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EDITORIAL

Mood alteration and heart rate variability in patients with cancer on treatment

Yun-Chen Chang, Wei-Nung Liu, Felicia Lin, Gen-Min Lin

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Abstract

In this article, Deng and Song showed compelling evidence on the connection between heart rate variability (HRV) alterations and cancer in 127 cancer patients compared with healthy reference individuals, highlighting autonomic nervous system dysfunction as a significant physiological manifestation in cancer patients. We discussed that the reduced HRV may be associated with cancer treatments, *e.g.*, operation, chemotherapy and pain control and psychological response such as depression and anxiety related to the affected cancer. A management such as medicine to mood disturbances related to cancer has been shown a benefit to improve HRV in cancer patients.

Key Words: Cancer; Chemotherapy; Heart rate variability; Mental stress; Heart

Core Tip: We discussed that the reduced heart rate variability may be associated with cancer treatments, *e.g.*, operation, chemotherapy and pain control and psychological response such as depression and anxiety related to the affected cancer. A management such as medicine to mood disturbances related to cancer has been shown a benefit to improve heart rate variability in cancer patients.

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INTRODUCTION

Deng and Song[1] presented compelling evidence on the connection between heart rate variability (HRV) alterations and cancer, highlighting autonomic nervous system dysfunction as a significant physiological manifestation in cancer patients. Their observational study of 127 cancer patients demonstrated that HRV, a non-invasive measure of autonomic function, is significantly abnormal in cancer patients compared to reference individuals, with pronounced reductions especially evident in advanced disease stages.

MECAHNISMS FOR REDUCED HRV IN CANCER AND MANAGEMENTS

Cancer treatments, including surgical interventions, chemotherapy, and pain management protocols, have substantial impacts on HRV patterns, reflecting treatment-induced autonomic modulation. Surgical procedures often trigger profound autonomic responses characterized by immediate sympathetic activation followed by gradual recovery, with HRV parameters frequently showing substantial reductions during the perioperative period[2]. These alterations can persist beyond the immediate recovery phase, indicating prolonged autonomic dysfunction. Chemotherapeutic agents, particularly anthracyclines, platinum compounds, and taxanes, have been associated with significant reductions in both time-domain and frequency-domain HRV parameters, suggesting these treatments may directly affect cardiac autonomic innervation[3,4]. The cardiotoxic effects of chemotherapy not only manifest as structural cardiac damage but also as functional autonomic dysregulation, potentially contributing to increased cardiovascular morbidity in cancer survivors. Furthermore, adequate pain control has emerged as a crucial factor influencing autonomic function in cancer patients. Uncontrolled pain triggers sympathetic hyperactivity, resulting in reduced HRV, while effective analgesic interventions can partially restore autonomic balance[5]. Notably, opioid analgesics demonstrate complex effects on HRV, with initial parasympathetic enhancement often followed by adaptation and potential long-term alterations in autonomic tone. These treatment-related autonomic changes highlight the importance of comprehensive cardiovascular monitoring throughout cancer treatment trajectories, with HRV assessment potentially serving as a valuable tool for early detection of treatment-induced cardiovascular complications.

Emerging evidence highlights the critical relationship between mood alterations in cancer patients and their impact on HRV, underscoring the complex interplay between psychological distress and autonomic nervous system regulation. A cancer diagnosis and subsequent treatments are frequently associated with heightened emotional stress, anxiety, and depression, which directly influence autonomic function, often manifesting as increased sympathetic activity and diminished parasympathetic tone, resulting in decreased HRV[6,7]. Chronic stress activation perpetuates autonomic imbalance, negatively affecting cardiovascular health, immune function, and potentially reducing overall prognosis and quality of life for cancer patients[8]. Given these implications, integrating psychological interventions into comprehensive cancer care has become increasingly critical. Mindfulness-based stress reduction[9], cognitive-behavioral therapy[10,11], supportive counseling[12], and structured psycho-oncological support have all demonstrated potential in modulating autonomic function, enhancing parasympathetic activity, and consequently improving HRV[12]. Mindfulness interventions, specifically, have shown promising results in reducing anxiety and depression, thereby attenuating sympathetic dominance and facilitating autonomic recovery[13]. Furthermore, relaxation techniques including yoga, meditation, and guided breathing exercises have proven effective in improving emotional well-being and autonomic regulation in cancer populations[11,13].

Pharmacological treatments, when indicated clinically, can complement psychological interventions, particularly in managing severe mood disturbances and their physiological consequences[14]. Additionally, adjunctive strategies such as music therapy and social support programs provide supplementary benefits, contributing significantly to emotional stabilization and physiological resilience, thereby supporting enhanced HRV outcomes[15,16]. Future research directions should aim at elucidating precise neurophysiological and psychological mechanisms linking mood disturbances to autonomic dysfunction, identifying potential patient-specific moderators, and rigorously evaluating intervention efficacy in long-term HRV improvement and cardiovascular risk mitigation. Embracing a biopsychosocial framework in oncology care can promote comprehensive patient management, fostering both emotional and physiological resilience, ultimately enhancing cancer patient outcomes and quality of life.

CONCLUSION

The intricate relationship between psychological distress and autonomic nervous system dysfunction underscores the importance of addressing mood alterations in cancer patients as a critical component of comprehensive oncology care. Persistent mood disturbances, such as anxiety and depression, significantly influence HRV, highlighting the necessity for integrative therapeutic approaches aimed at enhancing autonomic balance. Evidence-based psychological interventions, including mindfulness-based stress reduction, cognitive-behavioral therapy, and supportive counseling, demonstrate promising efficacy in restoring parasympathetic activity and mitigating sympathetic over activation. Additionally, complementary practices such as meditation, yoga, guided breathing exercises, and structured psycho-oncological support programs contribute substantially to emotional and physiological resilience. To optimize clinical outcomes, future research should further elucidate the mechanistic pathways linking psychological states to autonomic regulation, refine intervention modalities, and identify personalized factors that enhance responsiveness to these treatments. By recognizing and incorporating psychological well-being into cancer management, clinicians can foster a holistic, patient-centered approach that improves both cardiovascular function and overall quality of life for individuals affected by cancer.

FOOTNOTES

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EVIDENCE REVIEW

Navigating women with congenital heart disease during pregnancy: Management strategies and future directions

Bibhuti B Das, Varun Aggarwal, Shriprasad R Deshpande

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Abstract

Women with adult congenital heart disease (CHD) face unique challenges during pregnancy, as gestational cardiovascular (CV) and hemodynamic changes can exacerbate underlying cardiac conditions. While these adaptations are well tolerated in women with structurally and functionally normal hearts, they pose significant risks for those with adult CHD (ACHD), whether repaired, palliated, or with residual defects. Maternal CHD is associated with an increased risk of adverse CV events, including stroke, heart failure, arrhythmias, and thromboembolic complications during pregnancy and the peripartum period. Effective management requires a multidisciplinary team, including cardiologists, perinatologists, anesthesiologists, and other skilled care providers. Risk stratification tools such as the modified World Health Organization classification, CARPREG II, and ZAHARA scores are useful for predicting maternal and fetal outcomes and guiding clinical decision-making. Preconception counseling plays a critical role in assessing individual risks, optimizing cardiac function, and educating patients about potential complications. Future research should prioritize innovative therapies, including targeted pharmacological agents and minimally invasive interventions, alongside improved screening methods to identify high-risk patients before symptomatic disease manifests. This review synthesizes current literature on managing pregnant women with ACHD, highlights gaps in clinical practice, and explores future directions to enhance care. Addressing these challenges is essential to improving maternal and fetal outcomes and ensuring comprehensive, patient-centered care throughout the reproductive journey.

Key Words: Congenital heart disease; Pregnancy; Women with congenital heart disease;

Contraception; Postpartum care; Maternal & fetal outcomes

Core Tip: Managing adult congenital heart disease (ACHD) in pregnancy requires a multidisciplinary approach. Preconception counseling, risk stratification with the modified World Health Organization classification, and tailored monitoring optimize maternal and fetal outcomes. Hemodynamic changes can worsen ACHD complications, necessitating specialized cardio-obstetric team care. Individualized delivery plans, vigilant postpartum surveillance, and post-delivery contraception counseling are essential. Advances in imaging and interventions improve outcomes, but high-risk cases demand tertiary center expertise to address cardiac decompensation, arrhythmia, or heart failure, ensuring safe pregnancy management. Future directions emphasize AI-driven risk prediction to further enhance outcomes.

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INTRODUCTION

Advances in managing congenital heart disease (CHD) have led to an increased number of women with adult CHD (ACHD) reaching childbearing age. Pregnancy is a unique and complex physiological state that presents numerous challenges to women with pre-existing ACHD, whether unrepaired, repaired with residual defects, or palliated[1]. Currently, about 8 in every 10000 pregnant individuals have CHD[2]. Cardiovascular (CV) conditions, including ACHD, significantly contribute to maternal morbidity and mortality, stillbirths, premature births, and neonatal deaths, posing a growing public health concern[2,3]. Guideline-directed medical therapy (GDMT) for acquired heart diseases is not directly applicable to pregnant women who require special care to ensure optimal maternal and fetal outcomes. Several factors, including the complexity of CHD, unrepaired defects, and socioeconomic disparities, predict higher complication rates for pregnant women and their offspring. Most of the complications during pregnancy can be prevented through enhanced provider education and proper risk stratification, as recommended by leading societal guidelines, including those from the American College of Cardiology (ACC)/American Heart Association (AHA), European Society of Cardiology (ESC), Canadian Cardiovascular Society, International Society for Adult Congenital Heart Disease (ISACHD), and American College of Obstetricians and Gynecologists (ACOG)[4-9]. The evolving field of cardio-obstetrics (Figure 1) is a beacon of hope, involving a multidisciplinary team to surveil patients' CV health for preconception, antenatal, and postpartum care[10,11]. The cardio-obstetrics team includes perinatologists (maternal-fetal medicine physicians), ACHD cardiologists, heart failure (HF) cardiologists, cardiac and obstetric anesthesiologists, pharmacists, neonatologists, nurses, and social workers, and offers a comprehensive approach tailored to each patient's specific needs. This review emphasizes understanding pregnancy physiology, evaluating maternal and fetal risks during labor and delivery, management of CV complications such as stroke, HF, and arrhythmia, postpartum care, identifying areas for practice improvement, and exploring future directions (Figure 2).

NORMAL PHYSIOLOGICAL CHANGES DURING PREGNANCY

During pregnancy, the CV system undergoes significant changes (Table 1), characterized by an increase in cardiac output (CO), reaching its height between 16 and 28 weeks and rises an additional 30% during labor, due to an increased heart rate (HR) of 10-20 beats/minute and expanded blood volume[12]. Blood volume increases by 30% to 50%, and systemic vascular resistance (SVR) decreases due to higher levels of estradiol and prostacyclin, leading to lower blood pressure (BP) that peaks at 24 weeks of gestation before returning to preconception levels by term[13,14]. Pulmonary vascular resistance decreases by approximately 24% by the eighth week of gestation, accommodating a 47% increase in pulmonary flow[15,16]. Venous pressure, especially in the lower extremities, rises due to the growing uterus's pressure on pelvic veins and increased blood volume, leading to dependent edema, which can be confused with signs of HF[17]. Additionally, the dilutional effect of increased plasma volume can result in physiological anemia. These physiological changes are exacerbated in twin pregnancies[18]. The above physiologic adaptations ensure adequate fetal blood flow and are generally well-tolerated in healthy pregnant women. However, in patients with preexisting ACHD, these hemodynamic changes during pregnancy pose many challenges.

Table 1 Physiological changes during pregnancy and delivery

Changes	Variables	First trimester	Second trimester	Third trimester	Delivery
Hemodynamic	CO	Small increase	Moderate increase	Moderate increase	Significant increase
	SVR	Mild decrease	Moderate decrease	Moderate decrease	-
	PVR	Mild decrease	Mild decrease	Mild decrease	Mild increase
	HR	Small increase	Moderate increase	Significant increase	Very significant increase
	BP	Mild decrease	Mild decrease	No change	Mild increase
WBC	WBC count	-	-	-	High
RBC	RBC mass	Small increase	Moderate increase	Moderate increase	-
Blood volume	Plasma volume	Moderate increase	Moderate increase	Very significant increase	Extremely significant increase
Remodeling in heart	LV mass	Small increase	Small increase	Small increase	-
	Chamber sizes	-	-	4-chamber enlargement	-
Aorta	Distensibility	Increase	-	-	-
Respiratory minute ventilation	O_2 saturation[1]	Small increase	Moderate increase	Moderate increase	-
Cardiac biomarkers	BNP	No change	-	-	Mild increase
	cTn	No change	-	-	-
	CK-MB	Increase	-	-	-
	D-dimer	Small increase	Moderate increase	Significant increase	-
ECG changes	P wave	Small increase	Plateau	-	-
	Q wave	-	-	Prominent Q wave in inferior and anterolateral leads	-
	QTc	-	-	Mild increase	-
	ST changes	-	-	-	ST depression after cesarean section delivery
Arrhythmia	APC	Common	-	-	-
	PVC	Common	-	-	-

[1]O_2 saturation < 95% is abnormal during pregnancy and needs investigation.

CO: Cardiac output; SVR: Systemic vascular resistance; PVR: Pulmonary vascular resistance; HR: Heart rate; BP: Blood pressure; WBC: White blood cells; RBC: Red blood cells; LV: Left ventricle; BNP: Brain natriuretic peptide; CK-MB: Creatine kinase-isoenzyme MB; ECG: Electrocardiography; cTn: Cardiac troponin; APC: Atrial premature contraction; PVC: Premature ventricular contraction.

ASSESSMENT AND RISK STRATIFICATION

Highlighting the significance of preconception counseling for women with ACHD is essential due to the potential risks involved. These include hemodynamic deterioration with unplanned pregnancy, the risk of CHD in the offspring of parents with ACHD, and the potential teratogenicity of cardiac medications. A comprehensive evaluation, encompassing medical history for prior cardiac surgeries, history of arrhythmias, interventional procedures, physical examination, electrocardiogram, echocardiogram, and other relevant diagnostic tests such as serial monitoring of brain natriuretic peptide (BNP)/N-terminal fragment of the BNP precursor (NT-proBNP), forms the basis of effective care. Risk stratification, considering CHD's anatomic complexity and physiological stage[1], New York Heart Association (NYHA) functional class, and associated comorbidities, is the key to proactive management. Cardiopulmonary exercise testing (CPET) is a valuable tool for assessing functional capacity, evaluating cardiac and pulmonary pathology, and providing guidance on prognosis and interventional recommendations before pregnancy[19]. For parents with inherited cardiac conditions, a formal genetic evaluation is recommended to discuss the transmission of the disease to offspring[20].

Risk scoring systems, such as the modified World Health Organization (WHO) classification (adopted by the 2018 ESC guidelines)[6], Harris score[21], CARPREG II risk score[22], and ZAHARA risk score[23], estimate the risk of adverse maternal and fetal outcomes in pregnant women with ACHD. The modified WHO (mWHO) classification system for maternal CV risk offers the best approach to implementing risk assessment[24] and guiding management decisions (Figure 3). Patients are classified into minimal risk (class I), low to moderate risk (class II), high risk (class III), and extremely high risk (class IV), where pregnancy is contraindicated. Women in classes I and II can be cared for in a

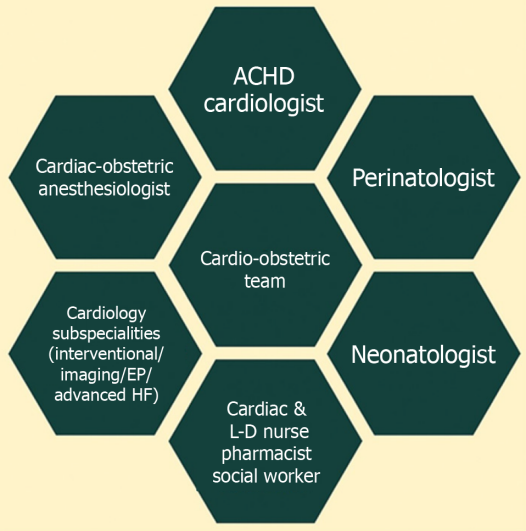

Figure 1 Cardio-obstetric team. ACHD: Adult congenital heart disease; EP: Electrophysiology; HF: Heart failure; L-D: Labor and delivery.

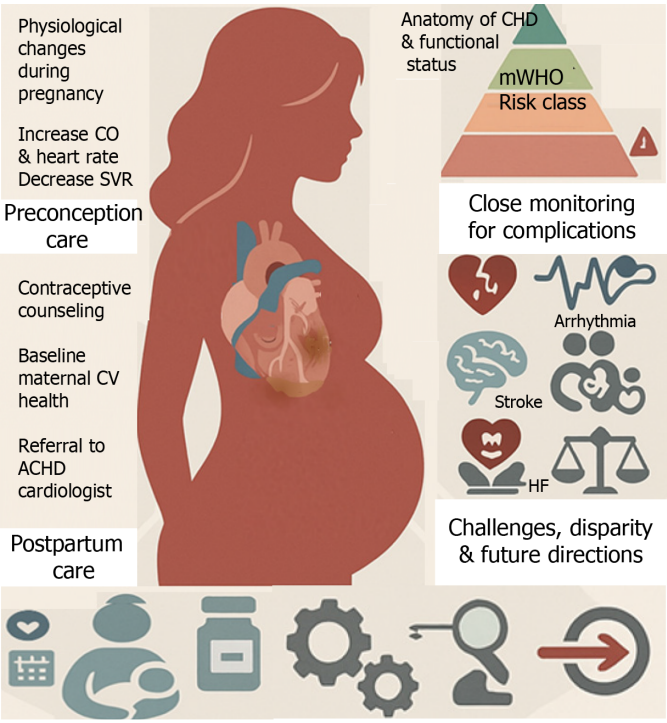

Figure 2 Overall summary of management of adult congenital heart disease during pregnancy. CO: Cardiac output; ACHD: Adult congenital heart disease; CV: Cardiovascular; SVR: systemic vascular resistance.

peripheral hospital, whereas those in classes II-III and III should be managed in a tertiary center with a cardio-obstetric team. Figure 4A illustrates the risk of cardiac events per mWHO class, and Figure 4B describes the composite risk of adverse effects by the integration of mWHO, CARPREG, ZAHARA, and ROPAC risk scores.

COMMON ACHD LESIONS IN PREGNANCY

The modified WHO classification emphasizes primary anatomic pathology rather than functional status, offering broader predictions about expected maternal outcomes. However, there is substantial diversity in ACHD patient anatomy, types of previous intervention/reconstruction, and physiology (including residual hemodynamically significant lesions and/or cyanosis), all of which collectively affect individual management. Table 2 describes key clinical features of different ACHD types.

Table 2 Common congenital and valvular heart disease encountered in pregnancy

ACHD type	Maternal risk	Fetal risk	Key clinical considerations
ASD	Low risk (< 5% arrhythmia, endocarditis, TE)	Low fetal mortality	DVT prophylaxis; consider anticoagulation if high-risk; aspirin in select cases
VSD	Similar to ASD	Low fetal mortality, CHD recurrence 27%	Standard management; low risk overall
Tetralogy of Fallot (repaired)	Low cardiac event rate, arrhythmia (2%-6%)	Low fetal risk	Elective PVR if RV dysfunction or dilation
CoA	HTN (5%-30%), rare dissection	Low fetal mortality, CHD recurrence 4%	Avoid pregnancy in severe CoA (mWHO IV); control BP carefully
Ebstein anomaly	HF 3%, arrhythmia 4%	Preterm 22%	Assess cyanosis, degree of TR, and RV function
d-transposition of great arteries s/p atrial switch	HF 10%, arrhythmia 15%	Preterm 34%-38%, low CHD recurrence	Assess systemic ventricular function and TR
ccTGA/l-TGA	HF 10%, cardiac event 2%	Preterm 9%, CHD recurrence 36%	Assess systemic RV, TR, and heart block risk
Cyanotic CHD (unrepaired)	High maternal risk (HF 19%, TE 3.6%)	Fetal mortality 12%, preterm 45%	Contraindicated for pregnancy; require thromboembolism prophylaxis, iron support
Eisenmenger syndrome	Very high maternal mortality (33%), TE 18%	Fetal mortality up to 30%, preterm 65%	Pregnancy is contraindicated; PDE-5i/prostanoids may be used, endothelin antagonists contraindicated
Fontan circulation	HF 3%-11%, arrhythmia up to 37%	Preterm 28%-59%, live birth only 45% of evidence of Fontan failure, postpartum hemorrhage 14%	Avoid pregnancy in complicated Fontan; anticoagulation recommended
Severe mitral stenosis	Mortality 3%, HF 37%, arrhythmia 16%	Fetal mortality 6%, preterm 18%	Severe MS = mWHO IV (contraindicated); moderate = mWHO III
Severe aortic stenosis	Mortality 2%, HF 9%, arrhythmia 4%	Fetal mortality 5%, preterm 4%	Severe symptomatic AS = mWHO IV; assisted delivery may be considered
Severe pulmonary stenosis	Generally well tolerated; worsening function possible	No significant fetal effects observed	Monitor for worsening symptoms; limited data
Moderate/severe AV valve regurgitation	Mortality < 1%, HF 8%-11%, arrhythmia 6%-8%	Fetal mortality 0%-1%, preterm 12%-15%	Worse prognosis with pulmonary hypertension or LV dysfunction
Moderate/severe semilunar valve regurgitation	Mortality < 1%, HF 1%-3%, arrhythmia 0%-3%	Fetal mortality 1%-8%, preterm 5%-10%	Same considerations as AV regurgitation

TE: Thromboembolism; DVT: Deep vein thrombosis; PVR: Pulmonary valve replacement, RV: Right ventricle; CoA: Coarctation of the aorta; mWHO: Modified world health organization classification; HTN: Hypertension; HF: Heart failure; TR: Tricuspid regurgitation; PDE-5i: Phosphodiesterase 5 inhibitor; AV: Atrioventricular valve regurgitation; s/p: Status post; CHD: Congenital heart disease; BP: Blood pressure; ACHD: Adult congenital heart disease; ASD: Atrial septal defect; ccTGA: Congenitally corrected transposition of the great arteries; l-TGA: L-transposition of great arteries; VSD: ventricular septal defect; MS: Mitral stenosis; AS: Aortic stenosis; LV: Left ventricle.

Left heart stenotic ACHD

Left heart stenotic ACHD includes aortic stenosis (AS), mitral stenosis (MS), and the coarctation of the aorta (CoA; Figure 5A).

AS: Pregnancy is contraindicated in symptomatic AS or severe asymptomatic AS with severely impaired left ventricular (LV) function [LV ejection fraction (LVEF) < 30%, mWHO-IV] due to high maternal morbidity and mortality risks[6,25,26]. It is important to highlight that, according to the CARPREG II[21] and ZAHARA[22] scores, a peak gradient ≥ 50 mmHg across the aortic valve, a subaortic gradient ≥ 30 mmHg, or an aortic valve area ≤ 1.5 cm² is deemed high risk during pregnancy[27]. Mild to moderate AS lesions are usually well-tolerated unless associated with LV dysfunction or aortic regurgitation (AR). Continuous invasive hemodynamic monitoring is required for severe AS. Diuretics should be used cautiously. Balloon dilatation or transcatheter aortic valve replacement (TAVR) may be considered in advanced pregnancy stages[27]. Surgery, if needed, is recommended to be done between the 13th and 28th weeks of gestation or should be considered after early cesarean delivery. Patients with LV outflow tract obstruction and CoA are at higher risk of small-for-gestational-age (SGA) infants and premature births[28]. Regional anesthesia is suitable, but single-shot spinal anesthesia should be avoided due to sudden hemodynamic changes. Postpartum care includes monitoring for HF and deterioration of LV function.

MS: MS poses a significant risk during pregnancy, with pulmonary edema being the most common complication[29]. Pre-

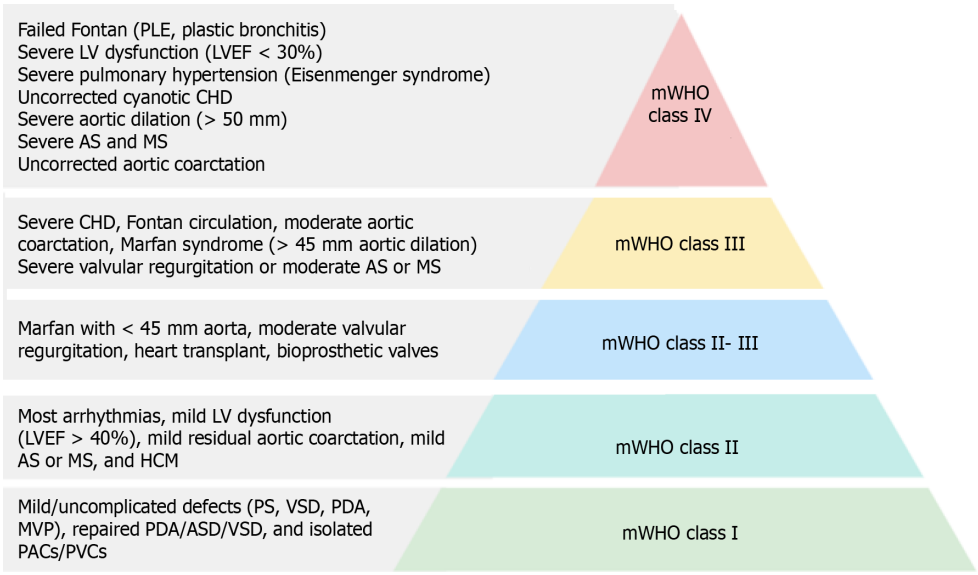

Figure 3 Modified World Health Organization classification for maternal risk associated with adult congenital heart disease. mWHO: Modified World Health Organization; PLE: Protein-losing enteropathy; CHD: Congenital heart disease; LV: Left ventricle; LVEF: Left ventricular ejection fraction; AS: Aortic stenosis; MS: Mitral stenosis; HCM: Hypertrophic cardiomyopathy; PS: Pulmonary stenosis; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; MVP: Mitral valve prolapse; ASD: Atrial septal defect; PAC: Premature atrial contraction; PVC: Premature ventricular contraction.

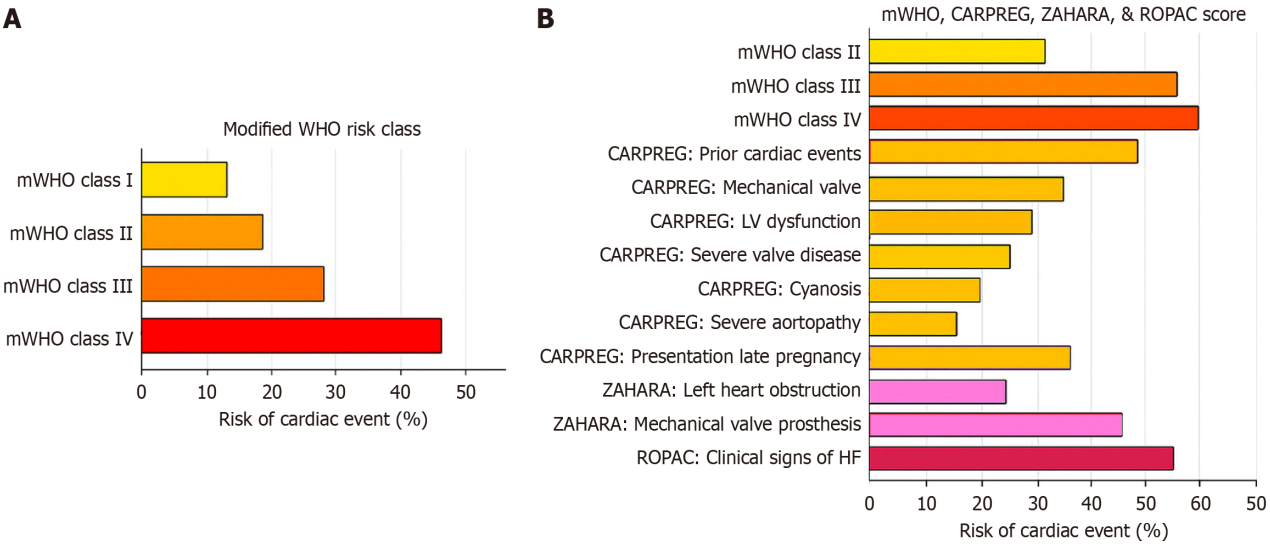

Figure 4 Risk stratification for women with ACHD during pregnancy. A: The risk of cardiac events per modified World Health Organization (mWHO) class; B: Composite risk comparison for cardiac events in women with adult congenital heart disease during pregnancy: mWHO class, CARPEG II, and ZAHARA scores. mWHO: Modified World Health Organization.

pregnancy severe MS (< 1.5 cm^2 valve area) should be corrected before pregnancy. Anticoagulation is indicated for atrial fibrillation, left atrial (LA) thrombosis, prior embolism, spontaneous echo contrast in the LA, LA volume index ≥ 60 mL/m^2, or when associated with HF. Mild MS is usually well-tolerated, while moderate or severe MS often leads to HF symptoms, especially in the second trimester. HR control is crucial, with beta blocker (BB; metoprolol) and calcium channel blocker (CCB; diltiazem), which are safe during pregnancy[30]. Diuretics should be used cautiously. Physical activity should be limited; bed rest is advised in moderate to severe cases. MS can cause atrial fibrillation, which is challenging to manage during pregnancy, and electrical cardioversion may be needed[31]. Balloon valvuloplasty is considered if medical management fails, preferably in the second trimester[27]. In most cases, congenital MS due to parachute mitral valve is not amenable to balloon valvuloplasty, highlighting the importance of accurate pre-conception valve characterization. Planned cesarean section is preferred for symptomatic severe MS, while mild MS can be managed with vaginal delivery and epidural analgesia. Maternal mortality is highest during labor and the immediate postpartum period. Postpartum care includes monitoring for pulmonary edema and fetal outcomes like intrauterine growth retardation (IUGR) and preterm delivery.

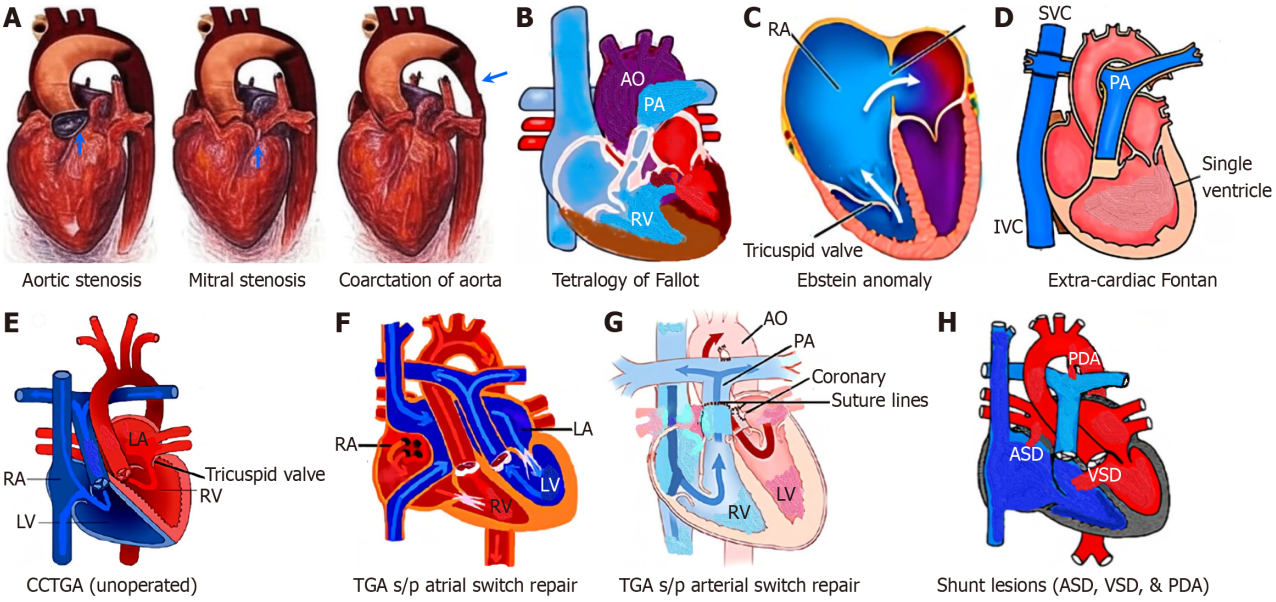

Figure 5 Adult congenital heart disease in women during pregnancy. A: Aortic stenosis, mitral stenosis, coarctation of the aorta; B: Unrepaired tetralogy of Fallot; C: Uncomplicated Ebstein anomaly; D: Extra-cardiac Fontan; E: Congenitally corrected transpositions of great arteries; F: Transposition of great arteries after Senning/mustard; G: Transposition of great arteries after arterial switch operation; H: Left to right shunt lesions (atrial septal defect, ventricular septal defect, and patent ductus arteriosus). ASD: Atrial septal defect; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; AO: Aorta; PA: Pulmonary artery; RV: Right ventricle; RA: Right atrium; LV: Left ventricle; LA: Left atrium; SVC: Superior venacava; IVC: Inferior venacava; TGA: Transposition of the great arteries arteries.

CoA: Women with unrepaired CoA, classified as mWHO class IV, are at risk for aortic dissection at the site of narrowing, placental hypoperfusion, and IUGR; therefore, pregnancy is contraindicated[6]. Before conception, it is recommended that patients undergo special imaging studies, such as computed tomography or cardiac magnetic resonance imaging (CMR), to assess aortic structure and dimensions. Consequently, unrepaired CoA or aortic aneurysm (aortic diameter > 5 cm) should be repaired before proceeding with pregnancy. According to the mWHO stratification, those with repaired CoA but having residual coarctation (> 20 mmHg gradient or aortic lumen < 1.2 cm) and aneurysm at the prior coarctation site fall into mWHO classes II and III. The primary concern for women with a history of prior CoA, even after repair, is the development of hypertension (30%) and preeclampsia during pregnancy[32,33]. Aspirin 81 mg daily beginning in the second trimester given increased risk of pre-eclampsia is recommended. During pregnancy, close BP monitoring should be conducted at least every trimester with careful measurement of all four extremities. Labetalol, nifedipine, and methyldopa are the preferred medications for managing hypertension[30]. During the second trimester, it may be necessary to reduce the dosage as a 5-10 mmHg decrease in systolic BP commonly occurs due to pregnancy-related physiological changes. Diuretics should be used cautiously as they can lead to placental hypoperfusion. Salt restrictions for pregnancy-related hypertension are not recommended because of concerns for poor fetal growth[34]. Hypertensive crises may require intravenous sodium nitroprusside or nitroglycerin. For cases of refractory BP control or maternal or fetal hemodynamic compromise, invasive interventions such as percutaneous stenting of re-coarctation sites may be considered[35].

Mechanical valve for valvular ACHD: Patients with a history of valve replacement who are hospitalized for delivery face a significant risk of adverse maternal and fetal events, irrespective of the valve type. Studies indicate that outcomes for mechanical heart valves and bioprosthetic heart valves are comparable[36]. Managing anticoagulation in women with mechanical valves is challenging due to the risk of valve thrombosis, and warfarin can cause teratogenic effects, particularly during weeks 6-12 of pregnancy. The risk to the fetus depends on the dose of warfarin, with lower risks observed when the daily dose is ≤ 5 mg before conception. Warfarin is preferred if the dose requirement is < 5 mg/day during the second and third trimesters[36]. Heparin and low molecular weight heparin (LMWH) can be used during the first trimester. Careful management of LMWH is crucial, with a peak anti-Xa target of 1.0-1.4 IU/mL taken 3-4 hours after a twice-daily LMWH dose[37]. Changes in anticoagulation regimen during pregnancy should be handled while hospitalized, providing a sense of security and reassurance. Women on warfarin should transition to LMWH or heparin at 36 weeks' gestation to minimize the risk of fetal hemorrhage and maternal bleeding during delivery. Regional anesthesia is contraindicated within 24 hours of the last LMWH dose. If labor begins while the mother is on warfarin, a cesarean delivery is advised. Administering vitamin K to the mother does not guarantee reversal of warfarin effects in the fetus.

Pulmonary stenosis

In pulmonary stenosis (PS), the increased CO during pregnancy leads to a rise in the transvalvular gradient but is typically well tolerated during pregnancy[38]. Medical optimization with diuretics to control right-sided HF is sometimes necessary. Balloon valvuloplasty may be considered in patients who remain symptomatic despite medical management. Vaginal delivery is recommended in medically optimized patients. However, it's crucial to stress the importance of

BP control, as women with isolated PS may be at increased risk for hypertensive disorder of pregnancy, underscoring the significance of this aspect[39].

Tetralogy of Fallot

For patients with unrepaired tetralogy of Fallot (TOF; Figure 5B), surgical repair is recommended before pregnancy. Pregnancy is not advised for women with unrepaired TOF whose oxygen (O_2) saturation is below 90%, due to the significant maternal and perinatal complications associated with cyanosis. However, women with repaired TOF generally tolerate pregnancy well (mWHO risk class II)[6]. However, up to 12% of these patients who had an initial repair with a transannular patch are particularly prone to severe pulmonary regurgitation (PR) and subsequent right ventricle (RV) dilation. RV dysfunction and/or moderate to severe PR are significant risk factors for right-sided HF, arrhythmia, and thromboembolism (TE)[40]. Treatment includes diuretics and afterload-reducing medications such as hydralazine. Pulmonary valve replacement may be required, although the best timing of this intervention is still a matter of debate[1]. Although uncommon, adverse maternal events can occur, often linked to LV dysfunction, severe pulmonary hypertension (PH), and significant PR with RV dysfunction[41]. Depending on the severity of symptoms and myocardial dysfunction, early delivery may be required, with potential escalation to admissions into the intensive care unit (ICU) and mechanical support. However, vaginal delivery is preferred in most women with repaired TOF except those with decompensated HF.

Valvular regurgitant ACHD

For pregnant women with mild to moderate mitral regurgitation (MR) and AR, it's important to focus on managing symptoms. Chronic mild to moderate AR and MR are typically well tolerated, but women with severe MR are at increased risk of HF, especially in the postpartum period, due to volume shifts[42]. Therefore, treatment should focus on using diuretics to maintain euvolemia, BB for HR control, and vasodilators like hydralazine and nitrates for afterload reduction[30]. Atenolol is not recommended due to the increased risk of fetal growth restriction. Renin-angiotensin-aldosterone system inhibitors are contraindicated in pregnancy due to their teratogenic effects. Labetalol, methyldopa, nifedipine, or amlodipine can be used safely for afterload reduction[30]. Patients with AR and/or MR with pre-existing symptoms or LV systolic dysfunction can progress to HF.

Pulmonic and tricuspid regurgitation (TR) are commonly associated with ACHD. TR is more frequent due to infective endocarditis or Ebstein anomaly. When there is no pre-existing right-sided HF before conception, women generally fare well during pregnancy. However, those who have undergone right-sided heart valve procedures are susceptible to atrial arrhythmias and right-sided HF, potentially necessitating diuretic therapy in the later stages of pregnancy and postpartum. Surgical intervention for regurgitant lesions is rarely required during pregnancy, except in cases of infective endocarditis complicated by valvular regurgitation due to the potentially life-threatening risks to the mother and fetus if it goes untreated. Maternal risk is largely determined by the presence of concomitant LV dysfunction or PH. Additionally, severe symptomatic TR or RV dysfunction can increase maternal risk, particularly through the development of atrial fibrillation. Vaginal delivery with epidural anesthesia and a shortened second stage of labor is advisable to minimize hemodynamic stress.

Ebstein anomaly

In women with uncomplicated Ebstein's anomaly (Figure 5C), pregnancy is often well-tolerated (mWHO risk class II)[6]. Ebstein anomaly is often associated with atrial septal defect (ASD), right atrial (RA) dilation, and Wolff-Parkinson-White syndrome. Consequently, pregnancy may lead to progressive cyanosis, TE and/or arrhythmias in women at risk. The prognosis is less favorable if RV dysfunction is already present before pregnancy. The fatal complication rate (3%-17%) correlates closely with the degree of HF and with associated left-sided valve disease or cyanosis[43-45]. It's crucial to advise against pregnancy for symptomatic patients with cyanosis and/or HF (mWHO risk class IV)[6]. Women with cyanosis (an arterial O_2 saturation < 90%) and hematocrit > 60% are indicators of a poor prognosis. Women with cyanotic ACHD face an elevated risk of miscarriage, preterm birth, fetal distress, and congenital anomalies in their children.

Fontan circulation

Fontan circulation represents a complex form of ACHD in which systemic venous blood flows passively into the pulmonary arteries without a subpulmonary ventricle[46]. Over the past two decades, most centers have transitioned to performing lateral tunnel or extracardiac conduit Fontan procedures (Figure 5D), given the long-term complications of the atrio-pulmonary Fontan approach, such as significant RA dilation, atrial arrhythmias, and increased risk for TE[47-49]. Pregnancy in women with Fontan circulation poses substantial challenges due to increased volume and pressure demands on the circuit[50]. This often leads to complications such as hepatic congestion, gastric congestion, and cardiorenal syndrome arising from renal venous congestion[51].

A comprehensive pre-pregnancy evaluation of Fontan physiology is critical and should include echocardiography, CMR, cardiac catheterization, and liver biochemical and ultrasound assessments[52]. Pregnancy is contraindicated (mWHO class IV) in the presence of severe complications like cyanosis, impaired ventricular function, atrioventricular valve (AV) regurgitation, arrhythmia, elevated Fontan pressures, protein-losing enteropathy, or plastic bronchitis[6]. Also, women with Fontan circulation face heightened risks of HF, TE, and hemorrhage during pregnancy and the postpartum period[53,54]. Expert consensus recommends therapeutic LMWH and aspirin for those with high thromboembolic risk and low-dose aspirin or prophylactic LMWH for those at lower risk[55]. Despite the complexity of management, maternal mortality during pregnancy is relatively low, and patients can often be managed effectively without significant long-term sequelae[56].

Fetal outcomes, however, tend to be less favorable. The live birth rate among women with Fontan circulation is reported at approximately 40%-50%[56]. Common complications include prematurity, IUGR, and SGA, driven by adverse hemodynamics, maternal medication effects, and the neurohormonal environment of Fontan circulation[57,58]. Additionally, BB (atenolol) is associated with risks such as IUGR, preterm birth, neonatal bradycardia, and hypoglycemia[30]. Placental abnormalities, including low weight, chorionic hematoma, and histological hypoxic changes, further contribute to poor fetal outcomes[59].

The postpartum period introduces additional hemodynamic challenges as uterine blood is auto-transfused back into circulation, and pressure on the inferior vena cava from the baby's mass is relieved. This 48-72-hour window is a critical time for monitoring, particularly in patients at risk of decompensation. Post-delivery, Fontan patients should remain in the ICU for at least 24-48 hours with close monitoring of fluid balance, HR, and BP. A thorough echocardiographic assessment before discharge is essential, focusing on Fontan conduit flow, thrombus detection, AV regurgitation, and ventricular function. TE prophylaxis should continue for at least six weeks postpartum[60]. Prolonged LMWH use is preferred to minimize the risk of severe bleeding, which can be unpredictable and difficult to manage with warfarin therapy.

Congenital systemic RV with bi-ventricular circulation

Patients with systemic morphological RV (sRV), including congenitally corrected transposition of the great arteries (ccTGA) or also called L-transposition of great arteries (Figure 5E) and dextro-transposition of the great arteries (d-TGA) with a Mustard or Senning atrial baffle repair (Figure 5F), have a high likelihood of maternal and neonatal morbidity and IUGR[61]. Pregnancy is generally well tolerated, but an sRV ejection fraction < 40% and clinical signs of HF and severe TR before pregnancy are significant risk factors for maternal complications[62]. These include maternal death, supraventricular or ventricular arrhythmias requiring treatment, HF, aortic dissection, endocarditis, ischemic coronary events, and other TE events[63].

Contrary to d-TGA after Senning and Mustard (which is no longer the preferred surgical procedure), women with a history of d-TGA and an arterial switch operation (Figure 5G), with normal LV function pre-pregnancy and normal CPET, pregnancy is tolerated relatively well (mWHO II)[64]. During preconception counseling, most women with a normal CPET should be reassured that the risk of pregnancy is low[65].

Left-to-right shunt ACHD

Left-to-right shunt lesions, such as ASD, ventricular septal defect (VSD), partial anomalous pulmonary venous return, and patent ductus arteriosus (PDA), result in increased pulmonary blood flow (Figure 5H) and are at risk of developing PH. ASD is the most common form of CHD observed during pregnancy. In contrast, undiagnosed moderate or large VSD and PDA are extremely rare. Most women with a small VSD or PDA, uncomplicated by PH, have a low risk (mWHO I) of hemodynamic deterioration during pregnancy, as these shunt lesions are highly resistant to flow[66]. Atrial arrhythmias are common in patients with a prior history of delayed ASD closure. In the rare case of marked clinical deterioration, catheter-based closure of the ASD is the first-line treatment. However, repaired atrioventricular septal defect (AVSD) with significant left AV valve regurgitation poses a higher risk of pregnancy complications (class III) and should be managed as described under MR[30,42]. Vaginal delivery is generally preferred, but cesarean delivery may be indicated in cases of severe ventricular dysfunction or hemodynamic instability. Close monitoring during the postpartum period is essential due to the significant hemodynamic changes after delivery.

Eisenmenger syndrome

Eisenmenger syndrome (ES) is a severe form of PH that arises in patients with AVSD, VSD, ASD, or PDA, leading to increased pulmonary blood flow and irreversible pulmonary vascular disease. Preconception counseling is essential for women with ES, emphasizing that pregnancy is contraindicated (mWHO class IV)[6]. This counseling involves a detailed discussion of the significant maternal and fetal risks associated with ES, including elevated maternal mortality, arrhythmias, HF, and fetal complications such as prematurity, IUGR, and stillbirth[67].

With advancements in PH treatment and new approaches to managing pregnant women during the peripartum period, maternal mortality has decreased but remains significant, ranging from 11% to 25%[68]. There have been reports of favorable pregnancy outcomes in women with ES[69]. Despite this, pregnancy remains associated with unpredictable risks and may accelerate the progression of PH. Women with PH can deteriorate at any time during or after pregnancy, necessitating that physicians inform patients about the risks so that women and their families can make informed decisions[70]. If pregnancy is continued, PH therapies need to be adjusted. It is recommended to discontinue endothelin receptor antagonists (ERA) such as bosentan, ambrisentan, macitentan, soluble guanylate cyclase stimulators such as riociguat, and oral prostaglandin receptor agonists such as selexipag due to potential or unknown teratogenicity[30,71]. Despite limited evidence, CCB (nifedipine), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), and parenteral and inhaled prostanoids are considered safe during pregnancy[30,72,73].

Delivery planning should be individualized based on the severity of PH, maternal and fetal status, and obstetric considerations. This individualized approach, which considers the unique circumstances of each patient, is a considerate and attentive way to manage the situation. Vaginal delivery is generally well-tolerated in women with well-compensated ES, but the mode of delivery should be determined in consultation with a multidisciplinary cardio-obstetrics team[74]. In some cases, cesarean section may be preferred to minimize the risk of hemodynamic changes during labor and delivery. Close monitoring should continue in the postpartum period to detect and manage any potential complications, such as HF exacerbation or arrhythmias[75]. Medications should be adjusted as the pharmacokinetics can change throughout gestation, and contraception should be discussed to prevent unplanned pregnancies in women with ongoing risks[76].

Aortopathies

Marfan syndrome: Marfan syndrome is diagnosed based on revised Ghent criteria and is confirmed by genetic testing [77]. The risk of aortic dissection during pregnancy in women with Marfan syndrome is approximately 3%[78]. Aortic size significantly influences this risk, with even those with an aortic root diameter of < 4 cm facing a 1% dissection risk. Although data is limited, it is generally advised that women with an aortic root diameter > 4.5 cm avoid pregnancy due to the heightened risk of dissection[79]. For those with an aortic root size between 4 and 4.5 cm, additional factors such as the family history of dissection and the rate of aortic growth (≥ 0.3 cm/year) are considered high-risk. Distal aortic dissection and dissection of other vessels also pose risks. Consequently, even after successful aortic root replacement, patients remain susceptible to further events in the abdominal aorta[80]. Studies on aortic growth during pregnancy in Marfan patients have shown mixed results; some indicate no significant increase, while others report growth exceeding 0.3 cm, with a partial decrease in diameter postpartum[81]. Other significant cardiac complications include progressive MR due to mitral valve prolapse, new arrhythmias, and HF resulting from ventricular dysfunction[82].

Bicuspid aortic valve: The bicuspid aortic valve is more common (2% of the population), but aortopathy associated with bicuspid aortic valve accounts for 6% of type A dissections during pregnancy[83]. The current evidence supports that hemodynamic wall stress, in combination with an underlying connective tissue disorder or genetic abnormality of the ascending aortic media, leads to bicuspid aortopathy, but overall, the risk of aortic dissection is small. There is a need for close monitoring of aortic dimensions with echocardiography or other imaging modalities to assess for aortic dilation in women planning for pregnancy[84]. Optimization of BP control during pregnancy, labor and delivery is warranted with medications, such as BB, to reduce the risk of aortic complications. Pregnancy should be avoided when the aorta diameter is > 5 cm with a pre-existing bicuspid aortic valve[6]. Careful management of chronic or gestational hypertension should include labetalol, nifedipine, and methyldopa during pregnancy.

Loeys-Dietz syndrome: Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder caused by mutations in *TGFβR1*, *TGFβR2*, *TGFβ2*, *TGFβ3*, and *SMAD3* genes[85]. It affects connective tissue and can lead to aortic dissection, with most dissections occurring in the third trimester (50%) or postpartum (33%)[86]. Vessel tortuosity in the head and neck is a hallmark finding for this disorder and may extend to the uterine vessels. Identification of women with LDS before or early in pregnancy is essential to allow for adequate surveillance of aortopathy and to ensure delivery at a tertiary care center with expertise in aortic surgery. Managing LDS during pregnancy requires a multidisciplinary approach to ensure both maternal and fetal safety. Optimization of BP control with medications, such as labetalol, nifedipine, and methyldopa, is needed to reduce the risk of aortic complications. Recent studies in LDS have not shown that vaginal delivery increases the risk of uterine rupture. Thus, vaginal delivery may be considered[87]. The ACC and ESC recommend CMR imaging for the aorta post-delivery and at six months postpartum to monitor aortopathy[6,88].

Turner syndrome: Turner syndrome (TS) is linked to a higher risk of CHD, aortic dilation, hypertension, diabetes, and atherosclerotic events[89]. Although aortic dissection is rare in TS, it occurs six times more frequently in younger individuals compared to the general population[90]. Pregnancies in women with TS, conceived with either autologous or donated oocytes, are considered high risk because of the risks of aortic dissection, especially when associated with bicuspid aortic valve and CoA. Pregnancy should be avoided if the aortic diameter index exceeds 2.5 cm/m^2. Even after aortic root surgery, patients remain at risk for type B dissection[91]. Effective BP control and diabetes management are crucial for all TS patients during pregnancy.

Vascular Ehlers-Danlos syndrome: Severe vascular complications are predominantly associated with type IV Ehlers-Danlos syndrome (EDS). Maternal mortality is notably high due to risks of uterine rupture and dissection of major arteries and veins. Consequently, pregnancy is considered extremely high risk and is generally not recommended. Women with EDS should participate in a shared decision-making process when considering pregnancy[92].

ROLE OF INVASIVE PROCEDURES

TAVR

Ideally, severe AS is identified and treated before conception. Preconception treatment options for native and bioprosthetic aortic valves include surgical aortic valve replacement (SAVR), TAVR, or a Ross procedure. During pregnancy, percutaneous balloon valvuloplasty can alleviate symptoms in native AS and may temporarily improve hemodynamics in patients with severe symptoms who do not respond to medical management. Balloon angioplasty typically serves as a palliative measure, postponing surgery until after childbirth. However, it carries the risk of significant AR and related hemodynamic instability. TAVR offers an alternative method for aortic valve replacement with lower immediate risks to both the mother and the fetus compared to SAVR.

The role of TAVR in pregnant women with AS is generally limited due to the potential for greater fetal exposure to radiation and the more critical nature of aortic valve function for the mother's overall health during pregnancy. Orwat *et al*[26] found that the peak aortic gradient of ≥ 50 mmHg before pregnancy was an independent predictor of complications during pregnancy. The development of symptoms such as dyspnea, near syncope or syncope, and arrhythmias is also an indicator of a complicated course[93]. The decision to proceed with TAVR during pregnancy should be made on a case-by-case basis, considering the potential risks and benefits to both the mother and the fetus in consultation with a cardio-obstetrics team. Fetal radiation exposure can cause miscarriage, IUGR, mental retardation, and major malformations. The risk to the fetus depends on the radiation dose and gestational age. The highest risk is during organogenesis (weeks 2-8)

and neuronal stem cell proliferation (weeks 8-14)[94]. There are anecdotal experiences of successful TAVR during pregnancy, but further research is needed to recommend TAVR as an option for the treatment of severe symptomatic AS during pregnancy[95-101]. There is limited data available in the literature on how women with a previous TAVR for severe AS or TAVR in prior SAVR will tolerate subsequent pregnancies[102].

Transcatheter pulmonary valve replacement

Like TAVR, transcatheter pulmonary valve replacement (TPVR) during pregnancy is classified as a high-risk procedure. However, it can be performed in specific scenarios where the mother's cardiac health is severely compromised by a failing RV, particularly when there is a history of prior surgical repair or intervention for RV outflow tract, such as TOF with residual PS and PR. Recently, there have been a few reported cases of successful TPVR during pregnancy[103,104]. For pregnant women with significant PS and PR who exhibit symptoms or are at risk of maternal or fetal complications, TPVR may be considered a viable alternative to surgical intervention[93]. Duarte *et al*[105] reported no major adverse cardiac events, including endocarditis or mortality, in nine pregnancies among seven women with various forms of ACHD who had undergone TPVR before pregnancy. From an obstetric perspective, it is important to note that preterm birth was common in these pregnancies, occurring in five out of nine cases[105].

MANAGEMENT OF CV COMPLICATIONS

Maternal history of ACHD increases the risk of stroke, HF, and arrhythmia during pregnancy and the peripartum period [2].

Stroke

Pregnant and postpartum women have a threefold increased risk of stroke compared to non-pregnant women of the same age, and this risk is further heightened by the presence of ACHD[106]. Physiological changes during pregnancy, including hemodynamic shifts, venous stasis, hypercoagulability, and immune modulation, contribute to this heightened risk. The immediate postpartum period presents the highest stroke risk for mothers[60,107]. Common causes of pregnancy-related strokes include TE associated with cyanotic ACHD and Fontan circulation, cervical artery dissection, cerebral venous thrombosis, cerebral vasospasm or subarachnoid hemorrhage from reversible cerebral vasoconstriction syndrome, and hypertensive intracerebral hemorrhage, often linked with posterior reversible encephalopathy syndrome [108]. Risk factors for stroke encompass migraines, hypertensive disorders of pregnancy, diabetes, infections, cerebrovascular malformations, moyamoya disease, antiphospholipid syndrome, and fibromuscular dysplasia[107,108]. Urgent neurological assessment is warranted for pregnant or postpartum women presenting with symptoms such as new-onset headache, high BP, severe pain, or focal neurological deficits. Managing high-risk cerebrovascular conditions in pregnant women demands personalized care and close monitoring by a multidisciplinary cardio-obstetrics team and neurologist. Delivery planning should focus on obstetric considerations, though cesarean delivery might be necessary for patients with recent acute stroke and elevated intracranial pressure[109]. Experiencing a stroke during pregnancy can lead to lasting health issues, making it crucial to transition postpartum care to either primary or specialty care to ensure optimal vascular health[110].

HF

HF is the most common complication among women with preexisting heart disease, regardless of the cause, whether related to valvular disorders, ventricular dysfunction, PH, or ACHD[5]. The ROPAC study identified several predictors for HF during pregnancy, including cardiomyopathy, left heart stenotic ACHD, d-TGA with Mustard or Senning operation, ccTGA, ES, Fontan, pre-existing HF, and PH[59,111]. Those with repaired TOF or pulmonary atresia with residual PS and PR, are more likely to develop right-sided HF[5,6]. Pregnancy is contraindicated in women with severe systemic ventricular dysfunction (LVEF < 30%), NYHA class III or IV)[6,112].

For pregnant women with stable HF on medications, monitoring during pregnancy includes echocardiograms every trimester and monthly after 24 weeks until delivery[113]. Drug levels should be monitored throughout pregnancy and postpartum due to changes in plasma volume. Medications such as angiotensin receptor-neprilysin inhibitors (ARNI), sodium-glucose cotransporter-2 inhibitors (SGLT2is), angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), carvedilol, statins, spironolactone, amiodarone, and atenolol should be discontinued during pregnancy due to potential or unknown fetotoxicity, and should be substituted with alternative afterload-reducing agents such as hydralazine and oral isosorbide dinitrate[30]. Selective BBs such as metoprolol and bisoprolol are favored[30]. Women with ventricular dysfunction require close monitoring throughout pregnancy and delivery at a specialized tertiary center with a cardio-obstetrics team. Patients should be instructed to rest in a lateral decubitus position. Symptomatic women may need bed rest and may require admission to the ICU.

Acute HF usually occurs in the late second or third trimester or early postpartum, often triggered by eclampsia or preeclampsia[113]. Differentiating between normal pregnancy symptoms and HF is vital. While avoiding radiation is preferable, a chest radiograph may be necessary to diagnose pulmonary edema. Regular transthoracic echocardiograms and serum NT-pro BNP help assess heart function. Treating potential triggers like hypertension or anemia is important. Loop diuretics like furosemide should be used carefully to avoid reducing placental flow[30]. Inotropic drugs like dopamine, dobutamine, or milrinone may be used if oral HF therapies are ineffective[114]. There is some concern for excessive vasodilation with milrinone in pregnancy in the setting of already decreased SVR. If HF is refractory, care should be provided at a center equipped for a ventricular assist device (VAD)[115-119]. Pregnancy is contraindicated for

women with a left VAD (LVAD), but unplanned pregnancies can still occur. In a review of nine pregnancies while on LVAD, one maternal death was reported[120]. During pregnancy, LVAD speed may need to be increased to provide adequate CO. Specific guidelines for anticoagulation for LVAD during pregnancy are not well-defined.

In select cases, pregnancy after heart transplantation can be considered[121]. Contraindications include being less than one year post-heart transplant, reduced graft function, nonadherence, presence of donor-specific antibodies, significant cardiac allograft vasculopathy, poorly controlled hypertension, diabetes, renal dysfunction, and active infections[122]. Mycophenolate mofetil and mycophenolic acid are teratogenic and should be discontinued, with azathioprine being a suitable alternative[123].

Labor induction should be based on clinical conditions, ideally after 37 weeks unless early delivery is necessary. In cases of refractory HF, early cesarean section delivery may be required. Fetal lung maturity should be addressed with corticosteroids if needed. O_2 saturation and BP should be monitored during labor, and Swan-Ganz catheterization may be used for acute HF or significant systemic ventricular dysfunction. Women should labor in the left lateral decubitus position to avoid fetal compression of the inferior vena cava, and intravenous fluids should be minimized to prevent volume overload. Post-delivery, volume status should be reassessed, and frequent clinical evaluations should continue in the postpartum period. The first 12 weeks postpartum are crucial for monitoring cardiac function, optimizing HF medications, anticoagulation, contraception, and transitioning care teams[113]. Since ARNI and SGLT2i, both carrying a class 1A recommendation in HF and offering mortality benefits[124], are unsafe for lactating women, it is important to discuss the potential cessation of breastfeeding to facilitate the rapid up-titration of GDMT for HF during the postpartum period.

Arrhythmia

According to the 2023 HRS expert consensus statement, pregnant patients with cardiac arrhythmias should be managed by a cardiac electrophysiologist[125]. Unstable arrhythmias in pregnancy should be managed with electrical cardioversion, avoiding antiarrhythmic medications in the first trimester if possible and using the lowest effective dose[31]. Amiodarone is contraindicated due to the risk of fetal thyroid and neurodevelopmental complications[30]. Supraventricular tachycardia can initially be treated with vagal maneuvers, followed by adenosine, metoprolol, and verapamil as third-line therapy[126]. Atrial fibrillation and atrial flutter can be managed with metoprolol, verapamil, and digoxin, while sotalol, flecainide, and propafenone are options if rhythm control is necessary[126]. Intravenous procainamide is used for atrial fibrillation with pre-excitation[126]. Flecainide is used during pregnancy but may cause maternal visual disturbances, prolonged QT intervals, neonatal HF at toxic levels, cholestasis, and decreased fetal HR variability[30]. Sotalol, used primarily for fetal arrhythmias, carries an increased risk of torsades de pointes due to QT prolongation [126]. ESC guidelines recommend procainamide, flecainide, or sotalol for ventricular tachycardia (VT), with electrical cardioversion for unstable VT during pregnancy[127]. Catheter ablation procedures during pregnancy should use techniques to minimize radiation exposure to as low as reasonably achievable[125]. General anesthesia is preferred over regional anesthesia for cardiac interventions performed during pregnancy. Invasive electrophysiology interventions should be carefully planned and executed with consideration for both maternal and fetal well-being.

FETAL DIAGNOSIS OF CHD IN WOMEN WITH ACHD DURING PREGNANCY

The complexity of the ACHD and whether it has been surgically repaired play crucial roles in determining the risk level of CHD in offspring[128]. Additionally, independent factors related to the cardiac and non-cardiac status of the patients, such as chromosomal anomalies in parents, cardiac treatments received during pregnancy, hypertensive disorders of pregnancy, smoking during pregnancy, gestational diabetes, and pre-pregnancy body mass index < 18.5 kg/m², also influence the outcomes[129]. First-trimester nuchal translucency screening is a significant step during routine obstetric ultrasound and can lead to a fetal echocardiogram to diagnose any CHD[130]. Babies whose parents have a chromosomal anomaly and mothers with CHD during pregnancy should have genetic counseling[131-133]. Cytogenetic fetal karyotyping was traditionally the gold standard of prenatal genetic testing, capable of detecting aneuploidy and large chromosomal rearrangements[134]. However, whole-exome sequencing (WES) has emerged as a powerful tool that sequences the entire coding region of the genome, known as the exome[135]. WES is particularly useful for identifying single-nucleotide variants, insertions, deletions, and copy number variants that may be responsible for fetal anomalies, including CHD [136]. The use of WES in prenatal diagnosis can significantly influence clinical decisions and treatment plans[137]. Prenatal diagnosis of CHD and associated chromosomal anomalies plays a crucial role in risk stratification and delivery planning. Fetal echocardiography helps predict the risk of hemodynamic compromise and identifies newborns who may require urgent cardiac interventions. This allows for the development of individualized perinatal management plans, ensuring that appropriate care is provided immediately after birth.

POSTPARTUM CARE

Figure 6 presents a holistic framework for postpartum care in women with ACHD. It highlights three domains of focus: (1) Postpartum monitoring, emphasizing the re-evaluation of cardiac function, arrhythmia surveillance, and medication optimization; (2) Obstetric risks, including considerations like maternal age, uterine rupture, prematurity, and fetal growth restrictions; and (3) Future CV risks, addressing potential complications such as hypertensive disorders, meta-

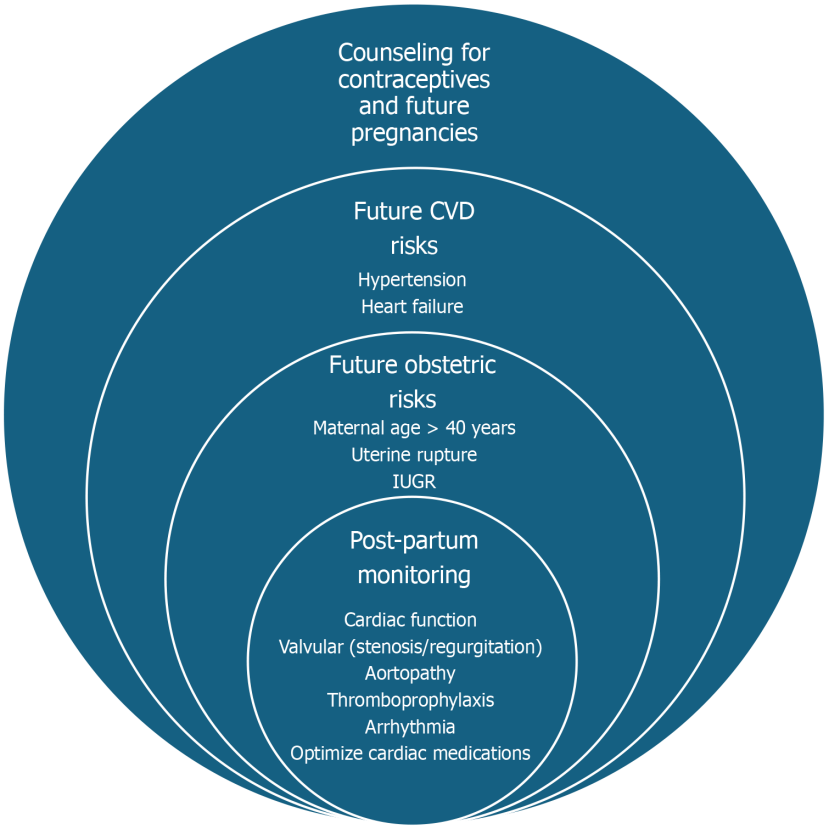

Figure 6 Postpartum care for women with adult congenital heart disease. CVD: Cardiovascular disease; IUGR: Intra-uterine growth retardation.

bolic syndrome, and HF. The foremost concern is the urgent need for counseling on contraception and future pregnancy planning. This approach underlines the importance of a multidisciplinary effort to balance cardiac health, obstetric safety, and long-term CV outcomes.

Close cardiac monitoring should be continued in the postpartum period, with specific frequency (*e.g.*, weekly for the first month, then bi-weekly for the next two months), to assess the mother's cardiac function, especially if she has a history of complex ACHD or has experienced any complications during pregnancy or delivery[138]. AHA statement recommends patient-centered holistic care and extending health coverage for one year postpartum to enhance maternal health outcomes and reduce disparities[139]. Women with ACHD should have a long-term care plan that includes regular cardiac evaluations and lifestyle modifications to reduce CV risks.

Medication management should be continued according to the mother's cardiac condition and the recommendations of her ACHD providers. This may involve adjusting or continuing medications for managing HF, arrhythmias, TE prophylaxis, and any potential drug interactions with breastfeeding[30,38,71]. Many medications, especially for HF, such as ACEi, ARB, ARNI, atenolol, statins, amiodarone, spironolactone, and NSAIDs, are contraindicated as these drugs are secreted in breast milk and can cause adverse effects in neonates[30]. A comprehensive resource for information on the safety of medications during lactation is available from the National Library of Medicine[140]. Discuss contraception options early in the postpartum period to prevent unintended pregnancies, which can pose significant risks for women with ACHD[141,142].

Emotional support: Women with ACHD often experience an increased prevalence of mental health issues such as depression, anxiety, or posttraumatic stress disorder related to complicated pregnancy or birth experiences[143]. Routine mental health screening, counseling, and support are essential components of care for women with ACHD[144]. If these mental health challenges go undetected and untreated, they can have significant consequences on the mother's well-being, her ability to parent, and consequently, on the cognitive and emotional development of her infant.

MANAGEMENT OF CONTRACEPTION FOR WOMEN WITH ACHD

Managing contraception for women with ACHD requires careful consideration of the individual patient's cardiac anatomic and physiologic status, reproductive goals, and potential risks associated with different contraceptive methods [141,142]. A thorough assessment of the patient's cardiac function, exercise tolerance, and risk factors for TE should be performed to guide the selection of an appropriate contraceptive method[145]. Women with ACHD should receive comprehensive counseling and education about the different contraceptive options available, their benefits, risks, potential interactions with cardiac medications, and the risk of unplanned pregnancy[145-147]. Combined hormonal contraceptives are generally considered high-risk for TE. However, they are still at a lower risk compared to pregnancy, so it's important

to weigh the risk/benefit ratio and establish another highly effective method of contraception before discontinuing[145-147]. Non-hormonal contraceptive methods, such as barrier methods (*e.g.*, condoms, diaphragms), copper intrauterine devices, or permanent methods (*e.g.*, tubal ligation), may also be considered in women with ACHD, particularly if hormonal methods are contraindicated or not preferred[145-147]. Highly effective contraception is recommended to prevent pregnancy in women with PH. Although progestin-only pills and medroxyprogesterone acetate injections are safe, they are less effective than long-acting, reversible, and permanent contraceptive options. ERA medications may decrease the potency of hormonal contraceptives[71]. If prescribed to women of childbearing age, dual contraceptive techniques with a mechanical barrier are recommended[30]. Finally, emergency contraception can be considered for instances of unprotected intercourse. Options include a single dose of levonorgestrel (which delays ovulation) or progesterone receptor modulators like mifepristone and ulipristal. These methods are generally considered safe for women with ACHD. However, there may be an interaction between warfarin and high-dose levonorgestrel, so monitoring of the INR is advised[147].

IDENTIFYING AREAS OF IMPROVEMENT

Pfaller *et al*[148] have found that provider-related factors are responsible for nearly three-quarters of preventable events in maternal and fetal outcomes in women with ACHD. These included accurately identifying and appropriately stratifying ACHD, as well as promptly recognizing and responding to worsening clinical status. This finding indicates that enhanced education of healthcare providers on cardiac risk stratification during pregnancy can significantly reduce adverse events. Davis *et al*[149] highlighted the necessity for establishing the foundational elements of cardio-obstetrics training. Their proposed framework for training encompasses traditional levels I, II, and III, mirroring competency structures in other cardiology subspecialties. The significant gaps in knowledge regarding how pregnancy influences ACHD and vice versa emphasize the urgent need for more comprehensive research on how ACHD workforce availability influences outcomes for women during pregnancy[150]. A study analyzed the workforce for both pediatric and adult congenital cardiology, emphasizing the need for more trained providers from minority populations in the US to improve disparity in the ACHD workforce[151].

Pregnant women with ACHD are more likely to undergo cesarean delivery, which increases the risk of infection and hemorrhage. Easter *et al*[152] have reported that planned vaginal births for patients with maternal cardiac disease, offering vaginal delivery with assisted second stage, when necessary, resulted in similar cardiac outcomes but lower rates of postpartum hemorrhage compared to cesarean deliveries. These findings suggest that obstetricians should consider reducing cesarean delivery rates for women with ACHD.

Socioeconomic factors also contribute to adverse maternal outcomes[153]. In the United States, non-Hispanic Black pregnant women tend to experience worse outcomes compared to others[154]. In general, women with ACHD face many public health issues, such as disparities and inequity in care towards racial and ethnic groups, and increasing healthcare costs[155]. The AHA supports federal public policy and legislative actions to improve health outcomes for these vulnerable groups during pregnancy[156]. The Further Consolidated Appropriations Act of 2024 allocated additional funding to the CDC, HRSA, NIH, and SAMHSA to enhance maternal health and reduce the nation's high maternal mortality rate, which has been advocated by ACOG committee since 2021[157]. This includes financial support, health insurance coverage, and subsidies for healthcare services, medications, and medical equipment for women with ACHD during pregnancy[158,159].

Studies have shown that increased diversity in the healthcare workforce, including those who provide care for women with ACHD, leads to improved critical thinking and improved scientific research output[160]. However, like many medical specialties, the ACHD subspecialty has an underrepresentation of women and ethnic minorities relative to their proportions in the United States[161]. Also, there has been a wide disparity in the geographic distribution and access to care by ACHD providers[162].

Restrictions on abortion and abortion pills can have significant implications for pregnancy outcomes in women with ACHD and increase total maternal mortality in the United States[163,164]. On June 24, 2022, the Supreme Court of the United States ruled that the constitution does not confer a right to abortion in Dobbs *vs* Jackson Women's Health Organization[165]. This landmark decision overturned the precedent set by United States Supreme Court[166], thus ending federal protection for abortion rights and allowing individual states to dictate abortion access for their residents. Under a complete abortion ban, one model predicts a 53.7% increase in single-ventricle cardiac defects, an additional 9 cases per 100000 Live births[167]. This increase would result in an extra 531 neonatal heart surgeries, 16 heart transplants, 77 extracorporeal membrane oxygenation utilizations, and 102 neonatal deaths annually in the United States. Women with hemodynamically significant ACHD (mWHO class III and IV) usually have high-risk pregnancies that pose significant health risks, including increased strain on the heart, risk of HF, arrhythmias, and death[168]. Overall, abortion bans will significantly affect both pregnancy-related and non-obstetric outcomes for pregnant women, such as mental health[169]. The inability to access abortion in high-risk situations could lead to significant psychological stress, anxiety, and trauma for women with ACHD, particularly if women are forced to continue a pregnancy that jeopardizes their health[170,171]. If the United States bans abortion, maternal mortality associated with pregnancy-related causes is expected to increase 21%, with Black women incurring a 33% increase compared with 13% among White women[172]. Findings demonstrate that black women at all educational levels and those with fewer years of education disproportionately experience adverse birth outcomes associated with restrictive abortion policies. Restrictive abortion policies may compound existing racial/ethnic, socioeconomic, and intersecting racial/ethnic and socioeconomic perinatal and infant health inequities[173]. Policymakers and healthcare systems would need to address these issues to mitigate the potential

harm to women with ACHD[174]. This vulnerable population may face increased health risks if they are unable to make informed decisions about their pregnancies based on their individual health needs.

FUTURE DIRECTIONS

Emerging evidence underscores the importance of innovative therapies, such as targeted pharmacological agents and minimally invasive interventions, as well as the development of improved screening methods to identify high-risk patients before ACHD worsens[175].

Non-invasive imaging, telemonitoring, and telehealth

Non-invasive imaging techniques, such as speckle-tracking echocardiography, strain imaging, three-dimensional echocardiography, and CMR, continue to advance and may provide more detailed information about the systemic ventricular function of pregnant women with ACHD, allowing for more accurate risk assessment and management decisions. There have also been notable advancements in fetal cardiac therapy, including transplacental pharmacologic treatments, enzyme replacement therapy, and fetal surgery for specific rare and severe CHD conditions such as hypoplastic left heart syndrome and others[176,177]. Advances in remote monitoring technologies, such as wearable devices and telehealth, provide opportunities for more frequent and convenient monitoring of women with ACHD during pregnancy[178]. Wearable devices, including mobile cardiac telemetry monitoring (MCT), enable earlier detection of potential arrhythmia and facilitate prompt intervention. Rodriguez and colleagues[179] researched to explore whether arrhythmia identified through 24-hour MCT monitoring, either before or early in pregnancy, was linked to negative pregnancy outcomes. Among the 141 pregnancies examined, 17% showed positive MCT findings, underscoring the high prevalence of arrhythmias in the ACHD population. Adverse cardiac outcomes were observed in 11% of the pregnancies, with clinically significant arrhythmia events occurring in 3.5%. Recent innovations in telemonitoring technology have expanded capabilities to assess critical metrics, including HR and its variability, O_2 saturation, CO, and SVR[180]. These enhanced evaluations are particularly valuable for complex ACHD patients experiencing chronic low O_2 levels and BP, as they allow for early detection of potential decompensation and timely intervention[181]. Furthermore, telehealth facilitates routine check-ups and specialist consultations, minimizing the need for in-person visits and improving access to care during pregnancy[182].

Patient education and empowerment

Greater emphasis on patient education and empowerment may become a cornerstone of care for women with ACHD, empowering them to take an active role in their care and make informed decisions. This may involve providing comprehensive education on ACHD, its impact on pregnancy, self-care strategies, and supporting patients in shared decision-making processes related to their care during pregnancy[183].

Role of father

Men can significantly influence supporting and advocating for women during their pregnancy, as they have a critical responsibility in child development[184]. In the mother-and-child dyad, the father's role often takes a backseat. Fathers, however, can serve as essential allies in creating better outcomes for mother and baby, and addressing their needs along the way can improve a family's overall well-being. The importance of family for CV health promotion, focusing on (1) Mutual interdependence of the family system; (2) Shared environment; (3) Parenting style; (4) Caregiver perceptions; and (5) Genomics, contributes to overall improvement in CV health[185]. Family-based approaches that target caregivers and children encourage communication among the family unit and address the structural and environmental conditions in which families live and operate are likely the most effective approaches to promote women's CV health[186].

CONCLUSION

Many women of childbearing age with ACHD now look forward to successful pregnancies and positive outcomes. However, these women still face a higher risk of cardiac complications during pregnancy and the postpartum period. It is crucial to tailor the management of these pregnancies based on the patient's specific ACHD, current health status, and other existing comorbidities. Managing pregnancies in women with ACHD should involve a multidisciplinary cardio-obstetrics team, comprehensive patient education beginning with preconception counseling and contraception management, and vigilant monitoring throughout pregnancy and the postpartum period. This approach aims to enhance long-term maternal health and reduce the risk of complications. Furthermore, it is important to address socioeconomic disparities among minority women with ACHD for healthcare access during pregnancy. This requires a multifaceted approach, advocating for policy changes that address disparity in healthcare and implementing targeted interventions to support minority women with ACHD. Future advancements in the care of pregnant women with ACHD should prioritize innovative therapies and refined screening strategies to enable the early detection of complications. By integrating predictive tools and personalized management approaches, healthcare providers can proactively mitigate risks, ultimately improving maternal and fetal outcomes.

FOOTNOTES

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REVIEW

Diagnosis and treatment options for sinus of Valsalva aneurysms: A narrative review

Kevan English

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Abstract

Sinus of Valsalva aneurysm (SoVA) is a rare cardiac defect that may be congenital or acquired. It is characterized by abnormal dilatation of the aortic root due to a weakened elastic lamina at the junction of the annulus fibrosus and the aortic media. SoVAs are present in approximately 0.09% of the general population and comprise up to 3.5% of all congenital cardiac defects. It is usually found incidentally on cardiac imaging, with a higher incidence observed in the Western populations and a male-to-female ratio of 4:1. A transthoracic two-dimensional echocardiogram is the initial diagnostic test of choice, which may reveal the characteristic "windsock deformity" that clinches the diagnosis. Other imaging modalities, such as transesophageal echocardiography and cardiac computed tomography angiography, help provide more extensive details of the aneurysm and its adjacent structures. Management options for ruptured and unruptured SoVA include surgical repair or transcatheter closure, which serves as a game-changing development in treatment. This article aims to provide background information on the epidemiology, pathophysiology, diagnosis, and recent advancements over the past decade in the management of SoVAs.

Key Words: Sinus of Valsalva aneurysm; Bicuspid aortic valve; Echocardiography; Cardiac computed tomography; Cardiac magnetic resonance imaging; Ventricular septal defect; Pulmonary stenosis; Atrial septal defect

Core Tip: Sinus of Valsalva aneurysm is a rare cardiac defect defined as an abnormal dilatation of the aortic root. This arises due to a weakened elastic lamina at the junction of the annulus fibrosus and the aortic media. Echocardiography is the first-line imaging of choice for diagnosis. Definitive management includes surgery. However, transcatheter closure is a newer minimally invasive technique that is now increasingly preferred over traditional surgical approaches in the treatment of both ruptured and unruptured aneurysms.

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INTRODUCTION

Sinus of Valsalva aneurysm (SoVA) is an uncommon cardiac defect characterized by an abnormal dilatation of the aortic root between the sinotubular ridge and the aortic valve annulus[1]. They can be congenital or acquired and are more common among men than women, with a reported incidence of 0.09% in the general population[1,2]. Congenital cases are commonly associated with other cardiac anomalies, such as bicuspid aortic valves (BAVs), pulmonary stenosis (PS), and ventricular septal defects (VSDs)[3,4]. Inherent deficiency of the elastic lamina in the affected aortic sinus is the common underlying mechanism of most SoVA[5]. Over time, this structural abnormality under long-standing pressure leads to progressive aneurysmal dilatation and eventual rupture[5,6].

SoVAs commonly originate from the right coronary sinus in 70% to 90% of cases, followed by the noncoronary sinus (10%-25%) and the left sinus (< 5%)[7]. Patients may present asymptomatic or symptomatic with symptoms suggestive of acute rupture, such as dyspnea, chest pain, cardiac murmurs, and palpitations[7,8]. Unruptured aneurysms are usually clinically silent and are commonly discovered incidentally on echocardiography or cross-sectional imaging performed for other reasons[7-9].

Treatment of SoVA has evolved over the last decade. Although surgical repair remains the definitive management option, transcatheter closure (TCC) is a minimally invasive technique that has emerged in the previous two decades[10]. This procedure treats both ruptured and unruptured aneurysms and has expanded the range of nonsurgical options for patients with SoVA[10,11]. In this article, we provide a narrative review of SoVA and its epidemiology, pathophysiology, diagnosis, and management.

EPIDEMIOLOGY

SoVAs are extremely rare, occurring in approximately 0.2% to 0.9% of patients undergoing cardiac surgery[5,12,13]. These aneurysms constitute up to 3.5% of all congenital cardiac anomalies, with an even lower reported incidence of 0.09% in the general population[14-16]. Due to its rarity, many cases of SoVAs remain clinically silent until an adverse event such as rupture occurs[17]. Congenital SoVAs typically occur in younger people and are 4 times more likely in men compared to women, with a higher reported incidence in the Western population[18,19]. This higher incidence in Western groups suggests a genetic predisposition[18-20].

Acquired SoVAs, in contrast, typically occur in older individuals, reflecting the additive effect of atherosclerosis or other risk factors such as infective endocarditis (IE), syphilis, vasculitis diseases, or trauma[21,22]. These aneurysms originate from the right coronary sinus in up to 90 of cases, followed by the noncoronary sinus (10%-25%) and the left sinus (< 5%)[3,23-25]. There is a significant increase in morbidity and mortality if ruptured SoVA occurs and remains untreated, owing to 1-year life expectancy[26].

ETIOLOGY AND RISK FACTORS

As mentioned above, SoVAs can be congenital or acquired[27]. Congenital SoVAs develop due to the absence of elastic lamina in the wall of the affected sinus, leading to an enlargement of the aortic root between the sinotubular ridge and the aortic valve annulus[28,29]. These aneurysms are frequently associated with other congenital heart anomalies such as BAV, VSD, and PS[30-32]. In fact, VSDs are present in up to 60% of cases[33]. Other associations include coarctation of the aorta, aortic insufficiency, atrial septal defect (ASD), and other rare coronary artery anomalies[34,35]. Aneurysmal dilatation of the sinus of Valsalva can occur due to connective tissue weakness in disorders such as Marfan syndrome, Ehler-Danlos syndrome, and other connective tissue diseases[36,37].

Acquired SoVAs, in contrast, occur due to several factors that diminish the strength of the aortic wall over time and are similarly associated with connective tissue pathologies[38-40]. Chronic changes of atherosclerosis leading to cystic media necrosis can weaken the intimal layer of the aorta, leading to SoVAs[41]. Infectious etiologies are well-known risk factors for the aneurysm, which include syphilis, tuberculosis, and IE[42]. Additionally, inflammatory conditions that damage

the proximal aorta, including inflammatory aortitis and Takayasu arteritis, have been implicated as causes of SoVA[43]. Chest trauma and iatrogenic injury during aortic valve replacement surgery have also been reported as secondary mechanisms of acquired SoVA[43-45].

PATHOPHYSIOLOGY

The pathophysiology of SoVA commonly occurs due to a complex interplay of physiological and anatomical factors, which leads to the creation and potential rupture of the aneurysm[5,46]. SoVAs occur at the three dilated sections of the aortic root area between the aortic valve annulus and the sinotubular junction[47]. These sections are termed the sinuses of Valsalva, which are normally reinforced by elastic lamina, which a thick fenestrated layer of elastin that provides structural integrity to the aortic wall[48]. The lack or defect in the elastic lamina at the sinuses, particularly at the junction of the aortic media and the annulus fibrosus, leads to the formation of SoVAs[49]. In congenital cases, the anomalous development of the bulbus cordis during embryogenesis results in a structurally weakened aortic wall, giving rise to aneurysmal dilatation[50]. Congenital SoVAs are commonly associated with other heart defects such as BAV, VSDs, ASDs, and PS[50,51].

Acquired SoVAs occur due to chronic degenerative changes of the aortic wall[52]. These changes arise due to several factors, including atherosclerosis, connective tissue disorders, and aging, leading to progressive weakness and an increased risk of aneurysmal formation[51-53]. Infectious etiologies such as IE and syphilis lead to inflammation and scarring of the aortic wall, increasing susceptibility to aneurysm formation[54,55]. Similarly, inflammatory conditions such as vasculitis can cause chronic inflammation and structural changes, leading to SoVAs[56]. Complications from cardiac surgeries and trauma can lead to physical damage to the aortic wall, which predisposes to the formation of aneurysms and rupture[57]. The aortic root is predisposed to massive hemodynamic stress due to high-pressure blood flow from the left ventricle. This stress is more pronounced at the sinuses of Valsalva, where the aortic valve cusps attach. The absence of the elastic lamina or prolonged stress in this area significantly increases the risk of aneurysm formation and rupture[58].

CLINICAL IMPLICATIONS

The most feared complication of SoVA is rupture[56-58]. These aneurysms typically enlarge over time, which leads to thin wall rupture, causing blood to spread to the nearby pericardial space or adjacent cardiac chambers, leading to heart failure and hemodynamic instability[59]. Depending on the aneurysm's physiologic location and function, it can present significant clinical consequences in both the rupture and unruptured state. Rupture of the right and noncoronary sinuses commonly results in communication between the right ventricular outflow tract and the aorta or the right atrium and the aorta[60,61]. This rupture, as a result, is susceptible to creating left-to-right shunts, which can lead to right-sided heart failure and right ventricular overload[60-62]. In contrast, rupture of a left SoVA is clinically less significant. This commonly results in communication to the left ventricular outflow tract and the left atrium[63].

Ruptures commonly occur between 20 and 40 years, with occasional outliers in late adulthood and early infancy[64]. In conjunction with the size and location, the speed at which rupture occurs is the major determinant of prognosis[65]. The right ventricle is the most common location of rupture, followed by the right atrium[66]. Historically, rupture across the interventricular septum has been associated with left ventricular outflow tract obstruction[65-67].

The size of SoVAs also has severe implications on clinical outcomes. Large SoVAs serve as a nest for thrombus formation[68]. Major coronary arteries have been occluded by SoVAs with thrombus formation, leading to ischemic heart disease. SoVAs in both the ruptured and unruptured states can be complicated by aortic regurgitation (AR), resulting in volume overload and heart failure[69]. AR as a complication occurs in up to 50% of patients with SoVAs[8,70]. For this reason, aortic valve replacement is usually done in conjunction with operative repair of the aneurysm at the time of surgery[71,72].

HISTORY AND PHYSICAL EXAMINATION

The clinical history of patients with SoVA is highly dependent upon whether the aneurysm is ruptured or unruptured. Patients with unruptured aneurysms are typically asymptomatic. The condition is frequently discovered incidentally in these patients while undergoing imaging for other reasons[73,74]. Symptomatic patients commonly express chest pain, dyspnea, and palpitations[75]. In cases where SoVA has ruptured, the history may include severe symptoms such as sudden onset chest pain, syncope, and severe shortness of breath. Patients may also report a history of syphilis, IE, cardiac surgery, and any other condition that predisposes them to SoVAs[76].

Physical examination is usually clinically unremarkable in asymptomatic patients. Patients with ruptured SoVAs typically have key examination findings such as murmurs. Diastolic murmurs indicate classic AR due to the aneurysm's effect on the aortic valve[77]. Continuous murmurs can be heard if communication exists between the aorta and the right atrium or ventricle[78]. In cases of acute rupture, additional objective findings may include hypotension, hypoxia, and tachycardia.

DIAGNOSIS

In conjunction with physical examination, the diagnosis (Figure 1) of SoVAs usually requires imaging. These imaging modalities are as follows (Table 1).

Echocardiography

Echocardiography has been the traditional first-line imaging study to detect SoVAs[79,80]. A transthoracic echocardiogram is routinely performed first in cases of suspected SoVAs, although more commonly obtained for other reasons, such as heart failure exacerbation. This imaging modality can identify the aneurysm, visualize the aortic root, and detect associated anomalies such as an ASD, VSD, or a BAV[81]. For further investigation on transthoracic echocardiogram findings, a transesophageal echocardiogram (TEE) is usually performed, which provides a more detailed anatomical delineation of the aneurysm's origin, which commonly appears on two-dimensional imaging as a thin-walled mobile structure that is circular in the short axis[82-84]. This structure commonly protrudes from above the plane of the coronary artery origins into an adjacent cardiac chamber, which produces a classical appearance known as a "windsock" deformity with enlargement during systole[84,85].

TEE also allows physicians to observe the filling of the aneurysm with color flow Doppler[86]. The additional use of contrast may help differentiate ruptured *vs* unruptured aneurysms and aid in visualizing the left-to-right shunt[86,87]. Spectral Doppler allows quantification of flow velocity and direction, where rupture into a cardiac chamber with subsequent shunting commonly yields a constant flow from the aorta to the lower pressure chambers through systole and diastole[88]. It is essential to recognize this pattern as it allows differentiation from other intracardiac shunts, such as VSDs[88,89].

Computed tomography

Cardiac computed tomography (CT) offers high-resolution images of the sinuses of Valsalva and provides quality images of the aorta[90]. This modality can delineate the morphology and size of the aneurysm and serve as a valuable tool for assessing cardiac and vascular structures in preparation for surgery[90,91]. Newer cardiac CT imaging, such as electrocardiogram gated angiography CT, can provide high-spatial resolution images of the aortic root[7]. This is an acquisition technique to obtain high-quality scans void of pulsation artifacts[7,92]. Electrocardiographic-gated CT offers several advantages to echocardiography in nonemergent situations. These include gaining an unrestricted field of view and obtaining multiplanar reformations to provide advanced anatomic delineation while assessing the coronary arteries[93,94]. Cardiac CT still possesses lower temporal resolution than magnetic resonance imaging (MRI) and cannot provide flow information, making CT inferior to MRI for valvular assessment[95].

MRI

MRI can provide a comprehensive assessment of cardiac morphology and is the gold standard technique for the evaluation of biventricular function[96]. It is considered the imaging study of choice, particularly in patients with infectious etiology, as a cause[96,97]. The saccular aneurysm can often be seen arising from one of the sinuses and protruding into an adjacent cardiac chamber. MRI has a higher temporal resolution than CT and offers excellent soft tissue contrast and anatomical delineation[98]. When used with multiplanar sequencing, it can further evaluate intracardiac shunts in ruptured SoVAs[99]. Although considered the gold standard for diagnosis, it is not required in cases where other imaging studies have already given the pertinent anatomic and physiologic details in conjunction with the diagnosis.

Cardiac catheterization

Angiography is not commonly used to diagnose SoVAs; however, it can provide detailed images of the coronary arteries and the aortic root[95]. Catheterization is particularly useful in patients with a planned surgical intervention and may aid the assessment of the hemodynamic impact of the aneurysm[95]. Patients who are at intermediate or high risk for coronary artery disease commonly undergo angiography to assess possible bypass grafting at the time of diagnosis[100,101].

MANAGEMENT

Medical management

For unruptured SoVAs, medical management is a temporary option for patients until definitive surgical intervention is possible. Medical therapy alone is insufficient as the optimal treatment for unruptured SoVAs. Management includes a serial echocardiogram to assess aneurysm morphology and size. In addition, blood pressure control is essential. Medications such as beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be used to lower blood pressure to the normal range and reduce aortic wall stress[102]. Patients should also be advised to limit activities that may increase intrathoracic pressure and precipitate rupture, such as heavy lifting and strenuous exercises[103]. In cases of acute rupture, medical stabilization with intravenous fluids and blood pressure support should be administered while managing heart failure or shock symptoms until surgical repair can be done.

Table 1 Comparison table of noninvasive imaging modalities used in the diagnosis and assessment of sinus of Valsalva aneurysms

Imaging modalities	General information	Strengths	Limitations
TTE	The first imaging modality of choice for diagnosis of SoVA	Possess > 90% accuracy for detecting SoVA. It is additionally safe, cost-effective, portable, and more widely available	Can sometimes incorrectly detect rupture site
TEE	Required as additional imaging in up to 25% of cases to further characterize the anatomy of the sinuses and their surrounding structures	Possesses better acoustic window and higher resolution, which facilitates more accurate characterization of the aneurysm and its surrounding structures	Contraindicated in patients with esophageal disease including known stricture, varices, diverticula, or tumors
ECG-gated MDCT	An acquisition technique that triggers a scan during a particular portion of the cardiac cycle	Provides high spatial resolution, elimination of motion artifacts, and improved temporal resolution in the nonemergent setting. Additionally, gated CT's ability to obtain multiplanar reformations provides superior anatomic delineation and can simultaneously assess the coronary arteries	More cost prohibitive. Additionally, retrospective ECG gating is needed to assess ventricular function and valvular motion, which carries a high radiation burden
Cardiac MRI	Plays an important role in SoVA assessment and is particularly important in the assessment of biventricular function	Gold standard imaging technique for SoVA due to its lack of ionizing radiation, better temporal resolution, ability to quantify ventricular function and aortic regurgitant fraction, and provides an assessment of wall motion abnormalities	More cost prohibitive

TTE: Transthoracic echocardiogram; SoVA: Sinus of Valsalva aneurysm; TEE: Transesophageal echocardiogram; ECG-gated MDCT: Electrocardiographic-gated multi detector computed tomography; CT: Computed tomography; ECG: Electrocardiogram; MRI: Magnetic resonance imaging.

Surgical management

Surgical repair is recommended for both ruptured SoVAs and SoVAs with associated intracardiac abnormalities such as VSD, PS, or significant AR[5,104,105]. Surgical intervention should also be considered for large SoVAs and patients with symptomatic unruptured aneurysms[106]. The main goal of repair is to prevent rupture and restore normal aortic and cardiac function. Although specific guidelines regarding SoVA repair are yet to be established, it is generally accepted to follow the abdominal aortic aneurysm algorithm[107]. According to the 2010 American Guidelines on Thoracic Aortic Disease, surgical repair should be considered in those with aneurysms > 5.5 cm, > 5 cm in patients with BAVs, > 4.5 cm in the setting of connective tissue disease, or a growth rate of more than 0.5 cm per year[108].

All surgical repairs are done with cardiopulmonary bypass and cardioplegic arrest[109]. Several operative approaches are available. However, the choice is determined by the size of the aneurysm, aortic valvular pathology such as aortic insufficiency, the cardiac chamber involved, and the associated intracardiac anomaly such as a VSD[110,111]. The primary operative approaches include through the cardiac chamber where the aneurysm has ruptured, through the aortic root *via* an aortotomy, or a combination of both, including an aortotomy and an incision into the involved cardiac chamber. Closure techniques include primary and patch closure[112]. Primary closure is commonly used for the repair of small SoVAs, while patch closure is preferred in the repair of larger SoVAs[112,113]. The use of primary closure in large SoVAs can distort the aortic sinus, resulting in valve incompetence or excessive tissue tension at the site of repair, which may increase the risk of recurrent rupture in the future[112-114]. Surgical repair overall has an operative mortality rate of up to 3.6%, with survival rates of close to 90% at 15 years[5,112].

TCC

TCC is a newer minimally invasive technique that is used to treat both ruptured and unruptured SoVAs[115]. This is an alternative approach to open heart surgery and is particularly useful in patients who are high-risk surgical candidates, including those who are older and patients with multiple comorbidities[115,116]. Clinical indications for TCC include both symptomatic and asymptomatic unruptured aneurysm and ruptured SoVAs causing heart failure or hemodynamic instability[115-117].

TCC offers several advantages, including avoiding open heart surgery, especially in high-risk surgical candidates. This avoidance reduces surgical risk and shortens hospital length and recovery time[118]. Several studies have demonstrated high success rates for TCC, resulting in effective aneurysm occlusion and relief of symptoms[118,119]. Complications such as residual shunt or embolization and device malposition are relatively low and can be treated with rapid intervention[120,121]. With the advancements in device technology and procedural techniques, TCC is becoming increasingly preferred over the traditional surgical approaches in managing SoVA. A comparison of treatment approaches with their respective advantages and disadvantages can be seen in Table 2.

Patient selection criteria for TCC

Patient selection criteria should be carefully considered prior to intervention for SoVA. Xiao *et al*[122] consider patients to be candidates for TCC if they meet the following: A bodyweight exceeding 10 kg, if the right or non-coronary sinus is the origin of the defect rupturing into the right atrium or ventricle, if the defect size is < 10 mm, if the ruptured SoVA does not involve the aortic valve has > 7 mm distance from the annulus of the aortic valve, if surgery is needed in the absence of other cardiac defects, and if a gap of > 5 mm exists between the ostium of the right coronary sinus and the ruptured

Table 2 Comparison table of treatment options for sinus of Valsalva aneurysms

Interventions	Recommendations	Advantages	Disadvantages
Medical management	Insufficient for definitive treatment. Blood pressure control with antihypertensives such as angiotensin-converting enzyme inhibitors, beta-blockers, or calcium channel blockers to reduce aortic wall stress should be used as a temporary measure until definitive surgical repair or transcatheter closure can be done	Reduces the chances of rupture for cases of unruptured SoVAs	Not definitive treatment
Surgical repair	Surgery remains the definitive treatment for SoVAs. Recommended for symptomatic, large, or rapidly progressive aneurysms and all ruptured aneurysms. The 2010 American Guidelines for Thoracic Aortic Disease recommend considering surgical repair for aneurysms greater than 5.5 cm, greater than 5 cm in patients with BAVs, greater than 4.5 cm in the setting of connective tissue disease, or a yearly growth rate that exceeds 0.5 cm	Can address concurrent cardiac issues such as VSDs or aortic valve dysfunction	Higher risk for complications such as bleeding, infection, or heart failure. Additionally, surgical repair prolongs hospital stay and recovery times compared to TCC
Transcatheter closure	Emerging minimally invasive technique used to treat both ruptured and unruptured aneurysms	Advantages include reduced surgical risks, avoiding heart surgery, and shortened hospital length and recovery times	Has potential complications such as residual shunt, embolization, or device malposition, which are generally manageable

SoVA: Sinus of Valsalva aneurysm; BAVs: Bicuspid aortic valve; VSDs: Ventricular septal defects; TCC: Transcatheter closure.

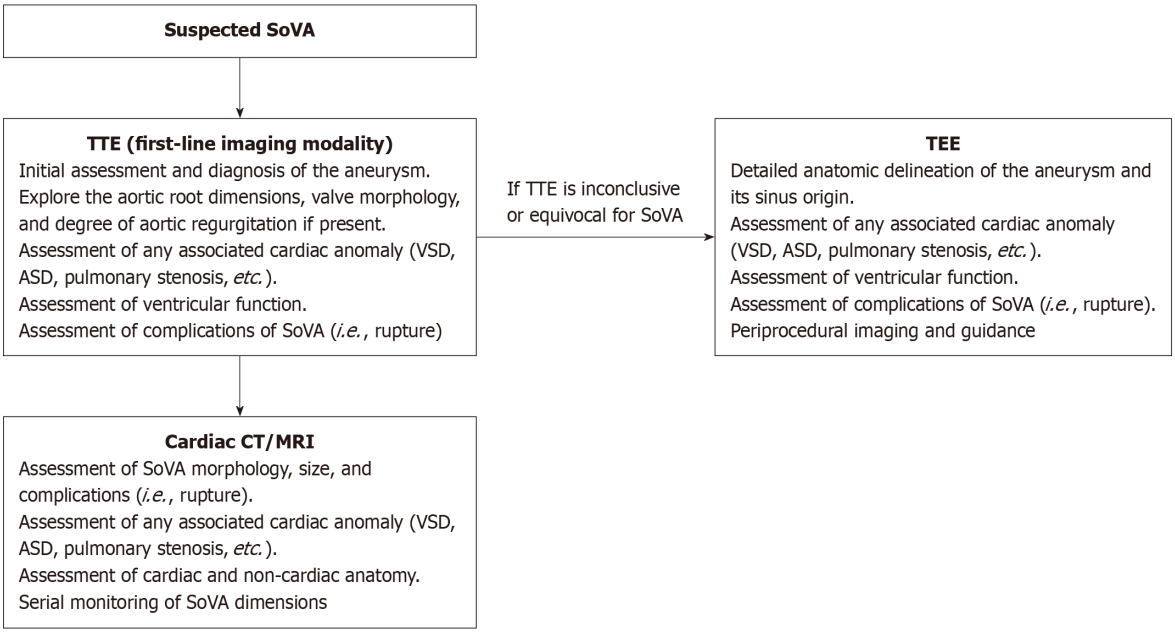

Figure 1 Proposed diagnostic algorithm for the assessment of suspected sinus of Valsalva aneurysm. Transthoracic echocardiogram is first line, followed by transesophageal echocardiogram if findings are not diagnostic or equivocal for the aneurysm. Cardiac computed tomography (CT) or magnetic resonance imaging (MRI) is used for further assessment after confirmation of diagnosis on echocardiography. MRI has a higher temporal resolution than CT and offers excellent soft tissue contrast and anatomical delineation. As such, MRI is preferred over CT for concurrent valvular assessment and flow information. TTE: Transthoracic echocardiogram; VSD: Ventricular septal defect; ASD: Atrial septal defect; SoVA: Sinus of Valsalva aneurysm; TEE: Transesophageal echocardiogram; CT: Computed tomography; MRI: Magnetic resonance imaging.

site. Liu *et al*[123] also suggested that patients with ruptured SoVAs with a European System for Cardiac Operative Risk Evaluation II score greater than 20% would benefit from catheter closure. Overall, indications for TCC *vs* surgery remain a topic of debate among the medical community. Further studies are needed to validate the inclusion and contraindications for patients with ruptured SoVAs.

TCC vs surgical outcomes

Since the initial case of TCC repair of a ruptured SoVA in 1994, evolving evidence, mostly in the form of case series and reports, has indicated the effectiveness of catheter closure as a suitable alternative to surgery[124-126]. TEE is valuable during the intervention because it provides real-time visualization of cardiac structures, particularly the aortic valve[82-88]. A systematic review by Ayati *et al*[120] revealed a post-interventional mortality of only 0.5% from a cohort of 407 patients who underwent TCC for ruptured SoVAs. In this review, 12% of patients developed complications, most notably from residual shunts (1.7%), new onset aortic insufficiency (1.5%), and rupture recurrence (1.5%). The study ultimately

concluded that while TCC is a valuable alternative to surgery, precise patient selection is mandatory as surgery still remains the first-line treatment option for patients with ruptured SoVA and accompanied heart defects, arrhythmias, infections, or outflow tract obstruction. This post-operative mortality is notably lower compared to the surgical mortality mentioned by Sarikaya *et al*[112] in their retrospective review. However, more systemic reviews and meta-analyses of larger patient cohorts are needed to clarify the mortality benefit between the two treatment approaches.

CONCLUSION

The diagnosis of SoVA requires a combination of history, physical examination, and imaging. The first line imaging study includes an echocardiogram to visualize the aortic root, identifying the aneurysm and any associated intracardiac abnormality. Additionally, cardiac studies such as CT and MRI can provide more precise information on the anatomic delineation of the aneurysm and its surrounding structures. Definite treatment of SoVAs includes surgery. However, TCC is an emerging technique used in managing both ruptured and unruptured SoVAs and is now increasingly preferred over traditional surgical approaches due to the reduction in surgical risk, shortened hospital course, and decreased recovery time.

Although inclusion criteria for TCC exist regarding the treatment of SoVAs, there are no evidence-based clinical guidelines that provide a census within the medical community. Therefore, clinicians should ultimately decide on treatment based on each clinical scenario. More research is needed to validate the indications and contraindications of TCC in patients with ruptured SoVAs. Larger studies are also needed to further assess mortality, complication rates, and recovery time between TCC and traditional surgery for SoVAs.

FOOTNOTES

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REVIEW

Metabolic-dysfunction associated steatotic liver disease and atrial fibrillation: A review of pathogenesis

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) significantly contributes to cardiovascular morbidity, with cardiovascular disease being the leading cause of mortality among affected individuals. Atrial fibrillation (AF), the most common cardiac arrhythmia, is frequently observed in patients with MASLD. While shared metabolic risk factors such as obesity, diabetes, dyslipidemia, and hypertension are implicated, underlying pathophysiological mechanisms that include systemic inflammation, oxidative stress, insulin resistance, endothelial dysfunction, and activation of the renin-angiotensin-aldosterone system (RAAS) are proposed to play significant part in the increased risk of AF in MASLD. The aim is to review the pathogenesis linking MASLD and AF. A comprehensive literature review was conducted, focusing on studies that explore the epidemiology, pathogenesis, and clinical implications of MASLD and AF. Databases searched included PubMed, Scopus, and Web of Science, with keywords such as "metabolic associated steatotic liver disease", "non fibrotic metabolic associated steatohepatitis", "Nonalcoholic fatty liver disease", "metabolic syndrome",

"atrial fibrillation", "antifibrotic therapies", "pathogenesis", and "cardiovascular risk". Chronic low-grade inflammation and oxidative stress in MASLD contribute to atrial structural and electrical remodeling, fostering an arrhythmogenic substrate. Insulin resistance, a hallmark of MASLD, exacerbates metabolic dysfunction and promotes atrial fibrosis. Dysregulated lipid metabolism and gut microbiota alterations further compound cardiovascular risk. Aldosterone dysregulation and systemic inflammation stemming from RAAS activation contributes to the shared pathophysiology. The severity of MASLD does not seem to directly influence the risk of AF, suggesting that even early stages of liver disease can increase susceptibility to this arrhythmia. Effective management of MASLD requires targeted risk-factor modification strategies, including weight management, glycemic control, and pharmacological interventions. A multidisciplinary approach is essential for comprehensive assessment and management of MASLD patients, with a focus on cardiovascular risk assessment and arrhythmia prevention. Future research should explore the impact of emerging MASLD therapeutic agents on the incidence and recurrence of cardiac arrhythmias. Early detection and comprehensive management of MASLD and AF are crucial to mitigate the dual burden of these conditions.

Key Words: Metabolic-dysfunction associated steatotic liver disease; Non-alcoholic fatty liver disease; Atrial fibrillation; Non-alcoholic steatohepatitis; Insulin resistance; Oxidative stress; Dyslipidemia; Obesity

Core Tip: Metabolic dysfunction-associated steatotic liver disease (MASLD) and atrial fibrillation (AF) share common metabolic risk factors, including obesity, diabetes, dyslipidemia, and hypertension. Pathophysiological mechanisms such as systemic inflammation, oxidative stress, insulin resistance, and renin-angiotensin-aldosterone system activation link MASLD to AF. Chronic inflammation and oxidative stress in MASLD lead to atrial remodeling, creating an arrhythmogenic substrate. Effective management of MASLD requires targeted risk-factor modification strategies and a multidisciplinary approach to reduce cardiovascular risk and prevent arrhythmias. Early detection and comprehensive management are crucial to mitigate the dual burden of MASLD and AF.

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INTRODUCTION

Metabolic associated steatotic liver disease (MASLD) is increasingly recognized as a significant risk factor for various cardiovascular conditions, particularly atrial fibrillation (AF)[1]. MASLD is the most common liver disease in the United States, affecting approximately 30% of the population, with a higher prevalence among diabetics[2]. Characterized by the accumulation of fat in the liver due to metabolic dysfunctions such as insulin resistance (IR) and chronic low-grade inflammation, MASLD is associated with a heightened risk of cardiovascular complications, including AF, which affects millions worldwide[3]. Due to common modifiable risk factors such as hypertension, diabetes, and obesity between AF and MASLD, researchers have been investigating the association that exists between these two heterogeneous conditions.

In recent years, the nomenclature surrounding fatty liver disease has undergone a significant transformation[4]. In 2020, hepatology experts acknowledged the need to update the terminology for non-alcoholic fatty liver disease (NAFLD) to better reflect its metabolic origins. The renaming of nonalcoholic steatohepatitis to metabolic dysfunction-associated steatohepatitis as well as NAFLD to MASLD signifies emphasis toward metabolic causes of liver disease, aiming to eliminate the stigma associated with "non-alcoholic" and highlight the metabolic dysfunction underlying the condition [4]. This shift was further solidified in June 2023 with the publication of a multi-society Delphi consensus statement, which formally retired the term NAFLD and introduced a more comprehensive classification system. While MASLD remains a broad category, MASH represents a more severe form, characterized by inflammation, liver damage, and an increased risk of fibrosis, cirrhosis, and liver cancer. This reclassification represents an effort to refine disease definitions to enhance patient care, improve diagnostic criteria, and streamline research efforts[4].

While some studies have reported an association[1,5], other studies in contrast have reported that liver stiffness and not steatosis is a risk factor for the development of AF[6]. Research highlights a significant link, showing that people with MASLD face a 19% higher likelihood of developing AF compared to those without the condition, with this risk increasing in individuals with more advanced liver disease[1,5] (Table 1). The underlying mechanisms linking MASLD and AF are complex, involving metabolic dysregulation, dyslipidemia, and endothelial dysfunction. Elevated pro-inflammatory cytokines contribute to systemic inflammation and vascular complications, promoting a pro-atherogenic state that can precipitate arrhythmias. Furthermore, hypertension, often exacerbated by MASLD, may serve as an additional pathway linking the two conditions[7-12]. AF, the most prevalent type of arrhythmia, often serves as the ultimate pathway for

Table 1 Summary of key studies that highlight the increased risk of atrial fibrillation in patients with metabolic-associated steatotic liver disease, non-alcoholic fatty liver disease, and metabolic-associated steatohepatitis

Study	Ref.	Year	Type	Population	Key findings
Incident cardiac arrhythmias associated with MASLD	Simon *et al* [18]	2023	Retrospective cohort	11206 Swedish adults with histologically-confirmed MASLD	MASLD patients had a significantly higher incidence of AF (aHR = 1.26, 95%CI: 1.18-1.35) compared to controls
MASLD is associated with an increased long-term risk of AF	Mantovani *et al*[21]	2024	Systematic review and meta-analysis	16 retrospective cohort studies with approximately 19.5 million individuals	MASLD is associated with an increased risk of developing AF
Cardiovascular disease and MASLD	Møller *et al* [20]	2025	Systematic review	General review of MASLD patients	MASLD is associated with increased risk of cardiovascular diseases, including AF
Non-alcoholic fatty liver disease and the risk of incident AF in young adults	Choi *et al*[23]	2022	Prospective cohort	5333907 young adults in South Korea	NAFLD patients had a higher risk of new-onset AF, which increased progressively with NAFLD severity
Association of NAFLD with new-onset AF stratified by age groups	Cho *et al*[1]	2024	Retrospective cohort	3179582 participants from the Korean National Health Screening Program	NAFLD patients had a higher risk of new-onset AF, which increased progressively with NAFLD severity

AF: Atrial fibrillation; MASLD: Metabolic dysfunction-associated steatotic liver disease; NAFLD: Non-alcoholic fatty liver disease; aHR: Adjusted hazard ratio.

numerous underlying cardiac and non-cardiac conditions. If not addressed, it can result in severe health complications such as stroke and heart failure[13]. Given the rising prevalence of both MASLD and AF, cardiovascular disease (CVD) being the leading cause of mortality in patients with MASLD and the healthcare burden associated with AF continuing to rise, understanding the interplay between MASLD and AF becomes crucial for public health initiatives and clinical practice[14,15]. This review examines the current literature, proposed pathogenetic mechanisms, and treatment implications for patients with MASLD and AF.

EPIDEMIOLOGY

AF is the most prevalent cardiac arrhythmia worldwide, posing a significant public health challenge. Recent studies estimate that 10.55 million American adults, or 4.48% of the United States population, are currently affected by AF[16]. These figures represent a staggering threefold rise compared to projections from the 1990s, underscoring the rapid rise in disease burden. AF affects approximately 37.6 million individuals globally, accounting for 0.51% of the global population. Alarmingly, the absolute burden of AF is expected to grow by more than 60% by 2050, driven by aging populations and the increasing prevalence of associated comorbidities[16]. Age remains a dominant risk factor for AF, with a lifetime incidence of approximately 33% in individuals aged 65 years and older[17]. However, age-related susceptibility is often compounded by metabolic and cardiovascular comorbidities, including obesity, diabetes, hypertension, and, most notably, MASLD. Emerging evidence highlights MASLD as a significant contributor to AF, by some estimates increasing the risk by 19%, mediated through shared risk factors and overlapping pathophysiologic mechanisms[18].

MASLD is a chronic condition the hallmark of which is fat deposition in the liver. It affects an estimated 80-100 million individuals in the United States alone and has a global prevalence that mirrors rising rates of obesity and metabolic syndrome[19]. Studies have reported MASLD prevalence among obese individuals in the United States approaches 75%, reflecting the interconnected nature of these conditions[19]. Several studies have established an epidemiological link between MASLD and AF[20-23]. A meta-analysis has demonstrated that patients with MASLD have a 19% greater risk of developing incident AF compared to those without MASLD, as indicated by an adjusted hazard ratio (aHR) of 1.19 (95%CI: 1.07-1.31)[18]. Furthermore, the association between MASLD and AF persists across various histological categories of liver disease. Patients diagnosed with simple steatosis have an aHR of 1.24 (95%CI: 1.14-1.35). In contrast, those suffering from non-fibrotic MASH and cirrhosis face even higher risks, with aHRs of 1.34 (95%CI: 1.07-1.68) and 1.59 (95%CI: 1.15-2.19), respectively[18]. This finding underscores the importance of fibrosis progression as a key determinant of arrhythmogenic risk in MASLD. Another study involving 238129 participants further corroborated these findings, showing that MASLD patients had a twofold increased risk of AF compared to those without the condition[15]. These studies highlight the interplay between liver disease severity and cardiac arrhythmogenesis, suggesting that MASLD progression may independently elevate AF risk, even when accounting for traditional cardiometabolic risk factors.

Both AF and MASLD share common risk factors, including obesity, diabetes, hypertension, and dyslipidemia, complicating efforts to delineate their causal relationship[20-24]. Obesity, a central driver of metabolic dysfunction, plays a particularly critical role[25]. Visceral fat accumulation is associated with IR, systemic inflammation, and hormonal imbalances, all of which contribute to both hepatic steatosis and atrial remodeling[25]. Up to 75% of obese individuals in the United States have MASLD, highlighting the high prevalence of this liver disease in populations at risk for AF[19]. Obesity significantly increases the likelihood of hepatic steatosis[26]. Patients meeting the criteria for metabolic syndrome demonstrate a notably higher risk of steatohepatitis and severe fibrosis. The growing obesity epidemic has thus driven

parallel increases in the prevalence of both MASLD and AF, particularly in Western countries and parts of Asia[26]. A recent meta-analysis to assess a study on the global impact of obesity across 73 World Health Organization member countries found that 37% of individuals were affected by overweight or obesity issues[27]. The research also indicated that nations with a strong economic standing tend to have a higher rate of overweight and obesity. In fact, an improvement in economic status could result in a 14% rise in these conditions[27].

MASLD and AF are interconnected public health challenges. While strong epidemiological and mechanistic evidence links these conditions, distinguishing the direct impact of MASLD on the risk of AF in the presence of overlapping factors remains challenging. As the evidence continues to accumulate, the need for targeted screening and interventions for MASLD patients at elevated risk of developing AF becomes increasingly clear, particularly as cardiovascular mortality has surpassed liver-related deaths in this patient group[24].

PATHOGENESIS

AF is a complex condition that can present as an isolated electrophysiological disorder or as a consequence of various cardiac and non-cardiac pathologies. The pathophysiological mechanisms that connect MASLD to an elevated risk of AF are intricate and encompass various processes, which will be elaborated upon in the subsequent sections.

SHARED RISK FACTORS

IR and diabetes mellitus

IR is a metabolic disorder characterized by the body's diminished ability to respond to insulin, leading to impaired glucose metabolism and elevated blood glucose levels. This condition serves as a significant precursor to various metabolic disorders, including type 2 diabetes and metabolic syndrome[28]. IR also affects vessels, leading to hypertension and vasoconstriction[29]. IR is increasingly being linked to the pathogenesis of AF and MASLD, highlighting its pivotal role in the development of these conditions.

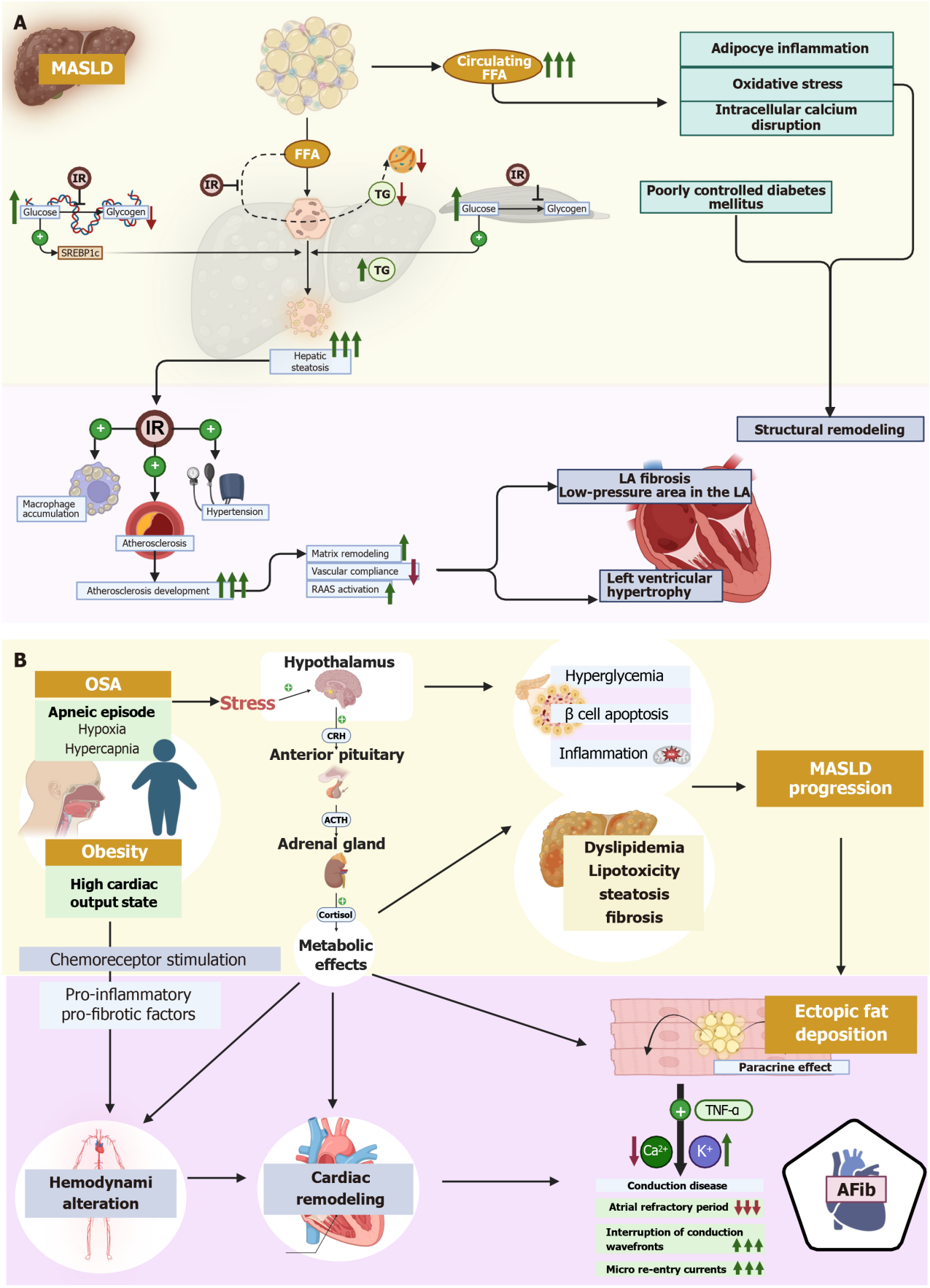
IR is a central feature of the onset of MASLD, affecting lipid metabolism and contributing to various metabolic disorders. IR disrupts the conversion of free fatty acids (FFAs) into triglycerides (TGs) and their incorporation into very low-density lipoprotein particles for storage or transport, resulting in fat buildup in liver cells and worsening hepatic steatosis [30] (Figure 1A). On a molecular level, the dysregulation of essential transcription factors, such as sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate regulatory element-binding protein, drives IR in MASLD. These factors regulate the expression of genes involved in lipogenesis and glucose metabolism[3]. Research indicates that elevated glucose levels can stimulate SREBP1c, which in turn enhances lipogenic gene expression and excess FFAs production, promoting lipid accumulation in hepatocytes which leads to hepatic steatosis or MASLD[31]. Decreased insulin action can result in decreased glycogen synthesis in skeletal muscle, increased hepatic *de novo* lipogenesis (DNL), and elevated TG synthesis, which collectively contribute to atherosclerotic dyslipidemia in individuals with MASLD[32].

IR has emerged as a significant risk factor for AF, influencing both the pathophysiology and progression of the condition. Several molecular mechanisms contribute to the association between IR and CVD s including AF[29]. Structural remodeling of the atria and disruption of intracellular calcium homeostasis is caused by adipocyte inflammation and oxidative stress which are linked to IR[33]. The increased oxidative stress and inflammation associated with impaired IR and insulin secretion contribute to left atrial (LA) fibrosis and the formation of a low-pressure area in the LA along with left ventricular hypertrophy (LVH), all of which are critical components in the pathophysiology of AF[28,34]. IR contributes to hyperinsulinemia, which can initiate mechanisms that modify vascular compliance and matrix remodeling. These physiological alterations enhance renal sodium reabsorption and activate the sympathetic nervous system, leading to left ventricular (LV) remodeling and the development of LVH[35]. Additionally, abnormal glucose tolerance and dyslipidemia related to IR have a cumulative effect on the risk of AF progression, thereby leading to recurrence after interventions such as radiofrequency catheter ablation[28].

Diabetes mellitus has been implicated as a significant risk factor for both AF and MASLD, highlighting a complex interplay among these conditions. The association between MASLD and type 2 diabetes mellitus (T2DM) is substantial, with over 70% of individuals with T2DM exhibiting MASLD[36]. Furthermore, the presence of MASLD in diabetic patients can complicate metabolic health and increase the risk of cardiovascular events[18,37]. A meta-analysis examining the association between MASLD and AF has demonstrated a significant increase in the risk of AF among middle-aged and elderly individuals with MASLD, with the risk being particularly elevated among diabetic patients[38]. Independent from MASLD, evidence suggests Diabetes Mellitus is a significant and independent risk factor for AF and flutter, as well as other CVDs, with some estimates indicating a 1.4- to 1.6-fold increased risk of AF[39-41]. Furthermore, a prolonged period of suboptimally controlled diabetes mellitus has been independently linked to a heightened risk of AF[37,41].

Obesity and obstructive sleep apnea

Obesity, characterized by excessive fat accumulation, plays a crucial role in the development of MASLD primarily through mechanisms that promote hepatic lipid accumulation and metabolic dysregulation. In obese individuals, excessive caloric intake and physical inactivity exacerbate the accumulation of fat deposits in the liver[25]. Dietary patterns high in sugars and unhealthy fats increase DNL, leading to further fat deposition in hepatocytes[42]. Obesity is also associated with obstructive sleep apnea (OSA) along with IR, T2DM, MASLD, and other related metabolic diseases[43,


A
MASLD
Circulating FFA
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Hepatic steatosis
Structural remodeling
Macrophage accumulation
Hypertension
Atherosclerosis
Atherosclerosis development
Matrix remodeling
Vascular compliance
RAAS activation
LA fibrosis
Low-pressure area in the LA
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B
OSA
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Hypoxia
Hypercapnia
Obesity
High cardiac output state
Stress
Hypothalamus
CRH
Anterior pituitary
ACTH
Adrenal gland
Cortisol
Metabolic effects
Hyperglycemia
β cell apoptosis
Inflammation
MASLD progression
Dyslipidemia
Lipotoxicity
steatosis
fibrosis
Chemoreceptor stimulation
Pro-inflammatory pro-fibrotic factors
Ectopic fat deposition
Paracrine effect
TNF-α
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Atrial refractory period
Interruption of conduction wavefronts
Micro re-entry currents
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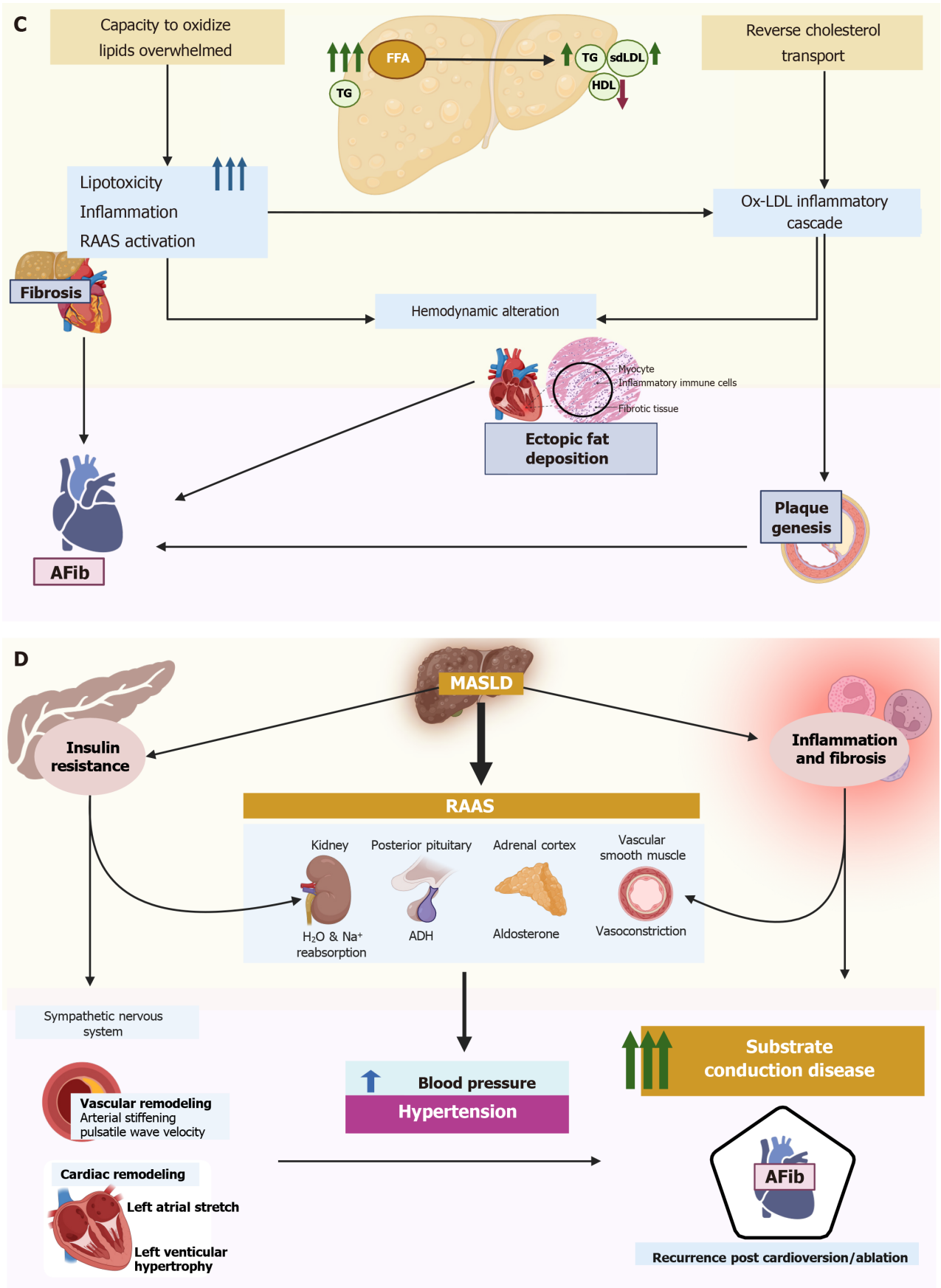
C
Capacity to oxidize lipids overwhelmed
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Inflammatory immune cells
Fibrotic tissue
Ectopic fat deposition
Plaque genesis
AFib
D
MASLD
Insulin resistance
Inflammation and fibrosis
RAAS
Kidney
Posterior pituitary
Adrenal cortex
Vascular smooth muscle
H2O & Na+ reabsorption
ADH
Aldosterone
Vasoconstriction
Sympathetic nervous system
Substrate conduction disease
Blood pressure
Hypertension
Vascular remodeling
Arterial stiffening
pulsatile wave velocity
Cardiac remodeling
Left atrial stretch
Left venticular hypertrophy
AFib
Recurrence post cardioversion/ablation

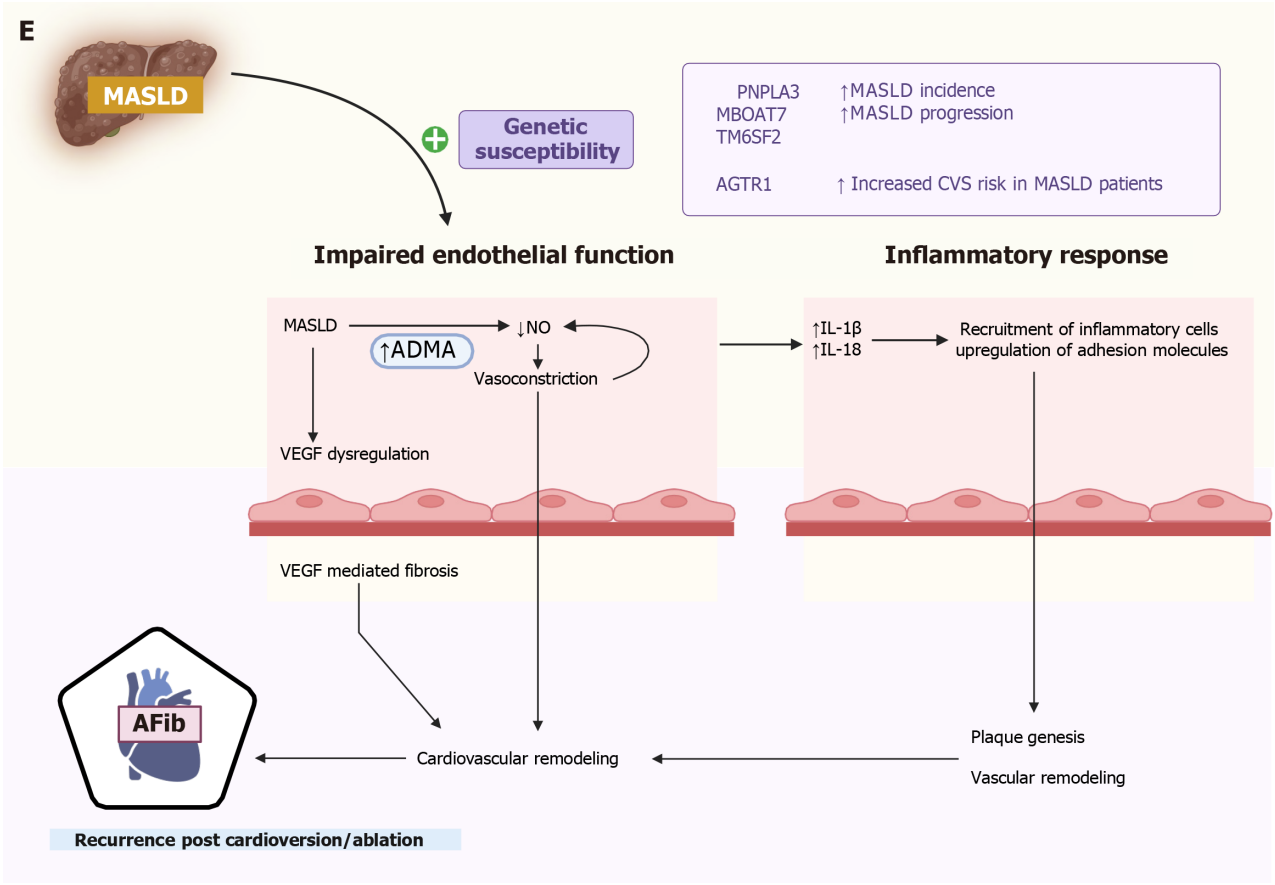

Figure 1 Role in atrial fibrillation and metabolic dysfunction-associated steatotic liver disease. A: Insulin resistance and diabetes mellitus; B: Obesity and obstructive sleep apnea; C; Dyslipidemia; D: Hypertension; E: Proposed role of endothelial dysfunction. AF: Atrial fibrillation; AFib: Atrial fibrillation; FFA: Free fatty acid; IR: Insulin resistance; LA: Left atrium; RAAS: Renin-angiotensin-aldosterone-system; TG: Triglycerides; SREBP1c: Sterol regulatory element binding protein 1c; K: Potassium; TNF: Tumor necrosis factor-α; HDL: High desnity lipoprotein; MASLD: Metabolic dysfunction-associated steatotic liver disease; Ox-LDL: Oxidized low-density lipoprotein; SdLDL: Small-density low-density lipoprotein; ADH: Antidiuretic hormone; ADMA: Asymmetric dimethylarginine; IL: Interleukin; VEGF: Vascular endothelial growth factor; Na: Sodium. Created in BioRender (Supplementary material).

44]. In fact, more severe OSA is associated with a higher prevalence of MASLD, body mass index (BMI), and oxygen desaturation index[45]. Intermittent awakening in OSA triggers the sympathetic system and hypothalamic-pituitary-adrenal axis to reduce glucose uptake, promote reactive oxygen species (ROS) generation, and trigger apoptosis of beta-cells in the pancreas[46]. The hypoxia in OSA induces TG and cholesterol ester synthesis, increased generation and decreased beta-oxidation of FFAs, and lipid mobilization from adipose to liver, predisposing patients to dyslipidemia[47,48]. This dysregulation often leads to lipotoxicity, triggering a cascade of pathophysiological changes that lead to liver damage as a consequence of oxidative stress, pro-inflammatory state, and activation of the renin-angiotensin axis and, ultimately, fibrosis[49,50]. High malondialdehyde levels have been observed in the liver as well as the serum of mice exposed to intermittent hypoxia[51]. These effects augment lipotoxicity which plays a critical role in the development and progression of MASLD. OSA impacts sleep quality and prior studies have found an association between low sleep duration and MASLD[52]. This is partly explained by the role of circadian rhythm in regulating insulin and lipid metabolism, the disturbance of which could promote inflammation and liver disease[53].

Obesity and OSA lead to systemic changes that may predispose individuals to AF (Figure 1B). In individuals with obesity, the increased cardiac output induces hemodynamic modifications that accelerate the progression of LVH and LV diastolic dysfunction[54]. LV dysfunction, along with hyper circulatory state, sleep apnea, sleep related hypoventilation and hypoxemia may result in involvement of the right heart, thereby further exacerbate alterations in cardiac morphology [55]. Moreover, the relative risk of incident AF increases by 19%-29% for each 5-unit increase in BMI above normal[56]. Furthermore, individuals with OSA exhibit a fourfold increase in the likelihood of developing AF. This elevated risk is quantified by an adjusted odds ratio, which, after adjusting for concurrent risk factors, ranges from 2.8 to 5.6[57,58]. The association of obesity and AF is two-fold, with the first pathway being through the excess adipose tissue and the second pathway involving the deposition of fat around the heart (epicardial fat). The pro-inflammatory and pro-fibrotic factors secreted by the former promote diastolic dysfunction, atrial inflammation, myocardial lipidosis, and atrial contractile dysfunction[25]. This is further complicated by intermittent nocturnal hypoxia in OSA that promotes endothelial dysfunction, hypercapnia, chemoreceptor stimulation and causes significantly elevated sympathetic activity along with severe blood pressure changes[59,60]. Furthermore, the inflammatory cytokine tumor necrosis factor-α (TNF-α) plays a pivotal role in this remodeling process by altering ion channel function characterized by a downregulation of calcium currents and increased outward potassium currents, leading to slowed conduction and shortened atrial refractory periods[61].

Collectively, these factors result in substantial alterations in cardiac chamber dimensions and transmural pressures, creating a substrate that facilitates the development and perpetuation of AF[8,62-64]. In contrast, epicardial fat, a type of ectopic adipose tissue, is metabolically active and secretes cytokines and chemokines that may contribute to the development of atrial arrhythmias[65]. Research indicates that inflammatory biomarkers, including interleukin (IL)-1β and TNF-α, may contribute to the development of atrial fibrosis by exerting paracrine effects on the surrounding myocardium. Furthermore, these biomarkers might lead to disruption of conduction wavefronts by fatty infiltration leading to the formation of micro reentry circuits[66]. OSA severity independently correlates with elevated markers of systemic inflammation, such as C-reactive protein (CRP). CRP, in turn, demonstrates a direct association with atrial remodeling and increased risk of arrhythmias including AF[67]. In addition, both hypoxemia and hypercapnia possess arrhythmogenic properties[68]. If left untreated for years, these recurring events may precipitate or increase susceptibility to AF[69,70]. In a population-based study, robust and graded correlations were identified between increased epicardial fat and AF, with the association potentially surpassing that of abdominal and overall adiposity[71]. Hence, the interplay between obesity, OSA, AF, and MASLD reveals a complex web of pathophysiological mechanisms that elevate the risk for CVDs.

Dyslipidemia

Dyslipidemia is a metabolic disorder characterized by abnormal lipid levels in the blood, and it plays a pivotal role in the pathogenesis of MASLD and AF (Figure 1C). Dyslipidemia is prevalent in approximately 60%-70% of individuals with MASLD[24]. The interplay between dyslipidemia and MASLD involves complex mechanisms, including genetic factors, impaired insulin sensitivity, and chronic inflammation[72,73]. Dyslipidemia is characterized by increased levels of TGs, the presence of small dense low-density lipoprotein cholesterol (sdLDL), and diminished high-density lipoprotein cholesterol (HDL-C) concentrations. The propensity of sdLDL to infiltrate the endothelium and undergo oxidation to form ox-LDL activates inflammatory cascades integral to atherosclerotic plaque genesis[72]. Due to their diminished affinity for LDL receptors, the reduced clearance of these particles amplifies their atherogenic potential[74]. Concomitantly, the decline in HDL levels compromises reverse cholesterol transport and attenuates HDL's antioxidant and anti-inflammatory properties, thereby impeding the breakdown of excess cholesterol[75]. This aberrant lipid profile not only aggravates liver disease but also heightens the susceptibility to cardiovascular complications, notably atherosclerosis and AF [24].

The development of dyslipidemia in MASLD can be influenced by both genetic predispositions and environmental factors. Specific genetic polymorphisms, such as the single nucleotide polymorphism (SNP) rs738409 in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene, have been associated with increased liver fat accumulation and a higher risk of progressive liver disease, which may in turn affect lipid metabolism[76]. The systemic inflammation and oxidative stress associated with MASLD and dyslipidemia contribute to cardiovascular pathologies, including AF. Elevated levels of inflammatory cytokines, such as TNF-α and IL-6, are not only linked to liver inflammation but also facilitate endothelial dysfunction, which is a precursor to AF[7]. The inflammatory milieu may induce electrical remodeling in the atria, increasing the risk of arrhythmias, including AF. Furthermore, the metabolic abnormalities seen in MASLD can disrupt cardiac autonomic function, which further exacerbates the likelihood of developing AF[7,77]. Dyslipidemia's association with AF is particularly notable yet controversial. While certain studies indicate that dyslipidemia may influence AF risk, higher levels of total cholesterol (TC) and LDL-C have been associated with a lower risk of AF in some studies, but this association appears to be time-dependent and may not persist beyond the initial years of follow-up [78]. Conversely, low levels of HDL-C and high TGs have been consistently associated with an increased risk of AF[79]. This indicates that further research is needed to understand the intricate dynamics between lipid metabolism and atrial arrhythmias.

Hypertension

The interplay between hypertension, AF, and MASLD reveals a complex relationship where each condition can worsen the other, establishing a vicious cycle that increases the risk of serious cardiovascular complications[80] (Figure 1D). MASLD is linked with various metabolic disturbances, including dyslipidemia and IR, which are often exacerbated by hypertension. IR is a defining characteristic of MASLD and can amplify the activity of the sympathetic nervous system, resulting in elevated blood pressure. In addition, IR may lead to the sodium and water renal retention, which intensifies hypertension by increasing blood volume. The persistent low-grade inflammation linked with MASLD can also influence the vascular system leading to vasoconstriction and further increase the blood pressure levels[81,82]. A cross sectional study in China demonstrated strong association of inflammatory indices, especially aggregate index of systemic inflammation with MASLD and opened the door for potential utility in risk stratification, thus reinforcing the role of chronic inflammation[83]. Recent findings suggest that MASLD not only increases the likelihood of developing hypertension but may also influence its onset at an early age, independent of other metabolic risk factors[24]. Furthermore, MASLD is associated with a gain-of-function variant in the angiotensin receptor type 1 gene in hypertensive individuals, specifically rs5186 A1166C. The findings indicate that MASLD may exacerbate the renin-angiotensin-aldosterone system (RAAS), resulting in elevated blood pressure through vasoconstriction and an increase in blood volume[84]. The positive correlation between elevated plasma aldosterone concentration (PAC) and the prevalence of MASLD in hypertensive patients supports this assertion[85]. Indeed, for every 5-unit increase in PAC, the risk of MASLD increased by a factor of 1.57[86]. Conversely, hypertension may contribute to the progression of MASLD, as evidenced by studies exhibiting an association of high blood pressure with liver scar tissue formation and worsening liver conditions, even when considering other factors like obesity and diabetes[87,88].

Hypertension is a well-recognized risk factor for AF, with evidence indicating that high blood pressure significantly contributes to the incidence of AF[89]. Individuals with hypertension face a 1.7-fold increased risk of developing AF compared to those with normal blood pressure, and hypertension is responsible for 1 in 6 AF cases[90]. High blood pressure

significantly strains the heart, leading to LVH[9]. This leads to disruption of the heart's electrical pathways, promoting the development of AF. Moreover, high blood pressure also leads to the stiffening of arteries. The elevated pressure pulsatility and increased pulse wave velocity worsen LVH, impair diastolic function, and raise LV filling pressure, which eventually causes the left atrium to stretch[9]. This atrial remodeling constitutes a substrate for AF onset and persistence of AF. This progression is facilitated by the interplay of inflammation, oxidative stress and RAAS activation, in addition to the aging process[91]. The association of hypertension with AF is further highlighted by the CHADS2VASc score, a clinical tool used to assess stroke risk in AF patients. It incorporates hypertension as a critical factor, underscoring its relevance in the clinical context[92]. Therefore, addressing hypertension is essential not only for the prevention of AF and MASLD but also for improving overall cardiovascular health.

PROPOSED HYPOTHESIS

Inflammation and oxidative stress

Inflammation has emerged as a crucial link between AF and MASLD, two increasingly prevalent conditions[24]. Chronic inflammation associated with MASLD is driven by elevated levels of pro-inflammatory cytokines, including TNF-α and IL-6. These cytokines not only contribute to hepatic damage but also play a significant role in the pathogenesis of CVDs, such as AF[6]. A mice model reported early non-obese MASH resulting from IR and hepatic inflammation through TNFα as the key regulator[11]. TNF-α secretion facilitates the upregulation of various pro-inflammatory mediators through activation of nuclear factor kappa-B (NF-κB) signaling pathway resulting in hepatic inflammation and steatosis. On the other hand, IL-6 activates the JAK/STAT signaling pathway, leading to the transcriptional upregulation of acute-phase reactants, such as CRP and serum amyloid A. This process subsequently amplifies the hepatic inflammatory response and exerts systemic effects beyond the liver[93]. A cross-sectional study revealed elevated levels of high-sensitivity CRP, an inflammatory marker that is indicative of an increased risk of MASLD[94].

Numerous research studies have identified a link between circulating inflammatory markers, such as CRP and ILs, and the severity of AF, including its chronicity, type, and burden[95,96]. Over two decades ago, research suggested a link between AF and inflammation, particularly in the context of postoperative AF following cardiac surgery, which occurred with a high frequency (20%-50%). The incidence of postoperative AF typically peaks 2 to 3 days post-surgery, coinciding with the activation of systemic inflammatory pathways. This is evidenced by early elevations in plasma IL-1β, followed by increases in IL-6 and CRP, the latter being a sensitive yet nonspecific marker of systemic inflammation[97]. Increased concentrations of inflammatory cytokines, including IL-6 and TNF-α, have been recognized as critical contributors to atrial remodeling and electrical instability[34]. The activation of cardiac fibroblasts by inflammatory factors leads to a vicious cycle of inflammation and fibrosis, reinforcing the substrate for AF maintenance[98]. The activation of pathways such as NF-κB signaling has also been implicated in the regulation of ion channels and gap junction proteins, thereby enhancing the susceptibility to AF[99]. Therefore, atrial fibrosis, characterized by conduction disturbances, is exacerbated by inflammatory mediators and contributes to atrial remodeling-a process that perpetuates AF and increases the risk of thromboembolic events. While some studies demonstrate a clear association between elevated inflammatory markers and AF incidence, others suggest the need for a more nuanced understanding of how these markers interact with additional risk factors, such as obesity and dyslipidemia[100].

Inflammation may result in oxidative stress that surpasses the capacity of antioxidant defenses. Oxidative stress has been reported to play a crucial role in the pathogenesis of both MASLD and AF, is a critical factor in atrial remodeling, which in turn leads to cellular damage and inflammation within the atrial tissue[12]. Mitochondrial dysfunction is a key contributor to oxidative stress, affecting cellular homeostasis and promoting the initiation of AF *via* altered ion channel dynamics[101]. Studies have shown that ROS produced by mitochondria can activate Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII), which in turn phosphorylates the ryanodine receptor 2. This phosphorylation event is a precursor to the onset of AF, as evidenced by research conducted using mouse models. Furthermore, oxidative stress is known to intensify AF and encourages CAMKII to mediate the interaction between Ca^{2+} and calmodulin, thereby activating calmodulin[102].

The presence of excessive hepatic fat in MASLD leads to an elevation in ROS production, which in turn induces cellular damage and contributes to the development of inflammation and fibrosis[103]. In addition, the pathogenesis of MASLD in OSA largely centers around chronic intermittent hypoxia, which leads to the release of ROS and inflammatory mediators that contribute to hepatic inflammation and fibrosis[103]. One factor that mediates this effect is macrophage specific hypoxia inducing factor (HIF-1α), which is increased in OSA as well as MASLD through oxidative stress and mitochondrial injury[103,104]. HIF-1α influences the release of lysyl oxidase (LOX), which plays a role in cross-linking of extracellular matrix proteins and promotes fibrosis[105]. This hypothesis is supported by the finding that LOX levels are higher in patients with hepatic fibrosis[106]. HIF-2 is also implicated and results in dysregulated lipid metabolism which leads to severe hepatic steatosis[107]. Generally, prolyl hydroxylase domain (PHD) enzymes degrade HIFs. Hypoxia results in decreased PHD activity, enabling excessive HIF activity and consequent liver injury[108]. Furthermore, MASH and MASLD are linked to decreased production of adiponectin which exhibits anti-inflammatory properties in adipose tissue and may also be associated with AF, although reports on this association are conflicting[109]. Hypoadiponectinemia may partially elucidate the role of obesity and systemic inflammation in the association between MASLD and AF [110]. Therefore, chronic inflammation and oxidative stress associated with MASLD can exacerbate atrial structural changes, thus creating a vicious cycle that accelerates the onset of AF.

Gut microbiome

Alterations in gut microbiota composition can significantly impact both MASLD and AF through mechanisms involving inflammation and metabolic dysfunction[111]. The gut microbiota, which comprises a complex community of microorganisms, is essential in maintaining human health by influencing metabolism, immune function, and inflammation. Dysbiosis, defined as an imbalance in gut microbial populations has been reported in multiple diseases and shown to activate the immune system, eliciting chronic diseases[112-115]. The concept of gut-immune-heart axis and gut-immune-liver axis have been proposed to explain the impact of dysbiosis on AF and MASLD[116,117]. The "multiple hit model" of MASLD development identifies several contributing factors, including fat accumulation, IR, and genetic or environmental influences that disrupt gut integrity leading to dysbiosis[118]. Dysbiosis in turn can lead to increased intestinal permeability and the translocation of microbial products into the bloodstream, triggering systemic inflammatory responses and contribute to its pathogenesis by exacerbating liver inflammation and fibrosis[119]. In patients with AF, the recruitment of monocytes and macrophages to the atrial myocardium can lead to the release of pro-inflammatory cytokines, which may precipitate arrhythmias[120]. Moreover, the interaction between gut microbiota and the autonomic nervous system may also play a role in AF progression, indicating a regulatory effect of the gut-brain-heart axis that warrants further investigation through clinical and preclinical studies[116]. The progression of MASLD has been linked to metabolites produced by gut microbiota, such as short-chain fatty acids, bile acids, and trimethylamine-N-oxide. These metabolites can affect liver metabolism and inflammatory responses, highlighting the intricate relationship between gut microbial composition and liver health[117]. Additionally, these metabolites of intestinal flora equally participate in AF occurrence[120-122]. Therefore, further research is necessary to explore whether targeted interventions in gut microbiota could mitigate AF progression and improve patient outcomes.

Endothelial dysfunction

The endothelium, forming the inner surface of blood vessels, plays a vital role in maintaining vascular homeostasis by controlling blood flow, coagulation processes and vascular tone. Under normal physiological conditions, the endothelium generates mediators that promote vasodilation and inhibit both platelet aggregation and the proliferation of smooth muscle cells[10]. However, this balance is disrupted in MASLD, leading to impaired endothelial function and an increased risk of cardiovascular events[123]. Key components of this interplay include inflammation, oxidative stress, and dysregulation of vascular endothelial growth factor (VEGF) signaling. In patients with MASLD, Nitric oxide (NO) production, a vital mediator of endothelial health, is often compromised due to increased oxidative stress and inflammation. Elevated Asymmetric dimethylarginine levels, an endogenous inhibitor of endothelial NO synthase, are prevalent in MASLD[124]. The reduction in NO leads to diminished vasodilation, increased vasoconstriction leading to further suppression of NO synthesis, and consequently increased vascular resistance and blood pressure, thereby escalating cardiovascular risks including arrhythmias like AF[124].

The inflammatory response exacerbated by endothelial dysfunction involves the upregulation of adhesion molecules and the recruitment of inflammatory cells, which are further influenced by cytokines such as IL-1β and IL-18. These cytokines promote plaque formation and vascular stiffness which exacerbate atrial remodelling and thus, promote arrhythmogenesis[18]. Moreover, the inflammatory VEGF signaling pathway is integral to the pathophysiology of AF [125]. VEGF has been implicated in atrial remodeling, inflammation, and fibrosis, potentially leading to the initiation and maintenance of AF. By interacting with fibroblasts and modulating fibrotic pathways, VEGF may contribute to the structural changes in the atria that promote arrhythmia[125]. Emerging evidence suggests that endothelial dysfunction contributes to the maintenance of an arrhythmic substrate in patients with AF undergoing cardioversion and ablation who have a high risk of recurrence, further highlighting its importance in the pathogenesis[126] (Figure 1E).

Genetic factors

Genetic factors are increasingly acknowledged as significant in the pathogenesis of AF. The presence of a family history of AF in a first-degree relative independently elevates the risk of developing AF by twofold[127]. While monogenic inheritance has been described for a variety of genes, polygenic inheritance is more common[128,129]. Recent research has highlighted the significance of genetic predisposition in the pathogenesis of elevated AF risk among individuals with metabolic disorders, including MASLD. This understanding is rooted in the polygenic risk associated with specific genetic variants that demonstrate a correlation with both AF and MASLD[130]. Genome-wide association studies have pinpointed several SNPs that are linked to these conditions, indicating a common susceptibility that may be related to the dysregulation of lipid metabolism and inflammatory processes[131]. Among the significant genetic variants linked to MASLD are those located in the membrane-bound O-acyltransferase domain 7, *PNPLA3*, transmembrane 6 superfamily member 2 genes[132]. These variants are implicated in the development and progression of MASLD, which is closely linked to the risk of CVDs, including AF[133]. Additionally, Variants in genes associated with hypertension and lipid metabolism, such as the angiotensin receptor type 1 gene, have been linked to MASLD and its cardiovascular complications[24,133,134]. The cumulative risk of developing AF was particularly pronounced in individuals with high polygenic risk scores (PRS) and rare genetic variants linked to MASLD, with a significant hazard ratio for incident AF when compared to lower-risk groups. The incidence of AF reached as high as 28.55% by age 80 among high-risk individuals [17]. However, controversies surrounding the applicability of PRS and their clinical utility persist, necessitating further research to validate these findings and refine risk evaluation methodologies.

Renin angiotensin axis

Historically, research on the RAAS has primarily concentrated on its role in blood pressure regulation. However, more recently, significant attention has been directed towards understanding RAAS's influence on a wider array of diseases,

particularly through its impact on local tissue dynamics[24]. RAAS can be divided into the traditional RAAS pathway (or classic RAAS) mediated by angiotensin II (AII), and the non-classic RAAS pathway mediated by angiotensin 1-7. Both pathways function within the heart and lungs. In the cardiac context, the classical RAAS predominates over the non-classical RAAS, significantly impacting hemodynamic processes and tissue remodeling. This predominance is linked to dysfunctions in cardiomyocytes and endothelial cells, thereby increasing the risk of AF[135,136]. AII, a key component of RAAS and a pro-inflammatory mediator, has the capacity to upregulate cytokines, stimulate cell proliferation, and modulate extracellular matrix metabolism through the AII type 1 receptor. The AII type 1 receptor is notably distributed across a range of organs, including blood vessels, the heart, the liver, the brain, the lungs, the kidneys, and the adrenal cortex. This widespread distribution suggests its potential involvement in the pathogenesis of both MASLD and AF[137]. AII causes vasoconstriction, stimulates aldosterone release, and promotes inflammation and fibrosis within the cardiac tissue[138]. This inturn leads to increased atrial pressure, fibrosis and electrical remodelling; all of which exacerbate the risk of AF[139].

Recent findings indicate that MASLD may exacerbate RAAS activity, resulting in increased vasoconstriction and elevated blood volume, which collectively elevate blood pressure[139]. Furthermore, RAAS plays a pivotal role as a lipid metabolism signaling pathway in the hepatic tissue of individuals with MASLD. In rodent studies, the suppression of RAAS has been found to reduce obesity caused by high-fat diets[140]. Moreover, rodent models with knockouts of RAAS-related genes, such as renin and angiotensin-converting enzyme, or those with a liver-specific deletion of the AT1 receptor, have shown improvements in hepatic steatosis[141]. RAAS activation downregulates the expression of genes associated with fatty acid oxidation, thereby suppressing the oxidative metabolism of fatty acids. Additionally, specific cytokines (TNF-α, MCP-1, and IL-6) and IR contribute to RAAS-mediated exacerbation of MASLD[110]. RAAS meditates the secretion of aldosterone that is essential in regulating the body's water and electrolyte balance[142]. Recent studies have linked elevated PAC to the development of MASLD[85,86]. In addition to chronic inflammation, oxidative stress, and IR, aldosterone contributes to the reduction of both circulating adiponectin and its expression in visceral adipose tissue. Moreover, this process initiates a direct sequence of events culminating in the activation of hepatic stellate cells, which in turn leads to liver fibrosis, primarily through NLRP3 inflammasome activation[143,144]. Given the interconnectedness of these conditions, understanding the role of RAAS becomes critical in addressing the pathogenesis of AF in patients with MASLD (Figure 2).

CLINICAL IMPLICATIONS

The clinical implications of MASLD extend beyond hepatic health, emphasizing the importance of a holistic understanding of its cardiovascular consequences[145]. This patient population is increasingly vulnerable to arrhythmias, necessitating comprehensive cardiovascular risk assessment and management strategies tailored to mitigate these risks [146]. Studies reported MASLD as an independent risk factor for recurrent arrhythmia following ablation after adjusting for body mass index and glycemic control[147,148]. This finding underscores the importance of integrating MASLD management into broader treatment strategies for cardiac arrhythmia prevention and management. In recognition of this, both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver advocate for the regular evaluation of cardiovascular risk factors in patients with MASLD. Physicians should, therefore, be vigilant about the potential cardiovascular implications of MASLD, including its association with arrhythmias such as AF.

Management of MASLD primarily revolves around lifestyle modifications and pharmacological interventions. Adopting lifestyle changes, such as altering one's diet, engaging in more physical exercise, managing body weight, and quitting smoking, is crucial for enhancing patient outcomes and controlling risk factors linked to both MASLD and AF [149]. Dietary management is one of the most significant nonpharmacologic strategies for MASLD. A balanced, nutrient-rich diet can influence mechanisms related to AF pathogenesis, including inflammation and oxidative stress[145]. The Mediterranean diet and the Dietary Approaches to Stop Hypertension diet have garnered significant attention for their efficacy in managing MASLD and enhancing cardiovascular health, while concurrently reducing hepatic fat accumulation [149]. Increasing physical activity is another critical intervention for patients with MASLD. Regular exercise has been shown to improve metabolic health, facilitate weight loss, and enhance overall cardiovascular fitness, which are vital for reducing AF risk[149]. Weight reduction is essential as it can result in improvements in liver health and reduction in AF risk factors[145]. This is further supported by reduction in arrhythmia recurrence noted in post-ablation patients with risk factor modification acknowledged as a crucial factor[56,150]. Finally, collaborative efforts implemented by a multidisciplinary care team, including dietitians, nurses, and pharmacists, could be vital for delivering comprehensive nutritional interventions and lifestyle modifications tailored to each patient's unique needs thereby enhancing adherence to the recommended lifestyle changes and improving clinical outcomes.

While diet and lifestyle interventions serve as the cornerstone of treatment, they are often insufficient or unsustainable for many patients[50]. Specific interventions targeting MASLD as part of arrhythmia management remain understudied. However, the relationship between AF and MASLD persists across various histological categories of MASLD, including simple steatosis and cirrhosis, indicating that the severity of liver fibrosis may be a crucial predictor for the development of AF[18]. Therefore, as the disease progresses, particularly in cases with significant fibrosis, patients may require pharmacological therapies aimed at reducing hepatic inflammation, fibrosis, and steatohepatitis. Resmetirom has emerged as the first Food and Drug Administration-approved drug for effective management of MASLD, functioning as a thyroid hormone receptor β (THR-β) agonist. This medicine helps by turning on the THR receptor in liver cells. This reduces the creation of new fats, increases the breakdown of fatty acids, and offers benefits against inflammation and

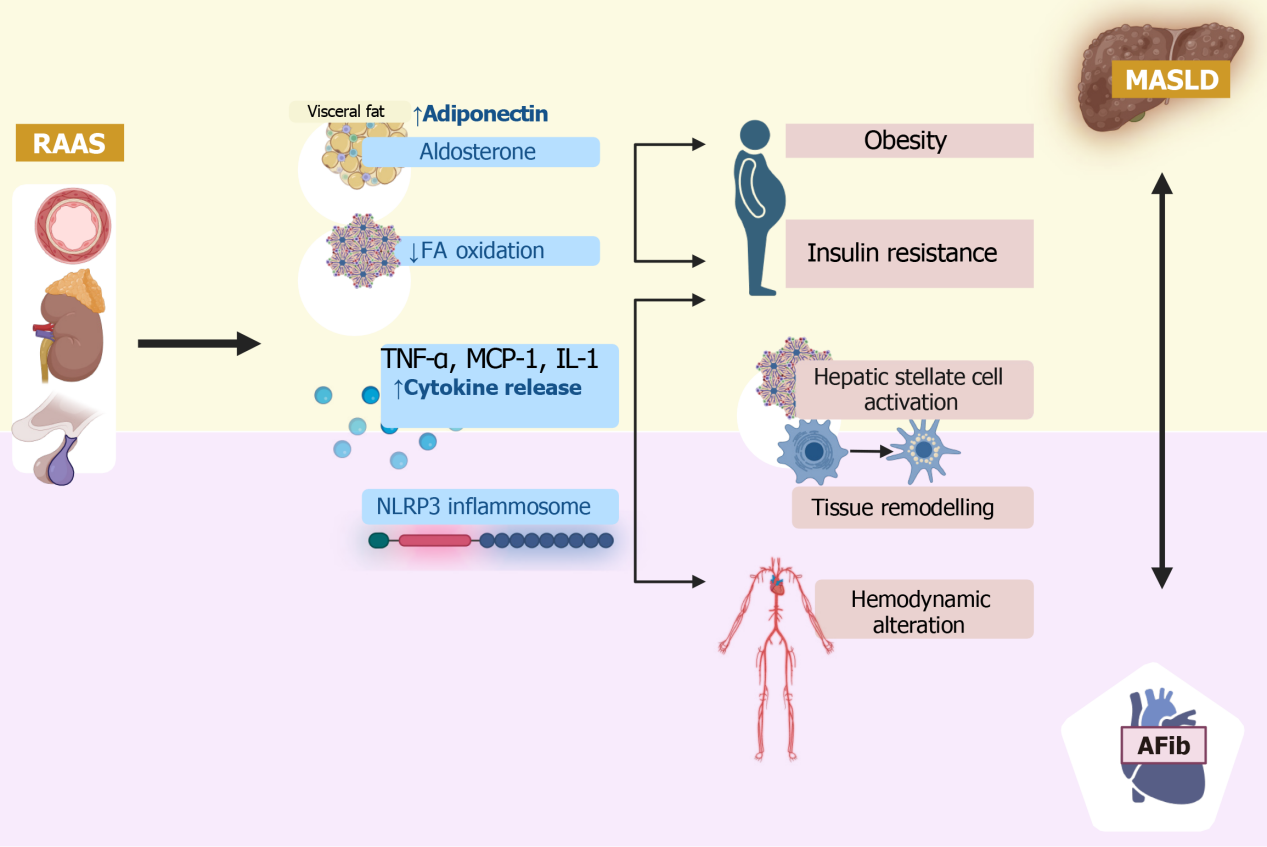

Figure 2 Association between metabolic dysfunction-associated steatotic liver disease and atrial fibrillation. AFib: Atrial fibrillation; FA: Fatty acid; CPAP: Continuous positive airway pressure; GLP-1RA; Glucagon like peptide-1 receptor agonist; iCa: Intracellular calcium; MASLD: Metabolic dysfunction-associated steatotic liver disease; OSA: Obstructive sleep apnea; RAAS: Renin-angiotensin-aldosterone-system; TNF-α: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor. Created in BioRender (Supplementary material).

scarring[151]. The direct impact of Resmeritom on the incidence of AF remains unstudied. The study noted that Resmetirom had no effect on heart rate and was not linked to arrhythmias, suggesting a favorable cardiovascular safety profile in this patient population, however, more research is required to establish risk reduction of AF in patients with MASLD [151].

Other potential pharmacological treatments include Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and thiazolidinediones (TZD). Multiple phase II and phase III trials have highlighted the efficacy of GLP-1RAs in reducing hepatic fat content and liver histological inflammation and fibrosis among MASLD patients[152-154]. These medications have been incorporated in the guidelines to manage diabetes, a major metabolic risk factor for arrhythmia[155,156]. Furthermore, obesity plays a notable role in the prognosis of AF among MASLD patients and is an independent risk factor for AF[56]. Thus, the weight loss effects linked to GLP-1RAs, especially when used in conjunction with glucose-dependent insulinotropic peptide or glucagon, could potentially lower the risk of AF in individuals with MASLD[157]. GLP-1RAs have been studied for their impact on AF in patients with T2DM and may have a beneficial effect on reducing the incidence of AF. A real-world cohort study found that GLP-1RA use was associated with a lower risk of AF compared to dipeptidyl peptidase-4 inhibitors but showed no significant difference when compared to sodium-glucose cotransporter 2 inhibitors[158]. Meta analysis of randomized clinical trials have provided mixed results however, one meta-analysis reported no significant increase in the risk of AF with GLP-1RA use while another meta-analysis specifically focusing on semaglutide found a significant reduction in the incidence of AF by 42% compared to placebo[159,160]. In the context of TZDs, Pioglitazone has been shown to decrease liver fat and/or improve liver histological features in patients with MASLD, in addition to raising the levels of circulating adiponectin[161-163]. The American Association of Clinical Endocrinologists and the American Association for the Study of Liver Diseases also recommend pioglitazone for patients with T2DM and biopsy-proven MASH, a condition closely related to MASLD, due to its efficacy in improving liver histology and cardiometabolic outcomes[164]. A meta-analysis examining the use of pioglitazone and its association with AF risk indicates that pioglitazone may offer protective effects against AF in patients with diabetes[165]. While specific data on the impact of pioglitazone on the risk of AF in patients with MASLD is limited, its overall cardiovascular benefits, including the reduction of AF incidence in broader populations, suggest a potential positive impact in this subgroup as well.

Management of underlying risk factors could have a role in mitigating the risk of AF in MASLD. The relationship between MASLD and hypertension is characterized by a reciprocal reinforcement, where each condition exacerbates the other. In the context of AF pathophysiology, a reduction in blood pressure diminishes the load on the LV. Therefore, implementing more stringent blood pressure control could be advantageous in reducing LVH, myocardial fibrosis,

diastolic dysfunction, and the retrograde stretching and structural remodeling of the atria. Recent research has indicated the potential role of RAAS blockers, including angiotensin receptor blockers and ACE inhibitors, in treating cardiovascular complications associated with MASLD. These agents can reduce hepatic inflammation and fibrosis, which are key components of MASLD, and also mitigate atrial structural remodeling and fibrosis, which are critical in the pathogenesis of AF[166,167]. The American College of Cardiology/American Heart Association guidelines suggest that RAAS blockers may have a role in preventing AF, particularly in patients with heart failure or hypertension, although the evidence is not robust enough to make a strong recommendation for their use solely for AF prevention[168]. In summary, RAAS blockade may reduce the risk of AF in patients with MASLD by addressing common pathophysiological pathways such as inflammation and fibrosis. However, while promising, the evidence is not yet conclusive, and further large-scale, long-term studies are needed to establish definitive clinical guidelines.

Statins, known for their cholesterol-lowering properties, are predominantly utilized in the treatment of atherosclerosis. Recently, there has been a growing interest in exploring their potential therapeutic role in managing MASLD[169,170]. A retrospective cohort study identified a protective association with the progression of fibrosis risk in primary care patients with MASLD who were prescribed moderate and high-intensity statins[169]. Statins have been shown to improve liver biochemistries and reduce cardiovascular events in patients with MASLD[171]. ACC and AHA recommend the use of statins in patients with chronic liver disease, including MASLD, when indicated for cardiovascular risk management [172]. Statins have been investigated for their potential role in the management of AF due to their pleiotropic effects, including anti-inflammatory and antioxidant properties. However, the evidence regarding their efficacy in preventing AF is mixed. In a study involving elderly patients diagnosed with AF, the American Heart Association identified that statin therapy is independently linked to a 13% to 17% reduction in stroke risk. This evidence indicates that statins may serve as an undervalued strategy for mitigating stroke risk in the AF population[173]. While retrospective data looks promising, a larger placebo-controlled trial of rosuvastatin did not demonstrate a reduction in postoperative AF[174]. The European Heart Rhythm Association, the European Association of Cardiovascular Prevention and Rehabilitation and Heart Rhythm Society have noted that while low HDL-C and high TG levels are associated with increased AF risk, the evidence for targeting LDL-C or TC to reduce AF risk is weak[90]. Therefore, while statins are beneficial for cardiovascular risk reduction in patients with MASLD, their role in specifically reducing the risk of AF in this population is not well-established. OSA is another risk factor implicated in shared pathogenesis of AF and MASLD. Research indicates that the implementation of continuous positive airway pressure (CPAP) therapy in individuals with OSA can markedly decrease the recurrence of AF. A meta-analysis involving 1087 patients demonstrated that CPAP therapy was associated with a marked decrease in AF recurrence rates following treatment for the arrhythmia, such as catheter ablation, thereby highlighting management of OSA for long-term treatment of AF[60].

An important aspect of management and mitigation of risk is screening. Liver stiffness measurement by transient elastography and FIB-4 score are recommended screening protocols for MASLD patients, as endorsed by the American Gastroenterological Association and the American Diabetes Association[175,176]. Regarding electrocardiogram screening for patients with MASLD, additional research is necessary before making recommendations. The USPSTF, in a 2022 update to their 2018 guidelines, determined that there is currently insufficient evidence to evaluate the advantages and disadvantages of screening for AF[177].

Future research should explore the impact of emerging MASLD therapeutic agents on the incidence and recurrence of cardiac arrhythmias. For example, gut microbiome and dysbiosis have garnered interest in the pathogenesis of AF and MASLD. Exploratory treatments for MASLD, such as dietary changes, prebiotics, probiotics, and fecal microbiota transplantation, are being investigated with the goal of reestablishing a balanced microbiota. This approach is intended to enhance liver function and alleviate metabolic dysfunction[118]. However, further investigations are warranted to fully understand the causal relationships and underlying mechanisms involved, as well as to identify specific microbial targets for clinical intervention. Understanding the role of these treatments in modifying arrhythmogenic risk may provide a new avenue for comprehensive management strategies targeting both MASLD and associated cardiovascular complications.

CONCLUSION

MASLD is increasingly recognized as a significant risk factor for various cardiovascular conditions, particularly AF. This association is independent of other common risk factors like age, sex, and diabetes (Figure 3). The severity of MASLD does not seem to directly influence the risk of AF, suggesting that even early stages of liver disease can increase susceptibility to this arrhythmia. Given the rising prevalence of both MASLD and AF, especially among aging populations, the clinical implications are profound, necessitating enhanced cardiovascular risk assessments and targeted management strategies for at-risk individuals. As the healthcare burden associated with AF continues to grow, understanding the interplay between MASLD and AF becomes crucial for public health initiatives and clinical practice. Strategies that integrate the management of both conditions may improve patient outcomes and reduce healthcare costs associated with cardiovascular events and complications related to liver disease.

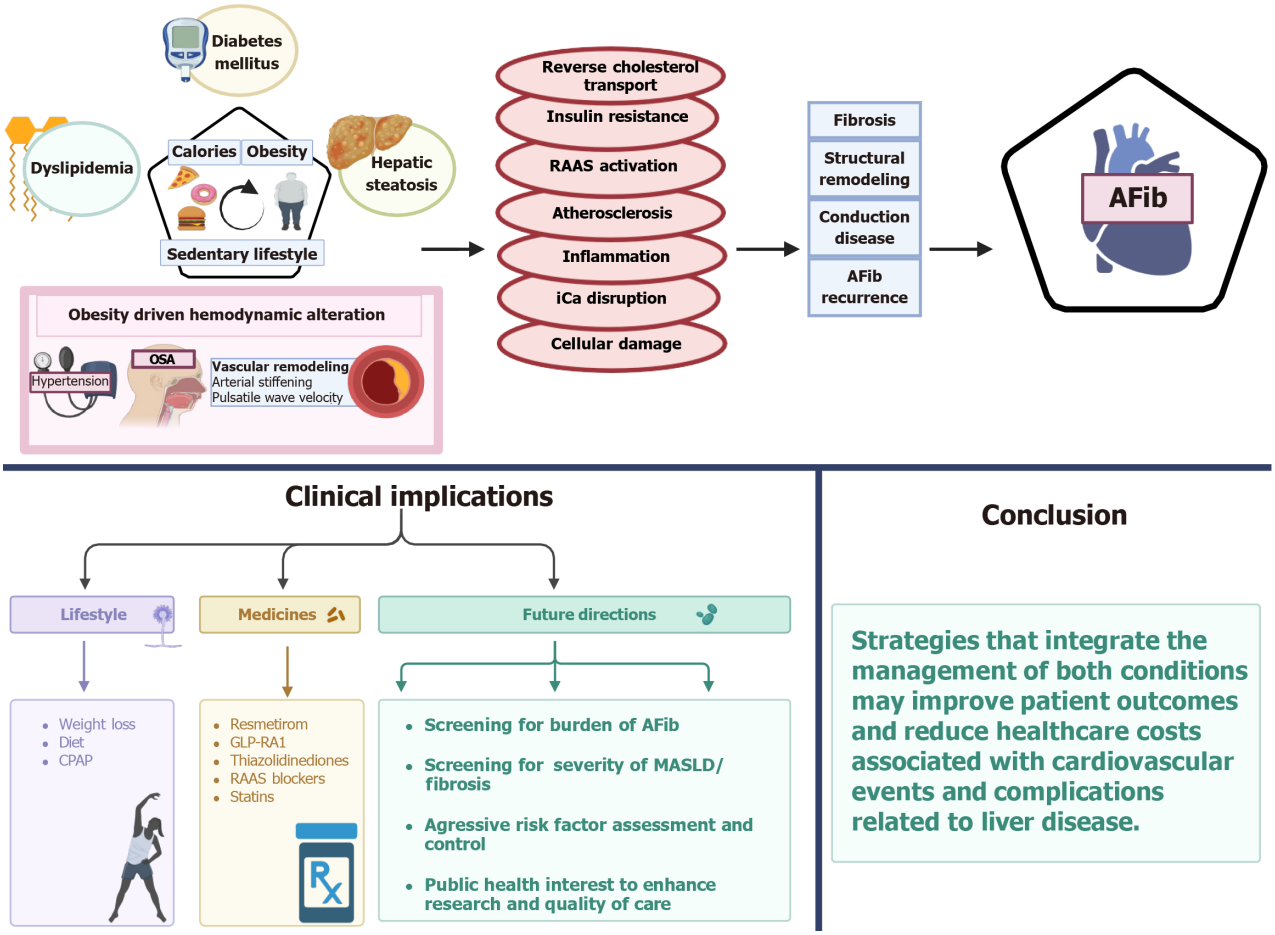

Figure 3 Central illustration. AFib: Atrial fibrillation; FA: Fatty acid; CPAP: Continuous positive airway pressure; GLP-1RA; Glucagon like peptide-1 receptor agonist; iCa: Intracellular calcium; MASLD: Metabolic dysfunction-associated steatotic liver disease; OSA: Obstructive sleep apnea; RAAS: Renin-angiotensin-aldosterone-system; TNF-α: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor. Created in BioRender (Supplementary material).

FOOTNOTES

Author contributions: Bharaj IS and Sohal A conceptualized and designed the study; Bharaj IS, Brar AS, Kahlon J, Hotwani P, Kumar V and Singh A conducted the literature review, interpreted data, created artwork, and drafted the original manuscript; Bharaj IS, Batta A and Sohal A supervised the study and made critical revisions.

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REVIEW

Impact of gut microbiome on atrial fibrillation: Mechanistic insights and future directions in individualized medicine

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Abstract

Atrial fibrillation (AF) is a growing global health burden, with a prevalence of over 52.55 million cases. Rising disability-adjusted life-years, increasing age, and disparities in care have contributed to the worsening severity and mortality of AF. Modifiable risk factors, such as hypertension, obesity, and diabetes mellitus, are associated with alterations in gut microbiota, making the gut-heart axis a potential therapeutic target. Gut dysbiosis influences AF pathogenesis through inflammation, metabolic disruption, and autonomic dysfunction. Key mechanisms include gut barrier dysfunction, short-chain fatty acid (SCFA) depletion, lipopolysaccharides (LPS)-induced inflammation, and ferroptosis-mediated atrial remodeling. Trimethylamine N-oxide, bile acids, and tryptophan metabolites contribute to arrhythmogenic remodeling. Emerging evidence suggests that dietary interventions, including prebiotics and probiotics, as well as gut

surveillance, may help mitigate AF progression. Clinical implications of gut modulation in AF include personalized dietary strategies, microbiome assessment through metagenomic sequencing, and targeted interventions such as SCFA-based therapies and ferroptosis inhibition. Metabolite surveillance, including LPS and indoxyl sulfate monitoring, may influence the effectiveness of anticoagulant and antiarrhythmic therapy. Despite growing mechanistic evidence linking gut dysbiosis to AF, clinical applications remain unexplored. This review summarizes the current understanding of the gut microbiome's role in AF.

Key Words: Atrial fibrillation; Gut microbiome; Dysbiosis; Inflammation; Short-chain-fatty-acid; Trimethylamine N-oxide; Ferroptosis; Lipopolysaccharides; Microbiome-based therapy; Individualized care

Core Tip: Gut microbiome alteration contributes to the generation of harmful metabolites, loss of gut integrity, and cardiac remodeling. Gut dysbiosis interacts with modifiable risk factors to promote cardiac tissue remodeling. Animal models and clinical studies indicate that microbial composition is associated with arrhythmogenesis, atrial fibrillation (AF) recurrence, and modulates medication response. Integrating microbiome surveillance and gut microbiome modulation therapy into AF management may slow disease progression and reduce the arrhythmia burden. However, clinical trials are needed to establish causality and support the incorporation of gut modulation into clinical care.

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INTRODUCTION

Atrial fibrillation (AF) affects an estimated 52.55 million people worldwide[1]. The rising number of disability-adjusted life-years (DALY), an indicator of disability, highlights the widening care gap in AF management and disease burden[1]. DALY rose from 3.3 million cases in 1990 to 8.3 million in 2021[1]. Over the past 30 years, increasing age, higher rates of modifiable risk factors, greater public awareness, and disparities in care have contributed to the growing severity and mortality of AF[1].

Gut dysbiosis is characterized by a high *Firmicutes*/*Bacteroidetes* (F/B) ratio and contributes to atrial tissue remodeling. Microbial imbalance (dysbiosis) interacts with modifiable AF risk factors, such as hypertension, obesity, and diabetes mellitus, which are linked to dietary factors (Figure 1)[2]. Chen *et al*[3] emphasizes that intestinal microbiome imbalance plays a significant role in the emergence and progression of AF[3]. The gut microbiota, a complex community of bacteria residing in the intestines, is directly influenced by dietary intake and can, when imbalanced, impact cardiovascular health [4]. Gut microbiome-targeted therapies are key areas for intervention.

This review examines the clinical significance of gut microbiota in AF, with a focus on current evidence and future implications. It reviews the mechanisms through which intestinal flora and their metabolites contribute to the onset of AF. We will also examine the bidirectional relationship between gut health and cardiac function. By correlating gut dysbiosis to established risk factors, this review underscores the potential for targeted interventions, the need for clinical evidence, and randomized controlled trials to characterize this association further.

Despite growing evidence linking gut dysbiosis to AF, a gap remains in clinical studies connecting gut microbiome-modulating therapies with improved AF outcomes[5]. This review discusses individualized therapeutic interventions to optimize AF management, including dietary modification, microbiome surveillance, and pharmacological strategies. Finally, we will highlight future research directions in this evolving field.

PATHOGENESIS

The gut microbiota is a complex community of bacteria, viruses, and fungi in our intestines[6]. It is primarily composed of *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria*. The F/B ratio is a relative estimate of intestinal microbial health (lower F/B ratio) or disease state (higher F/B ratio)(Figure 1)[7]. This ecosystem develops from birth and changes in response to diet, medication use, and overall health[8]. It produces substances crucial for the host's immune system development and regulation. Imbalances in the gut microbiota have been linked to various disorders, including cardiovascular diseases[9,10].

The gut microbiome is involved in cardiometabolic disease pathogenesis[11]. Diabetes, obesity, and hypertension increase AF risk and demonstrate gut dysbiosis[12–14]. However, the role of gut microbiota in AF within specific patient populations needs to be explored, and its potential as a therapeutic target warrants further investigation. Gut dysbiosis

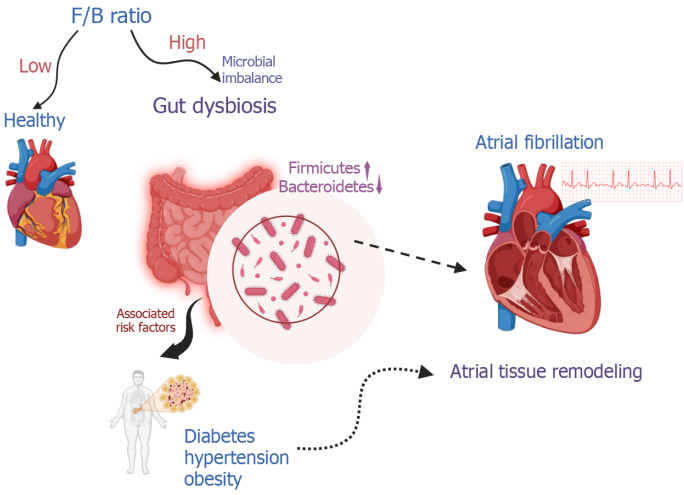

Figure 1 Gut dysbiosis and its role in atrial fibrillation. F/B: *Firmicutes*/*Bacteroidetes*.

has been observed in individuals with AF through observational and small cohort studies. Zuo *et al*[15] found that patients with paroxysmal and persistent AF have distinct gut microbiota and metabolite profiles compared to non-AF individuals[15].

Additionally, the composition of gut bacteria varies with AF duration and treatment modality. Persistent AF is linked with a decreased abundance of *Butyricicoccus* and *Paraprevotella* and an increased abundance of *Blautia*, *Dorea*, and *Coprococcus*. However, the exact nature of the causal relationship between AF and gut microbiota requires further exploration.

Gut dysbiosis contributes to AF through multiple interconnected pathways. Dysbiosis leads to a reduction in beneficial short-chain fatty acid (SCFA), loss of gut integrity, and leakage of harmful metabolites[10]. These disruptions trigger systemic inflammation, ferroptosis, and atrial remodeling, ultimately promoting AF (Figure 2). In the section below, we will discuss the various components involved in these pathways and their clinical relevance.

Gut lining

Gut dysbiosis damages the gut lining by triggering an inflammatory response and reducing the production of SCFAs. Low SCFA butyrate levels weaken the gut barrier, as butyrate increases tight junction proteins in the gut lining[10]. Harmful metabolites enter the circulation through dysfunctional mucosa. Reduced mucin production promotes AF through immunomodulation[16].

The endocannabinoid system dose-dependently improves gut integrity in mouse models[17]. It acts similarly on human coronary endothelial cell models. Enhanced integrity due to the endocannabinoid system prevents endothelial damage in response to hyperglycemia[18]. Dietary fibers and probiotics enhance gut integrity.

Ferroptosis cell death

Ferroptosis is a cell death mediated by iron-dependent lipid peroxidation and is involved in AF pathogenesis[19]. It is regulated by glutathione peroxidase 4 (GPX4), an enzyme that inhibits lipid peroxidation[20]. Decreased GPX4 promotes iron accumulation, leading to phospholipid membrane dysfunction[21]. Membrane lipid peroxidation releases reactive oxygen species (ROS) and harmful metabolites, damaging organelles[20]. Iron buildup in the body upregulates cardiac ferroptosis by increasing the availability of availability of activated iron. Additionally, damage-associated molecular patterns cause immunomodulation.

Gut bacteria upregulate ferroptosis in response to cell damage or inflammation[22]. They regulate ferroptosis locally by modulating iron absorption and storage[23]. Additionally, gut microbiota influences hepcidin[24].

Ferroptosis causes mitochondrial dysfunction, oxidative stress, electrical remodeling, ion channel dysregulation, and impaired autophagy, contributing to AF[19]. Loss of mitochondria depletes the energy available for contraction. Iron-dependent Fenton reactions generate ROS that remodel atria[25,26]. Cytoplasmic calcium leakage, rectifier potassium channel upregulation, and alterations in connexin propagate electrical remodeling. Cellular changes reduce conduction velocity and shorten the atrial refractory period[27]. Additionally, it triggers the interleukin (IL)-6/signal transducer and activator of transcription 3 pathway and plays a role in hypercoagulability[28].

Clinical implication: Probiotics can regulate iron absorption. Probiotics containing *Lactobacillus* alimentarus NKU556 have improved iron absorption[29]. *Bifidobacteria* and *Lactobacillus* may enhance iron bioavailability by decreasing pondus hydrogenii. Conversely, *Escherichia coli* (*E. coli*) downregulates the Fenton reaction to reduce inflammation[30]. *Lactobacillus* rhamnosis reduces ROS generation by influencing NADPH oxidase 1 (NOX1), and Butyrate-producing bacteria reduce ROS by inhibiting NOX2.

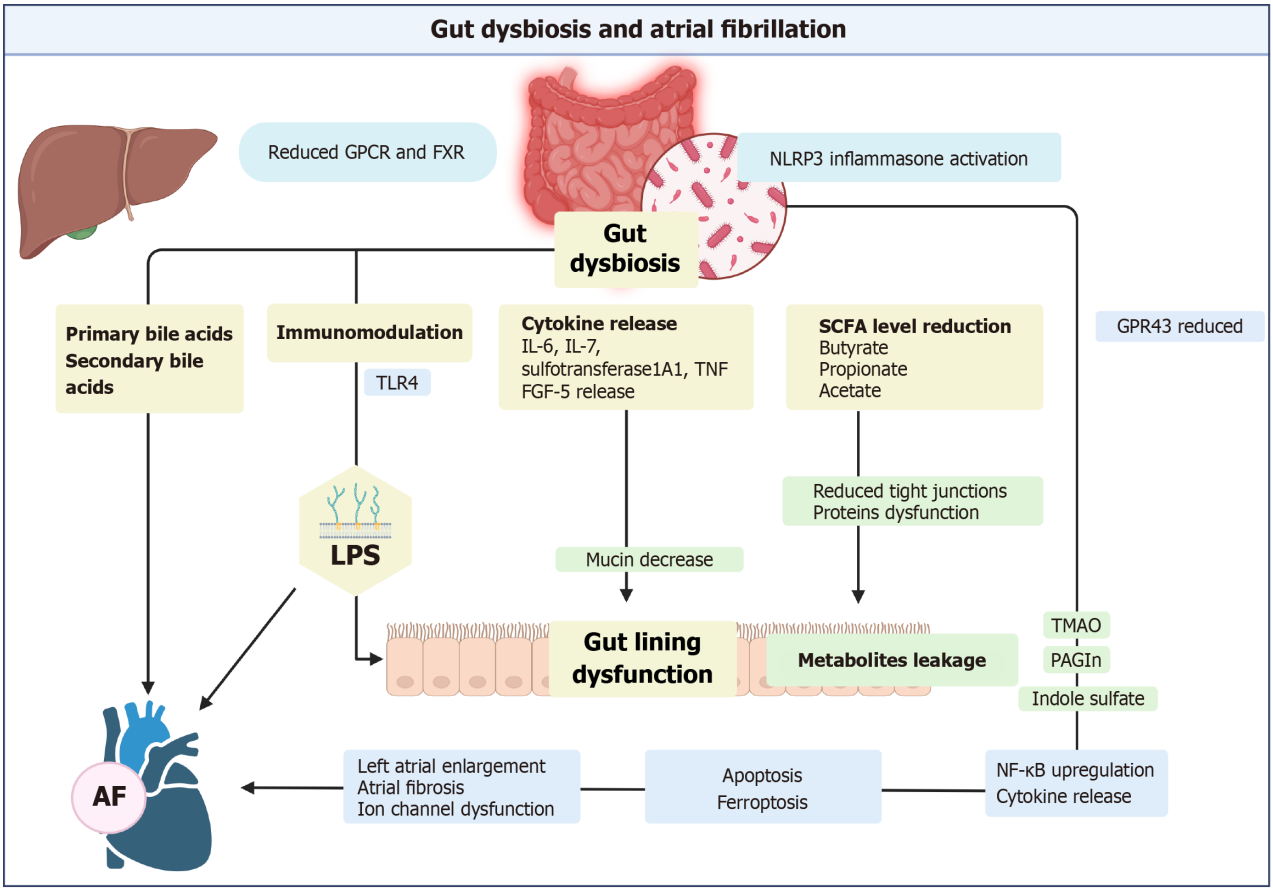

Figure 2 Pathological link between gut dysbiosis and atrial fibrillation. AF: Atrial Fibrillation; FGF: Fibroblast growth factor; GPCR: G-protein coupled receptor; GPR: G-protein-coupled receptor; IL: Interleukin; LPS: Lipopolysaccharides; NF-κB: Nuclear factor kappa B; NLRP3: Nod-like receptor protein 3; PAGIn Phenylacetylglutamine; SCFA: Short-chain fatty acids; TNF: Tumor necrosis factor; TLR: Toll-like receptor; TMAO: Trimethylamine N-oxide.

GUT METABOLITES

Gut bacteria contribute to the AF substrate through their influence on metabolite production. These metabolites cross the intestinal lining, modulate immune responses, and function as signaling molecules within the host[11]. Nod-like receptor protein 3 (NLRP3) inflammasome activation generates a substrate for AF both directly and indirectly[31,32]. Inflammasome activation leads to the release of inflammatory cytokines and the development of AF[33]. Gut dysbiosis activates signaling pathways nuclear factor kappa B (NF-κB), toll-like receptor (TLR)-4, and NLRP3[34]. These pathways interact with CD40L, leukemia inhibitory factor receptor, IL-2 receptor subunit Beta, and Fms-related tyrosine kinase-3 ligand, resulting in the release of IL-6, IL-7, sulfotransferase 1A1, tumor necrosis factor (TNF), and fibroblast growth factor 5. These molecules potentiate AF risk through complex interactions. Additionally, the autonomic nervous system sustains AF and is a target for research focusing on pulmonary vein and atrial tissue changes[35,36].

Trimethylamine N-oxide

The gut microbiota plays a crucial role in the production of trimethylamine N-oxide (TMAO). It converts dietary choline or L-carnitine into trimethylamine. This gaseous product enters the circulation and is oxidized into TMAO by hepatic flavin-containing monooxygenases[37]. MAO triggers inflammatory pathways, increasing autonomic activity and inducing AF. Yu *et al*[38] injected TMAO into specific nerve clusters in canine hearts, which resulted in rapid electrical changes compared to controls. Increased pro-inflammatory molecules, such as IL-1β, IL-6, and TNF-α, accompanied this. Similarly, elevated TMAO levels increased cardiac dysfunction, heart weight gain, and cardiac fibrosis in mice[39]. Cardiac changes were attributed to collagen accumulation, higher profibrotic markers, elevated inflammatory factors, and activation of the NLRP3 inflammasome.

While TMAO is linked to cardiovascular disease, its specific role in AF remains contested due to inconsistent findings across studies[40]. Svingen *et al*[41] noted that plasma TMAO levels and AF have a consistent association after adjusting for traditional AF risk factors and dietary choline intake. Conversely, Büttner *et al*[42] and Florea *et al*[43] observed no significant difference in plasma TMAO levels between individuals with and without AF when patients with coronary artery disease were removed from the analysis. The selection of the patients, the number of comorbidities, and the adjustment of confounders could explain the differences between the findings mentioned above.

Clinical implications: Due to the common risk factors shared by AF and many cardiac diseases, it is currently challenging to determine whether TMAO is a direct cause of AF or an incidental factor. Further clinical evidence is

needed to validate its potential as a therapeutic target in the future.

SCFAs

Colonic microbiota ferment glucose and dietary fiber, producing SCFAs. SCFA is an energy source utilized by the gut, resulting in secondary byproducts. The byproducts differentially modulate the host's immune system. Acetate, butyrate, and propionate are the most active and important, accounting for 95% of the SCFA[44]. Sodium butyrate exhibits anti-inflammatory properties against lipopolysaccharides (LPS), an endotoxin found in Gram-negative bacteria[45]. Butyrate lowers blood pressure by increasing the levels of nitric oxide synthase.

SCFA enhances T-cell differentiation into effector T cells, such as T helper (Th) 1 and Th17 cells, while also promoting the coexistence of anti-inflammatory IL-10+ regulatory T cells. SCFAs bind to G-protein-coupled receptor 43 (GPR43), significantly modulating inflammatory responses[46,47]. G-protein coupled receptor activation reduces the expression of genes implicated in cardiac hypertrophy, cardiorenal fibrosis, and inflammation[48–50]. Animal studies have demonstrated that stimulation of GPR43 by SCFAs is essential for reducing inflammation. Conversely, GPR43-deficient immune cells, particularly leukocytes, exhibit increased production of inflammatory mediators and enhanced immune cell recruitment[51].

AF, aging, and gut dysbiosis reduce SCFA production. AF lowers SCFA-producing bacterial species (prevotella), Kyoto Encyclopedia of Genes and Genomes orthologues, and enzymes involved in SCFA synthesis. Leukocyte GPR43/NLRP3 interactions may be utilized for microbiome evaluation, as they mediate the effect of SCFAs on AF[52,53]. Fang *et al*[54] demonstrated that reduced acetic acid disrupted GPR43 and NLRP3 expression in peripheral blood leukocytes and contributed to left atrial enlargement. GPR43 mRNA levels correlate positively with acetic acid levels in the fecal samples and negatively with NLRP3 mRNA expression. Crucially, GPR43 levels are inversely correlated with the diameter of the left atrium.

Clinical implication: Direct evidence linking SCFAs to AF is limited. Indirectly, low SCFA levels are associated with traditional AF risk factors such as hypertension, obesity, heart failure (HF), and atherosclerosis[55]. Gut surveillance through a constructed GPR43–NLRP3 score demonstrates the potential for predicting AF.

LPS

LPS are an endotoxin found in the outer layer of gram-negative bacteria. LPS-producing microbes are more prevalent in the gut of AF patients. They are implicated in AF development due to their role in immunomodulation, inflammation, and loss of gut integrity. Kong *et al*[56] noted that a high-fat diet alters gut microbiota and increases LPS production.

LPS decreases the expression of L-type calcium channel subunits (α1C and β2) and increases the expression of connexin 43. TLR-4 activation upregulates NF-κB activation, which increases pro-inflammatory cytokines in the atria[10]. These changes shorten the effective refractory period and induce AF[57,58]. Aging exerts a similar effect on the atrial tissue as a rise in LPS concentration[34].

Incorporating LPS measurements into risk models significantly enhances their ability to predict new-onset AF (NOAF) in specific sub-groups. Ren *et al*[57] observed that elevated LPS levels in patients with ST-elevation myocardial infarction (MI) predicted the development of NOAF. Similarly, Xu *et al*[59] correlated the risk of NOAF after lung cancer surgery with LPS elevation.

Clinical implication: Incorporating LPS measurement into standard risk assessment models may improve NOAF prediction. Following a Mediterranean diet rich in fruits and legumes reduces circulating LPS levels and warrants further clinical inquiry[60].

Primary and secondary bile acids

Bile acids (BAs) are systemic signaling molecules involved in fat and vitamin absorption[61]: Taurine and glycine conjugation in the liver results in primary BAs (cholic and chenodeoxycholic acid). Gut microbiota deconjugation produces secondary BAs, including deoxycholic and lithocholic acid, which are then reabsorbed[62]. Farnesoid X receptor (FXR), a nuclear transcription factor, regulates BAs. It prevents BA overload, reducing bile acid-mediated adverse effects on atrial cardiomyocytes[63].

Gut dysbiosis decreases secondary BAs and increases primary BAs. AF patients have elevated chenodeoxycholic acid levels, which are associated with atrial enlargement and electrical abnormalities. BA ratio alteration promotes atrial cardiomyocyte apoptosis[64–66]. Additionally, primary BA induces structural remodeling, cardiac fibrosis, and NLRP3 inflammasome activation[66]. In contrast, secondary BAs, such as ursodeoxycholic acid, exert antiarrhythmic effects through stabilization of the cell membrane potential[67,68]. However, specific secondary BAs (glycolithocholate sulfate and glycocholenate sulfate) are linked with AF risk in African-American cohorts, suggesting a complex interaction[69].

Clinical implication: Steroidal and Nonsteroidal FXR agonists are currently the subject of pre-clinical and clinical trials and may have a potential therapeutic role[63].

Tryptophan metabolite and indole derivatives

Tryptophan is an amino acid involved in obesity-mediated inflammation[70]. The gut microbiome differentially metabolizes tryptophan into either beneficial or harmful metabolites, depending on the available substrate[71]. Clostridium sporogenes metabolized tryptophan into beneficial indoleacetic acid and indole propionic acid (IPA). Conversely, *E. coli* metabolizes tryptophan into the harmful indole through the tnaA-encodedtryptophanasee enzyme.

The microbial composition determines whether tryptophan metabolism is detrimental or beneficial by regulating the metabolites formed. IPA maintains the gut lining by regulating the TLR pathway[72]. Downstream IPA inhibits atherosclerosis and exhibits an anti-inflammatory effect[73,74].

Indole sulfate is a harmful metabolite formed from indole in the liver and excreted by the kidneys[75]. It is implicated in arrhythmogenesis. In rabbit models, indoxyl sulfate (IS) promoted arrhythmogenesis in the arrhythmogenesis in the pulmonary veins and left atrium[76]. Arrhythmias are attributed to disruptions in cardiomyocyte calcium handling, profibrotic signaling, and oxidative stress[76,77]. However, discrepantly high IS plasma concentrations identified in animal models require contextual consideration, as humans have significantly lower circulating levels. Finally, kidney function regulates IS clearance; its accumulation in chronic kidney disease patients may create a proarrhythmic environment, as observed in animal models[75].

Clinical implication: The gut microbiome differentially metabolizes tryptophan into beneficial or harmful metabolites based on substrate availability.

Phenylacetylglutamine

Post-MI mouse models with gut dysfunction demonstrated Phenylacetylglutamine (PAGln) elevation and correlated it with the risk of NOAF in the cohort. PAGln-producing bacteria impair claudin-1 and occludin gut barrier proteins, resulting in PAGln translocation across the gut. PAGln activates the NLRP3 inflammasome in cardiac tissue, increasing atrial ectopy through the release of IL-1β, IL-6, and TNF-α[78]. Ferroptosis and PAGln-mediated collagen deposition impair electrical conduction through fibrosis and loss of ion channels[78].

Clinical implication: Improvement in gut integrity can reduce the risk of AF in post-MI patients.

CLINICAL IMPLICATIONS OF GUT MODULATION IN AF

Therapy targeting gut dysbiosis can decrease atrial tissue degeneration[55]. Compared to other cardiovascular diseases, gut microbiome surveillance, dietary alteration, and physical activity are underutilized in AF care. The lack of robust clinical evidence limits their use in clinical practice. Gut modulation therapy includes prebiotics, probiotics, dietary modification, supplementation, weight loss, and fecal microbiota transplantation. However, recent advances based on animal, clinical, and trial data highlight the potential of gut health in the care of AF (Table 1)[53,54,57,59,71,78,79].

Microbiome assessment techniques

Microbiome evaluation can be done through fecal sampling. Organism culture, 16S ribosomal sequencing, and mouse models have traditionally been used for assessment but are limited by their precision. Shotgun metagenomic sequencing has revolutionized microbiome assessment[80]. It leverages computing algorithms for data analysis and can identify species that cannot be cultured in the laboratory. Additionally, metaproteomics and metabolomics help us identify proteins involved and byproducts formed in the gut[81,82].

Metabolite surveillance is central to effective gut modulation. Human studies have noted a decrease in IS after successful catheter ablation. Higher IS levels increase the risk of AF recurrence after ablation[83]. Notably, kidney function influences IS levels. Future research warrants further investigation in groups stratified by kidney function[84]. The complex interactions of metabolites with the human body contribute to inaccuracies and limit their use.

GPX4, a regulator of ferroptosis, can predict AF recurrence. Adding GPX4 levels and TGF-β levels to the Left atrial diameter measurements enhances the predictive ability to detect AF recurrence, based on a study of 249 patients[85]. Recent advances can help design wearable sensors that continuously monitor the gut microbiome. Ingestible capsules are implantable chemical sensors being investigated to monitor gut health[86,87]. These sensors are independent circuits with bioreceptors that can analyze body fluids and provide continuous feedback remotely. A similar wearable biosensor was recently used to monitor C-reactive protein continuously through sweat[88]. However, no agreement exists on assessing the microbiota composition or dietary patterns. In the future, prediction models may leverage existing clinical evidence, epidemiologic data, and metabolite evaluation to provide recommendations.

Integration of gut microbiome in personalized AF management

Personalized AF management identifies patients who benefit from gut modulation based on genetic information and comorbidity clustering (Figure 3). Therefore, identifying high-risk or high-benefit groups through microbiome evaluation enables physicians to provide individualized care. Additionally, patients may be divided into subgroups such as older patients, HF patients, post-MI patients, alcohol users, post-ablation patients, or those on certain drugs.

Age-mediated gut dysbiosis increases the risk of AF in older patients[34]. Aging contributes to elevated LPS levels, loss of gut integrity, and increased serum levels of harmful metabolites. These patients may benefit from glucose management, tryptophan supplementation, a high-fiber diet, and monitoring of indole-sulfate levels.

In two recent nested case-control studies, tryptophan supplementation increased the (1) Kynurenine: Tryptophan ratio; and (2) Reduced AF risk[89,90]. In mouse models, tryptophan has been shown to protect against age-mediated dysbiosis [91]. Enhanced gut integrity, improved microbiome diversity, and decreased pro-inflammatory cytokines may explain its beneficial effects[92].

Indole sulfate monitoring can guide tryptophan requirements. The oral tryptophan challenge test (OTCT) categorizes patients into low IS or high IS producers by measuring IS levels 48 hours after tryptophan administration[93]. High IS

Table 1 Recently published evidence supporting the role of gut microbiome targeted therapy in atrial fibrillation management

Ref.	Study year	Category	Index	Key findings
Ren *et al*[57]	2024	Observational study	57	LPS levels associated with NOAF in ST-elevation MI patients
Xu *et al*[59]	2024	Observational study	59	Serum LPS linked to NOAF in cancer patients
Sinha *et al* [71]	2024	*In vivo* and *in vitro*	71	Gut microbiome alters tryptophan metabolism
Fang *et al* [54]	2024	Humans	54	SCFA-dependent G-protein-coupled receptor 43/Nod-like receptor protein 3 score is associated with AF risk
Liu *et al*[53]	2024	Animal model	53	Relationship between gut dysbiosis, aging, and AF risk. Use of SCFA and fecal microbiota transplant to mitigate damage
Shi *et al*[79]	2025	Animal model	126	*Lactobacillus* gasseri prevents ibrutinib-associated AF
Wang *et al* [78]	2025	Animal model	78	Phenylacetylglutamine is associated with increased AF risk in post-MI mice

AF: Atrial fibrillation; LPS: Lipopolysaccharides; MI: Myocardial infarction; NOAF: New-onset atrial fibrillation; SCFA: Short-chain fatty acids.

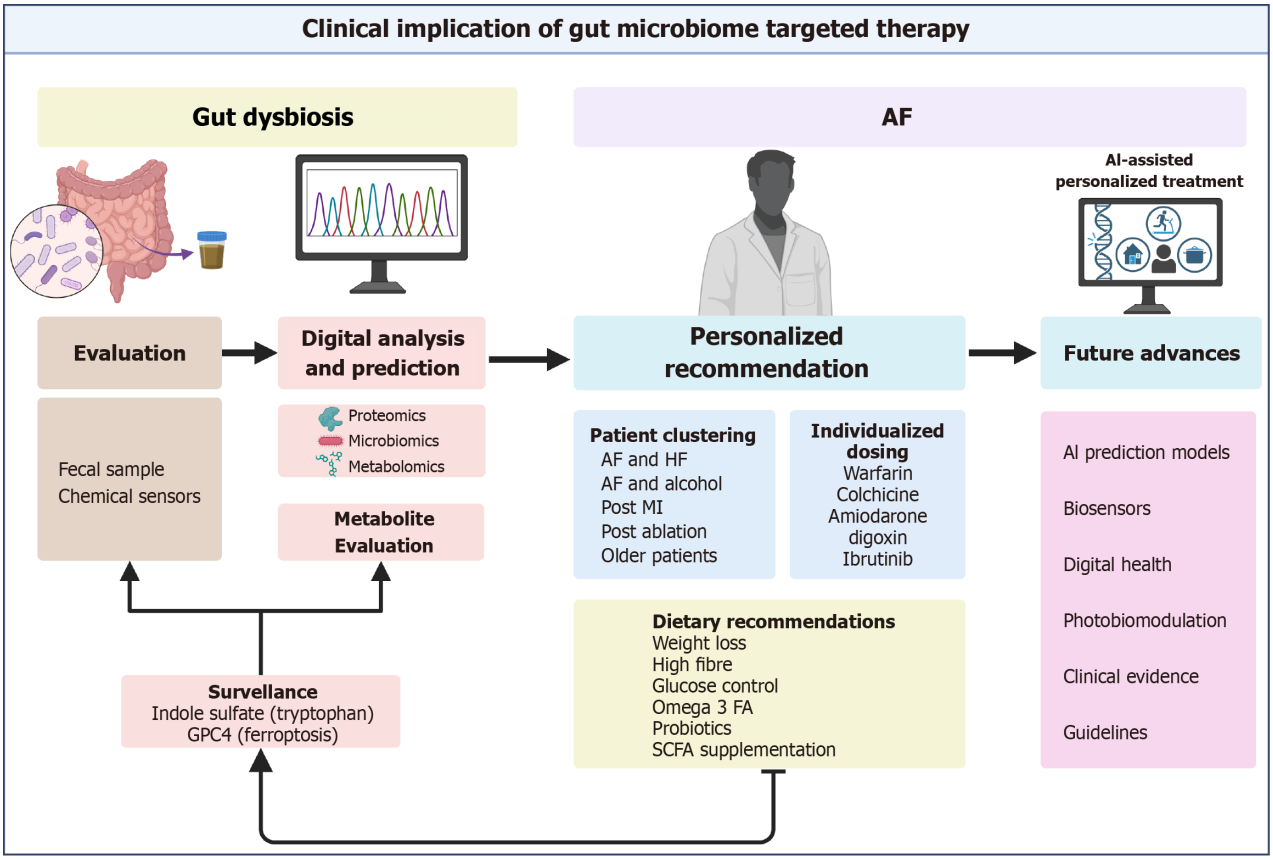

Figure 3 Gut modulation-based individualized care in atrial fibrillation. AF: Atrial fibrillation; GPC: G-protein coupled; HF: Heart failure; MI: Myocardial infarction; SCFA: Short-chain fatty acids.

producers are at an increased AF risk and could benefit from low-tryptophan diets. A high-fiber diet in high IS producers shifts tryptophan metabolism to reduce levels of IS. Further research is needed to explore the clinical applications of OTCT in precision nutrition.

HF-driven intestinal congestion damages the gut mucosa and alters the gut microbiome[94,95]. This congestion gives rise to cardiac cachexia and is associated with poor outcomes[96]. Gut modulation can reduce gut inflammation and improve integrity. Patients with concomitant AF and HF may benefit from gut microbiome-altering therapy.

Alcohol displays a strong link with increased AF risk[97,98]. In these patients, autonomic nervous system dysfunction, ion channel damage, and fibrosis contribute to atrial remodeling[99]. SIRT3 signaling and ferroptosis have been identified as potential therapeutic targets for the treatment of various diseases. Ferroptosis inhibition is a novel therapy to reduce the risk of AF in populations with high alcohol consumption[100].

Dietary strategies to modulate gut microbiome as part of AF management

To effectively implement dietary recommendations, healthcare providers must be grounded in clearly defined biochemical pathways that are tailored to specific patient subgroups and supported by evidence[101]. Clinical evidence suggests that weight loss, physical activity, increased fiber intake, and supplementation can improve gut health[102-104]. Clustering patients based on comorbidities and microbiome phenotypes enables targeted modulation of the gut microbiome for therapeutic benefit.

Weight loss in obese patients restores a healthier F/B ratio and increases beneficial *Rikenellaceae* levels[102]. The increase in *Rikenellaceae* is crucial, as it mediates IL-6, linking the gut microbiome alteration to obesity-related inflammation. Animal models of Metabolic dysfunction-associated steatotic liver disease consistently demonstrate that a high-fat diet correlates with reduced *Rikenellaceae* levels, whereas low body mass index correlates with increased *Rikenellaceae* levels[103,104].

Moreover, improved glucose control suppresses LPS-driven NLRP3-inflammasome activation, a mechanism central to gut dysbiosis[34]. Aging-related gut barrier dysfunction permits increased LPS translocation, underscoring the importance of tight glycemic control in mitigating gut dysbiosis, particularly in older adults.

Fibre slows colon transit time, improves carbohydrate availability, and promotes the microbiome to produce beneficial SCFA-producing metabolites. In contrast, rapid transition limits carbohydrate availability and shifts the substrate to protein, which generates harmful metabolites[105]. Qi *et al*[106] followed 9290 patients for 5.7 years and reported that a high-fiber diet shifted tryptophan metabolism toward the beneficial IPA.

A high-fiber diet offers distinct benefits for AF and HF and positively influences tryptophan metabolism[71]. At a microbial level, HF is associated with low SCFA producers, such as *Bifidobacterium* and *Lachnospiraceae*[107]. Dietary Fibre indirectly boosts SCFA-producing species. Higher SCFA consequently counters atherogenesis, dyslipidemia, and neurohormonal activation[108]. Omega-3 fatty acid (FA), found in fish oil, reduces the harmful metabolites and increases levels of SCFA, such as butyrate[109,110]. A pooled analysis of 54799 patients showed a reduced incidence of AF with omega-3 FA supplementation[111]. Omega-3 FA increased beneficial Akkermansia, restored a healthier F/B ratio, and reduced TMAO, collectively improving endothelial function in a randomized controlled trial[112]. Additionally, mouse models have shown that Akkermansia reduces AF by lowering TMAO[113].

EFA includes FAs such as omega-3 and omega-6 precursors, alpha-linolenic acid (ALA), and linoleic acid (LA). An omega-6/omega-3 ratio of 10/1 to 3/1 is optimal[114,115]. However, Western diets commonly exceed this ratio, with a 15:1 ratio. This results in an omega-3 deficiency because omega-3 and omega-6 compete for the same enzyme, delta-6 desaturase.

ALA supplementation of up to 2.5 g/day reduced AF risk in a cohort of 54260 over a 16-year follow-up[116]. Despite the substrate's preference for ALA, ALA and LA compete for delta-6-saturation reactions. Low ALA, compared to LA, increases anti-inflammatory Arachidonic acid production. Conversely, high ALA forms cell membranes and exhibits anti-inflammatory effects[117]. These findings highlight the gut microbiome's role in balancing the omega-3/omega-6 ratio and the benefits of ALA supplementation.

Pharmacomicrobiomics of AF

Harm from drugs with narrow therapeutic indexes and arrhythmogenic side effects of medications can be mitigated through gut modulation.

Warfarin

Vitamin K production by gut bacteria potentiates the effect of warfarin. Warfarin has a narrow therapeutic index requiring close monitoring. *Enterococcus* is associated with an increased response to warfarin[118]. Conversely, *Bacteroides*, *Shigella*, and *Klebsiella* are associated with a reduced response. Further exploration of warfarin's relationship with bacteria prevalent in patients with AF can improve individualized treatment regimens and enhance patient safety.

Colchicine

Omega-3 FAs are being investigated for their potential to improve gastrointestinal (GI) tolerability by influencing the gut microbiome[119]. Colchicine prevents AF recurrence after cardiac ablation; however, GI intolerance has limited its use [120,121]. GI side effects can be mitigated by using probiotics.

Digoxin

Actinobacterium Egerthella lenta metabolizes digoxin into inactive metabolite dihydro-digoxin through its action at the cardiac glycoside reductase (CGR) operon[122]. Digoxin has a narrow therapeutic index, with high concentrations correlated with mortality in AF patients[123,124]. The CGR protein to *Eggerthella lenta* ratio can predict the amount of digoxin lowered. Enhanced prediction of digoxin levels is critical to patients with HF and AF and requires continued inquiry[122].

Amiodarone

Based on mouse models, the Probiotic *E. coli*-induced cytochrome p450 2C activation alters amiodarone metabolism[125]. Conversely, amiodarone exhibits antibacterial activity against *E. coli*, highlighting a bidirectional relationship[126]. Amiodarone is frequently prescribed in AF, and gut modulation may influence its effectiveness in the future.

Ibrutinib

SCFA-producer *Lactobacillus* gasseri reduces the risk of Ibrutinib-induced AF[79]. Ibrutinib is an anti-cancer drug that increases AF risk *via* the C-terminal Src kinase-Src pathway[127]. It also damages gut integrity. As a result, the gut microbiome mediates Irutinib's effect on atrial tissue and electrophysiology.

CURRENT CHALLENGES

Gut modulation therapy is not yet well defined or integrated into standard care. Animal and clinical studies suggest that dysbiosis contributes to AF progression. However, several important issues must be addressed before gut microbiota can be considered a viable target for AF management.

Specifically, despite the correlation between gut dysbiosis and AF, the safety and efficacy of gut-modulating therapy are yet to be tested robustly in randomized controlled trials.

Most current studies on gut microbiota and AF have focused on bacteria, overlooking the potential involvement of other microorganisms such as fungi, viruses, archaea, and protists. The contribution of non-bacterial microorganisms, individually or as part of microbial communities, to AF development warrants further exploration. Additionally, extracting, sequencing, and identifying microorganisms with smaller genomes, such as bacteriophages, is challenging [128]. Instead of focusing on individual microbes, it is essential to explore the combined effects of microbial communities on gut microbiota.

Dietary habits significantly contribute to long-term changes in gut microbiota, but our understanding of this relationship remains limited. However, research indicates that nutritional patterns modulate the stability of gut microbiota over a six-month period[129]. More research is needed to determine the duration of dietary interventions required to produce lasting effects on gut microbiota.

Future studies should also consider whether certain probiotics and postbiotics can influence AF in humans and whether their use could be incorporated into risk factor modification programs for both primary and secondary prevention of AF[128,130].

Studies of association should be investigated through well-designed, randomized clinical trials that incorporate standardized, prospective microbiota analyses to establish causation. Future research should elucidate and characterize both the direct and indirect benefits of gut-modulating therapy in patients with AF.

FUTURE PERSPECTIVES AND EMERGING THERAPIES

Endocannabinoid system

Human research exploring the role of dysbiosis management in AF care is minimal[131]. The endocannabinoid system enhances gut integrity in mouse models in a dose-dependent manner[17]. It acts on tight junctions[132]. Human coronary endothelial cell models exhibit similar effects on membrane permeability at high glucose levels[18]. Decreased permeability mitigates endothelial damage in response to hyperglycemia. However, this needs human research.

Photobiomodulation

Photobiomodulation altered the gut microbiome in obese mouse models[133]. The infrared and red light projected on mice's abdomens over 2 weeks increased Allobaculum levels. Allobaculum improves gut integrity. Interestingly, exercise also increased Allobaculum levels in obese mice. However, this study was limited in number and requires further inquiry.

CONCLUSION

Gut dysbiosis plays a pivotal role in AF pathogenesis through inflammatory, metabolic, and autonomic pathways. Despite growing evidence linking gut microbiome alterations to the risk and progression of AF, clinical applications remain underexplored. Targeted interventions—such as dietary modifications, microbiome surveillance, and pharmacological strategies—offer promise for the prevention and management of AF.

Technological advancements in microbiome assessment, including metagenomics and wearable biosensors, offer new opportunities for personalized AF care. However, robust clinical trials are essential for validating gut-modulating therapies and establishing their role in routine AF management. Future research should focus on integrating microbiome-based precision medicine into AF care to bridge the evidence gap and improve patient outcomes.

FOOTNOTES

Author contributions: Brar AS, Vemula SL, Yanamaladoddi V, Sodhi S, and Hatwal J conducted the literature review, interpreted data, created artwork, and drafted the original manuscript; Brar AS and Sohal A conceptualized and designed the study; Sohal A and Batta A supervised the study and made critical revisions; all of the authors read and approved the final version of the manuscript to be published.

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MINIREVIEWS

Eosinophilic myocarditis due to parasitic infection: A case-based minireview

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Abstract

Eosinophilic myocarditis (EM) is a rare inflammatory condition of the heart, often associated with eosinophilic infiltration. While its causes range from allergies to autoimmune and infectious diseases, parasitic infections are an uncommon but critical etiology. This mini-review focuses on a case of EM in a 47-year-old male from Vietnam, linked to *Schistosoma spp.*, *Strongyloides stercoralis*, and *Toxocara spp.* infections. The patient presented with severe chest pain and recovered fully after treatment with corticosteroids and albendazole. Drawing insights from this case and existing literature, we discuss the pathophysiology, diagnostic approaches, and therapeutic strategies for parasite-induced EM. Early diagnosis and tailored treatment are essential to improve clinical outcomes, especially in endemic parasitic areas.

Key Words: Eosinophilic myocarditis; Parasitic infection; Corticosteroids; Albendazole; Diagnosis; Vietnam

Core Tip: Eosinophilic myocarditis induced by parasitic infections is often underrecognized despite its severity. A 47-year-old Vietnamese patient with *Schistosoma spp.*, *Strongyloides stercoralis*, and *Toxocara spp.* infections highlights that early diagnosis *via* serological and clinical evaluation, paired with corticosteroids and albendazole, can reverse cardiac dysfunction and prevent fatal outcomes, advocating for heightened awareness in endemic settings.

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INTRODUCTION

Eosinophilic myocarditis (EM) is a rare, potentially life-threatening inflammatory condition characterized by eosinophilic infiltration of the myocardium[1-3], with etiologies ranging from hypersensitivity[4,5] and autoimmune disorders to infections[6-9], including parasitic causes prevalent in endemic areas. This condition can lead to severe complications, including myocardial necrosis, heart failure, and sudden cardiac death, necessitating early diagnosis and intervention[10-13]. Clinically, EM poses diagnostic challenges due to its nonspecific presentation, ranging from chest pain to fulminant cardiac dysfunction, often requiring a combination of laboratory, imaging, and histopathological assessments[14]. This mini-review examines the clinical presentation, pathophysiology, diagnostic strategies, and management of EM, with a focus on its parasitic origins, using a real-world case to illustrate these complexities.

CASE PRESENTATION

A 47-year-old male with a medical history of gout and habitual consumption of fermented meats, raw fish dishes, and fresh vegetables presented to our clinic with severe retrosternal chest pain radiating to the back, associated with dyspnea on exertion. On admission, physical examination revealed tachycardia (heart rate: 108 beats/min), blood pressure of 90/60 mmHg, body temperature of 38 °C, and a respiratory rate of 22 breaths per minute. Cardiac auscultation disclosed muffled heart sounds, suggestive of pericardial involvement.

Initial laboratory investigations demonstrated normal creatine kinase levels but markedly elevated cardiac biomarkers, including high-sensitive cardiac troponin T (hs-cTnT) at 1.95 ng/mL (reference: < 0.014 ng/mL) and N-terminal pro B-type natriuretic peptide (NT-proBNP) at 12740 pg/mL (reference: < 125 pg/mL), which is consistent with myocardial injury and heart failure. Additional findings included hyperuricemia (uric acid: 469.5 μmol/L), hypokalemia (potassium: 2.95 mmol/L), and a normal cortisol level (283 nmol/L). Hematological analysis revealed a white blood cell count of 12.4 × 10^3/μL with significant eosinophilia (19.7%; reference range: 0%-7%). Inflammatory markers were elevated, with C-reactive protein (CRP) at 6.53 mg/L and interleukin (IL)-6 at 17.37 pg/mL.

Electrocardiography (ECG) on admission showed an irregular rhythm (110 beats/min), right axis deviation, QS waves in leads V1-V3, and inverted T waves in leads V4-V6, raising initial suspicion of subacute myocardial infarction with lateral ST elevation.

Transthoracic echocardiography was performed to evaluate cardiac structure and function, revealing hypokinesia of the anterior septum and apex, left ventricular systolic dysfunction with a left ventricular ejection fraction (EF) of 39%, and pericardial effusion, supporting a diagnosis of myocarditis with pericardial involvement. To exclude an ischemic etiology, coronary angiography was conducted, demonstrating no evidence of coronary artery stenosis (Figure 1A and B), effectively ruling out acute coronary syndrome.

Cardiac magnetic resonance (CMR) was subsequently undertaken to further characterize the myocardial pathology. CMR findings included reduced left ventricular end-diastolic volume (44.6 mL), and late gadolinium enhancement affecting > 75% of the myocardial wall thickness in the lateral wall, extending toward the apex (Figure 1C and D). Additionally, bone marrow examination, performed to investigate potential hematologic disorders, revealed eosinophilic hyperplasia (Figure 2).

Given the clinical presentation, eosinophilia, and imaging results, a diagnosis of EM was established. The patient's dietary history prompted serological testing for parasitic infections, which returned positive for *Schistosoma spp.*, *Strongyloides stercoralis*, and *Toxocara spp.* (Table 1). Detailed serological testing methodologies, including assay specifications, cutoff values, and local validation protocols, are provided in the Supplementary material. These findings strongly suggested a parasitic etiology as the underlying cause of EM in this case, guiding subsequent treatment decisions.

Treatment was initiated with a 5-day course of oral prednisolone (40 mg/day) and albendazole (400 mg/day), alongside standard heart failure therapy. Rapid clinical improvement ensued, with hs-cTnT decreasing to 0.051 ng/mL and NT-proBNP to 1311 pg/mL within days. The white blood cell count normalized to 5.2 × 10^3/μL, and eosinophilia resolved.

At one-month follow-up, repeat echocardiography demonstrated full recovery of left ventricular ejection fraction (EF: 64%). Eosinophil levels remained within normal limits, and the patient was asymptomatic, indicating a favorable response to therapy. A detailed timeline of the patient's clinical presentation, diagnostic workup, treatment, and follow-

Table 1 Results of serological testing for parasitic infections

Test name	Result	Reference range
Cysticercus cellulosae	Negative (6.265 NTU)	< 9.0 NTU; Grayzone: 9-11
Echinococcus granulosus	Negative (6.598 NTU)	< 9.0 NTU; Grayzone: 9-11
Fasciola gigantica	Grayzone (0.227 OD)	< 0.2 OD; Grayzone: 0.2-0.3
Schistosoma	Positive (1.127 OD)	< 0.2 OD; Grayzone: 0.2-0.3
Strongyloides stercoralis	Positive (0.865 OD)	< 0.2 OD; Grayzone: 0.2-0.3
Toxocara	Positive (32.445 NTU)	< 9.0 NTU; Grayzone: 9-11
Trichinella spiralis	Grayzone (0.351 OD)	< 0.3 OD; Grayzone: 0.3-0.4

up is provided in Figure 3.

DISCUSSION

Epidemiology of EM

EM is a rare subtype of myocarditis that can affect individuals across all age groups. It is defined by the presence of diffuse or localized myocardial inflammation accompanied by eosinophilic infiltration, typically associated with elevated peripheral eosinophil counts[1-3,15]. However, accurately determining the incidence of EM remains challenging due to its often nonspecific and subtle clinical presentation, which frequently results in diagnoses being made post-mortem through biopsy[16]. Among patients undergoing endomyocardial biopsy (EMB) for suspected myocarditis, EM is identified in 2%-46% of cases, highlighting its rarity and the limited understanding of its pathogenesis[17-21]. The true incidence of myocarditis remains uncertain, partly due to the infrequent use of EMB and the low sensitivity of the Dallas criteria[22]. Systematic studies have revealed that EM is more commonly observed in Caucasian populations, with a mean age of diagnosis around 41 years among those confirmed histologically[23]. Furthermore, two systematic reviews have consistently demonstrated that systemic disorders, such as hypereosinophilic syndrome (HES) or eosinophilic granulomatosis with polyangiitis (EGPA), are associated with EM in 64% to 71% of cases. The remaining cases are classified as idiopathic, where no specific underlying cause is identified[23,24]. Globally, EM is associated with a significant mortality risk of 22% in-hospital and up to 30% within five years if untreated-underscoring the urgency of early diagnosis, particularly in endemic regions[23,25].

Importance of early diagnosis

Early diagnosis of EM is essential for improving patient prognosis, although many complex and rare underlying clinical conditions may delay the diagnostic process. The first step involves hematologic and biochemical testing. Increase in cardiac biomarkers (particularly troponin and NT-proBNP), inflammatory markers (CRP, erythrocyte sedimentation rate, and procalcitonin), and leukocytes (especially eosinophils) are commonly observed[14,23]. It is important to maintain a high level of clinical suspicion, as eosinophilic cardiac involvement can occur even in the absence of peripheral eosinophilia or atopic manifestations at presentation. EM is not always associated with peripheral hypereosinophilia at time of evaluation. Getz *et al*[26] and Watanabe *et al*[27] described a patient with EM who never developed peripheral hypereosinophilia. Galiuto *et al*[28] similarly described a patient in whom EM was confirmed by cardiac biopsy, despite the fact that the initial peripheral blood eosinophil count was only 530/mm^3 and never exceeded 870/mm^3. However, patients without eosinophilia at admission could develop peripheral eosinophilia during hospitalization infiltration[15]. In our patient, laboratory findings of eosinophilia (19.7%), hs-cTnT (1.95 ng/mL), and NT-proBNP (12740 pg/mL) aligned with these expectations, indicating myocardial injury and heart failure.

Diagnostic criteria of EM

The definitive diagnosis of EM requires meeting at least two out of four standard criteria for myocarditis, as outlined by the European Society of Cardiology guidelines. First, the patient must fulfill the four standard criteria for diagnosing myocarditis: ECG, Holter, or stress test abnormalities; elevated myocardial injury markers (troponin I or T); evidence of functional or structural abnormalities on cardiac imaging; and myocardial tissue changes observed on cardiac magnetic resonance imaging (MRI), alongside histological evidence of inflammatory eosinophilic infiltration[14]. The degree of myocardial eosinophilic infiltration depends on the underlying cause, as well as the extent and duration of eosinophil exposure, with parasitic infections often inducing pronounced infiltration due to chronic antigenic stimulation[29,30].

Etiologies of EM

EM has been associated with various conditions. In cases where no specific cause is identified, the condition is considered idiopathic. One recognized form of EM is Loeffler endocarditis. EM is also associated with eosinophilic vasculitides, most notably EGPA (Churg-Strauss syndrome). Other causes include infections, allergic diseases, transplant rejection in heart transplants, and certain malignancies, particularly myeloproliferative disorders and hypersensitivity myocarditis, which

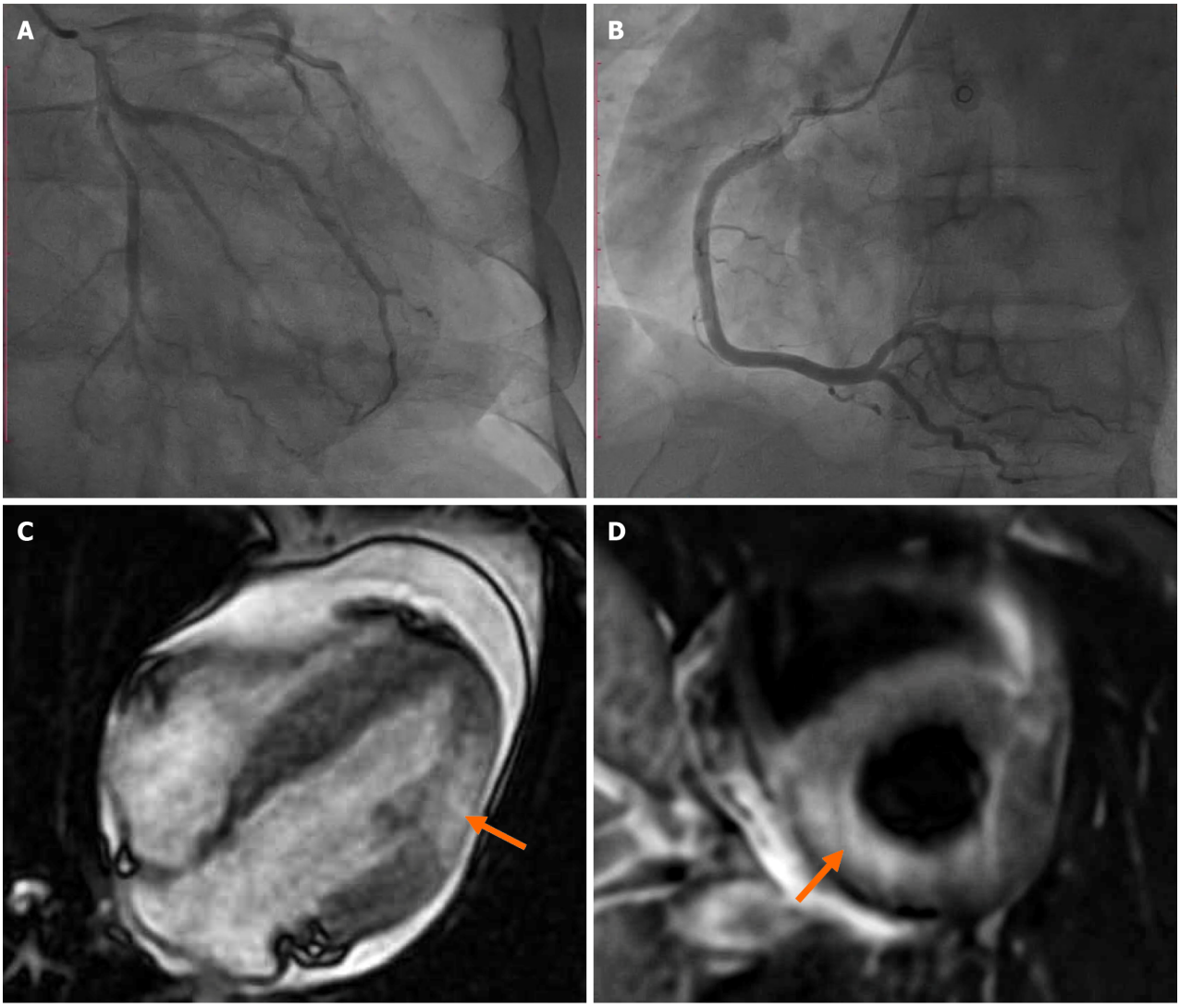

Figure 1 Coronary angiography and cardiac magnetic resonance imaging findings in a patient with suspected myocarditis. A and B: Coronary angiography reveals normal coronary anatomy with no evidence of luminal stenosis, effectively excluding obstructive coronary artery disease; C and D: Cardiac magnetic resonance imaging demonstrates focal myocardial injury indicated by arrows, characterized by increased signal intensity on T2-weighted imaging (edema) and late gadolinium enhancement in a subepicardial distribution of the lateral wall, consistent with acute myocarditis.

are among the most commonly reported etiologies[13,31]. A recent review of the literature indicated that idiopathic cases represented the largest share, approaching one-third of all reported cases. EGPA followed as the next most frequent etiology, accounting for close to one-fifth of all cases. Drug-induced EM and HES each contributed to roughly one in every eight cases. Less commonly, this condition has been linked to parasitic infections, malignancy-related eosinophilia, and post-vaccination reactions[32].

In our patient, marked eosinophilia suggested a possible association with parasitic infections, such as *Schistosoma spp*, *Strongyloides stercoralis*, and *Toxocara spp*. This link was further supported by positive serological results for specific antibodies. Nonetheless, we conducted a comprehensive evaluation, including medication history review and specialized testing, to rule out other common causes of eosinophilia and myocarditis. This evaluation helped exclude other etiologies, such as viral infections, malignancies, or vasculitis, ensuring a focused diagnostic approach[33]. The serological detection of *Schistosoma spp*, *Strongyloides stercoralis*, and *Toxocara spp* antibodies in our patient provides compelling but indirect evidence of parasitic etiology. While serologic testing remains the clinical mainstay in resource-limited settings, several diagnostic limitations warrant consideration. First, antibody tests cannot distinguish active infection from prior exposure, potentially overestimating disease causality. Second, cross-reactivity among helminth antigens may yield false positives.

In light of the eosinophilia and positive serological results, additional diagnostic methods could help support the presumed parasitic origin of myocarditis. These include both routine and advanced techniques-such as stool examination, cytokine profiling, and PCR-that may offer further diagnostic confirmation when invasive procedures like EMB are not feasible.

Stool ova and parasite examination remains a fundamental parasitological technique for detecting intestinal helminths and protozoa. It is widely used in endemic settings and for patients with eosinophilia. Although cost-effective, its sensitivity can be limited by intermittent parasite shedding and reliance on experienced microscopists, especially when only a single sample is tested. Therefore, collecting and examining multiple samples over consecutive days is recommended to

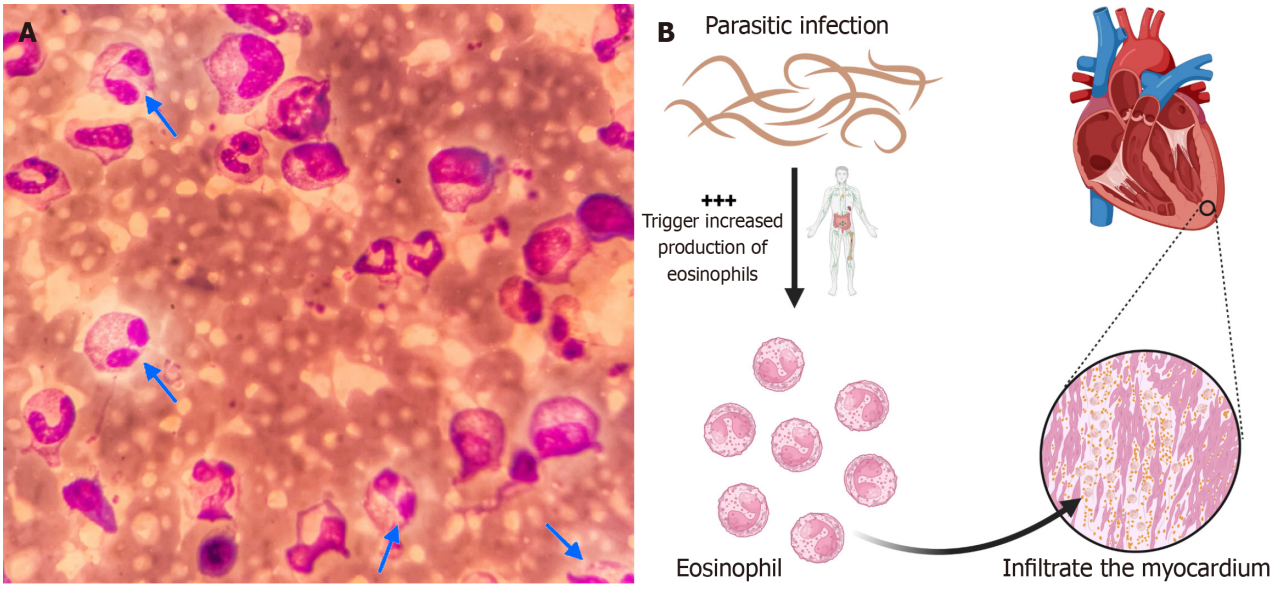

Figure 2 Eosinophilic activation and myocardial infiltration in the context of parasitic infection. A: Bone marrow smear from the patient reveals a markedly increased number of eosinophils, as demonstrated on the peripheral blood film, suggesting eosinophilic hyperplasia; B: Schematic illustration of the proposed pathophysiological mechanism: Parasitic infection triggers immune activation, leading to eosinophil proliferation and activation. Activated eosinophils subsequently infiltrate the myocardium, contributing to tissue inflammation and injury.

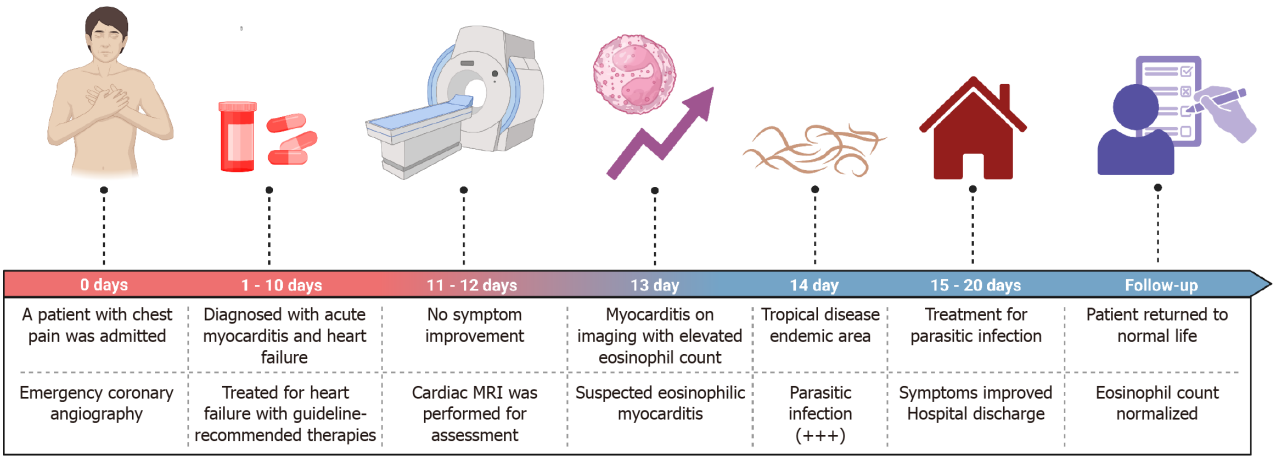

Figure 3 Timeline of clinical presentation, diagnostic workup, treatment, and follow-up in the reported case.

improve diagnostic sensitivity[34,35].

Cytokine profiling, particularly involving type 2 immune mediators such as IL-5, IL-13, IL-4, and eotaxin, has been proposed as a potential tool to better understand the pathophysiology of eosinophilia related to parasitic infections. IL-5 plays a central role in eosinophil activation and survival, while eotaxin facilitates eosinophil recruitment to inflamed tissues[36,37]. IL-4 and IL-13 contribute to Th2 immune polarization and promote IgE production. However, the evidence for their diagnostic utility remains limited, with most data derived from animal models and experimental studies. Notably, the roles of IL-4 and IL-13 in parasitic infections are complex and sometimes contradictory, as some studies suggest that they may impair host defense mechanisms[38]. To date, there are no established clinical guidelines recommending cytokine assays for diagnosing EM, and these biomarkers have not been integrated into routine clinical practice. Therefore, while cytokine profiling may offer insights into disease mechanisms and Th2-driven immune activation, its application remains investigational and requires further clinical validation before widespread use can be recommended.

PCR-based detection of parasitic DNA in blood, stool, or cardiac tissue can provide direct evidence of infection and may support the diagnosis of EM in suspected parasitic cases. Recent studies have demonstrated the value of PCR in detecting parasites with higher sensitivity than traditional microscopy or serology[35,39,40]. Moreover, multiplex and real-time PCR assays have improved diagnostic efficiency and the ability to detect co-infections[41]. Despite these benefits, PCR remains underutilized in routine clinical practice because of its high cost, lack of standardization for myocardial specimens, and limited availability of molecular diagnostic platforms in low-resource settings. Thus, while promising, its application in parasitic EM remains largely investigational.

Pathophysiology

Cardiac damage mechanisms related to eosinophilic infiltration progress through three stages (Figure 2). The initial phase, known as acute necrosis, is often clinically silent. In this stage, myocarditis is characterized by both inflammation and the presence of eosinophils within the myocardial tissue, occasionally accompanied by granulomatous formation [42]. Throughout this stage, a variety of cytotoxic molecules-such as eosinophil cationic protein, major basic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, and reactive oxygen species-are released. These agents contribute to mitochondrial dysfunction within cardiomyocytes[43-45]. These substances cause myocardial necrosis and programmed cell death (apoptosis). The second stage is thrombotic endocarditis, where eosinophil granule proteins act as potent procoagulants. They stimulate platelet aggregation and impair the anticoagulant properties of the endothelium, leading to thrombus formation adherent to blood vessel walls or cardiac chambers, which may result in embolic events[42]. Take *et al*[46] reported the finding of intraventricular thrombi in 15% of 110 cases of hypereosinophilia. The final stage is fibrosis, characterized by scarring in the damaged myocardium due to thrombus formation, ultimately leading to restrictive cardiomyopathy and atrioventricular valve dysfunction[47,48].

Clinical manifestations and complications

The manifestations of myocarditis are closely related to underlying pathogenic factors and inflammation, which can cause myocardial tissue damage of varying severity[49]. The clinical spectrum seen in EM is markedly heterogeneous, and disease severity often fails to correlate directly with the level of peripheral eosinophilia. Individuals may experience symptoms such as fever, skin eruption, palpitations, chest pain, and dyspnea, with more severe cases presenting with impaired cardiac function or hemodynamic collapse. Arrhythmias, abnormal impulse conduction, and alterations in ST and T waves have also been observed, although myocarditis does not present with a characteristic ECG phenotype[11]. Furthermore, complications such as arterial embolism, pericarditis, and sudden death can occur. EM is also associated with myocardial infarction through mechanisms such as coronary artery inflammation-induced stenosis, left coronary artery dissection, and coronary spasm. Eosinophil-derived proteins and vasoactive cytokines can cause vascular smooth muscle spasms, increasing the risk of myocardial infarction and serious cardiovascular events[28,50,51].

Diagnostic modalities

In some cases, differentiating myocarditis from a myocardial infarction can be challenging because of overlapping clinical features. The broad spectrum and nonspecific characteristics of clinical manifestations in EM, along with the absence of well-established diagnostic criteria, require a high level of clinical suspicion and the integration of multiple factors and tests for diagnosis[14]. First and foremost, a thorough patient history should always be reviewed, especially for allergies, systemic diseases, prior infections, travel history, and medication use before symptom onset[52]. Laboratory findings are also essential; although nonspecific and not always present, eosinophilia in blood tests may suggest EM[53,54]. Studies have demonstrated that eosinophil degranulation products and serum eosinophil cationic protein may serve as useful indicators for diagnosing and tracking disease progression during management[55]. Additionally, markers of inflammation and elevated cardiac troponin I and T levels are often present but are nonspecific. Even normal troponin levels do not entirely rule out myocarditis[56,57]. Echocardiographic findings in EM are diverse, depending on the disease's progression, and may manifest as dilated, hypertrophic, restrictive, or ischemic cardiomyopathy[16,58]. Our patient had normal chamber sizes but showed regional wall motion abnormalities in the anterior, anteroseptal, and apical left ventricular segments. Coronary angiography is mandatory to detect coronary artery disease, such as stenosis, arteritis, or thrombotic lesions[14]. CMR provides critical information regarding myocardial tissue characteristics, perfusion, ventricular function, and fibrosis[59]. It is the only non-invasive method that can be used before EMB to aid in diagnosing myocarditis and monitor disease progression during treatment[33]. Mavrogeni *et al*[60] also reported CMR as an emerging modality for evaluating Kawasaki disease, a type of systemic vasculitis, with the ability to visualize myocardial inflammation, blood flow, cardiac function, and fibrosis, providing essential and detailed clinical insight for diagnosing EM. Nonetheless, while CMR has been shown to outperform EMB in both sensitivity and specificity, it still cannot fully characterize the extent of inflammation or determine the precise etiology of the condition[33,61].

Role of EMB

EMB, using the Dallas criteria, is considered the gold standard for diagnosing and classifying myocarditis based on cellular infiltration[62]. In EM, EMB reveals diffuse myocardial necrosis associated with eosinophilic infiltration and interstitial fibrosis along with focal myocyte damage and perivascular infiltration[63]. The use of EMB in the routine evaluation of myocarditis has remained controversial. Despite being widely regarded as the definitive diagnostic modality, its clinical application is often limited due to factors such as low diagnostic yield, limited accessibility, elevated costs, and the procedural risks associated with its invasive nature. Nevertheless, EMB is still considered the diagnostic "gold standard" for confirming myocarditis[64]. EMB has limited sensitivity and specificity, around 50%, as the infiltrates are often localized[59]. EMB is advised in three clinical contexts. The first involves patients with acute-onset heart failure of less than two weeks' duration, accompanied by either normal ventricular dimensions or dilated ventricles and signs of hemodynamic compromise. The second applies to individuals experiencing heart failure for two to twelve weeks with left ventricular dilation, particularly when associated with new-onset ventricular arrhythmias, advanced atrioventricular block (second or third degree), or a lack of clinical improvement despite appropriate treatment within one to two weeks. The third scenario concerns cases of heart failure-regardless of its duration-in which dilated cardiomyopathy is suspected to be linked to hypersensitivity reactions and/or peripheral eosinophilia[65]. Acute myocardial infarction, left ventricular thrombus, or aneurysm formation are contraindications for myocardial biopsy. The risk of myocardial biopsy increases in cases of marked cardiomegaly, severe heart failure, or recent infection, especially when other pathologies cannot be

excluded[59]. Therefore, myocardial biopsy is limited. However, EMB is the only method capable of identifying the histologic characteristics and subgroups of cardiac inflammation. Specifically, acute myocarditis with interstitial eosinophilic infiltration can be detected through hematoxylin and eosin staining[65].

Application to our case

In our patient, who was admitted with acute chest pain, no risk factors for coronary artery disease were identified. Ischemic changes on the ECG and significantly elevated cardiac enzyme levels, along with regional wall motion abnormalities in the anterior, anteroseptal, and apical left ventricular segments on echocardiography, clearly indicated myocardial injury. CMR showed abnormal perfusion in the territories of the left anterior descending artery and left circumflex artery, pericardial effusion, and mild pericardial thickening. Normal coronary arteries excluded acute coronary artery disease, yet raised the issue of distinguishing myocarditis from myocardial infarction with non-obstructive coronary arteries (MINOCA). Diagnosing MINOCA is inadequate if myocarditis has not been excluded[66]. While myocarditis was yet to be ruled out, significant peripheral eosinophilia and positive serology for *Schistosoma spp.*, *Strongyloides stercoralis*, and *Toxocara spp.* pointed towards a likely diagnosis of parasitic EM in the patient, enabling prompt treatment with albendazole and prednisolone, which improved clinical symptoms, laboratory parameters, and normalized ECG and echocardiographic findings. In this case, myocardial biopsy was not conducted because the patient declined the procedure, despite the significant value of EMB in confirming the diagnosis.

Treatment

Currently, there are no clear guidelines or consensus for treating EM. Management depends on the underlying cause, clinical presentation, and disease stage, including discontinuing harmful factors, standard heart failure therapy, and early administration of high-dose steroids[51]. In many instances, the administration of glucocorticoids has led to significant improvement in clinical symptoms, likely attributable to their potent anti-inflammatory properties. Initiating steroid therapy at an early stage may help prevent progression to the subsequent phase characterized by thrombotic necrosis, mural thrombus formation, and fibrosis[59].

In most cases, glucocorticoids alleviate symptoms *via* potent anti-inflammatory effects, and early administration may help prevent disease progression[59]. Corticosteroids were administered in approximately four out of five EM cases associated with systemic conditions such as EGPA and HES, and in just over two-thirds of those related to hypersensitivity reactions. In many instances, cardiac function showed substantial improvement following treatment[23]. Although no clinical trials have evaluated steroid efficacy in parasitic EM, the use of antiparasitic drugs like albendazole is strongly recommended[59]. Globally, some EM case reports related to parasitic infections, such as *Ascaris lumbricoides*, *Trichinella spiralis*, and *Toxocara canis*, treated with dual therapy of high-dose albendazole and prednisolone, have demonstrated efficacy with favorable outcomes[51,67,68]. Additionally, symptomatic treatment to sustain life and prevent sudden death is essential, as most patients exhibit signs of cardiac dysfunction. Alongside conventional heart failure therapies, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and aldosterone receptor antagonists may aid in cardiac remodeling[59]. Furthermore, since most patients suffer from arrhythmias, close attention should be given to prevent malignant arrhythmias, which can lead to sudden cardiac death[69]. In cases where standard medical treatment is ineffective, mechanical support therapies, such as ventricular assist devices (VADs), intra-aortic balloon pump counterpulsation, and extracorporeal membrane oxygenation, may be considered to help patients overcome the most critical phase of heart failure[70]. After one month of this therapy, our patient showed significant improvement, with a left ventricular EF recovering from 39% to 64% and eosinophil counts returning to normal.

The therapeutic efficacy of corticosteroids combined with albendazole, while demonstrated in our patient should be interpreted as hypothesis-generating rather than definitive. Three key contextual factors may limit generalizability: (1) Treatment response appears optimal in early-stage disease before fibrotic myocardial remodeling occurs; (2) Therapeutic benefit requires confirmed parasitic etiology through serological or histopathological evidence; and (3) This approach may be particularly relevant in resource-limited settings where EMB remains inaccessible. Importantly, the absence of controlled clinical trials and potential confounding from concomitant cardiovascular therapies necessitates cautious interpretation. Future investigations should focus on prospective validation in endemic populations, with particular attention given to treatment duration optimization and identification of predictive biomarkers.

The role of immunosuppressive therapy in the treatment of EM remains controversial, but it may help prevent recurrence. Treatment with cytotoxic agents such as cyclophosphamide and imatinib can be employed as a specific therapeutic approach in EM associated with EGPA or myeloproliferative syndromes[51]. Recently, mepolizumab-a monoclonal antibody against IL-5-has emerged as a novel option in the management of EM associated with idiopathic HES, reducing eosinophil counts and mitigating the long-term side effects of corticosteroid therapy[71]. Inotropic agents and left VADs are valuable for patients with hemodynamic instability, heart failure, or arrhythmias[71]. The role of anticoagulation in acute EM for preventing intracardiac thrombi and arterial embolism is still under discussion; however, no studies have yet demonstrated the efficacy of this therapy[59].

CONCLUSION

EM caused by parasitic infections represents a rare but treatable cause of acute cardiac injury. Our case features eosinophilia and confirmed seropositivity for *Schistosoma spp.*, *Strongyloides stercoralis*, and *Toxocara spp.* - emphasizes that parasitic EM should be considered in patients presenting with chest pain, elevated cardiac markers, and peripheral eosinophilia, particularly in endemic regions. While cardiac MRI provides valuable diagnostic information and EMB

remains definitive, targeted serologic testing is crucial when parasitic etiology is suspected.

Early combined treatment with corticosteroids and antiparasitic agents (*e.g.*, albendazole) may lead to favorable outcomes, as observed in our patient. However, these therapeutic observations should be interpreted cautiously, as current evidence derives primarily from case reports rather than controlled studies. This approach appears most reasonable for patients with clear serological evidence of parasitic infection, especially when biopsy confirmation is not feasible. More robust clinical studies are needed to establish standardized treatment protocols and better define which patient populations would benefit most from this strategy.

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FOOTNOTES

Author contributions: Luong TV and Hoang TA were responsible for conceptualizing the study and writing the original draft of the manuscript; Dang HNN is designated as corresponding authors owing to their specific contributions. All the authors contributed to the writing, reviewing, editing, and drafting of the manuscript and have read and approved the final version. As co-first authors, Luong TV led the data analysis and interpretation, while Hoang TA coordinated the research methodology and data collection, with each making essential contributions to the study's completion.

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MINIREVIEWS

Rising trend of E-cigarettes among adolescents of Pakistan and cardiovascular implications of electronic nicotine delivery systems

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Abstract

It is a common misconception that e-cigarettes are safer than tobacco smoking, given their adverse cardiopulmonary effects, habituation, and the fact that it is only a fashion based manifestation to sell and use them. Therefore, the use of e cigarettes should not be encouraged as an alternative and pragmatic measure should be taken to profess this agenda.

Key Words: Adolescents; Cardiovascular implications; E-cigarettes; Nicotine

Core Tip: E-cigarette use among adolescents in Pakistan is rising rapidly, driven by misconceptions of safety and lax regulations. This trend poses serious cardiovascular risks due to nicotine, aldehydes, and toxic particles that induce inflammation, oxidative stress, and vascular dysfunction. Urgent public health measures are needed to curb use and prevent long-term cardiovascular harm.

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INTRODUCTION

The prevalence of e-cigarette use among Pakistani teenagers has become a source of rising worry due to the possible cardiovascular consequences. E-cigarettes, also known as electronic nicotine delivery systems (ENDS), have gained popularity globally, notably among young people in Pakistan[1]. Adolescents in Pakistan are increasingly turning to e-cigarettes, driven by certain reasons such as ease of access, aggressive marketing, and beliefs of lower damage compared to traditional tobacco products. However, the systemic effects especially the cardiovascular risks of e-cigarettes remain a major source of enigma and fretfulness. While conventional tobacco smoking is widely known as a risk factor for cardiovascular disease (CVD), cardiovascular effects of e-cigarette usage among Pakistani teenagers are not well recognized. This knowledge gap emphasizes the necessity for extensive study to investigate the cardiovascular consequences of e-cigarettes in this cohort[2-5].

The existing literature on e-cigarette usage and its cardiovascular repercussions is primarily based on studies undertaken in Western nations, with little study relevant to Pakistan. These findings, however, may not be completely applicable to the Pakistani teenage population due to cultural, environmental, and genetic variations. Thus, there is a significant need for localized research to clarify the cardiovascular consequences of e-cigarettes among teenagers in Pakistan[2,3,6]. Despite the increasing prevalence of e-cigarette use among Pakistani teenagers, there is an extensive gap in research on the cardiovascular consequences of this development. Existing research focuses mostly on Western populations, and there is no information on the particular cardiovascular consequences of e-cigarettes among Pakistani teenagers. Furthermore, the possible linkages between e-cigarette usage and other cardiovascular risk factors common in Pakistan, such as air pollution and dietary patterns, are unknown. Bridging this research gap is critical for informing public health policies and treatments targeted at reducing the cardiovascular hazards associated with e-cigarette use among Pakistan's adolescents[7].

BIOCHEMISTRY OF E-CIGARETTES

E-cigarette aerosols are characterized by a complex mixture of gases and particles that are influenced by a variety of elements such as the e-liquid's unique formulation, how it is puffed, and the device's operational parameters. The major aerosols emitted by an e-cigarette are composed primarily of propylene glycol, vegetable glycerin, ethylene glycol, 1,3-propanediol, and 1,2-propanediol, as well as a varying amount of nicotine. Experiments have identified thujon, ethyl vanillin, coumarin, camphor, safrole, menthol, and acetaldehydes as flavoring compounds[7-9].

E-cigarettes, also known as ENDS, are a diverse and perpetually expanding product category. Variability in physical parameters, such as tank style, battery power, and temperature settings, can have a substantial impact on vapor production. E-liquids are amalgamates of nicotine, flavorings, and carrier chemical substances. While some studies have discovered trace quantities of potential toxicants in both e-cigarette liquids and vapor, the extent of real human exposure remains comparatively underexplored compared to conventional cigarette smoking, which is believed to be around one-quarter as widespread[10,11].

RISING TRENDS OF E-CIGARETTES IN PAKISTAN

The worldwide e-cigarette and vape industry was valued at $22.45 billion in 2022 and is expected to rise significantly between 2023 and 2030, with a compound annual growth rate of 30.6%. This upsurge is especially noticeable in Western markets and Southeast Asian nations like as Bangladesh, Nepal, India, and, most importantly, Pakistan, which is quickly establishing itself as a major participant in the vaping business. Pakistan's e-cigarette income is expected to reach $77.2 million by 2024, with a 1.39% annual growth rate. Another study highlighted that 50.4% of students in colleges and universities had tried vaping, with 41.9% using e-cigarettes daily[12].

For several years, Pakistan has seen a steady increase in the popularity of vaping. A study carried out in Karachi in 2017 by medical students indicated that many consumers were using vaping devices without fully comprehending their contents and related health hazards. Unfortunately, a similar pattern appears to be occurring right now, implying that vaping might possibly turn into an epidemic in Pakistan before the negative impacts are completely understood[12]. The comparatively liberal restrictions governing vaping, including its use, advertising, promotional activities, sponsorship, and packaging, have made vaping more accessible to a more widespread population in Pakistan. Also, the availability of flavored e-liquids heightens its appeal, particularly among the youth, who are the major target demographic. Factors such as peer influence, the lack of societal shame, and ease of availability all contribute to its appeal among youth. This offers a challenging problem for Pakistan as it navigates economic challenges such as high inflation while also tackling the growing issue of vaping, which necessitates a balanced strategy that takes into account both public health concerns and economic factors[12].

CARDIOVASCULAR IMPLICATIONS: MECHANISMS, BIOMARKERS, AND LONG-TERM CONSEQUENCES

Nicotine, the primary addictive agent in e-cigarettes, contributes significantly to cardiovascular risk. It induces endothelial dysfunction, increases heart rate, blood pressure, and coronary resistance, and promotes atherosclerosis[13]. Carbonyl compounds like formaldehyde, acetaldehyde, and acrolein found in e-cigarette aerosols contribute to oxidative stress, vascular inflammation, and autonomic imbalance, further exacerbating cardiovascular risk[14,15]. Animal studies corroborate these effects, highlighting increased blood pressure, arrhythmias, and potential cardiac damage from chronic exposure to these substances[15]. Furthermore, ultrafine particles in EC aerosols can penetrate the circulatory system, potentially causing endothelial injury and accelerating cardiovascular pathologies[16]. Research has also indicated that chronic e-cigarette use may impair vascular reactivity, leading to arterial stiffness and impaired nitric oxide bioavailability, which are critical markers of cardiovascular dysfunction[17]. Additionally, biomarkers such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha have shown elevated levels in e-cigarette users, further affirming an inflammatory profile that supports the development of CVDs[18]. These effects are particularly concerning in adolescents whose cardiovascular systems are still in development, making them more vulnerable to long-term damage. Evidence also suggests that dual use of e-cigarettes and conventional cigarettes amplifies cardiovascular risk through cumulative toxic exposure and compounded oxidative stress[19]. Therefore, the cardiovascular threat posed by e-cigarettes among adolescents warrants urgent attention and preventive public health strategies.

MEASURES OF PREVENTION

Overall, while e-cigarettes may be less harmful than conventional cigarettes, they are not completely safe and can have negative health effects[20]. The non-linear dose-response relationship between smoking and cardiovascular mortality suggests that lowering the concentrations of HPHC in e-cigarette aerosols may not result in proportionate harm reduction, and that lower HPHC exposure may be counterbalanced by increased use by people who think e-cigarettes are less harmful than traditional cigarettes. As a result, the evidence at hand does not fully support the claim that e-cigarettes are safe products or successful smoking cessation aids[21]. Following measures should be taken to prevent use of e cigarettes: It should be made illegal for young people to use E-cigarettes. E-cigarettes cannot be advertised as a risk-free substitute for cigarette smoking. E-cigarettes might be useful as quitting aids, but more reliable data are needed to show how effective they are[22]. Aldehydes produced by e-cigarette aerosols should be rigorously monitored because they are harmful even at extremely low amounts in order to reduce cardiovascular damage[23]. Acrolein levels in e-cigarette aerosols should be below 0.008 ppm, at which chronic exposure has not been associated with any adverse effects. Acetaldehyde and formaldehyde concentrations should be below 0.025 and 0.40 ppm, respectively. To protect consumers from unnecessary injury, device attributes could be controlled to adhere to these requirements[22,23]. It is the best to prevent new, uninitiated, and young people from experimenting with e-cigarettes.

To assist adolescents in restraining use and assisting them in quitting, targeted interventions are required. Adolescents' awareness of potential risks can be raised through evidence-based curriculum and communication campaigns, the provision of counseling and cessation tools, a review of current policies, and instruction of school administrators in product identification[23,24].

PUBLIC HEALTH POLICY RECOMMENDATIONS

To counter this trend, several public health policy actions are necessary. These include enforcing strict age restrictions to prevent underage sales, regulating marketing strategies to eliminate youth-targeted advertising, and applying taxation to reduce affordability. Mandatory health warnings on packaging that clearly outline cardiovascular risks should be implemented. Public awareness campaigns focusing on the dangers of ENDS, especially for cardiovascular health, are essential. Establishing robust monitoring systems to track adolescent usage patterns and funding local research into long-term health outcomes will further inform policy. Additionally, integrating ENDS regulations into existing tobacco control frameworks and requiring retail licensing can strengthen enforcement and oversight[25].

SOCIOECONOMIC ISSUES LEADING TO INCREASED TRENDS

Socio-economic factors such as education, urbanization, and media exposure significantly influence adolescent uptake of ENDS. Lower educational attainment among adolescents or their parents is associated with reduced awareness of the health risks of vaping, making adolescents more susceptible to experimentation[25]. Urbanization also plays a key role, as adolescents in urban areas encounter greater availability of vape shops and social environments that normalize ENDS use. Furthermore, media, especially social media platforms like Instagram and TikTok, amplify the appeal of vaping by portraying it as fashionable and harmless, further encouraging adolescents to initiate use. Together, these socio-economic dynamics create a high-risk environment for increased ENDS adoption among youth[9]. The summary of Biochemistry to measures of prevention is given below in Table 1.

Table 1 Biochemistry to measures of prevention

Section	Key points
Biochemistry of E-cigarettes	E-cigarette aerosols contain propylene glycol, vegetable glycerin, nicotine, and flavoring agents like menthol, ethyl vanillin
	Variability in device design affects vapor production
	Some toxicants present, but extent of human exposure still unclear compared to traditional smoking
Rising trends of E-cigarettes in Pakistan	Pakistan's vaping market is growing rapidly, expected to generate $77.2 million by 2024
	Liberal regulations and flavored options increase youth appeal
	Socioeconomic and marketing factors drive the trend
Socioeconomic issues leading to increased trends	Lower education levels linked to poor awareness of vaping risks
	Urbanization increases access to vape shops
	Social media glamorizes vaping
	These factors create a high-risk environment for youth
Cardiovascular implications: Mechanisms, biomarkers, and long-term consequences	Nicotine induces endothelial dysfunction, raises heart rate and blood pressure
	Aerosols contain formaldehyde, acetaldehyde causing oxidative stress
	Ultrafine particles may cause endothelial injury
	Chronic use leads to arterial stiffness, inflammation (elevated CRP, IL-6, TNF-α)
	Adolescents more vulnerable due to developing systems
	Dual use (e-cigarettes + traditional cigarettes) amplifies risks
Measures of prevention	E-cigarette use among youth should be illegal
	E-cigarettes must not be advertised as safe alternatives
	Stricter control of harmful aldehyde levels
	Device regulations to limit toxic emissions
	Awareness campaigns, school interventions, and counseling are needed
	Evidence-based public health strategies required

CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha.

CONCLUSION

The emergence of e-cigarettes, also known as vaping, poses a multifaceted problem with significant consequences, especially among young people in Pakistan. E-cigarettes carry some risks even if they might be a less dangerous option than regular cigarettes. Strong regulations and oversight are essential given the carcinogens and other toxicants found in e-cigarette aerosols. Addressing the rising incidence of e-cigarette use among teenagers in Pakistan requires action to limit youth access, fight deceptive advertising, and support evidence-based cessation techniques.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Beyond initial recovery: Heart failure with transient *vs* sustained improvement in left ventricular ejection fraction

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Abstract

BACKGROUND

There is no available data about the trajectory of heart failure (HF) with improved ejection fraction (EF) and patient clinical outcomes in Qatar.

AIM

To explore the difference in characteristics and outcomes between patients with transient and sustained improvement in left ventricular ejection fraction (LVEF) and to determine the independent predictors for sustained improvement in LVEF.

METHODS

This is a retrospective cohort study that was conducted at the advanced HF clinic of a tertiary care hospital in Qatar between January 2017 and December 2018. This

study included adult patients with improved LVEF and had at least three echocardiographic studies. The patients were divided into two groups: HF with transient improvement in EF (HFtimpEF) and HF with sustained improvement in EF (HFsimpEF).

RESULTS

A total of 175 patients with HF and improved EF were included. Among them 136 (77.7%) patients showed sustained improvement in LVEF. The remaining patients with HFtimpEF were predominantly males [37 (94.9%) *vs* 101 (74.3%), $P = 0.005$] with a higher incidence of ischemic cardiomyopathy [32 (82.1%) *vs* 68 (50.4%), $P = 0.002$], dyslipidemia [24 (61.5%) *vs* 54 (39.7%), $P = 0.03$], and hypertension [34 (87.2%) *vs* 93 (68.4%), $P = 0.03$] than those with HFsimpEF. The latter experienced significantly lower rates of hospitalization [39 (28.7%) *vs* 20 (51.3%), $P = 0.01$] and diagnosis of new cardiovascular conditions during the follow-up (*e.g.*, acute coronary syndrome, stroke, decompensated HF, and atrial fibrillation) [14 (10.3%) *vs* 10 (25.6%), $P = 0.03$] without a difference in emergency department visits or in-hospital death. Sustained improvement in LVEF was positively associated with being female [adjusted odds ratio (aOR) = 6.8, 95% confidence interval (CI): 1.4-32.3, $P = 0.02$], having non-ischemic etiology of HF (aOR = 3.1, 95%CI: 1.03-9.3, $P = 0.04$), and using a mineralocorticoid receptor antagonist (aOR = 7.0, 95%CI: 1.50-31.8, $P = 0.01$).

CONCLUSION

Patients with HFsimpEF experienced significantly lower rates of hospitalization and diagnosis of new cardiovascular conditions than patients with HFtimpEF. Sustained improvement in LVEF was positively associated with being a female, having non-ischemic etiology of HF, and using a mineralocorticoid receptor antagonist.

Key Words: Asia; Cardiomyopathy; Improved ejection fraction; Middle East; Qatar

Core Tip: Our study reported observations from a population with heart failure in Qatar, a Middle Eastern country that is usually underrepresented in major clinical trials. This study was the first in the Middle East to characterize the clinical features and outcomes of patients with heart failure who demonstrate either sustained or temporary improvement in left ventricular ejection fraction.

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INTRODUCTION

Heart failure (HF) remains one of the key causes of cardiovascular mortality[1]. The current guidelines propose stratifying patients in phenotypes based on left ventricular ejection fraction (LVEF) to provide individualized care[2]. Guideline-directed medical therapy in HF with reduced EF (HFrEF) has resulted in improvements in cardiac function and left ventricular reverse remodeling[3,4]. Several studies have shown that these patients with HF and improved EF (HFimpEF) have a distinct HF phenotype and may carry favorable clinical outcomes[5-8].

Yet this improvement is not always sustained; reverse remodeling is often accompanied by detrimental neurohormonal changes that can precipitate fluctuations in EF[9]. This can lead to variations in EF over time and highlights the importance of longitudinal assessment of EF to further sub-stratify patients with HFimpEF into sustained improvement and transient improvement. This distinction has led to the need to further subclassify HFimpEF as HF with sustained improvement in EF (HFsimpEF) or HF with transient improvement in EF (HFtimpEF).

The factors that determine whether patients with HFrEF go on to become HFsimpEF or HFtimpEF has been an area of interest yet poorly studied. There is also a need to assess the long-term outcomes and prognosis of these patients. There is a lack of available data on the trajectory of HFimpEF and patient clinical outcomes in the Middle East. Hence, this study was conducted to explore several aspects related to patients with HFimpEF and their sustained improvement in LVEF. The hypothesis was that patients with sustained improvement in LVEF would have better clinical outcomes compared with those with transient improvement building on preliminary findings from previous studies exploring outcomes of patients with HFimpEF, who showed a generally favorable prognosis[10]. The main objective of this study was to explore the difference in characteristics and outcomes between patients with transient and sustained improvement in LVEF and to determine the independent predictors for sustained improvement in LVEF.

MATERIALS AND METHODS

This was a retrospective cohort study that was conducted at the advanced HF clinic in a tertiary care hospital in Qatar between January 1, 2017 and December 31, 2018. The study was approved by the Institutional Review Board of the Heart Hospital and the Medical Research Center, approval No. MRC-01-20-139. An informed consent was waived due to the retrospective nature of the study. The study was in line with the principles of the Declaration of Helsinki, Good Clinical Practice and the laws and regulations of the Ministry of Public Health in Qatar. This study included all adult patients (≥ 18 years) who were initially diagnosed with HFrEF, defined as LVEF < 40.0% at baseline, who demonstrated an initial improvement in LVEF and had at least three echocardiographic studies from their initial visit to the clinic.

The study population was selected from our previously published study that described the characteristics of patients with HFrEF who had improvement in their LVEF and analyzed the independent predictors of LVEF improvement. Our previous study screened all patients who visited the advanced HF clinic during the study period and included adult patients aged 18 years or older with a diagnosis of HFrEF and who had two echocardiographic examinations performed at least 6 months apart[11].

For the current study, all patients had a first (or baseline) echocardiogram (Echo-1) where the diagnosis of HFrEF was established and showed improvement in LVEF of at least 1.0% on the second echocardiogram (Echo-2) performed at least six months after Echo-1. Hence, Echo-2 would identify the HFimpEF cohort. The specific cutoff values for the improvement in LVEF have not been established yet by the international guidelines[12], and patients with improvement of any magnitude were included. A third echocardiogram (Echo-3) at least 12 months after from Echo-2 was included to distinguish patients with transient or sustained improvement in LVEF. An increase in LVEF by at least 1.0% in both the Echo-2 and the Echo-3 compared to the Echo-1 was defined as sustained improvement in EF (*i.e.* HFsimpEF). An initial improvement in LVEF of at least 1.0% in the Echo-2 followed by any reworsening of LVEF or lack of further improvement in the Echo-3 was defined as having transient improvement in EF (*i.e.* HFtimpEF). Thus, the patients were divided into two groups: HFtimpEF and HFsimpEF.

Furthermore, the improvement in LVEF was considered large if the increase or change in LVEF (Δ LVEF) was 10.0% or more and modest if Δ LVEF was 1.0%-9.0%[13]. A subgroup analysis for the patients with an initial large LVEF improvement (*i.e.* the difference between Echo-2 and Echo-1 of ≥ 10.0%) was conducted to compare the patients with HFtimpEF and HFsimpEF.

LVEF was measured using the Simpson biplane method, unless the Simpson method was not possible. This study excluded patients with specific cardiomyopathies (*e.g.*, hypertrophic, infiltrative, restrictive, stress-induced, or chemotherapy-induced), primary right-sided disease, congenital heart disease as the etiology of HF, cardiac transplant, left ventricular assist device, or primary valvular disease.

RESULTS

Baseline characteristics

Within the specified study duration, 582 patients with HFrEF underwent at least two echocardiograms. Of them, 175 patients (30.1%) showed any improvement in LVEF (*i.e.* ≥ 1.0%) between Echo-1 and Echo-2 and who had a second follow-up echocardiogram (*i.e.* Echo-3) performed at least 12 months after Echo-2. Among them, 136 patients (77.7%) showed sustained improvement in LVEF on Echo-3 while the remaining had reworsening of the LVEF (*i.e.* had transient improvement).

Patients with HFtimpEF were predominantly males (94.9% *vs* 74.3%, $P = 0.005$) with ischemic cardiomyopathy (82.1% *vs* 50.4%, $P = 0.002$). There were no differences between the groups in terms of age, body mass index, or duration of HF diagnosis. Patients with HFtimpEF had a higher incidence of dyslipidemia (61.5% *vs* 39.7%, $P = 0.03$) and hypertension (87.2% *vs* 68.4, $P = 0.03$) than those with HFsimpEF.

Table 1 presents details of baseline characteristics. At baseline, there were no differences between the groups in terms of blood pressure measurements, heart rate values, and the presence of left bundle branch block.

Similarly, there was no difference in the previous parameter measurements between the groups at follow-up except for the heart rate, which was significantly lower in patients with HFsimpEF [72.84 ± 12.90 *vs* 79.41 ± 15.45 beats per minute (bpm), $P = 0.02$] as shown in Table 2. Blood test parameters did not differ between the two groups at baseline and follow-up except for the estimated glomerular filtration rate, which was significantly higher in the sustained improvement group at both baseline (79.68 ± 33.27 *vs* 66.47 ± 27.79 mL/minute, $P = 0.03$) and follow-up (70.35 ± 29.24 *vs* 59.89 ± 28.49 mL/minute, $P = 0.05$) (Table 3).

Echocardiographic parameters

Upon initial diagnosis, mean LVEF was significantly lower in the sustained improvement group (26.77 ± 7.05% *vs* 30.56 ± 6.95%, $P = 0.003$) with no difference in other echocardiographic parameters. At follow-up, LVEF became significantly higher in the sustained improvement group (40.18 ± 0.12 *vs* 28.46 ± 6.59%, $P = 0.001$) with significant improvement in other parameters such as lower left atrium volume index (34.30 ± 11.26 *vs* 41.41 ± 12.92 mL/m^2, $P = 0.003$), left ventricular end-systolic diameter (4.50 ± 0.95 *vs* 4.99 ± 0.75 cm, $P = 0.004$), and right ventricular systolic pressure (RVSP; 33.10 ± 11.82 *vs* 38.78 ± 14.61 mmHg, $P = 0.04$). The initial improvement in LVEF (between Echo-1 and Echo-2) at almost 20 months of follow-up did not differ in magnitude between the groups (Echo-2 - Echo-1: Δ LVEF: 9.54 ± 7.69% *vs* 8.05 ± 6.53%, $P = 0.27$). After another 20 months of follow-up, the overall improvement in LVEF differed significantly between the groups (Echo-3 - Echo-1: Δ LVEF: 13.43% ± 9.09% *vs* 2.10% ± 5.05%, $P = 0.001$) (Table 4).

Table 1 Baseline characteristics of the included patients

Variable	Transient improvement (*n* = 39)	Sustained improvement (*n* = 136)	*P* value
Age (years), mean ± SD	58.15 ± 11.69	54.51 ± 13.52	0.13
BMI (kg/m^2), mean ± SD	28.36 ± 5.67	30.49 ± 7.20	0.09
Male	37 (94.9)	101 (74.3)	0.005
Female	2 (5.1)	35 (25.7)	-
HF etiology			
Ischemic	32 (82.1)	68 (50.4)	0.002
Dilated	5 (12.8)	57 (42.2)	
Others	2 (5.1)	10 (7.4)	
Duration of HF diagnosis, mean ± SD	7.05 ± 3.81	5.79 ± 4.0	0.08
Comorbidities			
Dyslipidemia	24 (61.5)	54 (39.7)	0.03
Hypertension	34 (87.2)	93 (68.4)	0.03
Diabetes	28 (71.8)	90 (66.2)	0.57
Atrial fibrillation	8 (20.5)	25 (18.4)	0.82
Ventricular arrhythmia	5 (12.8)	18 (13.2)	1.00
CVA/TIA	5 (12.8)	16 (11.8)	0.79
PAD	2 (5.1)	8 (5.9)	1.00
Renal impairment	17 (43.6)	35 (25.7)	0.05
Liver disease	2 (5.1)	5 (3.7)	0.65
Anemia	10 (25.6)	38 (27.9)	0.84
Sleep apnea	0 (0)	9 (6.6)	0.21
Chronic lung disease	6 (15.4)	21 (15.4)	1.00
Cancer	0 (0)	7 (5.1)	0.35
Dementia	2 (5.1)	3 (2.2)	0.31
Depression	0 (0)	6 (4.4)	0.34
Hypothyroidism	2 (5.1)	11 (8.1)	0.74
Hyperthyroidism	0 (0)	4 (2.9)	0.58

Data are presented as *n* (%). BMI: Body mass index; CVA: Cerebrovascular accident; HF: Heart failure; PAD: Peripheral artery disease; SD: Standard deviation; TIA: Transient ischemic attack.

Medications

At the time of diagnosis, more than half of the patients in both groups were on beta-blockers and renin-angiotensin-aldosterone system inhibitors without a difference between the two groups. Significantly more patients in the sustained improvement group were on mineralocorticoid receptor antagonists (MRA; 21.3% *vs* 5.1%, $P = 0.02$). At the second follow-up (Echo 3), the use of guideline-directed medical therapy for HF increased in both groups without a difference between them (Table 5).

Clinical outcomes

Patients with sustained improvement in LVEF demonstrated a significantly lower rate of all-cause hospitalization compared with those with transient improvement [39 (28.7%) *vs* 20 (51.3%) patients, $P = 0.01$]. Among all the hospitalizations, 28 were specifically due to HF with 16 occurring in the sustained improvement group and 12 in the transient improvement group. The incidence of developing new cardiovascular conditions during follow-up including acute coronary syndrome, stroke, decompensated HF, and atrial fibrillation, was also lower in the sustained improvement group [14 (10.3%) *vs* 10 (25.6%) patients, $P = 0.03$]. However, there was no statistically significant difference in the rates of emergency department visits [38 (27.9%) *vs* 16 (41.0%) patients, $P = 0.12$] or in-hospital deaths [6 (4.4%) *vs* 1 (2.6%) patient(s), $P = 1.00$] between the groups.

Table 2 Vital signs and electrocardiographic measures of the included patients

Variable	Transient improvement (*n* = 39)	Sustained improvement (*n* = 136)	*P* value
Baseline (Echo-1), mean ± SD			
Systolic BP (mmHg)	124.38 ± 22.41	125.30 ± 20.1 (*n* = 134)	0.81
Diastolic BP (mmHg)	72.64 ± 12.36	75.97 ± 12.99 (*n* = 134)	0.16
Heart rate (bpm)	86.43 ± 18.02 (*n* = 37)	89.69 ± 19.12 (*n* = 132)	0.36
Achieved target BP	26 (66.7)	87 (64.9)	1.00
Sinus rhythm	28 (90.3)	103 (86.6)	0.77
LBBB	7 (14.1)	19 (17.1)	0.42
QRS (ms), mean ± SD	109.45 ± 26.29 (*n* = 29)	109.43 ± 44.04 (*n* = 129)	1.0
QTc (ms), mean ± SD	468.86 ± 43.48 (*n* = 29)	462.84 ± 52.19 (*n* = 109)	0.57
Second follow-up (Echo-3), mean ± SD			
Systolic BP (mmHg)	127.87 ± 21.43	133.47 ± 98.18 (*n* = 129)	0.73
Diastolic BP (mmHg)	73.85 ± 13.62	73.81 ± 11.49 (*n* = 129)	0.99
Heart rate (bpm)	79.41 ± 15.45	72.84 ± 12.90 (*n* = 128)	0.02
Achieved target BP	26 (66.7)	90 (69.8)	0.67
Sinus rhythm	33 (89.2)	111 (88.8)	1.00
LBBB	7 (19.4)	21 (17.4)	0.81
QRS (ms), mean ± SD	112.00 ± 26.87 (*n* = 37)	110.07 ± 26.34 (*n* = 120)	0.70
QTc (ms), mean ± SD	455.08 ± 31.57 (*n* = 37)	448.91 ± 42.92 (*n* = 120)	0.35

Data are presented as *n* (%). Echo-1: First (or baseline) echocardiogram; BP: Blood pressure; bpm: Beats per minute; LBBB: Left bundle branch block; QTc: Corrected QT interval; QRS: QRS complex duration; Echo-3: Third echocardiogram; SD: Standard deviation.

Multivariate nominal logistic regression analysis was performed to identify factors associated with sustained improvement in LVEF. Female sex [adjusted odds ratio (aOR) = 6.8, 95% confidence interval (CI): 1.4-32.3, P = 0.02], non-ischemic etiology of HF (aOR = 3.1, 95%CI: 1.03-9.3, P = 0.04), and the use of MRA (aOR = 7.0, 95%CI: 1.50-31.8, P = 0.01) were significantly associated with sustained improvement of LVEF. Other factors such as age, hyperlipidemia, and hypertension did not show a significant association with sustained improvement (Table 6).

Subgroup analysis

A subgroup analysis was performed to identify the characteristics and outcomes of patients with HFimpEF and a large improvement in LVEF between the baseline (Echo-1) and first follow-up echocardiogram (Echo-2). Seventy-one (40.6%) patients had a large improvement in LVEF (*i.e.* Δ LVEF ≥ 10.0%) at Echo-2. Of them, 14 (19.3%) and 57 (80.3%) patients showed transient and sustained improvement in LVEF, respectively. Patients with transient improvement were significantly more dyslipidemic (71.4% *vs* 35.1%, P = 0.014) and hypertensive (92.9% *vs* 61.4%, P = 0.024) with significantly lower heart rates (79.92 ± 19.74 *vs* 94.18 ± 21.11 bpm, P = 0.030) and RVSP values (29.24 ± 7.29 *vs* 38.77 ± 12.87 mmHg, P = 0.010) at baseline. The heart rate was significantly lower (81.14 ± 15.37 *vs* 70.85 ± 11.77 bpm, P = 0.032) in patients with sustained improvement at the second follow-up.

Guideline-directed medications for HF did not differ between the sustained and transient improvement subgroups. The clinical outcome findings of the subgroups were in line with the overall study findings. Patients with sustained improvement in LVEF experienced a significantly lower incidence of new cardiovascular conditions (28.6% *vs* 7.0%, P = 0.022) without a difference in the emergency department visits (35.7% *vs* 29.8%, P = 0.750) or in-hospital deaths (7.1% *vs* 5.3%, P = 1.000). However, there was a trend towards lower hospitalizations in those with sustained improvement (50.0% *vs* 22.8%, P = 0.054).

DISCUSSION

This study explored the independent predictors for sustained improvement in LVEF at the advanced HF clinic in Qatar. One-quarter of our study population had reworsening in LVEF despite initial improvement. These patients with HFtimpEF were predominantly males with ischemic cardiomyopathy and higher incidence of hypertension and dyslipidemia compared with patients with HFsimpEF. The latter experienced significantly lower rates of hospitalization and

Table 3 Laboratory blood tests of the included patients

Variable	Transient improvement (*n* = 39)	Sustained improvement (*n* = 136)	*P* value
Baseline (Echo-1)			
NT-pro-BNP (pg/mL)	5106.63 ± 6035.19 (*n* = 27)	4730.48 ± 6792.82 (*n* = 93)	0.80
Hemoglobin (g/dL)	13.16 ± 2.22 (*n* = 38)	14.20 ± 12.89 (*n* = 132)	0.62
Urea (mmol/L)	8.16 ± 4.53 (*n* = 38)	7.15 ± 4.17 (*n* = 133)	0.20
Creatinine (μmol/L)	120.03 ± 56.87 (*n* = 38)	113.55 ± 114.84 (*n* = 132)	0.74
eGFR (mL/min)	66.47 ± 27.79 (*n* = 38)	79.68 ± 33.27 (*n* = 132)	0.03
HbA1c (%)	8.38 ± 2.34 (*n* = 26)	7.54 ± 2.19 (*n* = 102)	0.09
LDL-C (mmol/L)	2.69 ± 0.92 (*n* = 35)	2.57 ± 1.18 (*n* = 120)	0.56
Iron (μmol/L)	8.87 ± 3.69 (*n* = 10)	10.43 ± 6.49 (*n* = 37)	0.47
TSAT (%)	16.77 ± 5.42 (*n* = 10)	20.37 ± 15.74 (*n* = 35)	0.48
Ferritin (ug/L)	325.75 ± 347.95 (*n* = 8)	208.50 ± 277.71 (*n* = 30)	0.32
TSH (pmol/L)	1.76 ± 1.51 (*n* = 22)	2.38 ± 2.18 (*n* = 92)	0.21
T4 (mIU/L)	13.51 ± 1.70 (*n* = 23)	14.87 ± 3.58 (*n* = 87)	0.08
Second follow-up (Echo-3)			
NT-pro-BNP (pg/mL)	7672.15 ± 13459.32 (*n* = 27)	3184.52 ± 6564.79 (*n* = 81)	0.11
Hemoglobin (g/dL)	12.23 ± 2.25 (*n* = 37)	12.87 ± 2.08 (*n* = 120)	0.11
Urea (mmol/L)	10.28 ± 7.27 (*n* = 38)	8.50 ± 8.94 (*n* = 125)	0.26
Creatinine (μmol/L)	142.84 ± 88.49 (*n* = 38)	127.25 ± 126.01 (*n* = 128)	0.48
eGFR (mL/min)	59.89 ± 28.49 (*n* = 38)	70.35 ± 29.24 (*n* = 127)	0.05
HbA1c (%)	7.66 ± 2.04 (*n* = 33)	7.90 ± 4.88 (*n* = 103)	0.79
LDL-C (mmol/L)	1.81 ± 0.99 (*n* = 33)	2.03 ± 0.93 (*n* = 99)	0.25
Iron (μmol/L)	9.64 ± 4.33 (*n* = 18)	11.23 ± 6.24 (*n* = 41)	0.33
TSAT (%)	17.44 ± 8.69 (*n* = 18)	23.48 ± 16.53 (*n* = 41)	0.15
Ferritin (ug/L)	276.17 ± 489.76 (*n* = 14)	244.41 ± 429.58 (*n* = 30)	0.83
TSH (pmol/L)	2.43 ± 1.45 (*n* = 22)	3.22 ± 3.12 (*n* = 83)	0.26
T4 (mIU/L)	15.73 ± 2.23 (*n* = 19)	15.05 ± 3.86 (*n* = 73)	0.46

Data are presented as mean ± SD. Echo-1: First (or baseline) echocardiogram; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin; Echo-3: Third echocardiogram; LDL-C: Low-density lipoprotein cholesterol; NT-proBNP: N-terminal pro-brain natriuretic peptide; T4: Thyroxine hormone; TSAT: Transferrin saturation; TSH: Thyroid-stimulating hormone.

diagnosis of new cardiovascular conditions during the follow-up. Sustained improvement of LVEF was positively associated with being a female, having a non-ischemic etiology of HF, and using MRA (Figure 1).

Although the current diagnosis and management of HF depends on LVEF, it is important to consider that LVEF may vary over time. Many patients may erroneously be managed in the long-term as HFimpEF based on the initial improvement seen on their follow-up echocardiogram when in fact their LVEF may have later reworsened. This misclassification impacts their predicted mortality and hospitalizations. One study found that one-quarter of all patients in their cohort, similar to ours, had subsequent deterioration in their LVEF despite initial improvement[14]. This finding likely underpredicts the long-term course of LVEF owing to the lack of routine follow-up echocardiograms conducted in clinical practice once the patient is labelled to have recovered LVEF.

Currently, there is no consensus in the international guidelines on the exact cutoffs for LVEF improvement to define HFimpEF[12]. Due to the small sample size, we included all patients who demonstrated any (rather than large) improvement in LVEF on their first follow-up echocardiogram (Echo-2). However, our study found that the average initial improvement of LVEF was approximately 10.0% (Δ LVEF 8.1%-9.5%). Furthermore, the findings from subgroup analysis of patients who had an initial large improvement in LVEF of 10.0% or more were not different from the findings of the overall population.

Patients with HFsimpEF made up 77.7% of the total cohort in our study. Similarly, in a study that enrolled patients with dilated cardiomyopathy (*n* = 188), 46.0% of them showed an initial improvement in their LVEF (from 26.0 ± 7.0% to

Table 4 Echocardiographic parameters of the included patients

Variable	Transient improvement (*n* = 39)	Sustained improvement (*n* = 136)	*P* value
Baseline (Echo-1)			
LVEF (%)	30.56 ± 6.95	26.77 ± 7.05	0.003
Average E/e'	15.01 ± 5.88 (*n* = 20)	14.52 ± 5.78 (*n* = 67)	0.74
LA volume index (mL/m^2)	35.97 ± 12.51 (*n* = 25)	37.09 ± 11.35 (*n* = 82)	0.68
LVEDD (cm)	5.76 ± 0.79 (*n* = 37)	6.70 ± 4.17 (*n* = 130)	0.18
LVESD (cm)	4.76 ± 0.84 (*n* = 34)	5.08 ± 0.89 (*n* = 115)	0.80
RVSP (mmHg)	33.46 ± 11.06	37.35 ± 12.89 (*n* = 130)	0.13
Second follow-up (Echo-3)			
LVEF (%)	28.46 ± 6.59	40.18 ± 0.12	0.001
Average E/e'	13.12 ± 5.46 (*n* = 19)	12.08 ± 5.86 (*n* = 77)	0.49
LA volume index (mL/m^2)	41.41 ± 12.92 (*n* = 31)	34.30 ± 11.26 (*n* = 114)	0.003
LVEDD (cm)	6.06 ± 0.62 (*n* = 38)	5.81 ± 0.89 (*n* = 134)	0.05
LVESD (cm)	4.99 ± 0.75 (*n* = 37)	4.50 ± 0.95 (*n* = 131)	0.004
RVSP (mmHg)	38.78 ± 14.61 (*n* = 37)	33.10 ± 11.82 (*n* = 129)	0.04
LVEF (Echo-2)	38.59 ± 7.57	36.33 ± 7.69	0.11
Δ LVEF (Echo-2 - Echo-1) (%)	8.05 ± 6.53	9.54 ± 7.69	0.27
Duration between Echo-1 and Echo-2 (months)	19.82 ± 26.61	17.24 ± 21.15	0.53
Δ LVEF (Echo-3 - Echo-1) (%)	-2.10 ± 5.05	13.43 ± 9.09	0.001
Duration between Echo-2 and Echo-3 (months)	20.49 ± 13.40	21.79 ± 23.39	0.74

Data are presented as mean ± SD. Echo-1: First (or baseline) echocardiogram; Echo-2: Second echocardiographic examination at first follow-up; Echo-3: Third echocardiographic; LA: Left atrium/atrial; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular ejection fraction; RVSP: Right ventricular systolic pressure.

48.0 ± 10.0%). At 36 months of follow-up after Echo-2, most patients had Echo-3 (*n* = 183), which also showed sustained EF improvement in 70.0% of patients[15]. In contrast the reported frequency of HFtimpEF varies between 11.0% and 38.0% in prior studies[16]. This variation is thought to be due to different definitions of LVEF reworsening and variations in the timing and length of the follow-up echocardiograms. This led to increased rates of reported reworsening as the follow-up period was extended.

In our study patients with HFsimpEF showed concomitant improvement in echocardiographic parameters such as left atrium volume index, left ventricular end-systolic diameter, and RVSP despite having an initially lower LVEF than those with HFtimpEF. Similar findings have been observed in a study by Blechman *et al*[15]. In our study patients with HFsimpEF had a lower mean heart rate than those with HFtimpEF at follow-up, highlighting the continued use of beta-blockers despite initial improvement in patients with HFrEF. However, another study found no significant association between continued beta blocker therapy and sustained improvement in LVEF[17]. Hence, further studies are needed to confirm the long-term benefit of beta-blockers in HFsimpEF, especially to determine whether the benefits exist beyond just the lowering of heart rate.

Understanding the factors that lead to long-term sustained *vs* transient improvement followed by deterioration in LVEF is crucial for individualizing patient care. By recognizing the characteristics of such patients in each group, we can improve risk stratification and identify the vulnerable patients who may benefit from more aggressive treatment approaches. Currently, there is substantial evidence on the characteristics and outcomes of patients with HFimpEF. It is also known that patients with recovered EF have an improved prognosis after recovery[6,7,18]. However, it is not an entirely benign outlook. Despite experiencing improvement in their LVEF, these patients tend to have increased rates of all-cause hospitalizations and hospitalizations for HF[8]. Hence, HFimpEF should not be considered recovered. However, data is lacking about whether it is due to reworsening of the LVEF or whether there is a difference in the characteristics and clinical outcomes between those with HFtimpEF and those with HFsimpEF.

Our patients with HFsimpEF had favorable outcomes in terms of hospitalization rates and diagnosis of new cardiovascular diseases without an impact on mortality. In contrary other studies demonstrated a significant impact on mortality. Park *et al*[19] demonstrated that LVEF can be a predictor of mortality and that a declining LVEF was associated with a two-fold higher mortality. Sustained improvement of LVEF was positively associated with being female, having

Table 5 Medications at baseline and at second follow-up

Variable	Transient improvement (*n* = 39)	Sustained improvement (*n* = 136)	*P* value
Baseline (Echo-1)			
Beta-blockers	19 (48.7)	78 (57.4)	0.37
ACEI/ARB	25 (64.1)	81 (59.6)	0.71
MRA	2 (5.1)	29 (21.3)	0.02
Diuretics	13 (33.3)	62 (45.6)	0.20
HDZ/ISDN	1 (2.6)	4 (2.9)	1.00
Ivabradine	0 (0)	6 (4.4)	0.34
Digoxin	0 (0)	9 (6.6)	0.21
Antiplatelet therapy	24 (61.5)	78 (57.4)	0.71
LLA	24 (61.5)	72 (52.9)	0.38
Iron (IV)	7 (17.9)	17 (12.5)	0.43
Inotropes (hospital)	4 (10.3)	23 (16.9)	0.45
Second follow-up (Echo-3)			
Beta-blockers	36 (92.3)	126 (95.5)	0.43
ACEI/ARB	30 (76.9)	110 (80.9)	0.58
MRA	13 (33.3)	54 (40.9)	0.46
Diuretics	31 (79.5)	99 (75.0)	0.67
HDZ/ISDN	4 (10.3)	10 (7.6)	0.53
Ivabradine	3 (7.7)	11 (8.3)	1.00
Digoxin	2 (5.1)	7 (5.3)	1.00
Antiplatelet therapy	34 (87.2)	97 (73.5)	0.09
Lipid-lowering agents	36 (92.3)	106 (80.3)	0.08
Iron (IV)	4 (10.3)	5 (3.7)	0.12
Inotropes (hospital)	3 (7.7)	3 (2.2)	0.13

Echo-1: First (or baseline) echocardiogram; Echo-3: Third echocardiographic; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HDZ: Hydralazine; ISDN: Isosorbide dinitrate; IV: Intravenous; MRA: Mineralocorticoid receptor antagonists; LLA: Lipid lowering agents.

non-ischemic etiology of HF, and using MRA in our study.

In a recent study by McElderry *et al*[17], who recruited 7070 patients with HFimpEF, White race (OR = 1.31, 95%CI: 1.17-1.48) and continued use of renin-angiotensin-aldosterone system inhibitors or angiotensin receptor-neprilysin inhibitor (ARNi) (OR = 1.13, 95%CI: 1.03-1.25) were associated with increased odds of maintaining an improved LVEF. Male sex (OR = 0.84, 95%CI: 0.76-0.93), use of loop diuretics (OR = 0.79, 95%CI: 0.72-0.87), atrial fibrillation (OR = 0.85, 95%CI: 0.77-0.94), and history of myocardial infarction (OR = 0.76, 95%CI: 0.67-0.85) were correlated with a decline in LVEF over time in patients with HFimpEF[17].

Another study (*n* = 183) concluded that sustained improvement in LVEF was associated with a favorable long-term prognosis and reported the factors that were associated with the sustained improvement in patients with dilated cardiomyopathy. Pregnancy or chemotherapy-associated cardiomyopathy were associated with sustained improvement, but family history of dilated cardiomyopathy and long-standing disease had worse prognoses. Independent predictors of sustained improvement included pregnancy-associated disease, shorter disease duration, left ventricular hypertrophy by echocardiogram, and baseline LVEF of ≤ 25.0%. There was no difference in terms of medical therapy between the groups (HFsimpEF and HFtimpEF). However, beta-blocker dose was significantly higher in those with HFsimpEF. Interestingly, to predict sustained improvement in LVEF, the investigators established a score that assigned one point to each of the following variables: (1) Short disease duration (< 3.0 years) and no familial cardiomyopathy; (2) Baseline LVEF of ≤ 25.0%; (3) Pregnancy-associated presentation; and (4) Left ventricular wall thickness of ≥ 12.0 mm. A score of ≥ 3.0 reliably predicted sustained improvement in LVEF in 91.0% of patients[15]. It is important to recognize in our study that patients with pregnancy-associated cardiomyopathy were excluded. Yet most of our patients exhibited sustained improvement underscoring the importance of treatment-related factors in LVEF improvement.

Table 6 Multivariate nominal logistic regression analysis

Variable	Adjusted OR (95%CI)	*P* value
Age in years	0.99 (0.95-1.0)	0.42
Female	6.8 (1.4-32.3)	0.02
HF etiology		
Ischemic	1 (reference)	-
Dilated	3.1 (1.03-9.3)	0.04
Others	1.7 (0.30-9.3)	0.56
Hyperlipidemia	0.50 (0.21-1.11)	0.09
Hypertension	0.40 (0.13-1.16)	0.09
MRA use	7.0 (1.50-31.8)	0.01

CI: Confidence interval; OR: Odds ratio; HF: Heart failure; MRA: Mineralocorticoid receptor antagonists.

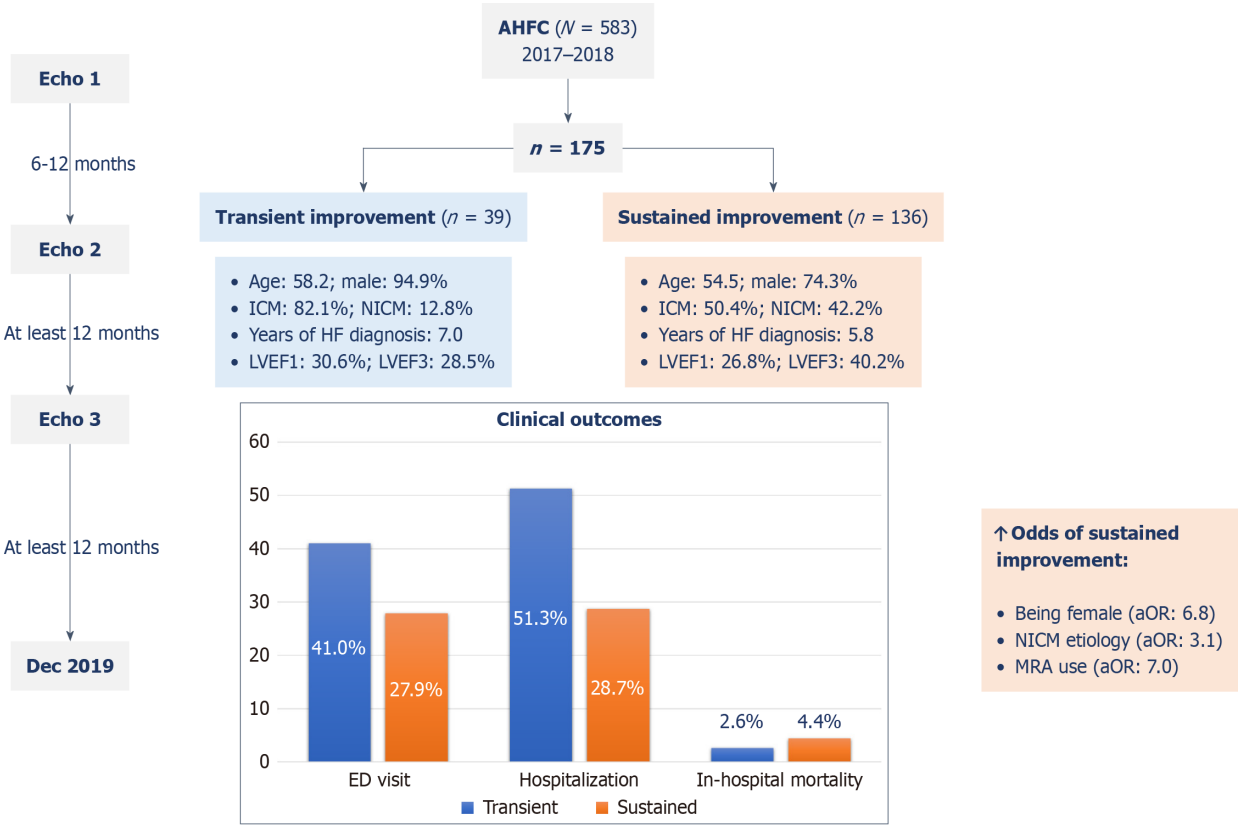

Figure 1 Characteristics and outcomes of patients with improved ejection fraction. AHFC: Advanced heart failure clinic; aOR: Adjusted odds ratio; Dec: December; ED: Emergency department; Echo 1: First (or baseline) echocardiogram; Echo 2: Second echocardiogram; Echo 3: Third echocardiogram; HF: Heart failure; ICM: Ischemic cardiomyopathy; LVEF: Left ventricular ejection fraction; LVEF1/3: LVEF at first (or baseline) echocardiogram/third echocardiogram; MRA: Mineralocorticoid receptor antagonists; NICM: Non-ischemic cardiomyopathy.

To the best of our knowledge, only a few studies have investigated the factors associated with sustained improvement in LVEF despite the accumulating studies examining the characteristics of patients with HFimpEF[17]. Enzan *et al*[20] concluded that beta-blocker therapy prevented the deterioration of LVEF (*i.e.* decrease in LVEF ≥ 10.0%) in patients with recovered dilated cardiomyopathy (*i.e.* mean LVEF was 49.3 ± 8.2%) at the 2-year follow-up (OR = 0.77, 95%CI: 0.63-0.95; $P = 0.013$). Chen *et al*[21] prospectively determined the safety of withdrawing spironolactone in patients with idiopathic dilated cardiomyopathy with improved LVEF (*i.e.* mean 44.0%-47.0%). Withdrawing spironolactone increased the likelihood of relapse (*i.e.* reduction in LVEF < 10.0%) within 12 months (relative risk = 4.31, 95%CI: 1.67-11.11; $P < 0.001$).

Halliday *et al*[22] in their pilot study concluded that tapering medications gradually can lead to relapses in patients with recovered dilated cardiomyopathy. Additionally, recent research identified echocardiographic parameters, namely

global longitudinal strain (GLS), that could predict sustained improvement in LVEF. Adamo *et al*[23] reported that a normal GLS was an indicator of maintaining a stable LVEF after its recovery and abnormal GLS was a predictor of a decrease in LVEF during follow-up. However, the authors defined a reduced LVEF as < 50.0%.

The results of our study should be interpreted in the context of the following potential limitations. Firstly, the retrospective observational design of the study may have introduced confounding by unmeasured variables, potentially affecting the reported associations between baseline characteristics and improvement in LVEF. Secondly, we defined improvement and sustained improvement in LVEF as 1.0% or greater on follow-up echocardiograms regardless of a specific cutoff for the final LVEF. Hence, interpreting the results must account for the inter-echocardiographer variability in the reporting of LVEF on each follow-up and must recognize the limitation of echocardiography as an imaging modality (*i.e.* it may be unable to recognize small improvements in LVEF of 1.0%). This has the potential to misclassify some patients between the two groups. Thirdly, the possibility of survival bias or lead-time bias cannot be fully excluded considering that patients who did not have a second follow-up echocardiogram (Echo-3) were excluded. Fourth, our study did not evaluate subjective measures of improvement to compare quality-of-life differences between HFsimpEF and HFtimpEF patients as such data were not available. It is also important to note that our study period concluded in 2018 when only a few of our patients were on an ARNi or a sodium-glucose cotransporter-2 inhibitors. This may result in potential underestimation of patients with long-term sustained improvement in LVEF considering their proven benefits in patients with HFrEF. Regarding clinical outcomes, our study investigated only the in-hospital death rates. Therefore, potential differences in the overall mortality rates between the groups remains to be elucidated. Finally, we did not evaluate other factors such as adherence to dietary recommendations, medication compliance, alcohol consumption, or smoking cessation, all of which can impact improvement in LVEF[24].

Despite these limitations, the key strength of our study was the inclusion of all patients from the largest tertiary care center for cardiovascular disease in Qatar, a country with a predominantly South East Asian and Middle Eastern/North African populations who are underrepresented in most HF studies. Other peripheral hospitals in Qatar share the same electronic medical records, hence the potential to miss a clinical outcome was reduced. Our study offers further baseline data for long-term longitudinal assessment of HFrEF patients with regular follow-up echocardiograms to prevent lack of recognition of HFtimpEF.

Further prospective studies are needed for the validation of the associated factors of improvement mentioned in this study to allow the creation of a risk stratification model and to identify patients at risk of reworsening LVEF to intensify their management strategy. In an era marked by extensive research demonstrating the benefits of ARNi and sodium-glucose cotransporter-2 in patients with HF, our study reported favorable outcomes despite the majority of patients not receiving these novel therapies. This highlights the need for future studies focusing on patients with improved LVEF who are treated with contemporary, guideline-directed HF therapies.

CONCLUSION

Patients with HFsimpEF experienced significantly lower rates of hospitalization and diagnosis of new cardiovascular conditions than patients with HFtimpEF. Sustained improvement in LVEF was positively associated with being female, having non-ischemic etiology of HF, and using an MRA.

FOOTNOTES

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment with verbal consent according to the usual standard of care.

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ORIGINAL ARTICLE

Retrospective Study

Incidence, risk factors and clinical outcomes of pericardial effusion in left ventricular assist device patients

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Abstract

BACKGROUND

Development of pericardial effusion in patients with left ventricular assist devices (LVADs) can be detrimental to health outcomes. This study aims to elucidate the prevalence and risk factors for pericardial effusion in patients with LVADs.

AIM

To elucidate risk factors associated with the presence of pericardial effusion in patients with LVADs and compare the clinical outcomes of those with and without pericardial effusion. The secondary goal is to determine the incidence of pericardiocentesis and pericardial window placement in patients with LVADs expe-

riencing pericardial effusion.

METHODS

Data were obtained from the National Inpatient Sample database between 2016 and 2018. Statistical analysis was performed using Pearson χ^2 test and multivariate logistic regression analysis to determine clinical outcomes of pericardial effusion and to identify variables associated with pericardial effusion in LVAD patients, respectively.

RESULTS

The prevalence of LVAD was 9850 (0.01%) among total study patients (n = 98112095). The incidence of pericardial effusion among LVAD patients was 640 (6.5%). The prevalence of liver disease (26.6% *vs* 17.4%), chronic kidney disease (CKD; 54.6% *vs* 49.4%), hypothyroidism (21.9% *vs* 18.1%), congestive heart failure (98.4% *vs* 96.5%), atrial fibrillation (Afib; 58.59% *vs* 50.5%), coronary artery disease (CAD; 11.7% *vs* 4.4%), dyslipidemia (31.3% *vs* 39.3%), and having undergone percutaneous coronary intervention (PCI; 1.6% *vs* 0.7%) was higher in the pericardial effusion cohort *vs* the non-pericardial effusion cohort. Multivariate regression analysis demonstrated that CAD (OR = 2.89) and PCI (OR = 2.2) had the greatest association with pericardial effusion in patients with LVADs. These were followed by liver disease (OR = 1.72), hypothyroidism (OR = 1.2), electrolyte derangement (OR = 1.2), Afib (OR = 1.1), and CKD (OR = 1.05). Among patients with LVADs, the median length of stay (33 days *vs* 27 days) and hospitalization cost (847525 USD *vs* 792616 USD) were significantly higher in the pericardial effusion cohort compared to the non-pericardial effusion cohort. There was no significant difference in mortality between cohorts. The prevalence of cardiac tamponade was 109 (17.9% of LVAD patients with pericardial effusion). Ten (9.2% of LVAD patients with cardiac tamponade) patients underwent pericardiocentesis and 44 (40.3%) received a pericardial window.

CONCLUSION

This study shows that liver disease, CKD, PCI, hypothyroidism, electrolyte derangement, Afib, and CAD had a significant association with pericardial effusion in LVAD patients. Hospitalization cost and length of stay were higher in the pericardial effusion group, but mortality was the same.

Key Words: Left ventricular assist device; Pericardial effusion; Cardiac tamponade; Pericardial window; Pericardiocentesis; Risk factors and clinical outcomes of pericardial effusion; Older age; Diabetes; Larger body mass index; Renal failure; malnutrition

Core Tip: Pericardial effusions in patients with left ventricular assist devices (LVADs) can lead to prolonged hospitalization and increased healthcare costs. Risk factors associated with the development of pericardial effusions include: Liver disease, chronic kidney disease (CAD), hypothyroidism, electrolyte derangement, atrial fibrillation, with the highest association found with CAD and percutaneous coronary intervention. While the presence of pericardial effusions did not have significant impact on mortality in our study, further studies are needed to elucidate whether the optimization of these co-morbidities would reduce the incidence of pericardial effusion in patients with LVADs.

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INTRODUCTION

Patients suffering from advanced end-stage heart failure who do not meet the criteria for heart transplantation can now benefit from mechanical circulatory support therapies such as left ventricular assist devices (LVADs). These devices improve quality of life and delay end-organ dysfunction; they can be used as bridging therapy until transplantation, or as destination therapy for patients who are ineligible for transplantation[1]. In the recent years, the use of LVADs as destination therapy has vastly increased, accounting for about 46% of all LVAD placements[1]. In the United States, the amount of LVAD implants is now approaching the number heart transplants[2]. As a result, the prevalence of LVADs and their associated complications are rapidly increasing. Topilsky *et al*[3] found that up to 60% of patients receiving LVADs experience an LVAD-related complication within 6 months of implantation, and 80% experience an adverse event within 2 years of implantation. Another study by Hillebrand *et al*[4] found that on average, patients were re-admitted 2.2 times in 11 months post-implant, with the median time to re-admission being just 35 days after initial discharge.

The most common LVAD-related complications include bleeding, device thrombosis, ischemic and hemorrhagic strokes, renal impairment, multi-organ failure and infection[5]. An equally important, but less studied complication of LVAD implantation, is the development of pericardial effusion which frequently requires pericardiocentesis or pericardial window placement.

Pericardial effusions can be found in patients with an initial myocardial infarction (MI) and are more often found in patients with an anterior ST segment MI, larger infarctions and congestive heart failure[6-8]. Pericardial effusions usually present within the first 5 days and slowly resolve over weeks to months[9]. In patients with acute MI or percutaneous coronary intervention (PCI), hemorrhagic pericardial effusions and cardiac tamponade may develop from coronary artery perforation during PCI, as well as hemorrhagic pericarditis, and cardiac rupture due to left ventricular free wall rupture.

Pericardial effusion is the abnormal accumulation of fluid within the pericardial cavity, and may be classified according to etiology, size, composition, duration, distribution and associated hemodynamics[10]. An effusion considered trivial is < 50 mL, effusions with an end-diastolic diameter less than 1 cm are considered mild (approximately 100 mL), effusions with a diameter > 1 cm and < 2 cm is considered moderate (100-500 mL), and those exceeding 2 cm are considered large[10-12].

LVAD placement carries a high risk of pericardial bleeding and cardiac tamponade[13]. Furthermore, LVADs confer a greater risk of bleed due to acquired von Willebrand syndrome, platelet dysfunction, arteriovenous malformation and angiodysplasia[14]. Additional risk of bleed is secondary to aggressive anticoagulation that is administered for the risk of pump thrombosis.

This study aims to elucidate risk factors associated with the presence of pericardial effusion in patients with LVADs and compare the clinical outcomes of those with and without pericardial effusion. The secondary goal is to determine the incidence of pericardiocentesis and pericardial window placement in patients with LVADs experiencing pericardial effusion.

MATERIALS AND METHODS

Data source

This study was conducted using the National Inpatient Sample (NIS) database which is part of the Healthcare Cost and Utilization Project, developed by the Agency for Healthcare Research and Quality[15]. The NIS is representative of over 97% of the human population, and the data encompasses an average of 7-8 million discharges per year, spanning 48 states. NIS data estimates more than 35 million hospitalizations nationally. Each of these admissions contain a myriad of patient information, including demographics, comorbidities, complications, the primary and secondary discharge diagnosis, and charge-to-cost ratio. The charges listed in the database represent the amount the hospital bills for services while the cost listed represents how much the service costs, including the utilities cost, supplies, and wages.

Study design

This study uses the International Classification of Disease (ICD), 10th revision, and Clinical Modification (ICD 10-CM) codes to identify diagnoses in the NIS database and included data obtained between January 2016 and December 2018. Only patients over the age of 18 years with were included in the study. Subjects excluded were patients under the age of 18 years, those heart transplant, intra-aortic balloon pump, and Impella device. ICD 10-CM codes were utilized to extract patients with LVAD from the NIS database. From within this subset of patients, ICD codes were again utilized to delineate those who had pericardial effusion and no pericardial effusion, as well as to identify those with specific comorbidities and baseline characteristics. This study was considered exempt from the formal approval of the Institutional Review Board, as the study cohort was derived from a publicly available database containing non-identifiable patient information.

Diagnosis code for LVAD, pericardial effusion, and other co-morbidities: The NIS data provides up to 30 Clinical Classifications Software (CCS) diagnoses for each inpatient visit. The CCS codes used for this study were: LVAD, pericardial effusion, cardiac tamponade, pericardial window, and pericardiocentesis (Supplementary Table 1). Patients were excluded if they were under 18 years old, had received heart transplants, intra-aortic balloon pumps, and/or Impella heart pumps.

Statistical analysis

The data analysis and extraction were done using SAS statistical software version 9.4. All continuous variables were compared using Student's *t*-test. These variables were presented as a mean ± SD for normally distributed variables. Median and interquartile ranges were used for non-Gaussian distributed variables. Categorical variables were analyzed using the Pearson χ^2 test. These variables were presented as a weighted frequency in percentages. A P value of < 0.05 was considered statistically significant. In the Table 1, age was analyzed using the Student's *t*-test, while the rest of variables in Table 1 were analyzed using the Pearson's χ^2 test. In Table 2, mortality was analyzed using Pearson's χ^2 test while length of stay and hospitalization cost were analyzed using the Student's *t*-test.

RESULTS

Between 2016 and 2018, there was a total of 115882699 hospitalizations in the United States. After excluding patients

Table 1 Patient-level characteristics of pericardial effusion *vs* no pericardial effusion in left ventricular assist device, *n* (%)

Characteristics	Pericardial effusion	No pericardial effusion	*P* value
Total number	640.00	9210.00	
Gender			
Male	445 (69.53)	7245 (78.66)	0.001
Female	195 (30.47)	1965 (21.34)	
Age (years)	57.57 ± 2.54	57.03 ± 3.63	0.649
Race			
White	345 (57.02)	5365 (62.21)	0.031
Black	165 (27.27)	2135 (24.75)	
Others	95 (15.7)	1125 (13.04)	
Co-morbidities			
Liver disease	170 (26.56)	1600 (17.37)	0.001
Obesity	150 (23.44)	1910 (20.74)	0.115
Chronic kidney disease	350 (54.69)	4550 (49.41)	0.010
Chronic obstructive pulmonary disease	90 (14.06)	1480 (16.07)	0.198
Carotid artery disease	10 (1.56)	1020 (11.07)	0.978
Percutaneous coronary intervention	10 (1.56)	65 (0.71)	0.029
CABG	5 (0.78)	135 (1.47)	0.214
Hypertension	65 (10.16)	1020 (11.07)	0.514
Peripheral vascular disease	15 (2.34)	370 (4.02)	0.044
Hypothyroidism	140 (21.88)	1665 (18.08)	0.018
Diabetes mellitus types 1&2	190 (29.69)	3555 (38.6)	0.001
Congestive heart failure	630 (98.44)	8890 (96.53)	0.013
Electrolyte derangement	455 (71.09)	6040 (65.58)	0.005
Smoking	25 (3.91)	520 (5.65)	0.076
Anemia	505 (78.91)	7055 (76.6)	0.198
Afib	375 (58.59)	4650 (50.49)	0.001
CAD	75 (11.72)	405 (4.41)	0.001
Dyslipidemia	200 (31.25)	3620 (39.31)	0.001

CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; Afib: Atrial fibrillation.

under 18 years (n = 17515974), patients with heart transplants (n = 67295), patients with intra-aortic balloon pumps (n = 139090) and patients with Impella heart pumps (n = 48245), 98112095 patients were eligible to be included in the study. Of the included patients, 9850 had LVADs with 640 (6.5%) patients having experienced a pericardial effusion (Figure 1).

Factors associated with the presence of pericardial effusion in patients with LVADs

Our results demonstrated a statistically significant correlation between multiple co-morbidities and the presence of pericardial effusion in patients with LVADs (Table 1).

These co-morbidities (percentage of pericardial effusion cohort *vs* percentage of no pericardial effusion cohort) included liver disease (26.56% *vs* 17.37%), chronic kidney disease (CKD; 54.69% *vs* 49.41%), hypothyroidism (21.88% *vs* 18.01%), congestive heart failure (98.44% *vs* 96.53%), atrial fibrillation (Afib; 58.59% *vs* 50.5%), coronary artery disease (CAD; 11.72% *vs* 4.41%), dyslipidemia (31.25% *vs* 39.31%), and having undergone PCI (1.56% *vs* 0.71%).

Multivariate regression analysis demonstrated that CAD (OR = 2.89, 95%CI = 2.21-3.72) and PCI (OR = 2.2, 95%CI = 1.08-4.23) had the greatest association with pericardial effusion in patients with LVADs. These were followed by liver disease (OR = 1.72, 95%CI = 1.42-2.06), hypothyroidism (OR = 1.26, 95%CI = 1.04-1.53), electrolyte derangement (OR = 1.2, 95%CI = 1.08-1.54), Afib (OR = 1.38, 95%CI = 1.17 -1.63), and CKD (OR = 1.23, 95%CI = 1.08-1.45; Table 2).

Table 2 Multivariate regression analysis for pericardial effusion group in left ventricular assist device

Comorbidity	Odds ratio (95%CI)	*P* value
Liver disease	1.721 (1.429- 2.063)	0.001
Chronic kidney disease	1.235 (1.052- 1.452)	0.009
Percutaneous coronary intervention	2.263 (1.083 -4.232)	0.015
Peripheral vascular disease	0.579 (0.328 -0.942)	0.034
Hypothyroidism	1.269 (1.041- 1.538)	0.016
Diabetes mellitus types 1&2	0.671 (0.563 -0.798)	0.001
Congestive heart failure	2.232 (1.249 -4.523)	0.009
Electrolyte derangement	1.290 (1.083-1.541)	0.004
Afib	1.387 (1.179-1.633)	0.001
CAD	2.890 (2.212-3.729)	0.001
Dyslipidemia	0.702 (0.590- 0.833)	0.001

CAD: Coronary artery disease; Afib: Atrial fibrillation.

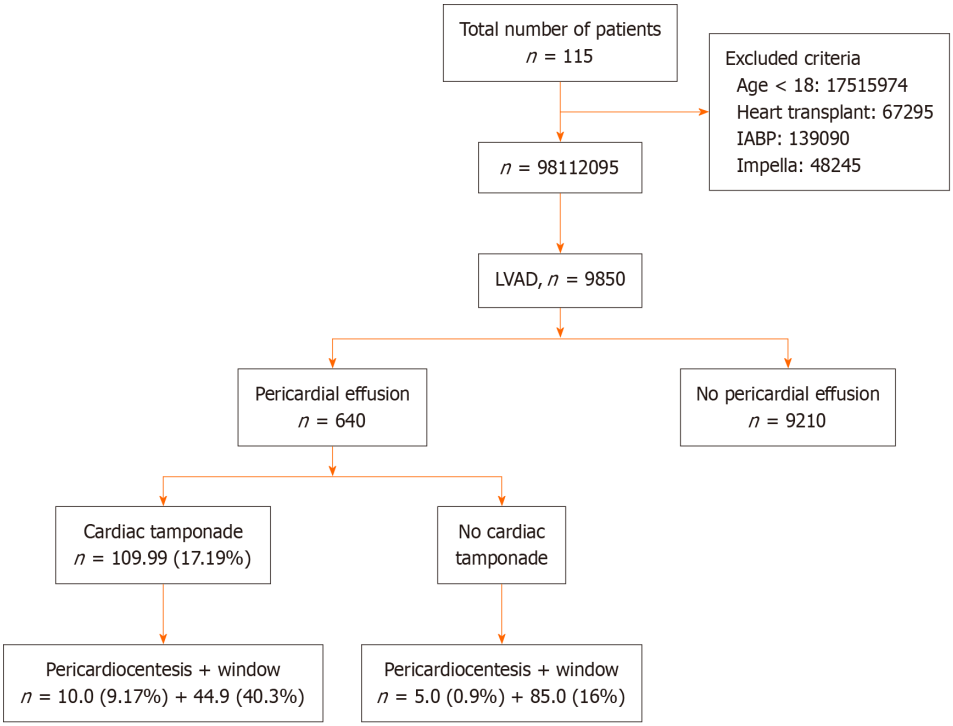

Figure 1 Flow chart of the study selection process. LVAD: Left ventricular assist device; IABP: Intra-Aortic Balloon Pump.

Clinical outcomes

Patients with LVADs who developed pericardial effusion experienced longer durations of hospitalization and higher hospitalization costs than patients without pericardial effusions. The median length of stay in LVAD patients with a pericardial effusion was 33 days compared to 27 days in those without a pericardial effusion (Table 3). The average hospitalization cost of LVAD patients with pericardial effusion was 847525 USD compared to 792616 USD in patients without pericardial effusion. Interestingly, there was no significant difference in mortality with a mortality of 9.38% in patients with pericardial effusion compared to 9.34% of patients without pericardial effusion. The annual trends of mean hospitalization cost and length of stay in the hospital were compared between pericardial effusion in patients with LVADs *vs* no pericardial effusion (Figure 2).

Cardiac tamponade and pericardiocentesis

Of the 9850 patients with implanted LVADs, 640 (6.5%) experienced a pericardial effusion. Within the pericardial effusion

Table 3 Clinical outcomes pericardial effusion *vs* no pericardial effusion in left ventricular assist device

	Pericardial effusion	No pericardial effusion	*P* value
Length of stay (days)	40.52 ± 6.06	34.08 ± 1.39	0.043
Hospitalization cost (USD)	847525 ± 93380	792616 ± 37959	0.035
Mortality	9.38 ± 2.26	9.34% ± 0.40	1

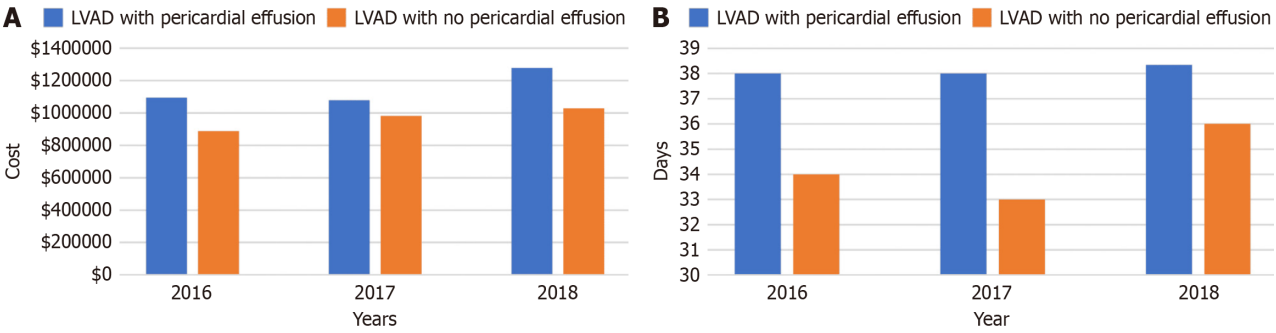

Figure 2 The annual trends of mean hospitalization cost and length of stay in the hospital were compared between pericardial effusion in patients with left ventricular assist devices *vs* no pericardial effusion. A: Trend in cost of care for left ventricular assist device with pericardial effusion and no pericardial effusion. $P < 0.001$ for the cost of care among pericardial effusion *vs* no pericardial effusion in 2016, 2017 and 2018; B: Trends in length of stay for left ventricular assist device with pericardial effusion and no pericardial effusion. $P < 0.001$ for length of stay among pericardial effusion *vs* no pericardial effusion in 2016, 2017 and 2018. LVAD: Left ventricular assist device.

cohort, 109 (17.0%) patients developed cardiac tamponade. Ten of these patients (9.2%) underwent pericardiocentesis and 45 patients (40.3%) received pericardial windows. Five-hundred and thirty-one patients experienced pericardial effusion without tamponade, of which 5 (0.9%) underwent pericardiocentesis, and 85 (16.3%) received pericardial windows.

DISCUSSION

This study demonstrates that LVAD patients with pericardial effusion experience longer hospitalization courses and higher hospitalization costs, however, there is no significant effect on mortality. Additionally, our results highlight a significant association between pericardial effusion and the presence of liver disease, CKD, hypothyroidism, electrolyte derangement, Afib, and CAD in LVAD patients.

To date, there are no large trials detailing the rate at which patients with LVADs develop pericardial effusion, however, several case studies over the years have attempted to quantify its prevalence. One Singaporean study analyzed the outcomes of 100 patients who underwent LVAD implantation and found that 14% developed pericardial effusions[16]. Topilsky *et al*[3] summarized that cardiac tamponade was a complication that occurred in 20% of patients receiving an LVAD, and Hillebrand *et al*[4] highlighted that 1 in 4 patients receiving LVAD implantation may develop pericardial effusion requiring re-exploration. Our study included 9850 patients with LVADs and found the prevalence of pericardial effusion to be 6.5%. The lower prevalence of pericardial effusion in our study may be due to our relatively large sample size, compared to previous case reports and may more accurately represent the prevalence of pericardial effusion in the general population.

One of the major concerns with developing pericardial effusion in a patient with an LVAD is that the device can mask the symptoms associated with cardiac effusion and tamponade, such as jugular venous distension, pulsus paradoxus, hypotension, and rest dyspnea[17]. This may be due to the set values of the LVAD preventing tachycardia or pulsus paradoxus, and is further complicated by the blurred echocardiogram windows in patients due to the LVAD flow, making rapid diagnosis difficult[18]. Both factors increase the risk of delayed diagnosis and management, leading to worse clinical outcomes. This was demonstrated by Al Shakaki *et al*'s case report of a patient with a ventricular assist device who suffered a massive pericardial effusion that was initially misdiagnosed as a thrombus of the outflow graft due to flow-limiting formation seen on CT. The patient received lysis therapy and subsequently clinically deteriorated, requiring emergent re-sternotomy and pericardiocentesis[19]. Our study relied upon ICD-10 coding of pericardial effusion and cardiac tamponade, which may have led to under-reporting of the true prevalence of pericardial effusion due to misdiagnosis.

This study found statistically significant correlations between a myriad of clinical conditions and the presence of pericardial effusion in patients with LVADs, including liver disease, CKD, hypothyroidism, electrolyte derangement, Afib, CAD, dyslipidemia, and those undergoing PCI. This correlation is not isolated to patients with LVADs and has been demonstrated to increase the risk of pericardial effusion in patients without mechanical circulatory support. Ashikhmina *et al*[20] found that patients who underwent cardiac surgery were at increased risk of developing a pericardial effusion if

they had a history of a high body mass index, pulmonary thromboembolism, hypertension, immunosuppression, or renal failure. Further research is required to determine whether optimization of these co-morbidities can reduce the incidence of pericardial effusion. It seems likely that a multidisciplinary approach to the management of patients with LVADs would lead to decreased incidence of pericardial effusion and improved clinical outcomes.

Pericardial effusion in patients with LVADs leads to an increased burden on the healthcare system through prolonging hospitalization and increasing the cost of healthcare delivery. Our study demonstrated that patients with pericardial effusion spent a median of 6 days longer in hospital and cost an additional 54909 USD per hospital stay compared to LVAD patients without pericardial effusion. These findings may be confounded by the fact that many of the co-morbidities associated with the presence of pericardial effusion also tend to prolong hospitalization and increase healthcare costs. This was highlighted by Cotts *et al*[21] who found that increased age, non-white race, history of CABG or valve surgery, diabetes, ascites, low albumin, high blood urea nitrogen, high right atrial pressure and concomitant surgery were all variables that increased length of stay and hospitalization costs in LVAD patients. If LVAD patients have co-morbidities that require additional non-cardiac surgery, then they are at very high risk of experiencing severe complications which would prolong their hospital course and increase costs[22]. Overall, it is imperative that the multidisciplinary team collaborates to minimize risk factors associated with pericardial effusion in patients with LVADs, and that pericardial effusion is identified appropriately and treated in a timely manner to prevent lengthy and costly hospitalization.

Limitations

Our study has several limitations. First of all, our data relied upon the correct diagnosis and use of ICD-10 codes by physicians across the country which may have led to some disease misclassification, as we were unable to validate the signs and symptoms experienced by the patients included in this study. Another limitation is that the study population is confined to inpatients and our results may not correlate with outcomes in patients with subclinical pericardial effusion who are managed in an outpatient setting. The NIS database provides information on hospital admissions and not individual patients. As a result, our data may be skewed by patients being admitted multiple times and artificially increasing the prevalence of pericardial effusion in our study population. In addition, LVAD type, implantation duration and anticoagulation therapy were not included in our study, and their inclusion could potentially influence the occurrence of pericardial effusion.

CONCLUSION

The development of pericardial effusion in patients with LVADs leads to prolonged hospitalization and increased healthcare costs, while the presence of pericardial effusion did not have significant impacts on mortality. The presence of liver disease, CKD, hypothyroidism, electrolyte derangement, Afib, CAD, and undergoing PCI have a significant association with development of pericardial effusion in patients with LVAD. Further research is required to elucidate whether optimization of co-morbidities in patients with LVADs reduces the incidence of pericardial effusion.

FOOTNOTES

Author contributions: Franklin S, Shah H were involved in the graphical abstract; Khan MZ, Brailovsky Y, Alvarez RJ contributed to the conceptualization of this manuscript; Khan MZ, Sircar A, O'Neill P, Waqas M, Brailovsky Y participated in the writing and review; Marhefka G, Alvarez RJ, Rajapreyar I, Rame JE contributed to the review and supervision of this manuscript; Franklin S, Shah H and Waqas M participated to make graphs and tables; Bhuiyan MAN and Faisal ASM did stastictics; all authors have read and approved the final manuscript.

Institutional review board statement: This study, entitled, "Incidence, Risk Factors and Clinical Outcomes of Pericardial Effusion in LVAD Patients," was considered exempt from the formal approval of the Institutional Review Board, as the study cohort was derived from a publicly available database containing non-identifiable patient information.

Informed consent statement: Our study meets the definition of Not Human Subject Research, as our study utilized de-identified data obtained from the National Inpatient Sample database between the years 2016 and 2018. We had no access to direct patient identifiers or identifiable information. Prior to obtaining the data from the NIS database utilized in our study, the data had already been de-identified. No data in our study can be used to identify any patients.

Conflict-of-interest statement: There are no conflicts of interest.

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ORIGINAL ARTICLE

Retrospective Study

Acute myocardial infarction in the young: A 3-year retrospective study

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Abstract

BACKGROUND

Acute myocardial infarction (AMI) is rare among patients aged ≤ 40 years but imposes significant morbidity, psychological distress, and economic burden. Approximately 10% of AMI hospitalizations involve patients under 45 years, underscoring the need to study this group. Compared to older patients, young AMI patients exhibit fewer traditional risk factors (*e.g.*, hypertension, diabetes) but higher rates of smoking, obesity, and non-atherosclerotic causes like spontaneous coronary artery dissection or coronary spasm, often linked to substance use. Global trends show rising obesity and dyslipidemia in young populations, with smoking contributing to 62%–90% of AMI cases in this age group. Family history of coronary artery disease also elevates risk, particularly in acute coronary syndrome. Studies like Bhardwaj *et al* report that young AMI patients are predominantly male with single-vessel disease, unlike the multi-vessel disease typical in older cohorts. This study characterizes AMI in young adults (≤ 40 years) at a single center, focusing on presentation, risk factors, angiographic findings, and management to guide preventive strategies.

AIM

To describe the characteristics of AMI in young patients, including presentation, risk factors, coronary angiography (CAG) findings, and management strategies.

METHODS

This retrospective cross-sectional study analyzed 91 patients aged 20–40 years diagnosed with AMI at Mouwasat Hospital Dammam, from June 2020 to May 2023. Data on clinical presentation, cardiovascular risk factors, CAG findings, and treatments were collected from medical records. Descriptive statistics were used to summarize findings.

RESULTS

Of 91 patients (96.7% male, mean age 35.9 years ± 3.4 years), 43.9% were obese

(body mass index > 30 kg/m²). Hyperlipidemia was the most prevalent risk factor (69.2%), followed by smoking (49.5%), diabetes mellitus (33.0%), and hypertension (26.4%). ST-elevation myocardial infarction (STEMI) was the most common presentation (57.1%). The left anterior descending artery was frequently affected (78.0%), with single-vessel disease predominant (72.5%). Most patients underwent percutaneous coronary intervention (PCI) (74.7%), while 8.8% required surgery.

CONCLUSION

Young AMI patients are predominantly obese males with hyperlipidemia and smoking as key risk factors, presenting with STEMI and single-vessel disease amenable to PCI.

Key Words: Acute myocardial infarction; Cardiovascular risk factors; Young adults; Coronary angiography; Coronary artery disease

Core Tip: This retrospective single-center study aimed to describe characteristics of acute myocardial infarction (AMI) in young patients, including presentation, risk factors, coronary angiography findings, and management strategies for AMI in a young population aged less than 40 years. The most common presenting diagnosis was ST-elevation myocardial infarction, with the left anterior descending artery being the most frequently affected artery. Most patients required percutaneous coronary intervention with single stent placement. Obesity and hyperlipidemia were identified as major risk factors for developing AMI in young individuals. Early screening for traditional risk factors and appropriate treatment in the young population is crucial for the primary prevention of AMI.

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INTRODUCTION

Acute myocardial infarction (AMI) is rare among patients aged ≤ 40 years but imposes significant morbidity, psychological distress, and economic burden[1]. Approximately 10% of AMI hospitalizations involve patients under 45 years, underscoring the need to study this group[2]. Compared to older patients, young AMI patients exhibit fewer traditional risk factors (*e.g.*, hypertension, diabetes) but higher rates of smoking, obesity, and non-atherosclerotic causes like spontaneous coronary artery dissection (SCAD) or coronary spasm, often linked to substance use[3,4].

Global trends show rising obesity and dyslipidemia in young populations, with smoking contributing to 62%–90% of AMI cases in this age group[5-7]. Family history of coronary artery disease (CAD) also elevates risk, particularly in acute coronary syndrome[2]. Studies like Bhardwaj *et al*[1] report that young AMI patients are predominantly male with single-vessel disease, unlike the multi-vessel disease typical in older cohorts. This study characterizes AMI in young adults (≤ 40 years) at a single center, focusing on presentation, risk factors, angiographic findings, and management to guide preventive strategies.

MATERIALS AND METHODS

This retrospective cross-sectional study analyzed data from the cardiovascular department archive at Mouwasat Hospital Dammam, Saudi Arabia. We included patients aged 20–40 years diagnosed with AMI from June 2020 to May 2023 who underwent coronary angiography (CAG). AMI was defined per the Fourth Universal Definition, requiring clinical evidence of acute myocardial ischemia and a rise and/or fall in cardiac troponin (cTn) above the 99th percentile, with or without ST-segment elevation[8]. Patients aged < 20 years or > 40 years or with undetectable cTn were excluded. Data on clinical presentation, cardiovascular risk factors (*e.g.*, hypertension, diabetes, smoking, obesity), CAG findings, and treatments were extracted from medical records. Obesity was defined as body mass index (BMI) > 30 kg/m². The age cutoff of 40 years aligned with prior studies defining "young" AMI patients, ensuring clinical relevance and adequate sample size[1,4]. The lower limit of 20 years excluded rare pediatric cases. Consecutive sampling included all eligible patients, yielding 91 cases over 3 years, consistent with an estimated 30–35 annual AMI cases in this age group at our center, which performs approximately 1200 percutaneous coronary intervention (PCI) annually. Data were analyzed using descriptive statistics (means ± SD for continuous variables, frequencies/percentages for categorical variables) in Statistical Package for the Social Sciences version 26. No inferential tests were conducted due to the study's descriptive design. The study was approved by the Institutional Review Board (No. 2023-D-002), with informed consent obtained

from all participants.

RESULTS

From June 2020 to May 2023, 91 patients with AMI (mean age 35.9 years ± 3.4 years, 96.7% male) were studied (Table 1). Most were obese (43.9%, BMI > 30 kg/m²) or overweight (35.2%). Hyperlipidemia was the most common risk factor (69.2%), followed by smoking (49.5%), diabetes mellitus (DM) (33.0%), hypertension (26.4%), and family history of CAD (20.9%) (Table 1).

Most patients had a high BMI (30.7 kg/m² ± 5.8 kg/m²). Of these, 40 (43.9%) patients were obese (BMI more than 30 kg/m²). A total of 32 (35.16%) patients were overweight (BMI ranging between 25- 29.9 kg/m²) (Table 2).

Traditional risk factors for ischemic heart disease were nearly similar to those in older patients. A total of 24 (26.37%) patients were hypertensive. DM was present in 30 (33.0%) patients, including 2 (2.2%) patients with type 1 DM, 28 (30.8%) patients with type 2 DM, and 8 (8.8%) patients newly diagnosed during admission. A total of 63 (69.2%) patients had hyperlipidemia, of whom 28 (36.7%) patients were newly diagnosed during admission. Total 49.45% of patients were smokers. Lastly, 20.88% of patients had a positive family history of ischemic heart disease in their first-degree relatives (Table 3).

ST-elevation myocardial infarction (STEMI) predominated (57.1%), with anterior STEMI most frequent (38.5%), followed by inferior STEMI in 16 (17.58%) patients. Non-STEMI was diagnosed in 42.86% of patients (Table 4).

Regarding the Echocardiographic assessment, mean ejection fraction was 47.8% ± 12.9%. Regarding segmental wall motion abnormality (SWMA), we found anterior and apical hypokinesia (21.98%), inferior/posterior hypokinesia (21.98%), anterior-septal hypokinesia (10.99%), apical akinesia (6.59%), global hypokinesia (13.19%) and lateral hypokinesia (6.59%) (Table 5).

CAG showed the left anterior descending artery (LAD) as the most affected (78.0%), followed by the right coronary artery (RCA) (54.9%), left circumflex artery (LCX) (44.0%), left main (LM) (5.5%) and ramus artery (5.5%) (Table 6).

Single-vessel disease was common (72.5%), followed by double-vessel (8.8%) and three-vessel disease (5.5%), LM and three vessel disease (4.4%), and the least common was LM and two vessel disease (1.1%). It is worth mentioning that this particular patient was a 25-year-old postpartum female who presented with extensive anterior STEMI and was found to have SCAD involving LM, LAD and LCX arteries (Table 6 and Figure 1).

Furthermore, we found that LAD was the most commonly affected culprit artery (56.04%), followed by RCA (18.68%), and lastly LCX (12.09%) (Table 6).

Obstructive CAD was observed in 83.5% of patients, while myocardial infarction with non-obstructive coronary arteries (MINOCA) occurred in 14.3%, and coronary artery dissection was identified in 2.2%. Among patients with normal coronary arteries, one (1.1%) was diagnosed with Takotsubo Cardiomyopathy, confirmed by Left Ventricle Angiogram (Figure 2), and another (1.1%) had Dilated Cardiomyopathy secondary to Aortic Valve Insufficiency (Table 7).

Management was classified into PCI with balloon dilatation and stenting (74.7%). Thrombus aspiration without stenting (2.2%). The 8.8% were referred for open-heart surgery, including coronary artery bypass graft (CABG) (6.6%), CABG with aortic valve replacement (AVR) (1.1%), and AVR with the Bentall procedure (1.1%). Conservative medical treatment (6.6%), and normal coronary arteries not requiring CAD treatment (7.7%). Of these, one was diagnosed with Takotsubo cardiomyopathy, and another had Dilated Cardiomyopathy due to severe Aortic Insufficiency (Table 8). The key positive findings of this study are summarized in Table 9.

DISCUSSION

This study characterizes AMI in young adults (≤ 40 years), revealing a predominance of male patients (96.7%) with obesity (43.9%) and traditional risk factors like hyperlipidemia (69.2%) and smoking (49.5%). These align with Bhardwaj *et al*[1], who noted AMI in young patients as primarily male with similar risk profiles. Regarding obesity, the guidelines recommend an ideal BMI of 25 kg/m² and suggest a reduction in body weight if BMI > 30 kg/m² or when waist circumference is > 102 cm for men and > 88 cm for women[5]. In the current study, we noticed that the mean BMI of the patients is high (30.7 kg/m² ± 5.8 kg/m²). Most of our patients (79.12%) were overweight or obese. Previous Literature found that obesity is the most prevalent risk factor in young adults[4]. Obese individuals have a higher incidence of cardiovascular risk factors, such as hypertension, DM and dyslipidemia. Therefore, this group of patients has higher morbidity and mortality associated with cardiovascular disorders[5]. Moreover, cigarette smoking is the most important and consistent risk factor for CAD, with contribution ranging from 62% to 90% in various literature[6,7]. In previous studies, smokers comprised 78.5% of the population[9]. Our study detected that 49.45% of patients were active smokers. Typically, a young AMI patient is an overweight or obese, hyperlipidemic and a smoker. Therefore, implementing targeted screening programs for young adults with obesity or family history of CAD, and promoting smoking cessation campaigns is crucial.

Unlike older AMI patients, where multi-vessel disease and hypertension are prevalent, our cohort showed single-vessel disease (72.5%) and lower hypertension rates (26.4%)[10]. This suggests a distinct pathophysiology driven by modifiable factors like smoking and obesity rather than chronic vascular changes.

The clinical significance lies in preventive opportunities. High rates of undiagnosed hyperlipidemia (39.7%) and diabetes (8.8%) highlight the need for routine screening in young adults, especially those with a family history of CAD (20.9%). Smoking, present in nearly half of cases, is a key target for public health interventions, as cessation could reduce AMI incidence significantly[6]. Our MINOCA rate (14.3%) matches prior studies (Al-Ali *et al*[11], 15.6%; von Korn *et al*

Table 1 Demographic Characteristics of study participants, *n* (%)

Parameter	Value
Age (mean ± SD) (years)	35.9 ± 3.38
Sex	
Male	88 (96.7)
Female	3 (3.3)

Total participants (*n*): 91.

Table 2 Body mass index summary, *n* (%)

Category (kg/m²)	
Underweight (< 18.5)	0
Healthy (18.5-24.9)	19 (20.87)
Overweight (25-29.9)	32 (35.16)
Obese (> 30)	40 (43.9)
Body mass index (mean ± SD)	30.7 ± 5.8

Table 3 Prevalence of cardiovascular risk factors, *n* (%)

Risk factor	Measure	
Hypertension	Yes	24 (26.37)
	No	67 (73.63)
DM	Yes	30 (32.97)
	No	61 (67.03)
Type 1 DM		2 (2.2)
Type 2 DM		28 (30.76)
Newly diagnosed DM		8 (8.79)
Dyslipidemia	Yes	63 (69.23)
	No	28 (30.76)
Newly diagnosed dyslipidemia		25 (39.68)
Smoking status	Yes	45 (49.45)
	No	46 (50.54)
Family history of ischemic heart disease	Yes	19 (20.88)
	No	72 (79.12)

Total participants (*n*): 91. DM: Diabetes mellitus.

[12], 8.8%), emphasizing the role of advanced diagnostics [*e.g.*, intravascular ultrasound (IVUS), optical coherence tomography (OCT)] for non-atherosclerotic causes like coronary spasm.

Angiographically, in young patients with AMI, STEMI was more prevalent than non-STEMI. CAD was more frequently detected in LAD than in other arteries. Moreover, LAD was the most frequently detected culprit artery, followed by RCA and LCX. Furthermore, SWMA was more frequently noticed in LAD territory. The same findings were described in Anjum *et al*[13] study and Fournier *et al*[14] study.

Compared to classic AMI populations, young patients required simpler interventions (62.6% needed one stent), reflecting less extensive CAD. The same finding was described in Andreenko *et al*[15] study. However, SCAD (2.2%) is an infrequent finding in young AMI patients in our study, notably in a postpartum female, underscores the need to consider non-traditional etiologies in young women, as reported by Tweet *et al*[16]. These differences advocate for tailored

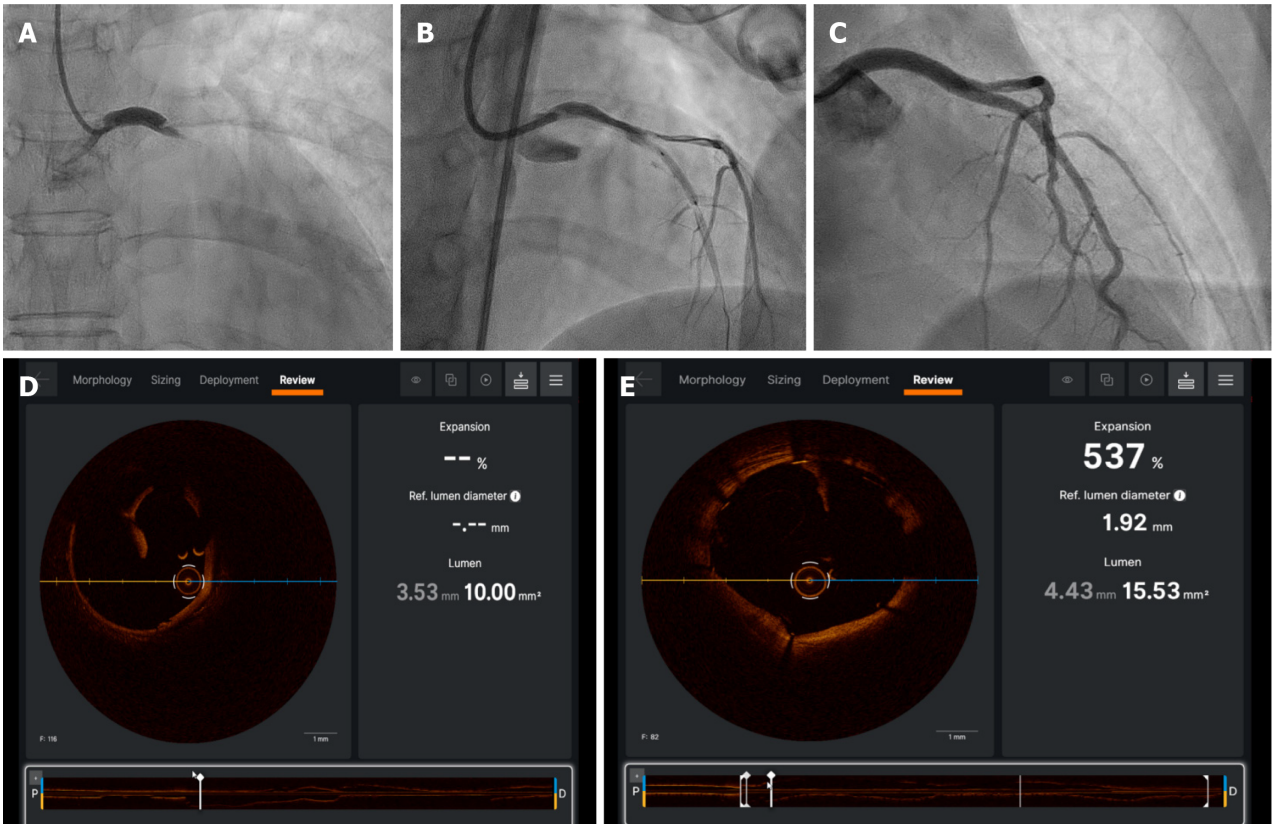

Figure 1 A 25-year-old postpartum female who presented with extensive anterior ST-elevation myocardial infarction and found to have spontaneous coronary artery dissection involving left main, left anterior descending artery and left circumflex artery. A: It shows distal left main (LM) dissection and left anterior descending artery (LAD)/left circumflex artery (LCX) total occlusion; B: It shows wiring of LAD/LCX; C: It shows post percutaneous coronary intervention to LM/LAD- LCX; D and E: They show optical coherence tomography imaging showing LM/LAD dissection.

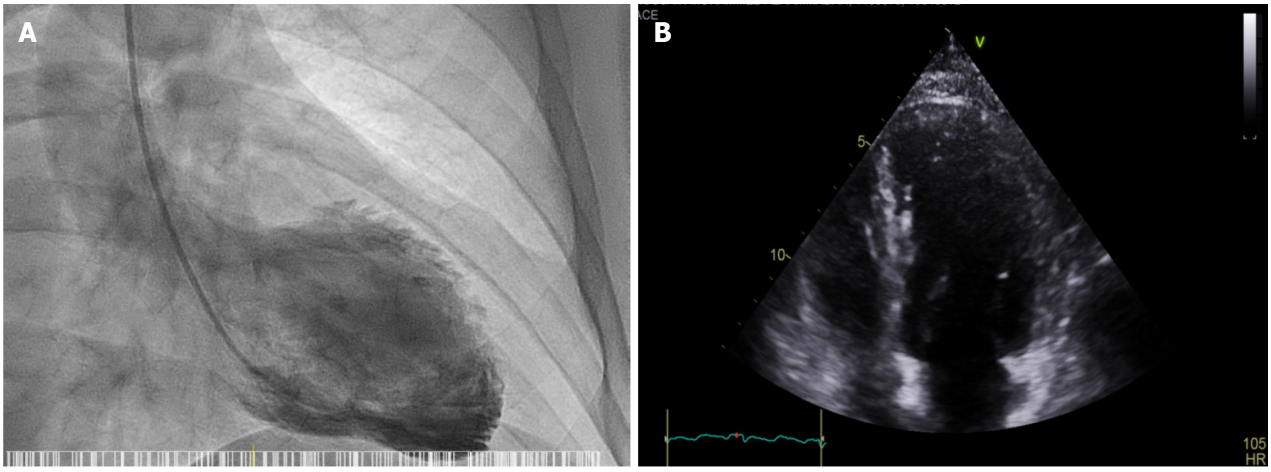

Figure 2 Left Ventricle Angiogram. A: It shows Left Ventricle Angiogram showing apical ballooning; B: Echocardiogram shows Apical ballooning.

diagnostic and management approaches to optimize outcomes in young AMI patients.

In order to properly evaluate and treat non-obstructive CAD, European guidelines put a clear definition for MINOCA. The diagnosis of MINOCA must meet 3 criteria. First, a definitive diagnosis of AMI must be made (the same as that of AMI caused by obstructive CAD). Second, CAG must show non-obstructive coronary disease, *i.e.*, no obstructive coronary disease (*i.e.*, no coronary stenosis ≥ 50%) is found in any possible infarction-related Angiography, including normal coronary arteries (no stenosis < 30%) and mild coronary atherosclerosis (stenosis > 30 and < 50%). Third, there is no clinical finding of other specific diseases that cause AMI, *e.g.*, myocarditis and pulmonary embolism[8]. Additional diagnostics, such as IVUS, OCT, and cardiovascular magnetic resonance, for accurate diagnosis.

Previous studies faced similar difficulties in building up the provisional diagnosis of this particular type of patients [17]. The current study revealed that 14.29% of the patients with AMI lacked significant coronary stenosis according to the CAG procedure performed during the hospital admission; which was consistent with the results of Al-Ali *et al*[11]

Table 4 Patient diagnosis on admission, *n* (%)

Cause of admission	Measure	
STEMI	Yes	52 (57.1)
	No	39 (42.86)
Anterior STEMI		35 (38.46)
Inferior STEMI		16 (17.58)
Lateral STEMI		1 (1.1)
Non-STEMI	Yes	39 (42.86)
	No	52 (57.1)

Total participants (*n*): 91. STEMI: ST elevation myocardial infarction.

Table 5 Echocardiographic findings, *n* (%)

Parameter	
Segmental wall motion	
Normal	17 (18.68)
Inferior/posterior hypokinesia	20 (21.98)
Anterior-septal hypokinesia	9 (10.99)
Apical akinesia	6 (6.59)
Anterior and apical hypokinesia	20 (21.98)
Global hypokinesia	12 (13.19)
Lateral hypokinesia	6 (6.59)
Ejection fraction range (mean ± SD)	47.8% ± 12.92%

Total participants (*n*): 91.

Table 6 Coronary angiography findings, *n* (%)

Parameter		*n* = 91
LM	Normal	86 (94.51)
	Significant lesion	4 (4.4)
	Total occlusion (dissection)	1 (1.1)
LAD	Normal	20 (21.98)
	Significant lesion	23 (25.28)
	Non-significant lesion	12 (13.19)
	Total occlusion	18 (19.78)
	Subtotal occlusion	9 (9.89)
	Thrombus	4 (4.39)
	Bridge	3 (3.3)
	Total D1	2 (2.2)
LCX	Normal	51 (56.04)
	Significant lesion	16 (17.58)
	Non-significant lesion	18 (19.78)

	Total occlusion	3 (3.3)
	Subtotal occlusion	2 (2.2)
	Dissection	1 (1.1)
RCA	Normal	41 (45.05)
	Significant lesion	11 (12.09)
	Non-significant lesion	20 (21.98)
	Total occlusion	9 (9.89)
	Subtotal occlusion	8 (8.79)
	Thrombus	2 (2.2)
Ramus	Normal	86 (94.51)
	Significant lesion	1 (1.1)
	Non-significant lesion	4 (4.4)
		n = 79
Culprit artery	LAD	51 (56.04)
	RCA	17 (18.68)
	LCX	11 (12.09)
		n = 84
Frequency of affected vessels	Single vessel disease	66 (72.53)
	Two vessel disease	8 (8.79)
	Three vessel disease	5 (5.49)
	LM + three vessel disease	4 (4.4)
	LM + two vessel disease	1(1.1)

LAD: Left anterior descending artery; LCX: Left circumflex artery; LM: Left main; RCA: Right coronary artery.

Table 7 Coronary angiography final diagnosis, *n* (%)

Final diagnosis	*n* = 91
Obstructive CAD	76 (83.51)
Myocardial infarction with non-obstructive coronary arteries	13 (14.28)
Non-obstructive CAD	5 (5.5)
Normal coronary	6 (6.59)
Takotsubo cardiomyopathy	1 (1.1)
Aortic valve insufficiency induced cardiomyopathy	1 (1.1)
Coronary artery dissection	2 (2.2)
With no obstructive lesion	1 (1.1)
With obstructive lesion	1 (1.1)

CAD: Coronary artery disease.

study (15.6%) and von Korn *et al*[12] study (8.8%).

Angina or ischemia with no obstructive CAD (ANOCA/INOCA) is another entity of non-obstructive CAD. It is frequently underdiagnosed and undertreated condition, primarily due to the limitations of current diagnostic tools. The condition is proposed to arise from two mechanisms: (1) Coronary microvascular dysfunction, leading to myocardial sub perfusion during stress; and (2) Microvascular spasm at rest. The definitive diagnostic approach involves invasive CAG with assessments of endothelial-independent microvascular dysfunction in response to adenosine, and endothelial-dependent microvascular dysfunction in response to acetylcholine, as well as evaluations for epicardial and microva-

Table 8 Management strategies, *n* (%)

Conclusion		*n* = 91
Intervention		78 (85.71)
PCI	Total number	68 (74.72)
	PCI with 1 DES	57 (62.64)
	PCI with 2 DES	6 (6.59)
	PCI with 3 DES	1 (1.1)
	PCI with 5 DES	1 (1.1)
	PCI with 1 DES and 1 DEB	1 (1.1)
	PCI with 2 DES and 1 DEB	1 (1.1)
	PCI with 1 DES and 3 DEB	1 (1.1)
Thrombus aspiration		2 (2.2)
Open heart surgery	Total number	8 (8.79)
	MVD for CABG	6 (6.59)
	MVD for CABG + AVR	1 (1.1)
	AVR and Bentall procedure	1 (1.1)
Medical treatment		6 (6.6)
Normal coronaries		7 (7.7)

AVR: Aortic valve replacement; CABG: Coronary artery bypass graft; DEB: Drug eluting balloon; DES: Drug eluting stent; MVD: Multi vessel disease; PCI: Percutaneous coronary intervention.

Table 9 Summary of patient characteristics, *n* (%)

Parameter	Value (*n* = 91)
Age (years, mean ± SD)	35.9 ± 3.4
Male	88 (96.7)
Body mass index (kg/m²) (mean ± SD)	30.7 ± 5.8
Obese (> 30)	40 (43.9)
Overweight (25–29.9)	32 (35.2)
Risk factors	
Hyperlipidemia	63 (69.2)
Smoking	45 (49.5)
Diabetes mellitus	30 (33.0)
Hypertension	24 (26.4)
Family history of CAD	18 (20.9)
Presentation	
STEMI	52 (57.1)
Non-STEMI	39 (42.9)
Coronary angiography findings	
Obstructive CAD	76 (83.51)
Myocardial infarction with non-obstructive coronary arteries	13 (14.28)
Coronary artery dissection	2 (2.2)
Management	

Percutaneous intervention	70 (76.92)
Surgery	8 (8.79)
Medical treatment	6 (6.6)
Normal coronaries	7 (7.7)

CAD: Coronary artery disease; STEMI: ST elevation myocardial infarction.

scular spasm[18]. Accurate diagnosis of coronary microvascular dysfunction is paramount, as it is associated with an increased risk of major adverse cardiovascular events. The assumption that normal CAG confirms normal coronary vasculature is now outdated. ANOCA/INOCA is linked to a heightened risk of significant cardiovascular incidents. This underscores the critical importance of comprehensive coronary vasculature testing in such patients[19].

CONCLUSION

Young AMI patients are predominantly obese males with hyperlipidemia and smoking as key risk factors, presenting with STEMI and single-vessel disease amenable to PCI. Traditional risk factors, such as hypertension, DM, and hyperlipidemia, are increasing in the young population, who are often not aware of their condition and its potential complications. Early detection through screening programs and proper treatment would significantly impact primary prevention of AMI in young adults. Smoking prevention and cessation remain crucial targets to reduce the incidence of AMI in this group.

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FOOTNOTES

Author contributions: Hegazi Abdelsamie A was responsible for data collection, analysis and interpretation, drafting of manuscript, data preparation and presentation; Hegazi Abdelsamie A and Abdelhadi HO were responsible for study design and conception; Hegazi Abdelsamie A and Abdelwahed AT were responsible for literature review; Abdelhadi HO was responsible for supervision of the research; Abdelwahed AT was responsible for revising and editing the manuscript critically for important intellectual contents; Hegazi Abdelsamie A, Abdelhadi HO, and Abdelwahed AT were responsible for research coordination and management; all of the authors read and approved the final version of the manuscript to be published.

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ORIGINAL ARTICLE

Prospective Study

Impact of optimal medical therapy in heart failure certification for hospitalists on guideline-directed medical therapy utilization

Farhan Ishaq, Duc T Nguyen, Edward A Graviss, Ebun Ebunlomo, Arvind Bhimaraj, Nadia Fida

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Abstract

BACKGROUND

Significant gaps in guideline-directed medical therapy (GDMT) for heart failure (HF) stem from shortages of cardiologists and advanced HF providers, as well as a lack of optimal HF management knowledge among hospitalists. This study compared the impact of optimal medical therapy in HF (OMT-HF) certification on GDMT implementation and patient outcomes between an intervention group (IG) of hospitalists and a standard-of-care comparison group (SOC-CG).

AIM

To evaluate if OMT-HF has a difference in GDMT and patients in outcomes between IG and SOC-CG.

METHODS

This study was implemented from November 2022 to May 2023. Hospitalized cardiology patients with HF and left ventricular ejection fraction ≤ 40% were randomized to IG or SOC-CG. Exclusion criteria included patients in cardiogenic shock, unable to consent, or at high risk. Follow-up was at 30 days post-discharge. Differences between groups were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank-sum or unpaired *t*-test for continuous variables. Changes in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores

were evaluated using a paired *t*-test.

RESULTS

IG patients had lower readmission rates [(9 (42.85%) *vs* 11 (17.46%), $P = 0.03$] and a decreased trend in mortality 30-day post discharge. IG patients also showed greater mean improvements in total (-27.03 ± 24.59 *vs* -5.85 ± 23.52, $P < 0.001$), physical (-13.8 ± 12.3 *vs* -2.71 ± 11.16, $P < 0.001$) and emotional (-4.76 ± 8.10 *vs* -1.42 ± 5.98) dimensions on the MLWHFQ compared to SOC-CG, however, change in emotional dimension did not reach statistical significance.

CONCLUSION

Hospitalist OMT-HF certification may lead to better 30-day outcomes in hospitalized HF patients including quality of life, mortality and readmission rates. Larger prospective studies are warranted to validate these findings.

Key Words: Heart failure education optimization; Guideline directed medical therapy; Heart failure; Quality of Life; Optimal medical therapy in heart failure

Core Tip: In patients with heart failure (HF) with reduced ejection fraction who are admitted to the hospital, seeing an optimal medical therapy in HF (OMT-HF) certified hospitalist can lead to improved guideline directed medical therapy scores, improved quality of life scores on the Milwaukee Living with Heart Failure Questionnaire 30 days post-discharge and lower 30-day readmission rates compared to those who did not see an OMT-HF certified hospitalist.

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INTRODUCTION

Heart failure (HF) is a public health issue that significantly impacts morbidity, mortality, and healthcare costs in the United States, with HF with reduced ejection fraction (HFrEF) representing about 50% of cases. HF is a leading cause of hospitalization in the United States[1]. A significant portion of HF patients are readmitted to the hospital, with 25 percent readmission within 30 days after discharge[2,3]. The mortality rate for patients admitted with HF is between 10% and 15%[4]. There are significant gaps in implementing evidence-based therapies, with less than 25% of HFrEF patients receiving all recommended guideline medications[5]. Hospitalization offers a key opportunity to optimize medications in HF patients; yet disparities remain. Data from Get With the Guidelines-Heart Failure registry show that patients from low-performing hospitals have a higher risk of mortality[6]. As hospitalists manage a large portion of HF admissions and face an increasing responsibility due to a projected shortage of cardiologists, their crucial role can be empowered through a Heart Failure Society of America (HFSA) initiative-optimal medical therapy in HF (OMT-HF) certification. OMT-HF offers online, evidence-based training for non-HF clinicians to optimize guideline-directed medical therapy. It emphasizes a comprehensive multidisciplinary approach and shared decision-making to improve medication compliance, quality of life (QoL), and reduce hospitalizations and mortality.

MATERIALS AND METHODS

This prospective, single-center study was implemented at Houston Methodist Baytown Hospital from November 2022 to May 2023. It is approximately a 320-bed multi-specialty hospital, sees approximately 800 HF admissions per year. The study was internally funded and approved by the Institutional Review Board (No. PRO00035436). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution's Human Research Committee.

A type-2 hybrid effectiveness-implementation study with a quasi-experimental design was used, including an interrupted time-series analysis to compare the impact of OMT-HF certification between intervention group (IG) and standard-of-care comparison group (SOC-CG). OMT-HF was offered to one of the two practicing hospitalist groups and their respective mid-level providers-(hospitalists IG), with the other group considered to be the SOC-CG (Figure 1). The IG group operates with cohorted staffing, assigning 2-3 physicians and 2-3 advanced practice providers (APPs) per quarter based on disease specialty. Typically, APPs manage patient admissions, while follow-ups are conducted by physicians. In contrast, the SOC-GC team staffs 2-3 medical doctors and 1-2 APPs at any time but covers patients hospital-wide without specialty cohorting. APPs admit patients, and physicians manage follow-ups. A total of 19 physicians and eight mid-level

providers in the IG completed the three-module course and rigorous post module assessment, which included: (1) Module 1: Available Medical Therapy for Heart Failure; (2) Module 2: Managing OMT to Target Doses; and (3) Module 3: Management Across the Care Continuum. Patients were naturally randomized to the two groups based on the hospital's predefined admission algorithm.

Patient enrollment

All patients were screened daily *via* electronic health record system [Epic (Epic Systems, Verona, WI)] and a database maintained in REDCap (Nashville, TN, United States). Adult patients with left ventricular ejection fraction ≤ 40% were included in the study. Patients who were in cardiogenic shock, unable to consent, at high risk per Acute Decompensated Heart Failure National Registry (systolic blood pressure < 115 mmHg, blood urea nitrogen ≥ 43 mg/dL, creatine ≥ 2.75 mg/dL) criteria[7], or being considered for advanced HF therapies were excluded. Informed consent was obtained according to institution guidelines.

Implementation

Implementation science shows that contextual factors affect the adoption of programs such as guideline-directed medical therapy (GDMT) optimization during HF hospitalization. We conducted an implementation needs assessment[8], identifying key stakeholders and summarizing personnel and process needs. After securing buy-in from leadership at Houston Methodist Baytown and collaboration with HFSA for a discounted certification course, hospitalists became OMT-HF certified, enhancing their credentials.

Statistical analysis

Data was collected at three key time points: (1) At baseline for what GDMT patients are on at home; (2) Within 48 hours of hospital admission; and (3) At discharge. We compared difference in GDMT scores between the IG and SOC-CG groups at discharge (and change from baseline to discharge) and evaluated outcomes of length of stay (LOS), 30-day mortality, readmission, and changes in QoL from baselines to 30-days post discharge.

The GDMT scores at discharge were categorized as sub-optimal (< 3), acceptable (3–4), and optimal (≥ 5), as previously described[9,10]. Minnesota Living with Heart Failure Questionnaire (MLWHFQ) responses were used for physical and emotional dimension scores on admission and at 30 days post-discharge[11]. Continuous variables were assessed for normality, with categorical variables reported as frequencies and proportions, and continuous variables reported as median and interquartile range (IQR). Differences between groups and physician certification status were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank-sum or unpaired *t*-test for continuous variables. Changes in MLWHFQ scores from admission to 30 days post-discharge were evaluated using a paired *t*-test. A decreased score from baseline to 30-days post discharge signified improvement in QoL. Analyses were conducted using Stata version 17.0 (StataCorp, College Station, TX), with a P value < 0.05 considered statistically significant.

RESULTS

Primary outcomes

A total of 84 patients with complete data and follow-up were included (63 IG, 21 SOC-CG). There was no statistical difference in the baseline demographics of the patients between the two groups. These include a median age of 62.5 years (IQR: 53.0–71.0 years), BMI of 30.44 kg/m^2 ± 8.120 kg/m^2, 55% male, 25% Black, and 24% Hispanic. Comorbidities included coronary artery disease (39%), atrial fibrillation (30%), diabetes (41%), hypertension (79%), hyperlipidemia (47%), sleep-disordered breathing (16%), chronic kidney disease (60%) and chronic obstructive airway disease (21%). A total of 16% had prior implantable cardioverter-defibrillator placement. Most patients were identified as New York Heart Association class 3. A total of 66% of the patients had Medicare/Medicaid, while 14% were uninsured.

Acute on chronic HFrEF was the most common diagnosis, with atrial fibrillation and non-ST-segment elevation myocardial infarction, being the most frequent conditions in that order.

The GDMT mean total score at admission was not significantly different between the two groups. IG patients were prescribed a higher average number of core medications at discharge than were SOC-CG patients (2.26 ± 1.2 *vs* 2 ± 0.95, P ≤ 0.01). At discharge, more IG patients (36, 57.1%) were prescribed mineralocorticoid receptor antagonist compared to SOC-CG patients (6, 28.57%) (P = 0.042). The differences in the prescription of other core GDMT medication groups were not significant. There was no statistically significant difference in the GDMT scores between the two groups (SOC-CG: 2.8 ± 1.7 *vs* IG: 3.4 ± 2.0, P = 0.19) (Table 1).

At admission, MLWHFQ scores were similar between SOC-CG and IG groups for total (53.09 ± 27.3 *vs* 55.80 ± 26.5, P = 0.69), physical (25 ± 11.22 *vs* 26.35 ± 12.11, P = 0.65), and emotional dimensions (12.76 ± 9.0 *vs* 12.71 ± 7.4, P = 0.98). At 30 days post-discharge, the IG group showed greater reductions in total (-27.03 ± 24.59 *vs* -5.85 ± 23.52, P < 0.001) (Figure 2) and physical scores (-13.8 ± 12.3 *vs* -2.71 ± 11.16, P < 0.001), while emotional score changes were not significant (-4.76 ± 8.10 *vs* -1.42 ± 5.98, P = 0.09). As lower MLWHFQ scores reflect better QoL, these results highlight significant improvements in the IG group.

Compared with SOC-CG patients, IG patients showed a greater improvement in the mean delta of their total (27.03 ± 24.59 *vs* -5.85 ± 23.52, P < 0.001), physical dimension (-13.8 ± 12.3 *vs* -2.71 ± 11.6, P < 0.001) and emotional dimension scores (-4.76 ± 8.10 *vs* -1.42 ± 5.98, P = 0.09) (Table 1).

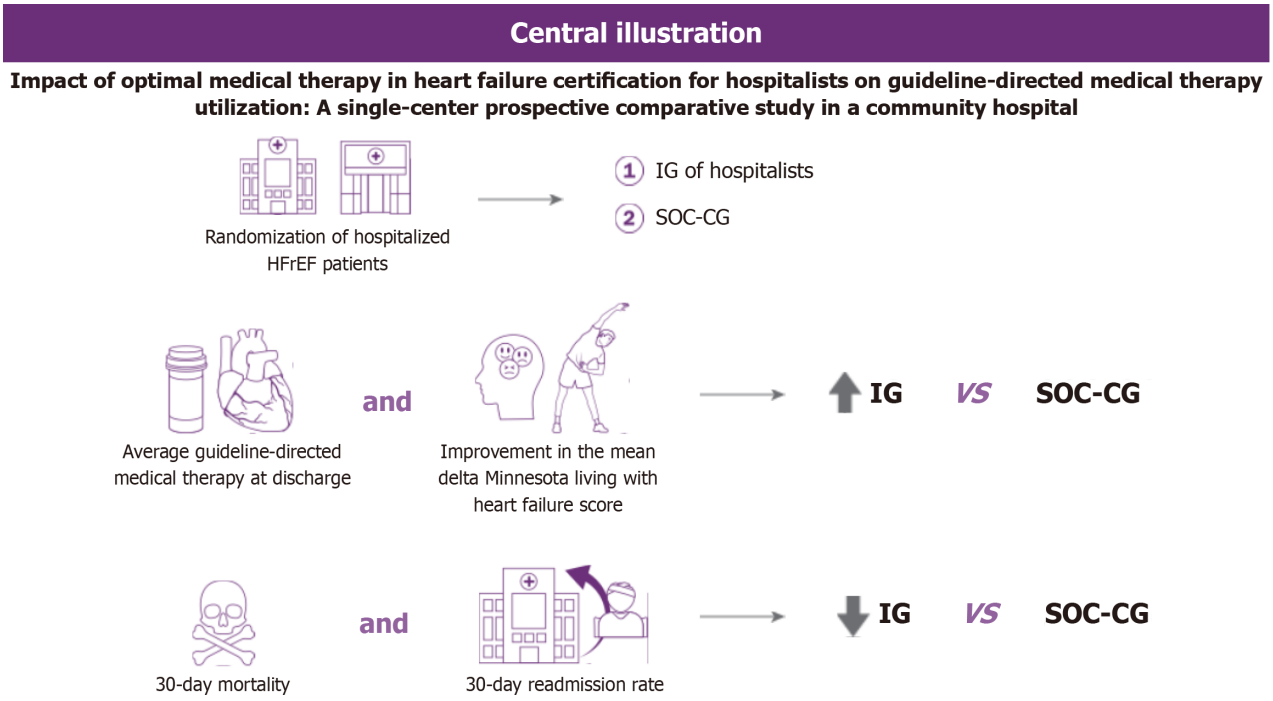

Figure 1 Central Illustration. IG: Intervention group; SOC-CG: Standard-of-care comparison group.

Provider assessment

Twelve physicians and seven mid-level providers completed the post OMT-HF course module feedback survey. Ten providers were early-career (0–5 years), three mid-career (6–15 years), and six senior-career (≥ 15 years). Provider demographics and receptiveness of this program initiative were evaluated per module assessment. This revealed 100% of the providers thought this initiative was helpful.

Secondary outcomes

In the total cohort, the LOS was longer for patients who saw the IG group compared to those who did not [median (IQR): 6.0 (3.0–8.0) *vs* 5.0 (3.0–6.0), $P \leq 0.01$] however, the 30-day readmission rate was lower for patients in the IG group [9 (42.85%) *vs* 11 (17.46%), $P = 0.03$].

We observed a trend toward higher 30-day all-cause mortality in SOC-CG patients compared to IG patients [1 (4.8%) *vs* 0 (0%), $P = 0.25$], though this difference was not statistically significant due to the low number of events.

DISCUSSION

Our study leverages hospitalists to optimize GDMT in HF patients during hospitalization which affords a critical opportunity to implement GDMT while the patient is being decongested and allows monitoring.

Cardiologists, given their focused expertise, often provide higher-quality HF care compared to internists, who may face challenges staying current with evolving management strategies across multiple chronic conditions[12,13]. Barriers to GDMT include clinician knowledge, patient and caregiver awareness, medication costs, and trials not fully representing real-world HF patients[14]. To address provider knowledge and workforce challenges, we equipped hospitalists with an OMT-HF certification focusing on GDMT fundamentals.

Participants responded positively to the program, with HFSA leadership, hospital administration and hospitalists collaborating to identify barriers and shaping implementation. Our study demonstrated improved trends in GDMT use, higher core medication prescriptions, and better QoL scores for patients treated by the IG. The IG also had a significantly lower 30-day readmission rate ($P = 0.035$), suggesting the OMT-HF course as a cost-effective method to bridge GDMT knowledge gaps, leading to improved outcomes. Prior studies have shown complex relationship between LOS and both readmission rate and mortality[15,16]. Extended LOS in IG patients may reflect the severity of illness or more mindful treatment, leading to improved decongestion[17,18], though this was difficult to evaluate[19]. A short LOS may lead to missed opportunities for up-titration of GDMT, patient education and post discharge planning, including early follow-up and care coordination[5,20]. Studies have shown that 57% of patients remain congested at 5 days of hospitalization, and premature discharge corelate with increased risk of cardiovascular death or rehospitalization within 180 days[19]. As mortality and readmission rates were lower in the IG group, it may reflect that a longer LOS with mindful treatment, in conjunction with optimal care across the continuum of care post discharge, can improve outcomes[20-23]. The mean delta in the emotional score on MLWHFQ did not reach statistical significance. This may be due to variance in resources available or adherence to the continuum of care. It may also be due to the emotional burden that HF and hospitalization for

Table 1 Baseline score, *n* (%)

	Did patient see an optimal medical therapy in heart failure certified provider		
	No (*n* = 21)	Yes (*n* = 63)	*P* value
GDMT score at discharge			
Number of core medications at discharge (mean ± SD)	2 ± 0.95	2.26 ± 1.2	< 0.001
Number of core medications at discharge			0.43
0	1 (4.76)	6 (9.52)	
1	5 (23.81)	10 (15.87)	
2	9 (42.86)	16 (25.39)	
3	5 (23.81)	23 (36.50)	
4	1 (4.76)	8 (12.7)	
On at least one core medication at discharge	20 (95.7)	57 (88.5)	0.67
GDMT total score, mean at admission (mean ± SD)	1.29 ± 1.8	1.32 ± 1.7	0.65
GDMT total score, mean at discharge (mean ± SD)	2.8 ± 1.7	3.44 ± 2.0	0.18
Optimal dosing of core medications at discharge			0.11
Sub-optimal (GDMT total score < 3)	13 (56.5)	19 (31.1)	
Acceptable (GDMT total score 3–4)	5 (21.7)	25 (41.0)	
Optimal (GDMT total score ≥ 5)	5 (21.7)	17 (27.9)	
Individual core medication used at discharge			
Beta-blocker	20 (95.2)	55 (87.3)	0.44
Mineralocorticoid receptor antagonist	6 (28.57)	36 (57.1)	0.04
Ace inhibitor, angiotensin receptor blocker or angiotensin receptor/neprilysin inhibitor	14 (66.6)	41(65.07)	1.00
Sodium-glucose cotransporter-2 inhibitor	2 (9.52)	11 (17.46)	0.50
Ivabradine	0 (0.0)	0 (0.0)	--
Vericiguat	0 (0.0)	0 (0.0)	--
Hydralazine/nitrates	4 (15.87)	10 (15.87)	0.74
Minnesota Living with Heart Failure Questionnaire			
Mean scores at admission			
Total score (mean ± SD)	53.09 ± 27.3	55.80 ± 26.5	0.69
Physical dimension score (items 2, 3, 4, 5, 6, 7, 12, 13) (mean ± SD)	25 ± 11.22	26.35 ± 12.11	0.65
Emotional dimension score (items 17, 18, 19, 20, 21) (mean ± SD)	12.76 ± 9.0	12.71 ± 7.4	0.98
Mean scores at 30 days after discharge			
Total score (mean ± SD)	47.23 ± 27.5	28.7 ± 25.93	< 0.001
Physical dimension score (items 2, 3, 4, 5, 6, 7, 12, 13) (mean ± SD)	22.28 ± 15.15	12.4 ± 12.3	< 0.01
Emotional dimension score (items 17, 18, 19, 20, 21) (mean ± SD)	11.33 ± 7.08	7.9 ± 7.8	0.08
Mean delta change from admission to 30 days after discharge			
Total score delta (mean ± SD)	-5.85 ± 23.52	-27.03 ± 24.59	< 0.001
Physical dimension score delta (items 2, 3, 4, 5, 6, 7, 12, 13) (mean ± SD)	-2.71 ± 11.16	-13.8 ± 12.3	< 0.001
Emotional dimension score delta (items 17, 18, 19, 20, 21) (mean ± SD)	-1.42 ± 5.98	-4.76 ± 8.10	0.09

GDMT: Guideline-directed medical therapy.

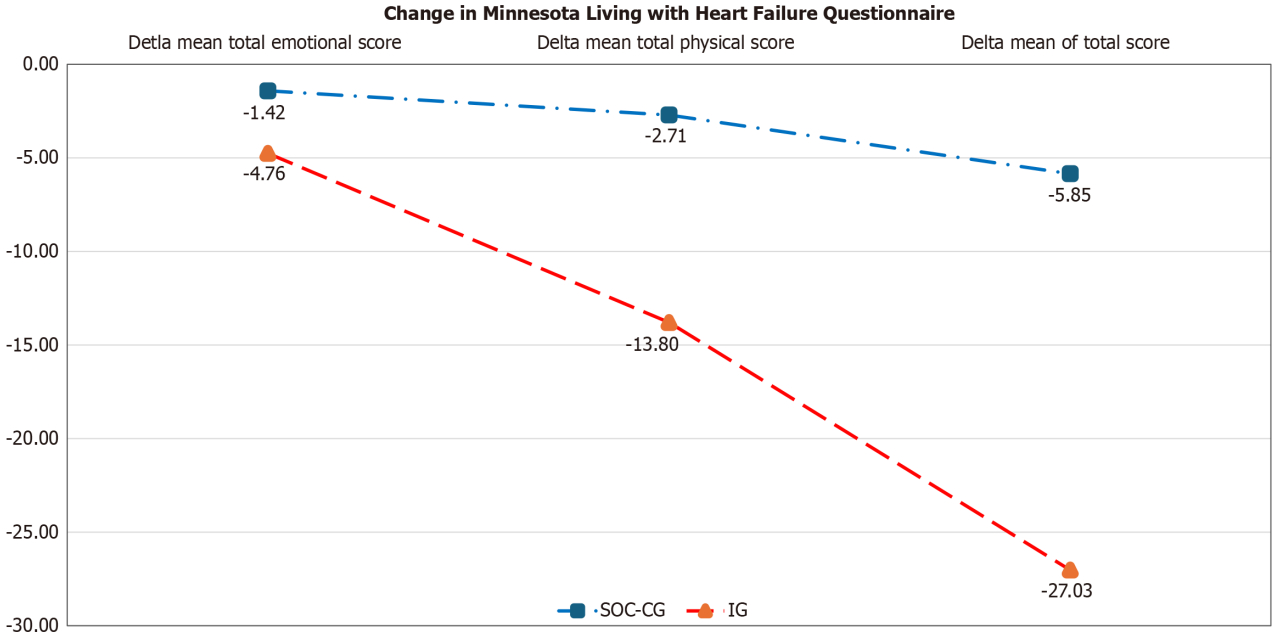

Figure 2 Delta change in Minnesota Living with Heart Failure Questionnaire. Changes in mean scores across emotional, physical, and total dimensions for the Standard of Care Group (SOC-CG) versus the Intervention Group (IG). The IG showed significantly greater declines in total score (−27.03 ± 24.59 *vs* −5.85 ± 23.52; $P < 0.001$) and physical dimension score (−13.80 ± 12.30 *vs* −2.71 ± 11.16; $P < 0.001$) compared to the SOC-CG. While the emotional dimension score also declined more in the IG (−4.76 ± 8.10 *vs* −1.42 ± 5.98), this difference was not statistically significant ($P = 0.09$). IG: Intervention group; SOC-CG: Standard-of-care comparison group.

HF can cause[24].

The MLHFQ is a widely used tool that assesses the physical and emotional dimensions of health-related QoL in HF patients. Higher scores indicate poorer QoL, and several studies have linked elevated scores to worse clinical outcomes [10]. Our results suggest that empowering hospitalists through focused programs such as OMT-HF can expedite patient care without the need to wait for a specialist; its application should be explored through other providers and settings. We did not exclude real-life conditions, such as consultation with cardiology, for external validity.

Limitations

The study faced several limitations: (1) A delayed start due to the severe acute respiratory syndrome coronavirus 2 pandemic; and (2) High staff turnover during the pandemic. However, the primary limitation of this study was the small sample size, which resulted in insufficient statistical power to draw conclusive data. Unfortunately, in the face of the pandemic our original projected sample size calculations could not hold; we remain committed to methodological rigor and hope these findings prompt further investigation.

Additionally, data contamination would have been difficult to prevent had natural randomization between groups not occurred. Second, data on sodium-glucose cotransporter 2 inhibitors were not available, as these therapies were incorporated into guideline-directed management after the study period began. Third, our sample size was limited, which may have contributed to some findings such as the impact of GDMT not reaching statistical significance. These results should therefore be interpreted with caution.

Audits and feedback were delivered through a single virtual seminar, which potentially may not have fully captured participant engagement or reception. While both hospitalist groups were well-established, we cannot exclude inherent differences in clinical practice that may have influenced outcomes.

Lastly, although the MLWHFQ is a widely validated tool, it remains a qualitative assessment. Improvements in perceived QoL may have been influenced by unmeasured factors such as additional provider time, education on care adherence, more complete diuresis, or increased use of medications—beyond actual clinical change.

Despite these limitations, we believe our initiative is replicable across other institutions and hope it inspires implementation and evaluation efforts in diverse settings and by a broad range of providers.

CONCLUSION

This study suggests that OMT-HF certification may contribute to improved GDMT adherence and QoL. Although the findings are encouraging, they are limited by the small sample size. Larger studies are needed to confirm these results, assess long-term outcomes, and explore strategies such as electronic health record alerts and structured feedback to optimize implementation. The results support the potential of hospitalist HF certification programs to help bridge gaps in care.

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FOOTNOTES

Author contributions: Ishaq F, Ebunlomo E, Bhimaraj A, and Fida N designed the study; Ishaq F and Fida N performed the research and wrote the manuscript; Nguyen DT and Graviss EA analyzed the data; Nguyen DT, Graviss EA, Ebunlomo E, and Bhimaraj A revised the manuscript; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Hydrogen alleviates right ventricular hypertrophy by inhibiting ferroptosis *via* restoration of the Nrf2/HO-1 signaling pathway

Jun-Cai Bai, Hong-Xiao Yang, Cheng-Chuang Zhan, Lu-Qi Zhao, Jia-Ren Liu, Wei Yang

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Abstract

BACKGROUND

Right ventricular hypertrophy (RVH) occurs because of volume or pressure overload within the right ventricular (RV) system. RVH is associated with complex pathological changes, including myocardial cell injury, apoptosis, myocardial fibrosis, neuroendocrine disturbances, and abnormal water and liquid metabolism. Ferroptosis, a novel type of iron-dependent cell death characterized by lipid peroxide accumulation, is an important mechanism of cardiomyocyte death. However, the role of ferroptosis in RVH has rarely been studied. We hypothesize that hydrogen (H_2), an experimental medical gas with superior distribution characteristics, inhibits ferroptosis.

AIM

To explore the protective effect of H_2 on RVH and the mechanism by which H_2 regulates ferroptosis.

METHODS

An *in vivo* RVH rat model was induced by monocrotaline (MCT) in 30 male Sprague-Dawley rats. An H9C2 cell model was treated with angiotensin II to simulate pressure overload in the RV system *in vitro*. H_2 was administered to rats

by inhalation (2% for 3 hours daily for 21 days) and added to the cell culture medium. The Nrf2 inhibitor ML385 (1 μM) was used to investigate anti-ferroptotic mechanisms.

RESULTS

In MCT-treated rats, H_2 inhalation decreased RVH; the RV wall thickness decreased from 3.5 ± 0.3 mm to 2.8 ± 0.2 mm ($P < 0.05$) and the RV ejection fraction increased from 45 ± 3% to 52 ± 4% ($P < 0.05$). In H9C2 cells, H_2 alleviated hypertrophy. H_2 inhibited ferroptosis by modulating the iron content, oxidative stress, and ferroptosis-related proteins, thereby restoring the Nrf2/HO-1 signaling pathway.

CONCLUSION

H_2 retards RVH by inhibiting ferroptosis *via* Nrf2/HO-1 restoration, suggesting a new treatment strategy.

Key Words: Hydrogen; Right ventricular hypertrophy; Nrf2/HO-1; Ferroptosis

Core Tip: This study explored the protective effects of hydrogen (H_2) on right ventricular hypertrophy (RVH) both *in vivo* and *in vitro*. The results revealed that H_2 inhibited ferroptosis, an iron-dependent cell death, by restoring the Nrf2/HO-1 pathway, offering new insights for treating RVH.

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INTRODUCTION

Right ventricular (RV) hypertrophy (RVH) is caused by volume or pressure overload and ultimately leads to RV dysfunction[1,2]. The right ventricle is more likely than the left ventricle to experience decreased cardiac function and even death under the same afterload[1]. Thus, improving RVH induced by pressure overload in the right cardiac system has great clinical significance. Although the clinical importance of RV function has been recognized, no effective therapies exist for RV dysfunction. Therefore, interventions should be developed to prevent RVH.

Several studies have suggested ferroptosis as a potential preventive target, particularly in diseases characterized by cardiomyocyte death[3]. Ferroptosis is a non-apoptotic form of cell death driven by the iron-dependent accumulation of lipid-based oxidative stress molecules[4]. Ferroptosis can induce cardiomyocyte injury, leading to cardiac remodeling. As ferroptosis contributes to heart damage, inhibiting ferroptosis can significantly improve the prognosis of myocardial damage[5-8]. System Xc- is the core antioxidant defense mechanism in ferroptosis[9]. The system Xc-/glutathione peroxidase 4 (GPX4) axis plays a central role in limiting lipid peroxidation. Disruption of system Xc-function can induce ferroptosis[10]. System Xc- is a heterodimer of member 11 of the light-chain solute carrier family 7 (SLC7A11) and member 2 of the heavy-chain solute carrier family 3 (SLC3A2), which are connected *via* disulfide bonds. SLC7A11 is an active subunit. Inhibition of SLC7A11, the light chain of system Xc-, attenuates glutathione (GSH) levels and GPX4 activity, leading to the accumulation of lethal lipid peroxides and the induction of ferroptosis[11,12]. Nrf2 has an anti-ferroptosis role and provides cardioprotection *via* an antioxidant effect[13]. Two critical targets associated with ferroptosis, system Xc and GPX4, are regulated by Nrf2. Nrf2 regulates the expression of various signaling proteins and enzymes by targeting downstream proteins such as SLC7A11, GPX4, and HO-1, thereby suppressing ferroptosis. Excess iron leads to ferroptosis through the regulation of iron metabolism[14]. TFR1 and FTH1 are important markers of ferroptosis[5,8]. TFR1 is considered a marker protein for ferroptosis. In addition, recent studies have confirmed that FTH1 is crucial for the initiation and promotion of cardiomyocyte ferroptosis[15]. Nrf2 induces SLC7A11 expression by directly binding to its promoter region, thereby regulating lipid peroxidation levels and morphological characteristics[16-18]. It is extremely important to elucidate the signaling pathways involved in cardiac hypertrophy and identify appropriate treatments to prevent or reverse this condition.

Hydrogen (H_2) is a safe, economical, and convenient antioxidant. Ohsawa *et al*[19] first reported that H_2 reduces the levels of cytotoxic oxygen free radicals. Our previous studies demonstrated that H_2 attenuates doxorubicin-induced inflammation and cell apoptosis and reduces pyroptosis and fibrosis in diabetic cardiomyopathy. H_2 also attenuates the production of reactive oxygen species (ROS) during thyroid hormone-induced cardiac hypertrophy[20-22]. However, whether H_2 inhibits ferroptosis and attenuates RV cardiomyocyte damage caused by pressure overload in the right cardiac system remains unclear. In this study, we investigated the potential preventive effects of H_2 against RVH in a monocrotaline (MCT) rat model simulating pressure overload of the right cardiac system and revealed that H_2 inhibits ferroptosis and restores the Nrf2/HO-1 signaling pathway.

MATERIALS AND METHODS

Animals

Considering the potential differences in cardiac function between male and female rats, and their different sensitivities to the model, only male rats were selected for this study. All procedures were performed in compliance with the guidelines of ARRIVE. The experimental protocol was performed in accordance with the Guide for the Care and Use of Laboratory Animals. This study was approved by the Animal Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University. Forty male Sprague-Dawley rats were housed in a controlled environment at the Animal Center of Harbin Medical University (Harbin, China) at a temperature of 22 ± 2 °C and a relative humidity of 55 ± 15% on a 12-hour light/dark cycle and were given ad libitum access to food and tap water.

In this study, a pressure overload model of the right cardiac system was established using a one-time subcutaneous injection of 60 mg/kg MCT. Subcutaneous injection of MCT causes minimal damage to animals during administration, is relatively simple to perform, has a high success rate, and is highly practical. Previous studies have reported 60 mg/kg as the most appropriate dose to induce pressure overload in the right heart system (MCT rat model). A dose that is too great leads to a significant increase in mortality; a dose that is too small does not effectively induce right heart failure and results in an experimental period that is too long[23,24]. The MCT rat model is a well-accepted model for studying the pathophysiology of pulmonary vascular remodeling and RV injury caused by pressure overload[25]. Forty male Sprague-Dawley rats (6-7 weeks old) were purchased from Liaoning Changsheng Biotechnology Co., Ltd. (Liaoning, China). Forty rats received a single subcutaneous injection of 60 mg/kg[26] of MCT (Absin Bioscience Inc, Shanghai, China) (n = 20) or saline (n = 20). The rats were divided into four groups: Control (n = 10), H_2 (n = 10), MCT (n = 10), and MCT + H_2 (n = 10) groups. The rats were weighed daily at 10:00 daily. Rats in the MCT and MCT + H_2 groups received MCT injections, whereas rats in the control and H_2 groups were injected with the same volume of saline. H_2 (2%) was administered to rats in the H_2 and MCT + H_2 groups by inhalation for 3 hours twice daily for 28 days after the injection. H_2 gas (2%) was deemed safe and effective and was produced and administered as reported previously[19-22,27]. Briefly, H_2 gas was produced using an H_2 generator (HA-300, SCDEALL, China). The H_2 concentration was monitored in real time and maintained at 2% using an H_2 detector (SDH-B101, Honeywell, United States). Rats and H_2 treatments were prepared as previously described[22]. In brief, high-purity H_2 was prepared using an H_2 generator (output pressure: 0.4 MPa, flow rate: 80 mL/min) and injected into a rat ventilator (44 cm × 74 cm × 23 cm). The concentration of H_2 was monitored using an H_2 sensor and maintained at 2% ± 0.02%. The other bellows are filled with air. A fan was installed in the ventilation compartment to facilitate the flow of air or H_2. The ventilation compartment contained food, water, and bedding so that the rats could live there for a long time. The rats were kept in the bellows for 6 hours per day for 28 days after MCT injection.

Echocardiography

After 28 days, all rats were treated with 1% pentobarbital sodium (40 mg/kg). Transthoracic echocardiography was performed after the rats were subjected to abdominal anesthesia and placed in a supine position. Transthoracic echocardiography was used to assess RV structure and function. The probe was placed on the left side of the chest, and indices were measured using an ultrasound system (Philips CX50, WA, United States). The measured indices were the left ventricular ejection fraction (LVEF), RV end-diastolic dimension (RVEDD), RV end-systolic volume (RV-ESV), RV end-diastolic volume (RV-EDV), RV ejection fraction (RVEF) and RV free-wall (RVFW) thickness[26]. The RVEDD assesses RV diastolic function. The RVEF is the ratio of the RV end-diastolic and end-systolic volume differences to the end-diastolic volume, which is a good quantitative measure of RV systolic function. RVEF can reflect RV systolic function[28]. All measurements were performed by three experienced technicians who were unaware of the identities of the groups for five consecutive cardiac cycles then averaged[27].

Serum parameters

The rats were administered an intraperitoneal injection of 0.1% 40 mg/kg sodium pentobarbital and fixed in the supine position. The abdominal cavity was opened layer-by-layer in the middle of the abdomen by incision, and the abdominal organs were moved to the right side with sterile cotton swabs to expose the abdominal aorta, which was separated with tweezers; blood samples were then collected through the abdominal aorta. Blood samples were centrifuged at 3000 × g and 4 °C for 15 minutes. The serum was collected and stored at −80 °C for further analysis. The brain natriuretic peptide (BNP) level is also a biomarker of cardiac function. Serum BNP, GSH, and GSH-Px levels were assessed using commercial kits (Nanjing Jiancheng Bioengineering Institute, China). The total superoxide dismutase (T-SOD) was assessed using a commercial kit (Wanlei, China) according to the manufacturer's instructions.

Detection of malonaldehyde and Fe^{2+} in RV tissue

Malonaldehyde (MDA) is an indicator of lipid peroxidation. The MDA content in the RV tissue was detected using a commercial kit according to the manufacturer's instructions (Nanjing Jiancheng Bioengineering Institute, China). Frozen RV samples were thawed on ice. The ratio of heart tissue weight (g) to normal saline volume (mL) ratio was 1:9. After mechanical homogenization on ice, the samples were centrifuged at 3000 × g and 4 °C for 15 minutes. Similarly, Fe^{2+} in the RV tissue was assessed using a commercial kit according to the manufacturer's instructions (Nanjing Jiancheng Bioengineering Institute, China).

Histology

Heart tissue was placed in a 4% paraformaldehyde fixative solution for light microscopy, and conventional paraffin embedding was used for morphological analysis. Tissue samples collected from the same area of the heart rapidly after sacrifice were cut into 4-μm-thick paraffin sections for histological analysis[29]. Paraffin sections were stained with hematoxylin-eosin (HE, Beyotime, China) according to the manufacturer's instructions. Antinatriuretic peptide A (ANP) and BNP levels are the classic diagnostic and prognostic indicators of cardiac hypertrophy[3]. Immunohistochemistry (IHC) was performed using ANP (ab225844, 1:2000, Abcam), rabbit anti-BNP (ab243440, 1:4000, Abcam), anti-Nrf2 (WL02135, 1:200, Wanlei), and anti-HO-1 (WL02400, 1:100, Wanlei) antibodies. To quantify HE staining, we randomly selected multiple fields under a light microscope at 100 × or 200 × magnification. The cardiomyocyte size was quantified by measuring the diameter of the cardiomyocytes in each field, with at least 10 cells measured per field, and averaged for each section. Interstitial fibrosis was assessed by calculating the percentage of fibrotic area relative to the total tissue area in the selected fields.

For IHC staining, staining intensity was scored from 0 to 3 by two observers who were blinded to the groups. At least five fields per sample were evaluated and the average intensity score was calculated. The percentage of positively stained cells was determined by counting the cells in each field, dividing by the total cell number, and averaging across fields. To compare antigen expression among the samples, the immunoreactivity score was obtained by multiplying the average intensity score by the average percentage of positively stained cells. For Nrf2 and HO-1, subcellular localization was noted as cytoplasmic, nuclear, or both by observation at higher magnification, and the proportion of cells with each pattern was calculated for further analysis of protein function.

HE staining was employed to visualize general tissue morphology, including cardiomyocyte size and interstitial fibrosis, whereas IHC staining was employed to precisely detect and quantify the expression levels and subcellular localization of specific proteins (ANP, BNP, Nrf2, HO-1) relevant to cardiac hypertrophy and its regulatory mechanisms.

Wheat germ agglutinin staining

Histological sections of heart tissue were stained with wheat germ agglutinin (WGA) according to the manufacturer's instructions (4 μg/mL, Thermo Fisher Scientific Inc., United States) for morphometric measurement[29]. The tissues were observed using a fluorescence microscope, and images were collected in a dark room. Semi-quantitative analysis of three randomly selected fields per section was performed using ImageJ software.

WGA staining can clearly show the contours of cardiomyocytes, which is helpful for accurately measuring the area of cardiomyocytes, thus providing intuitive and reliable data for evaluating the degree of myocardial hypertrophy.

Prussian blue staining

Paraffin sections of heart tissue were dewaxed for 1 hour and hydrated with tap and distilled water three times. Equal proportions of hydrochloric acid and potassium ferrocyanide were mixed to generate the Prussian blue staining solution. The tissues in the working solution were incubated for 3 minutes, then the samples were examined under an OLYMPUS (CX23) microscope, with images captured at 200 × magnification. The region of interest (total tissue area) was outlined using ImageJ software. The color threshold was adjusted to select areas with blue-stained iron deposits. The ratio of the blue-stained area to total area was calculated for each image. Multiple (5-10) random fields were analyzed per sample, and the average percentage value was computed to represent iron accumulation in the heart tissue.

Prussian blue staining enables the specific visualization and quantification of iron deposits in the heart tissue, which is crucial for assessing the level of iron accumulation related to ferroptosis and its potential impact on cardiac function.

Electron microscopy

Morphological changes in the mitochondria at the same position as the free wall of the right ventricle were observed by electron microscopy. The tissue was fixed at 4 °C with 2% glutaraldehyde in sodium bicarbonate buffer for 1 hour on ice with 1% osmium tetroxide. The sections were stained with uranyl acetate and observed under an H7650 transmission electron microscope (Hitachi, Japan).

Establishment of the cell model

H9C2 cells were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The cells were cultured in DMEM containing 10% fetal bovine serum and 1% penicillin/streptomycin in a humidified 5% CO_2 atmosphere at 37 °C. An angiotensin II (Ang II)-induced H9C2 cell model was constructed *in vitro* to study myocardial hypertrophy induced by pressure overload in the right cardiac system. The concentration gradients of Ang II were 0.01 μmol/L, 0.1 μmol/L, 1 μmol/L, 10 μmol/L, and 100 μmol/L. The degree of cell hypertrophy was most obvious at 1 mol/L after 24 h, which is consistent with previous research[30]. H9C2 cells were divided into different groups: Control, H_2, Ang II (1 μmol/L), and Ang II+H_2 groups. In addition, the Nrf2 inhibitor ML385 (1 μmol/L, HY-100523, MCE) was used in this study[24,31]. H9C2 cells were pretreated with ML385 for 2 hours then treated with Ang II plus H_2 (Ang II+ML385+H_2) for 24 hours. H_2 treatment was performed as previously described[21]. In brief, H_2 was dissolved in DMEM (H_2 medium) at 0.4 MPa, O_2 was dissolved in DMEM (O_2 medium) at 42.5 mg/L saturation, and CO_2 was dissolved in DMEM (CO_2 medium) at atmospheric pressure. The three media (H_2, O_2, and CO_2) were mixed proportionally with fetal bovine serum in a 75:20:5 vol.% ratio. The culture flask was then filled with a mixture of 75% H_2, 20% O_2, and 5% CO_2, and the cells were cultured in a closed flask at constant pressure.

Cell counting kit-8 assay and lactate dehydrogenase release

Cell viability was measured using the cell counting kit-8 (CCK-8, Beyotime, China) following the manufacturer's instructions. Briefly, 5 × 10^3 cells/well from the different groups were cultured in 96-well plates. After treatment, 10 μL CCK-8 solution was added to each well at 37 °C for 2 hours before analysis. In addition, a lactate dehydrogenase (LDH, Nanjing Jiancheng Bioengineering Institute, China) release test was used to assess cell damage according to the manufacturer's instructions.

Detection of MDA, antioxidative capacity, and Fe^{2+}

H9C2 cardiomyocytes were collected from each group, homogenized, and centrifuged for 10 minutes, and the supernatant was collected. The MDA content, T-SOD activity, GSH content, and GSH-Px activity were determined. The MDA content of H9C2 cells in each group was assessed using a commercial kit (Nanjing Jiancheng Bioengineering Institute, China). Similarly, the activities of antioxidant enzymes such as T-SOD, GSH, and GSH-Px were determined in H9C2 cells from each group (Nanjing Jiancheng Bioengineering Institute, China) according to the manufacturer's instructions. In addition, Fe^{2+} levels were detected using a commercial kit (Elabscience, China) according to the manufacturer's instructions.

Phalloidin staining

The surface area of H9C2 cells was measured using a phalloidin staining kit (Beyotime, China) according to the manufacturer's instructions. Briefly, H9C2 cells were fixed, permeabilized, and stained with phalloidin and 4,6-diamino-2-phenyl indole (DAPI, Beyotime, China) in a dark room. At least three images were captured using a fluorescence microscope. Subsequently, a sample size of no less than 30 cells was measured and analyzed using ImageJ software.

Phalloidin staining was used to specifically label actin filaments in H9C2 cells, enabling accurate measurement of the cell surface area, which is a key parameter for evaluating cell hypertrophy.

Detection of cellular ROS production and mitochondrial membrane potential

Cellular ROS production and mitochondrial membrane potential (MMP) in H9C2 cells were detected using an ROS assay kit (Solarbio, China) and a JC-1 assay kit (Beyotime, China) in accordance with the experimental protocol. In brief, H9C2 cells of different groups cultured in six-well plates were washed with phosphate-buffered saline (PBS) and incubated with DCFH-DA in a darkroom at 37 °C for 30 minutes. The DCFH-DA fluorescent probe concentration was 1:2000 according to the manufacturer's instructions. Subsequently, the cells were washed three times with PBS, and fluorescence intensity was detected using a fluorescence microscope. In addition, H9C2 cells were washed three times then stained with JC-1 in a darkroom at 37 °C for 20 minutes. Red fluorescence of JC-1 aggregates and green fluorescence of JC-1 monomers were captured under a fluorescence microscope and analyzed using ImageJ software.

Quantitative PCR

Quantitative PCR (qPCR) was performed according to the manufacturer's instructions. For each group, total RNA was extracted from H9C2 cells in a six-well plate using TRIzol reagent (Sigma-Aldrich, T9424). cDNA was synthesized using a ReverTra Ace qPCR RT kit (TOYOBO, No. FSQ-101, Japan) according to the manufacturer's instructions. The expression of *ANP* mRNA and *BNP* mRNA was normalized to β-actin. All samples were analyzed in triplicate. The primer sequences were as follows: ANP, forward, 5′-TCCGATAGATCTGCCCTCTT-3′; ANP, reverse, 5′-CTCCAATCCTGTCAATCCTACC-3′; BNP, forward, 5′-ATTCTGCTCCTGCTTTTCCT-3′; BNP, reverse, 5′-CCTTGGTCCTTTGAGAGCTGT-3′; β-actin, forward, 5′-GAGGTATCCTGACCCTGAAGTA-3′; β-actin, reverse, 5′-CACACGCAGCTCATTGTAGA-3.′

Western blotting

Protein from RV tissues and H9C2 cells was stored at −80 °C for western blotting[27]. Protein concentration was determined using a bicinchoninic acid assay kit (Beyotime, China). Each experiment was performed at least three times. Anti-ANP antibody (ab225844, 1:2000, Abcam), anti-BNP antibody (ab243440, 1:4000, Abcam), anti-Nrf2 antibody (A0674, 1:1000, ABclonal), anti-TFR1 antibody (sc-65882, 1:1000, Santa Cruz), anti-SLC7A11 antibody (A15604, 1:1000, ABclonal), anti-HO-1 antibody (A1346, 1:1000, ABclonal), anti-FTH1 antibody (WL05360, 1:500, Wanlei), anti-GPX4 antibody (A13309, 1:1000, ABclonal) and horseradish peroxidase-conjugated secondary antibodies (ZB-2301, ZB-2305, 1:1000, ZSGB) were used. Anti-β-actin (AC026, 1:50000, ABclonal) antibody was used as the internal control.

Statistics analysis

The normality of the data was first examined using the Shapiro-Wilk normality test with SPSS software (version 27.0; IBM, United States). If the data did not conform to a normal distribution, non-parametric statistical tests were used. To compare multiple groups, we used the Kruskal-Wallis test, which is a non-parametric alternative to one-way analysis of variance. Subsequently, Dunn's test was applied for post-hoc analysis to determine which specific groups differed from each other. After confirming that all data conformed to a normal distribution, further data analyses were performed.

Data are presented as the mean ± SD. One-way analysis of variance with GraphPad Prism (GraphPad Software, CA, United States) was used for groups, and Tukey's post-hoc test was used for statistical analysis. All experiments were repeated at least three times. The level of statistical significance was set to $P < 0.05$.

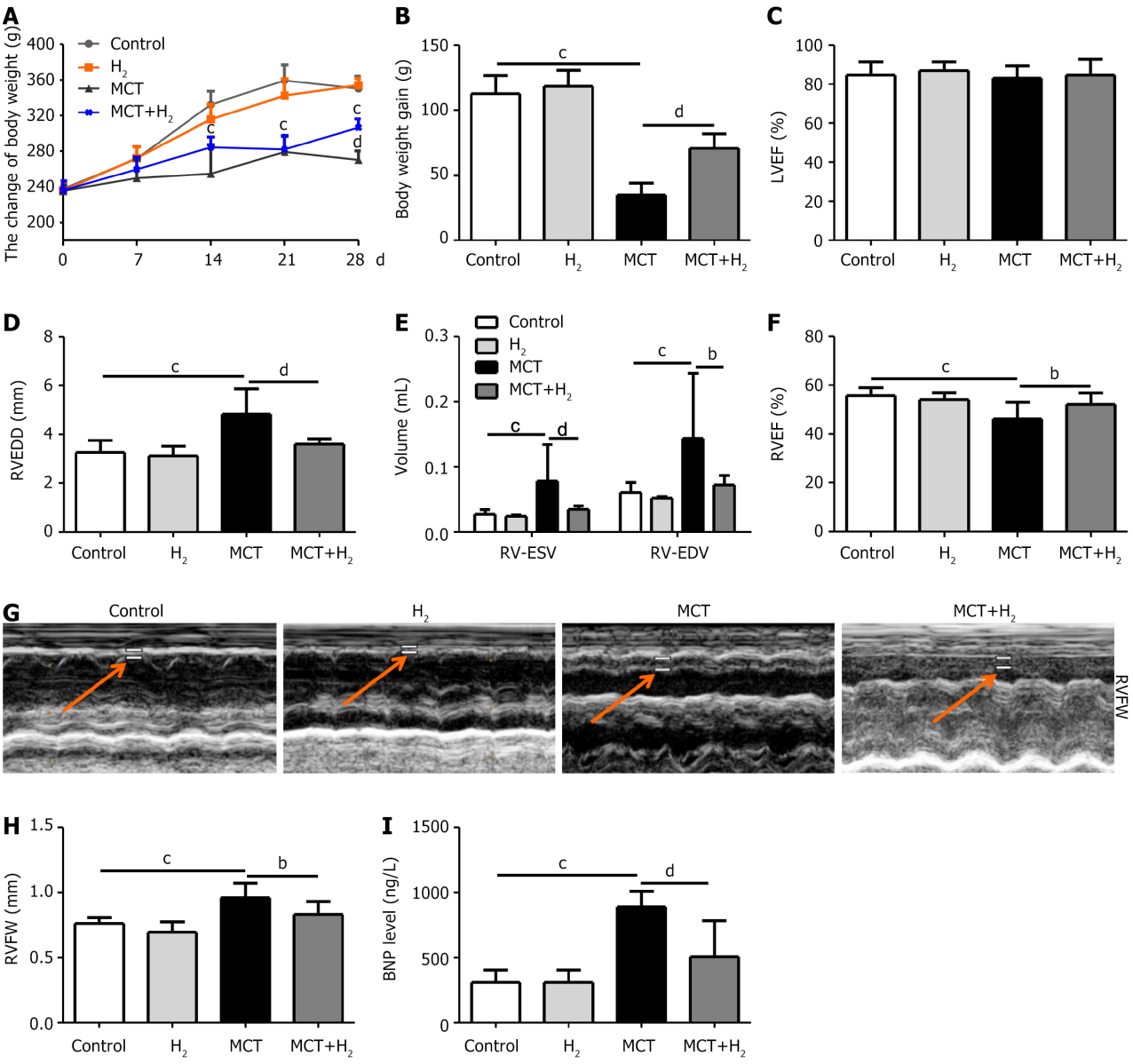

Figure 1 H_2 inhalation improved body weight and cardiac function in monocrotaline-treated rats. A: Body weight (BW) changes in each group; *n* = 10; B: BW gain of each group 28 days after monocrotaline (MCT) injection; *n* = 10; C: Right ventricular ejection fraction (RVEF) of all groups; *n* = 10; D: Right ventricular (RV) end-diastolic dimension of all groups; *n* = 10; E: RV end-systolic volume and RV end-diastolic volume of all groups; *n* = 10; F: RVEF of all groups; *n* = 10; G: Representative echocardiographic images showing the RV free-wall (RVFW) thickness (at orange arrow, between white lines); *n* = 10; H: RVFW of each group; *n* = 10; I: Serum brain natriuretic peptide levels, as assessed by ELISA; *n* = 10. Data are expressed as the mean ± SD. $^{c}P < 0.01$ MCT group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: MCT+H_2 group *vs* MCT group. MCT: Monocrotaline; LVEF: Left ventricular ejection fraction; RVEDD: RV end-diastolic dimension; RV-ESV: RV end-systolic volume; RV-EDV: RV end-diastolic volume; RVEF: RV ejection fraction; RVFW: RV free-wall; H_2: Hydrogen.

RESULTS

H_2 inhalation alleviated abnormal morphological hypertrophy and improved cardiac function in MCT-treated rats

The weight of the rats was measured weekly, their general condition was observed, and no spontaneous death occurred within 28 days after MCT administration. The condition of the MCT rats was worse than that of the control group (Figure 1A), and body weight (BW) gain (Figure 1B) was significantly decreased. Conversely, the condition of the MCT rats in the H_2 inhalation group was better than that of the MCT rats, with significantly increased BW and BW gains. The LVEF of the MCT group was lower than that of the other groups, but the difference was not significant, suggesting that the LVEF of MCT rats was not significantly decreased (Figure 1C), which was consistent with the model of RVH. We also evaluated the RV function in rats. RVEDD was significantly increased in the MCT group compared to that in the control group and was notably reduced by H_2 treatment (Figure 1D). RV-ESV and RV-EDV were notably increased in the MCT group compared to those in the control group, but were decreased by H_2 treatment (Figure 1E). RVEF was significantly decreased in the MCT group compared to that in the control group and was markedly increased by H_2 treatment (Figure 1F). H_2 inhalation alleviated abnormal morphological hypertrophy in MCT-treated rats. We assessed the RV structure in rats. RVFW thickness was increased in the MCT group compared to that in the control group, and this change

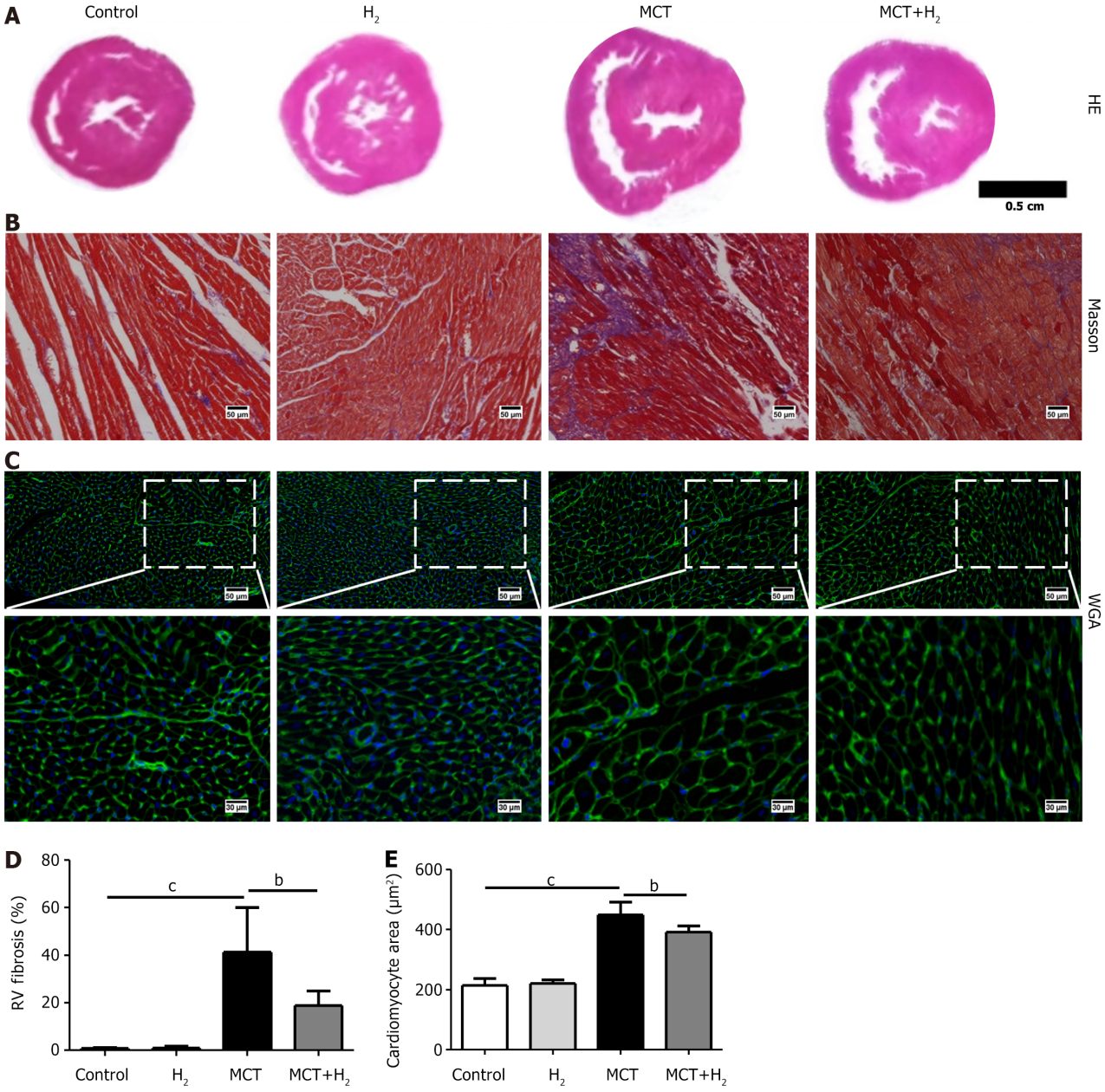

Figure 2 Hydrogen inhalation alleviated cardiomyocyte area and fibrosis in monocrotaline**-treated rats.** A: Representative images of hematoxylin-eosin staining of heart tissue; *n* = 4; B: Representative images of Masson staining of heart tissue; *n* = 4; C: Representative images of wheat germ agglutinin staining of right ventricular tissue. Magnification is 20 ×. Scale bar = 50 μm; D: Analysis of the Masson staining of heart tissue; *n* = 4; E: Analysis of the cardiomyocyte area; *n* = 4. Data are expressed as the mean ± SD. $^{b}P < 0.05$ MCT+H_2 group *vs* MCT group; $^{c}P < 0.01$: MCT group *vs* control group. MCT: Monocrotaline; H_2: Hydrogen; WGA: Wheat germ agglutinin.

was significantly alleviated by H_2 treatment (Figure 1G and H).

Serum BNP levels in the MCT group were notably increased compared to those in the control group, but were significantly decreased after H_2 treatment (Figure 1I). Thus, 28 days of H_2 treatment alleviated abnormal morphological hypertrophy and improved cardiac function in MCT-treated rats.

H_2 inhalation alleviated cardiomyocyte area and fibrosis in MCT-treated rats

Based on the results of HE staining (Figure 2A), Masson's trichrome staining (Figure 2B), and WGA staining (Figure 2C) of heart tissues, RV hypertrophy and fibrosis were significantly reduced in the MCT+H_2 group compared with the MCT group. Cardiomyocyte fibrosis (Figure 2D) and area (Figure 2E) were increased in the MCT group, but these changes were reversed by H_2 treatment.

H_2 inhalation further reduced the expression of hypertrophy-related indicators in MCT-treated rats

IHC staining showed that ANP and BNP levels in the MCT group were higher than those in the control group, and H_2 treatment prevented this increase (Figure 3A-D). Similarly, the western blotting results showed that the expression of ANP and BNP was increased in the MCT group compared to that in the control group but decreased after H_2 treatment

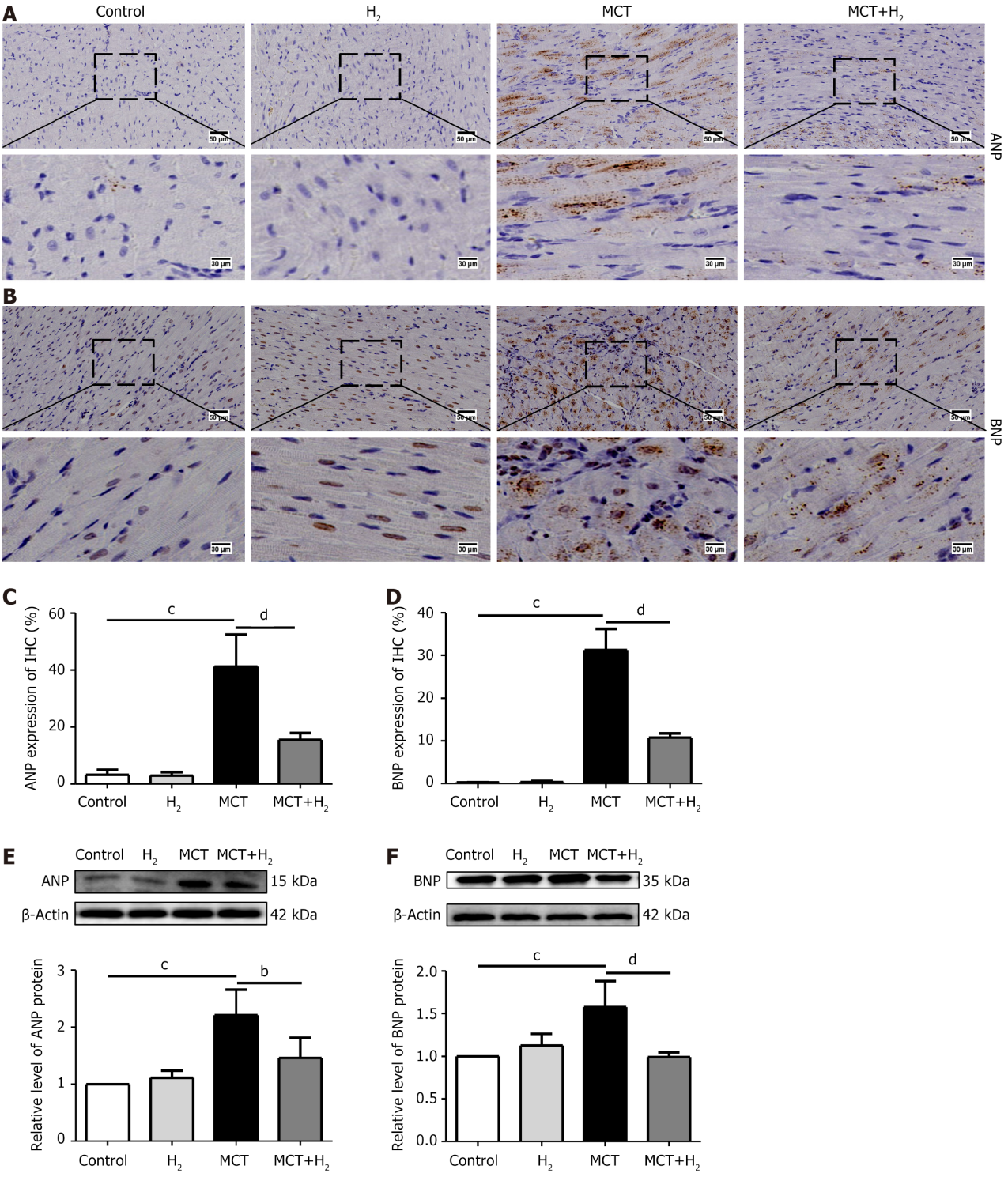

Figure 3 Hydrogen inhalation further reduced the expression of hypertrophy-related indicators in monocrotaline-treated rats. A: Representative images of immunohistochemistry (IHC) staining of Antinatriuretic peptide A (ANP). ANP proteins were stained brown. Magnification is 20 ×. Scale bar = 50 μm; B: Representative images of IHC staining of brain natriuretic peptide (BNP). BNP proteins were stained brown. Magnification is 20 ×. Scale bar = 50 μm; C: Quantitative analysis of IHC staining of ANP; n = 4; D: Quantitative analysis of IHC staining of BNP; n = 4; E and F: Representative western blotting bands of ANP and BNP proteins and their relative levels; n = 3. Data are expressed as the mean ± SD. $^{c}P < 0.01$: MCT group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: MCT+H_2 group *vs* MCT group. ANP: Antinatriuretic peptide A; BNP: Brain natriuretic peptide; MCT: Monocrotaline; H_2: Hydrogen.

(Figure 3E and F). These data confirmed that H_2 has a protective effect against hypertrophy in MCT-treated rats.

H_2 inhalation alleviated iron accumulation in MCT-treated rats

We assessed iron levels in the heart tissue, as iron is an important trigger of ferroptosis. Prussian blue staining showed that the number of iron-stained cells increased in MCT-treated rats. The iron content of RVH myocardial tissue was higher than that in normal rats. H_2 reduced the iron content and proportion of Prussian blue iron-stained cells in the myocardium of MCT-treated rats (Figure 4A and B). The iron content of the RV tissue in the MCT group was notably

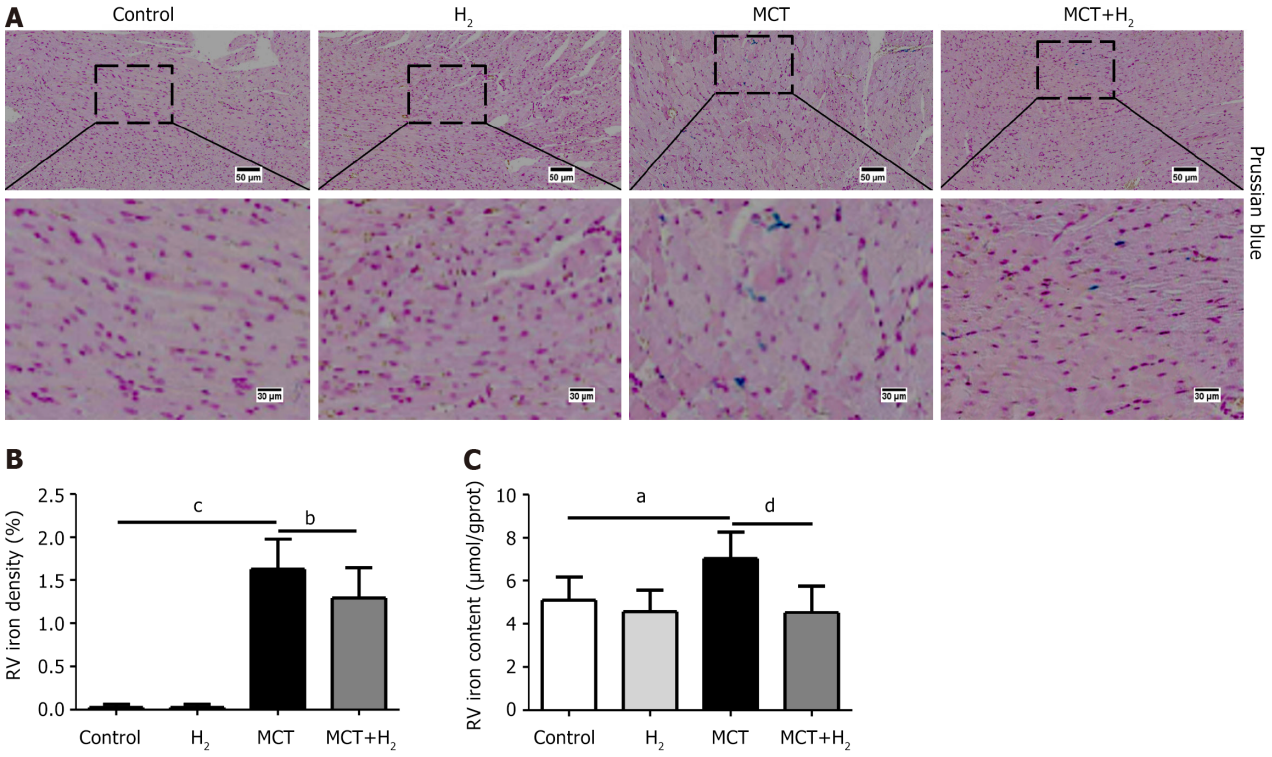

Figure 4 Hydrogen inhalation alleviated iron a[f]umulation in monocrotaline-treated rats. A: Representative images of Prussian blue staining. Magnification is 20 ×. Scale bar = 50 μm; B: Quantification of Prussian blue iron staining; *n* = 4; C: Right ventricular Fe content; *n* = 6. Data are expressed as the mean ± SD. [a]*P* < 0.05 and [c]*P* < 0.01: MCT group *vs* control group; [b]*P* < 0.05 and [d]*P* < 0.01: MCT+ H_2 group *vs* MCT group. MCT: Monocrotaline; H_2: Hydrogen.

elevated compared to that in the control group, but was reduced significantly after H_2 treatment (Figure 4C).

H_2 inhalation suppressed oxidative stress in MCT-treated rats

Next, we measured the mitochondrial morphology of the RV in each group using transmission electron microscopy (TEM) images. We observed that mitochondrial membrane density increased and mitochondrial cristae decreased or disappeared in MCT-treated rats compared to those in the control group. However, H_2 inhalation significantly inhibited this effect (Figure 5A). To investigate the effect of H_2 on MCT-induced oxidative stress, we assessed the levels of the oxidative stress-related indicators MDA, T-SOD, GSH, and GSH-Px. MDA is the primary marker of damage due to oxidative stress[32]. According to our results, MDA levels were significantly higher in the MCT group than in the control group and significantly lower in the MCT+H_2 group than in the MCT group (Figure 5B). In addition, compared with the control group, serum T-SOD, GSH, and GSH-Px activities were downregulated in the MCT group and upregulated after H_2 treatment (Figure 5C-E). In this regard, our results revealed that severe injury due to oxidative stress is an important mechanism underlying the occurrence and development of RVH, and that H_2 inhalation suppressed oxidative stress in MCT-treated rats.

H_2 inhalation alleviated ferroptosis by restoring the Nrf2/HO-1 pathway in MCT-treated rats

To elucidate the mechanisms involved in the prevention of RVH by H_2 inhalation, we examined the effects of H_2 on the core regulators of ferroptosis in the presence of RVH. IHC staining revealed the expression of Nrf2 (Figure 6A), and HO-1 (Figure 6B) in the MCT group was downregulated compared to that in the control group, and H_2 treatment prevented this downregulation. Figure 6C and D also confirm this result. The expression levels of the ferroptosis-associated proteins Nrf2, HO-1, SLC7A11, FTH1, and GPX4 decreased after MCT administration, whereas the expression level of TFR1 increased. The levels of Nrf2, HO-1, SLC7A11, FTH1, and GPX4 were upregulated, whereas those of TFR1 were downregulated after H_2 inhalation (Figure 6E and F). Ferroptosis occurred in the MCT rat model with pressure overload in the right cardiac system. H_2 inhalation reduced right cardiac hypertrophy in MCT rats and improved cardiac function.

H_2 alleviated Fe^{2+} content and oxidative stress in Ang II-treated H9C2 cells

Hypertrophy was induced in H9C2 cells by administering different concentrations of Ang II (0, 0.01, 0.1, 1, 10, and 100 μmol/L) after 24 hours of serum starvation. Ang II-induced hypertrophy was obvious at a concentration of 1 μmol/L. A CCK-8 assay was performed to confirm the activity of H9C2 cells, and the degree of H9C2 cell damage was determined using an LDH release assay. The Fe^{2+} content in the Ang II group was higher than that in the control group, but was reduced after H_2 treatment (Figure 7A-D). We then detected the oxidation-related indicators MDA, T-SOD, GSH, and GSH-Px, and the Fe^{2+} content in H9C2 cells. Our results suggest that MDA levels were higher in the Ang II group than in the control group and were lower after H_2 treatment (Figure 7E). In addition, compared to the control group, T-SOD, GSH, and GSH-Px activities were downregulated in the Ang II group and upregulated after H_2 treatment (Figure 7F-H).

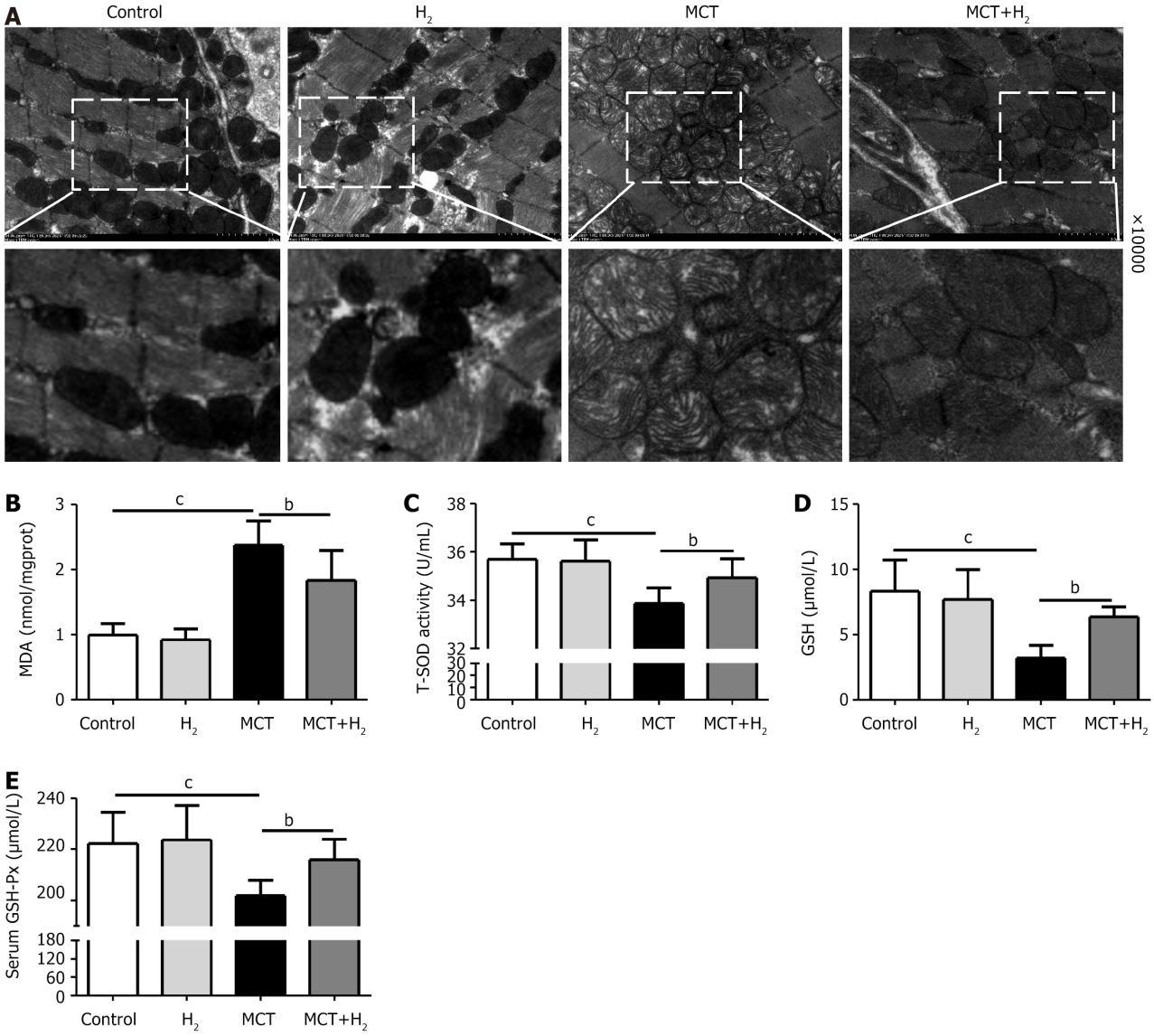

Figure 5 Hydrogen inhalation suppressed oxidative stress in monocrotaline-treated rats. A: Representative TEM images of mitochondrial morphology. The magnification is 10000 ×. Scale bar = 2 μm; B: Malonaldehyde content in right ventricular tissue; n = 6; C: Total superoxide dismutase activity in the serum; n = 10; D: Serum glutathione levels; n = 6; E: GSH-Px activity in the serum; n = 10. Data are expressed as the mean ± SD. $^{b}P < 0.05$: MCT+H_2 group *vs* MCT group; $^{c}P < 0.01$: MCT group *vs* control group. MCT: Monocrotaline; H_2: Hydrogen; MDA: Malonaldehyde; T-SOD: Total superoxide dismutase; GSH: Glutathione.

In this study, we confirmed that H_2 alleviates iron accumulation and oxidative stress in Ang II-treated H9C2 cells.

H_2 inhibited Ang II-treated cardiomyocyte hypertrophy in H9C2 cells

The effects of H_2 on cardiomyocyte hypertrophy were assessed using phalloidin staining. Phalloidin and DAPI staining were combined (Figure 8A). The surface area of H9C2 cells in the different groups was measured. The cell surface areas were increased after Ang II induction, but decreased after H_2 treatment (Figure 8B). We investigated the mRNA levels of hypertrophy-related indicators in H9C2 cells using qPCR. The qPCR results showed that the levels of ANP mRNA in the Ang II group were higher than those in the control group, but H_2 treatment prevented this increase (Figure 8C). Furthermore, the mRNA expression of BNP increased in the Ang II group compared to that in the control group but decreased after H_2 treatment (Figure 8D). We confirmed the ameliorative effect of H_2 on the excessive growth of Ang II-treated H9C2 cells.

H_2 ameliorated oxidative stress and suppressed ROS overproduction in H9C2 cells

The levels of ROS (green fluorescent signal) in the H9C2 cells of each group were detected by DCFH-DA staining (Figure 9A). ROS levels were higher in the Ang II group than in the control group. H_2 treatment significantly reversed this trend (Figure 9A). MMP levels were measured by JC-1 staining. An increased red/green fluorescence ratio indicates an increase in MMP. We analyzed the ratio of red-to-green fluorescence intensity (aggregates/monomers). The MMP in H9C2 cells was significantly decreased after Ang II treatment, but recovered by H_2 treatment (Figure 9B). The same result can be found in Figure 9C and D.

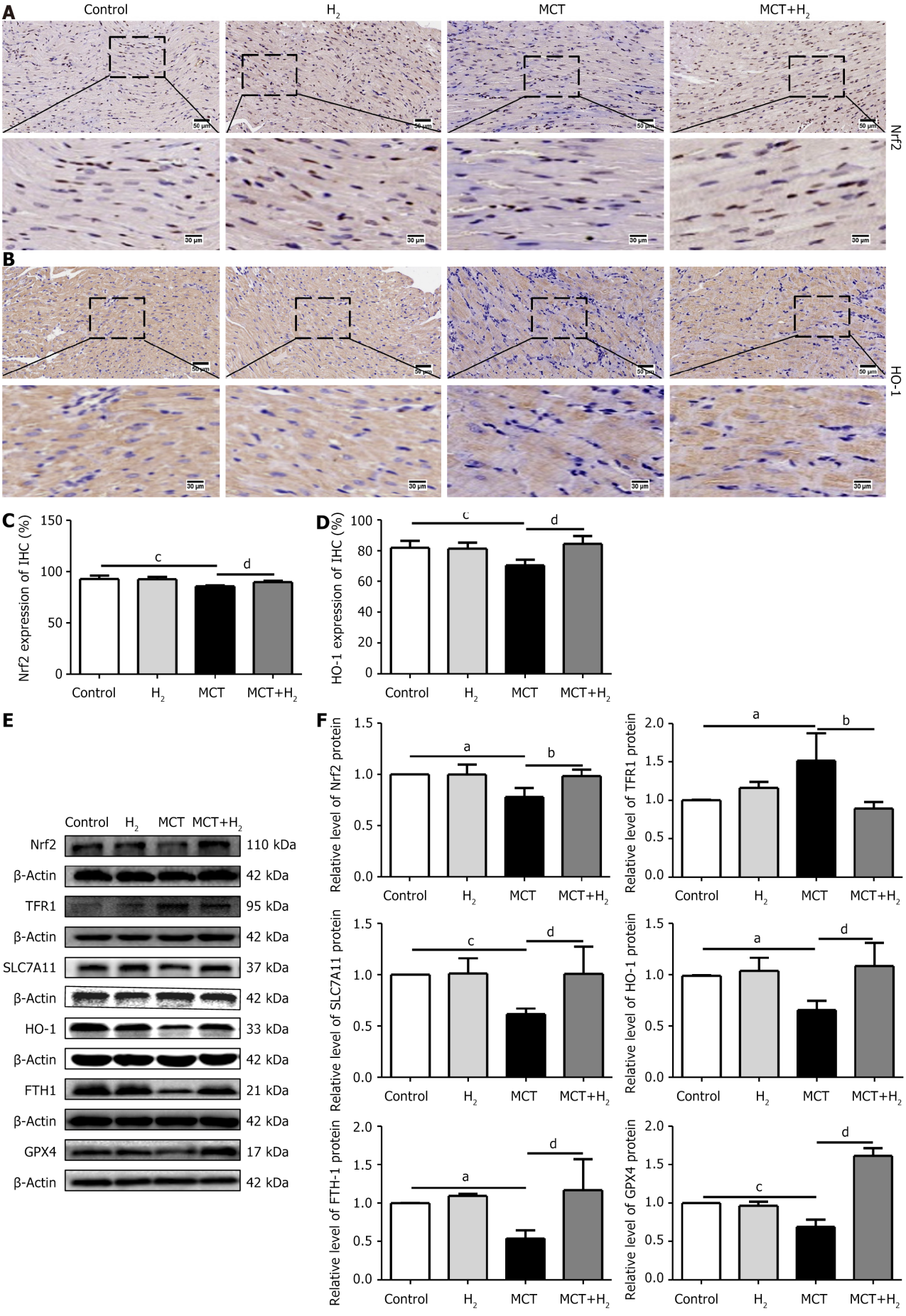

Figure 6 Hydrogen inhalation alleviated ferroptosis by restoring the Nrf2/HO-1 pathway in monocrotaline-treated rats. A: Representative

images of immunohistochemistry (IHC) staining of Nrf2. Nrf2-positive cell nuclei are stained brown. Magnification is 20 ×. Scale bar = 50 μm; B: Representative images of IHC staining of HO-1. HO-1-positive area is stained brown. Magnification is 20 ×. Scale bar = 50 μm; C: Quantitative analysis of IHC staining of Nrf2; *n* = 4; D: Quantitative analysis of IHC staining of HO-1; *n* = 4; E: Representative western blotting of Nrf2, TFR1, SLC7A11, HO-1, FTH1 and GPX4 proteins; F: Relative levels of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4 proteins. Data are expressed as the mean ± SD; *n* ≥ 3. $^{a}P < 0.05$ and $^{c}P < 0.01$: MCT group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: MCT+H_2 group *vs* MCT group. MCT: Monocrotaline; H_2: Hydrogen.

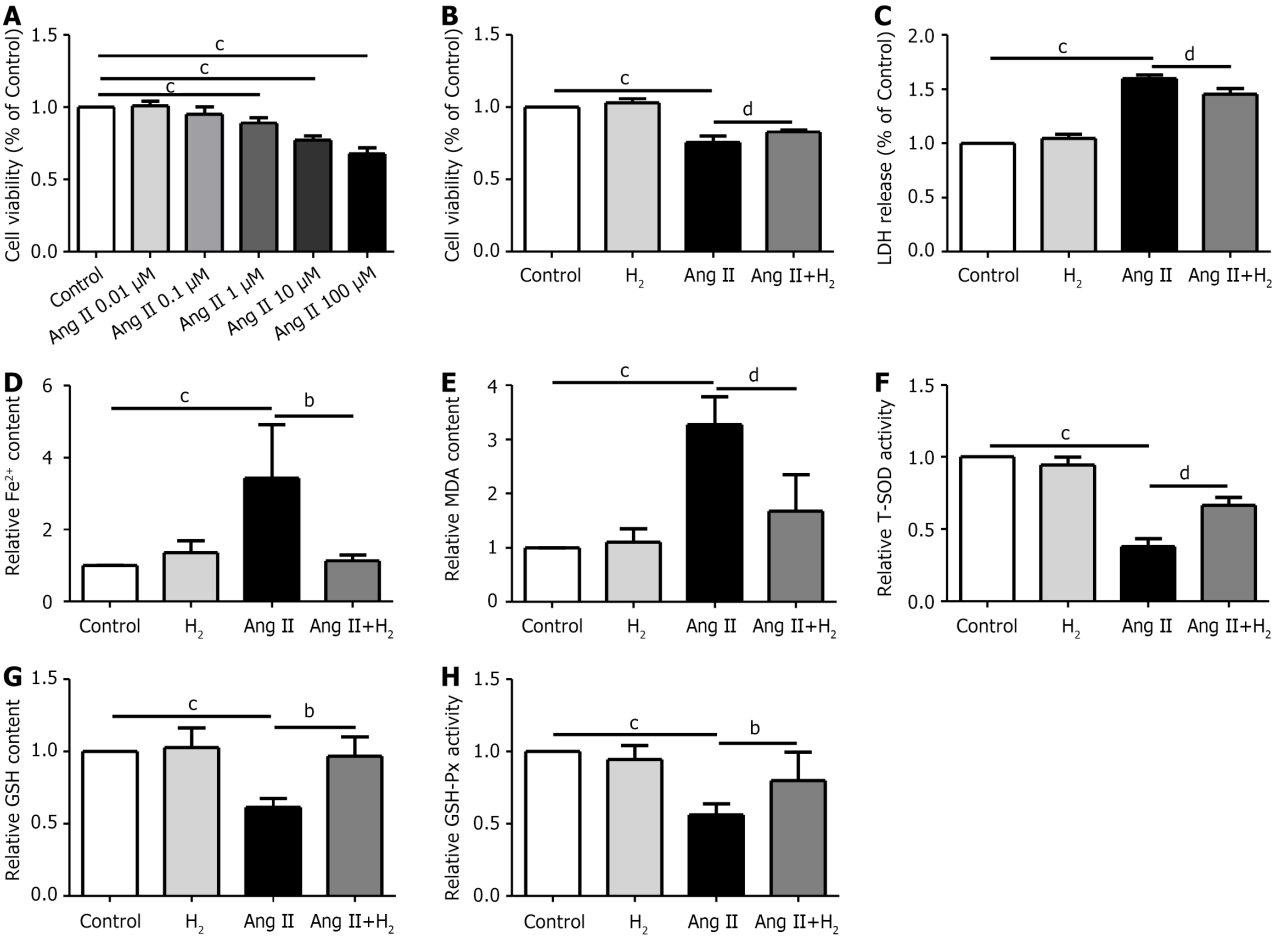

Figure 7 Hydrogen alleviates Fe^{2+} content and oxidative stress in an angiotensin II-treated H9C2 cells. A: Cell viability with different An angiotensin II concentrations (0, 0.01, 0.1, 1, 10, and 100 μmol/L) relative to the control; B: Relative cell viability in each group; C: Relative lactate dehydrogenase release in each group; D: Relative Fe^{2+} content in each group, *n* = 4; E: Relative malonaldehyde content in each group; *n* = 4; F: Relative total superoxide dismutase activity in each group; *n* = 4; G: Relative glutathione content of each group; *n* = 4; H: Relative GSH-Px activity in each group; *n* = 4. Data are expressed as the mean ± SD. $^{c}P < 0.01$: Ang II group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: Ang II+H_2 group *vs* Ang II group. MCT: Monocrotaline; H_2: Hydrogen; MDA: Malonaldehyde; LDH: lactate dehydrogenase; T-SOD: total superoxide dismutase; Ang II: An angiotensin II.

H_2 alleviated ferroptosis by restoring the Nrf2/HO-1 pathway in Ang II-treated H9C2 cells

To determine the mechanism by which H_2 prevents cardiomyocyte hypertrophy in H9C2 cells, we examined ferroptosis-related indicators. The expression levels of proteins associated with ferroptosis, Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4, decreased after Ang II administration, whereas the expression of TFR1 protein was upregulated. After H_2 treatment, the levels of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4 proteins were upregulated, whereas the expression of TFR1 protein was downregulated (Figure 10). Overall, H_2 reduced ferroptosis in H9C2 cells and increased the expression of components of the Nrf2/HO-1 pathway. Ferroptosis occurred in an Ang II cell model of right heart system pressure overload, and H_2 reduced Ang II-induced cell hypertrophy. H_2 inhibits ferroptosis by reducing the iron content, inhibiting oxidative stress, enhancing antioxidant activity, regulating the expression of various ferroptosis-related proteins, and alleviating myocardial hypertrophy caused by pressure overload.

ML385 inhibited restoration of the Nrf2/HO-1 signaling pathway in Ang II-treated H9C2 cells treated with H_2

Mechanistically, the anti-ferroptotic effect of H_2 is achieved by restoring the Nrf2/HO-1 signaling pathway. In particular, H_2 treatment increased the expression of Nrf2 in Ang II-treated H9C2 cells. The specific Nrf2 inhibitor ML385 (1 μmol/L) was used in our study. Consistently, the Ang II+H_2 group showed decreased ferroptosis compared to the control group, whereas ML385 treatment inhibited restoration of the Nrf2/HO-1 signaling pathway and negated the protective effects of H_2 (Figure 11). In the pressure overload model of the right cardiac system, the inhibitory effect of H_2 on ferroptosis was

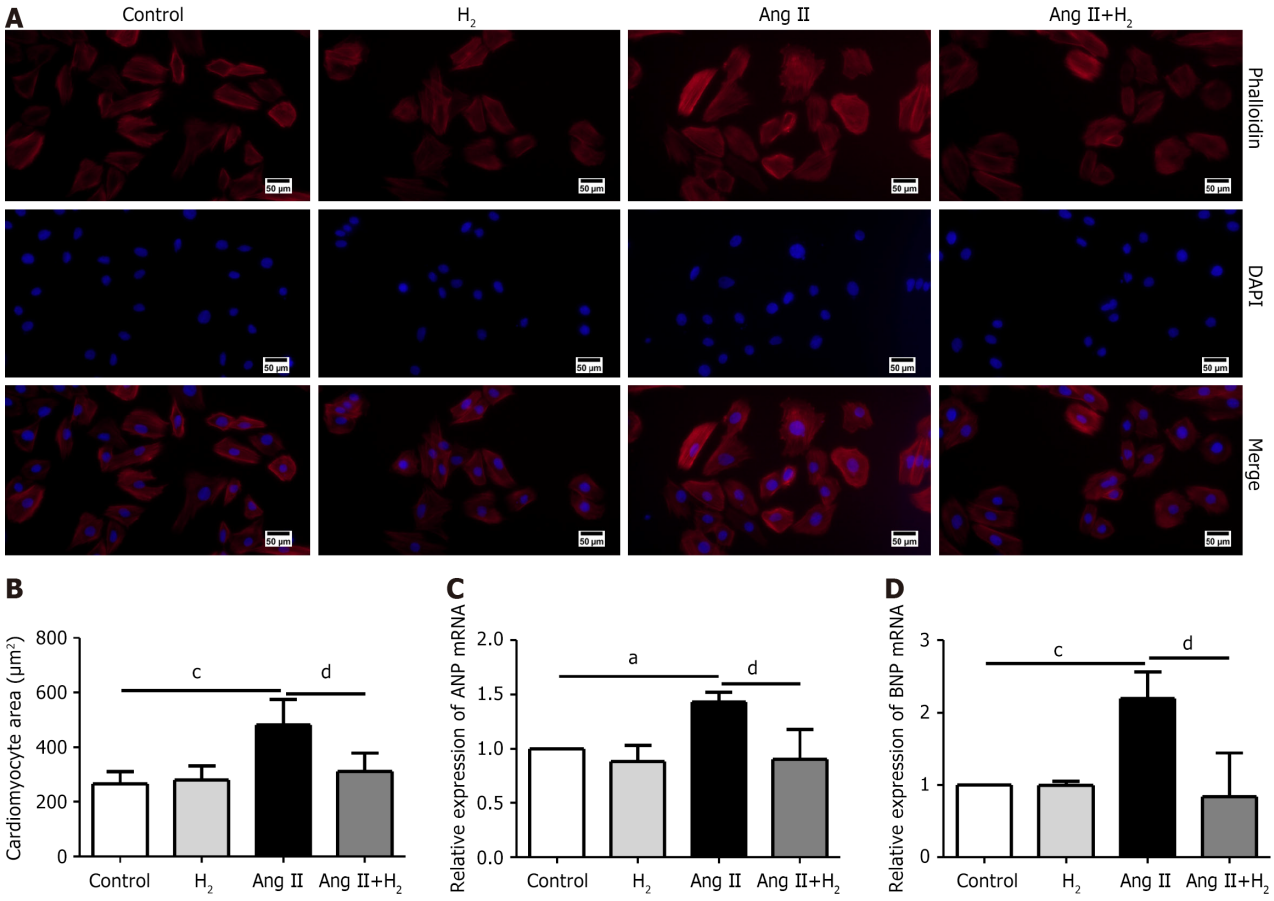

Figure 8 Hydrogen inhibited an angiotensin II-induced cardiomyocyte hypertrophy in H9C2 cells. A: Representative images of phalloidin staining in H9C2 cells from different groups. Phalloidin and DAPI staining images were merged. Magnification is 20 ×. Scale bar = 50 μm; B: Surface area of H9C2 cells in different groups; *n* = 4; C: Relative expression levels of *ANP* mRNA in each group; *n* = 3; D: Relative *BNP* mRNA expression in each group; *n* = 3. Data are expressed as the mean ± SD. $^{a}P < 0.01$ and $^{c}P < 0.01$: Ang II group *vs* control group; $^{d}P < 0.01$: Ang II+H_2 group *vs* Ang II group. MCT: Monocrotaline; H_2: Hydrogen; Ang II: An angiotensin II; ANP: Antinatriuretic peptide A; BNP: Brain natriuretic peptide.

related to restoration of the Nrf2/HO-1 signaling pathway.

DISCUSSION

RVH is caused by long-term overload, which mainly refers to hypertrophy and enlargement of the RV, ultimately leading to right heart failure or even death[33]. RHV is easily overlooked in the early stages and associated with poor clinical prognosis and high mortality. RV function is the main determinant of survival in patients with pulmonary arterial hypertension[34]. The right ventricle is more susceptible to oxidative stress-induced damage than the left ventricle[35-37]. Effective treatment is important to prevent RVH; however, clinical options are limited. H_2 is a biological antioxidant and can significantly inhibit injury in multiple organs by alleviating oxidative stress[19,38-40]. Based on previous studies, we investigated the protective effects of H_2 against cardiac hypertrophy by inhibiting ferroptosis. Here, we present the first evidence that H_2 alleviates RV hypertrophy and dysfunction by inhibiting ferroptosis *in vivo*. Furthermore, we confirmed that H_2 inhibits ferroptosis by restoring the Nrf2/HO-1 signaling pathway *in vitro* in MCT-treated rats. H_2 suppresses RVH through several key mechanisms. First, H_2 inhibited ROS production. As depicted in Figure 12, ROS contributes to lipid peroxidation, which is a crucial step in ferroptosis. Thus, H_2 prevents ferroptosis initiation by reducing ROS levels. Second, H_2 likely interacts with Fe^{2+} ions. As Fe^{2+} contributes to the generation of ROS, interference with Fe^{2+} activity by H_2 can decrease the formation of ROS and subsequent lipid peroxidation. Third, H_2 restores the Nrf2 pathway. Once activated, Nrf2 translocates to the nucleus and induces the expression of HO-1, which has antioxidant properties that counteract oxidative stress and reduce ferroptosis. Finally, H_2 helps maintain the GSH–GPX4 axis, which is essential for preventing lipid peroxidation because GSH and GPX4 work together to reduce lipid peroxidation. By preserving this axis, H_2 prevents the progression of ferroptosis associated with RVH (Figure 12). It has been established that reducing agents like H_2 can act on the redox-sensitive cysteine residues within KEAP1. The structure and function of KEAP1 are altered by specific chemical modifications of these residues. This alteration disrupts the normal inhibitory interaction between KEAP1 and NRF2 in the cytoplasm. Once the ability of KEAP1 to bind and sequester NRF2 is compromised, NRF2 is free to translocate to the nucleus. Inside the nucleus, NRF2 can bind to specific antioxidant response elements on DNA, initiating the transcription of a series of downstream target genes, including HO-1, which

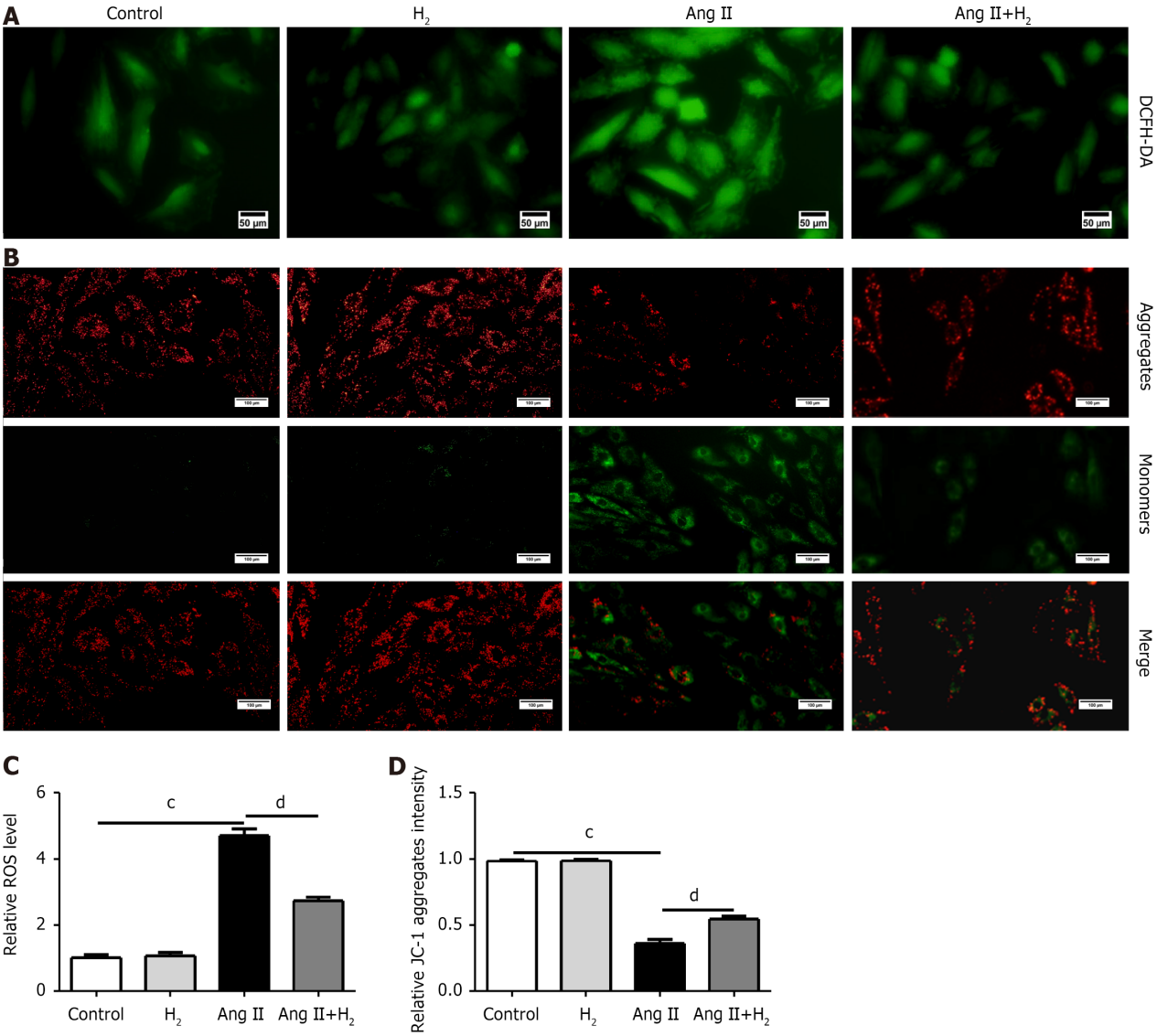

Figure 9 Hydrogen ameliorated oxidative stress and suppresses reactive oxygen species overproduction in H9C2 cells. A: Representative images of the DCFH-DA staining. Magnification is 20 ×. Scale bar = 50 μm; B: Representative images of JC-1 staining. Magnification is 10 ×. Scale bar = 100 μm; C: Relative reactive oxygen species levels in each group; n = 4; D: Relative JC-1 aggregate intensity in each group; n = 4. Data are expressed as the mean ± SD. ^{c}P < 0.01: Ang II group *vs* control group; ^{d}P < 0.01: Ang II+H_2 group *vs* Ang II group. MCT: Monocrotaline; H_2: Hydrogen; Ang II: An angiotensin II; ROS: Reactive oxygen species.

plays a crucial role in counteracting oxidative stress and regulating various physiological and pathological processes related to our observed outcomes.

The weights of the rats were measured weekly and their BW increased gradually every week. The rats in all groups were weighed and the average weekly weight and weight gain were calculated. Compared with the control group, BW was reduced at 14, 21, and 28 days after MCT injection, and weight increased after H_2 inhalation. Comparing weight gain among rats in each group, weight gain 28 days after H_2 administration was significantly lower than that in the MCT group. We suggest that a decrease in the heart function of rats led to impaired appetite and digestive system function, which resulted in a decrease in BW and weight gain.

Studies have investigated specific cardiac morphometric changes in MCT-induced RVH[26,31]. Echocardiography results showed that the LVEF in MCT rats was not significantly decreased, which was consistent with the RVH model. In addition, RVEDD, RV-ESV, RV-EDV, RVEF, and RVFW are indicators of RV structure and function[26,31]. We evaluated the RVEDD, RV-ESV, RV-EDV, RVEF, and RVFW using echocardiography. Consistent with prior studies, H_2 inhalation improved RV function in MCT-treated rats, as determined by the decrease in RVEDD, RV-ESV, RV-EDV, RVFW, and BNP, and the increase in RVEF.

RVFW is an indicator of RV structural abnormalities[26,41]. To investigate the effect of H_2 in RVH rats, RVFW was compared between groups and found to be increased in MCT-treated rats and decreased after H_2 treatment. H_2 inhalation alleviated the cardiomyocyte area and fibrosis in MCT-treated rats. HE staining showed that RVH was increased in MCT-treated rats and decreased by H_2 inhalation. Masson staining showed that fibrosis in the right ventricle was increased in MCT-treated rats and decreased by H_2 inhalation. In addition, WGA staining showed that H_2 treatment significantly suppressed enlargement of the cardiomyocyte area caused by MCT. The cardiomyocyte area was severely increased in

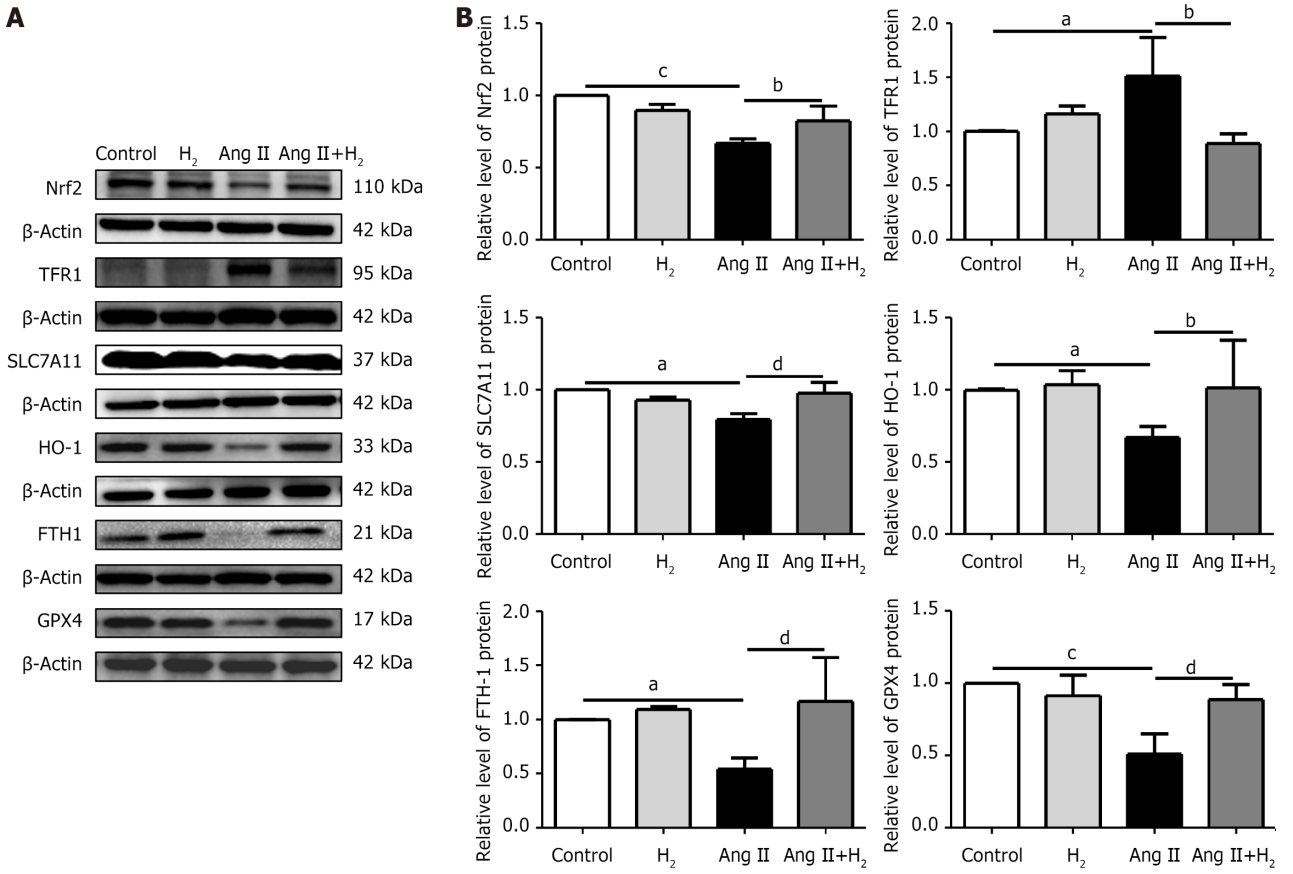

Figure 10 Hydrogen alleviates ferroptosis by inhibiting the Nrf2/HO-1 pathway in an angiotensin II-treated H9C2 cells. A: Representative western blotting of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4 proteins; B: Relative protein levels of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4. Data are expressed as the mean ± SD; $n \geq 3$. $^{a}P < 0.05$ and $^{c}P < 0.01$: Ang II group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: Ang II+H_2 group *vs* Ang II group. MCT: Monocrotaline; H_2: Hydrogen; Ang II: An angiotensin II.

RVH rats and was significantly suppressed by H_2 treatment. Furthermore, the hypertrophy-related markers ANP and BNP increased in the model group but decreased after H_2. These results supported our hypothesis that the H_2 strategy has a preventive effect against hypertrophy caused by pressure overload in the right cardiac system.

H_2 has been explored in various diseases. In the central nervous system, H_2 shows potential for treating conditions such as Parkinson's and Alzheimer's diseases, as well as neonatal hypoxic-ischemic encephalopathy. The cardiovascular system improves heart function in myocardial infarction and reduces oxidative stress[]. It also shows promise for the treatment of acute pancreatitis, sepsis, respiratory diseases, and other diseases. In China, the "H_2 therapy instrument" has been approved as a class III medical device by the National Medical Products Administration for the auxiliary treatment of several diseases including cerebral ischemia, pulmonary ischemia, and others. Although the regulatory authorities in most countries have not achieved a widespread global consensus, existing research and partial approval indicate the potential of H_2 for future clinical use.

Ferroptosis is typically characterized by iron accumulation, lipid peroxidation and mitochondrial dysfunction[3,42,43]. Iron is an essential element for many biological processes, including oxygen transport and storage, oxidative phosphorylation, and redox reactions. Excessive iron accumulation causes abnormal redox reactions leading to organ dysfunction. Excess iron produces ROS *via* the Fenton reaction, leading to ferroptosis. We found that the accumulation of iron and MDA led to ferroptosis and subsequent myocardial damage and deterioration. H_2 regulates iron metabolism in MCT-treated rats. In our study, the regulation of iron metabolism and maintenance of iron homeostasis were decreased in MCT-treated rats. Ferroptosis mainly occurs because of inactivation of the cellular antioxidant system[44]. The activities of T-SOD, GSH, and GSH-Px antioxidant systems were significantly decreased *in vivo* and *in vitro* (Figure 7). Similarly, mitochondria in the RV tissue and H9C2 cells were identified using TEM and JC-1 assays. The results showed that the ameliorative effect of H_2 on cardiohypertrophy was related to its ability to suppress oxidative stress.

Disruption of system Xc-function can induce ferroptosis[10]. The downregulation of SLC7A11 is believed to contribute to ferroptosis[3,45]. Our data suggest that SLC7A11 downregulation promotes ferroptosis in cardiomyocytes, which is consistent with previous studies[9,46]. In addition, GPX4 protein expression was significantly decreased in the model group, but significantly increased after H_2 treatment. In our study, the iron content in the model group was higher than that in the control group and reduced after H_2 administration. TFR1 is a ferroptosis marker. Recent studies confirmed that FTH1 is crucial for initiating and promoting cardiomyocyte ferroptosis[3]. Decreased FTH1 Levels indicate increased iron uptake and decreased iron storage. Thus, decreased FTH1 Levels may contribute to iron overload during ferroptosis. The model group showed decreased expression of FTH1 compared to the control group, which significantly increased after H_2

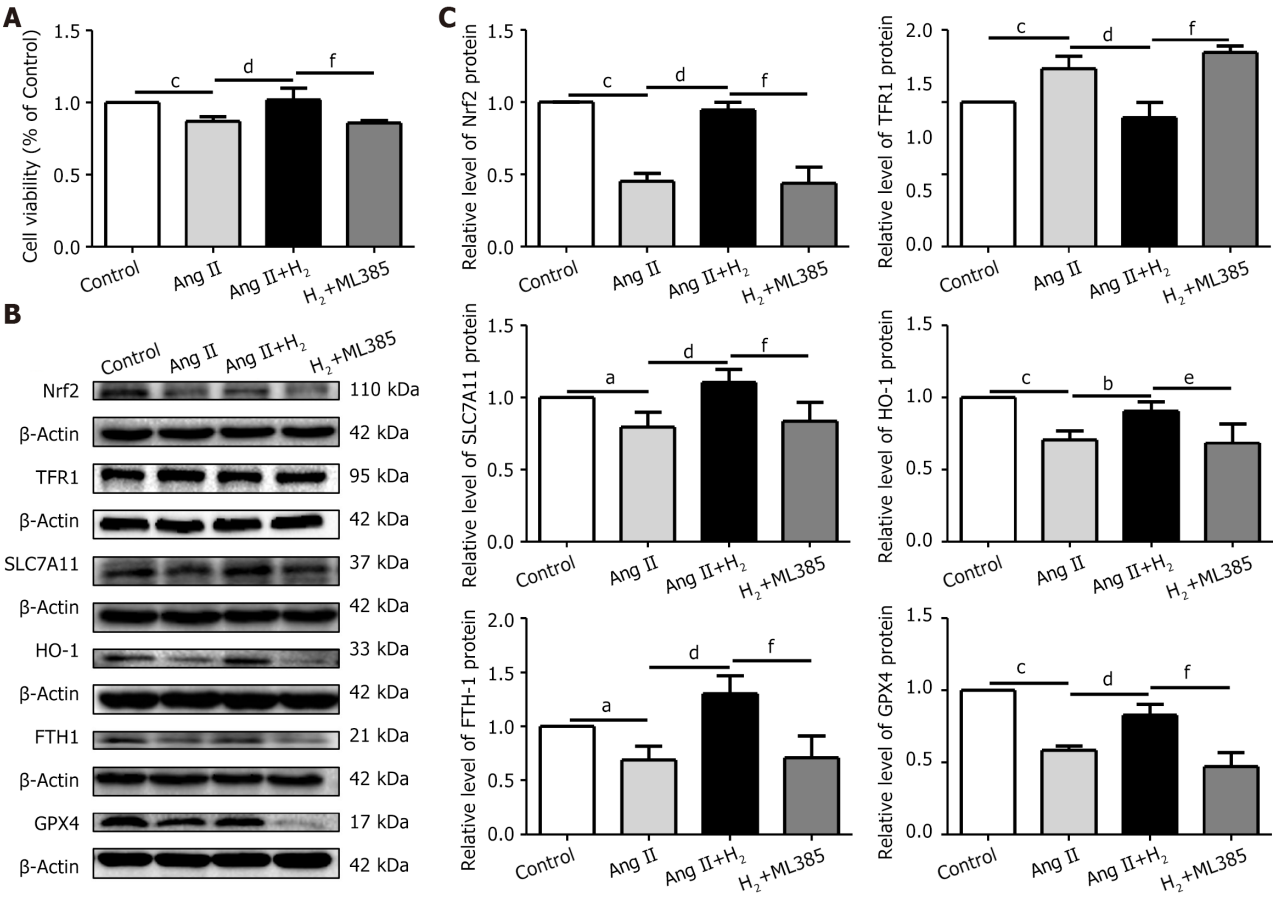

Figure 11 The Nrf2 inhibitor ML385 (1 μmol/L) inhibited restoration of the Nrf2/HO-1 signaling pathway in an angiotensin II-treated H9C2 cells after Hydrogen treatment. A: Cell viability in each group; B: Representative western blotting of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4 proteins; C: Relative levels of Nrf2, TFR1, SLC7A11, HO-1, FTH1, and GPX4 proteins. Data are expressed as the mean ± SD; $n \geq 3$. $^{a}P < 0.05$ and $^{c}P < 0.01$: Ang II group *vs* control group; $^{b}P < 0.05$ and $^{d}P < 0.01$: Ang II+H_2 group *vs* Ang II group; $^{e}P < 0.05$ and $^{f}P < 0.01$: Ang II+H_2+ML385 group *vs* Ang II+H_2 group. MCT: Monocrotaline; H_2: Hydrogen; Ang II: An angiotensin II.

treatment. In addition, the model group showed increased TFR1 expression compared to the control group, which was decreased after H_2 treatment.

We clarified that the cardioprotective effects of H_2 depend on ferroptosis and Nrf2/HO-1 restoration during cardiomyocyte hypertrophy. Nrf2 is an important transcription factor activated during regulation of the antioxidant response[30,47]. Similar to previous studies, we found that Nrf2 promotes the expression of HO-1 after H_2 treatment. In our study, the protein expression levels of Nrf2 and HO-1 in the model group were downregulated compared to those in the control group, whereas H_2 treatment prevented this downregulation.

In RVH, ferroptosis is caused by a pressure overload in the right cardiac system. H_2 can inhibit ferroptosis by upregulating the Nrf2/HO-1 signaling pathway, reducing the iron content, inhibiting oxidative stress, enhancing antioxidant activity, and regulating a variety of ferroptosis-related proteins. The inhibitory effect of H_2 on ferroptosis may be related to restoration of the Nrf2/HO-1 signaling pathway. H_2 restores the Nrf2/HO-1 signaling pathway and inhibits the ferroptosis of cardiomyocytes caused by pressure overload in the right cardiac system, thereby reducing RVH.

This study has several limitations. The exact proportion of cardiomyocytes affected by ferroptosis or cell death *in vivo* and *in vitro* remains unclear because we did not perform TUNEL assays or blotting of cleaved caspase-3. Moreover, the role of Ang II in RVH is debatable in the MCT model, with incomplete exploration of the related physiological responses. Experiments on Nrf2 overexpression and knockout in mice are also lacking. In addition, the effects of H_2 inhalation on ventricular wall thickness and Nrf2 activation, along with its relationship with ferroptosis and the Nrf2/HO-1 pathway, require further in-depth studies. For further research, we suggest applying a TUNEL assay and caspase-3 blotting, refining the model to better understand the role of Ang II, establishing Nrf2 gene-manipulated mouse models, and conducting more detailed studies on H_2-related effects.

CONCLUSION

In conclusion, our study provides evidence that H_2 retards the progression of cardiac hypertrophy caused by pressure overload in the right cardiac system by inhibiting ferroptosis and restoring the Nrf2/HO-1 signaling pathway. Our findings suggest that H_2 inhalation represents a simple and convenient candidate strategy for protection against RVH.

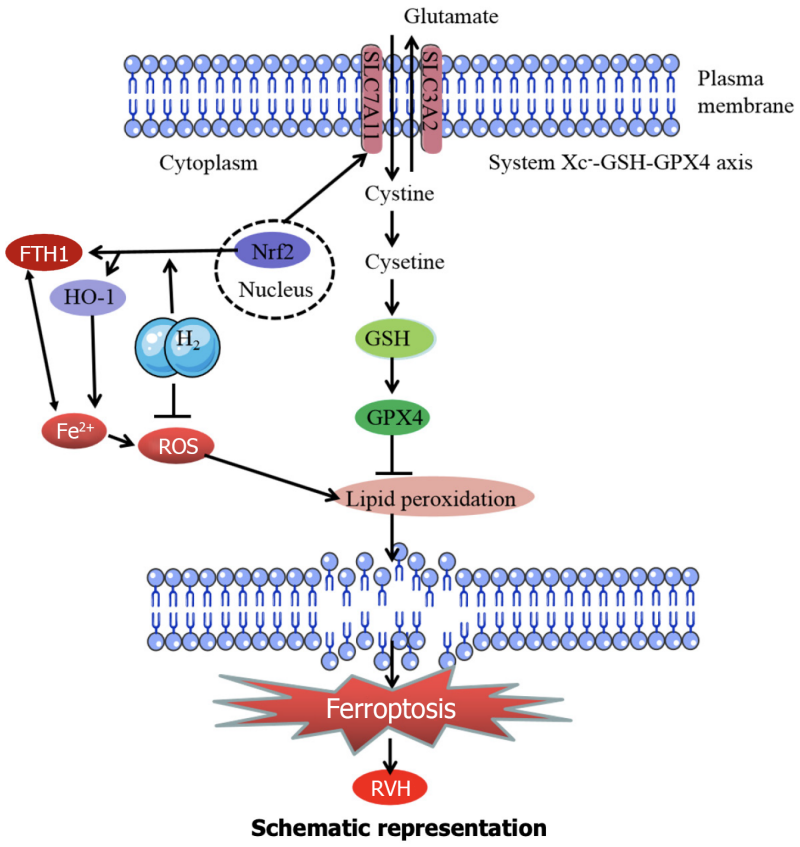

Figure 12 Graphical abstract of the mechanism by which hydrogen suppresses right ventricular hypertrophy in monocrotaline-treated rats.

This approach shows potential for addressing RVH and warrants further exploration.

FOOTNOTES

Author contributions: Bai JC, Yang HX, and Zhan CC performed the experiments; Bai JC, Yang HX, and Zhan CC analyzed the data; Bai JC, Yang HX, Zhan CC, and Zhao LQ wrote the manuscript; Yang HX, Zhan CC, Zhao LQ, and Liu JR edited the manuscript; Liu JR and Yang HX critically revised the manuscript; Yang W designed the study and is the corresponding author. All the authors have read and approved the final manuscript. Bai JC and Yang HX contributed equally to this study.

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META-ANALYSIS

Long-term prognostic role of adiponectin in stable coronary artery disease: A meta-analysis of prospective studies

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Abstract

BACKGROUND

The persistent burden of cardiovascular (CV) disease in the United States requires innovative and cost-effective prognostic markers that can be relied upon.

AIM

To provide insights into how adiponectin can predict all-cause mortality and major adverse CV events (MACE) in patients with coronary artery disease (CAD) and to determine the prognostic value of adiponectin in predicting all-cause mortality and MACE in patients with stable CAD.

METHODS

We conducted a systematic search on PubMed, Scopus, and Google Scholar to find relevant studies published through June 2023 evaluating the long-term prognostic role of adiponectin in patients with stable CAD. Using a random effects model with 95%CI, we estimated the odds ratio (OR) while assessing heterogeneity through I^2 statistics. To ensure robustness, we performed a sensitivity analysis using the leave-one-out approach.

RESULTS

After screening, we included five prospective studies involving 3225 patients who were followed up for a median duration of 3.8 years. Within the study population, prevalent risk factors included hypertension, diabetes, hyperlipidemia, and smoking. The commonly prescribed medications were angiotensin-converting enzyme inhibitors, beta blockers, and statins. The combined adjusted OR for all-cause mortality was found to be 2.51 (95%CI: 1.36–4.62), showing heterogeneity (I^2 = 65.51%, P = 0.03). On the other hand, the combined adjusted OR for MACE was determined to be 1.04 (95%CI: 1.02–1.06) with no significant heterogeneity observed (I^2 = 0%, P = 0.68). Through a sensitivity analysis, it was discovered that none of the studies significantly impacted the overall results of the meta-analysis, thus indicating their robustness.

CONCLUSION

Higher levels of adiponectin were found to be associated with an increased risk of long-term mortality and MACE in patients with CAD, which highlights its potential as a cost-effective marker for risk assessment and guiding treatment strategies. Further research on the role of adiponectin could greatly influence decision-making and resource allocation in CV care.

Key Words: Adiponectin; Stable coronary artery disease; Coronary artery disease; Major adverse cardiac and cerebrovascular events; Mortality; Long-term; Systematic review; Meta-analysis

Core Tip: The persistent burden of cardiovascular (CV) disease in the United States requires innovative and cost-effective prognostic markers that can be relied upon. Higher levels of adiponectin are associated with increased long-term mortality and major adverse CV events in patients with coronary artery disease. This highlights adiponectin as a potential cost-effective prognostic marker for risk assessment and treatment guidance.

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INTRODUCTION

Adiponectin is a 244-amino acid protein hormone, first identified in 1995, with a molecular mass of approximately 28 kDa. In circulation, it primarily exists as a dimer[1] but it can also assemble into trimers, as well as higher molecular weight hexamers and multimers (90 kDa, 180 kDa, and > 400 kDa). Structurally, adiponectin forms a single-chain trimer composed of a variable N-terminal region, a collagen-like domain, and a globular C-terminal domain resembling complement component C1. The three globular regions are located at the N-termini and C-termini and are connected through the Pro104–Tyr109 region. This trimeric unit is encapsulated within a gong-shaped shell[2].

Adiponectin exerts its biological effects by modulating signaling pathways in various target cells, thereby counteracting inflammatory stimuli. Its anti-inflammatory properties are central to its beneficial effects on the cardiovascular (CV) system and metabolic conditions, including insulin resistance and atherosclerosis in the vascular endothelium[3,4],

as well as obesity, type 2 diabetes mellitus, and coronary artery disease (CAD). Additionally, adiponectin maintains vascular homeostasis by regulating key signaling pathways in endothelial cells and modulating inflammatory processes within the subendothelial space[5].

The predictive role of adiponectin in long-term outcomes for patients with CAD is based on its complex involvement in metabolic and CV processes. Recent research has highlighted its importance as a biomarker for CV disease risk assessment. Higher levels of adiponectin have been associated with an increased risk of all-cause mortality in CAD patients, indicating its potential as a predictor of unfavorable results. However, the adiponectin paradox persists, as certain investigations suggest a protective role against CV events. Complexities arise from differences in study design, patient cohorts, and testing methods. This paradox highlights the intricate nature of adiponectin's involvement in CV health and its potential multifaceted impact[6,7].

The relationship between adiponectin levels and CV risk appears complex, as both higher and lower levels have been associated with adverse outcomes. Elevated adiponectin levels have been paradoxically linked to major adverse CV events (MACE), including ischemic stroke[8]. In contrast, reduced adiponectin levels have been implicated in increased CV complications in conditions such as obesity, insulin resistance, and diabetes[9]. This paradox underscores the intricate interplay between adiponectin's protective mechanisms and its potential role in promoting vascular dysfunction.

Previous research has delved into unraveling the adiponectin paradox. Some studies suggest that higher circulating adiponectin concentrations might serve as a marker of lower risk for myocardial infarction in men[10]. On the other hand, meta-analyses have indicated that both high and low adiponectin levels could be associated with increased CV mortality risk[11]. While adiponectin's anti-inflammatory and vasculoprotective properties could contribute to its beneficial effects, the paradoxical outcomes highlight the need for a deeper understanding of its complex mechanisms in CV pathophysiology[12]. In essence, the role of adiponectin, in predicting the risk of CAD, myocardial infarction, or stroke is complex. It highlights the connection between its levels and CV outcomes. The conventional understanding of how adiponectin exerts its effects on health is often derived from studies conducted on animal models or from early human research. However, these recent unexpected findings from genetic studies highlight the importance of rigorously examining and validating biomarkers, in real world clinical settings. Further research is necessary to elucidate its involvement in these diseases, especially in patients with stable CAD. This systematic review and meta-analysis aims to evaluate prospective trials with long-term follow-up.

MATERIALS AND METHODS

Search strategy and selection criteria

For this analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (Figure 1). We conducted a search on PubMed, Scopus, and Google Scholar databases, including studies up until June 2023. To ensure a search, we used specific keywords such as "adiponectin", "stable coronary artery disease", "major adverse cardiac and cerebrovascular events", "mortality", "prospective studies" and "systematic review/meta-analysis". We excluded comments, editorials, case reports, reviews, proceedings, personal communications, and non-English publications. Only prospective studies that provided data on the predictive role of adiponectin and outcomes related to MACE (major adverse cardiac and cerebrovascular events) as well as all-cause mortality were included (Figure 2)[13-17].

Study selection and data extraction

Two reviewers independently screened the studies to determine their eligibility for inclusion. In cases where there were uncertainties or disagreements between the two reviewers, a third reviewer was consulted to reach a consensus. The extracted data included information such as author names, publication year, study design details, participant numbers, and their age, sex distribution, and comorbidities. Additionally, we collected data on adiponectin levels measured during the study period as well as information on follow-up duration and outcome measures related to all-cause mortality, or MACE.

Quality assessment

We assessed the quality of each study using the Newcastle Ottawa Scale, which employs criteria to evaluate potential biases, in research design (Table 1). Two independent reviewers conducted the assessment process, and any discrepancies or disagreements were resolved through discussion until a consensus was reached.

Statistical analyses

The study focused on two outcomes; MACE and all-cause mortality. To analyze the data, we used OpenMeta[Analyst] software and applied the random effects model to combine effect sizes. The results were visually presented using forest plots. We also measured heterogeneity using the I^2 statistics. To examine the impact of studies, we conducted a sensitivity analysis by leaving out one study at a time. Additionally, we used funnel plots to assess publication bias, considering P values greater than 0.05, as statistically significant.

RESULTS

After screening, we included five prospective studies[13-17] involving 3225 patients who were followed up for a median

Table 1 Newcastle Ottawa Scale for critical appraisal of included studies

Criteria		Study 1	Study 2	Study 3	Study 4	Study 5
Selection						
Representativeness of the exposed cohort	Were the included patient's representative of the population with stable CAD	Yes	Yes	Yes	Yes	Yes
Selection of the non-exposed cohort	Were appropriate comparison groups selected to evaluate the association between adiponectin and outcomes in stable CAD patients	-	-	Yes	-	Yes
Ascertainment of exposure	Were adiponectin levels accurately measured and defined in the studies	Yes	Yes	Yes	Yes	Yes
Demonstration that outcome of interest was not present at the start of the study	Were patients with pre-existing conditions or adverse outcomes excluded or adequately accounted for at baseline	Yes	Yes	Yes	Yes	Yes
Comparability						
Comparability of cohorts on the basis of the design or analysis	Did the studies control for only for main factor or all potential confounding factors or perform appropriate adjustments when examining the association between adiponectin and outcomes in stable CAD patients	Yes	Yes	Yes	Yes	Yes
Outcome						
Assessment of outcome	Were the outcomes of interest (*e.g.*, cardiovascular events, mortality) clearly defined and assessed using standardized criteria across the studies	Yes	Yes	Yes	Yes	Yes
Was follow-up long enough for outcomes to occur	Did the studies have a sufficient follow-up period to capture the occurrence of outcomes in stable CAD patients with adiponectin levels	Yes	Yes	Yes	Yes	Yes
Adequacy of follow-up of cohorts	Did the studies achieve a high follow-up rate for both the exposed and non-exposed cohorts throughout the follow-up period	-	-	Yes	-	Yes

CAD: Coronary artery disease.

duration of 3.8 years. Within the study population, prevalent risk factors included hypertension, diabetes, hyperlipidemia, and smoking. The commonly prescribed medications were angiotensin converting enzyme inhibitors, beta blockers, and statins. The baseline characteristics of the study population are reported in Table 2[13-17].

The combined adjusted odds ratio (OR) for all-cause mortality was found to be 2.51 (95%CI: 1.36–4.62), showing heterogeneity (I^2 = 65.51%, P = 0.03). On the other hand, the combined adjusted OR for MACE was determined to be 1.04 (95%CI: 1.02–1.06) with no significant heterogeneity observed (I^2 = 0%, P = 0.68). Through a sensitivity analysis, it was discovered that none of the studies significantly impacted the overall results of the meta-analysis thus indicating their robustness. Concisely, higher levels of adiponectin were found to be associated with an increased risk of long-term mortality and MACE in patients with CAD, which highlights its potential as a cost-effective marker for risk assessment and guiding treatment strategies.

We acknowledge that Pratesi *et al*[16] reported adiponectin cut-off levels in ng/mL (13.2 ng/mL), whereas others, such as Hascoet *et al*[14], used μg/mL (9.1 μg/mL). Despite this unit discrepancy, our leave-one-out sensitivity analysis for all-cause mortality confirmed that the association between elevated adiponectin and increased mortality remained statistically significant even after excluding the study performed by Pratesi *et al*[16] [OR: 1.78 (1.35–2.36)]. This indicates that differences in units or cut-off values did not materially impact our findings. Additionally, the consistency of results across studies, despite slight methodological variations in adiponectin measurement, supports the robustness of our meta-analysis.

DISCUSSION

This systematic review and meta-analysis of prospective studies showed a link between higher levels of adiponectin and an increased likelihood of long-term mortality and adverse CV events in stable CAD patients. This finding supports the emerging evidence that suggests adiponectin could be a cost-effective marker for assessing risk and making management decisions[8,13]. The overall adjusted OR for all-cause mortality was 2.51 (95%CI: 1.36-4.62) with some variation among the studies (I^2 = 65.51%, P = 0.03). The pooled adjusted OR for events was 1.04 (95%CI: 1.02-1.06), showing no significant variation across the studies (I^2 = 0%, P = 0.68). Sensitivity analysis confirmed the reliability of these results, indicating that no individual study had an influence on the observed outcomes. Given the increased risk of mortality and adverse events associated with adiponectin levels, further research is warranted to understand its role in CAD pathophysiology.

Table 2 Characteristics of study population, *n* (%)

Ref.	Location	Study design	Cohort	Sample size	Mean/median age (years)	Median follow-up (years)	Male participants	Hypertension	Hyperlipidemia	DM	Obesity (BMI > 25 kg/m²)	History of myocardial infarction	Smoking	Adiponectin cut offs	Outcomes reported (ACM, MACE)	Multivariable regression analysis was adjusted for which variables/confounders
Marino *et al*[15], 2018	Netherlands	Prospective	Total: 570, ACS: 309, SAP: 261	261	N/A	1	203 (77.8)	161(61.70)	Hypercholesterolemia: 180 (69)	59 (22.60)	N/A	N/A	49 (18.8)	In ACS patients-median IQR: 2.9 (1.8-4.1 μg/mL) μg/mL. In SAP patients-median IQR: 2.9 (1.9-3.9 μg/mL) μg/mL	ACM adjusted OR/HR = 8.48 (0.92-78.03), MACE adjusted OR/HR = 1.33 (0.41-4.28)	ACS and SAP-adjusted for age, gender, diabetes, hypertension, and CRP. Additionally, adjusted for indication for coronary angiography in the total cohort
Pratesi *et al*[16], 2016	Italy	Prospective	Stable CAD	138	69.3 ± 10.4	3.8	122 (89.7)	98 (71)	99 (71.70)	61 (42.20)	Mean level of BMI was 26.8 kg/m² ± 4.1 kg/m²	114 (82.60)	91 (65.94)	13.2 ng/mL	ACM adjusted OR/HR = 11.31 (2.89-44.28)	Model 1 (ACM), age, gender, BMI, Inflammatory Disease Score, previous percutaneous transluminal coronary angioplasty, atrial fibrillation, peripheral artery disease, NYHA class, EF, hemoglobin, NT-proBNP, eGFR. Model 2 (cardiovascular hospitalisation rate): age, gender, BMI, smoking, NYHA class, hemoglobin, NT-proBNP, EF
Hascoet *et al*[14], 2013	France	Prospective	Stable CAD	715	60.2 ± 8	8.1	715 (100)	44.60%	64.90%	24.8%	N/A	N/A	82.50%	9.1 μg/mL	ACM adjusted OR/HR = 1.71 (1.16-2.52)	Diabetes mellitus, dyslipidaemia, and hypertension, systolic blood pressure, resting heart rate, tobacco consumption, hsCRP, HDL cholesterol, lipoprotein (a), ankle-arm index, and physical activity
Beatty *et al*[13], 2012	United States	Prospective	Stable ischemic heart disease	981	64 ± 10.5, 64.9 ± 10.2, 67.6 ± 10.9, 70.5 ± 11.2	7.1	800 (81.5)	691	N/A	259	N/A	N/A	N/A	Lowest detectable: 145.4 pg/mL. Median: 21.3 μg/mL	ACM adjusted OR/HR = 1.77 (1.12-2.67)	Model 1 adjusts for Demographics (age, sex, race). Model 2 adjusts for model 1 + clinical risk factors (diabetes, eGFR,

															beta-blocker, aspirin, statin). Model 3 adjusts for model 2 + metabolic markers (BMI, hemoglobin A1c, insulin, glucose, non-HDL cholesterol, HDL, triglycerides). Model 4 adjusts for model 3 + measures of baseline cardiac disease severity (left ventricle ejection fraction, diastolic dysfunction, inducible ischemia, log CRP, log NT-proBNP)
Schnabel *et al*[17], 2008	Germany	Prospective	Total: 1890; stable CAD: 1130; ACS: 760	1130	63	2.5	906 (80.2)	896	Total cholesterol: 194; HDL: 48; low density lipoprotein: 121; triglycerides: 129	DM: None or diet: 929; oral: 103; insulin: 98	N/A	N/A	No: 413; past: 523; present: 194	Not mentioned but concentrations were similar in patients presenting with SAP [9.03 μg/mL (6.7-13.45 μg/mL)] or ACS [(9.19 μg/mL (6.72-13.15 μg/mL)]	MACE adjusted OR/HR = 1.04 (1.008-1.062)	Model 1, univariate analysis. Model 2 is adjusted for age, sex, BMI, hypertension, diabetes mellitus, smoking, status, HDL cholesterol family history, ACS (only for total population). Model 3 is adjusted for age, sex, BMI, hypertension, diabetes mellitus, smoking, status, family history, ACS, statins, and beta blocker. Model 4 is adjusted for age, sex, BMI, hypertension, diabetes mellitus, smoking, status, family history, statins and beta blocker, BNP, and CRP

ACM: All cause mortality; ACS: Acute coronary syndrome; BMI: Body mass index; CAD: Coronary artery disease; CRP: C-reactive protein; DM: Diabetes mellitus; EF: Ejection fraction; EGFR: Estimated glomerular filtration rate; HDL: High density lipoprotein; HR: Hazard ratio; NT-proBNP: N-terminal pro B-type Natriuretic Peptide; NYHA: New York Heart Association; IQR: Interquartile range; MACE: Major adverse cardiovascular events; N/A: Not available; OR: Odds ratio; SAP: Stable angina pectoris.

The combined ORs for all-cause mortality and adverse CV events were determined based on data from five studies involving 3225 patients who were followed up for an average of 3.8 years. The study participants had risk factors such as hypertension, diabetes, hyperlipidemia, and smoking, while prescribed medications included angiotensin-converting enzyme inhibitors, beta blockers, and statins.

Adiponectin, first identified by Scherer P in 1995, is a hormone released by adipocytes. It exists in three oligomeric multimers in the body: (1) A low-molecular-weight trimer; (2) A medium-molecular-weight hexamer; and (3) A high-molecular-weight multimer. The high-molecular-weight form is the active form that exerts its effects on multiple organs.

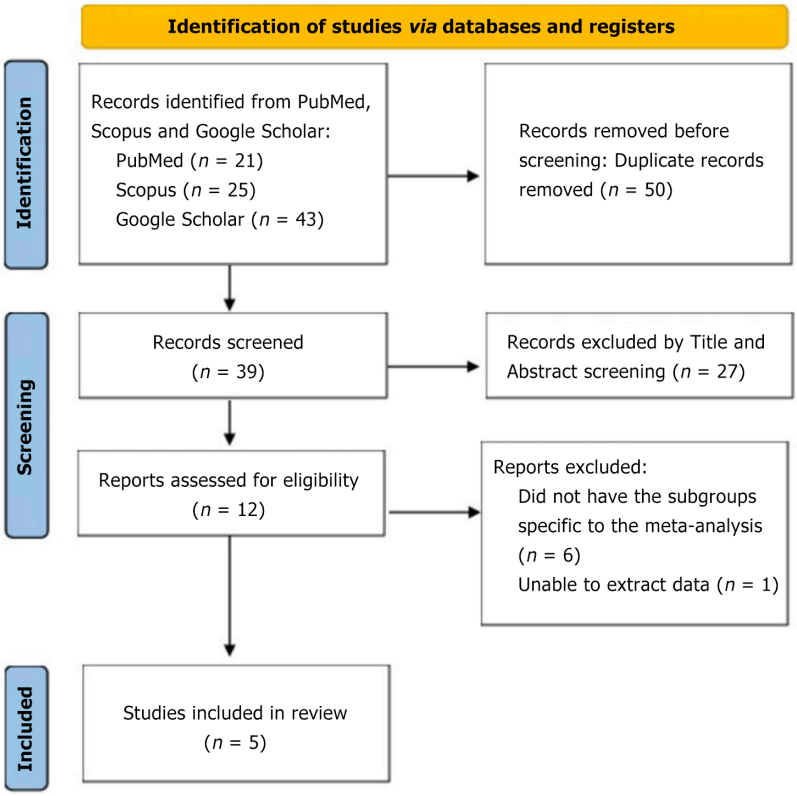

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta Analyses flow diagram for study population selection.

Adiponectin levels are inversely related to body fat content. While numerous studies have reported an association between low adiponectin levels and CV outcomes, our meta-analysis revealed a significant association between higher levels of adiponectin and the long-term MACE of CV origin. The discrepancy in the results can be explained by a requirement of intricate balance on the level of maintaining an equilibrium between body metabolism and excess active hormones. There is a similar adipokine, leptin, a nonglycosylated protein that plays a key role in maintaining the harmony of fat metabolism and working anti-synergistically with adiponectin.

In a post-hoc analysis of ATTEMPT-CVD by Kim-Mitsuyama *et al*[18], high total adiponectin levels were identified as an independent marker of CV and renal outcomes in hypertensive patients. A total of 1228 patients were enrolled, and subgroups were stratified into four quartiles based on total adiponectin levels. Patients with higher adiponectin levels exhibited a higher incidence of renal and CV events, with a statistically significant *P* value of 0.0135. Similarly, Beatty *et al* [13] followed 981 patients with existing ischemic heart disease for 7.1 years and observed an increased incidence of heart failure hospitalization (23%) and mortality (49%), but a lower incidence of myocardial infarction (12%), resulting in a combined CV event rate of 56% in groups with higher adiponectin levels. Another study by Cavusoglu *et al*[19] enrolled 324 patients, showing a higher incidence of CV and all-cause mortality in patients with higher adiponectin levels and existing CV risk factors.

According to a prior review, individuals with CVD who have higher levels of adiponectin in their plasma are at an increased risk of mortality. Additionally, another study found that patients with myocardial ischemia who had elevated levels of plasma adiponectin during their hospital discharge had a higher likelihood of all-cause mortality, after more than a decade of follow up period[14,16]. The results of our analysis align, with studies that suggest adiponectin could be a useful biomarker for evaluating CV risk[20,21]. However, there are some complexities in the field of adiponectin research, with studies indicating a protective role against CV events.

Prior reports also indicated that adiponectin possesses anti-inflammatory properties and metabolic benefits that could contribute to its protective role against CV disease. It may modulate insulin resistance, dyslipidemia, and non-alcoholic fatty liver disease[1,22]. Moreover, the impact of adiponectin on metabolic issues and its connection with controls who have the obesity level offer valuable understanding into its complex function among patients with CAD[1]. The intricate nature of adiponectin's significance calls for investigations that take into account factors like gender-specific effects and correlations with particular CV results[23]. These conflicting findings may arise from differences in study design, patient groups, or testing methods. Our meta-analysis contributes by bringing together evidence from studies, enhancing our conclusions' reliability and applicability[24].

While our meta-analysis highlights the potential of adiponectin as a predictor of risk, it's important to recognize the gaps in our understanding. We still have limited knowledge about how exactly adiponectin influences the progression of CAD. The intriguing paradox surrounding the role of adiponectin in cardiometabolic health has triggered discussions, opening up fascinating avenues for future research. While initial preclinical studies indicate that adiponectin has effects on various aspects such as glucose regulation, inflammation, cell death, oxidative stress, and atherosclerosis, recent comprehensive human studies have presented a challenge to this traditional view. Surprisingly, these studies propose

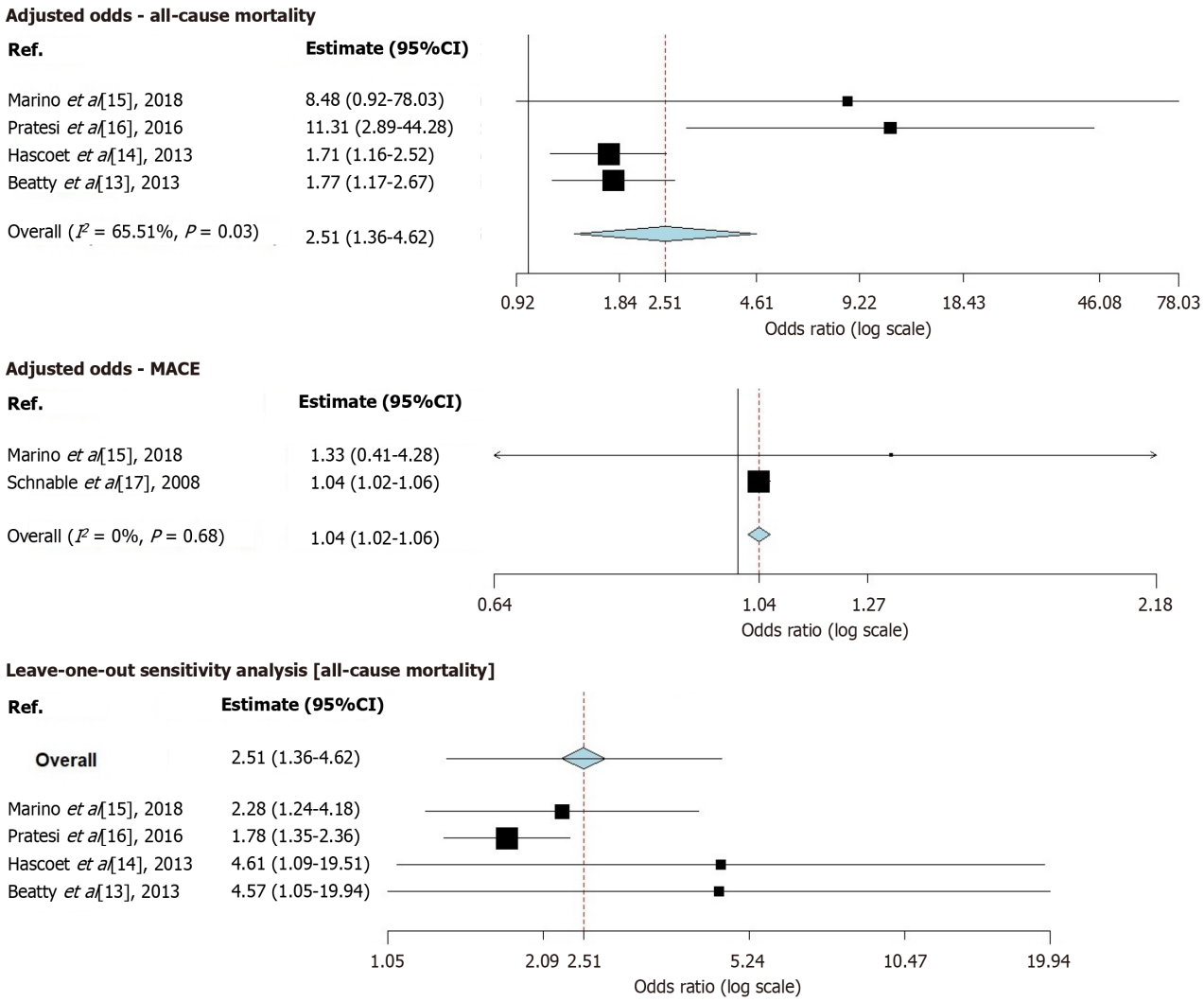

Figure 2 Role of Adiponectin in predicting long-term mortality and major adverse cardiovascular events in patients with stable coronary artery disease: A meta-analysis of prospective studies. MACE: Major adverse cardiovascular events.

that adiponectin might primarily serve as a marker for insulin sensitivity and glucose regulation rather than directly influencing the risk of developing type 2 diabetes and CV disease[25].

Adiponectin is emerging as a powerful multidimensional biomarker for mortality risk prediction, particularly in individuals with cardiometabolic comorbidities. Unlike conventional markers such as N-terminal pro B-type Natriuretic Peptide (NT-proBNP), which reflects hemodynamic stress, or troponins, which signal acute myocardial injury, adiponectin captures a broader pathophysiological profile, including metabolic dysfunction, endothelial stress, and chronic inflammation[1,26]. This unique biological footprint enables identification of high-risk phenotypes often missed by cardiac-specific markers, especially in patients with diabetes, obesity, or subclinical vascular disease. Its inverse relationship with insulin resistance, atherogenesis, and systemic inflammation further positions it as a valuable tool for early prognostication and long-term risk stratification, even among asymptomatic individuals. Several studies have demonstrated its predictive value for CV and all-cause mortality, independent of traditional risk factors[27,28]. However, the standalone clinical utility of this method is restricted by a variety of challenges, such as the lack of standardized thresholds, assay heterogeneity, and paradoxically elevated levels in chronic illness and frailty. Consequently, adiponectin could prove to be particularly valuable when utilized in conjunction with NT-proBNP or troponins, providing enhanced understanding of residual CV risk. Furthermore, investigating cost-effective biomarkers in conjunction with adiponectin could enhance risk stratification and inform tailored treatment strategies. With the increasing emphasis on residual risk in contemporary cardiology, adiponectin emerges as a significant factor due to its comprehensive potential. Comprehensive large-scale studies are crucial for standardizing its measurement and confirming its additional predictive value across various populations for long-term follow-ups.

The robustness and credibility of our findings, corroborated by sensitivity analysis, bolster the notion that assessing adiponectin levels may yield valuable insights into long-term mortality and MACE risk prediction. Incorporating adiponectin measurements into risk assessment models may improve their precision, aiding clinicians in identifying patients who would benefit from enhanced interventions and more rigorous monitoring. Irrespective of the outcomes, it is crucial to acknowledge that this meta-analysis possesses certain limitations. The quantity of studies and patients incorporated in our research may limit the applicability of our findings to a broader population. The discrepancies in

characteristics and methodologies among studies may explain the variations in overall mortality outcomes. To substantiate our conclusions, it is imperative to conduct prospective randomized studies.

CONCLUSION

Based on our meta-analysis, we have discovered a link between rising adiponectin levels and higher risks of long-term mortality and MACE among stable CAD patients. These findings highlight the potential role of adiponectin as a cost-effective biomarker, supporting its integration into risk assessment and management strategies. It is crucial to investigate further the mechanisms by which adiponectin affects CAD pathophysiology, as it holds promise in shaping CV care. In conjunction with our study into the role of adiponectin, we underscore the significance of examining additional cost-effective biomarkers to augment risk assessment and enhance patient management.

FOOTNOTES

Author contributions: Jitta SR, Vatsavayi P, Tera CR, Krishnamurthy S, Adla Jala SR, Pasnoor DS, Dasari U, Farooq A, Maramreddy S, Jammula K, Kesani MR, and Tripuraneni S were responsible for writing original draft, writing review, editing, data curation, and visualization; Jena N, Desai R were responsible for conceptualization, methodology, software, formal analysis, resources, data curation, writing original draft, writing review, editing, project administration, and supervision; all of the authors read and approved the final version of the manuscript to be published.

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CASE REPORT

RAF1 mutation expands the cardiac phenotypic spectrum of Noonan syndrome: A case report

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Abstract

BACKGROUND

Noonan syndrome is a relatively common autosomal dominant genetic disorder characterized by cardiovascular defects owing to functional abnormalities in key genes such as *RAF1*. Mutations in *RAF1* are typically associated with hypertrophic cardiomyopathy (HCM). However, in this case, the patient exhibited atrial and ventricular septal defects (VSDs).

CASE SUMMARY

This case report describes an 11-year-old boy diagnosed with Noonan syndrome, in whom genetic testing revealed a c.770C>T (p.Ser257 Leu) mutation in *RAF1*. The patient presented with intermittent chest discomfort and shortness of breath, symptoms that significantly worsened after physical activity. Clinical evaluation revealed marked growth retardation and multiple physical abnormalities. Electrocardiographic and echocardiographic assessments revealed VSDs, atrial septal defects, and left ventricular outflow tract obstruction. Following multidisciplinary consultation, the patient underwent cardiac surgical intervention, which led to clinical improvement; however, they subsequently developed a third-degree atrioventricular block, necessitating the implantation of a permanent pacemaker. During follow-up, echocardiographic findings demonstrated near-complete resolution of the shunt across the atrial and ventricular septa, significant improvement in left ventricular outflow tract obstruction, and notable reduction in ventricular

septal thickness. A genetic mutation at the c.770C>T (p.Ser257 Leu) locus of *RAF1* is typically associated with HCM and pulmonary hypertension. However, this patient's clinical phenotype manifested as HCM, atrial septal defect, and VSD, suggesting that this mutation may involve a different pathophysiological mechanism.

CONCLUSION

This case confirms the genotype-phenotype heterogeneity of Noonan syndrome and highlights the complex management requirements of *RAF1* mutation-associated cardiac pathologies. Early surgical intervention can ameliorate structural defects, but it must be integrated with genetic counseling and lifelong monitoring to optimize patient outcomes.

Key Words: Noonan syndrome; *RAF1* gene mutation; Hypertrophic cardiomyopathy; Atrial septal defect; Ventricular septal defect; Case report

Core Tip: This case report elucidates the unique clinical heterogeneity of the *RAF1* c.770C>T (p.Ser257 Leu) mutation in Noonan syndrome. While this variant is classically associated with severe hypertrophic cardiomyopathy and pulmonary hypertension, our patient exhibited atypical congenital heart defects - including atrial septal defect and ventricular septal defect - coexisting with hypertrophic cardiomyopathy, suggesting potential dysregulation of alternative molecular pathways in cardiac morphogenesis. Notably, this case expands the phenotypic spectrum of *RAF1* mutations, underscoring the necessity for comprehensive genetic counseling even in carriers of "classic" mutations, as genotype-phenotype correlations remain incompletely defined. Mechanistically, we propose that this mutation disrupts RAF1 protein-mediated mitogen-activated protein kinase signaling, thereby contributing to aberrant cardiac developmental pathways.

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INTRODUCTION

Noonan syndrome is a relatively common autosomal dominant genetic disorder characterized by short stature, thoracic deformities, congenital heart disease, and distinctive facial features[1]. Common manifestations of Noonan syndrome are cardiovascular defects, including atrial septal defects (ASDs), ventricular septal defects (VSDs), and pulmonary stenosis. These cardiac defects are closely related to the genetic background of Noonan syndrome and functional abnormalities in key genes. Mutations in genes such as *PTPN11*, *KRAS*, *SOS1*, *RAF1*, *BRAF*, and *NRAS* have been associated with Noonan syndrome. Approximately 50%-60%, 20%, 5%-15%, and 2% of Noonan syndrome cases are linked to *PTPN11*, *SOS1*, *RAF1*, and *KRAS* mutations, respectively. Moreover, mutations in genes such as *SHOC2*, *BRAF*, *RIT1*, and *CBL* are rare. This case report presents a patient with Noonan syndrome caused by a mutation in *RAF1* [the child, owing to global developmental delay accompanied by a distinctive facial appearance, was clinically suspected to have a hereditary rare disease. On August 5, 2019, a peripheral blood sample (ethylenediaminetetraacetic acid anticoagulant tube) was collected and transported *via* cold chain to Beijing Maijino Medical Laboratory. The testing institution used the Illumina NovaSeq 6000 sequencing system to perform whole exome sequencing version 4 (MyGenostics CapV4 capture panel). The testing was completed through a standardized process, leading to the conclusion of a *RAF1* gene mutation, with the following details: Chromosome position: Chr3: 12645699; transcript exon: NM_002880: Exon7; nucleotide change: C.770C>T (p.S257 L); heterozygous status: Het; inheritance pattern: Autosomal dominant; disease/phenotype: 1. Noonan syndrome type 5, 2. Multiple lentigines syndrome type[2,3]. Dilated cardiomyopathy type 1NN. The *RAF1* variant was validated by segrega-tion analysis in family members, and the results showed that neither parent carried the variant, indicating that the variant in the child was of spontaneous origin]. However, in this case of *RAF1* mutation, the phenotype included hypertrophic cardiomyopathy (HCM) [left ventricular outflow tract (LVOT) obstruction], VSD (membranous type), and ASD type II (central type). However, no study has reported VSD and ASD in this context; notably, the patient did present pulmonary arterial hypertension (PAH).

CASE PRESENTATION

Chief complaints

An 11-year-old boy presented with intermittent chest tightness and shortness of breath.

History of present illness
The symptoms had persisted for 4 years and were exacerbated by physical exertion and alleviated during rest.

History of past illness
The patient had previously received treatment at a hospital in Beijing, where genetic testing revealed a *RAF1* mutation [chromosomal location: Chr3: 12645699; transcript exon: NM_002880.3: Exon 7; nucleotide and amino acid change: C.770C>T (p.Ser257 Leu)]. The patient's family was advised to consider septal defect repair (ventricular and atrial) and LVOT resection. However, the patient's family opted for surgery and the patient was discharged. Over the following 4 years, the patient's chest tightness and shortness of breath gradually worsened to a point where even mild physical activity could trigger symptoms.

Personal and family history
The patient was born at full term *via* vaginal delivery but had a low Apgar score (exact value unknown) and experienced perinatal hypoxia. Since infancy, their food intake had been minimal, and complementary foods were introduced at 9 months. Their motor development was delayed, with no signs of rolling, crawling, or sitting during infancy. They began teething at 7 months and walking at 13 months, with an overall developmental delay compared to peers. Their intellectual abilities were average, and, at the time of this report, they were in the 5th grade of primary school with average academic performance. They presented with amblyopia, and school vision tests revealed bilateral visual acuity of 0.4, while hearing was within normal limits. The patient had a history of cryptorchidism.

Physical examination
The patient's body temperature was 36.5 °C, pulse was 95 beats per minute, respiratory rate was 21 breaths per minute, and blood pressure was 87/54 mmHg. The patient had a height of 127 cm (< P3) and weight of 26 kg (< P3). Their father's height was 173 cm, their mother's height was 168 cm, and their older brother, aged 21 years, was 182 cm tall with normal growth and development. The patient had short stature, and their facial features included a prominent forehead, low posterior hairline, widened interocular distance, ptosis, broad nasal tip, low nasal bridge, thick auricles, low-set and posteriorly rotated ears, thick lips, misaligned teeth, missing teeth, protruding jaw, and short neck. A café-au-lait spot measuring approximately 2 mm × 4 mm was observed in the middle of their chest with scattered pigmented nevi across their body. Their lung sounds were clear bilaterally, with no dry or wet rales. Their cardiac rhythm was regular, with a 4/6 systolic murmur auscultated over all valve areas. Muscle strength in all four limbs was normal, and there was no edema in their lower extremities. The patient's penis was approximately 4 cm long, and their testicular volume was approximately 2.5 mL.

Laboratory examinations
Laboratory examinations are shown in Table 1.

Imaging examinations
The following tests were performed on the patient echocardiography, cardiac magnetic resonance imaging, computed tomography angiography of thoracic great vessels, chest X-ray and electrocardiogram.

FINAL DIAGNOSIS
Patient was diagnosed with Noonan syndrome; ASD; VSD; ventricular septal hypertrophy; hypertrophic obstructive cardiomyopathy; post ASD repair; post VSD repair; residual stenosis after LVOT relief; third-degree atrioventricular block; sinus tachycardia; pacemaker implantation; atrial premature contraction; thyroid nodule; emphysema; and pulmonary artery dilation.

TREATMENT
After consultation with a multidisciplinary team, it was unanimously recommended that the patient undergo cardiac surgery under general anesthesia, including ASD repair, VSD repair, and LVOT resection. Subsequently, the patient was transferred to the Department of Cardiovascular Surgery. Postoperative echocardiography showed that the shunts across the atrial and ventricular septa had almost disappeared; however, left ventricular wall thickening, LVOT obstruction, and reduced left ventricular diastolic function were observed. Specific measurements indicated that the thickness of the interventricular septum in different regions was 10.7 mm, 11.9 mm, 10.6 mm, and 12.6 mm in areas I, II, III, and IV, while the left ventricular lateral wall was 10.6 mm thick. The patient's first postoperative electrocardiogram revealed third-degree atrioventricular block (Figure 1), with no clinical improvement (Figure 1B). Despite aggressive medical therapy, the patient's condition failed to improve, prompting the decision to implant a permanent pacemaker (Figure 1C). Compared with preoperative doppler echocardiography findings (Figure 2), postoperative evaluation demonstrated significant relief of LVOT obstruction, with near-complete closure of both the ASD and VSD (Figure 2E and F). Following intensive monitoring and treatment, the patient's condition gradually improved, and was ultimately discharged in stable condition.

Table 1 Laboratory examinations

Test date	Test item	Result	Reference range	Note
July 11, 2024	NT-proBNP (pg/mL)	2487	< 125	Pre-surgery
July 11, 2024	High-sensitivity troponin I (ng/mL)	0.001	< 0.0262	Pre-surgery
July 13, 2024	Growth hormone (ng/mL)	6.58	0.09-1.95	Pre-surgery
July 13, 2024	Insulin-like growth factor 1 (ng/mL)	147	50-286	Pre-surgery
July 24, 2024	NT-proBNP (pg/mL)	6396	< 125	Post-surgery
July 24, 2024	High-sensitivity troponin I (ng/mL)	15.79	< 0.0262	Post-surgery
July 24, 2024	Interleukin-6 (pg/mL)	37.73	< 7	Post-surgery
July 24, 2024	PCT (ng/mL)	0.961	< 0.065	Post-surgery

NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCT: Procalcitonin.

OUTCOME AND FOLLOW-UP

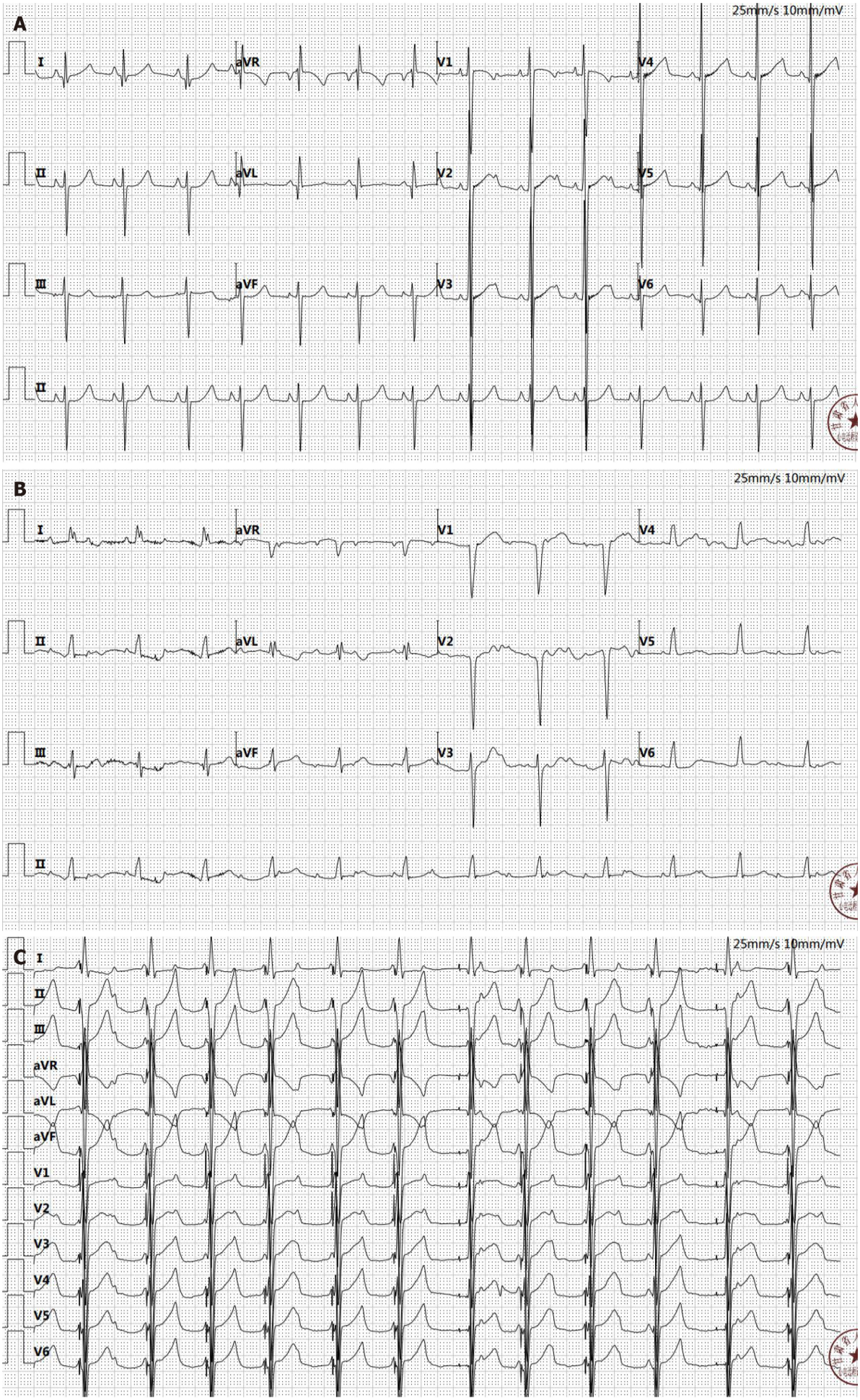
The patient visited our center in July 2023. As of the date of this response (March 2024), a total of 8 months have passed, during which four follow-up visits have been conducted.

Preoperative echocardiography indicated the following findings

Preoperative echocardiography (on July 11, 2024) indicated the following findings: (1) The interventricular septum and the thickness of the left ventricular posterior wall were increased, with the thickened interventricular septum protruding into the LVOT, resulting in LVOT obstruction. No abnormalities were observed in the left ventricular wall echo or motion amplitude; (2) The anterior and posterior leaflets of the mitral valve were elongated and thickened (notably at the leaflet tips), with the anterior leaflet tip showing malalignment. The systolic anterior motion (SAM) phenomenon was observed at the mitral valve anterior leaflet and chordae tendineae during systole, with adequate leaflet opening but poor closure. The tricuspid valve leaflets appeared thickened, with adequate leaflet opening but suboptimal closure; no significant abnormalities were noted in the remaining membrane morphology; (3) In the parasternal four-chamber view, the echo of the atrial septum was interrupted by approximately 3.8 mm, with a residual end of 13.5 mm on the atrioventricular valve side and a residual end of 21.9 mm (soft residual end) at the top of the atrium; in the short-axis view of the great arteries: The echo of the atrial septum was interrupted by approximately 4.1 mm, with no residual end on the aortic valve side, and a residual end of 19.5 mm (soft residual end) on the opposite side of the aorta; in the subxiphoid two-chamber view, the echo of the atrial septum was interrupted by approximately 4.2 mm, with a residual end of 17.6 mm on the superior vena cava side and 24.0 mm on the inferior vena cava side, with a total length of the atrial septum of 41.5 mm. The echo of the membranous part of the interventricular septum was interrupted, with a left ventricular base of 9.5 mm, and the membranous part of the interventricular septum adhered to the tricuspid valve septal leaflet and chordae tendineae, presenting a tumor-like bulge, approximately 9.5 mm × 5.9 mm in size, with a rupture extending approximately 7 mm. There was almost no residual end at the defect site near the aortic valve, about 5.7 mm from the tricuspid septal leaflet. The aorta arose from the left ventricle; the pulmonary artery arose from the right ventricle; no abnormal channels were observed in the great vessels; and (4) There was a left-to-right shunt at the atrial level and a left-to-right shunt at the ventricular level, with velocity maximum (Vmax) = 4.4 m/second and peak gradient maximum (PGmax) = 77 mmHg, estimating the pulmonary artery systolic pressure within the normal range; under resting conditions, the forward blood flow velocity in the LVOT was significantly increased: Vmax = 4.7 m/second, PGmax = 89 mmHg; there was a small amount of regurgitation at the mitral valve; a small amount of regurgitation at the tricuspid valve, with Vmax = 3.2 m/second and PGmax = 40 mmHg.

The first postoperative echocardiography indicated the following findings

The first postoperative echocardiography (on July 30, 2024) indicated the following findings: (1) Left atrial enlargement; (2) Increased thickness of the interventricular septum and left ventricular posterior wall: The thickened interventricular septum protruded into the LVOT, causing LVOT obstruction. The maximum thickness measurements of the interventricular septum were as follows: Zone I: 10.7 mm; zone II: 11.9 mm; zone III: 10.6 mm; zone IV: 12.6 mm; and left ventricular lateral wall: 10.6 mm; (3) "SAM" phenomenon: The anterior leaflet of the mitral valve and its subvalvular apparatus exhibited SAM during systole. While leaflet opening was adequate, poor closure was noted, likely due to altered tension in the chordae tendineae. No significant abnormalities were observed in the remaining valve morphology; (4) Residual shunt: An echo of the patch used for atrial septal repair was observed, with a residual shunt approximately 1.2 mm wide on the inferior side of the patch. An echo of the patch was also noted on the interventricular septum, with no significant gaps around it; and (5) Atrial and ventricular shunts essentially disappeared; under resting conditions, the forward blood flow velocity in the LVOT was increased: Vmax = 3.8 m/second, PGmax = 57 mmHg. There was a small amount of regurgitation at the mitral valve; a small amount of regurgitation at the aortic valve; and a small amount of regurgitation at the tricuspid valve, with Vmax = 2.6 m/second and PGmax = 27 mmHg, estimating the pulmonary artery systolic


A
25mm/s 10mm/mV
I
aVR
V1
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II
aVL
V2
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III
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B
25mm/s 10mm/mV
I
aVR
V1
V4
II
aVL
V2
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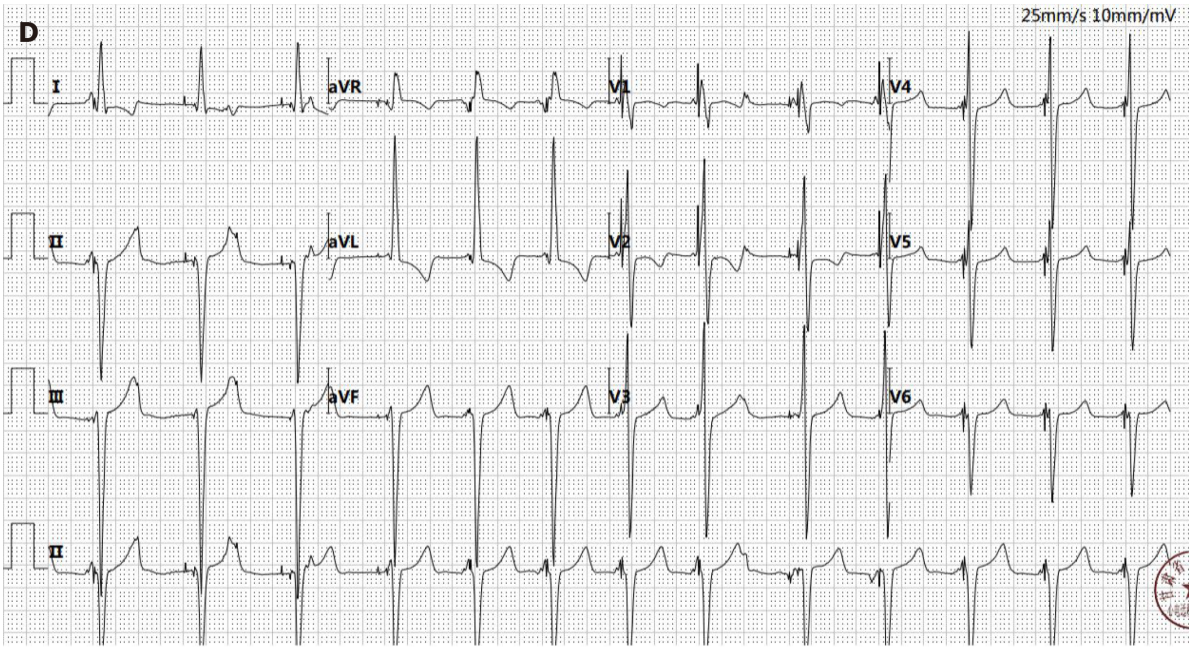

Figure 1 Sequential electrocardiogram changes in the clinical course: from admission to post-discharge follow up. A: The initial electrocardiogram (ECG) upon admission; B: Postoperative ECG on the first recording after surgical intervention; C: ECG post-permanent pacemaker implantation; D: ECG upon follow-up visit one month after hospital discharge.

pressure at 32 mmHg.

The second postoperative echocardiography indicated the following findings

The second postoperative echocardiography (on August 31, 2024) indicated the following findings: (1) Strong echo from the pacemaker electrode was visible in the right atrium and right ventricle, with left atrial enlargement; (2) Increased thickness of the interventricular septum and left ventricular posterior wall: The thickened interventricular septum protruded into the LVOT, causing LVOT obstruction. The maximum thickness measurements of the interventricular septum are as follows: Zone I: 10.7 mm; zone II: 11.9 mm; zone III: 10.6 mm; zone IV: 12.6 mm; and left ventricular lateral wall: 10.6 mm; (3) The SAM phenomenon was observed during systole at the mitral valve anterior leaflet and chordae tendineae, with adequate leaflet opening but poor closure; (4) An echo of the patch used for atrial septal repair was observed, with a residual shunt approximately 0.8 mm wide on the inferior side of the patch. An echo of the patch was also noted on the interventricular septum, with no significant gaps around it; and (5) Atrial and ventricular shunts essentially disappeared; under resting conditions, the forward blood flow velocity in the LVOT was increased: Vmax = 3.4 m/second, PGmax = 47 mmHg. There was a small amount of regurgitation at the mitral valve; a minimal amount of regurgitation at the aortic valve; and a small amount of regurgitation at the tricuspid valve, with Vmax = 2.0 m/second and PGmax = 17 mmHg, estimating the pulmonary artery systolic pressure at 22 mmHg.

The third postoperative echocardiography indicated the following findings

The third postoperative echocardiography (on September 11, 2024) indicated the following findings: (1) Strong echo from the pacemaker electrode was visible in the right atrium and right ventricle, with left atrial enlargement; (2) Increased thickness of the interventricular septum and left ventricular posterior wall: The thickened interventricular septum protruded into the LVOT, causing LVOT obstruction. The maximum thickness measurements of the interventricular septum were as follows: Zone I: 10.7 mm; zone II: 11.9 mm; zone III: 10.6 mm; zone IV: 12.6 mm; and left ventricular lateral wall: 10.6 mm; (3) The SAM phenomenon was observed during systole at the mitral valve anterior leaflet and chordae tendineae, with adequate leaflet opening but poor closure; (4) An echo of the patch used for atrial septal repair was observed, with a residual shunt approximately 0.8 mm wide on the inferior side of the patch. An echo of the patch was also noted on the interventricular septum, with no significant gaps around it; and (5) Atrial and ventricular shunts essentially disappeared; under resting conditions, the forward blood flow velocity in the LVOT was increased: Vmax = 3.4 m/second, PGmax = 45 mmHg. There was a small amount of regurgitation at the mitral valve; a minimal amount of regurgitation at the aortic valve; and a small amount of regurgitation at the tricuspid valve, with Vmax = 2.0 m/second and PGmax = 17 mmHg, estimating the pulmonary artery systolic pressure at 22 mmHg.

The fourth postoperative echocardiography indicated the following findings

The fourth postoperative echocardiography (on February 12, 2025) indicated the following findings: (1) Strong echo from the pacemaker electrode was visible in the right atrium and right ventricle, with left atrial enlargement; (2) Increased thickness of the interventricular septum and left ventricular posterior wall: The thickened interventricular septum protruded into the LVOT, causing LVOT obstruction. The maximum thickness measurements of the interventricular

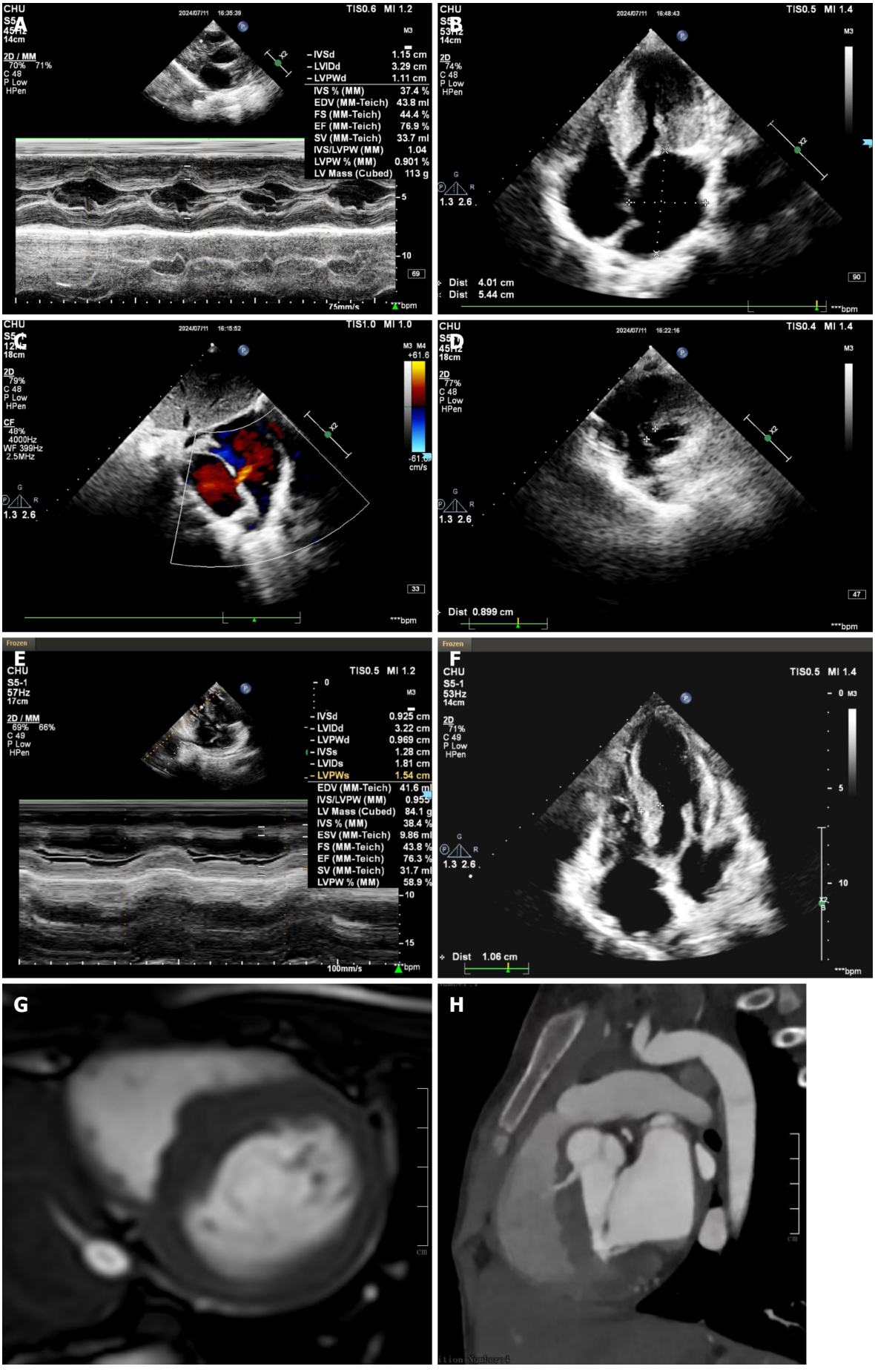

Figure 2 Echocardiographic and cardiac magnetic resonance imaging findings: from pre-operative diagnosis to post-discharge

resolution in cardiac pathology. A: Preoperative echocardiogram indicates significant left ventricular wall thickening; B: Echocardiogram showing dilation left atrium left ventricular outflow tract obstruction; C: Echocardiogram: Atrial septal echo dropout with left-to-right shunt at the atrial level; D: Echocardiogram: Membranous part of the interventricular septum echo dropout measuring 89 mm; E: One month post-discharge, the echocardiogram reveals a septal thickness of 0.925 cm at end-diastole; F: Interventricular septum after alleviation of the obstruction; G: Short-axis cine end-diastolic frame of the heart; H: Cardiac magnetic resonance imaging showing hypertrophied interventricular septum and ventricular septal defect.

septum were as follows: Zone I: 9.1 mm; zone II: 11.5 mm; zone III: 11.7 mm; zone IV: 12.3 mm; (3) The anterior and posterior leaflets of the mitral valve were elongated and relaxed, adhering to the interventricular septum during systole, causing malalignment of the anterior leaflet. The "SAM" phenomenon was visible during systole, with adequate leaflet opening but poor closure; (4) An echo of the patch used for atrial septal repair was observed, and an echo of the patch was also noted on the interventricular septum, with no significant gaps around it; (5) Atrial and ventricular shunts disappeared; under resting conditions, the forward blood flow velocity in the LVOT was normal: Vmax = 1.8 m/second, PGmax = 13 mmHg. During the Valsalva maneuver, the forward blood flow velocity in the LVOT increased: Vmax = 2.7 m/second, PGmax = 29 mmHg. There was a small amount of regurgitation at the mitral valve; a minimal amount of regurgitation at the aortic valve; and a small amount of regurgitation at the tricuspid valve, with Vmax = 2.2 m/second and PGmax = 20 mmHg, estimating the pulmonary artery pressure at 25 mmHg; and (6) The child's height was 130 cm, weight was 27 kg, and body surface area was 0.99 m^2.

Based on the results of the four echocardiograms, the highest pulmonary artery pressure was 32 mmHg, and the maximum forward blood flow velocity in the LVOT has been progressively decreasing under resting conditions, along with a decrease in pressure (Table 2). The velocity and pressure of tricuspid regurgitation have significantly reduced compared to preoperative levels. The observable conclusion is that the child has shown good recovery after the interventricular septal repair surgery, with gradually decreasing flow velocity and pressure in the LVOT, as well as decreasing velocity and pressure of tricuspid regurgitation, and no recurrence has been detected postoperatively (Table 3).

DISCUSSION

The diagnosis of Noonan syndrome relies on clinical features and genetic testing results. During the initial screening phase, physicians primarily suspect the syndrome based on distinctive facial features, growth retardation, developmental abnormalities, and physical examination findings. Further diagnostic evaluation can be performed using echocardiography to identify specific cardiac anomalies such as ASDs, VSDs, or pulmonary valve stenosis. These findings further strengthen the suspicion of Noonan syndrome. Finally, a diagnosis is confirmed using genetic testing.

In this case, the patient harbored an *RAF1* mutation. The *RAF1* gene is located on chromosome 3p25. Patients with Noonan syndrome carrying *RAF1* mutations typically exhibit a distinct set of phenotypic features, such as cardiovascular defects and growth retardation. These characteristics differ from the phenotypes caused by mutations in other genes, such as *PTPN11* or *KRAS*, leading to varying clinical manifestations.

The patient's preoperative electrocardiogram indicated sinus rhythm and left ventricular hypertrophy, with no third-degree atrioventricular block present. Previous case reports also did not show any instances of third-degree atrioventricular block. During the surgical procedure, the child developed third-degree atrioventricular block, and a temporary pacemaker was implanted. The heart rhythm was closely monitored for 5 days, and after the cardiac edema subsided, an assessment was made to determine whether the atrioventricular block had resolved or improved. No significant improvement was observed, leading to the decision to implant a permanent pacemaker. Therefore, this complication is considered to be caused by surgical trauma.

RAF1 variants are commonly associated with HCM and pulmonary hypertension. An observational retrospective analysis revealed that among children with NM_002880.4: C.770C>T and NP_002871.1: P.Ser257 Leu mutations, 92% were diagnosed with HCM, with most receiving a definitive diagnosis within the first year of life[2]. The study found that 30% of these patients were premature, and 47% of newborns required treatment in the neonatal intensive care unit for complications related to HCM or pulmonary hypertension, with a mortality rate of approximately 13%. This study indicated that patients with the pathogenic variant c.770C>T in the *RAF1* gene exhibited particularly severe phenotypes characterized by rapid progression of neonatal HCM and high mortality rates[2]. Further investigation of this mutation site revealed that the *RAF1* gene mutation (c.770C>T, p.Ser257 Leu) affects patients with Noonan syndrome through alterations in cardiac ultrastructure, abnormal calcium handling, and excessive activation of signaling pathways[3]. For instance, mutations at this site significantly affect cardiac function, leading to prominent ultrastructural defects in cardiomyocytes, particularly the shortening of the I-band. In addition, it is associated with cardiac calcium transients and reduced contractile tension. These changes may result in myocardial hypertrophy, decreased cardiac function, and heart failure in patients with Noonan syndrome. Our patient also exhibited HCM and declining cardiac function (preoperative NT-Pro-BNP 2487 pg/mL).

The *RAF1* mutation reported in this case (NM_002880.4: C.770C>T, p.Ser257 Leu) has also been reported in previous studies. Research has indicated that the most common pathogenic variant among *RAF1* mutations is c.770C>T, which accounts for approximately 37.5% of the patients with *RAF1* mutations[4]. The c.770C>T variant is typically associated with HCM and pulmonary hypertension[5]. However, in the present case, although HCM was present, pulmonary hypertension was not observed; instead, ASDs and VSDs were observed.

Table 2 Follow-up data on the child's left ventricular outflow tract, tricuspid valve flow velocity, and pressure

Date	Left ventricular outflow tract (resting state)	Vmax (m/second)	PGmax (mmHg)	Tricuspid regurgitation Vmax (m/second)	Tricuspid regurgitation PGmax (mmHg)	Pulmonary artery systolic pressure (mmHg)
July 11, 2024	Significantly increased	4.7	89	3.2	40	-
July 30, 2024	Increased	3.8	57	2.6	27	32
August 31, 2024	Increased	3.4	47	2.0	17	22
September 11, 2024	Increased	3.4	45	2.0	17	22
February 12, 2025	Normal	1.8	13	2.2	20	25

PGmax: Peak gradient maximum; Vmax: Velocity maximum.

Table 3 Analysis of the child's interventricular septal thickness

Date	Zone I (mm)	Zone II (mm)	Zone III (mm)	Zone IV (mm)
July 11, 2024	-	-	-	-
July 30, 2024	10.7	11.9	10.6	12.6
August 31, 2024	10.7	11.9	10.6	12.6
September 11, 2024	10.7	11.9	10.6	12.6
February 12, 2025	9.1	11.5	11.7	12.3

The RAF1: C.770C>T mutation is closely related to the mechanism of PAH through the excessive activation of the mitogen-activated protein kinase (MAPK) signaling pathway. This mutation is located in the conserved region of *RAF1* (Ser257 Leu) and significantly enhances *RAF1* kinase activity by relieving the self-inhibitory effect at the Ser259 phosphorylation site, leading to sustained activation of the MAPK/extracellular signal-regulated kinase signaling pathway[2]. This abnormal signaling induces myofibrillar disarray, sarcomere structural abnormalities, and HCM in cardiomyocytes, while in the pulmonary vascular system, it may lead to PAH through the following mechanisms: (1) Indirect effects of HCM: LVOT obstruction and mitral valve abnormalities caused by HCM can lead to increased left atrial pressure, which subsequently increases pulmonary artery pressure through retrograde transmission *via* the pulmonary veins[2]; (2) Direct pulmonary vascular remodeling mechanism: The excessive activation of the MAPK signaling pathway may directly promote the proliferation of pulmonary vascular smooth muscle cells and vascular remodeling. *RAF1* plays a critical role in vascular development, and its gain-of-function mutations may affect pulmonary vascular function through similar mechanisms[2]; and (3) Synergistic effects of hemodynamics and hypoxia: The reduction in cardiac output and left ventricular diastolic dysfunction caused by HCM can lead to pulmonary venous congestion and hypoxia, further stimulating pulmonary vascular contraction and remodeling. Studies have shown that 62% of death cases are directly related to cardiopulmonary complications associated with HCM, with an average age of death at only 7.5 months, highlighting the rapid progression of the pathological process[2].

In this case, the child's pulmonary artery pressure reached a maximum of 32 mmHg, which may be attributed to the presence of ASD and VSDs. In this context, the defects in the atrial and ventricular septa act as shunt valves, reducing pulmonary artery pressure. We aimed to identify the potential mechanisms by which the c.770C>T (p.Ser257 Leu) mutation causes ASDs and VSDs by analyzing and summarizing previous studies related to *RAF1*. Dysregulation of signal transduction caused by the c.770C > T (p.Ser257 Leu) mutation typically manifests as aberrant activation of the rat sarcoma viral oncogene homolog-mitogen-activated protein kinase (RAS)-MAPK signaling pathway, which is the core mechanism underlying the various symptoms in patients with Noonan syndrome[2]. This mutation generally acts as a positive regulator, enhancing signal transmission and subsequently influencing cell growth and differentiation.

The rapidly accelerated fibrosarcoma-mitogen-activated protein kinase kinase-extracellular signal-regulated kinase cascade within the RAS-MAPK signaling pathway is a core component of signal transduction and is involved in the regulation of cellular functions. *RAF1* plays a crucial role in the RAS-MAPK signaling pathway through mechanisms such as signal amplification, kinase activity, gene expression regulation, and feedback modulation. Overactivation of *RAF1* may lead to VSDs and myocardial hypertrophy. The patient presented with VSDs, ventricular septal hypertrophy, and LVOT obstruction.

CONCLUSION

The c.770C>T (p.Ser257 Leu) mutation in *RAF1* is associated with HCM and pulmonary hypertension. This case report describes an 11-year-old patient with Noonan syndrome whose genetic testing revealed chromosome position chr3: 12645699, transcript exon NM_002880, and the nucleotide change c.770C>T (p.Ser257 Leu). The patient's phenotypes included HCM, ASDs, and VSDs.

FOOTNOTES

Author contributions: Ma N performed patient management, manuscript writing and data collection; Li ZW performed clinical diagnosis and treatment planning; Liu JJ contributed to the manuscript with serial echocardiographic assessment; Liu XG contributed to the cardiac surgical intervention; Zhou X contributed to the radiological assessment; Wang BW performed permanent pacemaker implantation; Li YL performed pacemaker programming and follow-up; Zhang TC performed intraoperative electrophysiological monitoring; Xie P revised the manuscript and provided treatment instructions; and all authors thoroughly reviewed and endorsed the final manuscript.

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Informed consent statement: Written informed consent was obtained from the patient's parents (legal guardians) for the publication of this case report, including all clinical data and anonymized medical images. Patient identity was protected through strict de-identification measures in accordance with privacy protection standards.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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