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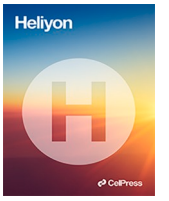

Review article

Current understanding of cardiovascular autonomic dysfunction in multiple sclerosis

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ABSTRACT

Autoimmune diseases, including multiple sclerosis (MS), are proven to increase the likelihood of developing cardiovascular disease (CVD) due to a robust systemic immune response and inflammation. MS can lead to cardiovascular abnormalities that are related to autonomic nervous system dysfunction by causing inflammatory lesions surrounding tracts of the autonomic nervous system in the brain and spinal cord. CVD in MS patients can affect an already damaged brain, thus worsening the disease course by causing brain atrophy and white matter disease. Currently, the true prevalence of cardiovascular dysfunction and associated death rates in patients with MS are mostly unknown and inconsistent. Treating vascular risk factors is recommended to improve the management of this disease. This review provides an updated summary of CVD prevalence in patients with MS, emphasizing the need for more preclinical studies using animal models to understand the pathogenesis of MS better. However, no distinct studies exist that explore the

Abbreviations: APC, antigen-presenting cells; Ach, acetylcholine; BBB, blood–brain barrier; CHT, choline transporter; CNS, central nervous system; CVD, cardiovascular diseases; CYP27B1, 25-hydroxyvitamin D-1 alpha hydroxylase; DAMP, damage-associated molecular patterns; DMT, disease-modifying therapies; EAE, experimental autoimmune encephalomyelitis; EBV, epstein Barr virus; EtBr, ethidium bromide; FDA, Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; GWAS, genome-wide association studies; HEM, Holter electrocardiography monitoring; HLA, human leukocyte antigen; IFN-γ, interferon-γ; IL-17, interleukin-17; IL2RA, interleukin-2 receptor alpha; IL7RA, interleukin-7 receptor alpha; LPC, lysophosphatidylcholine; LKB1, liver kinase B1; Ly6c, lymphocyte antigen six complexes; MS, multiple sclerosis; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MI, myocardial infraction; MIF, migration inhibitory factor; MOG, myelin oligodendrocyte glycoprotein; MSNA, muscle sympathetic nerve activity; MUGA, multigated acquisition scan; NSM, neurogenic myocardium; PLP, proteolipid protein; PRR, pattern recognition receptors; ROS, reactive oxygen species; SCH, spinal cord homogenate; S1P, sphingosine-1-phosphate; STK11, serine-threonine-kinase 11; Th, T helper; T reg, T regulatory; TMEV, Theiler's murine encephalomyelitis virus; TNF-α, tissue necrosis factor-α; TNFRSF1A, tumor necrosis factor receptor superfamily member1A.

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temporal effects and etiopathogenesis of immune/inflammatory cells on cardiac damage and dysfunction associated with MS, particularly in the cardiac myocardium. To this end, a thorough investigation into the clinical presentation and underlying mechanisms of CVD must be conducted in patients with MS and preclinical animal models. Additionally, clinicians should monitor for cardiovascular complications while prescribing medications to MS patients, as some MS drugs cause severe CVD.

1. Introduction

Multiple sclerosis (MS) is one of the most common inflammatory and neurodegenerative diseases in young adults aged between 20 and 45 years, particularly in European and North American populations, and leads to the development of neurological defects with irreversible disabilities [1–3]. The global prevalence of MS has increased from 2.3 million to 2.9 million in 2023, with a substantial increase in age-standardized prevalence in recent years, with a prevalence rate of 288/100,000 in the North American population (MSIF, [4]; https://www.msif.org/resource/atlas-of-ms-2023/). Nearly more than 1 million people are living with MS in the U.S. Reports suggest an increase in the global occurrence of this disease, which has strongly impacted the socioeconomic indicators of disease burden [3,5].

MS is generally accompanied by chronic inflammation, demyelination, activation of astrocytes and microglia, progressive destruction of oligodendrocytes, and axonal loss in the central nervous system (CNS), largely affecting motor, visual, cerebellar, autonomic, and sensory functions of the body [6]. The overall consequence of persistent inflammation is obliteration of the CNS, which includes myelin, neurons, axons, white matter, and blood vessels [7,8]. There are reports of an increasing incidence of MS globally, which has strongly impacted socioeconomic indicators of disease burden [9,10]. Furthermore, genetic and pathological studies have thoroughly proven the profound role of the immune system in disease pathogenesis, as it is a crucial part of the adaptive arm, comprised of T cells and B cells [11–13]. However, cells of the innate immune system, such as monocytes, neutrophils, macrophages, and microglia, also contribute to disease pathogenesis [14–17]. Based on the revised recommendations, a typical disease course includes a clinically isolated syndrome, relapse following remission, secondary-progressive, and primary-progressive disease. However, these phases are broadly categorized into relapsing and progressive phenotypes, which differ from each other based on disease activity [18]. Revelations of the immune mechanisms underlying MS development have come from different preclinical disease models, with major contributions coming from experimental autoimmune encephalomyelitis (EAE) commonly induced in rats and mice through various antigens [19].

The etiology of MS is convoluted since the exact trigger and mechanism of pathogenesis is vague [20]. Epidemiological studies have demonstrated the role of environmental, genetic, and epigenetic factors in disease pathogenesis [12] (Fig. 1). Some of the leading environmental factors include viral infections, such as Epstein–Barr virus (EBV) [21], cigarette smoking [21,22], adolescent obesity [23], and vitamin D deficiency [24]. Ongoing research has primarily focused on understanding the exact role of environmental factors that contribute to MS development. There are also convincing reports suggesting the role of genetic backgrounds towards MS predisposition in the form of congenital and somatic variations to significant candidate genes, such as human leukocyte antigen (HLA). These variants contribute to an increased disease risk, with HLA-DRB1 (HLA-DRB1*15:01 haplotype) showing a consistent association with MS across studies [25–28]. Furthermore, genetic studies have linked polymorphic variations in several non-HLA genes with

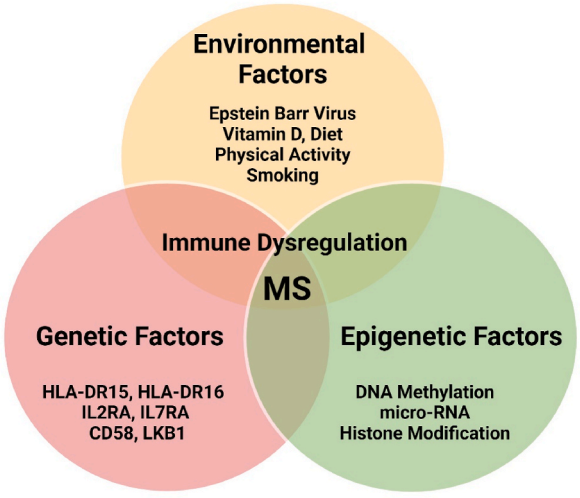

Fig. 1. Overview of multiple sclerosis (MS) etiology. The interplay between different components is involved in the etiopathogenesis of MS, with each factor modifying disease risk through a combination of genetic, environmental, and epigenetic factors (Created with BioRender.com).

disease susceptibility; these mainly include interleukin-2 receptor alpha (IL2RA) [29], tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) [30], 25-hydroxyvitamin D-1 alpha-hydroxylase (CYP27B1) [31], interleukin-7 receptor alpha (IL7RA) [32], and serine-threonine-kinase 11 (STK11), which encodes liver kinase B1 (LKB1) [33]; although these polymorphisms have a small effect individually. To date, genome-wide association studies (GWASs) and meta-analyses have recognized more than 200 loci that are positively correlated with MS risk [27,34]. Additionally, various epigenetic factors play essential roles in disease risk and impact the disease course [35]. However, the interacting mechanisms of various etiologic factors that ameliorate overall disease risk have not been fully elucidated.

Apart from etiologic influences on MS predisposition and pathogenesis, a plethora of epidemiologic and clinical studies have reported comorbid conditions in patients with MS and their grave clinical, health, and financial implications, which could directly impact disease burden and the quality of life [36–38]. In general, people with MS have a higher prevalence of conditions such as cardiovascular, respiratory, renal, sexual, diabetic neuropathy, autoimmune, seizure, gastrointestinal, and mood disorders ([39]; [40]; [38,38,38,38,38,41–43]). Chronic symptoms of these diseases can impact the quality of life and thereby influence overall disease management strategies [44–46].

2. Autonomic dysfunction and cardiovascular diseases in MS

Studies have suggested the impact of autonomic nervous system dysfunction on the immune system, which could influence MS pathogenesis, progression, and comorbid disease predisposition [47]. In some initial cases, spectral analysis of heart rate variability in MS patients has also revealed disturbances in parasympathetic and sympathetic pathways [48–50]. Autonomic dysfunction in MS has been associated with lesions in CNS areas that control autonomic regulation, such as the brainstem and spinal cord, which could directly affect the autonomic parameters and clinical outcomes of this disease [51,52]. Several reports have linked nervous system dysfunction with disease status and fatigue in patients with MS. However, during acute exacerbations, only parasympathetic dysfunction tends to increase in parallel with deterioration and disease severity [53–55]. The primary function of the autonomic nervous system is to maintain homeostasis between different physiologic parameters, such as heart rate, blood pressure, heart rhythm, systolic function, respiration, bladder, and bowel control [56]. As such, autonomic dysfunction can cause dysregulation of the autonomic pathways related to vital physiologies of the body, thereby disturbing normal homeostasis and leading to cardiovascular abnormalities associated with cardiovascular disease (CVD) in patients with MS [36,57–60].

CVD represents a group of several diseases: ischemic heart disease, myocardial infarction (MI), angina, and sudden cardiac death. There is a higher risk of ischemic heart disease in people with chronic immune-mediated diseases, suggesting the role of inflammation in regulating atherosclerotic plaques and associated thrombotic disturbances [61]. Sympathetic cardiovascular autonomic dysfunction is common in MS, in addition to sudomotor and parasympathetic impairment [62]. It is unclear how prolonged pathophysiological inflammation, brainstem lesions, the spinal cord, and immobility from disability during the progressive disease stage increase the prevalence of CVD in patients suffering from MS [59,63]. There are certain limitations to understanding the true disease burden in patients with MS, contributing to a lack of prevalence data distributed by demographic features, including age, sex, ethnicity, immigration status, and disease duration. Epidemiological studies are vital to public health research and contribute to improving the clinical management of this disease, as well as investigations into the underlying disease etiology. In this review, we present a detailed account of CVD in patients with MS, the potential of future studies using MS animal models and surveillance, as well as therapeutic strategies that could be employed to alleviate cardiovascular dysfunction. This approach could provide a rationale for comprehensive research that investigates the pathogenic role of the underlying derailed immune system as a contributor to CVD in MS patients.

The underlying mechanisms of cardiovascular dysfunction have not been entirely elucidated, as only hypothetical explanations are available, rather than experimental outcomes based on epidemiological studies. A few reports are suggesting that impaired carotid baroreceptor blood pressure control (baroreflex dysfunction) is responsible for orthostasis-related symptoms and abnormal sympathetic modulation of blood vessels in patients with MS [50,64]. Another study reported reduced muscle sympathetic nerve activity (MSNA) in patients with MS, contributing to autonomic cardiovascular dysfunction [65]. Preliminary findings from the most recent study published by the European Society of Cardiology Congress in 2019, and the World Congress of Cardiology, reported a high incidence of neurogenic stunned myocardium (NSM) in patients with MS [66]. This was attributed to demyelinating plaques in the lateral horn of the lower cervical (C5-7) and upper thoracic regions (Th1-4). These plaques are associated with clinical manifestations of autonomic dysfunction and spinal cord injuries in these locations due to a loss of supraspinal control of the sympathetic nervous system, resulting in unopposed parasympathetic activity. The peculiar location of plaques appears to correlate with abnormalities in the autonomic nervous system and may be used to identify patients at greater risk of developing NSM. This could also be used to assess cardiovascular abnormalities in patients with MS. These findings are supported by Palladino et al., reporting a higher risk of death caused by CVD in patients with MS, with a 1.5-2-fold greater mortality rate than those without MS (Palladino et al., 2020; Palladino et al., 2023). Additional studies show that the risk of MI is 2.5 times greater in female patients with MS than in male patients [41]. These findings reflect the need for timely monitoring of cardiovascular risk factors in patients with MS. A recent systematic review and meta-analysis of observational studies strongly recommended monitoring for myocardial infarction and heart failure in patients with MS during follow-up examinations [67].

There are fewer reports on the association of vascular risk factors and brain loss volume in MS. Marrie et al. revealed that higher Framingham risk scores are associated with lower brain volume, or greater loss of brain volume, as MS progresses, which suggests effective management of comorbidities related to vascular risk in people affected with MS (Marrie et al., 2021). Furthermore, a recent study by Yang et al. provided genetic evidence for causal associations between MS and an increased risk of cardiovascular abnormalities, including coronary artery disease, myocardial infarction, heart failure, and ischemic stroke, through a GWAS involving

115,803 individuals. These findings highlight the significance of active monitoring for cardiovascular risk factors to combat cardiovascular comorbidities in patients with MS [68]. Similarly, another study concluded that patients with a controlled MS disease course have a greater risk of CVD than non-MS controls, emphasizing the use of CVD risk indexes to monitor and manage CVD risk in these patients (Albuquerque et al., 2021). Interestingly, a recent report shows an association between uncomplicated myocarditis development and COVID-19 vaccines in both healthy individuals and MS patients with a prior diagnosis of myocarditis [69]. However, there has been little attention on the prevalence of cardiovascular disorders in MS, prompting in-depth epidemiological, preclinical, and clinical studies [70].

Whether cardiovascular dysfunction is the cause or consequence of MS-related lesions in the CNS is unknown. Although there is substantial evidence confirming a higher prevalence of CVD in MS patients, standardized methods for continuous monitoring of cardiovascular abnormalities in such patients are lacking. Additionally, there are potentially confounding effects of various medications on MS incidence. Furthermore, the limited number of observational studies on human subjects prevents the ability to reach definitive conclusions. MS may have unpredictable variable disease courses and human-study-associated ethical concerns. All of these factors make *in vivo* preclinical animal models the best option for understanding the "chicken-or-egg" relationship between cardiovascular dysfunction and MS. Animal models have been instrumental in investigations into disease mechanisms, including inflammation, autoimmunity, and demyelination, as well as testing disease-modifying therapies (DMTs) and identifying drug targets, by understanding the role of different antigens and disease-mediating molecules [71]. However, there have been few studies on cardiovascular disease and CVD in preclinical models of MS. These findings compel us to provide a further overview of preclinical model applications to elucidate the mechanisms underlying cardiovascular and cerebrovascular dysfunction, which can also serve as indispensable tools for studying the pathophysiology of MS. The mechanism by which an overactive immune system leads to CVD and cerebrovascular dysfunction in MS must be explored. This information would surely help in devising mitigation strategies to prevent cardiac damage in MS patients.

3. Clinical studies on the status of cardiovascular diseases in MS

Cardiovascular dysfunction in MS patients is not well understood. MS may be an underlying cause of CVD through immune dysfunction, along with inflammatory processes, vascular pathology, and neurodegenerative disease processes, highlighting the importance of in-depth investigations into its role by unraveling the hidden facets of MS (Fig. 2) [72–78]. There have been mixed outcomes from investigating the pathophysiological association between autonomic dysfunction in MS patients, advanced brain atrophy, and demyelinating lesions in the CNS [79,80]. The presence of cardiac abnormalities in patients with MS is often attributed to underlying causative risk factors such as age, physical inactivity, arterial hypertension, diabetes, dyslipidemia, obesity, psychosocial stress, procoagulant status, smoking, oxidative stress, and inflammation [60,81–83]. The occurrence of hypertension, diabetes, and hyperlipidemia in patients with MS has increased more rapidly than in the general population ([84]; [85]). Few studies have shown that CVD can affect the quality of life, reduce patients' overall life expectancy, worsen disease presentation, and even affect immunotherapy treatment [45,63,86], although cardiovascular autonomic dysfunction can be clinical or subclinical [59,87,88].

To date, there have been multiple reports, with variable outcomes, on the symptoms of cardiovascular autonomic dysfunction in patients with MS. Two independent studies from Croatia and Turkey reported orthostatic symptoms in 61 % and 24 % of patients with clinically isolated syndromes and MS, respectively [62,89]. A noteworthy study from Iraq analyzed symptoms of cardiovascular dysfunction in 55 patients with MS and 40 healthy controls. These authors reported postural dizziness in 67 % of patients and 33 % of controls, syncope/presyncope in 18 % of patients and 0 % of controls, and palpitations in 64 % of patients and 23 % of controls [90]. Another study from Turkey, analyzing 22 relapsing/remitting MS patients and 22 healthy controls, reported orthostatic dizziness in 9 patients and 6 controls [91]. Similarly, a German study reported orthostatic dizziness in 50 % of MS patients and 17 % of controls [92].

Interestingly, a report by Kanjwal et al. published the presence of postural orthostatic tachycardia syndrome, representing

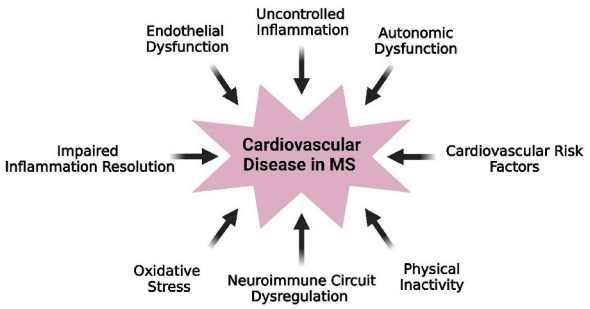

Fig. 2. Factors causing cardiovascular abnormalities in patients with multiple sclerosis (MS). The primary factors that contribute to cardiovascular dysfunction in patients with MS include an imbalance between inflammation and resolution, along with underlying cardiovascular risk factors and autonomic nervous system dysfunction caused by MS plaques. Additionally, prolonged inflammation due to impaired resolution can cause severe oxidative stress, which might have detrimental effects on the endothelial lining of blood vessels via the cardiac myocardium. Other risk factors that might contribute to developing CVD include dysregulation of neuroimmune circuit interactions, reduced mobility, nutritional status, race, age, and sex (Created with BioRender.com).

autonomic dysfunction in patients with MS [93]. However, few reports have mentioned rare complications associated with cardiovascular dysfunction in MS patients, such as Tako-Tsubo cardiomyopathy and Brugada syndrome [94–97]. Additionally, cardiac symptoms, including sinus bradycardia, have been associated with MS disease relapse in a 20-year-old woman with no underlying cardiovascular pathology [98]. One of the most common findings related to cardiovascular dysfunction in MS is impaired heart rate variability. Several studies in the 1990s reported a significant reduction in heart rate variability in patients with MS because of increased disturbance to the sympathetic cardiovascular pathway [49,99]. This decline was even more significant ($p < 0.05$) for long-term, 24-h Holter monitoring in 34 patients with MS and 20 healthy controls [100]. Given the importance of background information for cardiovascular abnormalities in patients with MS, results from studies conducted thus far are conflicting [36,38,101–104].

A nationwide study from Denmark followed patients with MS from 1980 to 2005 and reported a greater incidence of CVD after an MS diagnosis than before the diagnosis [105]. This highlights the role of a common pathological process that drives cardiovascular abnormalities in this highly inflammatory disease; however, it is not yet known whether cardiovascular autonomic dysfunction is the cause, or consequence, of MS-related lesions in the CNS, and the increase in vascular risk factors as patients become less mobile. Another study analyzed data from electronic medical records at a tertiary center and showed the cumulative and independent impact of comorbid diseases such as hypertension, diabetes, and obstructive lung disease on the clinical course of MS [106]. A comprehensive European study by Jadidi et al. applied Poisson regression to investigate the association between MS diagnosis and CVD (MI, stroke, heart failure, and atrial fibrillation) risk in 8281 first-time MS patients between 1987 and 2009, along with 76,640 healthy subjects from Sweden, as controls [58]. They found an increased risk of MI (1.85 incidence rate ratio, 95 % confidence interval: 1.59 to 2.15), stroke (1.71 incidence rate ratio, 95 % confidence interval: 1.46 to 2.00), and heart failure (1.97 incidence rate ratio, 95 % confidence interval: 1.52 to 2.56), but a lower risk of atrial fibrillation (0.63 incidence rate ratio, 95 % confidence interval: 0.46 to 0.87) in MS patients compared to controls. The higher risks were consistent after stratification by sex, age, ethnicity, and immigration status. However, the sex distribution of risk was greater for females than for males. This study is considered significant because of the large sample size of demographically and ethnically diverse populations and the inclusion of non-CVD patient follow-ups. These findings were somewhat consistent with CVD risk in patients with MS in a previous report from Europe [102]. CVD occurrence in patients with MS is also significant when regarding regional variation [38]. However, the estimates of risk in North American populations vary due to the influence of geographic factors on overall disease burden and distribution across regions [107].

It has been observed that ischemic heart disease leads to increased disability in patients with MS [108]. Based on this concept, a population-based validation study by Marrie et al. measured the incidence and prevalence of ischemic heart disease in 2366 MS patients and 11,786 healthy individuals by using data obtained from 1984 to 2005 [109]. They concluded that the age-standardized incidence of ischemic heart disease was 6.77 % (95 % confidence interval: 5.48–8.07 %) in the MS population compared to 6.11 % (95 % confidence interval: 5.56–6.66 %) in healthy controls. The incidence was notably greater in patients aged 20–44 years (prevalence ratio 1.87; 95 % confidence interval: 1.65–2.12) and those aged 45–59 years (prevalence ratio 1.21; 95 % confidence interval: 1.08–1.35). Similarly, the overall incidence was also greater among patients with MS, with an incidence rate ratio of 1.24. Ischemic heart disease was present in more than 5 % of patients, with a higher incidence in people under 60 years old [109]. A more recent retrospective study in Canada by the same group examined the risk of acute myocardial infarction in 14,565 patients with MS and 72,825 healthy subjects, all of whom were over 30 years old [74]. The adjusted risk of acute myocardial infarction was 60 % greater in patients with MS than healthy individuals, with a crude incidence rate of 146.2 per 100,000 in the MS population and 128.8 in the control population. After adjusting for age, the incidence rate ratio was approximately 1.18. They concluded that myocardial infarction risk is greater in adult patients with MS than in healthy individuals,and invalidated the exclusive role of traditional risk factors when defining CVD risk across subjects [74].

However, another study in Sweden by Roshanisefat et al. analyzed 7667 patients with MS that were recorded in the Swedish Multiple Sclerosis Register between 1965 and 2005, along with 76,045 healthy subjects as matched controls [42]. Using Poisson regression, they observed a significantly greater adjusted relative risk of CVD in the MS cohort (1.31 relative risk; 95 % confidence interval: 1.22–1.41). However, there was a slight variation in the distribution across different disease stages. The increased relative risk was highly significant for venous thromboembolic disorders in patients with progressive MS compared to those with relapsing MS, suggesting the potential role of immobility during the advanced disease stage. Additionally, these findings reflected the absence of an increased relative risk for ischemic heart disease with a low presence of atrial fibrillation in patients with MS compared to the general population. The exact data on the incidence and prevalence of CVD in people after MS diagnosis are lacking. This is particularly true for ischemic heart diseases. The results are inconclusive because different studies have reported varying rates of cardiovascular abnormalities in patients with MS compared to a non-MS cohort. A meta-analysis by Racosta and colleagues revealed a 42.1 %, or 18.8 %, prevalence of cardiovascular autonomic dysfunction in 611 patients with MS from 16 studies, based on the outcome of one or two autonomic tests, respectively [56]. Some studies have even shown an 18 %–85 % risk for patients with MS [58,74,102], while others have reported the risk of ischemic heart disease to be the same [84], or 12 % lower than that in the non-MS cohort [42]. Mincu et al. evaluated ventricular function by measuring cardiac function parameters using noninvasive echocardiographic techniques in 67 patients with MS and 36 healthy subjects [110]. They observed reduced left and right ventricular function in patients with MS compared to healthy subjects. Furthermore, they also found reduced diastolic and left atrial function in patients. Overall, they concluded that patients with MS have biventricular dysfunction, accompanied by decreased left atrial function, with normal arterial and endothelial function, which is suggestive of endogenous myocardial damage. However, this was a small study that necessitates replication of the findings in a large data set.

A two-year follow-up study by Habek et al. reported that progressive sympathetic adrenergic and sudomotor dysfunction is responsible for CVD in patients with a clinically isolated syndrome of MS, which is recognized as a first demyelinating event [111]. A

more recent multi-database study by Persson et al. assessed the risk of new CVD in patients with MS who were enrolled between 2004 and 2017 into large databases of the United States Department of Defense Military Health Care System and the United Kingdom's Clinical Practice Research Datalink GOLD [41]. The study included 6406 (US) and 5726 (UK) patients with MS and 66,281 and 57,331 healthy subjects, respectively. These authors reported a 2-fold greater risk of cardiac abnormalities in patients with MS from the US and UK, with venous thromboembolism and peripheral vascular disease in the MS cohort, and a 2.5-fold greater risk of myocardial infarction for female patients.

There is a potential impact of cardiovascular abnormalities on heightened neurodegenerative damage in patients with MS. This is reflected by worse outcomes monitored through magnetic resonance imaging (MRI) in terms of increased lesion burden and brain atrophy [112,113]. In a five-year longitudinal study by Jakimovski et al. involving 194 patients with MS and 43 controls, the effect of CVD on disease outcomes in the MS cohort was assessed by observing clinical and MRI parameters [114]. The participants were recruited from 2009 to 2013 and followed up between 2014 and 2017. They found that patients with MS and heart disease exhibited an increased loss of white matter and whole-brain volume compared to those with no heart disease. They also observed a greater percentage of lateral ventricle volume changes in hypertensive patients (24.5 %) than in nonhypertensive patients (14.1 %). This study is one of the first to show the contribution of hypertension and heart disease to heightened central, whole-brain, and white matter atrophy in patients with MS. However, they did not notice more progressive disability even with more advanced brain atrophy throughout the five-year study. Overall, these findings are significant because CVD may contribute to neurodegenerative tissue damage, which can be monitored with regular brain MRIs [114]. There is significant evidence that MS has a female preponderance [115], but most CVDs are more prevalent in males than in females [116,117]. However, whether CVD risk is biased by sex in patients with MS has yet to be ascertained. While a few studies have shown a higher death rate caused by CVD among female patients with MS, others suggest that CVD predominates in male patients [118–120]. There have been thorough analyses associating cardiovascular autonomic dysfunction with the type of MS, as well as patient experienced disease characteristics. A consensus has been established that there is a significantly greater burden of autonomic dysfunction in patients with progressive MS, compared to relapsing-remitting patients, as reflected by altered heart rate variability in progressive cases. This could be related to the variable inflammatory activity associated with the disease course of MS [42,121–123].

4. Cardiac effects of MS treatment

Several disease-modifying therapies (DMTs), such as mitoxantrone, S1P receptor modulators (fingolimod, siponimod, and ozanimod), alemtuzumab, and corticosteroids, can cause cardiovascular complications in patients with MS. There are concerns with cardiac toxicity that is associated with second-line therapy in patients treated with the immunomodulatory drug mitoxantrone [124], which is an anthracene-dione derivative used to reduce lymphocyte proliferation, macrophage numbers, and proinflammatory cytokine production [125]. Over time, mitoxantrone-treated patients have an increased risk of developing cardiovascular complications, including cardiomyopathy, congestive heart failure, and reduced left ventricular function [126,127]. The use of mitoxantrone in the United States fell out of favor as the number of MS drug choices has increased in the last few years. Initially, a multigated acquisition scan (MUGA) was required before each infusion treatment, and cardiac monitoring was performed periodically after treatment discontinuation. A study by Le Page et al. reported prolonged dose-dependent asymptomatic left ventricular function reductions (to $<$50 %) in 39 out of 802 patients with MS, treated with mitoxantrone, over a one-year follow-up period [128]. Data from three clinical trials testing mitoxantrone doses in patients with MS have shown a 3-fold lower, dose-dependent, asymptomatic left ventricular function reduction at a cumulative dose of less than 100 mg/m^2 than at higher doses [129]. Another cohort study in 2017 by Ragonese et al. reported the rate of adverse cardiac effects associated with mitoxantrone in 264 Sicilian patients with MS [130]. Cardiac function was impacted in 12.4 % of treated patients, and congestive heart failure was observed in 2.7 % of treated patients with MS. A total of 3.1 % of treated patients had abnormal electrocardiographs, and only one had MI. This study provided crucial evidence of cardiac toxicity associated with mitoxantrone treatment.

A thorough assessment of cardiac abnormalities in patients with MS should be performed using proper diagnostic approaches prior to designing a treatment plan [63]. It has been observed that comorbid CVD can negatively affect the use of some MS therapies, raising concerns about their safety over the disease course ([131]; [132]). According to the FREEDOMS and TRANSFORMS phase III clinical trials, cardiac complications such as bradycardia and atrioventricular (AV) conduction blockage have been associated with fingolimod (FTY720; brand name: Gilenya®, Novartis Pharma AG, Basel, Switzerland) treatment after the first dose [133–135]. Patients in these trials experienced worsening cardiac function with increasing doses of fingolimod from the standard dose of 0.5 mg, prohibiting approval of 1.25 mg by the US Food and Drug Administration (FDA). A 2011 report by the FDA explains the case of a patient with MS who died within 24 h of taking the first dose of fingolimod. However, the exact cause of death was never determined, as the patient had also been treated with metoprolol and amlodipine ([136]). A recent study by Feige and colleagues reported prolonged a high-grade AV block in a 63-year-old patient with late-onset, relapsing MS after 450 days of immunomodulatory treatment using the FDA approved 0.5 mg dose of fingolimod, eventually requiring permanent implantation of a pacemaker. There was no prior history of cardiac dysfunction as revealed by cardiac examination and was not taking any other medication except fingolimod. Cardiac dysfunction persisted even after fingolimod was stopped for 3 months [137]. This study provides additional evidence for persistent cardiac complications and adverse effects caused by vagomimetic cardiac activity from fingolimod, as revealed in other studies [138–140].

Akbulak and colleagues have reported acute and long-term effects of fingolimod on heart rhythm and heart rate variability in 64 patients with relapsing-remitting MS who were followed for three months [138]. They performed Holter electrocardiography (HEM) and heart rate variability analyses 24 h before fingolimod treatment, 6 h during treatment, and 72 h after the initial dose. A statistically significant decrease in heart rate ($p < 0.001$) was observed after fingolimod treatment for up to 72 h. They observed AV block in 7.8 %

of their patients, and the mean heart rate was still lower ($p = 0.002$) after following patients for 14.1 ± 9.6 months, at which point the heart rate could not be restored to baseline after treatment. The authors recommended an additional 24 h of HEM after starting an initial dose of fingolimod in MS patients. Although there have been multiple reports on cardiovascular abnormalities associated with fingolimod, the definitive association has yet to be ascertained [141–146]. However, the FDA has issued various recommendations and guidelines for regular monitoring of cardiac symptoms while prescribing fingolimod to patients with MS and cardiovascular abnormalities ([147]). The other important cardiac side effect of fingolimod is elevated blood pressure [142].

The detrimental effects of fingolimod on cardiovascular function are linked to its ability to modulate the sphingosine-1-phosphate (S1P) receptor by acting as an agonist (S1PR1, S1PR3 – 5). S1PR1 – S1PR3 contribute to maintaining cardiac function through their presence on cardiomyocytes. The binding of fingolimod to these receptors can activate potassium channels, hindering electrical excitability, heart rate (bradycardia), and atrioventricular conduction [59]. A nationwide cohort study of 2095 patients in Denmark reported a higher risk of CVD in patients with MS who were treated with fingolimod, which was attributed to hypertension [148]. Second-generation S1P modulators (siponimod and ozanimod) are more specific for S1PR1 and S1PR5, with fewer cardiac effects [149]. In line with the results of the abovementioned studies, cardiovascular symptoms are usually asymptomatic and mild in most patients during initial treatment with fingolimod. Per recommendations from the FDA, cardiac monitoring is required with the first dose [142].

In addition to DMTs, patients with MS are often on other symptomatic medications (benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, amantadine, tizanidine, or methylphenidate) to treat other MS symptoms. Benzodiazepines can cause hypotension; corticosteroids, methylphenidate, and tricyclic antidepressants may induce hypertension; tricyclic antidepressants, oxybutinine, tizanidine, baclofen, and methylphenidate may cause tachycardia; beta-blocking agents can cause bradycardia; and amantadine and tizanidine can cause peripheral vasodilation [150–155]. Based on the outcomes of the abovementioned studies, monitoring cardiovascular disturbances in patients with MS before initiating any treatment is common practice for better disease management and preventing early mortality caused by life-threatening complications.

5. Potential of cardiovascular studies in animal models of MS

Over the past decade, significant research has developed preclinical animal models for MS that could effectively mimic different levels of pathophysiological features and immunological aspects in disease development. Although there are many models available for studying MS, they have certain inherent limitations that limit their use as approximate options due to the inability to completely replicate the complexity and heterogeneity of the MS disease process [156]. However, they can still efficiently replicate certain stages of disease development. Depending on the mode of disease induction, preclinical models are broadly categorized as immune-mediated, virus-induced, or toxin-induced models [157–159]. Toxin-induced models are generated using chemical agents such as ethidium bromide (EtBr), lysophosphatidylcholine (LPC), and cuprizone [160]. Virus-induced models are generated with Theiler's virus, canine distemper virus, and mouse hepatitis virus [161]. A widely used virus-induced demyelination model uses the Theiler's murine encephalomyelitis virus (TMEV) [157]. A novel zebrafish model for MS has been developed recently with the potential for carrying out preclinical screenings [162]. However, there are pitfalls associated with each of these models, limiting their use as universal models of MS.

One of the best-characterized and most widely studied preclinical animal models of MS was the experimental autoimmune encephalomyelitis (EAE), which was induced in mice more than 60 years ago [163,164]. It has been extensively used to study classical T-cell- and B-cell-mediated immune responses in MS, making it very constructive to develop several options for treating conventional DMT [165]. EAE is an inflammatory disease of the CNS that can be induced in a range of animals, from rodents such as rats, mice, and guinea pigs to nonhuman primates. It is induced by active immunization via myelin peptides (myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), myelin basic protein (MBP), myelin-associated glycoprotein (MAG), spinal cord homogenate (SCH), and myelin-associated oligodendrocytic basic protein, as well as through passive immunization via the adoptive transfer of encephalitogenic T cells [166–168]. The clinical signs, disease severity, and course of EAE varies between animal species, strains used, the CNS antigen for disease induction, the type of adjuvant, timing, and dosages of the antigen and adjuvant. Disease onset usually occurs 10–15 days postimmunization, with typical signs such as ruffled fur and weight loss followed by hind limb/forelimb weakness and subsequent paralysis [169,170]. Over time, the disease course worsens, and severely ill animals develop quadriparesis and respiratory problems, leading to death. The disease course and severity of EAE are typically gauged and followed overtime on a clinical scoring scale ranging from 0 to 5.

The pathophysiological changes that occur after disease induction mimic the stages observed in patients with MS [165]. The initial injection of CNS antigens leads to the activation of peripheral $CD4^+$ T cells, followed by their proliferation and differentiation into effector T cells [171]. These effector T cells then migrate into the CNS by crossing the blood-brain barrier (BBB), assisted by integrin proteins, where they are reactivated by resident antigen-presenting cells (APCs) [171,172]. This process leads to microglial activation and the release of pathogenic chemokines and the proinflammatory cytokines, interferon-γ (IFN-γ), interleukin-17 (IL-17), tissue necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF). This then leads to the recruitment of T cells, B cells, macrophages, monocytes, neutrophils, and dendritic cells into the CNS [173,174]. Immune cell trafficking enhances proinflammatory cytokine production, reactive oxygen species (ROS) formation, and complement activation, ultimately leading to myelin sheath attack and resulting in the onset of clinical signs for EAE [175]. There is little information about the effector mechanisms operating within the CNS; however, it is believed that the leading players in propagating the immune response are IFN-γ-producing $CD4^+$, or T helper (Th) 1 cells. It was recently shown that other T cells, such as IL-17-producing Th17 cells and $CD8^+$ T cells, also play substantial roles in neuroinflammation [176]. Due to extensive applications of EAE towards understanding MS as a disease of the

overactive immune system, with manifestations in the nervous system, this approach can be used to understand the pathogenesis of CVD, aid in timely diagnoses, test potential treatment options, and find novel therapeutic targets.

There is extensive cross-talk between cardiovascular and neuronal dysfunction, and the immune system, which appear to be linked through a plethora of chemical mediators, such as cytokines, hormones, and neurotransmitters [177,178]. T-cell stimulation, and the resulting acetylcholine (Ach) release, dampens cytokine production and thus, enhances the course of inflammatory processes (Rosas-Ballina et al., 2011). Our study revealed that human T cells express the neuronal choline transporter **(**CHT) and contain all proteins involved in neuronal ACh synthesis [179]. The immune system plays a crucial role in the initiation and progression of cardiac damage and dysfunction. Interestingly, the neuroimmune system also plays a role in the modulation of cardiac conduction through cardiovascular disturbances, such as rhythm and conduction disorders [180]. Sequelae of events set up an inflammatory response that results in cardiac damage, beginning with injury at the site of infarction. This initiates inflammation followed by other responses, including the recruitment of neutrophils and proinflammatory macrophages, clearance of necrotic cells and debris, production of ROS, and oxidative stress [181]. This process is followed by reparative responses, ultimately resulting in angiogenesis and cardiac tissue healing.

The first event in the immune response against cardiac injury is triggered by cardiac cell death, including cardiomyocytes, followed by the recognition of exposed damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs). These are expressed by neutrophils, macrophages, and dendritic cells with the subsequent release of inflammatory chemokines and cytokines [177]. This is followed by the migration of immune cells to the site of infarction. The migrated neutrophils clear debris and release ROS, leading to oxidative stress. Proinflammatory M1 macrophages expressing lymphocyte antigen six complex (Ly6c) populate the infarcted tissue for 3–4 days after the onset of ischemic injury [178,182,183]. These cells release proteolytic enzymes and proinflammatory mediators that facilitate the clearance of necrotic tissue and apoptotic neutrophils by phagocytosis. This induces the anti-inflammatory reparative M2 phenotype from M1, which eventually promotes healing and scar formation [184]. In conjunction with neutrophils and lymphocytes, monocytes and macrophages play a well-established role in mediating the onset and development of atherosclerosis [185]. However, monocytes/macrophages play a central role in regulating tissue damage and repair after myocardial infarction. In addition to the innate immune system, the adaptive immune system also plays an essential role in the later stages of cardiac damage and repair [177]. Reports suggest there is a shift toward a Th1 response in the later stages of myocardial infarction. Activated $CD4^+$ T cells are recruited from heart-draining lymph nodes to the infarct zone [186]. Activated T cells are IFN-γ-producing Th1 cells that stimulate the proliferation of classical $CD4^+$ Foxp3-cells and regulatory $CD4^+$ Foxp3+ cells. Yan and colleagues observed the temporal distribution of immune cells in mice after infarction. It has been reported that the proportions of different types of immune cells, including $CD4^+$ T cells, Foxp3+ T cells, $CD8^+$ T cells, γδ T cells, and B cells, increase by the 7th day of infarction. However, there was no significant change in the number of IL-17- or IL-4-producing T cells. Moreover, reports have shown increased numbers of activated Th1 and Th17 cells and a decreased number of regulatory T (T reg) cells in patients with acute coronary syndrome and MI [187,188]. The cytokine macrophage migration inhibitory factor (MIF) participates in fundamental events of both innate and adaptive immunity. The profile of MIF mechanisms, both *in vivo* and *in vitro,* strongly suggest its pivotal role in the pathogenesis of many inflammatory diseases, including MS and rheumatoid arthritis (RA). MIF activity also contributes to the underlying inflammatory pathogenesis of atherosclerosis and, interestingly, has protective and pathological roles in cardiovascular ischemia and stroke [189,190]. In murine models of atheroma, MS, and other inflammatory diseases, MIF deficiency has been associated with significant inhibition of disease, as has been the case in animal models of RA. A similar case has been made for anti-inflammatory strategies that block MIF from binding to its cognate receptor CD74, which resulted in increased therapeutic activity in EAE mice [191,192]. Understanding the immune mechanisms underlying cardiovascular disturbances can help identify a common link between MS and CVD pathophysiology. The role of the immune system in CVD pathogenesis can be studied through preclinical models that can provide molecular targets for immunomodulatory therapy.

The EAE model can be used to understand the underlying cardiovascular autonomic disturbances that occur in different stages of the MS disease course by monitoring associated physiological changes. Telemetric monitoring of physiological disturbances caused by autonomic dysfunction has been used to detect changes in relevant functional parameters such as heart rate, blood pressure, body temperature, and activity. Telemetric devices can be implanted in mice to record physiological data associated with disease status, induction and progression, and the therapeutic efficacy of drugs for MS [193–195]. Buenafe et al. analyzed physiological data, including heart rate, blood pressure, motor activity, and heart rate variability, in both healthy mice and EAE (SJL strain) mice exhibiting a relapsing-remitting disease course [196]. They observed a striking disturbance in physiological data before and after the onset of EAE, and ensured that device implantation did not affect the disease course. These models can provide novel mechanistic insights into the pathophysiological process of cardiovascular abnormalities observed in MS, and can provide options to manipulate the critical molecules involved in damage and repair pathways.

6. Conclusions, future perspectives, and recommendations

MS is associated with comorbid diseases, affecting its timely and accurate diagnosis, prognosis, and therapeutic intervention. Other autoimmune diseases, including diabetes, autoimmune thyroid disease, uveitis, ulcerative colitis, and other rheumatological disorders, co-occur in patients with MS. There is substantial evidence suggesting a higher prevalence of CVD in people with MS due to cardiovascular autonomic dysfunction, which is often undetected. Studies indicate that mindfulness based stress reduction can have fatal implications for disease symptoms, disease course, severity, and overall management. However, the severe impact of MS on motor, visual, and cerebellar function is overwhelming, and insidious or subtle symptoms of autonomic dysfunction are overlooked by patients and providers. Indeed, in older patients, CVD findings on MRI could mimic MS, impacting an accurate diagnosis. Available

literature suggests that factors such as inflammation, CNS lesions, heightened oxidative stress, endothelial dysfunction, physical disability, altered cardiomyocyte structure, and the presence of other cardiovascular risk factors in MS can cause cardiovascular autonomic dysfunction, resulting in CVD [59]. Studying the pathophysiology of CVD in patients with MS and how uncontrolled and unresolved inflammation leads to cardiac dysfunction is obligatory. It would be impactful to perform an in-depth analysis of the factors that influence CVD risk in patients with MS in addition to general cardiovascular risk factors. Advanced knowledge about comorbid diseases in patients with MS is crucial since the resulting cardio- and peripheral-vascular complications contribute to the enhanced risk of premature death, necessitating a better CVD risk characterization in patients with MS.

In this review, we have highlighted an essential aspect of MS that continues to be understudied. The inconsistency observed could be due to bias in methodology and data interpretation across studies. More rigorous epidemiological studies are needed to explore the causal relationship between vascular pathology and MS. It will be intriguing to examine the effect of treatment on patients with cardiac abnormalities and observe any impact on disease severity and progression. Prior knowledge of underlying cardiac complications in patients with MS is crucial to guide clinicians while prescribing immunotherapies, as some complications could lead to cardiac toxicity. Even though cardiac evaluation is mandatory for the clinical use of fingolimod, mitoxantrone, siponimod, and ozanimod to treat MS, cardiac side effects should be considered, in addition to other predisposing risk factors, when planning for comorbid disease management in people with MS and to alleviate any associated complications. There is an evident gap between clinical and preclinical studies, which can be addressed by creating, and adopting, preclinical MS disease models with cardiac dysfunction. Different strategies can be used to develop a novel disease model with both autoimmune demyelinating disease and CVD. To this end, EAE is the most promising model for studying MS. By inducing myocardial infarction, diabetes mellitus, hypertension, volume overload, and myocarditis in EAE animals, we can study CVD in patients with MS. Furthermore, we can provide new mechanistic insights that may lead to the development of effective, anti-inflammatory, therapeutic strategies. In conclusion, CVD is a critical component of MS, and additional research is necessary to understand the pathophysiology of this phenomenon. Studying the pathophysiology of CVD as a consequence of the unbefitting in immune responses in MS would be intriguing. This approach could undoubtedly aid in the timely detection and screening of CVD patients and help reduce deaths associated with this consequence of MS.

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CRediT authorship contribution statement

Insha Zahoor: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Guodong Pan:** Writing – review & editing. **Mirela Cerghet:** Writing – review & editing, Supervision. **Tamer Elbayoumi:** Writing – review & editing. **Yang Mao-Draayer:** Writing – review & editing, Conceptualization. **Shailendra Giri:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Suresh Selvaraj Palaniyandi:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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