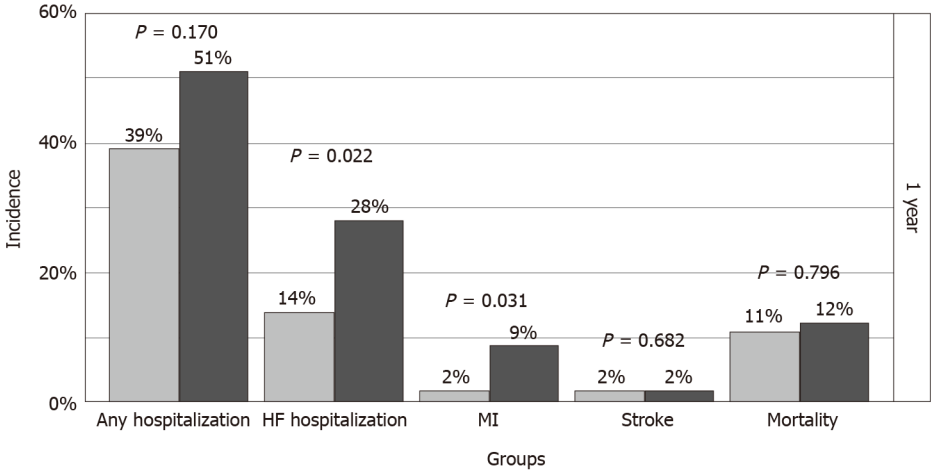

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Figure 3 Clinical outcomes of transcatheter aortic valve replacement patients for permanent pacemakers and no permanent pacemakers patients. MI: Myocardial infarction; HF: Heart failure.

Novel and traditional predictors of PPM placement

Several studies have reported demographic, clinical, anatomic, EKG, and valve-related risk factors for conduction abnormalities requiring pacemakers after TAVR[6,8,12,16,19,20,37,38]. Siontis *et al*[18] from the systematic review and meta-analysis, reported that male sex, baseline first-degree AV block, RBBB, LBBB, left anterior hemiblock, intraprocedural AV block was associated with a high incidence of PPM placement post-TAVR[18]. Several other similar multiple-center studies, systematic reviews, and meta-analyses have shown similar risk factors for post-TAVR pacemaker requirements. However, none to our knowledge investigated the impact of nonspecific interventricular conduction defect on post-TAVR pacemaker requirement (defined in the study as QRS > 120 without LBBB and RBBB), which we found to be predictive of PPM placement[6,8,12,16,19,20,37,38].

Due to the potential correlation between RBBB, LBBB, and QRS duration, we evaluated PPM incidence by prolonged QRS stratified by prior conduction abnormalities and found that patients without prior RBBB or LBBB but had QRS ≥ 120 ms had a higher PPM incidence compared to those with QRS interval < 120 ms (23% *vs* 11%; $P = 0.05$). Also, stratifying PPM incidence by baseline prolonged QTc interval [> 470 ms], abnormal QRS canceled the effect of QTC on PPM requirement due to collinearity between the QRS duration and QTc interval. Further multivariate analysis revealed a consistently significant increase in the OR of the PPM requirement for every 20 ms increase in the QRS duration above 100 ms, as shown in Figure 2. Overall, in patients with QRS > 120 ms, our study was found to have an adjusted OR of 2.18 (95%CI: 1.02-4.66, $P = 0.045$) for post-TAVR PPM placement.

Another interesting finding in our study is that baseline type 2 DM was a significant predictor of PPM placement with an adjusted OR of 2.16 [95%CI; 1.18-3.94, $P = 0.012$], a finding that was scarcely reported in several studies. Notably, Sammour *et al*[16], in a recent systematic review, reported that type 2 DM was a pre-procedural predictor of new-onset LBBB, which is a known indication for PPM requirement. This further supports the findings of our study[16].

Among the traditional risk factors for PPM implantation, our study found that the odds of pacemaker placement in patients with prior RBBB was 3.73 (95%CI: 1.92-7.26; $P < 0.001$) times those without prior RBBB in the unadjusted model which tended towards significance following multivariate analysis (aOR: 2.15; 95%CI: 0.91-5.09; $P = 0.081$). Contrary to the widely reported increased PPM implantation risk inherent with the use of SEV[8,6,16], our study did not demonstrate a significantly higher risk of PPM placement with the SEV when compared to the balloon-expandable ESV (OR: 1.25; CI: 0.71-2.20; $P = 0.4.42$). This finding can be explained by the fact that our institution started implanting self-expandable

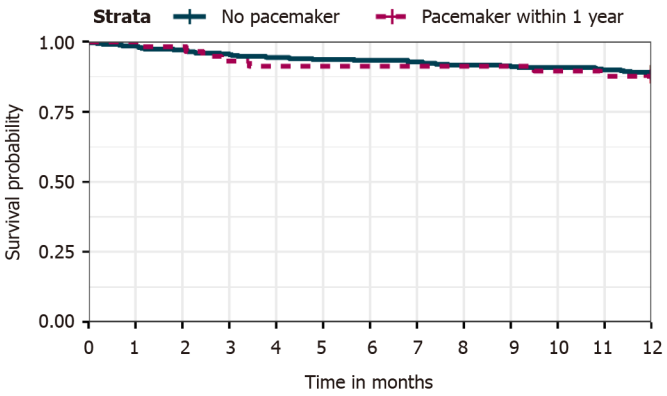

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Figure 4 Kaplan-Meier survival curve for one year following transcatheter aortic valve replacement.

valves in 2015, three years after they started the balloon-expandable valve; this delay presumably helps the TAVR operators advance in the learning curve and gain considerable experience with the TAVR procedure[39]. Also, over the last few years, there have been manufacturer-assisted modifications of self-expandable valve implantation techniques in our health system, which emphasize shallow valve implantation depth and cusp overlap in order to avoid the anatomical vicinity of the conduction tissues during TAVR procedures. This performance improvement process, which resulted in lower SEV-related PPM implantation, was informed by contemporary studies that demonstrated that implantation depth relative to membranous septum length is an independent risk factor for post-TAVR PPM implantation[12,40].

An essential clinical significance of the findings of our study is its ability to enhance clinical decision-making prior to TAVR procedures, assist in patients' overall PPM risk evaluation, and choice of valve system to implant. A notable risk prediction score that can be refined by our findings of increased PPM risk for QRS > 100 ms is the Emory risk score for the prediction of PPM requirement following TAVR developed by Kiani *et al*[41]. This scoring system incorporates the history of RBBB (2 points), QRS interval ≥ 140 ms (one-point), syncope (one-point), valve oversizing ≥ 16% (1 point) and has an OR of 2.2 per every point increase ($P < 0.001$)[41]. Adjusting the QRS duration cut-off may increase the sensitivity of this scoring system. However, given the relatively small size of our cohort, further, more extensive studies will be needed to validate this finding.

Clinical outcomes

Although PPM implantation in the non-TAVR population has been associated with complications like device infection, pocket erosion or hematoma, lead failure, right ventricular perforation, and lead-induced tricuspid regurgitation which might lead to higher mortality[42,43], studies on clinical outcomes in TAVR patients with pacemaker have shown conflicting results with the majority of studies showing no mortality impact of PPM implantation at 1 year[6,16].

At 30 d post TAVR, our study showed no significant increase in clinical outcomes of all-cause mortality, hospitalization for HF, nonfatal MI, and stroke. However, at 1 year post-TAVR, relative to the no PPM cohort, the PPM patients had a significantly higher incidence of hospitalization for HF (28% *vs* 14% $P = 0.022$), and nonfatal MI (9% *vs* 2%; $P = 0.031$) with no mortality difference Figure 3. Further evaluation of one-year survival using a Kaplan-Meier curve showed no survival difference between the two cohorts (Figure 4). This lack of impact of PPM implantation all-cause mortality or survival was also echoed by several multiple studies[44-51].

Similar to our finding of higher odds of HF hospitalization (aOR: 3.9; CI: 1.1-14; $P = 0.031$), López-Aguilera *et al*[52] in a single-center prospective study, and Chamandi *et al*[53] in the multicenter retrospective study both showed an increased risk of hospitalization due to HF in post-TAVR PPM patients[52,53].

Study limitations

This study is a single-center retrospective analysis of our experience as a tertiary cardiology referral health center in the Midwestern United States. Our findings may not reflect the experience in other regions. Also, there was no randomization of the valves to patients based on established criteria but based on the decision of the multidisciplinary TAVR team. As a result, the distribution of valves, patient selection, and valve sizes in each cohort might have been affected. However, the observed relatively equal distribution of these and other patient-related variables between each cohort suggests that this factor might not have significantly contributed to our study findings.

CONCLUSION

Patients with baseline type 2 DM and QRS duration > 100 ms, regardless of the presence of right or left bundle branch morhology, are at increased risk of permanent pacemaker implantation post-TAVR. A linear association may exist between post-TAVR PPM incidence and every 20 ms prolongation in QRS duration > 100 ms. Patients with PPM implantation may have higher risks of HF hospitalization and non-fatal MI at 1 year post TAVR. In light of the expanded

indication of TAVR and the clinical and economic impact of PPM implantation, multidisciplinary heart teams should meticulously risk-stratify pre-TAVR patients regarding PPM requirements using this new evidence.

ARTICLE HIGHLIGHTS

Research background

Conduction abnormalities requiring permanent pacemakers (PPM) are short-term complications following transcatheter aortic valve replacement (TAVR), and their clinical outcomes remain conflicting. Potential novel predictors of post-TAVR PPM, like QRS duration, QTc prolongation, and supraventricular arrhythmias, have been poorly studied.

Research motivation

The evaluation of novel predictors of PPM placement post TAVR light nonspecific interventricular conduction defect, will enhance clinical decision making prior to the TAVR procedure, assist in patient pacemaker risk evaluation, and further refine the indications of pacemaker placement.

Research objectives

To determine the timing, incidence and novel predictors of PPM implantation post TAVR. To evaluate and compare clinical outcomes of length of hospitalization, heart failure (HF) hospitalization, myocardial infarction (MI) and cardiovascular death post TAVR between patients requiring permanent pacemaker implantation and others without pacemaker at 1 year post TAVR procedure.

Research methods

A retrospective cohort study that identified patients with TAVR between January 1, 2012 to December 31, 2019. The cohort was divides into those with post-TAVR PPM and those without PPM. Both groups were followed for one year.

Research results

Of 357 patients that met inclusion criteria, the mean age was 80 years, 188 (52.7%) were male, and 57 (16%) had a PPM implantation. Baseline demographics, valve type, and cardiovascular risk factors were similar except for type II diabetes mellitus (DM), which was more prevalent in the PPM cohort (59.6% *vs* 40.7%; $P = 0.009$). The PPM cohort had a significantly higher rate of pre-procedure right bundle branch block, prolonged QRS > 120 ms, prolonged QTc > 470 ms, and supraventricular arrhythmias. There was a consistently significant increase in the odds ratio (OR) of PPM implantation for every 20 ms increase in the QRS duration above 100 ms: QRS 101-120 (OR: 2.44; CI: 1.14-5.25; $P = 0.022$), QRS 121-140 (OR: 3.25; CI: 1.32-7.98; $P = 0.010$), QRS 141-160 (OR: 6.98; CI: 3.10-15.61; $P < 0.001$). After model adjustment for baseline risk factors, the OR remained significant for type II DM and QRS > 120. The PPM cohort had a higher OR of HF hospitalization and nonfatal MI without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; $P = 0.796$) at one year.

Research conclusions

Pre-TAVR type II DM and QRS duration > 120, regardless of the presence of bundle branch blocks, are predictors of post-TAVR PPM. Post-TAVR, patients with PPM implantation may have higher odds of HF hospitalization and non-fatal MI at 1 year.

Research perspectives

In light of the expanded indication of TAVR to involve lower risk patients and the clinical impact of PPM implantation, risk assessment using the predictors outlined in the study will help optimize pre-procedural risk stratification. Further larger multicenter studies will be needed to further investigate the impact of this number predictors and post-TAVR pacemaker requirement.

FOOTNOTES

Author contributions: Nwaedozie S and Garcia-Montilla R designed the research study; Zhang H and Najjar Mojarrab J assisted in the data abstraction; Gabor R did the data analysis; Sharma P, Yeung P, Umukoro P, Anderson K, and Soodi D reviewed and edited the final manuscript.

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Informed consent statement: The requirement to obtain authorization is waived. The waiver is for the specific PHI and uses/disclosures described in your waiver request. Any change to the type of PHI to be collected, used or shared, or to the uses and disclosures described in the waiver request, require prior IRB approval.

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Country/Territory of origin: United States

ORCID number: Somto Nwaedozie 0000-0002-8598-0559.

Corresponding Author's Membership in Professional Societies: American Heart Association, No. 298575465.

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Observational Study

Clinical impact of portal vein pulsatility on the prognosis of hospitalized patients with acute heart failure

Naoya Kuwahara, Tomoyuki Honjo, Naohiko Sone, Junichi Imanishi, Kazuhiko Nakayama, Kohei Kamemura, Masanori Iwahashi, Soichiro Ohta, Kenji Kaihotsu

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Naoya Kuwahara, Tomoyuki Honjo, Naohiko Sone, Junichi Imanishi, Kazuhiko Nakayama, Kohei Kamemura, Masanori Iwahashi, Soichiro Ohta, Kenji Kaihotsu, Department of Cardiology, Shinko Hospital, Kobe 651-0072, Japan

Corresponding author: Tomoyuki Honjo, MD, PhD, Doctor, Department of Cardiology, Shinko Hospital, 1-4-47, Wakinohamacho, Chuo-ku, Kobe 651-0072, Japan. thonjo@honjo-iin.com

Abstract

BACKGROUND

Heart failure (HF) causes extracardiac organ congestion, including in the hepatic portal system. Reducing venous congestion is essential for HF treatment, but evaluating venous congestion is sometimes difficult in patients with chronic HF. The portal vein (PV) flow pattern can be influenced by right atrial pressure. Ultrasound images of the PV are quite easy to obtain and are reproducible among sonographers. However, the association between PV pulsatility and the condition of HF remains unclear. We hypothesize that PV pulsatility at discharge reflects the condition of HF.

AIM

To evaluate the usefulness of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

METHODS

This observational study was conducted from April 2016 to January 2017 and April 2018 to April 2019 at Shinko Hospital. We enrolled 56 patients with acute HF, and 17 patients without HF served as controls. PV flow velocity was measured by ultrasonography on admission and at discharge. We calculated the PV pulsatility ratio (PVPR) as the ratio of the difference between the peak and minimum velocity to the peak velocity. The primary endpoint was cardiac death and HF re-hospitalization. The observation period was 1 year from the first hospitalization. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups.

RESULTS

On admission, the PVPR was significantly higher in patients with acute HF than

controls (HF: 0.29 ± 0.20 *vs* controls: 0.08 ± 0.07, $P < 0.01$). However, the PVPR was significantly decreased after the improvement in HF (admission: 0.29 ± 0.20 *vs* discharge: 0.18 ± 0.15, $P < 0.01$) due to the increase in minimum velocity (admission: 12.6 ± 4.5 *vs* discharge: 14.6 ± 4.6 cm/s, $P = 0.03$). To elucidate the association between the PVPR and cardiovascular outcomes, the patients were divided into three groups according to the PVPR tertile at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). The Kaplan-Meier analysis showed that patients with a higher PVPR at discharge had the worst prognosis among the groups.

CONCLUSION

PVPR at discharge reflects the condition of HF. It is also a novel prognostic marker for hospitalized patients with acute HF.

Key Words: Heart failure; Venous congestion; Atrial pressure; Ultrasonography; Portal vein; Prognosis

Core Tip: Although reducing venous congestion is essential for heart failure (HF) treatment, the assessment of venous congestion is sometimes difficult, especially in patients with recurrent HF. Interestingly, a previous study demonstrated a correlation between right atrial pressure and portal vein (PV) flow pattern. However, the association between PV flow and the condition of HF remains unclear. Therefore, we investigated the clinical usefulness of PV pulsatility in hospitalized patients with HF. We found that PV pulsatility reflected not only the condition of HF but also cardiovascular outcomes. Therefore, PV pulsatility may be a novel prognostic marker for hospitalized patients with HF.

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INTRODUCTION

The prevalence of heart failure (HF) is increasing worldwide, especially in the aging population. Previous studies have reported that patients with HF have more severe frailty and a poorer prognosis than patients with several common diseases, including cancer[1,2]. Therefore, prevention of recurrent acute decompensated HF is of paramount importance.

Extracardiac organ congestion is seen in the advanced stages of chronic HF[3]. When severe right-sided HF is present, liver congestion develops followed by an increase in serum liver aminotransferase and total bilirubin concentrations, indicating a poor prognosis[3]. Thus, reducing venous congestion is essential for HF treatment. However, the assessment of venous congestion is sometimes difficult, especially in patients with recurrent HF.

To evaluate venous congestion, right atrial pressure (RAP) measured by right heart catheterization (RHC) is the most reliable parameter. RHC is difficult to repeat because the process is invasive and costly[4]. For non-invasive assessment, measuring the inferior vena cava (IVC) using ultrasound is the standard method. However, the ultrasound image quality of the IVC is often poor in patients with obesity[4]. Although a previous study reported that intrarenal venous flow has been proposed as venous congestion, reproducible images are difficult to obtain[5]. Therefore, there is a strong demand for a non-invasive and easy-to-use technique for reliable measurement of venous congestion.

The portal vein (PV) is interposed between the capillary network of the splanchnic circulation and the hepatic sinusoids[6]. Ultrasound images of the PV are quite easy to obtain and reproducible among sonographers. Interestingly, previous studies have demonstrated a correlation between RAP and PV flow[7,8]. However, the association between PV flow and the condition of HF remains unclear.

In this study, we aimed to identify the changes in PV flow pattern by the condition of HF and to evaluate the ability of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

MATERIALS AND METHODS

Patients

This study was conducted with hospitalized patients with acute HF starting in April 2016, with the total of 56 enrolled by April 2019. The European Society of Cardiology guideline was used to confirm the diagnosis of HF[9]. We also included 17 patients without HF, such as patients with urinary tract infection, dehydration, and other conditions, who were admitted during the same follow-up period as the acute HF patients and who served as controls. Patients in the control group were always in sinus rhythm. We excluded patients with liver cirrhosis, acute coronary syndrome, carbon dioxide narcosis due to chronic obstructive pulmonary disease, a malignant tumor diagnosed in the past 5 years, and renal

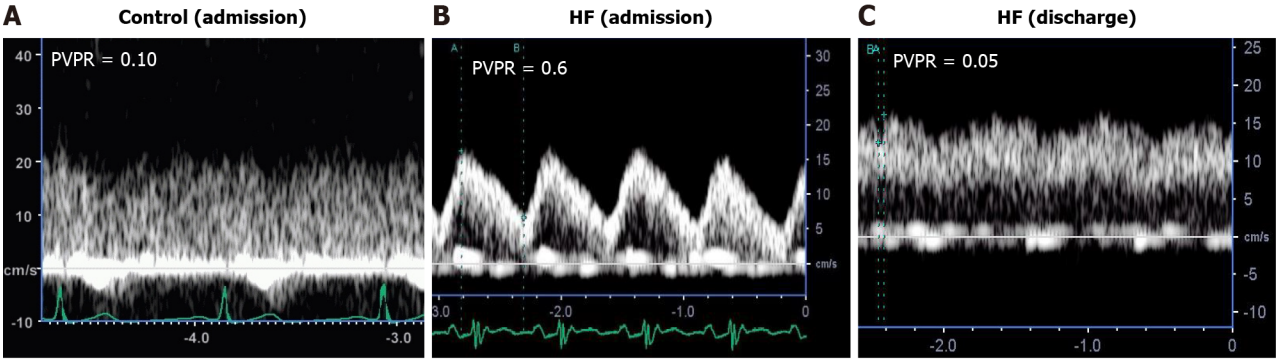

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Figure 1 Portal vein flow in the control and heart failure groups. A and B: Representative portal vein (PV) flow waveform in the control (A) and heart failure (HF) (B) groups at admission. Patients with HF had a pulsatile PV flow waveform. Patients in the control group had a continuous PV flow waveform with a significantly higher minimum PV velocity; C: Representative PV flow waveform in a patient with HF at discharge. At discharge, the waveform turned into a continuous pattern. HF: Heart failure; PVPR: Portal vein pulsatility ratio.

replacement therapy.

This study was approved by the Institutional Review Board of Shinko Hospital, and all requirements for written informed consent were waived for the use of the patients' clinical and imaging data.

Study protocol

All of the patients underwent blood tests and ultrasonography on admission and at discharge. The patients with HF were treated according to current guidelines[9]. The treatment goal was to improve clinical HF symptoms and physical examination findings. The primary endpoint was cardiac death and unexpected re-hospitalization for recurrent HF. The observation period was 1 year from discharge. We investigated the prognosis of all patients by outpatient clinic visit and by telephone conversation.

Ultrasound examination

Ultrasound examinations were performed using ultrasound devices (Vivid S5; GE Healthcare, Wauwatosa, WI, United States). Doppler images of PV flow were obtained from right-sided intercostal scanning using a 1.9-6-MHz convex array, and the waveform of PV flow was assessed from the right portal branch (Supplementary Figure 1)[6]. Doppler traces were recorded at the end of expiration. We calculated the PV pulsatility ratio (PVPR) by dividing the difference between the peak velocity and minimum velocity by the peak velocity [(peak velocity - minimum velocity)/peak velocity]. In patients with atrial fibrillation (AF), PV velocity was measured for five heartbeats, and the mean value was used for the analysis.

Statistical analysis

Continuous variables are reported as the mean ± SD, and categorical variables are reported as number and percentage. For comparisons between groups, we used the Student's *t*-test. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc statistical software, version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Table 1 shows that there were no significant differences in the baseline characteristics between the HF group and the control group, except for age and duration of hospital stay. Among the patients with HF, 32% had a history of HF and 89% had severe symptoms and were classified as New York Heart Association functional class III or IV. Regarding the etiology of HF, 23% of patients with HF had ischemic cardiomyopathy, 25% had non-ischemic cardiomyopathy (including tachycardia-induced cardiomyopathy, idiopathic cardiomyopathy, and cardiac sarcoidosis), and 20% had valvular heart disease.

PV flow reflects RAP[7,8,10]; therefore, we preliminarily confirmed that the minimum PV velocity was negatively correlated with RAP assessed by RHC (data not shown). As shown in Figure 1A and B, the HF group had a pulsatile PV flow waveform, whereas the control group had a continuous PV flow waveform because of the higher minimum PV velocity, indicating a low RAP. Regarding the PVPR, the control group had a significantly lower PVPR than the HF group (Table 2; control: 0.08 ± 0.07 *vs* HF: 0.29 ± 0.20, $P < 0.01$).

Next, we investigated how AF affected venous congestion in the setting of HF because AF was a major baseline characteristic in the HF group. There were no significant differences in the tricuspid regurgitation pressure gradient (TRPG), IVC diameter, tricuspid annular plane systolic excursion, and PVPR at admission between the HF group in sinus rhythm

Table 1 Patients' baseline characteristics

Characteristic	HF	Control	*P* value
No. of patients	56	17	
Age (yr)	78.1 ± 13.1	70.3 ± 12.8	0.03
Male	36 (66)	12 (70)	0.85
Body mass index (kg/m^2)	22.8 ± 4.5	24.4 ± 3.7	0.18
Systolic blood pressure (mmHg)	138.9 ± 33.3	132.2 ± 26.2	0.45
Diastolic blood pressure (mmHg)	84.1 ± 22.3	87 ± 21.3	0.18
Duration of hospital stay (d)	16.9 ± 8.5	8.1 ± 5.2	< 0.01
NYHA classification			
Class II	1 (2)	-	-
Class III	35 (65)	-	-
Class IV	13 (24)	-	-
Atrial fibrillation	29 (51)	0 (0)	-
Etiology of HF			
Ischemic cardiomyopathy	13 (23)	-	-
Non-ischemic cardiomyopathy	14 (25)	-	-
Valvar heart disease	11 (20)	-	-
Other	18 (32)	-	-
History of HF	18 (32)	-	-
In-hospital death	0 (0)	0 (0)	-

Data are *n* (%) or mean ± SD. HF: Heart failure; NYHA: New York Heart Association.

Table 2 Changes in the portal vein pulsatility ratio in control patients and patients with heart failure

Parameter	Control (admission)	HF (admission)	*P* value
Minimal velocity (cm/s)	14.4 ± 2.3	12.6 ± 4.5	< 0.01
Peak velocity (cm/s)	15.7 ± 2.5	18.6 ± 6.2	0.12
PVPR	0.08 ± 0.07	0.29 ± 0.2	< 0.01

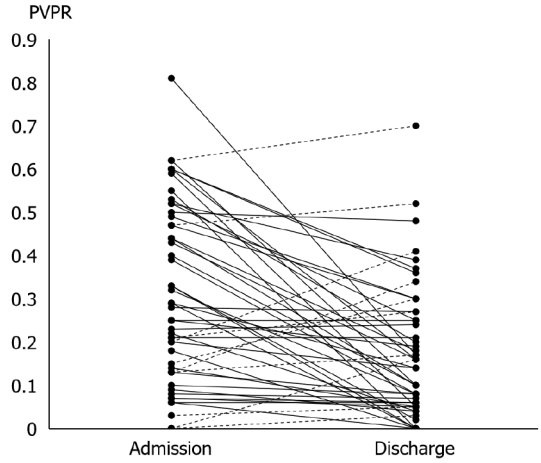
HF: Heart failure; PVPR: Portal vein pulsatility ratio.

and those with AF (TRPG: 29.8 ± 12.5 mmHg *vs* 32.3 ± 10.6 mmHg, respectively, $P = 0.66$; IVC diameter: 15.6 ± 4.1 mm *vs* 17.5 ± 4.3 mm, respectively, $P = 0.15$; tricuspid annular plane systolic excursion: 17.9 ± 5.1 mm *vs* 16.1 ± 3.4 mm, respectively, $P = 0.18$; PVPR: 0.27 ± 0.19 *vs* 0.28 ± 0.23, respectively, $P = 0.43$).

In all patients with HF, clinical symptoms and physical examination findings improved after optimal treatment. At discharge, blood tests showed that total bilirubin and brain natriuretic peptide concentrations were significantly decreased. Transthoracic echocardiography also demonstrated that right heart overload findings, such as the TRPG and IVC diameter, improved significantly after HF treatment (TRPG: 31.3 ± 12.1 mmHg *vs* 25.2 ± 8.9 mmHg, respectively, $P < 0.01$; IVC diameter: 16.5 ± 4.2 mm *vs* 14.2 ± 2.9 mm, respectively, $P < 0.01$) (Table 3).

Figure 1B and C depicts the representative PV flow waveforms of patients with HF before and after optimal treatment, respectively. Figure 2 shows the changes in the PVPR from admission to discharge in patients with HF. The PVPR decreased after the improvement in HF (admission: 0.29 ± 0.20 *vs* discharge: 0.18 ± 0.15, $P < 0.01$) due to the increase in minimum velocity (admission: 12.6 ± 4.5 cm/s *vs* discharge: 14.6 ± 4.6 cm/s, $P = 0.03$). The minimum velocity was negatively correlated with RAP; therefore, RAP also decreased. However, 14% of patients with HF did not demonstrate an improvement in the PVPR, even after HF treatment.

To elucidate the association between the PVPR at discharge and cardiovascular outcomes, we divided the patients with HF into three groups according to the PVPR tertile at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). Surprisingly, the Kaplan–Meier analysis found that patients with a high PVPR at discharge had a



	Admission	Discharge	*P* value
Minimal velocity, cm/s	12.6 ± 4.5	14.6 ± 4.6	0.03[a]
Peak velocity, cm/s	18.6 ± 6.2	18.1 ± 5.6	0.72
PVPR	0.29 ± 0.20	0.18 ± 0.15	< 0.01[a]

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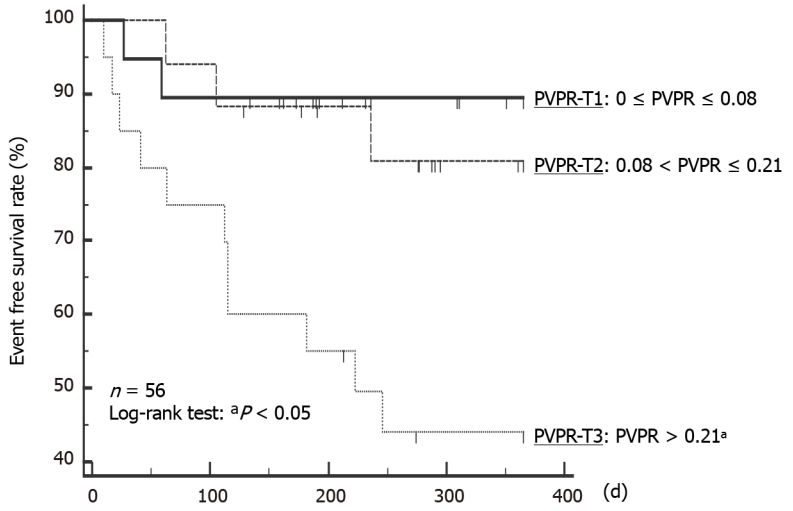
Figure 2 Changes in the portal vein pulsatility ratio from admission to discharge in patients with heart failure. The portal vein (PV) pulsatility ratio (PVPR) was significantly decreased after the improvement in heart failure (HF) due to the significant increase in minimum PV velocity. Some patients with HF (14%) did not demonstrate an improvement in the PVPR at discharge. [a]*P* < 0.05. Solid line: PVPR decreased at discharge. Dotted line: PVPR increased at discharge. PVPR: Portal vein pulsatility ratio.



Patients at risk

PVPR-T1	20	15	11	7	0
PVPR-T2	17	16	12	6	0
PVPR-T3	19	17	9	6	0

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Figure 3 Kaplan–Meier curve for prognosis in patients with heart failure. Patients with heart failure were divided into three groups according to the portal vein pulsatility ratio (PVPR) at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). PVPR-T3 had a worse prognosis than the lower PVPR tertiles (log-rank test: [a]*P* < 0.05 *vs* PVPR-T1). PVPR: Portal vein pulsatility ratio.

significantly worse prognosis than patients with a low PVPR ($P < 0.05$; Figure 3). There were no significant differences in the biochemical and echocardiographic data among the tertiles (Table 4).

DISCUSSION

In this study, we showed that the PV flow pattern differed between the control group and the HF group. The high PVPR pulsatile pattern was often seen in the HF group but not in the control group. The PVPR was significantly decreased after

Table 3 Changes in the biochemical and echocardiographic data of patients with heart failure

Parameter	Admission	Discharge	*P* value
Laboratory data			
Albumin (mg/dL)	3.5 ± 0.4	3.4 ± 0.5	0.14
AST (IU/L)	61.4 ± 17.8	23.8 ± 15.0	0.06
ALT (IU/L)	46 ± 12.4	19 ± 2.0	0.06
Total bilirubin (mg/dL)	1.0 ± 0.6	0.8 ± 0.4	< 0.01
BUN (mg/dL)	28.3 ± 12.1	28.4 ± 12.4	0.50
Creatinine (mg/dL)	1.5 ± 1.4	1.4 ± 0.9	0.30
eGFR (mL/min/1.73 m^2)	43.7 ± 18.1	43.7 ± 18.5	0.99
Hb (g/dL)	11.8 ± 2.5	11.6 ± 2.4	0.30
BNP (pg/mL)	1010 ± 1181	396 ± 626	< 0.01
TTE			
EF (%)	42 ± 16	44 ± 14	0.51
TRPG (mmHg)	31.3 ± 12.1	25.2 ± 8.9	< 0.01
TAPSE (mmHg)	16.5 ± 4.9	17.4 ± 3.7	0.43
IVC (mm)	16.5 ± 4.2	14.2 ± 2.9	< 0.01

Data are mean ± SD. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; IVC: Inferior vena cava; TAPSE: Tricuspid annular plane systolic excursion; TRPG: Tricuspid regurgitation pressure gradient; TTE: Transthoracic echocardiography.

the improvement in HF and venous congestion. Furthermore, patients with a high PVPR at discharge had a significantly worse prognosis than patients with a low PVPR.

Patients with HF had a high RAP and hepatic venous pressure, representing venous congestion[11]. Previous studies have demonstrated that the PV flow pattern is affected by not only hepatic venous pressure but also RAP[7,8,12,13]. These findings are consistent with our preliminary data showing that the minimum PV velocity was negatively correlated with the RAP assessed by RHC. In this study, patients in the control group had a low PVPR with a high minimum PV velocity, whereas patients with congestive HF had a high PVPR with a low minimum PV velocity at admission. After the improvement in HF, the PVPR was significantly decreased due to the increase in the minimum PV velocity, indicating a decrease in RAP. We also found that there was no significant difference in the PVPR between patients with HF in sinus rhythm and patients with AF. This indicated that there was no correlation between AF and high RAP, which is in agreement with the findings of a previous study[14].

The timing of the minimum PV velocity was synchronized with the peak of the v-wave in the right atrium (RA) (Figure 4). The v-wave represents passive venous filling of the RA when the tricuspid valve is closed. In patients with congestive HF, a high RAP obstructs passive venous blood return into the RA. As a result, we speculate that the velocity of venous blood return from the PV and the IVC decreases. Thus, the minimum PV velocity would be low in patients with congestive HF. When RAP decreases along with HF treatment, the velocity of passive venous return from the PV increases, followed by a continuous PV flow pattern. Given that the PV flow pattern reflects RAP, the PVPR would be a promising marker for evaluating the condition of HF.

The PVPR decreased significantly after HF treatment due to the increase in the minimum PV velocity. However, 14% of the patients with HF did not demonstrate an improvement in the PVPR, even at discharge. In other words, a decrease in the PVPR was not seen in every patient with HF. Given that a high PVPR with a low minimum velocity would indicate a high RAP, we compared the cardiovascular outcomes among the PVPR tertiles. Interestingly, patients with a high PVPR at discharge had a significantly poorer prognosis than patients with a low PVPR (Figure 3). This indicated that patients with a high PVPR still had venous congestion at discharge, even after guideline-based optimal treatment.

IVC diameter and TRPG measurements are standard methods for evaluation for venous congestion and RAP. However, our study demonstrated that the IVC diameter and TRPG did not correlate with cardiovascular outcomes in patients with HF (Supplementary Figures 2 and 3). These findings suggest that the PVPR is a simpler and more reliable non-invasive method to identify the condition of HF than traditional measurements.

Limitations

This study had some limitations. This was a retrospective study that was performed without randomization of patient selection. Moreover, although the two groups of patients demonstrated no significant differences in terms of sex, body mass index, and blood pressure, undetermined factors could have influenced the results.

Table 4 Biochemical and echocardiographic data of patients with heart failure categorized by portal vein pulsatility ratio at discharge

Parameter	PVPR-T1	PVPR-T2	PVPR-T3	*P* value
Age (yr)	81.3 ± 11.6	78.7 ± 13.7	76.6 ± 14.8	0.54
Male	11 (55)	8 (61)	14 (56)	0.92
Laboratory data				
Albumin (mg/dL)	3.4 ± 0.7	3.5 ± 0.5	3.3 ± 0.4	0.84
AST (IU/L)	24 ± 8.7	22.1 ± 6.5	25.2 ± 24.5	0.85
ALT (IU/L)	20.6 ± 17.1	19.6 ± 11.1	17.2 ± 27.4	0.86
Total bilirubin (mg/dL)	0.7 ± 0.3	0.9 ± 0.5	0.7 ± 0.3	0.08
BUN (mg/dL)	31.2 ± 13.1	24.8 ± 12.2	29.0 ± 14.0	0.34
Creatinine (mg/dL)	1.5 ± 0.9	1.2 ± 0.6	1.5 ± 1.1	0.52
eGFR (mL/min/1.73 m^2)	39.4 ± 15.3	48.2 ± 15.6	46.9 ± 23.7	0.28
Hb (g/dL)	11.5 ± 2.4	13.0 ± 2.5	10.6 ± 2.0	0.08
BNP (pg/mL)	200 ± 178	350 ± 342	682 ± 1030	0.12
TTE				
EF (%)	48 ± 13	42 ± 15	42 ± 17	0.40
TRPG (mmHg)	22.1 ± 5.2	27 ± 7.3	26.1 ± 10.9	0.24
TAPSE (mmHg)	22 ± 5.2	22.2 ± 7.5	21.9 ± 10.8	0.84
IVC (mm)	13.3 ± 2.6	14.7 ± 3.0	14.9 ± 3.1	0.21

Data are *n* (%) or mean ± SD. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; IVC: Inferior vena cava; TAPSE: Tricuspid annular plane systolic excursion; TRPG: Tricuspid regurgitation pressure gradient; TTE: Transthoracic echocardiography; PVPR-T1: 0 ≤ portal vein pulsatility ratio ≤ 0.08; PVPR-T2: 0.08 < portal vein pulsatility ratio ≤ 0.21; PVPR-T3: 0.21 > portal vein pulsatility ratio.

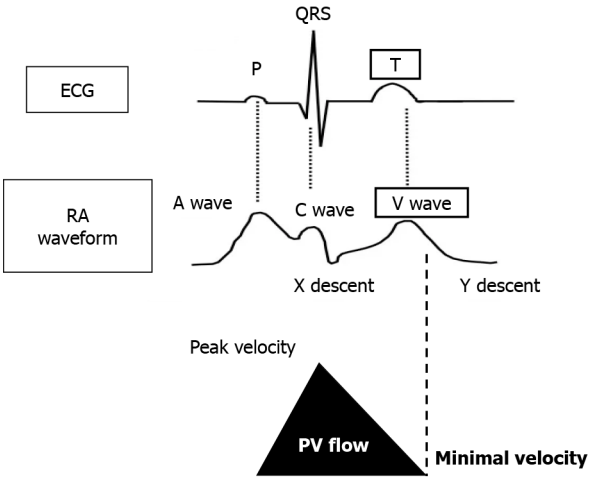

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Figure 4 Relationship between electrocardiography, right atrium waveform, and portal vein flow. The timing of minimum portal vein velocity was synchronized with the V-wave in the right atrium. ECG: Electrocardiography; RA: Right atrium; PV: Portal vein.

CONCLUSION

The PVPR at discharge in hospitalized patients with acute HF reflected venous congestion and the condition of HF. Therefore, the PVPR may be a novel prognostic marker for hospitalized patients with acute HF. We also propose that hospitalized patients with acute HF with a low PVPR at discharge require more careful treatment and close follow-up (Figure 5).

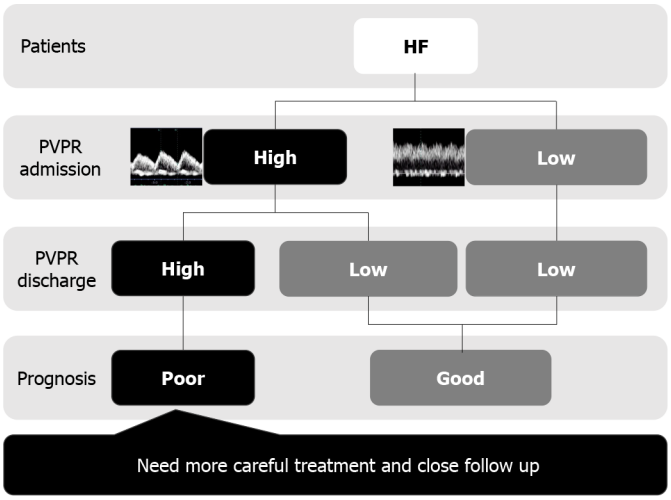

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Figure 5 Summary of the study. HF: Heart failure; PVPR: Portal vein pulsatility ratio.

ARTICLE HIGHLIGHTS

Research background

Heart failure (HF) causes extracardiac organ congestion, including in the hepatic portal system. Reducing venous congestion is essential for HF treatment, but evaluating venous congestion is sometimes difficult in patients with chronic HF.

Research motivation

The portal vein (PV) flow pattern can be influenced by right atrial pressure. Ultrasound images of the PV are quite easy to obtain and are reproducible among sonographers. However, the association between PV pulsatility and the condition of HF remains unclear. We hypothesize that PV pulsatility at discharge reflects the condition of HF.

Research objectives

To evaluate the usefulness of PV pulsatility as a prognostic marker for hospitalized patients with acute HF.

Research methods

This observational study was conducted from April 2016 to January 2017 and April 2018 to April 2019 at Shinko Hospital. We enrolled 56 patients with acute HF, and 17 patients without HF served as controls. PV flow velocity was measured by ultrasonography on admission and at discharge. We calculated the PV pulsatility ratio (PVPR) as the ratio of the difference between the peak and minimum velocity to the peak velocity. The primary endpoint was cardiac death and HF re-hospitalization. The observation period was 1 year from the first hospitalization. The Kaplan-Meier method was used to determine the stratified composite event-free rates, and the log-rank test was used for comparisons between groups.

Research results

On admission, the PVPR was significantly higher in patients with acute HF than controls (HF: 0.29 ± 0.20 *vs* controls: 0.08 ± 0.07, $P < 0.01$). However, the PVPR was significantly decreased after the improvement in HF (admission: 0.29 ± 0.20 *vs* discharge: 0.18 ± 0.15, $P < 0.01$) due to the increase in minimum velocity (admission: 12.6 ± 4.5 *vs* discharge: 14.6 ± 4.6 cm/s, $P = 0.03$). To elucidate the association between the PVPR and cardiovascular outcomes, the patients were divided into three groups according to the PVPR tertile at discharge (PVPR-T1: 0 ≤ PVPR ≤ 0.08, PVPR-T2: 0.08 < PVPR ≤ 0.21, PVPR-T3: PVPR > 0.21). The Kaplan–Meier analysis showed that patients with a higher PVPR at discharge had the worst prognosis among the groups.

Research conclusions

The PVPR at discharge reflects the condition of HF.

Research perspectives

The PVPR is also a novel prognostic marker for hospitalized patients with acute HF.

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FOOTNOTES

Author contributions: Honjo T, Sone N, and Kaihotsu K substantially contributed to the study conceptualization; Kuwahara N and Honjo T substantially contributed to data analysis and interpretation; Honjo T substantially contributed to the manuscript drafting; all authors critically reviewed and revised the manuscript draft and approved the final version for submission.

Institutional review board statement: This study was reviewed and approved by the ethics committee of Shinko Hospital (approval No. 1524).

Informed consent statement: This study was approved by the Institutional Review Board of Shinko Hospital, and all requirements for written informed consent were waived for the use of the patients' clinical and imaging data.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Country/Territory of origin: Japan

ORCID number: Naoya Kuwahara 0000-0001-8805-8212; Tomoyuki Honjo 0000-0002-3167-5903; Naohiko Sone 0009-0005-4949-929X; Junichi Imanishi 0000-0002-1488-1545; Kazuhiko Nakayama 0000-0001-8619-400X; Kohei Kamemura 0009-0008-2162-3705; Masanori Iwahashi 0000-0003-1607-8331; Soichiro Ohta 0009-0003-0960-7474; Kenji Kaihotsu 0009-0008-3276-5362.

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CASE REPORT

Hypertrophic cardiomyopathy secondary to deficiency in lysosome-associated membrane protein-2: A case report

Ye-Tong Zhao, Xiu-Qun Cao, Xiao-Lin Mu

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Ye-Tong Zhao, Xiao-Lin Mu, Department of Radiology, Central Hospital of Dalian University of Technology, Dalian 116033, Liaoning Province, China

Ye-Tong Zhao, Graduate School, Dalian Medical University, Dalian 116000, Liaoning Province, China

Xiu-Qun Cao, Departments of Ultrasound and Health Medicine, Central Hospital of Dalian University of Technology, Dalian 116033, Liaoning Province, China

Corresponding author: Xiao-Lin Mu, MS, Doctor, Department of Radiology, Central Hospital of Dalian University of Technology, No. 826 Southwest Road, Shahekou District, Dalian 116033, Liaoning Province, China. dugumuxin@163.com

Abstract

BACKGROUND

Danon disease (DD), in which mutations in the X-linked lysosome-associated membrane protein-2 (LAMP-2) gene result in hypertrophic cardiomyopathy, is a rare disease, reported primarily in small samples or cases. However, with the development of cardiac magnetic resonance imaging and genetic technology in recent years, the number of reports has increased.

CASE SUMMARY

We report a case of DD in an adolescent male patient, confirmed by genetic testing. The patient was admitted to our hospital with complaints of a three-year history of chest tightness and shortness of breath. His preliminary clinical diagnosis is hypertrophic cardiomyopathy. Our report includes the patient's clinical course from hospital admission to death, step-by-step diagnosis, treatment course, and noninvasive imaging features. We highlight how a noninvasive diagnostic approach, based solely on clinical and imaging "red flags" for DD, can be used to achieve a diagnosis of DD with a high degree of confidence.

CONCLUSION

DD is a very dangerous cardiomyopathy, and it is necessary to achieve early diagnosis and treatment.

Key Words: Danon disease; Lysosome-associated membrane protein-2 gene; Cardiomyopathy; Hypertrophy; Cardiac magnetic resonance imaging; Myocardial strain; Case report

Core Tip: Danon disease (DD) is a rare X-linked disorder caused by a deficiency of lysosome-associated membrane protein-2. DD is clinically characterized by severe cardiomyopathy, skeletal muscle disease, and intellectual disability. The most frequent high-risk form of DD is cardiomyopathy, which can result in arrhythmia(s), early-onset heart failure, and even sudden cardiac death. Our case report intents to raise the awareness of DD and improve the clinical suspicion of DD.

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INTRODUCTION

Danon disease (DD) is a rare, hereditary, X-linked, and dominant lysosomal glycogen storage disease, caused by a deficiency in lysosome-associated membrane protein-2 (LAMP-2)[1]. The disease predominantly affects men, who usually exhibit more severe clinical manifestations and present at an earlier age than women. Clinical manifestations of DD include myocardial enlargement, skeletal myopathy, and mental aberrations[2], and the most frequent high-risk form of DD is cardiomyopathy, which can manifest as arrhythmia(s), early onset heart failure, or even sudden cardiac death. Young male patients with DD typically present with left ventricular hypertrophy, which, unfortunately, is frequently mistaken for hypertrophic cardiomyopathy or other secondary conditions related to left ventricular hypertrophy. Characterized by rapid progression and a propensity for high mortality at an early age, DD may be the most lethal cardiomyopathy in young male patients[3]. In the present case study, we describe the patient's clinical course from hospital admission to death, including all diagnostic work-ups, his treatment course, and any notable noninvasive imaging features. Herein, we emphasize the importance of utilizing unique clinical signs and imaging features for the early recognition and diagnosis of DD.

CASE PRESENTATION

Chief complaints

An 18-year-old adolescent male patient was admitted to our hospital with complaints of a three-year history of chest tightness and shortness of breath.

History of present illness

The patient's symptoms became noticeably worse one week before his admission, with increased chest tightness, an inability to lie supine, and anuria.

History of past illness

The patient was seen at a hospital in Beijing with complaints of chest tightness and was diagnosed with non-obstructive hypertrophic cardiomyopathy, a small pericardial effusion, and chronic bilateral lung inflammation with a few interstitial changes. Additionally, the patient suffered a cerebral infarction during the hospitalization, which improved slightly after treatment.

Personal and family history

The patient denied any family history of genetic disorders or similar conditions.

Physical examination

Upon physical examination, the patient exhibited evidence of hypotension, with a blood pressure of 92/62 mmHg. He exhibited normal development, intelligence, consciousness, and retinal features. Limb muscle strength was graded as level 5 upon the first hospitalization, and muscle tone was normal; however, at the time of the final hospitalization, muscle strength in the right upper limb was grade 4, while muscle strength in the left lower, left upper, and right lower limbs were grade 1. Unfortunately, the hospital staff did not perform electromyography, skeletal muscle magnetic resonance imaging (MRI), or a pathological examination. Atrial/ventricular premature beats and ventricular blocks were visible on resting electrocardiography, although no pre-excitation was observed.

Laboratory examinations

Laboratory testing revealed elevated levels of high-sensitivity cardiac troponin T (0.187 ng/mL) and N-terminal pro-B-type brain natriuretic peptide (NT-proBNP; 6,554 pg/mL), while liver function tests revealed elevated levels of creatine

kinase (1075 U/L, 1545 U/L, and 936 U/L), creatine kinase-MB (63 U/L, 61 U/L, and 58 U/L), lactate dehydrogenase (728 U/L), alanine transpeptidase (206 U/L), and aspartate aminotransferase (273 U/L). The patient's troponin T and myocardial enzyme levels were also elevated, suggesting secondary myocardial damage.

Imaging examinations

Left ventricular centripetal and right ventricular hypertrophy were observed on transthoracic echocardiography (ventricular septal thickness, 20-31 mm; lateral wall thickness, 26 mm) (Figures 1A-C). Tissue Doppler imaging revealed increased end-diastolic filling pressure, with an E value of 70 cm/s (Figure 1D), a ventricular septum e' value of 3 cm/s, and a lateral wall e' value of 4 cm/s (Figures 1E and F).

The patient underwent coronary computed tomography (CT) angiography with maximum intensity projection, excluding acute coronary syndrome, which revealed the patency of the lumen of the coronary trunk and its branches (Figure 1G). To further characterize the cardiac phenotype, a cardiac MRI (CMRI) was performed, which revealed bilateral ventricular hypertrophy, severe trabecularization of the biventricular wall, and minor pericardial effusion. Additionally, myocardial strain analyses of the entire left ventricle (Figure 2A), as well as each segment, were performed. The 16-segment bullseye diagram and longitudinal strain map revealed varying degrees of strain reduction in each segment of the patient's left ventricle, indicating myocardial injury (Figures 2B and C). The ventricular myocardium exhibited substantial late gadolinium enhancement (LGE) on MRI, sparing the mid-basal septum but involving the apex (Figures 1H and I), which is a unique imaging characteristic of DD[4].

FINAL DIAGNOSIS

After reviewing the patient's gene sequencing, in conjunction with the aforementioned data, the patient's final diagnosis was DD.

TREATMENT

The patient experienced ventricular thrombosis, pulmonary thrombosis, pulmonary hypertension, and cerebral infarction in previous hospitalization, which required the administration of the cardiotonic medication digoxin and the anticoagulant warfarin. The patient and his family approved a therapeutic regimen; however, after undergoing treatment with the medications for > 1 mo, the patient's chest tightness worsened, anuria developed, and his lungs started to crackle. Additionally, paroxysmal atrial fibrillation was detected on resting electrocardiography and laboratory results showed an additional elevation in high-sensitivity cardiac troponin T (0.527 ng/mL) and NT-proBNP (84, 072.43 pg/mL) concentrations, as well as hyperkalemia (potassium level, 6.4 mmol/L). Multislice chest CT revealed serious infection in both lungs. The patient was treated with diuretics, nutritional supplementation for the myocardium, anticoagulants, and anti-infection therapy for one week. However, he did not show any significant improvement.

OUTCOME AND FOLLOW-UP

The patient's prognosis continued to be poor, and he subsequently exhibited signs of entering a deep coma and died, despite attempts at active resuscitation.

DISCUSSION

DD is a highly penetrant vacuolar myopathy caused by a primary deficiency in LAMP-2[5]. This condition usually involves the skeletal muscle and myocardium and can be definitively diagnosed through a biopsy. The characteristic pathological features of DD include intracytoplasmic vacuoles harboring autophagic components and glycogen[1]. The classic "trifecta," which includes cardiac enlargement, skeletal myopathy, and abnormal liver function, is used to definitively diagnose patients with suspected DD[5]. Other red flags, such as pre-excitation on resting electrocardiography, are not always present in patients with DD. Although the patient presented herein did not undergo a skeletal muscle biopsy, his decreased muscle strength, in combination with an increase in creatine kinase concentrations, indicated the presence of skeletal muscle damage.

A distinctive LGE pattern and basal septum preservation, seen on CMRI, may help distinguish DD from sarcomeric or other hypertrophic cardiomyopathy phenotypes[4,6] and strengthen a suspected diagnosis of DD. Physicians should confirm cardiac hypertrophy, impaired liver function, and a genuine pattern of progressive gadolinium enhancement on CMRI to diagnose DD. To date, CMRI findings in patients with DD have been described in only a few case reports[4]. CMRI provides accurate imaging of morphological structures and tissue characteristics, such as unusual LGE patterns, which may have practical utility in the identification and differential diagnosis of cardiomyopathy in patients with DD. Additionally, adding myocardial fibrosis to the list of indicators of DD may be appropriate. For the first time, we added feature-tracking technology to investigate cases of DD. The analysis of global and segmental longitudinal myocardial

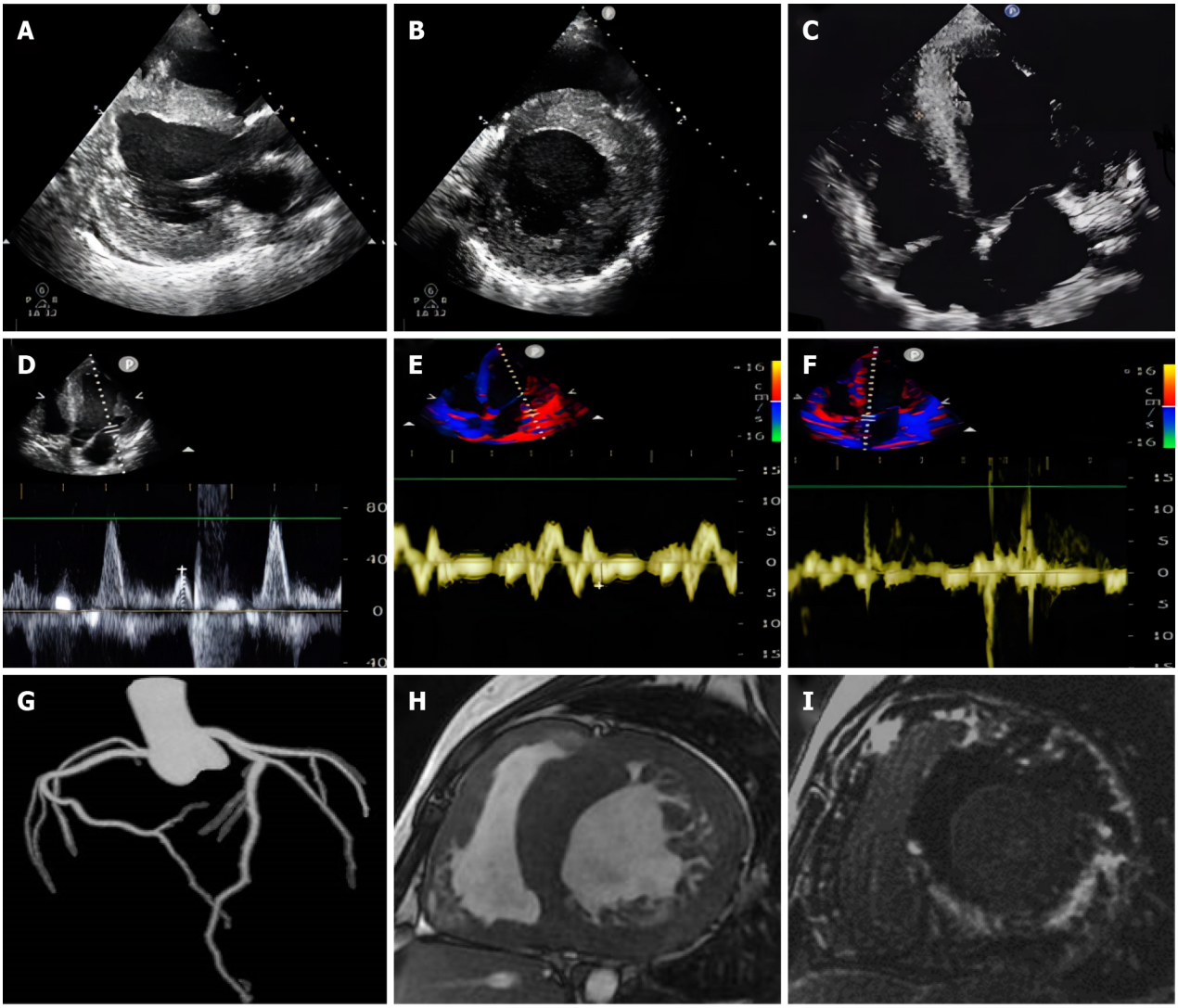

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Figure 1 Imaging features of the male patient. A: Transthoracic echocardiography shows left ventricular centripetal hypertrophy in parasternal long axis view; B: Transthoracic echocardiography shows left ventricular centripetal hypertrophy in parasternal short axis view; C: Transthoracic echocardiography shows left ventricular centripetal hypertrophy and right ventricular hypertrophy in long axis view; D: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with an E value of 70 cm/second; E: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with e' (lateral wall) value of 4 cm/second; F: Tissue Doppler imaging shows increased end-diastolic filling pressure in the left ventricle, with e' (ventricular septum) value of 3 cm/second; G: The coronary tree's maximum intensity projection displays the patency of each branch lumen; H: Cardiac magnetic resonance short-axis cine shows diffuse thickening of the biventricular wall, excessive myocardial trabeculation, and pericardial effusion; I: Late gadolinium enhancement of the short axis demonstrates extensive late gadolinium enhancement of the biventricular wall, sparing only the basal segment septum.

strain using CMRI-feature tracking revealed that both were damaged; however, no other unique features were observed. We speculate that the patient presented herein was in the late stage of heart failure, although he had left ventricular non-compaction, which differs from the preservation of normal apical strain patterns described in previous reports. We hope that more patients with DD will undergo feature-tracking analysis in the future, to further characterize the unique features of cardiac strain seen in these patients.

The clinical results of treating DD depend on the severity of cardiomyopathy, which can be difficult to identify, frequently being discovered only in the presence of clinically significant symptoms. In the case presented herein, substantial myocardial injury, cardiac insufficiency, and arrhythmia were the secondary causes of numerous organ disorders that ultimately led to the patient's death. Physicians should be aware that young males exhibiting myocardial hypertrophic changes, elevated plasma creatine kinase levels, pre-excitation syndrome on electrocardiography, and/or distinctive LGE on CMRI may have DD; therefore, abnormal clinical or laboratory results and CMRI features can be used to diagnose and distinguish DD from other diseases. Furthermore, the aforementioned data allow a diagnosis to be made in a noninvasive manner, providing an alternative to the current gold standard for the diagnosis of DD – genetic testing for LAMP-2 deficiency/mutations. Although there is currently no specific gene therapy for DD, the adenovirus-mediated delivery of a functional LAMP2B transgene has been achieved in a mice model, the efficacy of which is being tested in adolescent male patients with DD.

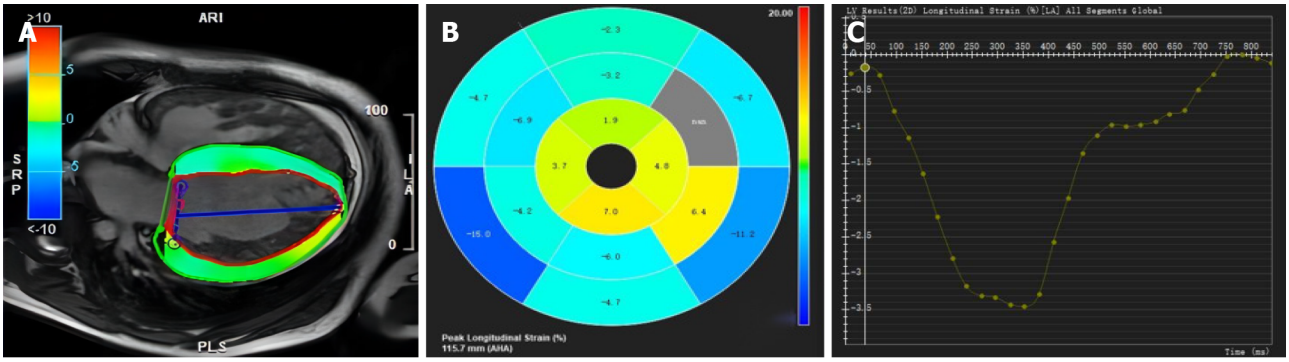

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Figure 2 Feature Tracking strain measurements. A: Cardiac magnetic resonance feature tracking with longitudinal strain overlay on a four-chamber cine steady-state free procession image; B: Bull's- eye diagram of strain in each segment in the left ventricular myocardium of the same patient; C: The map show the longitudinal strain values. The vertical axis shows longitudinal strain (%), and the horizontal axis shows the time in ms.

The Dalian Municipal Central Hospital Affiliated to Dalian Medical University Ethics Committee approved the present case study (No. YN2023-003-04). The patient's parents consented to the publication of anonymized case details.

CONCLUSION

In summary, the authors would like to emphasize the importance of the early diagnosis of DD, which facilitates advanced treatments, such as targeted gene therapy, cardiac transplantation, or the installation of an implantable cardioverter defibrillator. A deeper understanding of the unique clinical signs and imaging features of DD is needed, particularly with the use of CMRI. Genetic testing should also be performed as early as possible to increase diagnostic accuracy.

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FOOTNOTES

Author contributions: Cao XQ and Mu XL collected the clinical data; Mu XL and Zhao YT analyzed and interpreted the clinical data; Zhao YT drafted the manuscript; Mu XL guided the completion of this article, supervising and revising the manuscript for intellectual content; All of the authors have read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Xiao-Lin Mu 0000-0003-3449-9658.

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CASE REPORT

Down syndrome child with multiple heart diseases: A case report

Mo-Wei Kong, Yi-Jing Li, Jun Li, Zhen-Ying Pei, Yu-Yu Xie, Guo-Xiang He

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Mo-Wei Kong, Yi-Jing Li, Jun Li, Zhen-Ying Pei, Guo-Xiang He, Department of Cardiology, Guiqian International General Hospital, Guiyang 550018, Guizhou Province, China

Yu-Yu Xie, Department of Dermatology, Guiqian International General Hospital, Guiyang 550018, Guizhou Province, China

Corresponding author: Jun Li, MD, Doctor, Department of Cardiology, Guiqian International General Hospital, No. 1 Dongfeng Avenue, Wudang Distract, Guiyang 550018, Guizhou Province, China. 492847537@qq.com

Abstract

BACKGROUND

Down syndrome, also known as trisomy 21 syndrome, is commonly associated with congenital heart disease, and can often result in early formation of pulmonary hypertension. The development of pulmonary hypertension can result from factors such as intracardiac and macrovascular shunts, and upper airway obstruction or hypoplasia of lung tissue. Individuals with Down syndrome and congenital heart disease have a significantly lower average life expectancy, with surgical intervention being the most viable treatment option to improve longevity.

CASE SUMMARY

We report the case of a 13-year-old boy with Down syndrome presenting with atrial septal defect and patent ductus arteriosus along with severe pulmonary hypertension. The electrocardiogram shows sinus rhythm and right ventricular hypertrophy. The echocardiogram shows an atrial septal defect with interrupted echo in the interatrial septum, measuring 0.813 cm in length. The patient was initially refused to be offered surgical treatment by many hospitals due to the high surgical risk and pulmonary artery resistance. After discussing the patient's diagnosis and treatment options, we ultimately recommended surgical treatment. However, the patient and their family declined this recommendation and chose to be discharged. During the follow-up period of 6 mo, there were no significant improvements or deteriorations in the patient's condition.

CONCLUSION

In conclusion, this case highlights the challenges faced by individuals with Down syndrome and congenital heart disease complicated by severe pulmonary hypertension. Timely intervention and a multidisciplinary approach are crucial for improving prognosis and life expectancy. Further research is needed to enhance our understanding and develop effective interventions for this population.

Key Words: Down syndrome; Trisomy 21 syndrome; Atrial septal defect; Pulmonary hypertension; Review; Patent ductus arteriosus; Case report

Core Tip: This case study presents a 13-year-old boy diagnosed with Down syndrome alongside atrial septal defect, patent ductus arteriosus, and severe pulmonary hypertension. A complex condition initially met with surgical treatment denial due to high risks, highlights the significant challenges faced by individuals with Down syndrome and congenital heart disease. This case highlights the discussion and educational value surrounding the decision to undergo surgery in complex congenital heart diseases. The educational value lies in the diagnostic and therapeutic approaches demonstrated by our team. Due to the relatively common occurrence of this case in the field of cardiology, our decision-making process holds significant value and applicability.

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INTRODUCTION

Down syndrome (DS), also known as trisomy 21 syndrome (Figure 1), is the most prevalent genetic disorder among Chinese children. The disease arises due to a mutation of the 21st pair of chromosomes, resulting in the duplication of genetic material. Common clinical manifestations include developmental abnormalities, intellectual disability, and an increased propensity for digestive tract and cardiovascular malformations[1]. Reports suggest that the incidence of congenital heart disease (CHD) in DS patients ranges from 40%-60% and can lead to heart failure, pulmonary vascular disease (PVD), and pneumonia[2,3]. Early diagnosis and surgical intervention are vital to prolong survival and enhance the quality of life of these children[4]. However, DS is a chromosomal disease impacting multiple systems, and opinions differ on the effectiveness of surgical intervention.

In the present case, the patient was refused to be offered surgical intervention by multiple hospitals due to the high risk of pulmonary arterial resistance. However, after extensive consultation, our hospital reassessed the patient's situation and proposed a promising treatment plan that ultimately gave the child a chance at life. This case may serve as a valuable reference for the management and treatment of similar cases.

CASE PRESENTATION

Chief complaints

A 13-year-old boy presented to our hospital for further evaluation and treatment.

History of present illness

The patient was diagnosed as having DS with CHD. A patent ductus arteriosus (PDA) closure was successfully performed, but atrial septal defect (ASD) closure was withheld due to the patient's complicated pulmonary arterial hypertension. After treatment, the patient's activity tolerance improved. On July 29, 2020, the patient sought medical care at the Yan'an Hospital of Kunming City, where cardiac catheterization revealed a pulmonary artery pressure of 95/41/66 mmHg and a right ventricular pressure of 97/-10/38 mmHg. He was diagnosed with ASD complicated with severe pulmonary arterial hypertension, and continuation of oral Bosentan and Sildenafil for the management of pulmonary arterial hypertension was recommended.

History of past illness

The patient's medical history revealed that at 2 mo of age, he was diagnosed at another hospital with CHD characterized by ASD and PDA. However, no treatment was provided. In 2018, the patient developed "cyanosis of the lips and shortness of breath after exercise" and was admitted to Fuwai Hospital, where he was diagnosed with ASD and PDA, along with an enlarged heart, severe pulmonary hypertension (PH), and cardiac function Grade II.

Physical examination

Physical examination revealed a pulse rate of 95 bpm, blood pressure of 113/55 mmHg, and pale purplish lips. Cardiac percussion examination revealed leftward expansion of the heart border. Auscultation revealed regular heart rhythm with mild hyperactivity of P2, but no discernible noise.

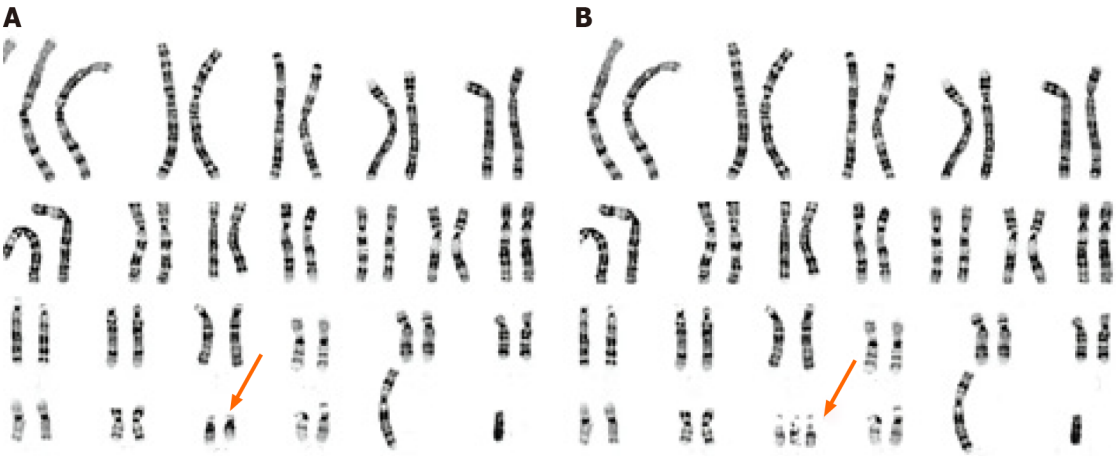

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Figure 1 Differences between the chromosomes of normal individuals and Down syndrome patients. A: Normal human chromosome sequence; B: Down syndrome patients chromosome sequence.

Imaging examinations

Frontal and lateral chest digital radiography (DR) revealed the presence of reticular shadows in the mediastinal area indicative of postoperative changes (Figure 2). A conventional 12-lead electrocardiogram (ECG) (Figure 3) was conducted during the outpatient visit, which revealed sinus rhythm and right chamber hypertrophy. An echocardiogram was also performed, which showed an ASD (central secondary foramen) with an interrupted middle echo in the atrial septum measuring 0.813 cm. The position and functionality of the PDA interventional closing device were normal, the right atrium and ventricle show enlarged diameters and increased wall thickness in the right ventricle (Figure 4). According to subsequent reports, the patient exhibits blood flow signals indicating left-to-right shunting that can be visualized in the atrium. Additionally, a small regurgitant jet can be observed at the tricuspid valve during atrial contraction, with peak flow velocity of 398cm/s and a peak pressure gradient of 63mmHg. Following these assessments, the patient was referred to our department for the management of "ASD and associated PH".

FINAL DIAGNOSIS

The patient was finally diagnosed with: (1) ASD (central foramen secundum type); (2) moderate PH; (3) PDA (after interventional closure); and (4) DS.

TREATMENT

For patients with inconsistent severe PH following the results of physical examination, ECG, chest DR, right cardiac catheterization, and cardiac ultrasound, it is necessary to consider the possibility of measurement instrument errors and judgment bias. We also considered the possibility of heart-lung combined transplantation. However, due to the high surgical trauma and shortage of donors, we took a conservative approach when discussing this option. Further surgical plans will be presented in the "DISCUSSION" section.

OUTCOME AND FOLLOW-UP

The patient ultimately did not accept our surgical recommendation and opted for conservative treatment (oral PH medication) before being discharged.

We conducted a 6-mo follow-up during which the patient did not show significant improvement or worsening of his condition. During the follow-up period, the patient sought medical care at two other hospitals and continued to decline surgical treatment.

DISCUSSION

After extensive discussion by our hospital's expert group, the following findings in this case are summarized. The child had been diagnosed with DS associated with CHD. Despite a previous diagnosis by other medical facilities of severe PH

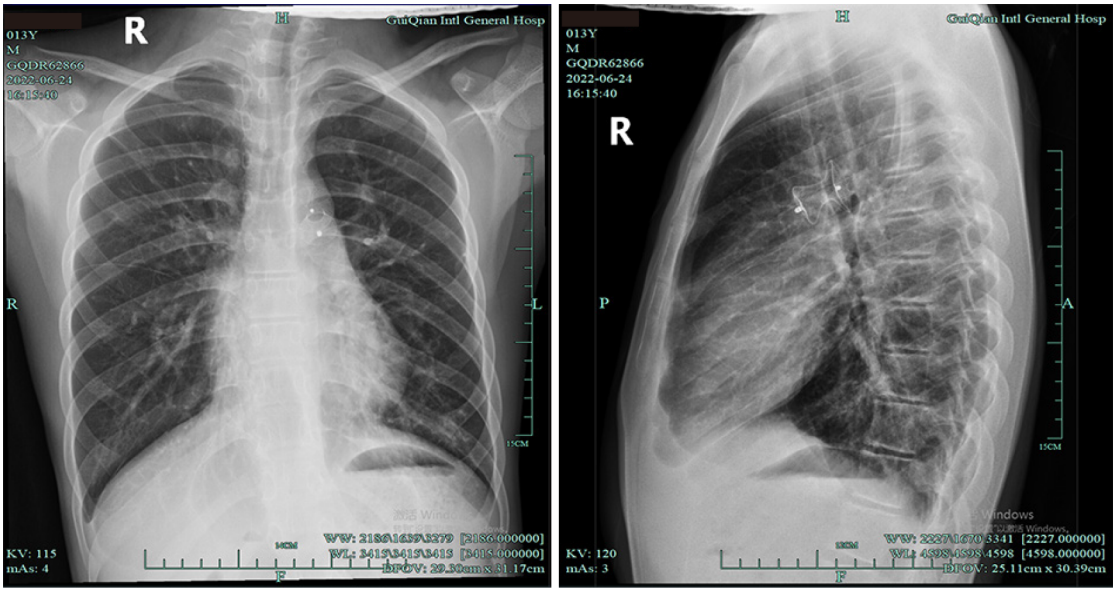

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Figure 2 Anteroposterior and lateral digital radiography of the chest.

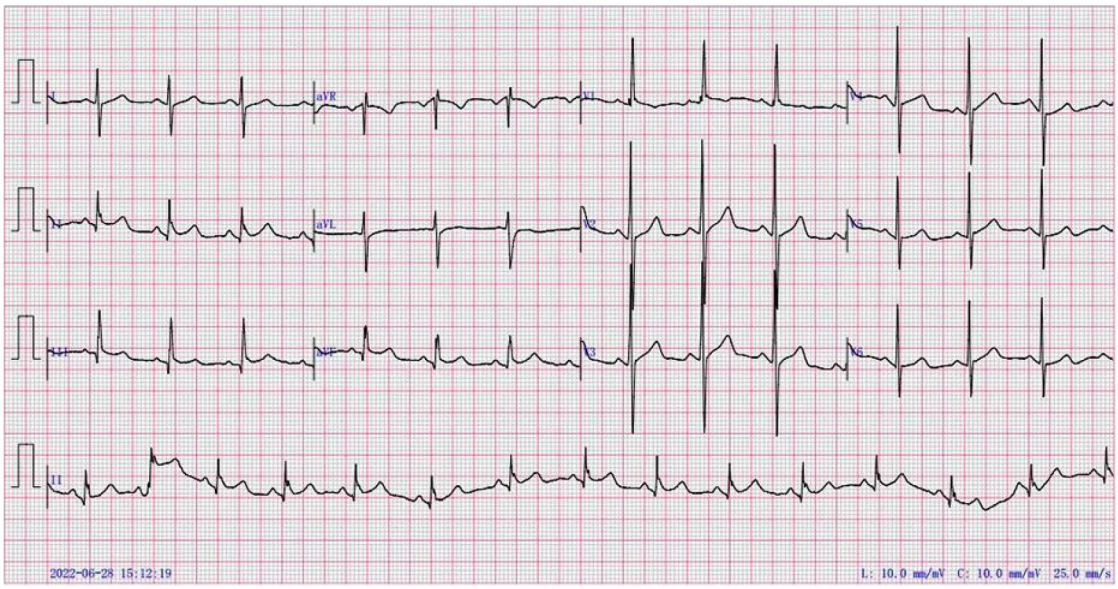

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Figure 3 Conventional 12-lead electrocardiogram.

(systolic pulmonary pressure > 70 mmHg), our physical examination only noted mild accentuated P2 heart sound, suggesting that the patient's actual PH may be mild or nonexistent, or potentially present with a two-way shunt. And the child's ECG demonstrated right ventricular high voltage without any signs of right bundle branch block, and with a low or upside-down ST-T wave, which suggests that the right ventricular hypertrophy may not have been significant. Chest DR indicated slightly expanded pulmonary artery sections without any sparse blood vessels indicative of the "no truncating phenomenon." Therefore, further evaluation was necessary *via* right-heart catheterization to obtain critical indicators for assessing the patient's pulmonary artery pressure. Further investigation was conducted to analyze the relationship between the patient's PDA and ASD. In children with PDA, blood enters the pulmonary arteries through the ASD, leading to a significant increase in pulmonary blood flow (PBF) and left ventricular overload, resulting in an increase in long-term PBF and pulmonary vascular resistance (PVR), eventually leading to PH in later stages. As PH worsens, right-to-left shunting occurs at the atrial level, known as the Eisenmenger syndrome, indicated by clinical cyanosis. However, the child's ultrasonic display did not show a significant increase in the left ventricle. This may be due to the merged ASD, which leads to an increase in the left heart load and the occurrence of left-to-right shunting at the atrial level. After interventional closure of the PDA, the left-to-right shunt in the atrium was reduced, and the systolic pulmonary pressure decreased compared to that previously, significantly improving the patient's symptoms.

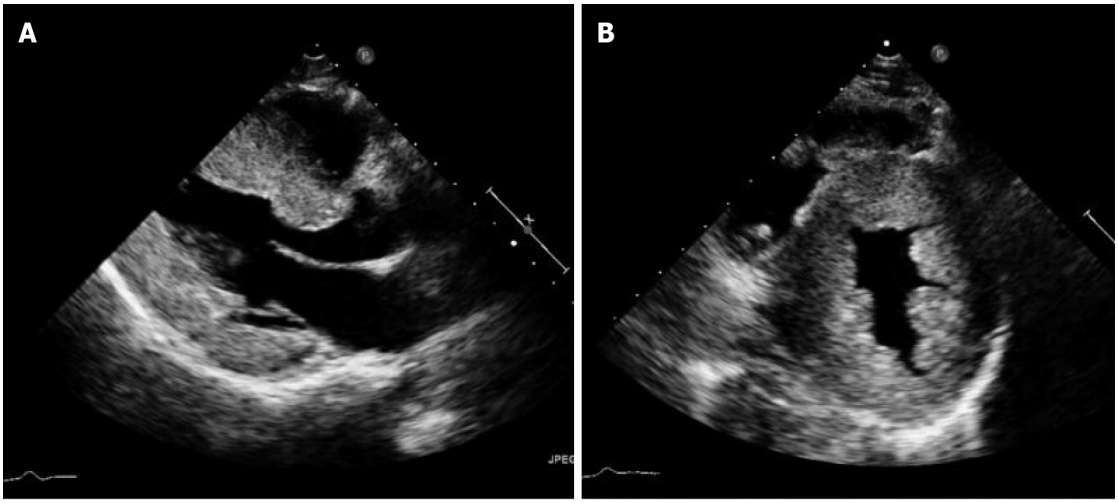

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Figure 4 Echocardiography demonstrated the presence of an atrial septal defect and associated left to right shunt.

It is important to exercise caution and conduct proper communication and evaluation before considering the closure of an ASD in a child with DS combined with CHD, as the prognosis is poor, and the risks associated with anesthesia and surgery are substantial. It is also possible that, even after right heart catheterization, there still may not be any indication for interventional closure or surgery. If a patient's parents fully understand their child's medical condition, treatment plan, surgical risks and benefits, as well as prognosis, but still desire right heart catheterization and any necessary interventional therapy, it is advisable to arrange for general anesthesia appropriate for the cardiac catheterization procedure.

Unfortunately, the patient's parents were unaware of the above situation and declined the surgical recommendation. Therefore, further cardiac catheterization for examination and treatment was not performed, and he continued to take pulmonary artery pressure-lowering drugs and was discharged from the hospital for follow-up.

We also performed a review of the related literature. CHD is the most common type of malformation associated with DS and is a significant cause of mortality in DS patients. The early onset of PH resulting from cardiac defects and respiratory tract hypoplasia can lead to PVD and heart failure, further worsening the timing of surgery and prognosis. Early diagnosis and timely intervention are crucial in prolonging the survival and improving the quality of life of DS patients.

DS is frequently associated with malformations across multiple organ systems, with CHD being the most significant factor affecting patient survival. Approximately 40%-60% of DS cases are associated with CHD[5]. The specific types of CHD associated with DS and their respective composition ratios vary across different countries and regions. In North East England, atrioventricular septal defect (AVSD) is the most common (42%) type of CHD associated with DS, followed by ventricular septal defect (VSD) at 31%. Other types such as ASD, tetralogy of Fallot (TOF), and PDA account for 15%, 5%, and 4%, respectively[5]. In Mexico, ASD is the most common type, accounting for approximately 38%, while VSD and PDA make up 30% and 21%, respectively[6]. In Germany, the most frequently observed type of CHD in DS cases is AVSD (51.2%), followed by VSD (25.1%), TOF (6.7%), and ASD (8.9%)[7]. In Asia, VSD is the most common type of CHD associated with DS, accounting for 43%, followed by AVSD (15.4%), ASD (13.4%), and TOF (13.4%)[8]. The reasons for these regional differences remain unclear.

The pathogenesis of PH in patients with DS and CHD is multifaceted and may be related to both anatomical and physiological changes in the lung circulation[9]. Abnormal shunting caused by heart malformations and other factors, such as upper respiratory tract obstruction and lung tissue development in DS children, contribute to the formation of PH. Deformities in the heart structure result in abnormal shunting, with shunts flowing from left to right causing an increase in PBF[10]. This creates additional shear force on the pulmonary vascular endothelium, leading to irreversible internal cellular damage. Forward-looking studies have found that more than half of DS children show signs of PH, with AVSD often being linked to its formation. Large internal defects cause a significant amount of blood to shunt from left to right after birth, resulting in pulmonary vascular bed damage and the formation of PVD[11,12].

Furthermore, the abnormal blood shunt in the heart increases the blood flow in small arteries, leading to early reflection spasm in the pulmonary arteries and increased pulmonary circulation resistance[13]. The prolonged high flow in the pulmonary circulation leads to the main pathological change of blood vessel remodeling, eventually resulting in irreversible PVD. Studies have demonstrated that, before the age of one year, DS children show lower average PBF and average PVR levels compared to non-DS children[14,15]. Approximately 10% of DS children are diagnosed with pulmonary vascular obstructive diseases (PVOD) before the age of one year, which is not observed in non-DS children. Furthermore, compared to non-DS children with CHDs, DS children with CHDs exhibit a faster increase in PVR and an equivalent trend towards PVOD in the first year after birth[16].

Endothelial progenitor cell dysfunction is also involved in the formation of PH in children with DS. Endothelial progenitor cells maintain the stability of blood vessels and participate in the production of vascular endothelial cells[17]. Their dysfunction is mainly reflected in a reduction of cell number and physiological function, leading to damage in

Table 1 Basic characteristics of included studies evaluated not suitable for surgery

Ref.	Case	Not suitable for surgery (%)	Death without surgery (%)
Liu *et al*[22], 2015	77	17 (22.1)	5 (6.5)
Gu *et al*[5], 2016	96	38 (39.6)	4 (4.2)
Xu *et al*[23], 2019	30	0 (0)	0 (0)
Guo *et al*[24], 2015	25	0 (0)	0 (0)
Zahari *et al*[25], 2019	414	270 (65.1)	37 (9.0)
Evans *et al*[26], 2014	4231	2200 (52.4)	85 (1.9)
Baban *et al*[27], 2020	859	245 (28.5)	34 (4.0)
Aziz *et al*[28], 2020	18	6 (33.3)	-
Santos *et al*[29], 2019	139	48 (34.5)	10 (6.8)
Dias *et al*[30], 2016	102	-	3 (2.9)

maintaining the stability of blood vessels and resulting in severe or irreversible damage in the early stages of pulmonary vessel development[18]. Furthermore, several studies have indicated higher levels of various inflammatory mediators in DS children, including tumor necrosis factor-α, interleukin-6, and C-reactive protein, among others. This is also considered to impact the number of endothelial progenitor cells circulating in the blood[19].

Early onset, severe disease, and rapid progression of PH are observed in patients with DS and CHD. Therefore, early evaluation and diagnosis are critical to improving their prognosis. The assessment process involves echocardiography to determine the morphological changes in the heart and detect the presence of PH. Generally, evaluation of pulmonary arterial compression is conducted using the three-pointed reflux peak speed and Doppler ultrasonic images in combination with other ultrasonic indicators that could potentially indicate PH, such as increased pulmonary valve reflux speed, enlargement of the right heart cavity, and enlargement of the main pulmonary artery[20]. Evaluation also includes clinical manifestations, peripheral blood oxygen saturation, and other indicators to determine the level of PH.

In some cases, cardiac catheterization and acute pulmonary vascular dilation tests may be necessary to determine the level of PVD[21]. A pulmonary artery pressure of ≥ 25 mmHg under right cardiac catheterization in a static state is diagnostic for PH. Severe PH patients who cannot undergo surgery can lower their pulmonary artery pressure by taking oral diuretics and vasodilators, and partially benefit from targeted therapies[21].

Children with DS and CHD often experience repeated lung infections, weight loss, and advanced heart failure in the early stages before undergoing surgical treatment to correct cardiovascular malformations. Delayed treatment can result in an increased risk of mortality[16-18]. To investigate the status of DS with CHD over the past decade, we conducted a search of Chinese and international databases to identify cases who underwent surgical treatment. However, we found that some of these cases were deemed unsuitable for surgery (Table 1). It is important to recognize that delaying surgical treatment can increase the risk of severe complications and mortality. This highlights the need for early assessment and diagnosis to improve the prognosis of DS children with CHD.

CONCLUSION

The data in Table 1 highlight a notable discrepancy between those deemed "unsuitable for surgery" and those who passed away without undergoing surgery in various studies. This difference may be due to the various types of combined heart diseases observed in different regions or sample size differences. Nevertheless, some children are unable to receive surgical treatment and may even pass away while waiting for surgery.

FOOTNOTES

Co-first authors: Mo-Wei Kong and Yi-Jing Li.

Co-corresponding authors: Jun Li and Guo-Xiang He.

Author contributions: Kong MW and Li YJ conceived and designed the study protocol and drafted the manuscript; Li J and He GX were involved in the data collection; Pei ZY and Xie YY analyzed the data; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Kong MW and Li YJ contributed equally to this work as co-first authors. Li J and He GX contributed equally to this work as co-corresponding authors. The reasons for designating Kong MW and Li YJ as co-first authors, and Li J and He GX as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed

authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, the co-first authors and co-corresponding authors contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors or co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Kong MW and Li YJ as co-first authors, and Li J and He GX as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORCID number: Mo-Wei Kong 0000-0002-1214-164X; Jun Li 0009-0003-1481-9914; Guo-Xiang He 0009-0005-2285-6947.

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