THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 2

REVIEW ARTICLE

Cardiovascular involvement in COVID-19: A review

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OPEN ACCESS

PUBLISHED
28 February 2025

CITATION
Osmani, Z., Baljic, R., et al., 2025. Cardiovascular involvement in COVID-19: A review. Medical Research Archives, [online] 13(2). https://doi.org/10.18103/mra.v13i2.6208

DOI
https://doi.org/10.18103/mra.v13i2.6208

ISSN
2375-1924

ABSTRACT

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has underscored the significant role of cardiovascular risk factors in determining the severity and outcomes of the disease. Pre-existing conditions such as hypertension, diabetes, obesity, and cardiovascular diseases have emerged as key contributors to increased susceptibility to severe forms of COVID-19, influencing both short-term and long-term health outcomes. This review examines the complex interplay between these risk factors and the virus's direct impact on the cardiovascular system. Key findings suggest that conditions like hypertension, diabetes, and obesity not only predispose individuals to more severe disease but also exacerbate complications such as myocardial injury, arrhythmias, and heart failure. Furthermore, the long-term cardiovascular effects of COVID-19, including myocarditis and pericarditis, are of growing concern, particularly in patients with pre-existing cardiovascular conditions. The virus's ability to induce myocardial damage through mechanisms involving ACE2 receptor binding and inflammatory cytokine storms has been well-documented. The pandemic has also highlighted significant cardiovascular complications, including left and right ventricular dysfunction, myocardial injury, and elevated pulmonary arterial pressure, with the right ventricle being particularly affected due to pulmonary damage. Imaging modalities such as echocardiography and cardiac magnetic resonance have proven valuable for diagnosing myocardial injury and complications, although accessibility may be limited in routine clinical practice. Survivors of severe COVID-19, especially those with pre-existing cardiovascular conditions, face an elevated risk of major adverse cardiovascular events for up to two years post-infection. Evaluation of post-COVID patients includes ECGs, laboratory tests, echocardiography, and cardiac MRI, which provide critical insights into myocardial injury and complications. Preventive measures, including vaccination, regular monitoring of cardiovascular health, and lifestyle modifications, play a crucial role in reducing the long-term risk of cardiovascular complications. The role of vaccination in mitigating the risk of severe disease and cardiovascular complications is well-established, despite rare cases of vaccine-related myocarditis. Understanding these interactions is essential for developing targeted management strategies, improving patient outcomes in both acute and long-term COVID-19 effects, and addressing the broader challenges posed by COVID-19's impact on cardiovascular health.

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had an unprecedented global impact, challenging healthcare systems and scientific communities worldwide. While the clinical spectrum of COVID-19 ranges from asymptomatic cases to severe respiratory failure and death, soon after a pandemic outbreak it has become increasingly evident that pre-existing conditions significantly influence disease severity and outcomes[1]. Among these, cardiovascular risk factors such as hypertension, diabetes, obesity, and established cardiovascular diseases have emerged as critical determinants of susceptibility to severe COVID-19[2]. In addition, COVID-19 has a range of direct cardiac effects that can lead to serious cardiovascular complications, particularly in patients with pre-existing cardiovascular disease or those experiencing severe infection. Beyond the acute phase, COVID-19 has sparked concerns about long-term cardiovascular effects, with growing evidence suggesting that the severity of the initial illness is linked to an increased risk of developing heart-related issues in the post-acute phase[3].

Understanding the interplay between these risk factors and the pathophysiological mechanisms of COVID-19, as well as the virus effects on heart is essential for developing effective management strategies and improving patient outcomes. This review aims to synthesize the current evidence on cardiovascular risk factors associated with severe forms of COVID-19 as well as all the major effect of new coronavirus on heart, exploring the underlying mechanisms, clinical implications, and potential therapeutic interventions. By providing a comprehensive overview, this article seeks to inform ongoing research and clinical practice in the intersection of cardiology and infectious diseases.

Cardiovascular risk factors for severe COVID-19

ARTERIAL HYPERTENSION AND COVID-19

Numerous studies have identified specific cardiovascular conditions that significantly increase the risk of severe manifestations of COVID-19, including hospitalization, intensive care unit (ICU) admission, and mortality. Arterial hypertension (AH) was more frequently observed in severe COVID-19 patients compared to nonsevere patients[4,5].

The prevalence of AH in COVID-19 patients ranged, in different studies, from 15% to 35%. The cohort of the patients with increased prevalence of AH also had significantly higher average age, which suggests that age is the most important reason for the difference in the proportion of hypertensive COVID-19 patients among the studies. Advanced age was associated with higher prevalence of other comorbidities as well, such as diabetes, renal deficiency, and obesity that occur in a large proportion of the hypertensive population[6]. AH could either play a direct role as a salient clinical predictor of disease severity or be a contributing factor to the deterioration late in the disease course, which is characterized by ARDS and systemic inflammatory response syndrome and/or multiple organ failure.

ACE2 is a key component of the renin-angiotensin-aldosterone system (RAAS), a critical pathway involved in the pathophysiology of arterial hypertension (AH)[7]. An imbalance between the two major RAAS pathways—downregulated angiotensin-converting enzyme 2 (ACE2)/ angiotensin-(1-7) and upregulated ACE/ angiotensin II—may contribute to an increased risk of severe COVID-19 in patients with comorbidities and advanced age[8].

OBESITY AND COVID-19

According to WHO, the prevalence of obesity has nearly tripled in the last four decades amounting to 13% of the entire world's adult population[9], which is a cause for concern during the pandemic. The interplay between obesity and other disease conditions has been established for a long time. Many studies have reported increased rates of hospitalization, mechanical ventilation, and mortality in patients with a higher BMI[10-13].

During the pandemic, due to worldwide lockdowns lasting several months, compromised

work routine, increased calorie intake, lack of exercise options, and stress due to uncertainty, people are at an increased risk of becoming overweight and developing obesity[14]. Research indicates that individuals with obesity are more likely to experience severe COVID-19 outcomes due to associated respiratory dysfunctions and cardiovascular issues.

DIABETES AND COVID-19

Diabetes mellitus was recognized as one of the most significant risk factors for developing severe symptoms of COVID-19. According to numerous studies, COVID-19 patients with preexisting presence of diabetes mellitus (type 1 or 2) have reduced survival rate and heightened mortality, as well as morbidity rate. Research has shown that chances of greater illness severity and hospitalization are three to four times greater in diabetic population in comparison to non-diabetic population[15]. Causes of adverse outcomes in diabetic patients are the result of chronic inflammatory and hyperglycemic environment in the organism[16]. These abnormal conditions cause cellular-level alterations that predispose greater viral penetration and facilitate the impact of the virus.

SARS-CoV-2 enters the cell by binding to angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor[17]. The virus is further being internalized and achieves effect on an infected cell. Research has shown that hyperglycemic conditions increase expression of ACE2[18], thus potentially enhancing the effect of the virus.

Diabetes mellitus is characterized by presence of endothelial dysfunction, microvascular and macrovascular defects, chronic inflammation and increased prothrombogenicity. All of the stated factors can negatively affect the course of the infection. The infection of COVID-19 itself triggers numerous mechanisms that alter the balance towards hypercoagulative and prothrombogenic states, consequently facilitating the underlying vascular pathology in diabetic patients and potentially resulting in severe thromboembolic outcomes[19].

It has been recognised that SARS-CoV-2 induces loss of pancreatic beta-cells via direct and indirect mechanisms, possibly harming insulin secretion and consequently contributing to hyperglycemia and its negative effects on the human body[16].

Diabetes is also closely related to increased BMI and obesity. Adipocytes express ACE2 receptors, therefore higher adiposity leads to increased number of receptors and greater viral penetration[20]. Multiple studies confirmed a significant correlation between severe obesity and increased mortality rates when it comes do COVID-19. Consequently, obesity appears to be a self-standing risk factor in leading to unfavorable results. Since the association between the two is yet to be investigated, coexisting conditions and comorbidities must be taken into consideration as potential contributors[21].

Prevalence of diabetes increases with age. Diabetic patients are usually older than patients with regulated blood glucose levels. Not only older age stands as an independent factor for poorer outcome, but it also contributes to increased levels of morbidity and mortality in diabetic patients[22].

It is of great significance to note that diabetic patients are also often presented with coexisting arterial hypertension, coronary heart disease, congestive heart failure, coronary or cerebrovascular incidents, valvular disease or other associated cardiovascular conditions, potentially elevating the rates of morbidity and mortality throughout the period of concurrent COVID-19.

CHRONIC KIDNEY DISEASE AND COVID-19

Cardiovascular disease is a common complication and the leading cause of death among patients with chronic kidney disease (CKD)[23]. Despite notable medical advancements, CKD patients experience a cardiovascular mortality rate that is 20 times higher than that of the general population. This concerning disparity is primarily due to the high prevalence of both traditional and nontraditional cardiovascular risk factors in this group. Nontraditional factors, including metabolic imbalances, hormonal dysregulation, and inflammatory processes, further heighten their vulnerability.

The global COVID-19 pandemic has added new challenges in managing cardiovascular health for CKD patients. Emerging evidence suggests that COVID-19 not only increases the risk of cardiovascular events but may also exacerbate preexisting risk factors in this population. Preexisting CKD and end-stage kidney disease have consistently emerged as strong predictors of severe and critical illness in COVID-19 patients. A prospective cohort study involving 701 hospitalized COVID-19 patients found that those with kidney disease faced a 2 to 4-fold higher risk of in-hospital death, depending on the severity of their kidney condition[24]. These interactions highlight the complexity of managing cardiovascular complications in CKD patients during the pandemic.

AGE AND COMORBIDITIES

Age is a significant risk factor for severe COVID-19, and this risk is magnified in individuals with cardiovascular comorbidities. Older adults often have multiple chronic conditions, including obesity and diabetes, which further increase their vulnerability. The combination of aging and cardiovascular disease leads to a higher incidence of severe respiratory symptoms, prolonged hospitalization, and increased mortality rates. Patients aged ≥60 years showed heavier clinical manifestations, greater severity and longer disease courses compared with those aged <60 years[25].

In summary, the cardiovascular risk factors for severe COVID-19 include hypertension, diabetes, obesity, and pre-existing cardiovascular diseases. These conditions not only predispose individuals to more severe forms of the disease but also complicate recovery and increase the risk of long-term cardiovascular sequelae. The interplay between COVID-19 and these risk factors underscores the necessity for targeted interventions and management strategies for affected populations.

CARDIOVASCULAR DISEASES AND COVID-19

The interplay between COVID-19 and pre-existing cardiovascular conditions is complex; for instance, the virus can exacerbate existing heart conditions, leading to increased myocardial injury.

CORONARY ARTERY DISEASE (CAD) AND HEART FAILURE

Patients with previous long-term coronary artery disease (CAD) or risk factors for atherosclerotic disease are at hightened risk of acute coronary synfdromens (ACS) if infected with SARS-CoV2. They are at an increased risk due to the compromised blood flow to the heart muscle. This can lead to ischemic episodes during viral infection, exacerbating cardiovascular stress and increasing the likelihood of heart attacks or other severe complications. CAD, indeed, has been identified as an established risk factor for severe illness and mortality in COVID-19 patients[26].

Individuals with heart failure often have reduced cardiac reserve, which makes it challenging for their bodies to handle the additional stress caused by COVID-19. The inflammatory response triggered by the virus can further impair cardiac function, leading to worsened heart failure symptoms. The presence of heart failure, independently increases the risk of mortality in COVID-19 patients[27], regardless of other adverse prognostic factors[28]. The overall cardiovascular disease burden—comprising acute cardiac injury, coronary artery disease, heart failure, and arrhythmias—has been strongly linked to higher mortality rates and increased need for intensive care in COVID-19 patients[29].

DIRECT CARDIAC EFFECTS OF COVID-19

Although, the hallmark of COVID-19 is respiratory involvement, ranging from mild upper respiratory symptoms to acute respiratory distress syndrome[30], severe COVID-19 has been implicated in multi-organ involvement, with several observational case series showing a significant proportion of cardiac involvement among hospitalized patients[31-33]. COVID-19 appears to associate with a wide spectrum of cardiovascular sequelae, including acute-onset heart failure, dysrhythmias, acute coronary syndrome, myocarditis, venous thromboembolic events and cardiac arrest[34]. Moreover, the acute cardiac injury seems to be significantly correlated with increased in-hospital mortality in COVID-19 patients[31].

PATHOPHYSIOLOGY OF COVID-19 IN IMPACTING THE CARDIOVASCULAR SYSTEM

COVID-19 can damage the heart through several mechanisms, including the binding of the virus to cardiac myocytes and endothelial cell injury. The SARS-CoV-2 coronavirus enters host cells by interaction of its spike glycoprotein with the host's cell ACE2 receptor, sialic acid receptor, transmembrane serine protease 2 (TMPRSS2), and extracellular matrix metaloproteinase inducer (CD147)[35]. The ACE2 receptors convert Angiotensin II, a product of the renin-angiotensin-aldosterone system (RAAS), to Angiotensin 1-7. ACE2 receptors exist throughout the body, including in the pulmonary, gastrointestinal, renal, and cardiac tissues[36].

Cardiac myocytes contain a high density of ACE2 receptors, second only to lung tissue cells, making them highly vulnerable to SARS-CoV-2 binding, entry, and infection[36]. The virus damages these cells, leading to dysregulation and dysfunction that can result in myocardial injury and subsequent inflammatory effects[37]. Additionally, endothelial cell damage plays a key role in the pathophysiology of COVID-19. Endothelial cells in both the heart and vasculature are targeted, contributing to cardiovascular and systemic complications[38]. Some studies suggest that ACE2 receptors are also present on endothelial cells, facilitating direct infection similar to that seen in myocytes[39-41]. Endothelial cells may be harmed by systemic processes, such as reactive immune responses and inflammatory cytokine storms triggered by the virus.

MYOCARDIAL INJURY IN COVID-19

Individuals infected with SARS-CoV-2 appear to be more susceptible to various forms of myocardial injury[42]. Myocardial injury during COVID-19 can manifest through a large spectrum of pathologies (myocarditis, myocardial infarction, Takotsubo syndrome and multisystem inflamatory syndrome in adults and children (MIS-A and MIS-C). Cardiac damage during SARS-CoV-2 infection can arise in patients with no previous hystory of heart disease or in the absence of symptoms and is therefore challenging to diagnose.

A study conducted in Wuhan found evidence of cardiac damage, indicated by high circulating troponin levels, in up to 28% of patients with SARS-CoV-2 infection. Moreover, patients who exhibited signs of cardiac injury had significantly higher mortality rates compared to those without cardiac involvement (51.2% vs. 4.55%, $P < 0.001$). Furthermore, there is a positive correlation between increased cardiac troponin levels and disease severity, suggesting that troponin is a clinically relevant biomarker for a more severe disease course[37]. Complications such as acute respiratory distress syndrome, electrolyte imbalances, and acute kidney injury were more common in patients with cardiac injury, suggesting that cardiac involvement worsens the prognosis for these individuals[31].

A systematic review published in 2021 estimated the rate of new cardiac injury to be between 7.2% and 77% in live and deceased SARS-CoV-2–infected patients, further reinforcing the association between cardiac injury, poorer outcomes, and higher mortality rates. This is primarily driven by the development of shock and malignant arrhythmias. Notably, troponin I levels appeared to be inversely correlated with survival duration[43].

Patients with more severe myocardial damage face more than a three-fold increase in the risk of mortality. Those with preexisting cardiovascular disease (CVD) are also more likely to experience myocardial injury compared to those without[44]. Therefore, patients who develop myocardial injury during a COVID-19 infection should undergo regular follow-up through clinical evaluations and imaging, with tailored protocols based on their individual risk profiles.

MYOCARDITIS AND PERICARDITIS IN COVID-19

Viral infections are a leading cause of myocarditis and pericarditis worldwide, conditions that frequently coexist. Myocarditis and pericarditis were some of the early comorbidities associated with SARS-CoV-2 infection and COVID-19. Many epidemiologic studies have been conducted since that time concluding that SARS-CoV-2 increased the incidence of myocarditis/pericarditis at least

15× over pre-COVID levels although the condition remains rare[45,46].

The incidence of myocarditis has been detected in up to 36% of patients; however, the actual incidence of myocarditis remains uncertain due to discrepancies in laboratory and clinical findings[47]. Isolated pericarditis is rarely described; therefore, its incidence cannot yet be determined.

The pathophysiological mechanisms behind the development of COVID-19-related myocarditis remain the subject of ongoing research. Observations suggest both direct and indirect viral effects. Myocardiocytes express ACE2 receptors, facilitating viral penetration. Consequently, the immune system intervenes by releasing proinflammatory cytokines and recruiting inflammatory cells—predominantly macrophages and T-lymphocytes—which infiltrate the cardiac tissue. It is therefore suggested that inflammatory responses to a viral infection could play a significant role in developing fulminant myocarditis. Pathohistological findings have also shown an interstitial inflammatory reaction in cardiac tissue without infected myocytes, indicating potentially diverse mechanisms of myocardial injury[47].

Patients with myocarditis due to COVID-19 present similarly to those with other forms of viral myocarditis, with symptoms including elevated body temperature, sternal pain, syncope, and dyspnea. During patient assessments, additional manifestations such as electrocardiogram abnormalities and/or arrhythmias have been detected, as well as signs of cardiac dysfunction observed through echocardiogram and cardiac MRI[47,45].

The presence of myocardial infection in COVID-19 is associated with poorer outcomes. However, given the variability in collected data and differences between cases, the prognosis for these patients remains uncertain[47,48].

VACCINE RELATED MYOCARDITIS

A small proportion of individuals who received mRNA-based vaccines developed mild myocarditis. In these cases, the vaccine is hypothesized to act as an immune trigger for subsequent myocardial inflammation[49]. Rare but similar vaccine-triggered inflammatory events have been documented historically, such as with the smallpox vaccine in the 1940s, where individuals receiving their first vaccination were at the highest risk of occurrence[50-52].

A descriptive study reported 1,626 cases of myocarditis out of 192,405,448 doses of COVID-19 vaccines administered. The study concluded that the risk of myocarditis after receiving an mRNA-based COVID-19 vaccine increased across various age and sex groups, with the highest risk observed after the second dose in adolescent males and young men[49]. Notably, in most patients who developed myocarditis, the clinical course was mild, with preserved cardiac function, rapid recovery (typically within six days), and no short-term complications[53].

It is important to note that both thrombosis and myocarditis are significantly more likely to occur following COVID-19 infection than after vaccination[54].

Globally, the introduction of various COVID-19 vaccines has led to a substantial decline in COVID-19-related morbidity and mortality. All approved vaccines have demonstrated benefits that far outweigh potential risks, including myocarditis, across all age groups[53-57].

CARDIOVASCULAR IMAGING DURING COVID-19 INFECTION

Evaluation of patients via echocardiography has demonstrated myocardial injury with left ventricular (LV) dysfunction, specifically diastolic dysfunction, decreased left ventricular ejection fraction (LVEF), and right ventricular (RV) dilatation, with or without accompanying dysfunction[58–60]. Evidence suggests that RV afterload increases due to lung damage, and elevated troponin levels are associated with worsened RV dysfunction[58,59].

A meta-analysis summarizing common cardiac abnormalities observed via echocardiography and cardiac magnetic resonance (CMR) revealed that many patients with COVID-19 exhibit elevated pulmonary arterial systolic pressure (PASP)[59]. This analysis also indicated that lung damage caused by

the virus could lead to increased pulmonary artery pressure and, ultimately, RV dysfunction[61]. While LV dysfunction and LV global longitudinal strain (LV-GLS) are frequently reported, RV dysfunction appears more prevalent and is likely the primary contributor to observed elevated troponin levels[61,62].

A systematic review of echocardiographic findings demonstrated that systolic LV dysfunction was present in fewer than 10% of patients with abnormal cardiac findings[58]. Evaluating RV strain patterns could provide significant prognostic value, particularly as they are impaired early, even in mild forms of the disease[59].

Electrocardiograms (ECGs) are also clinically relevant for patient assessment. The detection of T-wave inversion can assist in identifying stress cardiomyopathy and myocarditis[63].

Overall, echocardiography and CMR have proven to be precise tools for assessing myocardial injury and cardiac complications in COVID-19 patients. However, these imaging modalities are not always accessible or commonly used in routine clinical practice. In such cases, cardiac biomarkers, including troponin and creatine kinase, as well as ultrasound imaging, offer readily available diagnostic alternatives for identifying cardiovascular complications[61].

LONG-TERM CARDIOVASCULAR IMPLICATIONS

The COVID-19 pandemic, which began less than four years ago, makes it premature to fully comprehend the chronic, long-term effects of the virus, particularly on the respiratory and cardiovascular systems. Nevertheless, patients across all levels of COVID-19 severity—from those who were only PCR-positive for SARS-CoV-2 to those who required hospitalization—face a significantly elevated long-term risk of major adverse cardiovascular events (MACE)[32]. These risks have been observed in individuals categorized by one-year intervals post-infection, as well as in those with pre-existing conditions such as cardiovascular disease, diabetes, obesity, and other comorbidities.

Long COVID's impact on the cardiovascular system is expected to substantially influence the global healthcare landscape as survivors contend with persistent disease sequelae. Research into cardiovascular function following COVID-19 infection has highlighted alarming findings. For instance, a cohort study of German patients by Putmann et al. revealed that 60% of recently recovered patients experienced ongoing myocardial inflammation, while 78% exhibited reduced left ventricular ejection fraction and increased left ventricular volumes compared to controls[64].

Importantly, the likelihood and severity of MACE and its components were significantly higher among patients who required hospitalization for COVID-19. These results align with findings from two of the largest published studies, which reported similar long-term outcomes persisting up to two years[65].

The structured approach helps to comprehensively evaluate and manage cardiac symptoms in post-COVID-19 patients. For patients with intermittent or persistent cardiopulmonary symptoms, such as palpitations, or generalized symptoms like weakness or fatigue, a 12-lead ECG should be performed. If ischemic heart disease or heart failure is suspected, basic laboratory tests are also conducted, including a complete blood count, basic metabolic panel, cardiac troponin, D-dimer, brain natriuretic peptide (BNP), and C-reactive protein (CRP). Transthoracic echocardiography (TTE) is indicated for patients with a history or biochemical evidence of myocardial injury or myocarditis during acute illness. It is also recommended for patients with dyspnea or signs of underlying cardiac disorders. Limited data indicate that 10 percent of patients admitted to the ICU with COVID-19 and experiencing persistent symptoms at four months post-discharge have an ejection fraction less than 50%[66]. The clinical utility of cardiac magnetic resonance imaging (MRI) for identifying myocarditis that was not clinically evident during the acute phase of COVID-19 remains controversial. Patients with suspected myocarditis are typically referred to a cardiologist for further evaluation. For patients with persistent palpitations

or symptoms of dysautonomia, such as dizziness upon standing, despite an unremarkable ECG, the recommendations of the ACC consensus decision pathway are followed[67]. These include performing an active 10-minute stand test with heart rate and blood pressure measurements taken after lying supine for 5 minutes and at intervals of 2, 5, and 10 minutes after standing. Symptoms should be correlated with vital sign changes. Extended Holter monitoring may also be appropriate.

Preventive Measures

Given the heightened risk for individuals with cardiovascular disease, preventive measures are crucial. Vaccination against COVID-19 has been shown to reduce the severity of illness, hospitalization, and mortality in at-risk populations. It is particularly recommended for those with cardiovascular conditions[68]. Regular monitoring and management of blood pressure, cholesterol levels, and diabetes are essential. Lifestyle modifications, including a heart-healthy diet, regular exercise, and smoking cessation, can significantly improve cardiovascular health and resilience against reinfections with SARS-CoV-2.

Conclusion

The COVID-19 pandemic has underscored the critical intersection of infectious diseases and cardiovascular health. Cardiovascular risk factors such as hypertension, obesity, diabetes, and chronic kidney disease significantly predispose individuals to severe COVID-19 outcomes, while the virus itself can directly damage cardiac tissue and exacerbate pre-existing conditions. Identifying cardiovascular risk factors for worsened COVID-19 prognosis is important to identify high-risk patient groups and targeting of intervention strategies. Many of the risk factors identified as significantly associated with adverse outcomes with COVID-19 are potentially modifiable. Emerging evidence also highlights the long-term cardiovascular sequelae of COVID-19, including myocardial inflammation and an elevated risk of major adverse cardiovascular events. Preventive strategies, including vaccination, regular health monitoring, and lifestyle modifications, are vital for mitigating these risks. As the pandemic evolves, ongoing research and tailored clinical interventions will be essential to improving outcomes for at-risk populations.

Conflict of Interest:

None.

Funding Statement:

None.

Acknowledgements:

None.

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