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MINIREVIEWS

COVID-19 vaccine-associated myocarditis

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Abstract

Myocarditis is now recognized as a rare complication of coronavirus disease 2019 (COVID-19) mRNA vaccination, particularly in adolescent and young adult males. Since the authorization of the Pfizer-BioNTech™ and Moderna™ mRNA vaccines targeting the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein, the Centers for Disease Control and Prevention (CDC) has reported 1175 confirmed cases of myocarditis after COVID-19 vaccination in individuals ages 30 years and younger as of January 2022. According to CDC data in June 2021, the incidence of vaccine-mediated myocarditis in males ages 12-29 years old was estimated to be 40.6 cases *per* million second doses of COVID-19 mRNA vaccination administered. Individuals with cases of COVID-19 vaccine-mediated myocarditis typically present with acute chest pain and elevated serum troponin levels, often within one week of receiving the second dose of mRNA COVID-19 vaccination. Most cases follow a benign clinical course with prompt resolution of symptoms. Proposed mechanisms of COVID-19 vaccine myocarditis include molecular mimicry between SARS-CoV-2 spike protein and self-antigens and the triggering of preexisting dysregulated immune pathways in predisposed individuals. The higher incidence of COVID-19 vaccine myocarditis in young males may be explained by testosterone and its role in modulating the immune response in myocarditis. There is limited data on long-term outcomes in these cases given the recency of their occurrence. The CDC continues to recommend COVID-19 vaccination for everyone 5 years of age and older given the greater risk of serious complications related to natural COVID-19 infection including hospitalization, multisystem organ dysfunction, and death. Further study is needed to better understand the immunopathology and long-term outcomes behind COVID-19 mRNA vaccine-mediated myocarditis.

Key Words: COVID-19; SARS-CoV-2; mRNA vaccine; Myocarditis; Pericarditis

Core Tip: In this review article, we aim to synthesize the current literature surrounding coronavirus disease 2019 (COVID-19) vaccine-mediated myocarditis. COVID-19 mRNA vaccination has been associated with increased cases of myocarditis, particularly in the adolescent and young adult male population. Presentation typically occurs several days following administration of the second dose of a COVID-19 mRNA vaccination. As the world continues to vaccinate against COVID-19, understanding this vaccine-related adverse event is clinically important. Potential mechanisms are reviewed, and current clinical recommendations are discussed.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the novel virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has impacted the entire globe and continues to spread. On December 11, 2020, the United States Food and Drug Administration granted an emergency use authorization (EUA) for the Pfizer-BioNTech™ COVID-19 vaccine in individuals 16 years of age or older. Seven days later, another EUA was released for the Moderna™ vaccine in adults 18 years of age or older[1]. Since their introduction, the mRNA vaccines against the SARS-CoV-2 virus have been highly effective in preventing both symptomatic and asymptomatic infections along with COVID-19-related hospitalizations and death[2]. Despite the great success of these vaccines, they have not come onto the public stage without controversy. In May 2021, the first case of myocarditis following mRNA vaccination was identified, and as of January 12, 2022, the Vaccine Adverse Events Reporting System (VAERS) had received 2077 reports of myocarditis or pericarditis among people ages 30 and younger who received a COVID-19 vaccine with 1175 confirmed cases[3]. This article aims to review the current literature regarding COVID-19 vaccine-related myocarditis.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

While the possibility for developing myocarditis or pericarditis following COVID-19 vaccination is concerning, it is important to emphasize that the incidence of this adverse effect is rare. Since January 2022 there have been over 502 million doses of COVID-19 mRNA vaccines administered across the United States with less than 1175 confirmed cases of myocarditis or pericarditis[3]. The primary group being impacted by this adverse event is the male adolescent and young adult population, ages 12-29[4-8]. The principal window of risk for the development of COVID-19 vaccine-mediated myocarditis appears to be within a week of receipt of the vaccine and occurs most commonly following the second dose of an mRNA vaccine[4,5,7,9]. Affected young men are predominately healthy individuals without a history of COVID-19 infection or comorbidities. Resolution of clinical symptoms usually occurs within 6 d with preservation of cardiac function, indicative of overall fast recovery with no short-term complications[4,5,8].

It is challenging to calculate the true incidence of vaccine-related myocarditis in the United States, as currently reported case series are not population-based. Based on crude data with both confirmed and unconfirmed cases reported to the VAERS, the CDC has estimated the incidence rates of myocarditis to be 40.6 cases *per* million second doses of mRNA COVID-19 vaccines administered to males between 12 and 29 years old[1]. Females in the same age group had an estimated incidence of 4.2 cases of myocarditis *per* million second doses. In adults 30 years and older, rates of myocarditis were reported as 2.4 cases *per* million second doses in males and 1.0 case *per* million second doses in females. As of December 31, 2021, VAERS has processed 4317 reported events of COVID-19 vaccine-associated myocarditis and pericarditis across all age groups with the highest number of cases reported for both myocarditis and pericarditis in the age group 18-29 (Figure 1A)[9].

Investigators from Israel queried the database of the largest Israeli healthcare organization that contains data related to 2.5 million vaccinated individuals. They determined that post-vaccine myocarditis had an estimated incidence rate of 2.13 cases [95% confidence interval (CI): 1.56-2.70] *per*

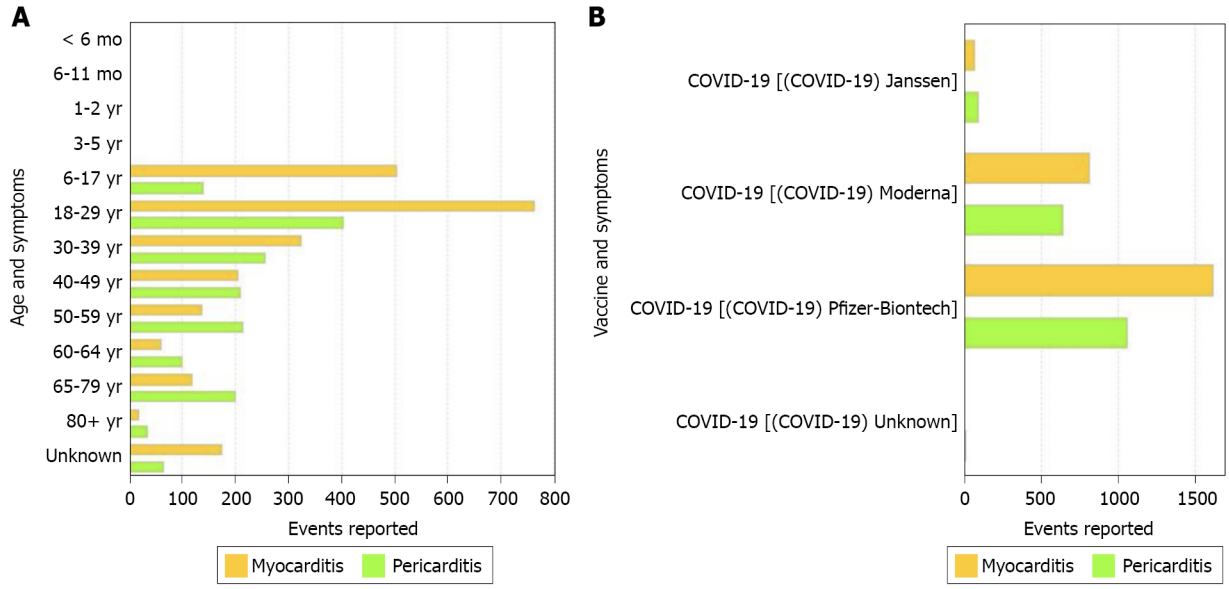

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Figure 1 Coronavirus disease 2019 vaccine-mediated myocarditis and pericarditis cases reported to Vaccine Adverse Event Reporting System. A: Age. A total of 4317 events of myocarditis and pericarditis after receiving coronavirus disease 2019 (COVID-19) vaccine were reported to Vaccine Adverse Event Reporting System (VAERS) as of December 31, 2021. Age group 18-29 had the highest number of cases reported for myocarditis (763 cases) as well as pericarditis (404 cases). Adapted from centers for disease control and prevention (CDC) WONDER and VAERS which is updated weekly for continuous updates including revisions and new reports for preceding time periods[9]; B: Vaccine manufacturer. A total of 2512 cases of myocarditis and 1805 cases pericarditis after receiving COVID-19 vaccine were reported to VAERS as of December 31, 2021. Pfizer-BioNTech™ had the highest number of cases reported for myocarditis (1615 cases) as well as pericarditis (1063 cases). Adapted from CDC WONDER and VAERS which is updated weekly for continuous updates including revisions and new reports for preceding time periods[11]. COVID-19: Coronavirus disease 2019.

100000 individuals who had received at least one dose of the Pfizer-BioNTech™ vaccine[10]. Additionally, the incidence increased to 10.69 cases *per* 100000 individuals (95%CI: 6.93-14.46) among males between 16 and 29 years old.

To compare the three types of vaccines, a systematic review of 6 case reports and 2 case series with a total of 15 patients reported that 60% of the myocarditis-related COVID-19 vaccine cases were associated with the Pfizer-BioNTech™ vaccine, 33% were associated with the Moderna™ vaccine, and 7% were associated with the Johnson & Johnson™ vaccine[5]. Similarly, as of December 31, 2021, VAERS indicated Pfizer-BioNTech™ had the highest number of cases reported for myocarditis and pericarditis, 1615 and 1063 cases respectively (Figure 1B)[11]. The clinical presentation of post-vaccine myocarditis is similar to other forms of myocarditis, most commonly featuring acute chest pain combined with other symptoms such as shortness of breath, fever, and palpitations[6,8,9,12,13]. Evidence of myocardial injury *via* serum troponin elevations was present in all cases. Electrocardiogram (EKG) findings were varied but often showed ST segment elevations. Echocardiogram findings ranged from preserved ejection fraction to varying degrees of wall motion abnormalities. When cardiac magnetic resonance imaging (MRI) was performed, findings were consistent with acute myocarditis with late gadolinium enhancement being the most commonly cited abnormality. Figure 2 displays a cardiac MRI consistent with myocarditis following COVID-19 vaccination in a 21-year-old male. Notably, most cases resulted in normalization of symptoms, troponin levels, and EKG/echocardiogram abnormalities upon discharge or at follow-up (Table 1). The CDC Vaccine Safety Technical Work Group Report on August 30, 2021, reviewed 98 cases with chest pain, pressure, and discomfort of which 56% of the cases met confirmatory criteria for myocarditis within 0-21 d of vaccination with elevated troponin, abnormal EKG findings, and abnormal MRI commonly found. It was determined that all of these included cases were discharged home, with 76% of them being discharged within 0-2 d[14].

POTENTIAL MECHANISMS OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

The mechanism underlying COVID-19 vaccine-mediated myocarditis is poorly understood. SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA encoding for the virus's spike protein encapsulated in lipid nanoparticles which aid in delivery of the mRNA into the cell. The cell then produces the spike protein, and a subsequent adaptive immune response ensues generating antibodies against the spike protein. The nucleoside modification of the mRNA aids in reducing the mRNA's immunogenicity, however in some individuals with an unknown genetic predisposition, exposure to

Table 1 Summary of coronavirus disease 2019 vaccine-associated myocarditis studies

Ref.	Study design	Sample size	Main findings	Analysis
Salah and Mehta[5], 2021	Systematic review of 6 case reports and 2 case series with a total of 15 patients	15 individuals who developed myocarditis following a COVID-19 vaccine, regardless of the type or dose of the vaccine	(1) 60% of the myocarditis related COVID-19 vaccine cases were associated with the Pfizer-BioNTech™ vaccine, 33% were associated with the Moderna™ vaccine, and 7% were associated with the Johnson & Johnson™ vaccine; (2) All the myocarditis related to the Moderna™ vaccine (5/5) occurred following the second dose of the vaccine, whereas 6/9 (66.7%) of the myocarditis related to the Pfizer-BioNTech™ vaccine occurred following the second dose of the vaccine; (3) Peak cardiac troponin I level (ng/mL) was reported in 13/15 patients, and it ranged between 0.37 and 51.37 ng/mL (mean 12.9 ng/mL). Peak troponin T levels were reported in the other 2/15 patients and were 854 ng/L and 1693 ng/L; (4) Transthoracic echocardiogram in all these patients showed preserved LVEF; exact LVEF value was reported in 13/15 patients with a mean LVEF of 53.5% and a range of 48% to 65%. In the other 2/15 patients, the LVEF was reported as normal with no value; (5) There were no regional wall abnormalities in 14/15 of the patients; 1 patient had subtle apical septal and apical lateral hypokinesis with a LVEF of 52%; and (6) All patients recovered within 6 d of their presentation with complications reported	(1) Myocarditis related to COVID-19 vaccines mostly occurs in young male individuals following the 2nd dose of the vaccine; (2) Myocarditis related to COVID-19 vaccines mostly occurs with mRNA vaccines (*i.e.*, Pfizer-BioNTech™ and Moderna™ COVID-19 vaccines); (3) In all the reported cases of myocarditis related to COVID-19 vaccine, clinical symptoms resolved within 6 d with preservation of the cardiac function; and (4) No complications were reported in any of these patients showing that myocarditis related to COVID-19 vaccine has an overall fast recovery with no short-term complications
Mevorach *et al*[4], 2021	Retrospective review of myocarditis cases from the Israeli Ministry of Health database between December 2020 and May 2021	142 Israeli patients diagnosed with myocarditis within 21 d of receiving the first dose of Pfizer-BioNTech™ vaccine or 30 d of receiving the second dose	(1) In the 136 cases of definite or probable myocarditis with recent vaccination, the clinical presentation in 129 was generally mild, with resolution of myocarditis in most cases, as judged by clinical symptoms and inflammatory markers and troponin elevation, electrocardiographic and echocardiographic normalization, and a relatively short length of hospital stay; one fulminant case was fatal; (2) As compared with the expected incidence of myocarditis based on historical data, the standardized incidence ratio was 5.34 (95%CI: 4.48-6.40) and was highest after the second dose in male recipients between the ages of 16 and 19 yr (13.60; 95%CI: 9.30-19.20); and (3) Definite or probable cases of myocarditis among persons between the ages of 16 and 19 yr within 21 d after the second vaccine dose occurred in approximately 1 of 6637 male recipients and in 1 of 99853 female recipients	(1) There was a slight increase in the incidence of myocarditis after the Pfizer-BioNTech™ vaccine, particularly after the second dose among young male recipients; and (2) The incidence of myocarditis after two doses of the Pfizer-BioNTech™ mRNA vaccine was low but higher than the incidence among unvaccinated persons and among historical controls, driven primarily by young males after receiving their second dose
Rosner *et al*[6], 2021	Case series of 7 patients hospitalized for acute myocarditis-like illness after COVID-19 vaccination from 2 United States medical centers	Seven males, all < 40 years old	(1) Six patients received an mRNA vaccine (Moderna™ or Pfizer-BioNTech™), and 1 received the adenovirus vaccine (Johnson and Johnson™); (2) All patients presented 3 to 7 d after vaccination with acute onset chest pain and troponin elevations; EKG varied from normal to 1 mm ST segment elevations; Echocardiograms showed left ventricular ejection fraction ranging from 35% to 62%, with 5 of 7 having some degree of hypokinesis; (3) Multifocal subepicardial late gadolinium enhancement was present in 7 of 7 patients and additional midmyocardial late gadolinium enhancement was found in 4 of 7 patients; and (4) Treatment included β-blocker and anti-inflammatory medication. Hospital length of stay was 3 ± 1 d, and all patients' symptoms resolved by hospital discharge	(1) There is a potential causal association with vaccination given the temporal relationship, clinical presentation, and cardiac magnetic resonance imaging findings; (2) Vaccine-associated myocarditis appears to have a favorable clinical course; and (3) The benefits of vaccination outweigh the risks of vaccine-related myocarditis in younger adults given the potential morbidity of COVID-19 infection
Dionne *et al*[7], 2021	Case series of 15 adolescents at single United States center	15 adolescents ages 12-18 years old hospitalized with myocarditis after receiving Pfizer-BioNTech™ COVID-19 vaccine	(1) 14 children were male, and 1 child was female; (2) Symptoms started 1-6 d following vaccine administration (14 of 15 occurring after second dose); common symptoms included chest pain, fever, myalgia, and headache; (3) Elevated troponins found in all 15 cases; (4) Cardiac MRI findings were consistent with myocarditis in 13 patients, with 12 patients showing evidence of late gadolinium enhancement; (5) No patients required intensive care and the median length of hospital stay was 2 d (range 1-5 d); and (6) At 1-to-13-d follow-up after hospital discharge, 11 patients had full resolution, 1 patient had persistent borderline low LV systolic dysfunction (EF = 54%), 3 patients had mildly elevated troponins, 1 patient had nonsustained ventricular tachycardia on ambulatory monitor	(1) Following Pfizer-BioNTech™ vaccination, most cases of myocarditis were diagnosed in male children after the second dose; (2) All patients had a benign clinical course; and (3) Long-term risks of post-vaccine myocarditis in the child population remains unknown

COVID-19: Coronavirus disease 2019; MRI: Magnetic resonance imaging; EKG: Electrocardiogram; LVEF: Left ventricular ejection fraction.

the mRNA may result in an overactivated immune response *via* dendritic cells and Toll-like receptors of the innate immune system leading to proinflammatory immune cascades and cytokine activation[15]. This inflammatory response is thought to play a role in COVID-19 vaccine-associated myocarditis. The role of mRNA in the development of vaccine-mediated myocarditis is further supported by the evidence that the incidence of myocarditis occurs at a much higher rate following mRNA vaccination compared to the adenovirus vector vaccine of Johnson and Johnson™[4].

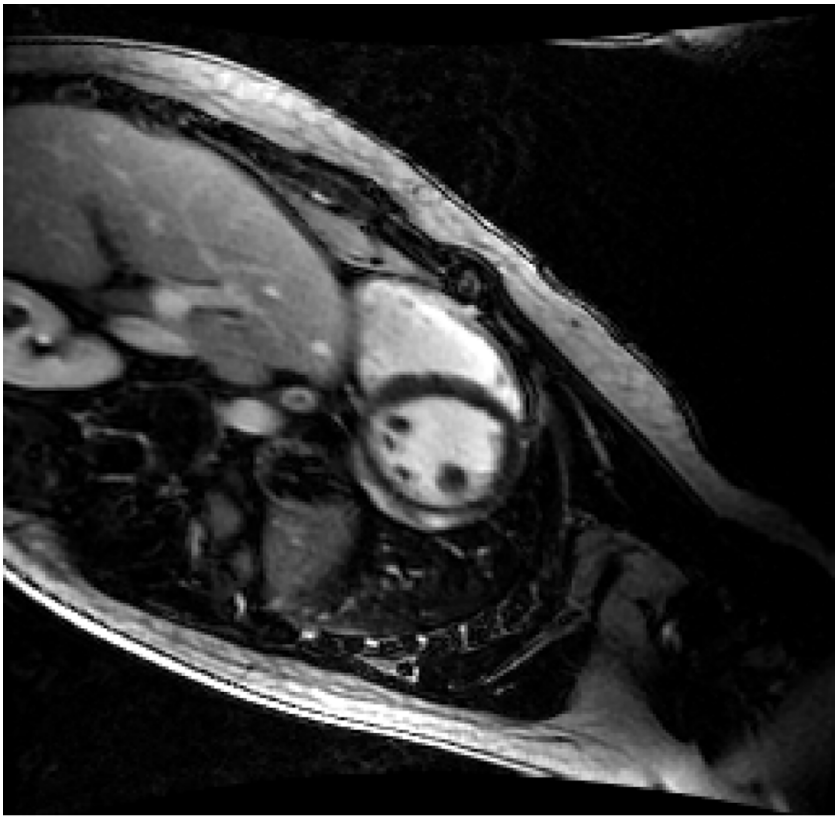

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Figure 2 Cardiac magnetic resonance imaging of coronavirus disease 2019 vaccine-associated myocarditis. Cardiac magnetic resonance imaging slice of a 21-year-old male six days after receiving his second dose of the Moderna™ mRNA coronavirus disease 2019 vaccination showing evidence of significant diffuse late gadolinium enhancement and myocardial edema consistent with myocarditis.

Another potential mechanism for COVID-19 vaccine myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens. Antibodies of the SARS-CoV-2 spike protein have been shown to cross-react with human proteins of similar structure including α-myosin in experimental studies[16]. It appears more likely that the immune-mediated adverse effects of mRNA vaccination are due to the triggering of preexisting dysregulated pathways in certain predisposed individuals rather than the inherent immunogenicity of the vaccine itself[15]. Polymorphisms in interleukin-6 have been suggested as an important genetic component for determining autoinflammatory dysregulation that may ensue upon exposure to SARS-CoV-2, however further study is needed to elucidate these theories [17].

Young men have been found to be most susceptible to the development of myocarditis outside the setting of COVID-19 vaccination as well. Kytö *et al*[18] have presented evidence that testosterone appears to play a major role in the pathogenesis of myocarditis identifying testosterone-mediated mechanisms such as inhibition of anti-inflammatory cell populations promoting cardiac inflammation, a preference towards a Th1 immune response, and increased transcription of cardiac fibrotic remodeling genes[18]. Conversely, estrogen appears to play a protective role *via* the preference of a Th2 immune response, stimulation of inhibitory regulatory T cells, and inhibition of proinflammatory T cells[18]. These mechanisms may contribute to why the young male population has the highest incidence of post-vaccine myocarditis.

COVID-19 VACCINE ASSOCIATED MYOCARDITIS IN CHILDREN AND ADOLESCENTS

Cases of myocarditis have also been reported in the childhood population since the Pfizer-BioNTech™ COVID-19 vaccine was authorized for emergency use on May 10, 2021, for children ages 12 and older. A case series of 15 adolescents who developed myocarditis following administration of the Pfizer-BioNTech™ vaccine found that, similar to the adult population, the most commonly affected group were young males ages 12-18 years old following administration of the second dose[7]. All patients in this study had an uncomplicated short-term clinical course, however the long-term prognosis of these adolescent patients remains unclear, emphasizing the importance of continued follow-up and monitoring.

A case series published by Marshall *et al*[19] reported myocarditis or pericarditis in 7 male adolescents ages 14-19 years old, all within 4 d of receiving the second dose of the Pfizer-BioNTech™ COVID-19 vaccine[19]. All 7 patients presented with elevated troponin levels. ST segment elevation was the most common EKG and was observed in 6/7 individuals. Echocardiogram results were normal in 5 of 7 patients; however, all patients had cardiac MRI findings consistent with acute myocarditis. Investigatory studies for other etiologies of myocarditis including respiratory pathogen panels, serum polymerase chain reaction (PCR) tests, and infectious serologies all returned negative, and multisystem inflammatory syndrome in children was excluded based on cardiac MRI findings.

EVALUATION AND MANAGEMENT OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

Given the increased incidence of myocarditis following mRNA vaccination in adolescent and young adult males, clinicians should have a high index of suspicion for myocarditis in this demographic who present with symptoms such as acute chest pain, shortness of breath, or palpitations. Initial evaluation should include obtaining an EKG, serum troponin levels, complete blood count with differential, chest x-ray, inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate, brain natriuretic peptide, and an echocardiogram (Figure 3). If this initial workup supports a diagnosis of myocarditis, cardiology consultation should take place in conjunction with studies seeking to determine potential alternative etiologies of myocarditis. Consultation with infectious disease and/or rheumatology may also be considered to aid in this process[20]. PCR testing for acute COVID-19 infection and SARS-CoV-2 antibody testing for prior COVID-19 infection are of particular importance. Obtaining enterovirus PCR along with a respiratory pathogen panel can assist in ruling out other potential viral etiologies (*e.g*. Coxsackievirus, Epstein-Barr virus, cytomegalovirus, respiratory syncytial virus, parvovirus) and autoimmune serologies such as antinuclear antibodies may be indicated depending on clinical presentation. Cardiac MRI may be utilized to aid in diagnosing suspected myocarditis without the need for obtaining invasive endomyocardial biopsy.

The clinical management of COVID-19 vaccine-mediated myocarditis is largely supportive, and patients frequently exhibit rapid resolution of symptoms and normalization of cardiac biomarkers. Those with persistent mild symptoms and no signs of arrhythmia, left ventricular systolic dysfunction, or hemodynamic instability may benefit from therapy with nonsteroidal anti-inflammatory drugs, colchicine, or steroids. In more serious cases of myocarditis, such as those patients showing signs of hemodynamic instability, new-onset arrhythmia, or worsening systolic dysfunction, intravenous steroids or intravenous immunoglobulin may be considered[15]. Patients with reduced ejection fraction should be placed on beta-blockers and angiotensin-converting enzyme inhibitors according to guideline-directed medical therapy. The majority of cases from prior reports resulted in a resolution of symptoms and abnormal cardiac studies prior to discharge following a short hospital stay with supportive care or a short course of nonsteroidal anti-inflammatory. Close monitoring and avoidance of strenuous exercise until a complete resolution of symptoms and normalization of cardiac biomarkers, EKG, and echocardiogram is an important measure, especially in the young age group who may be eager to return to a normal exercise routine. If a patient develops myocarditis following a first dose of mRNA vaccination, the CDC recommends the second dose be delayed and reconsidered later following the complete resolution of signs and symptoms[20]. Of note, there are currently no randomized controlled trials examining the management of post-vaccine myocarditis which highlights the importance of the inclusion of cardiovascular specialists in the management and follow-up of these patients.

The concerted efforts of the biomedical community to develop safe and efficacious vaccinations in such a short time frame have been extraordinary. SARS-CoV-2 virus mRNA vaccines have been tremendously successful in curtailing the morbidity and mortality associated with COVID-19[21]. Healthy adolescents and young adults are not immune to serious complications from COVID-19 infection and rising adolescent hospitalization rates from COVID-19 infection have been observed[22]. Despite media attention regarding adverse effects of these vaccines, it is important to emphasize the low incidence in which these events occur. The benefits of vaccination to prevent both the spread and possible complications of COVID-19 infection including hospitalization, multisystem organ dysfunction, and death far outweigh the potential risk of post-vaccine myocarditis while this global pandemic persists.

The diagnosis of myocarditis is a serious one as cardiac myocytes do not regenerate, and an insult at a young age can lead to an increased risk of developing cardiac disease later on in life[23]. While myocarditis has been linked to COVID-19 mRNA vaccination, it is important to compare the risk of developing myocarditis following vaccination to the risk following natural COVID-19 infection. A large study in Israel used data from the nation's largest healthcare organization to determine the risk of myocarditis following vaccination after adequately matching vaccinated individuals to unvaccinated individuals[24]. 42 d after vaccination, they found a risk ratio of 3.24; 95%CI: 1.55-12.44, and a risk difference of 2.7 events *per* 100000 persons; 95%CI: 1.0-4.6. To put this in context, they then determined the risk of myocarditis among SARS-CoV-2 infected individuals matched to uninfected individuals.

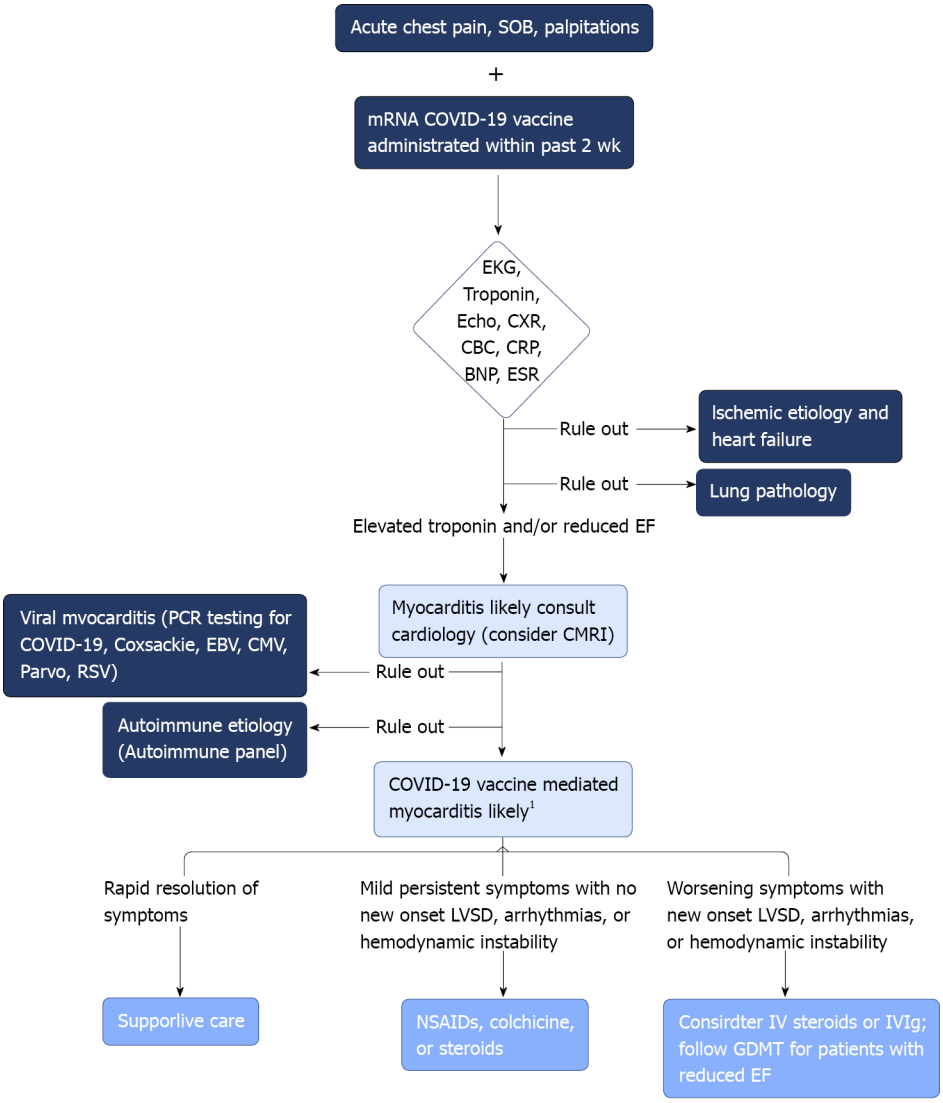

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Figure 3 Clinical decision-making algorithm for diagnosis and management of suspected coronavirus disease 2019 vaccine-associated myocarditis. [1]All cases should have monitoring with close cardiology follow up. Initial evaluation should include a basic workup in addition to ruling out other etiologies that can present similarly. Early cardiac consultation should occur for suspected coronavirus disease 2019 vaccine myocarditis along with close cardiac monitoring and follow-up. SOB: Shortness of breath; EKG: Electrocardiogram; Echo: Echocardiogram; CXR: Chest x-ray; CBC: Complete blood count; CRP: C-reactive protein; BNP: Brain natriuretic peptide; ESR: Erythrocyte sedimentation rate; CMRI: Cardiac magnetic resonance imaging; EBV: Epstein-barr virus; CMV: Cytomegalovirus; Parvo: Parvovirus; RSV: Respiratory syncytial virus.

COVID-19 infection was associated with a much higher risk of myocarditis with a risk ratio of 18.28; 95%CI: 3.95-25.12 and a risk difference of 11.0 events *per* 100000 persons; 95%CI: 5.6-15.8[24]. This large-scale study supports the notion that the risk of myocarditis is much higher in the setting of natural COVID-19 infection compared to myocarditis following vaccination. Given the widespread transmissibility of this virus, it stands to reason that an individual should receive a vaccine to safeguard against the increased risk of myocardial injury associated with COVID-19 infection.

Underreporting of myocarditis in the adolescent and young adult male population is possible, as there may be a low index of suspicion in this relatively healthy age group. Mild cases of post-vaccine myocarditis are likely to go unreported as there is currently no routine screening protocol in place. However, as public awareness of post-vaccine myocarditis continues to grow, there may also be a potential for overreporting as well, emphasizing the need for effective surveillance systems to confirm suspected cases.

Based on the current available data, the CDC is continuing to recommend that patients aged 5 years and older be vaccinated against COVID-19, stating that the known risks and potential complications associated with COVID-19 infection far outweigh the rare chance of developing an adverse reaction to vaccination including myocarditis. Vaccine-mediated myocarditis has a low incidence, and while clinicians should be vigilant for its occurrence, this adverse effect should not deter vaccination efforts during this pandemic based on current data. Continued monitoring and reporting to the Vaccine

Adverse Event Reporting System is strongly encouraged. Additional guidance from the American Heart Association for follow-up of patients with myocarditis emphasizes the use of cardiac MRI to examine the heart *in vivo*[25].

One of the major limitations of many of the studies describing post-vaccine myocarditis is the lack of follow-up data given the recency of vaccine approval and administration. There is minimal long-term data available to date which limits our ability to interpret long-term outcomes of patients who receive a diagnosis of COVID-19 vaccine-associated myocarditis. However the availability of long-term data will accumulate with time. Additionally, many of these studies were case reports compiled *via* colleague communication rather than surveillance systems which allow for more complete diagnostic evaluation to exclude other potential etiologies of myocarditis. Many of the cases reported were presumed to be a result of the COVID-19 vaccine purely based on temporal association. While feasible, this assumption might result in the overestimation of myocarditis as a result of COVID-19 vaccination. Similarly, many studies used negative antibody tests to rule out active or prior COVID-19 infection which could be problematic due to false negatives or waning immunity.

With third dose eligibility for the Pfizer-BioNTech™ and Moderna™ mRNA vaccines recently expanding to include much of the adult general public, careful prospective observation of the rate of vaccine-mediated myocarditis following the third dose compared to rates following the second dose is needed. While there is limited data currently available, data obtained by the Israel Ministry of Health have reported lower rates of myocarditis following the third dose compared to the second dose. Proactive surveillance efforts have discovered 17 total myocarditis/perimyocarditis cases among ages 16-59 years following administration of over 2.5 million third doses of the Pfizer-BioNTech™ mRNA vaccine[26].

CONCLUSION

Vaccine-mediated myocarditis following vaccination against COVID-19 using mRNA vaccines is a rare, but potentially serious occurrence. Clinicians should be aware of the potential development of vaccine-mediated myocarditis, particularly in young males. Early consultation with cardiologists and further investigation *via* serum biomarkers and imaging with cardiac MRI may confirm the diagnosis. Long-term follow up of those patients developing vaccine-mediated myocarditis is necessary to assess the potential for chronic complications of this rare phenomenon. Despite the potential for vaccine-mediated myocarditis, vaccination continues to be recommended against COVID-19 in all eligible populations.

FOOTNOTES

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MINIREVIEWS

Heart failure in general and cardiac transplant patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is primarily an infection of the respiratory tract, but it can have multisystem manifestations. Cardiac complications of COVID-19 can range from acute myocardial injury, cardiac arrhythmias, or heart failure, amongst others. Heart failure (HF) in COVID-19 can be a de novo process or due to worsening of pre-existing cardiovascular ailment. HF in a patient with COVID-19 not only poses challenges in clinical presentation and management of COVID-19 but also affect prognosis of the patient. This article aims to succinctly revisit the implications of this pandemic regarding pre-existing HF or new-onset HF based on prevailing data. It also focuses on the management and special recommendations from prior studies and guidelines.

Key Words: COVID-19; Coronavirus; Cardiomyopathy; Heart failure; Cardiomyopathy

Core Tip: The mini-review is composed of assimilation of guidelines and current literature recommendations for managing heart failure in coronavirus disease 2019 (COVID-19) patients. We discuss many important aspects of heart-failure in COVID-19 from epidemiology to post recovery rehabilitation.

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INTRODUCTION

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected all continents. The case count of coronavirus disease 2019 (COVID-19) continues to soar to-date, as evident by more than 300 million global caseloads[1]. COVID-19 typically presents as a respiratory tract infection, but we have witnessed it herald a multisystem disorder in a lot of patients, including but not limited to the cardiovascular system. Cardiac manifestations of COVID-19 can be broad, and symptoms generally stem from myocardial injury, cardiac arrhythmias, cardiogenic shock, heart failure (HF), or sudden cardiac death[2-5]. This article attempts to provide a brief review of all the major topics related to heart failure and covid-19 from epidemiology, diagnostic tools to the important management options, and post-recovery rehabilitation. It gives insights on breakthrough vaccination and cardiac complications post COVID-19. It attempts to touch on treatment options in various situations encountered while treating heart failure patients.

EPIDEMIOLOGY

An accurate incidence of HF in COVID-19 is difficult to determine as there are not abundant definitive data on it. HF in COVID-19 can be due to worsening of preexisting known or undiagnosed heart disease. Besides, it could also be a new onset HF due to hemodynamic stress, ischemic cardiomyopathy, or nonischemic cardiomyopathy. Available studies have not always clearly discerned a new-onset HF from worsening of chronic HF. As evident in Table 1, HF was present at baseline in up to 23% of cases while up to 7% of patients with COVID-19 had a new-onset HF as a complication of the infection[6-9]. However, we must bear in mind that there seems to be a wider range in these data reported. The other caveat is that not all studies have clearly demarcated the incidence and acuity of pure right heart failure from left heart failure to biventricular loss. Creel-Bulos C *et al*[10], described five patients with acute right HF in their case series from March 23 to April 4, 2020, in an intensive care unit in Georgia, United States. With the progression of the pandemic, Corica *et al*[11] conducted a combined pooled analysis of 3813 patients and found to have right HF in as high as 20.4% of patients with COVID-19.

ETIOPATHOLOGY

Two types of mechanisms for myocardial injury are described in prior literature. ie direct or specific and indirect effects[24].

SARS-CoV-2 directly attaches to the ACE2 on the myocardium and causes cell damage and death. It also decreases the protective and anti-inflammatory properties of ACE2 on the myocardium through its downregulation.

Sympathetic activity causing Tachycardia from underlying infection, prolonged immobility causing coagulopathy, hypoxemia, hemodynamic changes are indirect effects worsening the cardiac status[24]. Severe inflammatory response causing surge of cytokines like Interleukins, Tumor necrosis factor, interferons' play a major role in the pathogenesis of pulmonary and myocardial damage leading to acute respiratory distress syndrome (ARDS) and various cardiac complications[25]. It can precipitate new cardiac failure and worsen the course in underlying failure patients[25].

Pre-existing HF can exacerbate during COVID-19, as evident in other viral illnesses such as Influenza [15]. Stress cardiomyopathy, vasculitis, thrombosis of coronary arteries, fissuring, and rupture of atheromatous plaque leading to acute myocardial ischemia can be some of the ischemic and nonischemic causes of acute cardiomyopathy and subsequent HF[16,17]. One study evaluated that cardiogenic shock resulting from myocardial injury occurred in up to 10% of patients in shock and can result in worse prognosis compared to hypovolemic or distributive shock in COVID-19 patients[26]. 48% of patients had normal Ejection fraction and low cardiac index shock from low end diastolic volumes which was

Table 1 It shows data on incidences of acute, chronic heart failure, and acute heart failure

Ref.	Study type	Country of origin	Incidences
Zhou *et al*[6], 2020	Retrospective cohort study	China	Total patients 191. deceased 54 patients (28 had chronic hf exacerbation, *i.e.*, 52%) survived 137 patients (16 had chronic hf exacerbation, *i.e.*, 12%) $P < 0.0001$
Arentz *et al*[7], 2020	Case series	United states	Total patients 21. nine patients (42.9%) acute on chronic hf
Ruan *et al*[8], 2020	Multicenter retrospective analysis	China	Total patients 150. death 68 acute on chronic hf 5 (7%)
Shis *et al*[9], 2020	Single-center cohort jan 2020 - feb 2020	China	Total patients 416. new-onset heart failure 4.1%
Chen *et al*[12], 2020	Retrospective study	China	Total patients 274. acute on chronic hf 1 (< 1%) new-onset hf 21 (7.7%). 1 recovered and 20 died
Inciardi *et al* [13], 2020	Retrospective study	Italy	Total patients 99. acute on chronic hf 21 (21%)

due to use of Peak end expiratory pressures and mechanical ventilation causing decreased venous return. Cytokine storm detailed above can result in distributive shock[26]. Pulmonary embolism from coagulopathy and pericardial tamponade can cause obstructive shock which are reported in COVID-19. Worsening of chronic kidney disease or onset of acute kidney injury leading to volume overload has been reported in up to 29% of patients with COVID-19 and chronic HF[6,18].

Acute right heart failure (RHF) in COVID-19 has been primarily thought to be due to ARDS and severe hypoxemia. RHF due to acute pulmonary embolism has also been reported in 5%-22% of cases by different authors[19,20]. High clot burden was also found in patients with right heart strain from pulmonary embolism[21]. Patients with COVID-19 are several times at higher risk of pulmonary embolism compared to non-COVID-19 patients and is also associated with higher mortality[20]. Severe Acute Respiratory distress syndrome may lead to pulmonary hypertension and cause right-sided heart failure. Myocardial injury and myocarditis can also weaken the right heart ventricle in COVID-19. Right heart failure in COVID-19 is associated with increased mortality[22,23] Etiopathology of HF in COVID-19 has been summarized in inline diagrams in Figures 1 and 2.

Clinical evaluation and utility of diagnostic tools

Symptoms of HF, in general, can be due to reduced cardiac output causing fatigue and weakness. It could also be due to excessive fluid accumulation resulting in dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, and edema. Patients in cardiogenic shock could have a low cardiac output state. Overall, it can be difficult to accurately distinguish most of the symptoms of HF from COVID-19 itself, so careful examination and use of diagnostic tools are imperative. Signs of fluid overload like weight gain, Jugular venous distension, fine crackles at lung bases, wheezing, third heart sound, abdominal distension, ascites, and pitting pedal edema can be used as important clues at the bedside to determine new-onset or exacerbation of HF in COVID-19 patients.

Plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro BNP) are useful laboratory markers in suspected HF. High sensitivity troponins (hs-cTn) are often elevated as a marker of myocardial inflammation[16]. BNP less than 100 pg/mL and NT-proBNP less than 450 pg/mL have high negative predictive for HF[27]. Elevated plasma BNP and NT-proBNP also indicate poor prognosis in general, and this relationship holds true for HF in COVID-19 as well[28]. Elevated NT-proBNP level was detected in 12.9% of 3219 patients in a study from Wuhan, China. The adjusted hazard ratio for NT-proBNP was 5.71 (95%CI 3.50-7.47)[29]. In another study conducted on 397 patients with COVID-19 in Milan, Italy, 14.9% had elevated BNP levels, and the mortality rate was higher by 33.9% in these patients [30]. Elevation of BNP, NT-Pro BNP or troponin, hs-cTn should be interpreted with caution. It should not trigger evaluation for heart failure or Myocardial infarction unless patients have accompanying signs and symptoms or EKG changes to suggest diagnosis.

Electrocardiogram (EKG) may not receive ample attention in the diagnosis of HF beyond the milieu of a cardiologist. Perhaps, it is highly unlikely that a patient with a normal EKG will have a dysfunctional left ventricle (LV). Atrial fibrillation, old myocardial infarction, left ventricular hypertrophy, axis deviation, bundle branch block, and ST-T wave abnormalities may hint towards underlying acute or chronic HF in patients with COVID-19[16]. EKG changes commonly observed in COVID-19 patients were atrial fibrillation or flutter, Premature atrial (APCs) and ventricular contractions, Bundle branch block, interventricular conduction delay, and repolarization abnormalities[31]. Abnormal EKGs changes like APCs, Right BBB/Intraventricular block, Ischemic T wave inversions, and non-specific repolarization abnormalities were associated with an increased risk of adverse cardiac events or death in patients with underlying comorbidities like cardiovascular or renal diseases[31,32].

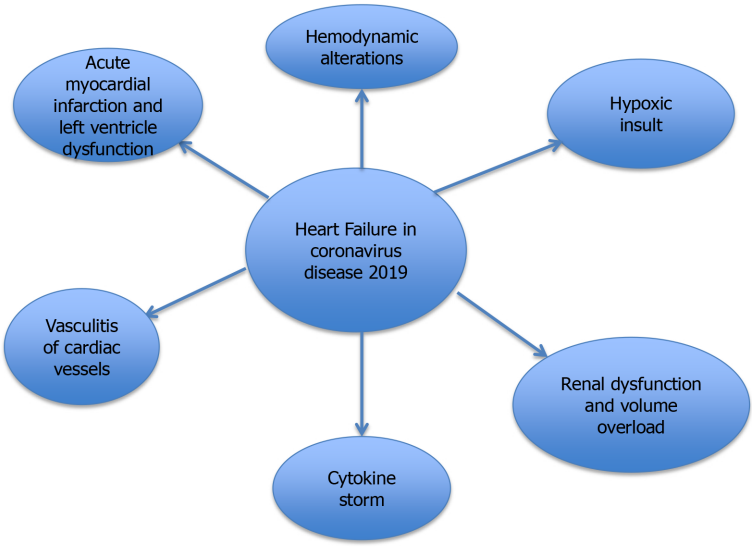

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Figure 1 Pathogenesis of heart failure in coronavirus disease 2019.

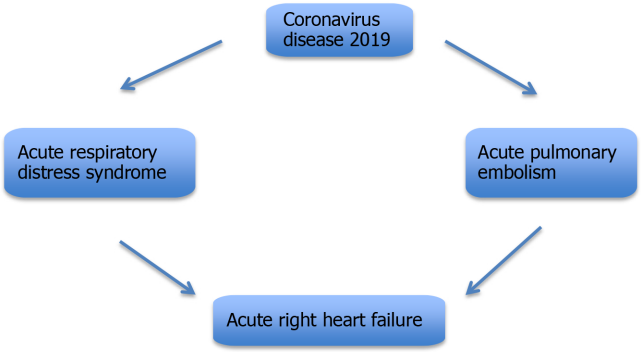

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Figure 2 Causes of acute right heart failure in coronavirus disease 2019.

An echocardiogram is one of the most important diagnostic tools for HF. There have been some studies utilizing echocardiograms in patients with COVID-19. Szekely *et al*[33], performed an echocardiogram in 100 patients within 24 h of hospitalization with COVID-19. 32% of patients had a normal echocardiogram, 39% had right ventricle (RV) dilatation and dysfunction, 16% had LV diastolic dysfunction, and 10% had LV systolic abnormality. Reassessment with echocardiogram due to deterioration during hospital course showed worsening of RV failure in 12 patients and LV systolic failure in 5 patients[33]. In a prospective international study of 1216 patients from 69 countries, 667 patients (55%) were found to have an abnormal echocardiogram. 479 (39%) had LV dysfunction while 397 (33%) had RV dysfunction. Echocardiography findings changed management in 33% of these patients[34]. In an International multicenter study of 305 patients admitted with COVID-19, RV dysfunction was found in 26.3%, LV diastolic dysfunction in 13.2%, and LV global systolic dysfunction in 18.4% of patients. Moreover, multivariate adjustments showed that myocardial injury with abnormal echocardiograms represented higher mortality in comparison to normal echocardiograms[35]. Hence, an echocardiogram is a vital diagnostic tool that should be used by clinicians taking care of COVID-19 patients in a timely and appropriate manner. The Trans-thoracic echocardiogram has also been performed successfully among COVID-19 patients with ARDS who were in prone position by temporarily deflating the lower thoracic portion of the air mattress. This helps in placing the probe between the thorax and the mattress surface[36].

The role of cardiac magnetic resonance imaging (MRI) has been so far more relevant in patients that are on the road to recovery from acute COVID-19 illness. Because of inflammatory cardiomyopathy, some of these patients can develop HF as a sequela. In a German study of 100 patients that were in the recovery phase from acute COVID-19 illness, cardiac MRI was abnormal in 78% of patients at an average of 71 days from initial diagnosis. Compared to the control group, these patients had lower LV and RV ejection fractions. Furthermore, endomyocardial biopsy in three patients with elevated T1/T2 signal, late gadolinium enhancement, and LV ejection fraction less than 50% revealed lymphocytic infilt-

ration with no detection of the viral genome[37]. In another study of 148 patients with severe COVID-19 infection, cardiac MRI was done at a median of 68 days post-discharge from the hospital. The myocarditis-like scar was seen in 26%, and infarction was found in 54%, but 89% of these patients had normal LV function[38]. Thus, cardiac MRI and endomyocardial biopsy in selected COVID-19 patients may be of value in timely diagnosis and initiation of goal-directed medical therapy where HF arises as a late complication in subacute and chronic recovery phases (Table 2).

MANAGEMENT

Management of HF exacerbation during COVID-19 should be based on the volume status, the previous history of heart failure, and vital signs. Patients with heart failure and COVID-19 have worse hospitalization and in-hospital mortality outcomes in a systematic review and meta-analysis of 18 studies[39].

Shared decision-making among consultants is necessary to guide clinical management regarding immunosuppression, multiple treatments, multiorgan involvement, and associated complications in COVID-19.

Chronic heart failure patients have a higher risk of in-hospital complications like acute heart failure, acute renal failure, sepsis and length of stay, and in-hospital mortality[40,41].

Medications should be initiated per Guideline-directed medical therapy and continued. Special considerations exist for each class of drugs which are discussed below.

Diuretics

Diuretics in heart failure and COVID-19 help to decongest the lungs. Prior to starting diuretics, they require careful monitoring of the volume status by physical examination, BNP, and bedside ultrasound assessment for the IVC (inferior vena cava) collapsibility[42]. Pulmonary artery catheter, Echocardiography, and cardiac output monitoring are other methods for advanced hemodynamic monitoring in patients with complex hemodynamics. Conservative fluid strategy with judicious initiation or up-titration of diuretics with daily weights is recommended[43]. Aiming for a negative fluid balance is necessary for these patients. Watching for signs of hypotension and over diuresis which can result in kidney injury is necessary. Nephrotoxic medications should be used carefully along with diuretics, *i.e.*, NSAIDs, Remdesivir, or nephrotoxic antibiotics like vancomycin[42,44]. If there is diuretic resistance, then ultrafiltration can be considered to treat heart failure and AKI[42].

It was hypothesized that medications associated with upregulation of ACE2 receptors could worsen the COVID-19 infection, which was not proven in further studies. Outcomes among heart failure patients were similar regardless of ACE inhibitor or ARB use[40].

Heart failure society of America/American College of Cardiology/American Heart Association guidelines recommends against adding or discontinuing these medications beyond the standard of practice in patients with preexisting heart failure, hypertension, or ischemic heart disease. However, careful decision-making and medication discontinuation should be done in acute kidney injury, hypotension, hyperkalemia, and shock on a patient-to-patient basis[45].

Beta-blockers

Carvedilol is the recommended beta-blocker in patients with heart failure and COVID-19 due to its anti-cytokine action[46,47]. However, these medications should not be started for COVID-19 and HF beyond the standard of practice. Assessment of hemodynamic stability is necessary before the initiation of beta-blockers[42]. Patients previously on beta-blockers can have inappropriate bradycardia with COVID-19. Dose changes should be made if patients develop a low output state[45]. Betablockers also help patients with sinus tachycardia and tachyarrhythmias[45]. Antiviral medications like Remdesivir and Tocilizumab can influence the pharmacokinetics of cardiovascular medications, increasing the risk of toxicities and arrhythmias.

Digoxin

Most of the indications for digoxin in HF with reduced ejection fraction are as a rate control agent in those with low blood pressure and atrial fibrillation[48]. Digoxin has antiviral and anti-inflammatory properties per prior literature[46]. Again, there is no recommendation to start patients with new-onset HF and COVID-19 on these medications beyond clinical practice. Digoxin levels should be closely monitored when given anti-viral medications and immunomodulators that may interact with it[42].

Anticoagulation therapy

Consideration should be given for interaction between anticoagulants' current and emerging COVID-19 therapies. Monitoring the liver and kidney function is also necessary. Unfractionated Heparin or Low molecular weight heparin (LMWH) is the preferred anticoagulant in hospitalized patients with prior anticoagulation for other causes. It is particularly preferred in sick patients due to drug interactions with oral anticoagulants[45]. If oral anticoagulants are needed in less sick patients, switching to direct oral anticoagulants is preferred over Vitamin K antagonists. Prophylactic Anticoagulation with LMWH can

Table 2 A late complication in subacute and chronic recovery phases

Diagnostic tools	Likely heart failure	Likely COVID/ARDS
BNP/NT-Pro BNP and clinical findings	BNP > 100 pg/mL or NT-Pro BNP > 450 pg/mL Signs and symptoms of right and left heart failure	< 450 pg/mL Absence of signs and symptoms of volume overload
EKG	Abnormal ekg findings of LVH, LAE, Sinus tachycardia, LAD, RAD, AF, PVCs, BBB	Nonspecific findings or symptoms of pulmonary embolism, Right heart strain or myocardial ischemia
ECHO	Ejection Fraction%, RV dilatation and dysfunction, LV Diastolic dysfunction, LV global systolic dysfunction	Findings of pulmonary arterial hypertension; RV dysfunction, enlargement and abnormal contraction, septal dyskinesia. Acute Cor pulmonale
CMRI	Establishes ischemic *vs* nonischemic heart failure, quantification of ventricular function and scar burden	Distinguishes pulmonary *vs* extrapulmonary causes for acute respiratory distress syndrome

LVH: Left ventricular hypertrophy; LAE: Left atrial Enlargement; LAD: Left axis deviation; RAD: Right axis deviation; AF: Atrial fibrillation; PVCs: Premature ventricular complexes; BBB: Bundle branch blocks.

be considered in all inpatients if there is no hemorrhagic risk[49].

Mineralocorticoid receptor antagonists

Careful use in heart failure patients based on volume status and kidney function. Electrolytes should also be monitored.

Recommendations regarding guideline-directed medical therapy

Stopping GDMT, *i.e.*, Beta-blockers, ACE/ARB, and mineralocorticoid receptor antagonists in patients with chronic heart failure with COVID, are associated with increased in-hospital mortality per prior studies[50]. If GDMT therapy has been discontinued inpatient for AKI or hemodynamic instability, during discharge of patients post heart failure exacerbation, they should be restarted as they have favorable outcomes in heart failure patients[50].They should follow up with the cardiologist or physician for heart failure to review and adjust the dose of GDMT.

Ionotropic/ vasopressor medications and respiratory support

Patients with heart failure have pulmonary edema superimposed on COVID-19 pneumonia. High BNP levels elevation in patients with ARDS indicates cardiogenic shock and pulmonary edema. Use of non-invasive ventilation and prone ventilation help to decrease pulmonary edema. Heart Failure patients are susceptible to hypoxia and ARDS and therefore may require intubation and lung-protective ventilation. These methods also help to manage right heart failure from ARDS[51].

The shock from sepsis and heart failure can develop. Dehydration and hypoperfusion can worsen symptoms. Clinical assessment, bedside echo, and monitoring of hemodynamics help in assessing the pathophysiology of shock. Volume status assessment, careful use of diuretics, and intravenous fluid repletion are needed. The greatest benefit of fluid resuscitation was seen in patients with signs of hypoperfusion who are in hypovolemic shock[26]. In patients with Mixed shock (cardiogenic and septic), vasopressors or inotropes should be started.

Norepinephrine is the preferred vasopressor agent for septic and cardiogenic shock, especially in hypotensive patients[51].If there are signs of low organ perfusion or severe decreased cardiac output, inotropes such as dobutamine and epinephrine can be added[51].Cardiac output monitoring helps in the selection and titration of inotropes and vasopressors.

Bedside, Intra-aortic balloon pump should be considered in severe cardiogenic shock refractory to vasopressors or inotropes[52]. ECMO as mechanical circulatory support is used in the setting of ARDS/hypoxemia with refractory cardiogenic shock in available centers[45,51].

Myocarditis in COVID-19: Patients can present with Heart failure symptoms. Inotropes and vasopressors, mechanical circulatory support, and mechanical ventilation can be used in severe cases.

COVID-19 with HF in heart and lung transplant recipients

Heart Transplant and Heart and lung transplant recipients are on immunosuppression with medications like calcineurin inhibitors, prednisone, and antimetabolites. They are prone to COVID-19 infection from immunosuppression and can have severe symptoms and outcomes[53,54]. For patients with mild symptoms, supportive treatment with the continuation of immunosuppression is recommended.

In patients with moderate to severe illness, anti-metabolites such as azathioprine and mycophenolate mofetil can be held inpatient per the international society of heart and lung transplantation recommendations[55].

Table 3 Summary of management

Management of heart failure
We should know that the development of heart failure in COVID-19 patients can complicate management and worsen the prognosis; Chronic heart failure patients have adverse outcomes compared to new-onset heart failure patients; GDMT guided medical therapy should be used in heart failure with individualized patient decision making based on hemodynamic status and development of complications; Avoiding over diuresis to prevent kidney injury and hypoperfusion is necessary; Watching for signs of deterioration and shock with early initiation of vasopressors in mixed shock should be practiced; Cardiac arrhythmias and acute myocardial infarction are some major complications to look out for.; Advanced hemodynamic monitoring helps to guide management in these patients; Post-recovery cardiac, pulmonary rehabilitation with psychological support and nutritional interventions is necessary

COVID-19: Coronavirus disease 2019.

These patients should be treated at a heart transplant center. After the infection resolves, careful monitoring is required when restarting immunosuppression in these patients due to effects from the allograft[53].

Breakthrough infection

Breakthrough infections after the COVID-19 vaccination have been frequently observed in older patients and those with comorbidities. One study described close to 12% of breakthrough infections after vaccination[56]. In another study of 700 breakthrough cases close to 49% of the patients were symptomatic[57]. Despite increased breakthrough infection in this patient population, they did not develop disease severe enough to require supplemental oxygen or ICU admission[56,58].

Vaccinated people have a shorter duration of virus transmission, short symptom duration, and restricted tissue dissemination[59].

Chronic heart failure patients with breakthrough infections who are stable can be treated as outpatients with GDMT.

Rehabilitation post-recovery

In the Post-Acute phase, exercise training should be done in these patients, considering oxygen saturation, heart rate, systolic blood pressure, and symptoms[60]. Cardiac rehabilitation includes a variety of programs such as aerobic endurance training, interval training (IT), High intensity IT and resistance training done around 2-5 times per week[60].Thoracic expansion exercises to increase lung ventilation and airway clearance are some of the recommended methods for respiratory rehabilitation in these patients. Home-based cardiac telerehabilitation- is another alternative strategy to follow for these patients. Psychological support and nutritional interventions should also be a part of rehabilitation programs[60].

Complications

Direct viral infection of the myocardium can cause myocardial injury and complications such as myocarditis and myocardial interstitial fibrosis[61,62]. System-wide inflammatory response and release of pro-inflammatory markers like Tumor necrosis factor, interleukin-6, and interleukin-1β are associated with direct myocardial injury and can cause myocardial infarction[24,63]. The prothrombotic state can result in acute coronary events[61,62]. Cardiac Arrhythmias such as atrial arrhythmias, bradyarrhythmia, and non-sustained ventricular tachycardia can occur due to inflammation of the myocardium, fibrosis, edema of interstitial tissues, medication side-effects, and myocarditis[61,62]. Atrial fibrillation can predispose patients to cardiogenic shock[62].

Patients who recover after severe COVID-19 are at high risk of Pulmonary hypertension, Diastolic dysfunction, and right heart failure[9,64]. Stress-induced cardiomyopathy or Takutsubo cardiomyopathy can develop from microvascular dysfunction and inflammatory response[65,66]. The summary of management is illustrated in Table 3.

CONCLUSION

Heart Failure can occur as a complication in patients with COVID-19 infection. It can worsen the course of COVID-19 and is associated with poor outcomes. It requires early diagnosis and appropriate management on a patient-to-patient basis. Continuing Guideline Directed medical therapy is recommended. We need to watch out for complications during its management. Post the acute phase of COVID physical, psychological and nutritional rehabilitation for these individuals is necessary to aid in recovery.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Is there a window of opportunity to optimize trastuzumab cardiac monitoring?

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Abstract

BACKGROUND

It remains unclear whether the current arbitrary screening recommendations of trastuzumab-related cardiotoxicity provides an adequate balance between preventing heart damage and curtailing a curative treatment.

AIM

To determine the incidence rate and consequences of trastuzumab-induced cardiotoxicity as adjuvant treatment in a real-world scenario.

METHODS

We present a retrospective analysis of cardiac function measured by echocardiogram at baseline and every 3 mo during trastuzumab treatment. Cardiotoxicity was defined as a drop in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and/or any drop < 50%.

RESULTS

Between January 2011 and December 2014, 407 patients were selected. Most (93.6%) were treated with an anthracycline followed by a taxane-based regimen and trastuzumab for 12 mo. Forty patients (9.8%) had cardiotoxicity. None of

them were symptomatic, and 28 (72.5%) completely recovered LVEF. Cardiotoxicity happened early as shown by LVEF measured on echocardiogram 2 to 4 as compared to 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). There were 54 deaths (13.3%) during the 70-mo follow-up period; 1 (0.2%) was attributed to late cardiotoxicity (4 years after treatment). The absence of symptomatic cardiotoxicity during trastuzumab treatment and moreover the early occurrence on the treatment period may translate into a strategy to evaluate less frequently.

CONCLUSION

We observed a 10% rate of asymptomatic cardiotoxicity, which mirrors the results from the large adjuvant trials. Despite being transient, an LVEF drop led to frequent treatment delays and interruptions. It remains unclear whether LVEF decline is predictive of late cardiotoxicity, and treatment efficacy is compromised.

Key Words: Cardiac toxicity; Ventricular Dysfunction; Heart failure; Trastuzumab; Breast cancer

Core Tip: It remains unclear whether the current arbitrary screening recommendations for trastuzumab-related cardiotoxicity in early-stage HER2-positive breast cancer provides an adequate balance between preventing heart damage and curtailing a curative treatment. Real world data showed that despite a low rate of mainly early, asymptomatic and transient cardiotoxicity, treatment delays and interruptions occur due to these findings. The study results suggest optimization of cardiac monitoring after an initial period without a decrease in cardiac function.

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INTRODUCTION

Trastuzumab, a monoclonal antibody targeting HER2, represents a milestone in breast cancer treatment. The drug improves the progression-free and overall survival in metastatic and localized HER2-positive breast cancer[1,2]. Cardiotoxicity remains the most compromising side effect[3]. Myocardial HER2 receptors are associated with cardiac function protection physiologically[4]. Therefore, the drug administration could lead to a decrease in left ventricular ejection fraction (LVEF), usually reversible, although a few patients need to delay or permanently stop their ongoing treatment[4,5]. The incidence is around a quarter of patients receiving the drug, with a small percentage experiencing heart failure (1%-4%)[6]. Several factors can contribute, such as the chemotherapy regimen, particularly anthracycline, patient characteristics such as age, previous cardiovascular disease and low ejection fraction prior to treatment initiation[7].

Cardiotoxicity of anti-cancer treatment includes any toxicity affecting the heart[8] and suggested by biomarkers, such as decrease of LVEF or signs of heart failure[9]. Guidelines suggest a baseline pre-treatment evaluation and risk stratification, during treatment monitoring and post-treatment surveillance[2,10]. Although these recommendations mimic the schedules used in the clinical trials, the cardiac assessment was not supported by prospective data. Our study aimed to evaluate the cardiac function during trastuzumab treatment for early-stage breast cancer in a real-world scenario.

MATERIALS AND METHODS

Materials and methods

A retrospective chart review was performed using patient medical files from January 2010 to December 2014, at the Instituto Nacional de Cancer, Brazil. Patients had tissue confirmation of HER2-positive breast cancer, stage I to III, treatment with chemotherapy combined with and followed by trastuzumab. Exclusion criteria included loss to follow-up in less than 3 mo after treatment initiation.

Echocardiogram was performed at baseline and every 3 mo during trastuzumab treatment. It was performed by the same examiner and device [Siemens SONOLINE G 60, with P 4-2 cardiac probe (4.0-2.0 MHz)]. The analyses performed included the M-mode, 2D-mode, spectral doppler, color Doppler

and tissue doppler imaging. The cavities dimensions were obtained according to the recommendation of the American Society of Echocardiography[11]. LVEF was calculated though the Teichholz Formulae. Cardiotoxicity was defined as: a 10% drop in LVEF from the baseline echo, a drop below 50% or symptoms according to the New York Heart Association class III or IV[12,30].

The study was approved by the institutional review board and conducted in accordance with the Good Clinical Practice Guidelines and the Helsinki declaration.

Statistical analysis

Numerical variables were reported by central tendency measures, and categorical variables were represented by absolute frequency and percentages. A bar plot containing the percentage of cardiotoxicity detected by echocardiograms at each scheduled measurement was performed to describe differences between patients that developed cardiotoxicity. A univariate analysis using the χ^2 method for categorical variables and two sample *t*-test for continuous variables were initially performed to test the association between cardiotoxicity and potential confounders in clinical practice (age, comorbidities, body mass index).

To verify statistical differences in cardiotoxicity during the follow-up time, odds ratio was calculated to show differences in cardiac event odds in the beginning *vs* end of screening period. The prevalence ratio was calculated using the Wald[13] and Score[14] methods. The R statistical software was used to calculate the odds ratio and prevalence measures using the epiR package[15].

RESULTS

From 423 eligible patients, 16 were excluded (7 with metastatic disease and 9 lost to follow-up), with 407 remaining for the final analysis. The median age was 52 years, and the body mass index was 27.54 kg/m^2. The stage at presentation was predominantly stage III: 59.47%. Most tumors were invasive ductal carcinoma (98.64%), and an anthracycline followed by taxane-based regimen was the most common treatment (93.6%). Almost all patients received trastuzumab for the whole 1-year period (97.0%) (Table 1).

Forty patients (9.8%) had cardiotoxicity at a median time of 289 d (114-680 dc) from treatment initiation, and a wider variation of LVEF was seen in cardiotoxicity patients as shown by Figure 1. Although none of these patients were symptomatic, all of them had their treatment delayed due to the echocardiogram findings. Twenty-nine patients (72.5%) recovered the LVEF, for which the drug was restarted, and 11 (27.5%) had trastuzumab suspended. The rates of cardiotoxicity did not vary according to age (P = 0.58), comorbidities (P = 0.81) or body mass index (P = 0.64).

Cardiotoxicity occurred early, as shown in Figure 2. The prevalence in echocardiograms 2 to 4 was 2.7% against 1.1% prevalence ratio in echocardiograms 5 to 7. The odds of cardiotoxicity were 2.5 times higher when echocardiogram 2 to 4 were compared to echocardiogram 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). The median follow-up time was 70 mo, and there were 54 deaths (13.3%). Overall, survival did not vary according to cardiotoxicity (P = 0.08). One death (0.2%) was attributed to heart failure. However, it occurred 4 years after the end of trastuzumab treatment, possibly related to late anthracycline cardiotoxicity.

DISCUSSION

We showed a 9.8% cardiotoxicity rate detected by routine echocardiogram during trastuzumab-based treatment for early-stage breast cancer. To our knowledge, this is the largest real-world cohort reported in South America. Our results were similar to the ones presented by the large breast cancer adjuvant clinical trial 3, which varied from 6.0% to 35.4%[16,17]. This wide variation could be explained by the different chemotherapy regimens but more likely attributed to patient selection and diverse definitions of cardiotoxicity[18]. Whilst contemporary studies focus on predictive biomarkers (*i.e.* plasma levels of troponin and/or brain natriuretic peptide) and more costly imaging studies (*i.e.* cardiac magnetic resonance imaging), transthoracic echocardiogram is widely available with an affordable cost, which allows its widespread use[19]. Although the pathophysiology of cardiotoxicity is being elucidated, and players such as neuregulin[20] have been suggested. Reliable and validated biomarkers with a better cost-effectiveness than LVEF estimation are awaited[21].

Recommendations to withhold trastuzumab in Europe (absolute LVEF decrease > 20% or > 10% to < 50% or symptomatic heart failure)[22] and America (LVEF decrease ≥ 16% from baseline or LVEF below institutional limits of normality and ≥ 10% absolute LVEF decreased from baseline)[23] are roughly similar in not considering borderline asymptomatic decrease in LVEF. None of the patients in this cohort had symptoms at the time of the abnormal echocardiographic findings. Notwithstanding, it led to treatment delays and interruptions based on the guidelines available. The consequences of asymptomatic LVEF drop are unknown as well as whether early trastuzumab treatment interruption

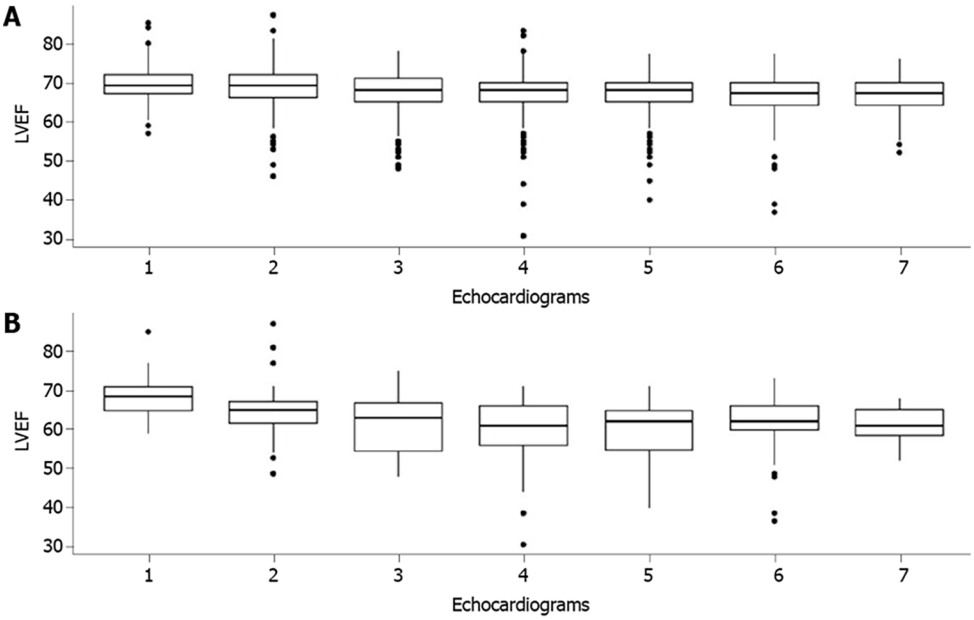

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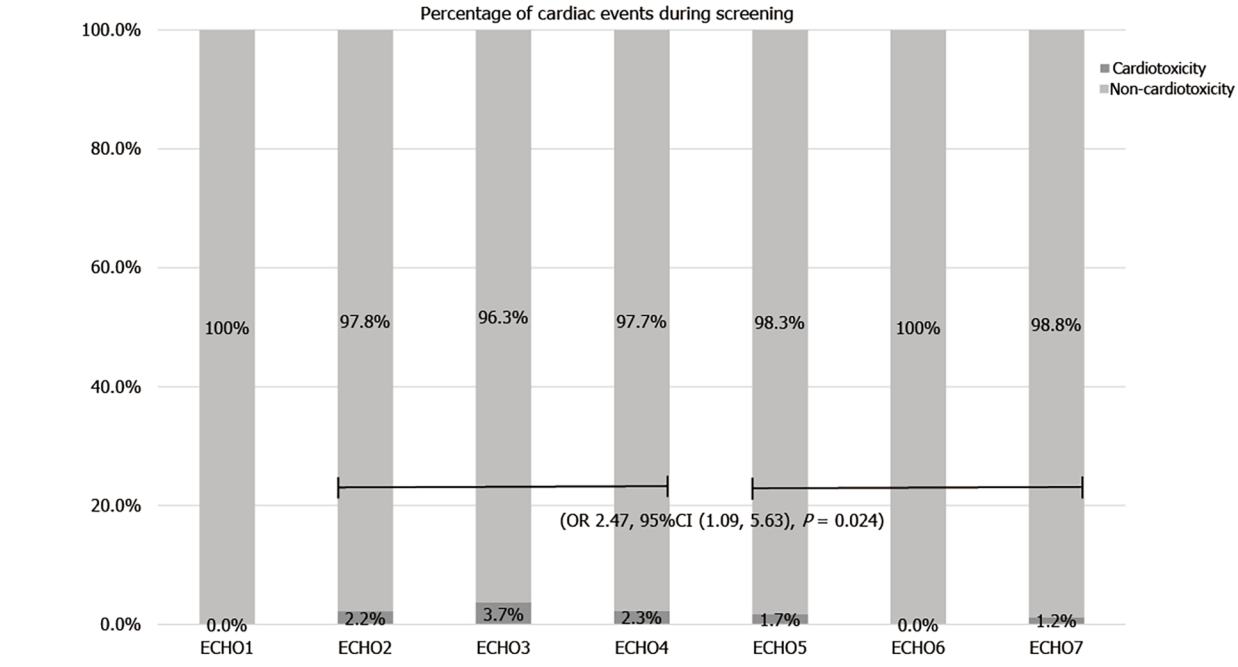
Figure 1 Left ventricular ejection fraction over trastuzumab cardiotoxicity monitor. A: Total sample; B: Cardiotoxicity group. LVEF: Left ventricular ejection fraction.



Status	Frist (Baseline)	Second	Third	Fourth	Third	Sixth	Seventh
Non-cardiotoxicity	407	397	392	398	348	195	80
Cardiotoxicity	0	9	15	9	6	0	1

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Figure 2 Percentage of cardiac event over time. OR: Odds ratio; CI: Confidence interval.

may compromise its efficacy[24,25]. More recent trials showed less clinical cardiac dysfunction in shorter trastuzumab treatment duration compared to longer trastuzumab treatment duration[26].

There are known risk factors associated with trastuzumab-related cardiotoxicity such as age above 65, Ile655Val HER2 polymorphism, previous cardiovascular disease, radiation therapy and the use of anthracycline, especially high cumulative doses[27,28]. In our cohort, we were unable to show such a correlation. The studies on the other hand are conflicting about other factors such as other comorbidities (diabetes or kidney function impaired) or baseline LVEF (high or low)[3]. We interpret these factors

Table 1 Patients and treatment characteristics

Variable	Absolute number	Percentage
Age		
Minimum	18	-
Median	52	-
Maximum	79	-
Body mass index		
Minimum	14.27	-
Median	27.54	-
Maximum	50.58	-
Comorbidities		
Hypertension	56	13.75
Diabetes	19	4.66
Lack of other comorbidities reported	330	81.10
Menopausal status		
Post-menopausal	304	74.69
Pre-menopausal	103	25.31
Histological subtypes		
Invasive ductal carcinoma	400	98.28
Invasive lobular carcinoma	5	1.22
Others	2	0.50
Clinical stage		
I	36	8.86
II	129	31.69
III	242	59.45
Chemotherapy regimen		
Anthracycline and taxane based	381	93.61
Non-anthracycline based	26	6.39
Chemotherapy purpose		
Neoadjuvant	204	50.12
Adjuvant	203	48.88
Adjuvant radiotherapy		
Yes	213	52.33
No	194	47.67
Trastuzumab duration		
1 yr	395	97.06
Less than 1 yr	12	2.94

with caution once the standard of care population is significantly heterogeneous and frequently differs from the subjects included in clinical trials. Moreover, specific recommendations to adapt cardiac monitoring is lacking, unless the patient has a high cardiotoxicity risk[29].

Of note, we showed an increased incidence of cardiotoxicity in the early monitoring as compared to the later cardiac function evaluation through echocardiogram. As there is a lack of prospective randomized clinical trials for optimal cardiac monitoring[30], our results provide an opportunity to such an endeavor. Our study limitations included its retrospective nature, the limited number of patients and the lack of standard reporting of comorbidities. On the other hand, similar studies suggest that a

population to optimize monitoring might exist[31].

CONCLUSION

The cardiotoxicity rates in a real-world population were similar to those reported by the large adjuvant trastuzumab trials. Most events occurred early during the initial monitoring examinations. As these findings led to treatment changes with unknown long-term consequences. These results deserve a prospective confirmation to assess the optimal way to monitor and manage trastuzumab-related cardiac events.

ARTICLE HIGHLIGHTS

Research background

It remains unclear whether the current arbitrary screening recommendations of trastuzumab-related cardiotoxicity provides an adequate balance between preventing heart damage and curtailing a curative treatment.

Research motivation

There is an urgent need to optimize monitoring of cardiotoxicity.

Research objectives

This study aimed to determine the incidence rate and consequences of trastuzumab-induced cardiotoxicity as adjuvant treatment in a real-world scenario.

Research methods

A retrospective chart review was performed using patient medical files during 5 years at a single institution in Brazil. Patients had tissue confirmation of HER2-positive breast cancer, stage I to III, treatment with chemotherapy combined with and followed by trastuzumab. Exclusion criteria included loss to follow-up in less than 3 mo after treatment initiation.

Research results

Forty patients (9.8%) had cardiotoxicity (out of 407 included). None of them were symptomatic, and 28 (72.5%) completely recovered left ventricular ejection fraction. Cardiotoxicity happened early as shown by left ventricular ejection fraction measured on echocardiogram 2 to 4 as compared to 5 to 7 (odds ratio = 2.47, 95% confidence interval: 1.09, 5.63, P = 0.024). There were 54 deaths (13.3%) during the 70-mo follow-up period; 1 (0.2%) was attributed to late cardiotoxicity (4 years after treatment).

Research conclusions

The absence of symptomatic cardiotoxicity during trastuzumab treatment and moreover the early occurrence on the treatment period may translate into a strategy to evaluate less frequent cardiac monitoring.

Research perspectives

This data alongside similar studies in the literature warrants a prospective evaluation of a de-escalation of cardiotoxicity monitoring in a selected population.

FOOTNOTES

Author contributions: Rala de Paula BH, Costa METF and Bines J contributed to data collection; Rala de Paula BH, de Sousa CAM and Bines J were in charge of statistical analysis; All authors participated in the study plan, paper writing and reviewing and approved the final manuscript.

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Observational Study

Vitamin d deficiency and metabolic syndrome: The joint effect on cardiovascular and all-cause mortality in the United States adults

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Abstract

BACKGROUND

The long-term impact of vitamin D deficiency and metabolic syndrome (MetS) on cardiovascular disease (CVD) and all-cause mortality are still a matter of debate.

AIM

To test the hypotheses that lower serum 25 hydroxyvitamin D [25(OH)D] concentrations (a marker of vitamin D level) and MetS have a long-term impact on the risk of CVD and all-cause mortality, and individuals with vitamin D deficiency can be identified by multiple factors.

METHODS

A sample of 9094 adults, 20 to 90 years of age, who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) were followed through December 2015 was analyzed. The associations of serum

25(OH)D concentrations and MetS with CVD and all-cause mortality were analyzed longitudinally using Cox regression models. Classification and regression tree (CART) for machine learning was applied to classify individuals with vitamin D deficiency.

RESULTS

Of 9094 participants, 30% had serum 25(OH)D concentrations < 20 ng/mL (defined as vitamin D deficiency), 39% had serum 25(OH)D concentrations between 20 to 29 ng/mL (insufficiency), and 31% had serum 25(OH)D concentrations ≥30 ng/mL (sufficiency). Prevalence of MetS was 28.4%. During a mean of 18 years follow-up, vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. Subjects with both vitamin D deficiency and MetS had the highest risk of CVD mortality (HR = 1.77, 95%CI: 1.22-2.58) and all-cause mortality (HR = 1.62, 95%CI: 1.26-2.09), followed by those with both vitamin D insufficiency and MetS for CVD mortality (HR = 1.59, 95%CI: 1.12-2.24), and all-cause mortality (HR = 1.41, 95%CI: 1.08-1.85). Meanwhile, vitamin D sufficiency significantly decreased the risk of CVD and all-cause mortality for those who even had MetS. Among the total study sample, CART analysis suggests that being non-Hispanic Black, having lower serum folate level, and being female were the first three predictors for those with serum 25(OH)D deficiency.

CONCLUSION

Vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. There was a significant joint effect of vitamin D deficiency and MetS on the risk of mortality. Findings of the CART analysis may be useful to identify individuals positioned to benefit from interventions to reduce the risk of CVD and all-cause mortality.

Key Words: Joint effect; Serum 25 hydroxyvitamin D concentration; Metabolic syndrome; Cardiovascular and all-cause mortality; Cox model and machine learning

Core Tip: To investigate the long-term effect of vitamin D deficiency and metabolic syndrome on the risk of cardiovascular disease and all-cause mortality using a nationally representative sample. Standard measurements of the study exposures, co-variables and outcomes are processed. Multivariate Cox's proportional hazards regression analysis was used to prospectively test the associations between the exposures and outcomes. Classification and regression tree for machine learning was applied to classify subjects with higher risk of lower serum vitamin D concentrations.

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INTRODUCTION

The classical function of vitamin D is to increase the intestinal absorption of calcium for proper bone mineralization. Vitamin D can be obtained by the diet or synthesized on the skin with exposure to ultraviolet-B from the sun. The best method to determine vitamin D status is through measurement of serum 25 hydroxyvitamin D [25(OH)D] concentrations[1,2]. Recent evidence has demonstrated that individuals with vitamin D deficiency are more likely to have cardiovascular disease (CVD), and are associated with CVD risk factors, including metabolic syndrome (MetS)[3-7]. However, most studies examined the cross-sectional association of serum 25(OH)D concentrations and MetS with the prevalence of CVD. Few studies, with a longitudinal study design, estimated the causal association between vitamin D deficiency and the risk of CVD. Furthermore, the findings of the previous studies are inconsistent. For example, the Women's Health Initiative calcium-vitamin D trial, a randomized clinical trial, observed a weak association between vitamin D supplementation and CVD risk reduction among postmenopausal women[8,9]. Meanwhile, the characteristics of the population with vitamin D deficiency varied by different studies[2]. In our early report in 2012, we tested the medium-term effect of serum vitamin D deficiency and risk of heart failure and premature mortality[4]. In the present study, we aimed to examine the long-term effect of vitamin D and MetS on the risk of CVD and all-cause

mortality using data from the third National Health and Nutrition Examination Survey (NHANES III). The NHANES III started in 1988 to 1994 and is an ongoing follow-up study for the participants' vital status through the national Linked Mortality Files (LMFs). The NHANES III provides us a unique opportunity to prospectively examine the association between baseline serum 25(OH)D concentrations and risk of disease-specific and all-cause mortality among community-dwelling residents in the United States[10,11]. In this study, we aimed to test two hypotheses: (1) Serum 25(OH)D deficiency and MetS are significantly associated with risk of CVD and all-cause mortality; and (2) serum 25(OH)D deficiency varies by age, sex, race/ethnicity, poverty and key measures of serum biomarkers.

MATERIALS AND METHODS

The NHANES III is a nationwide survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in the United States[10,12]. The baseline survey was conducted from October 1988 through October 1994 in two phases (phase 1: 1988-1991, and phase 2: 1991-1994) gathering information representing the health and nutritional status of the noninstitutionalized civilian United States residents ages 2 mo and older. Participants were recruited based on a nationwide probability sample across four regions of the USA (Northeast, Midwest, South, and West). The study consisted of (1) household interviews on sociodemographic factors, health behaviors, and history of medical conditions through standard survey instruments; (2) physical examinations in mobile examination centers (MEC); and (3) laboratory measures from blood and urine samples. Blood samples were obtained at the MEC for measurements of serum and urinary biomarkers. To minimize hemolysis of blood samples in the measures of serum lipid profiles and glucose concentrations, participants were asked to fast for 12 hours before a morning examination, or 6 hours before an afternoon or evening examination. All phlebotomists were certified and trained in standardized laboratory procedures. Detailed information on the NHANES III has been provided elsewhere[10,12].

Follow-up data for participants' survival status or disease-specific and all-cause mortality were extracted from the NHANES III Linked Mortality File (LMF). The LMF was linked by the NCHS working with the State's Offices of Vital Statistics to link NHANES III data with death certificate records using the National Death Index (NDI)[13]. The NDI is a central computerized index of death record information on files. This standard and technique-supported linkage process provide an opportunity to conduct longitudinal analyses between measures at baseline and outcomes through the follow-up period. In the present study, we used data from the recently available follow-up of the LMF for the NHANES III from baseline 1988-1994 through December 31, 2015. The NHANES III survey was approved by the CDC NCHS institutional review board. Data obtained from the NCHS for the present study were de-identified for participants' private information security. The study, using the deidentified NHANES III and its LMF to examine risk factors for mortality has been approved by the Drexel University Office of Institutional Review Board (#2105008546). Of 18799 participants, 23 without follow-up and 2869 without serum 25(OH)D measures were excluded. Of the rest 15907, we further excluded 6251 who had fasting blood sample < 8 hours (to assess triglycerides and glucose concentrations), and 562 who had no measurements of five MetS components. That, the final study sample size was 9094 for those who had serum 25(OH)D concentrations measured, had valid follow-up records for their vital status, and had full measurements of MetS components [waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and fasting glucose concentrations]. Figure 1A shows the sample size flowchart.

Exposures

Measurements of serum 25(OH)D concentrations were performed as part of the nutritional biomarkers of the NHANES III (1988 to 1994)[10]. Serum 25(OH)D concentrations were measured at the National Center for Environmental Health, CDC, Atlanta GA, using the DiaSorin RIA kit (Stillwater MN). In the study, we analyzed serum 25(OH)D concentrations as a categorical variable in the Cox regression models to examine hazard ratios of serum 25(OH)D concentrations for risk of mortality. We applied the commonly used cut-off points to categorize serum 25(OH)D levels into three groups: (1) Vitamin D deficiency was defined as serum 25(OH)D concentrations < 20 ng/mL (< 50 nmol/L); (2) Vitamin D insufficiency was defined as serum 25(OH)D concentration 20 to 29 ng/mL (50 to 74 nmol/L); and (3) Vitamin D sufficiency was defined as serum 25(OH)D concentrations ≥ 30 ng/mL (≥ 75 nmol/L)[1,4,14,15]

On MetS, five components are included. These are waist circumference (WC), which was measured using a standard flexible and tension-regulated tape measure. Systolic and diastolic blood pressure (SBP and DBP, respectively), were measured with an automated blood pressure monitor after five minutes of rest, with the last two of three readings, averaged and recorded. Blood samples collected at least 8 hours fasting were used to assess TG, and fasting glucose concentrations. To define MetS, we applied the cut-off criteria modified from the American Heart Association (AHA), the American Diabetes Association (ADA), and the Adult Treatment Panel III (ATP III)[16]. Individuals with MetS were defined by the presence of 3 of five MetS components: (1) Large WC (a marker of abdominal adiposity): WC > 102 cm

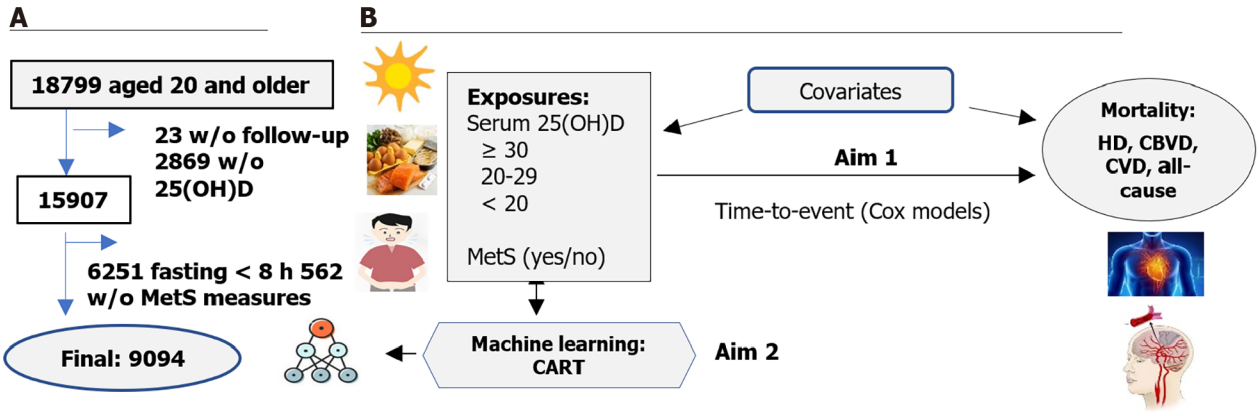

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Figure 1 Participant flowchart (A) and the analysis conceptual model (B) in the study. Serum 25(OH)D: Serum 25 hydroxyvitamin D (a marker of vitamin D level in blood); MetS: Metabolic syndrome; CART: Classification and regression tree; HD: Heart disease; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease.

in males and > 88 cm in females; (2) Elevated BP: SBP ≥ 130 or DBP ≥ 85 mmHg or under antihypertensive medication use; (3) Elevated TG: TG ≥ 150 mg/dL; (4) Elevated glucose: fasting glucose ≥ 100 mg/dL or use of glucose-lowering medications; and (5) Low HDL-C: HDL-C < 40 mg/dL in males and HDL-C < 50 mg/dL in females.

Outcomes

The study outcomes included mortality from (1) Heart disease (HD) (*International Classification of Disease, Tenth Revision, ICD-10* codes: I00-I09, I11, I13, I20-I51); (2) Cerebrovascular diseases (CBVD, ICD-10 codes: I60-I69); (3) CVD (included either HD and CBVD); and (4) All-cause mortality. Follow-up time (years) was calculated from the baseline interview to the end of follow-up (December 31, 2015), or until the date of death if a participant died before the end of follow-up, whichever occurred first.

Covariates

We included the following factors as covariates in the analysis. These variables are: age (years), sex (males, and females), race/ethnicity, educational attainments, smoking status, alcohol consumption, physical activity, and chronic conditions. Race/ethnicity are classified based on participants' self-reports using standard survey questionnaire. Three groups are recorded: non-Hispanic White, non-Hispanic Black (*i.e.*, African American), and the other groups (including Hispanic or Latino, Asian, native Hawaiian or other Pacific Islander). Educational attainments are classified into three groups (less than high school, high school, and colleges or higher levels), smoking status, alcohol consumption, physical activity, and chronic condition. Smoking was categorized as "never", "former", and "current smokers". Alcohol consumption was defined by a question, "Have you had at least 12 drinks in the last 12 mo?" (*i.e.*, at least once a month, "yes" or "no"). Physical activity was categorized as more activity, about the same, or less activity from a survey question: "How does the amount of activity that you reported for the past month compare with your physical activity for the past 12 mo?" Chronic conditions were self-reported diagnoses on questions: "Have you been told by a doctor that you have the following disease(s): hypertension, diabetes mellitus, coronary heart disease, heart failure or stroke?" ("yes" or "no").

Statistical analysis

We conducted a serial analysis to examine the two specific aims (Figure 1B). In the first set of analyses, we described the characteristics of the study participants across three groups of serum 25(OH)D concentrations (*i.e.*, serum 25(OH)D < 20, 20 to 29, and ≥ 30 ng/mL, respectively). Differences in MetS rates, sex, race/ethnicity, education attainment, smoking status, alcohol consumption, and history of chronic conditions at baseline were tested using the Chi-squared test. Differences in continuous variables were tested using analysis of variance. In the second-set analyses, we estimated age-sex-adjusted mortality rates (per 10000 person-years) from HD, CBVD, CVD, and all-cause mortality by serum 25(OH)D concentrations and MetS using Poisson regression models in SAS GENMOD procedure. In the third-set analyses, we estimated the hazard ratio and its 95% confidence interval of serum 25(OH)D concentrations and MetS for HD, CBVD, CVD, and all-cause mortalities using time-to-event Cox proportional hazards regression (Cox) models. In the analyses, follow-up time (years) and mortality (yes or no) were the dependent variables, and serum 25(OH)D concentrations (reference to 25(OH)D ≥ 30 ng/mL) and MetS (yes *vs* no) were the independent variables. To test Cox proportional hazard assumption, we applied plots of log(-log) survival curves and Schoenfeld residuals methods. To control potential

confounders, we performed two multivariate-adjusted models. Model 1 adjusted for age (years), sex (males and females), race/ethnicity [non-Hispanic White (NHW), non-Hispanic Black (NHB), and the others], education (< high school, high school, and > high school), and living in regions of the United Stated (Northeast, Midwest, South, and West). We included the adjustment for regions for control potential difference in the exposures to sunshine across the nation because sunshine is one of the possible resources for a human to get vitamin D. Model 2 further adjusted for covariates including smoking (never, former, and current smokers), alcohol consumption (yes or no), physical activity (more activity, about the same, or less activity) and baseline prevalence of CVD (yes or no) because these lifestyle and baseline health conditions were associated with the study exposures and outcomes. We tested the interaction effects of serum 25(OH)D and MetS on mortality risk as well. In the fourth-set analyses, because we did not observe a significant interaction effect of serum 25(OH)D and MetS on the risk of CVD and all-cause mortality, we further estimated their joint effect on the risk of HD, CBVD, CVD, and all-cause mortality.

In the fifth-set analyses, we applied classification and regression trees (CART), a predictive algorithm in machine learning techniques, to test the characteristics of participants with different serum 25(OH)D concentrations to use classification tree analysis to identify individuals who are at higher risk of vitamin D deficiency. CART analysis is a standard decision tree analysis in machine learning introduced by Breiman *et al*[17] and Bzdok *et al*[18]. CART analysis does not request data with a certain mathematical distribution (*i.e.*, distribution-free). Compared to Principal Component Analysis and Factor Analysis, CART analysis more easily handles noisy data, such as outliers from multiple variables, because CART's splitting algorithms can isolate outliers into a separate node[17]. In CART analysis, data are partitioned along the predictor axes into subsets with homogeneous values of the outcome variable. A decision tree is created, which can be used to make predictions from new observations[18]. The selection of important predictors can be assessed by mean decrease in Gini (MDG) index. MDG index is an average of a variable's total decrease in node impurity, weighted by the proportion of samples reaching that node in each decision tree in the random forest. A higher MDG index indicates higher variable importance. To valid the classification process, we used two sub-datasets: (1) 20% of the total participants were randomly selected serving as the validation dataset; and (2) The remaining 80% served as the training dataset to construct the predicting models. In the analysis, serum 25(OH)D concentrations in two and three categorical groups as the dependent variable and the other 46 variables as the independent variables (Supplementary Table 1). Serum 25(OH)D concentrations were categorized as: (1) Serum 25(OH)D ≥ 20 *vs* < 20 ng/mL; (2) Serum 25(OH)D ≥ 30, *vs* 20 to 29, *vs* < 20 ng/mL; and (3) Serum 25(OH)D ≥ 30 *vs* < 30 ng/mL.

Statistical analyses were performed using SAS 9.14 (SAS Institute, Cary, North Carolina). SAS analyses for complex sample surveys were used by taking into consideration the NHANES III's complex, multistage, probability sampling design. CART analyses were performed using R programming[19], and "rpart" package[20]. A 2-sided P value < 0.05 was considered statistically significant in all data analyses.

Finally, we conducted a sensitivity analysis by the exclusion of those who died within the first year of follow-up to avoid a potential over-estimate of the association of serum 25(OH)D concentrations and MetS with mortality risk because patients with serious health conditions might die within the first year of the follow-up.

RESULTS

Participants' characteristics

Of 9094 participants, 30% had serum 25(OH)D concentrations less than 20 ng/mL (defined as vitamin D deficiency), 39% had serum 25(OH)D concentrations in the 20 to 29 ng/mL range (insufficiency), and 31% had serum 25(OH)D concentrations ≥ 30 ng/mL (sufficiency). The total prevalence of MetS was 28.4%. Table 1 shows that across the three groups of serum 25(OH)D concentrations, the highest prevalence of MetS (35.3%) was observed among participants with serum 25(OH)D < 20 ng/mL, followed by 29.2% and 20.7%, respectively, among those with serum 25(OH)D concentrations in the 20 to 29 ng/mL range and those with serum 25(OH)D concentrations ≥ 30 ng/mL (testing for rates differences, P < 0.001). The mean ages were 45.8, 44.7, and 40.3 years older among those with serum 25(OH)D concentrations of < 20 ng/mL, 20 to 29 ng/mL, and ≥ 30 ng/mL, respectively (P < 0.001).

Participants with the lowest serum 25(OH)D concentrations had the highest mean waist circumference (WC), body mass index (BMI), SBP and DBP, serum TG, and glucose concentrations, but slightly lower HDL-C concentrations compared to those with serum 25(OH)D ≥ 30 ng/mL. Among those with serum 25(OH)D concentrations < 20 ng/mL, 61.7% were females. The proportions of race/ethnicity, education attachments, and alcohol consumption by serum 25(OH)D concentrations were significantly different (P < 0.001). Meanwhile, participants with serum 25(OH)D concentration < 20 ng/mL had a significantly higher prevalence of hypertension (36.5%), diabetes mellitus (9.3%), and CVD (6.3%) compared to those with serum 25(OH)D 20-29 ng/mL and those with serum 25(OH)D ≥30 ng/mL, respectively (P < 0.01).

Table 1 Characteristics of participants at baseline

	Serum 25(OH)D concentrations									*P* value
	< 20 ng/mL			20 to 29 ng/mL			≥ 30 ng/mL			
	No.	mean, %	(SE)	No.	mean, %	(SE)	No.	mean, %	(SE)	
MetS, %										< 0.001
No	2640	64.7		2230	70.8		1276	79.3		
Yes	1394	35.3		1089	29.2		465	20.7		
Age, yr	4034	45.8	(0.6)	3319	44.7	(0.6)	1741	40.3	(0.6)	< 0.001
Waist circumference, cm	4034	94.2	(0.4)	3319	92.2	(0.3)	1741	88.3	(0.4)	< 0.001
Body mass index, kg/m^2	4033	27.8	(0.2)	3318	26.5	(0.1)	1739	25.0	(0.1)	< 0.001
Systolic BP, mmHg	4034	123.4	(0.6)	3319	122.0	(0.6)	1741	119.0	(0.6)	<0.001
Diastolic BP, mmHg	4034	74.7	(0.3)	3317	74.1	(0.3)	1741	72.9	(0.4)	< 0.001
Triglycerides, mg/dL	4034	138.9	(4.1)	3319	136.4	(2.6)	1741	126.5	(3.8)	< 0.001
HDL-C, mg/dL	4034	51.0	(0.5)	3319	49.3	(0.4)	1741	51.5	(0.6)	< 0.001
Glucose, mg/dL	4034	100.7	(0.7)	3319	98.4	(0.5)	1741	94.7	(0.4)	< 0.001
Categorical variable, %										
Sex, male, %	1561	38.3		178	51.9		975	55.4		< 0.001
Race/ethnicity, %										< 0.001
NHW	894	55.1		1557	79.7		1213	92.0		
NHB	1788	25.8		575	6.0		139	1.9		
Others	1352	19.1		1187	14.3		389	6.1		
Region										< 0.001
Northeast	490	15.8		429	20.6		303	26.7		
Midwest	651	18.9		709	24.5		434	28.1		
South	1933	40.3		1299	33.2		685	29.1		
West	960	25.0		882	21.6		319	16.1		
Education level										0.001
< High school	930	13.1		818	11.8		355	8.2		
High school	1971	49.2		1532	45.8		788	46.1		
> High school	1113	37.7		949	42.4		592	45.6		
Smoking										0.07
Never	2562	62.1		2230	63.9		1130	62.5		
Former	193	5.5		191	6.0		105	4.0		
Current	1279	32.4		898	30.2		506	33.5		
Alcohol consumption, yes	1704	44.8		1592	55.9		910	63.7		< 0.001
Exercise, yes										0.13
More activity	559	14.1		475	16.3		287	18.4		
About the same	2433	58.3		1998	56.2		1005	52.7		
Less activity	1040	27.6		841	27.5		445	28.9		
Health conditions										
Hypertension, yes	1489	36.5		1129	29.6		565	25.5		< 0.001

Diabetes mellitus	465	9.3	312	6.7	105	3.3	< 0.001
CVD	278	6.3	252	5.3	124	3.4	0.001

Weighted mean and percentage are estimated because NHANES III applied a complex, multistage, probability sampling design. SE: Standard error; MetS: Metabolic syndrome; BP: Blood pressure; HDL-C: High-density lipoprotein cholesterol; NHW: Non-Hispanic White; NHB: Non-Hispanic Black; Others: Including all the other race/ethnicity groups; CVD: Cardiovascular disease included those with coronary heart disease, heart failure, or stroke.

Mortality rate by serum 25(OH)D concentrations and MetS status

Table 2 shows that during a mean of 18 years follow-up, participants with serum 25(OH)D concentrations < 20 ng/mL had significantly higher age-sex-adjusted mortality from HD (17.4 per 10000 person-years), CVD (21.3 per 10000 person-years), and all-cause mortality (103.9 per 10000 person-years) compared to those with serum 25(OH)D concentrations ≥ 30 ng/mL. Participants with MetS had significantly higher age-sex-adjusted mortality from HD (16.7 per 10000 person-years), CVD (22.0 per 10000 person-years), and all-cause mortality (102.4 per 10000 person-years) compared to those without MetS.

Multivariate-adjusted hazard ratios of serum 25(OH)D and MetS for mortality

Table 3 shows that, after adjusting for age, sex, race/ethnicity, and region (Model 1), and additional adjusting for health behaviors and baseline CVD (Model 2), participants with serum 25(OH)D concentrations < 20 ng/mL had a significantly higher risk of HD, CVD, and all-cause mortality compared to those with serum 25(OH)D concentrations ≥ 30 ng/mL. The corresponding hazard ratios [HRs and 95% confidence intervals (CI)] in Model 2 were 1.43 (1.07-1.91, P = 0.017) for HD, 1.36 (1.04-1.78, P = 0.028) for CVD, and 1.32 (1.10-1.58, P = 0.004) for all-cause mortality, respectively.

Participants with MetS had a significantly higher risk of CVD and all-cause mortality compared to those without MetS in Models 1 and 2. The corresponding HRs (95%CI) in Model 2 were 1.29 (1.05-1.59, P = 0.017) for CVD, and 1.20 (1.05-1.36, P = 0.01) for all-cause mortality.

No significant association of serum 25(OH)D concentrations and MetS with the risk of CBVD mortality, and no significant interaction effects of serum 25(OH)D concentrations and MetS on the risk of HD, CBVD, CVD, and all-cause mortality were observed (P > 0.05).

Joint effects of serum 25(OH)D concentrations and MetS on mortality risk

We further estimated the joint effect of those who had lower serum 25(OH)D concentrations and MetS on mortality risk. Figure 2 depicts that individuals with serum 25(OH)D concentrations < 20 ng/mL and MetS had the highest risk of CVD (HR = 1.77, 95%CI: 1.22-2.58, P < 0.01, Figure 2A) and all-cause mortality (HR = 1.62, 95%CI: 1.26-2.09, P < 0.01, Figure 2B), followed by those with serum 25(OH)D concentrations 20 to 29 ng/mL and with MetS [1.59 (1.12-2.24, P = 0.01) for CVD, and 1.41 (1.08-1.85, P = 0.01) for all-cause mortality] as compared to those with serum 25(OH)D ≥ 30 ng/mL and without MetS (the reference group). Figure 2 also shows that individuals with MetS, but with serum 25(OH)D concentrations ≥ 30 ng/mL, did not have a significantly higher risk of CVD (HR = 1.44, 95%CI: 0.96-2.22, P = 0.008) and all-cause mortality (HR = 1.30, 95%CI: 0.95-1.78, P = 0.09) compared to the reference group (shown as green bars in Figure 2), indicating a higher protective effect of serum 25(OH)D concentrations ≥30 ng/mL on CVD and all-cause mortality compared to MetS.

Identifying the main predictors for those with lower serum 25(OH)D concentrations

We used CART to identify the top 10 important predictors from 46 variables (Supplementary Table 1) for participants with serum 25(OH)D at different concentrations and by sex. Table 4 shows the overall results. Figure 3 depicts an example of CART analysis for serum 25(OH)D concentrations ≥ 20 ng/mL *vs* < 20 ng/mL among the total sample (S1 of Table 4). Racegp (race/ethnicity) is grouped as racegp = 1 for non-Hispanic White (NHW), 2 for non-Hispanic Black (NHB), and 3 for the other racial/ethnic groups. Figure 3A indicates that the classification tree starts from node 1 (also called the root) and ended in node 5 (*i.e.*, the "leaves"). Under each oval-shaped box, the values on the left-listed indicate the percentage of individuals with serum 25(OH)D concentrations ≥ 20 ng/mL [such as under node 1, 55% of individuals had serum 25(OH)D concentrations ≥20 ng/mL]. It should be noted that if the left-listed value is more than 0.5 (*i.e.*, > 50%), the oval-shaped box will be labeled as 25(OH)D ≥ 20 ng/mL, otherwise labeled as 25(OH)D < 20 ng/mL (such as 5a and 5b of node 5, *i.e.*, 0.29 and 0.38 are less than 0.50). Under each box, the value on the right-listed indicates the percentage of the participants included in the node (such as 100% in node 1). Figure 3A depicts that among the randomly selected training sample, 55% of them had serum 25(OH)D concentrations ≥20 ng/mL. In the analysis, race/ethnicity was first selected by the CART algorithm as a predictor. Of the sample, 28% (the value showing on the right-listed under box 5a of node 5) were NHB (*i.e.*, racegp = 2). Among NHB, 29% (on the left-listed value) had serum 25(OH)D concentrations ≥ 20 ng/mL (note: the oval-shaped box is labeled as 25(OH)D < 20 ng/mL because 0.29 is less than 0.5). In other words, 71% of NHB had serum 25(OH)D concentrations < 20 ng/mL. Of the total training sample, 72% were NHW and other racial/ethnic groups (*i.e.*, racegp ≠ 2), and 66% of them had

Table 2 Age-sex-adjusted mortality from heart disease, cerebrovascular disease, cardiovascular disease, and all-cause mortality

	Observed number		Weighted mortalityrate per 10000 PY		*P* value
	No. at risk	Case	Rate	(95%CI)	
Heart Disease					
25(OH)D, ng/mL					
≥ 30	1741	130	11.7	(8.2-16.6)	Ref.
20-29	3319	272	13.2	(10.3-16.9)	0.43
< 20	4034	292	17.4	(13.1-23.0)	0.012
CBVD					
25(OH)D, ng/mL					
≥ 30	1741	34	3.6	(2.0-6.6)	Ref.
20-29	3319	83	3.6	(2.5-5.1)	0.97
< 20	4034	88	4.5	(2.5-7.9)	0.53
CVD					
25(OH)D, ng/mL					
≥ 30	1741	164	15.3	(11.4-20.5)	Ref.
20-29	3319	355	16.6	(13.3-20.7)	0.56
< 20	4034	382	21.3	(16.6-27.3)	0.023
All-cause					
25(OH)D, ng/mL					
≥ 30	1741	545	75.9	(64.9-88.8)	Ref.
20-29	3319	1141	87.5	(79.4-96.3)	0.066
< 20	4034	1290	103.9	(93.2-115.8)	< 0.001
MetS status					
Heart Disease					
MetS, no	6146	327	12.5	(9.7-16.2)	Ref.
MetS, yes	2948	369	16.7	(12.9-21.7)	0.002
CBVD					
MetS, no	6146	97	3.2	(2.2-4.7)	Ref.
MetS, yes	2948	108	5.1	(2.9-8.9)	0.059
CVD					
MetS, no	6146	424	15.9	(13.0-19.5)	Ref.
MetS, yes	2948	477	22.0	(16.9-28.6)	< 0.001
All-cause					
MetS, no	6146	1490	82.5	(75.3-90.5)	Ref.
MetS, yes	2948	1486	102.4	(91.0-115.3)	< 0.001

PY: Person-years; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease; 25(OH)D: Serum 25 hydroxyvitamin D concentration; MetS: Metabolic syndrome.

serum 25(OH)D concentrations ≥20 ng/mL (these values showing under the box of node 2). Of the 72% sample (*i.e.*, racegp ≠ 2), 32% were the other race/ethnicity (*i.e.*, racegp = 3), and 54% of them had serum 25(OH)D concentrations ≥20 ng/mL. The rest 40% (racegp ≠ 2 and racegp ≠ 3) were NHW, and 75% of NHW had serum 25(OH)D concentrations ≥ 20 ng/mL (Box 5e of node 5). Thirty-two percent (32%) of the total sample were other racial/ethnic groups (racegp = 3, node 3), 16% of the total sample were other racial/ethnic females (racegp = 3 and sex = 2, node 4), and of them, 43% had serum 25(OH)D concen-

Table 3 Hazard ratios of serum 25 hydroxyvitamin D concentration and metabolic syndrome for heart disease, cerebrovascular disease, cardiovascular disease, and all-cause mortality

	Model 1			Model 2		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Ref to 25(OH)D ≥ 30 ng/dL						
25(OH)D for HD						
20-29	1.13	(0.82-1.55)	0.45	1.13	(0.83-1.52)	0.43
< 20	1.54	(1.14-2.08)	0.005	1.43	(1.07-1.91)	0.017
25(OH)D for CBVD						
20-29	0.97	(0.61-1.53)	0.88	0.98	(0.62-1.56)	0.94
< 20	1.15	(0.58-2.26)	0.69	1.14	(0.58-2.25)	0.69
25(OH)D for CVD						
20-29	1.09	(0.82-1.46)	0.54	1.10	(0.82-1.46)	0.52
< 20	1.44	(1.09-1.91)	0.011	1.36	(1.04-1.78)	0.028
25(OH)D for all-cause mortality						
20-29	1.16	(0.99-1.35)	0.06	1.16	(0.99-1.36)	0.07
< 20	1.38	(1.16-1.64)	0.001	1.32	(1.10-1.58)	0.004
Ref to Non-MetS						
MetS for HD	1.31	(1.09-1.58)	0.005	1.22	(1.00-1.49)	0.053
MetS for CBVD	1.58	(0.94-2.66)	0.083	1.60	(0.96-2.65)	0.069
MetS for CVD	1.37	(1.12-1.66)	0.002	1.29	(1.05-1.59)	0.017
MetS for all-cause mortality	1.22	(1.08-1.37)	0.002	1.20	(1.05-1.36)	0.008
Interaction of						
25(OH)D x MetS on						
HD	0.91	(0.72-1.17)	0.46	0.91	(0.72-1.15)	0.41
CBVD	0.80	(0.39-1.66)	0.54	0.79	(0.38-1.62)	0.50
CVD	0.89	(0.71-1.12)	0.31	0.88	(0.70-1.11)	0.28
All-cause	0.98	(0.84-1.14)	0.78	0.96	(0.82-1.13)	0.63

Model 1 adjusted for age, sex, race/ethnicity, education, and regions; Model 2 adjusted covariate in Model 1 plus smoking status, physical activity, alcohol consumption, and baseline CVD. HR: Hazard ratio; 25(OH)D: Serum 25 Hydroxyvitamin D concentration; HD: Heart disease; CBVD: Cerebrovascular disease; CVD: Cardiovascular disease; MetS: Metabolic syndrome.

trations ≥ 20 ng/mL (note: the oval-shaped box is labeled as 25(OH)D < 20 ng/mL because 0.43 is less than 0.5). The rest 16% of the total sample were other racial/ethnic males (racegp = 3 and sex = 1). Of the males, 65% had serum 25(OH)D concentrations ≥ 20 ng/mL (Box 5d of node 5). Among the females (node 4), the CART algorithm further identified serum folate concentrations (FOP, a marker of folate intake) as an important factor to continue the classification. Sixteen percent (16%) of the total sample were other racial/ethnic females, 14% of them had serum folate concentrations (FOP) < 8.9 ng/mL, and 38% of them had serum 25(OH)D concentrations ≥ 20 ng/mL. Overall, node 3 it suggests that sex and serum folate level play a role in the further classification among the other racial/ethnic groups. The classified rates for those with serum 25(OH)D concentrations ≥ 20 range from 62% [*i.e.*, (1-0.38 = 0.62), Box 5b of node 5] to 75% (box 5e of node 5). Figure 3B depicts the top 10 important factors that predicted those with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL. These ranks are assigned based on the values of their MDG indexes, a larger bubbler size indicating a stronger predictor.

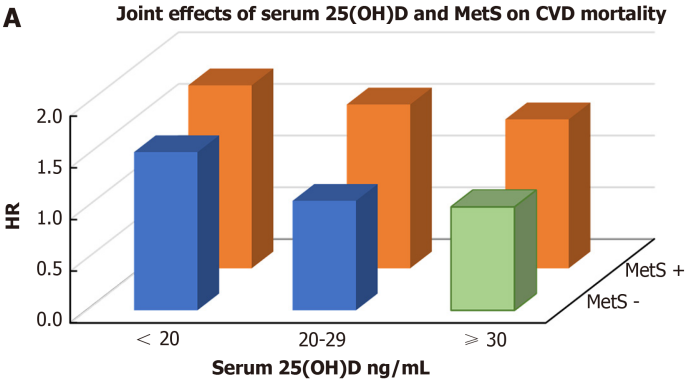
Table 4 shows the final selected top 10 predictors. Race/ethnicity was consistently selected as one of the important predictors in sample 1 (S1, the total sample) to sample 6 (in females). In S1, the top 10 important predictors for classifying those with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL were: race, serum folate level, sex, region, red blood cell folate (RBP, a marker of tissue stores of folate), poverty, educational level, glomerular filtration rate (GFR), serum uric acid (UAP), and alcohol

Table 4 Top 10 important predicators for classifying serum 25 Hydroxyvitamin D levels in the total and sex-specific samples

	S1: In both sex		S2: In males		S3: In females		S4: In both sex		S5: In males		S6: In females	
	≥ 20 *vs* < 20		≥ 20 *vs* < 20		≥ 20 *vs* < 20		≥ 30 *vs* < 30		≥ 30 *vs* < 30		≥ 30 *vs* < 30	
Rank	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG	Predictor	MDG
1	Race	519.5	Race	229.7	Race	267.7	Race	200.0	Race	95.2	Race	103.9
2	Folate	90.4	RBP	19.6	Folate	101.3	Age	97.5	WC	34.0	Age	79.4
3	Sex	57.3	Age	14.8	Age	77.5	Folate	65.1	BMI	29.0	GFR	50.6
4	Region	34.3	Glucose	14.2	GFR	73.7	GFR	54.8	AGE	28.9	Folate	49.6
5	RBP	34.0	GFR	13.1	RBP	50.7	BMI	48.8	Region	24.8	RBP	34.1
6	Poverty	33.3	Poverty	12.8	Poverty	50.1	WC	42.2	GFR	22.7	WC	32.0
7	Edu	30.3	Region	11.9	WC	22.9	Poverty	41.4	Insulin	18.9	SBP	26.9
8	GFR	29.6	WC	11.1	VEP	21.1	RBP	39.8	C1P	18.8	BMI	23.2
9	UAP	27.7	Folate	10.9	SBP	16.1	Glucose	22.0	RBP	18.6	VEP	22.0
10	Alcoh	21.6	Edu	9.8	A1C	14.6	DairyHEI	20.8	Poverty	17.4	Poverty	18.8
Accuracy,%	71.1		70.8		68.0		81.5		79.3		81.8	
Precision, %	68.4		68.2		68.2		83.0		82.4		85.6	
Recall,%	63.0		47.5		68.5		97.0		93.5		94.0	
F1 score, %	65.6		56.0		68.3		89.5		87.6		89.6	

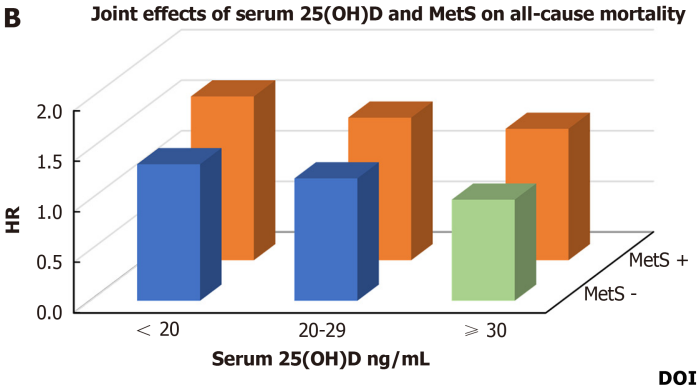
S1-S3: Samples 1 to 3. S1 to S3 for the classification of serum 25(OH)D ≥ 20 *vs* <20 ng/mL. Of them, S1: In the total sample. S2: In males. S3: In females. S4-S6: Samples 4 to 6. S4 to S6 for the classification of serum 25(OH)D ≥ 30 *vs* <30 ng/mL. Of them, S4: in the total sample. S5: In males. S6: In females. MDG: Mean decrease in Gini index. A higher MDG index indicates higher variable importance; RBP: Red blood cell folate; Edu: Educational level; GFR: Glomerular filtration rate; UAP: Serum uric acid; Alcohol: Alcohol consumption; WC: Waist circumference; BMI: Body mass index; VEP: Serum concentrations of vitamin E; SBP: Systolic blood pressure; A1C: Hemoglobin A1c; DairyHEI: Dairy healthy eating index; C1P: Serum C-peptide.

consumption. Table 4 also gives the prediction accuracy rate (the proportion of the correct predictions for both true positives and true negatives), precision rate (the proportion of the correct predictions for the true positives among the total positive predications), the recall rate (the proportion of the true positive predictions among the total true (observed) cases, and F1 score (a weighted average of the precision and recall rates, where an F1 score reaches its best value at 1 and worst at 0). For example, in S1, the average accuracy rate to classify individuals with serum 25(OH)D concentrations ≥ 20 *vs* < 20 ng/mL was 71.1%, the precision rate was 68.4%, the recall rate was 63%, and the F1 score was 65.6%. These rates vary with sex-stratified samples and by the cutoffs of serum 25(OH)D concentrations.



Vitamin D and MetS for CVD

25(OH)D	MetS	HR	(95%CI)	*P* value
≥ 30	No	1		
20-29	No	1.06	(0.69 – 1.62)	
		0.79		
< 20	No	1.53	(1.08 – 2.17)	0.02
≥ 30	Yes	1.44	(0.96 – 2.22)	0.08
20-29	Yes	1.59	(1.12 – 2.24)	0.01
< 20	Yes	1.77	(.122 – 2.58)	< 0.01



Vitamin D and MetSyn for All-cause

25(OH)D	MetSyn	HR	(95%CI)	*P* value
≥ 30	No	1		
20-29	No	1.21	(1.01 – 1.46)	0.04
< 20	No	1.35	(1.07 – 1.72)	0.02
≥ 30	Yes	1.30	(0.95 – 1.78)	0.09
20-29	Yes	1.41	(1.08 – 1.85)	0.01
< 20	Yes	1.62	(.126 – 2.09)	< 0.01

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Figure 2 Joint effect of serum 25 hydroxyvitamin D and metabolic syndrome on the risk of cardiovascular disease (A) and all-cause mortality (B). Serum 25(OH)D: Serum 25-hydroxyvitamin D; MetS: Metabolic syndrome; CVD: Cardiovascular disease; HR: Hazard ratio.

In the CART analyses, race/ethnicity, sex, age, and serum folate level were included as the important predictors in most prediction models (S1-S6). Figure 4 further depicts these associations that non-Hispanic Black (NHB) had significantly lower mean serum 25(OH)D concentrations (16 ng/mL in females, and 18.5 ng/mL in males, Figure 4A) than NHW and the other race/ethnicity groups in both males and females. Overall, a decreased trend of serum 25(OH)D concentrations by age was observed in NHW (Figure 4B). However, among female NHB and males in the other racial/ethnic groups, serum 25(OH)D concentrations decreased after age 65 years older (Figure 4B). An increasing trend of mean 25(OH)D concentration was observed among females in the other racial/ethnic groups (Figure 4B). Figure 4C indicates an overall increasing trend of serum 25(OH)D concentrations with the increase in serum folate levels in both males and females and NHW, NHB, and the other racial/ethnic groups, except for male NHB with a decreased trend of serum 25(OH)D concentrations at around 10 ng/mL of serum folate concentrations, and with a decreased trend for male NHW and males in the other racial/ethnic groups at around 15 ng/mL of serum folate concentrations.

Finally, results from the sensitivity analysis, by the exclusion of those who died within the first year of follow-up from the longitudinal analysis, do not change the overall results. Therefore, we present the results without this exclusion in the report.

DISCUSSION

The main findings from this study indicate that: (1) Individuals with serum 25(OH)D deficiency and MetS had a significantly higher risk of CVD and all-cause mortality; (2) There was a significant joint effect of serum 25(OH)D concentrations and MetS on the mortality risk; and (3) Among both males and females (sample 1 of Table 4), the top 10 predictors were race/ethnicity, serum folate concentrations, sex, region, serum retinol-binding protein, poverty, educational level, glomerular filtration rate (GFR), serum uric acid, and alcohol consumption.

The impact of vitamin D deficiency on the risk of a variety of chronic diseases, including diabetes mellitus, multiple sclerosis, cancer, and CVD, has been reported in recent decades but is still a matter of debate[21-23]. Because findings from previous studies are inconsistent[9,22,24]. For example, in meta-analyses of eight prospective cohort studies, in which 2624 participants died of CVD during follow-up, individuals in the lowest quantile of serum 25 (OH)D concentrations had an increased risk of CVD and all-cause mortality[24]. However, this finding may be confounded by the heterogeneity of data from different study designs, adjustment for different covariates in each study, several studies were possibly

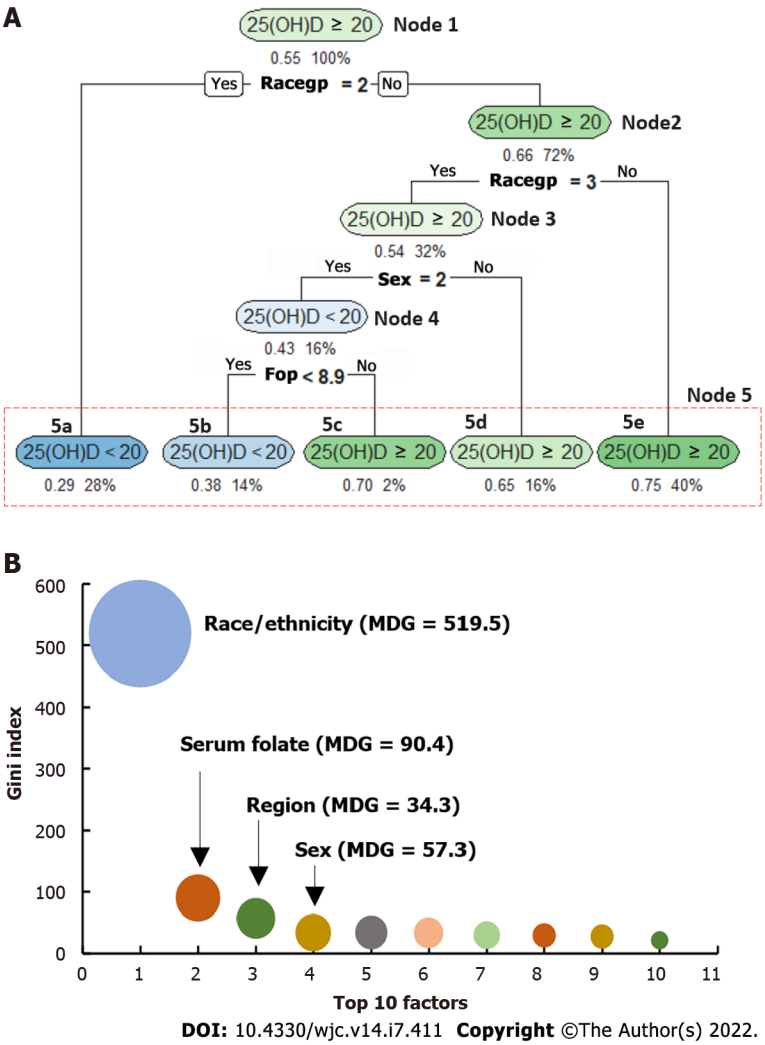

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Figure 3 Example of classification and regression trees with serum 25 hydroxyvitamin D ≥ 20 *vs* < 20 ng/dL in both sexes. A: Decision tree. Node 1: is the "root" node. Nodes 2 to 5 are the "leaves". Node 5 is also called as the terminal node, including five sub-nodes (5a – 5e). Each "leaf" is a classification labeled for the output variable {serum 25-hydroxyvitamin D [25(OH)D]}, showing in each oval-shaped box. Under each box, the values listed on right indicates the % of total sample size, and the value listed on the left indicates the % of those with serum 25(OH)D concentration ≥ 20 ng/mL. If the value on the left-listed is > 0.5 then the corresponding oval-shaped box is labeled as 25(OH) ≥ 20 ng/mL, otherwise labeled as < 20 ng/mL; B: An example of top 10 important variables presented by their mean decrease in Gini (MDG) index, a higher MDG indicates a stronger predictor for the output variable. 25(OH)D: 25-hydroxyvitamin D; RACEGP: Race group, coded as racegp = 1 for non-Hispanic White, racegp = 2 for non-Hispanic Black, and racegp = 3 for all the other race groups; Sex = 1 for male, and sex = 2 for female; FOP: Serum folate level; MDG: Mean decrease in Gini index.

confounded by other lifestyle-related factors, such as body weight and physical activity. Studies have shown that serum 25(OH)D concentrations are significantly associated with obesity and physical activity[5,25], as well as MetS is significantly associated with other CVD risks[2]. In our analysis, we adjusted key covariates and further examined the joint effect of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality, which also demonstrated that individuals with vitamin D sufficiency [serum 25(OH)D concentration ≥ 30 ng/mL] had a significant protective effect on CVD and all-cause mortality reduction even among those with positive MetS.

The mechanism by which vitamin D deficiency and MetS lead to an increased risk of CVD and all-cause mortality has not been fully elucidated. Several potential mechanisms have been hypothesized. First, the heart and the vasculature possess vitamin D receptors as well as the 1α–hydroxylase enzyme to activate serum 25(OH)D to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and thus are important target tissues for vitamin D. Second, several vitamin D effects on the electrophysiology, contractility, and structure of the heart suggest that vitamin D deficiency might be a causal factor for myocardial diseases [22,26]. Third, significant associations of vitamin D deficiency with obesity, hypertension, insulin resistance, and dyslipidemia (*i.e.*, the major components of MetS) have been reported by several researchers[5,24]. Although the complex association of vitamin D and MetS with risk of CVD requests more studies, findings of the joint effect of vitamin D deficiency and MetS, as well as a strong protective effect of vitamin D on CVD and all-cause mortality risk highlight the importance to control vitamin D deficiency and MetS for risk reduction of CVD and all-cause mortality.

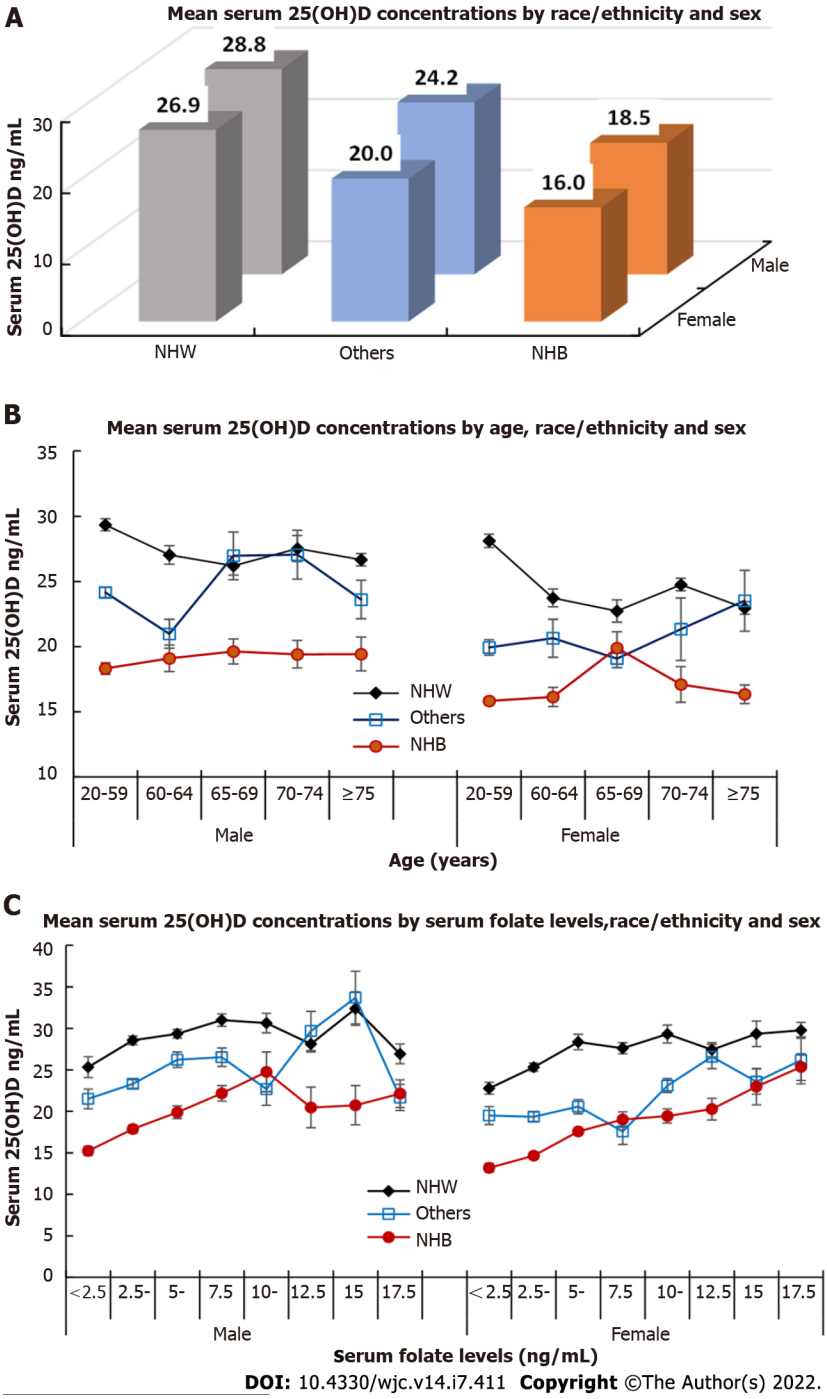

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Figure 4 Mean Serum 25-hydroxyvitamin D concentrations (ng/mL) by race/ethnicity and sex (A), and by age (B), and serum folate levels (C). Serum 25(OH)D: Serum 25-hydroxyvitamin D; NHW: Non-Hispanic White; NHB: Non-Hispanic Black; Other: All other race/ethnicity.

In CART analysis, we observe that the top 10 important predictors varied by the study samples, and the cutoffs of the output variables [*i.e.*, serum 25(OH)D concentrations]. The main results indicate that race/ethnicity was one of the most important predictors. NHB had the lowest mean of serum 25(OH)D concentrations followed by the other racial/ethnic groups, and NHW. Differences in socioeconomic status and biological factors may explain the race/ethnic difference in mean serum 25(OH)D concentrations as well, including education, overweight and obesity, and prevalence of chronic conditions of hypertension, diabetes mellitus, and chronic kidney disease. Findings from the CART analysis suggest that to classify individuals with different serum 25(OH)D concentrations, sociodemographic factors (age, sex, poverty level, and regions) and biomarkers (BMI, waist circumference, glomerular filtration rate, and serum total folate, red blood folate, glucose, insulin, C-peptide, triglyceride, and serum vitamin E concentrations) were potential predictors. Of these biomarkers, serum folate and red blood cell folate concentrations had a relatively higher mean decrease in the GINI index (*i.e.*, a higher impact on the classification analysis) than several other biomarkers (Table 4). Folate is an essential micronu-

trient from diet or diet supplementation and is also synthesized locally by the intestinal microbiome [27]. A positive association between serum folate and serum 25(OH)D concentrations and a significant association between serum folate and muscle strength have been reported by other studies[28,29]. Although a detailed analysis of potential interactions of these biomarkers is beyond the scope of the present study, the role of serum folate with serum 25(OH)D in cardiovascular health and mortality warrants further study.

It should be noted that there are several limitations of the study when interpreting the main findings. First, the NHANES III does not include participants who were hospitalized at the time of the baseline survey, which may lead to an underestimation of the association between serum 25(OH)D concentrations and mortality risk. Because individuals with the severe disease might have been hospitalized or have died before the baseline survey. Second, the estimated associations of serum 25(OH)D concentrations and MetS with risk of CVD and all-cause mortality may be under-or over-estimated if the values of baseline serum 25(OH)D concentrations and MetS components changed during the follow-up. Third, the nonsignificant association of serum 25(OH)D concentrations and MetS with risk of cerebrovascular disease (CBVD) was possibly due to the small sample size of CBVD cases. Further studies are needed to focus on CBVD risk using a larger sample size. Last but not the least, although Machine Learning (ML) offers a useful tool to develop a prediction algorithm, findings from ML, including CART analysis offer an overall and useful data mining approach. For example, the results from Table 4 suggest that stratified samples are needed to improve the CART algorithms.

This study also has several strengths. First, the NHANES III, using a complex survey sampling approach, provides a nationally representative sample of residents living in the United States. Second, the survey design, process, and laboratory measures employed standard protocols that are supported and coordinated by the CDC. Third, the measures of CVD and all-cause mortality were highly reliable by using a standardized record process of the National Death Index system[13,30]. Fourth, we analyzed the association prospectively, which allowed us to test a potential causal association of baseline serum 25(OH)D concentrations and MetS with CVD and all-cause mortality risk. Last, to the best of our knowledge, the study is the first to examine the joint effect of vitamin D and MetS on the risk of CVD and all-cause mortality using a nationally representative sample and has the longest follow-up by using the NHANES III. Findings from the CART analysis add to new insights into classifying high-risk groups with lower vitamin D concentrations.

CONCLUSION

In conclusion, vitamin D deficiency and MetS were significantly associated with increased risk of CVD and all-cause mortality. There was a significant joint effect of vitamin D deficiency and MetS on the risk of mortality. Findings of the CART analysis may be useful to identify individuals positioned to benefit from interventions to reduce the risk of CVD and all-cause mortality.

ARTICLE HIGHLIGHTS

Research background

Studies that tested whether there is a significant joint effect of vitamin D intake and metabolic syndrome (MetS) on the risk of cardiovascular disease (CVD) and all-cause mortality are sparse.

Research motivation

The third National Health and Nutrition Examination Survey provides us an unique opportunity to test the research questions using a large-scale population sample size, with an average of 18 years follow-up. An integrated analysis approach of standard statistics methods and Machine Learning may provide new insights into the study field and add new evidence of clustering risk factors to control CVD and all-cause mortality.

Research objectives

To test the hypotheses that lower serum 25 hydroxyvitamin D [25(OH)D] concentrations (a marker of decreased vitamin D intake) and MetS have a long-term impact on the risk of CVD and all-cause mortality, and individuals with vitamin D deficiency can be detected by key covariates.

Research methods

A prospective analysis of 9094 adults who participated in the Third National Health and Nutrition Examination Survey in 1988 to 1994 and were followed for each participant's vital status by December 31, 2015, was conducted.

Research results

Findings from the study add new evidence to the body of research by highlighting the joint effects of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality among the United States adults. A comprehensive intervention for both groups of risk factors are necessary to reduce the risk of CVD and all-cause mortality.

Research conclusions

There is a significant joint effect of vitamin D deficiency and MetS on the risk of CVD and all-cause mortality. The application of standard bio-statistics and Machine Learning techniques provides a new tool to test research hypothesis and provide new insights into health promotion for individuals who are at high risk of unhealthy exposures and risk of CVD and all-cause mortality.

Research perspectives

A high proportion of populations who have lower vitamin D levels and prevalent MetS poses a serious public health issue. Further studies are needed to examine the potential mechanisms by which that may cause vitamin D deficiency and MetS.

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FOOTNOTES

Author contributions: Liu L conceptualized the study and analysis designs, and performed the data analysis and drafted the manuscript; Cui S performed the machine learning analysis. Volpe SL, May NS, Sukumar D, DiMaria-Ghalili RA, Cui S, and Eisen H critically reviewed the study design and analysis methods, and carefully reviewed the results and edited the manuscript. All authors contributed to the study and approved the submission.

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ORIGINAL ARTICLE

Observational Study

National trend of heart failure and other cardiovascular diseases in people living with human immunodeficiency virus

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Abstract

BACKGROUND

As people living with human immunodeficiency virus (HIV) (PLWH) enjoy longer life expectancy with highly effective antiretroviral therapy, they are encountering challenging cardiovascular health risks.

AIM

To retrospectively examine the increasing burden of cardiovascular diseases in PLWH over the past decade.

METHODS

All hospitalizations for heart failure (HF), ischemic heart disease (IHD), and cerebrovascular disease (CeVD) in PLWH were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes in the National Inpatient Sample from 2008 to 2018. Outcomes included number of hospitalizations, in-hospital mortality, length of stay, and total hospital charge. Trend of the outcomes from 2008 to 2018 were analyzed using Cochran-Armitage trend test and simple linear regression.

RESULTS

The number of hospitalizations for HF in PLWH increased from 4212 in 2008 to 6700 in 2018 (P_{trend} < 0.01). Similar increasing trend was seen with those for IHD and CeVD over the decade (P_{trend} < 0.01). A decreasing trend of in-hospital mortality was observed in all hospitalizations of PLWH (P_{trend} < 0.01) and CeVD in PLWH (P_{trend} < 0.01), but not in those for HF (P_{trend} = 0.67) and IHD (P_{trend} = 0.13). The trend of length of stay was decreasing in all hospitalizations of PLWH (P_{trend} <

0.01), but increasing in those for HF in PLWH (P_{trend} < 0.01). An increasing trend of total hospital charge was observed in hospitalizations for HF, IHD, and CeVD (P_{trend} < 0.01).

CONCLUSION

The burden of cardiovascular diseases has significantly increased in hospitalizations of PLWH from 2008 to 2018. Continued efforts are needed to address the additional cardiovascular risks in this vulnerable population.

Key Words: Cardiovascular; Heart failure; Trend; Human immunodeficiency virus; People living with human immunodeficiency virus

Core Tip: People living with human immunodeficiency virus (HIV) are at risk of developing cardiovascular diseases, including heart failure, but recent trends in the number of hospitalizations for various cardiovascular causes have not been examined on a national level. This study sought to analyze the trend in the number of hospitalizations for different cardiovascular diseases in people living with HIV to highlight the rising importance of cardiovascular diseases in this vulnerable population. More studies are needed to address the additional cardiovascular risks in people living with HIV, and tailored approach may be beneficial when managing and treating this population.

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INTRODUCTION

As of the year 2020, human immunodeficiency virus (HIV) affected 37.7 million people worldwide with 1.5 million new diagnoses and 680000 deaths due to illnesses associated with acquired immunodeficiency syndrome (AIDS)[1]. HIV infection used to be a debilitating disease leading to fatal infectious diseases, but with the advent of highly effective antiretroviral therapy, life expectancy for people living with HIV (PLWH) has increased by up to 10 years, approaching near-normal life expectancy especially in compliant patients[2,3]. As a result, the importance of cardiovascular diseases (CVDs) in PLWH is continually increasing, especially with new studies suggesting that inflammation and immune activation associated with HIV infection are contributing to additional cardiovascular risk[4].

Many previous studies have indicated that HIV infection is an independent risk factor for CVDs and cerebrovascular diseases (CeVDs), including heart failure (HF), myocardial infarction, and stroke[5-7]. However, studies on yearly dynamic changes brought about by CVDs in PLWH are lacking. Given the increasing burden of CVDs in PLWH, this study serves to elucidate the yearly trend of CVDs in PLWH by examining associated hospitalizations and in-hospital mortality from 2008 to 2018. Heart failure, along with ischemic heart disease (IHD) and CeVD, was used to represent the burden of CVDs in PLWH changing over the years[8].

MATERIALS AND METHODS

Data source

All data used in this study are openly available in the public website of Healthcare Cost and Utilization Project (HCUP) at https://www.hcup-us.ahrq.gov/nisoverview.jsp. The National Inpatient Sample (NIS), a retrospective cohort study developed for the HCUP, is the largest publicly available inpatient database that covers more than 97% of the U.S. population stratified by hospital region and type of insurance[9]. The NIS consists of demographic and hospital characteristics at discharge, which are searchable using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes[10]. As the NIS is fully de-identified and public, ethics committee approval was not required in this study. The datasets used and analyzed during this study are available at https://www.hcup-us.ahrq.gov/databases.jsp[9].

Study population

Total number of hospitalizations of PLWH was calculated as the sum of all hospitalizations with primary or secondary diagnosis of HIV: ICD-9-CM codes 042 and V08, or ICD-10-CM codes B20-24, R75, and Z21. Primary discharge diagnoses of CVDs were defined as follows: HF (ICD-9-CM codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428; ICD-10-CM codes I11.0, I13.0, I13.2, I09.81, I50), IHD (ICD-9-CM codes 410-411; ICD-10-CM codes I20-I25), and CeVD (ICD-9-CM codes 430-438; ICD-10-CM codes I60-I70). HF was chosen as the main CVD of interest as it comprised the largest proportion among the three. Other CVDs, including IHD and CeVD, were also included. The proportion of each CVD among all hospitalizations of PLWH was then calculated for each year. Only patients above 18 years were included, and hospitalizations with missing information on age, sex, and mortality status were excluded (Figure 1).

Outcome measures

The primary outcome of this study was the in-hospital mortality of hospitalizations due to each of the selected CVDs in PLWH. Secondary outcomes included length of hospital stay and total hospital charges.

Statistical analysis

To calculate estimates that represent total nationwide numbers, survey analysis methods were used based on the weights of hospital-level discharge provided by the NIS. The baseline demographic and hospital characteristics including sex, age, race, comorbidities, Charlson comorbidity index, hospital region, hospital bed size, and location were summarized as percentages for categorical variables and as means with standardized error for continuous variables. The crude mortality rate was calculated by each year and linear trends were examined using the Cochran-Armitage trend test. The trends in continuous outcomes were tested based on simple linear regression. A *P* value of less than or equal to 0.05 was considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

From 2008 to 2018, 54987 hospitalizations of adults (> 18 years) with a primary diagnosis of heart failure and secondary diagnosis of HIV were examined. Hospitalization with a primary diagnosis of HF and secondary diagnosis of HIV steadily increased from 4212 in 2008 to 6,700 in 2018 (P_{trend} < 0.001). The yearly demographics and comorbidities are shown in Table 1. About two-thirds of the population were male (65.5% in 2008 and 69.6% in 2018). In the year 2008, age less than 50 years was the largest group, but with progression of time, age group spanning from 50 to 59 years became the largest group. Majority of the population consisted of black race, which decreased over the years from 74.6% in 2008 to 71.5% in 2018 (P_{trend} < 0.001). Comorbidities of hypertension, diabetes mellitus, chronic kidney disease, obesity, and chronic obstructive pulmonary disease all significantly increased from 2008 to 2018 (P_{trend} < 0.001). Of note, hypertension and obesity markedly increased from 65.9% and 7.3% in 2008 to 91.2% and 17.1% in 2018, respectively. Such phenomenon was redemonstrated in the significantly increasing trend of Charlson comorbidity index over the years (P_{trend} < 0.001). These findings are shown in Table 1.

A total of 2,483,868 hospitalizations of PLWH with either primary or secondary diagnosis of HIV were reported from 2008 to 2018. Hospitalizations due to HF in PLWH increased from 4212 in 2008 to 6700 in 2018 (P_{trend} < 0.001). IHD (3921 in 2008 and 4,350 in 2018) and CeVD (2927 in 2008 and 3960 in 2018) followed the same pattern (both P_{trend} < 0.001). However, the overall hospitalizations of PLWH decreased from 236,809 in 2008 to 215,410 in 2018 (P_{trend} < 0.001). At the same time, the proportion of HF, IHD, and CeVD over all hospitalizations of PLWH increased from 4.7% in 2008 to 7.0% in 2018 (all P_{trend} < 0.001). These findings are illustrated in Figure 2.

There was a statistically significant decline in the in-hospital mortality of all hospitalizations of PLWH (P_{trend} < 0.001) from 3.40% in 2008 to 2.28% in 2018. A similar decline was observed in the in-hospital mortality of CeVD in PLWH (P_{trend} < 0.001) from 7.14% in 2008 to 3.67% in 2018. On the other hand, no significant difference was found in the trend of in-hospital mortality rate in hospitalizations due to HF or IHD in PLWH. In-hospital mortality rate was 1.84% in 2008 and 1.49% in 2018 for heart failure (P_{trend} = 0.672), and 1.61% in 2008 and 2.87% in 2018 for IHD (P_{trend} = 0.13). Figure 3 illustrates these findings.

Average length of hospital stay in all hospitalizations of PLWH decreased from 6.74 days in 2008 to 6.18 days in 2018 (P_{trend} < 0.001). However, that of HF in PLWH increased from 4.85 days in 2008 to 5.32 days in 2018 (P_{trend} < 0.001). No significant trend was found with IHD (P_{trend} = 0.294) and CeVD (P_{trend} = 0.341). These trends are illustrated in Figure 4.

Statistically significant increase in average total hospital charge was observed in all hospitalizations of PLWH from 2008 to 2018. Similar trend was seen in hospitalizations for HF, IHD, and CeVD in PLWH (Figure 5). In absolute terms, IHD showed the greatest increase by $53500 from $57324 in 2008 to $110824. In relative terms, HF increased by 123% from $28503 in 2008 to $63566 in 2018. The order of

Table 1 Baseline characteristics of hospitalizations due to heart failure in people living with human immunodeficiency virus from 2008 to 2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P_{trend}
n (sample)	869	954	1021	910	825	868	928	979	1074	1248	1340	< 0.001
n (weighted)	4212	4878	5225	4362	4125	4340	4640	4895	5370	6240	6700	< 0.001
Sex (%)												
Male	65.5	67.1	68.5	64.8	69.0	68.4	65.7	67.4	68.0	67.2	69.6	< 0.001
Female	34.5	32.9	31.5	35.2	31.0	31.6	34.3	32.6	32.0	32.8	30.4	< 0.001
Age (%)												
< 50	41.8	38.8	41.2	36.7	29.7	27.2	29.1	27.4	28.1	25.0	24.9	< 0.001
50-59	35.2	38.5	36.2	41.3	41.1	42.5	42.0	39.6	37.9	37.3	35.1	< 0.001
60-69	16.7	16.7	16.5	16.5	20.8	22.8	22.2	24.8	26.9	28.8	29.0	< 0.001
≥ 70	6.3	6.0	6.1	5.5	8.4	7.5	6.7	8.2	7.1	8.9	10.0	< 0.001
Race (%)												
White	11.8	12.0	12.8	13.6	16.9	15.5	18.1	16.9	17.3	17.6	15.9	< 0.001
Black	74.6	74.5	76.2	76.4	71.7	72.1	70.2	73.8	71.5	69.2	71.5	0.002
Hispanic	10.9	8.9	8.3	6.2	6.6	7.9	8.5	5.6	7.7	8.8	9.5	0.203
Asian	0.6	0.1	0.3	0.3	0.5	0.5	0.2	0.3	0.7	1.1	0.7	< 0.001
AI/AN	0.1	0.0	0.1	0.0	0.1	0.4	0.2	0.2	0.0	0.1	0.3	< 0.001
Other	2.0	4.5	2.3	3.5	4.2	3.6	2.8	3.2	2.7	3.2	2.1	< 0.001
Comorbidities (%)												
Hypertension	65.9	67.9	64.7	67.5	81.8	80.1	68.4	69.7	86.6	73.4	91.2	< 0.001
Diabetes mellitus	33.4	33.2	31.3	32.5	34.4	35.1	37.8	37.4	38.0	37.9	36.7	< 0.001
CKD	53.1	50.4	50.4	49.2	53.9	56.9	54.5	58.1	60.6	62.6	61.0	< 0.001
Obesity	7.3	7.9	11.8	11.3	10.1	12.4	14.4	18.8	16.3	16.3	17.1	< 0.001
COPD	31.2	32.7	33.0	38.1	43.8	47.1	39.4	42.2	41.4	42.6	43.4	< 0.001
Charlson comorbidity index												
Mean (SD)	NR	NR	6.18 (0.10)	6.17 (0.11)	6.11 (0.12)	6.28 (0.11)	6.27 (0.11)	5.37 (0.11)	6.86 (0.10)	7.19 (0.09)	6.99 (0.09)	< 0.001
Hospital characteristics												

Hospital region (%)												
Northwest	25.4	35.3	35.9	30.9	32.1	31.8	28.0	274	24.8	25.8	26.3	< 0.001
Midwest	11.5	11.1	13.1	11.4	11.6	9.7	13.6	11.7	10.4	9.3	11.6	< 0.001
South	58.6	48.9	44.7	52.5	46.1	49.8	50.7	54.4	54.5	54.3	53.7	< 0.001
West	4.5	4.7	6.4	5.2	10.2	8.8	7.7	6.4	10.3	10.7	8.4	< 0.001
Hospital bed size (%)												
Small	8.1	9.5	9.6	6.0	11.5	10.3	16.8	13.3	14.4	17.0	17.8	< 0.001
Medium	21.7	25.0	24.6	23.5	30.3	28.8	26.4	30.6	29.9	27.0	27.6	< 0.001
Large	70.2	65.5	65.8	70.5	58.2	60.9	56.8	56.1	55.7	56.0	54.6	< 0.001
Urban location (%)												
Rural	5.5	3.8	2.9	3.4	2.9	3.6	2.6	3.4	3.1	3.8	4.0	< 0.001
Urban nonteaching	28.0	28.7	29.2	33.3	26.4	24.3	16.9	18.0	18.0	13.9	14.1	< 0.001
Urban teaching	66.5	67.5	68.0	63.3	70.7	72.1	80.5	78.6	78.9	82.2	81.9	< 0.001

AI/AN: American Indian/Alaska Native; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus; NR: Not reported; SD: Standard deviation.

total hospital charge was IHD, CeVD, and HF from highest to lowest.

DISCUSSION

PLWH have increased risks of CVDs, including myocardial infarction, HF, sudden cardiac death, peripheral artery disease, and CeVD[11,12]. The mechanism of this increased risk has been explained by a combination of factors in HIV tropism in cardiac myocytes and effects related to the immunologic response triggered by HIV[13,14]. In addition, traditional cardiovascular risk factors, such as dyslipidemia, diabetes, smoking, and HTN are more prevalent in PLWH[15]. Genetic factors and the association of antiretroviral and metabolic abnormalities may also be playing a role in increasing cardiovascular risks in PLWH[16,17,18]. On the other hand, immune activation and chronic inflammation mediated by HIV contribute to the progression of CVD. Ongoing viral replication and release of inflammatory markers, such as hsCRP, IL-6, and D-Dimer, trigger subclinical atherosclerosis and increase CV events[4]. HIV-associated atherosclerosis is known to have its own features, such as non-calcified plaques, given this chronic inflammation[11,19]. Even with HIV suppression with antiretroviral therapy, chronic inflammation persists, putting PLWH at risk of more cardiovascular events[4].

According to the trends described in the present study, hospitalizations due to HF, IHD, and CeVD in PLWH increased while overall hospitalizations of PLWH decreased. This is likely related to the impact

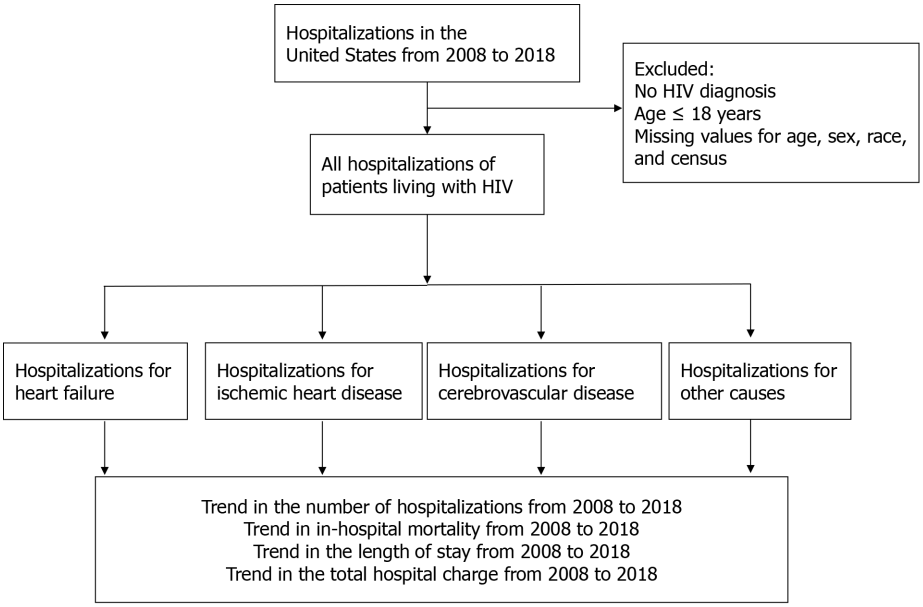

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Figure 1 Flow chart of this study. The flow chart illustrates the underlying design of the present study. HIV: Human immunodeficiency virus.

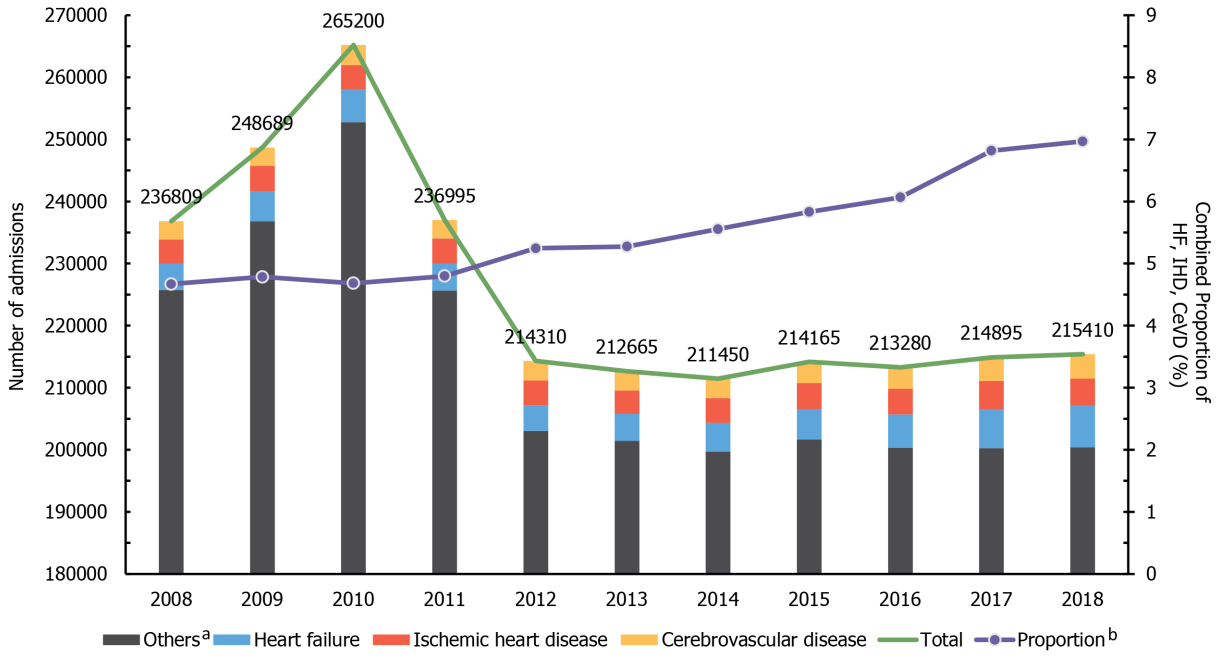

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Figure 2 Yearly trend of heart failure and other cardiovascular diseases in all admissions of people living with human immunodeficiency virus. Bar graph shows the yearly trend in the admissions of heart failure (HF) (blue), ischemic heart disease (IHD) (red), and cerebrovascular disease (CeVD) (yellow) in people living with human immunodeficiency virus (HIV). Gray bars show the number of all admissions of people living with human immunodeficiency virus (PLWH) for reasons other than HF, IHD, and CeVD. Violet line represents the combined proportion of HF, IHD, and CeVD among all hospitalizations of PLWH. Green line shows the total number of hospitalizations occurring in PLWH. [a]"Others" refer to all admissions of PLWH for reasons other than HF, IHF, and CeVD. [b]"Proportion" refers to the combined proportion of HF, IHD, and CeVD among all hospitalizations of PLWH. CeVD: Cerebrovascular disease; HF: Heart failure; IHD: Ischemic heart disease; PLWH: People living with human immunodeficiency virus.

of highly effective antiretroviral therapy, which allowed PLWH to have near-normal life expectancy and resulted in a rise in morbidity and mortality associated with age-related causes[20,21]. The dramatic changes brought about by antiretroviral therapy is shown by how the annual mortality of PLWH exceeded 20% prior to 1996 but declined to less than 2% only after a decade later[22]. With improvement in life expectancy, reduction of infectious burden, and changes in lifestyle, the prevalence of CVD is also expected to increase[23]. Increase in the prevalence of comorbidities among PLWH was also noted in the

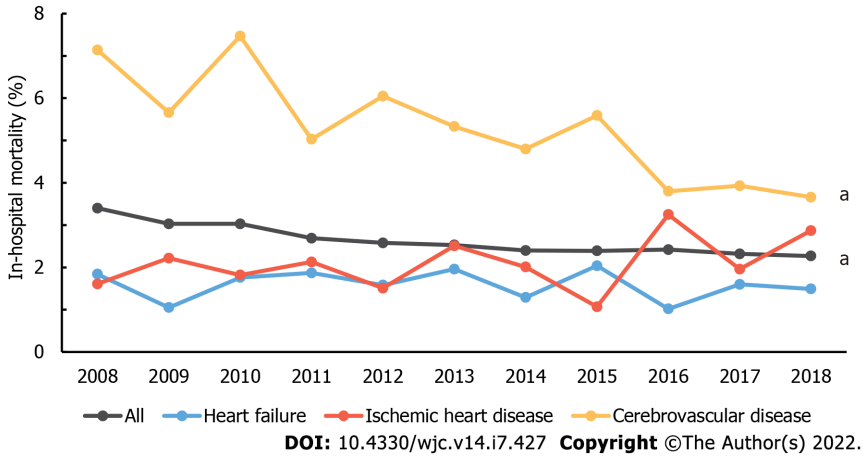

Figure 3 Yearly trend of average in-hospital mortality rate in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of in-hospital mortality in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the in-hospital mortality of all admissions occurring in people living with human immunodeficiency virus. Significant P_{trend} < 0.05 is marked with an asterisk (a) at the end of the linear graph.

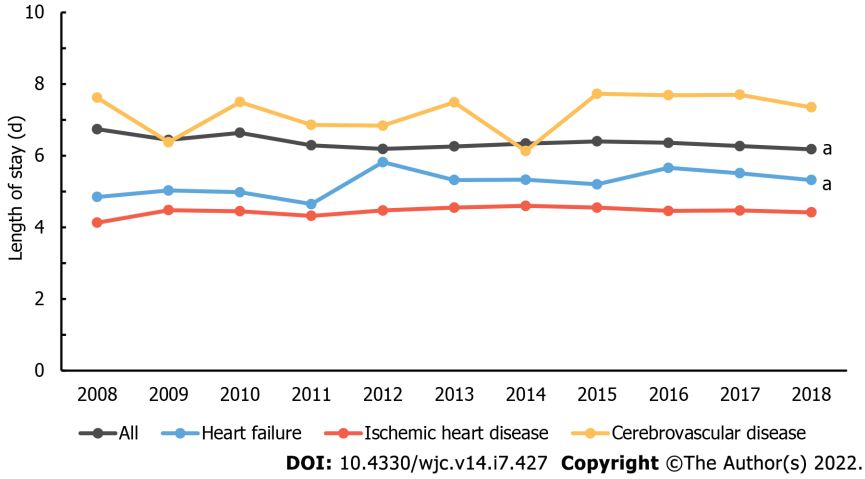

Figure 4 Yearly trend of average length of hospital stay in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of length of hospital stay in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the length of hospital stay in all admissions occurring in PLWH. Significant P_{trend} < 0.05 is marked with an asterisk (a) at the end of the linear graph.

present study (Table 1).

Interestingly, a precipitous reduction in hospitalizations of PLWH from 2010 to 2012 was observed. This may be due to the National HIV/AIDS Strategy implemented in 2010, intensifying HIV prevention efforts, facilitating access to care for PLWH, and creating a coordinated national response to the HIV epidemic[24,25]. The President's Emergency Plan for AIDS Relief in the U.S., whereby the government supported high active antiretroviral therapy (HAART) for more than 3.9 million people and provided care for nearly 13 million people, was also expanded in the year 2011[26]. With these national efforts to combat HIV, hospitalizations of PLWH have been subdued since 2012 and has been remaining relatively stable.

The trend analysis from this present study coincides with those seen in previous studies. According to a population-based cohort study from 1999 to 2018, diagnosis and mortality rate of HIV infection underwent annual decrease of 5% and 8%, respectively[27]. Earlier diagnosis, lower probability of AIDS-associated infections, and antiretroviral therapy factored into this decline[27]. The decline of in-hospital mortality of CeVD in PLWH seen in this study may be due to the reduced severity of stroke among PLHW explained by the effectiveness of HAART and better tools for stroke diagnosis and treatment[28]. This study did not show significant changes in the in-hospital mortality of HF and IHD in PLWH despite other epidemiological studies showing a decrease in the general population[29,30]. From such finding, one can hypothesize that additional cardiovascular risk factors are present in PLWH, which are not being sufficiently addressed.

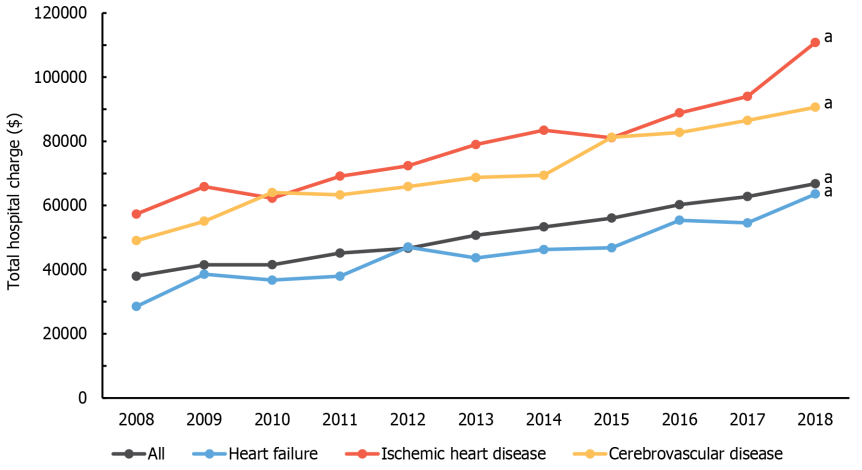

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Figure 5 Yearly trend of average total hospital charge in admissions due to heart failure and other cardiovascular diseases in people living with human immunodeficiency virus. Line graphs illustrate the trend of total hospital charge in all admissions due to heart failure (blue), ischemic heart disease (red), and cerebrovascular disease (yellow). Gray line shows the total hospital charge in all admissions occurring in PLWH. Significant P-trend < 0.05 is marked with an asterisk (a) at the end of the linear graph.

The decrease in average length of hospital stay in PLWH over time has also been reported by a retrospective study of more than 700,000 admissions in three hospitals in New York City[31]. Rowell-Cunsolo *et al*[31] reported decreases in length of stay from 2006 to 2014, but noted that the length of stay was greater in PLWH than the general population. Other studies have also produced comparable results, including Berry *et al*[32] who reported decline in hospitalizations due to AIDS-defining illnesses from 6.7 to 2.7 per 100 person-years from 2001 to 2008 and Heslin *et al*[33] who reported 10% decrease in length stay from 2006 to 2013[32,33].

To the best of authors' knowledge, the present study was the first to use the largest inpatient database in the U.S. to examine the trend in the number of hospitalizations, stratified to cardiovascular causes, in people living with HIV. In addition, trends in the in-hospital mortality, length of hospital stay, and total hospital charge were also uniquely examined. By analyzing the yearly trend of CVDs in PLWH, the objective of this study is to increase the awareness of burden of CVD in this more vulnerable population. Hospitalizations due to CVD has increased in PLWH, highlighting the importance of evaluating and managing cardiovascular risks factors imparted by HIV. Meanwhile, more research investigating the underlying mechanisms that link HIV and CVD must continue to provide potential solutions to this problem of additional risk. Mechanisms whereby antiretrovirals may contribute to this risk should also be studied. With better understanding of the association between HIV infection and CVD, tailored approaches may be warranted in managing cardiovascular risk factors in PLWH.

This study contains several limitations. Administrative data was used for clinical outcomes by using NIS in analyzing yearly trends for CVDs in PLWH. NIS data can have varying degrees of accuracy since cardiovascular events can be coded differently, leading to underestimation of event rates and misclassification[34]. As this study relied on NIS data, there was no control in either exposure or outcome. Not all cardiovascular diseases were included in the analysis. Age-standardized in-hospital mortality could not be calculated due to the skewed distribution of mortalities in different age groups. Prospective cohort studies should be implemented to better examine the burden of CVD in PLWH.

CONCLUSION

The present study used a national representative sample of U.S. hospital admissions from 2008 to 2018 to reach the following conclusions. First, hospitalizations due to HF, IHD, and CeVD in PLWH increased while total hospitalizations of PLWH decreased. Second, hospitalizations due to HF in PLWH steadily increased over 11 years along with the concomitant increase in the prevalence of comorbidities. Third, declining trends in the in-hospital mortality rate of overall hospitalizations in PLWH and those due to CeVD in PLWH were observed, whereas no change in trend was present with HF and IHD. Fourth, while the length of hospital stay in all hospitalizations of PLWH decreased, that due to HF increased. Finally, the healthcare costs increased for all admissions for all HF, IHD, and CeVD in PLWH. The results from this study demonstrate the increasing burden of CVD in PLWH as demonstrated by increasing hospitalizations, lack of improvement in in-hospital mortality, and increased length of hospital stay in those with HF.

ARTICLE HIGHLIGHTS

Research background

Recent studies have reported a strong association between human immunodeficiency virus (HIV) infection and cardiovascular diseases. However, studies examining the trend of cardiovascular diseases in people living with HIV on a national level have been lacking.

Research motivation

The trends of cardiovascular diseases in people living with HIV have not been sufficiently examined using nationally representative database.

Research objectives

To demonstrate that the burden of cardiovascular disease in people living with HIV has been increasing in the recent decade, emphasizing the need for continual efforts to address the excess cardiovascular risks in this vulnerable population.

Research methods

We retrospectively examined the National Inpatient Sample from 2008 to 2018 to analyze the trends in the hospitalizations for various cardiovascular diseases in people living with HIV. In addition, we looked at the trends of in-hospital mortality, length of hospital stay, and total hospital charge. Cochran-Armitage test and simple linear regression were used to examine the trends of categorical and continuous variables, respectively.

Research results

Hospitalizations for heart failure, ischemic heart disease, and cerebrovascular disease in people living with HIV showed an increasing trend, while the total number of hospitalizations in people with living HIV showed a decreasing trend from 2008 to 2018. The trend of in-hospital mortality and length of stay were variable in contrast to total hospital charge, which demonstrated a substantially increasing trend over the decade.

Research conclusions

Nationally representative data showed that the burden of cardiovascular diseases in people living with HIV has been significantly.

Research perspectives

Further studies and preventative measures are needed to mitigate the additional cardiovascular burden in people living with HIV.

FOOTNOTES

Author contributions: Park DY and An SK designed the research; Park DY and An SK performed the research; Park DY and An SK contributed analytic tools; Park DY and An SK analyzed the data; Park DY, An SK, Romero ME, Murthi M, and Atluri R wrote the paper, validated the results, and reviewed and edited the drafts.

Institutional review board statement: This study was exempt from institutional review board as it solely used deidentified data openly and readily available in a public database.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest relevant to this study.

Data sharing statement: All data used in this study are openly available in the public website of Healthcare Cost and Utilization Project (HCUP) at https://www.hcup-us.ahrq.gov/nisoverview.jsp.

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

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LETTER TO THE EDITOR

Heart failure with reduced, mildly reduced, or preserved left ventricular ejection fraction: Has reasoning been lost?

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Abstract

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by end-diastolic volume, has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this LVEF-based terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions in HF, especially at the higher end of the LVEF spectrum.

Key Words: Arbitrary; Cut off; Guidelines; Limitations; Normal left ventricular ejection fraction range; Phenotypic persistence

Core Tip: Left ventricular ejection fraction (LVEF) has been consistently used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF is classified as HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cutoffs. A prerequisite for using this terminology is knowledge of the LVEF normal range, which is lacking and may lead to erroneous conclusions, especially at the higher end of the LVEF spectrum.

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TO THE EDITOR

Left ventricular (LV) ejection fraction (LVEF), defined as LV stroke volume divided by LV end-diastolic volume, is the only biomarker that has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades[1]. Accordingly, HF has been classified into HF with reduced LVEF (HFrEF), HF with midrange or mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF) using various, continuously changing LVEF cutoffs. A mandatory prerequisite for the use of this LVEF-based terminology is the definition of the normal LVEF range, which is lacking. From this perspective, we discuss the limitations related to the current LVEF-based classification of HF and provide examples of erroneous conclusions that can be drawn, especially in HF patients at the higher end of the HF spectrum.

The LVEF-based classification of HF was initially applied several decades ago in the clinical trials of neurohormonal inhibitors in which LVEF cutoffs of < 35% or 40% were chosen arbitrarily to define patients with HF perceived to be at greatest risk (HFrEF). Several years later, clinical trials with similar agents and endpoints were conducted in patients with HF with an LVEF of ≥ 40%-50% (HFpEF), but they were considered unsuccessful for various reasons[2,3]. Recently, another HF phenotype (HFmrEF) was added based on the underrepresentation of patients with HF with an LVEF of 40%-50% in clinical trials. The LVEF cutoffs used for HF classification have varied continuously in the guidelines issued by scientific societies (Figure 1)[4]. The 2013 American College of Cardiology Foundation/American Heart Association guidelines defined HFrEF by an LVEF of ≤ 40%, borderline HFpEF by an LVEF of 41%-49%, and HFpEF by an LVEF of ≥ 50%[5]. By contrast, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines defined HFrEF and HFpEF by an LVEF of < 50% and ≥ 50%, respectively, and did not recognize borderline HFpEF or HFmrEF as a distinct entity[6]. Furthermore, in the recent Universal Definition and Classification of Heart Failure[7], which was adopted by the European Society of Cardiology[8], HF classification includes HFrEF with an LVEF of ≤ 40%, HFmrEF with an LVEF of 41%-49%, and HFpEF with an LVEF of ≥ 50%. Subsequently, another classification of HF was proposed, which defines HFrEF by an LVEF of < 40%, HFmrEF by 40% ≤ LVEF < normal, and HF with normal EF by an LVEF of ≥ 55% in men and ≥ 60% in women[9]. LVEF can be reduced, mildly reduced, preserved, or normal; however, what is the normal LVEF range? According to the 2015 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the normal reference range for LVEF is 52%-72% for males and 54%-74% for females[10]. The latest guidelines from the British Society of Echocardiography define LVEF ≥ 55% as normal (preserved)[11]. However, several recent studies have raised serious concerns regarding the normal LVEF range as proposed by echocardiographic societies. Wehner *et al*[12] investigated the relationship between LVEF and survival by linking physician-reported LVEF on 403977 echocardiograms obtained from 203135 patients to all-cause mortality in the United States, and validated their findings in a dataset including 45531 echocardiograms and 35976 patients from New Zealand. During follow-up, unadjusted hazard ratios for mortality showed a U-shaped relationship for LVEF with a nadir of risk at an LVEF of 60%-65% in both datasets. The results were similar after adjusting for conditions associated with an elevated LVEF, including mitral regurgitation, increased wall thickness, and anemia and when restricted to patients reported to have HF at the time of the echocardiogram (Figure 2). Slightly different but trending in the same direction were the findings of another study including approximately 500000 participants, which reported that in both women and men, mortality was lowest at an LVEF of 65.0%–69.9%[13]. However, in the same study, sex-dependent differences in the relationship between LVEF and mortality were observed. In women, an increased risk of cardiovascular-related mortality persisted to an LVEF of 60.0%–64.9%, whereas in men, the equivalent LVEF was lower (55.0%–59.9%) (Figure 3)[13]. Sex-related differences were also reported in 4632 patients from coronary computed tomography angiography evaluation for clinical outcomes, namely, an international multicenter registry in which LVEF was measured by cardiac computed tomography and participants were categorized according to LVEF (low < 55%, normal 55%–65%, and high > 65%) [14]. After 6 years of follow-up, no difference in mortality was observed in patients with high LVEF in the overall cohort. However, when data were stratified by sex, women with high LVEF died more often from any cause compared to women with normal LVEF, while an opposite trend was observed in men [14]. Thus, the LVEF-based terminology for HF classification is challenged based on recent evidence.

Therefore, it is not surprising that the LVEF-based classification might lead to erroneous conclusions when interpreting the results of various studies enrolling HF patients at the upper end of the LVEF spectrum (Table 1). A typical example is the recently published Empagliflozin outcome trial in patients with chronic HF with preserved EF (EMPEROR-preserved trial), which reported a benefit with

Table 1 Heart failure studies including patients with mildly reduced and preserved left ventricular ejection fraction

Ref.		Drug	LVEF cut off
Registries			
Yancy *et al*[22]	ADHERE	-	≥ 40
Fonarow *et al*[23]	OPTIMIZE-HF	-	≥ 40%; ≥ 50%
Steinberg *et al*[24]	GWTG-HF	-	≥ 50%; 40%-50%
Randomized controlled trials			
Yusuf *et al*[25]	CHARM-PRESERVED	Candesartan	> 40%
Cleland *et al*[26]	PEP-CHF	Perindopril	> 40%
Massie *et al*[27]	I-PRESERVE	Irbesartan	≥ 45%
van Veldhuisen *et al*[28]	SENIORS	Nebivolol	> 35%
Redfield *et al*[29]	RELAX Trial	Phosphodiesterase-5 inhibitors	≥ 50
Yamamoto *et al*[30]	J-DHF	Carvedilol	> 40%
Ahmed *et al*[31]	DIG-PEF	Digitalis	> 45%
Pitt *et al*[32]	TOPCAT	Spironolactone	≥ 45%
Solomon *et al*[33]	PARAMOUNT	Sacubitril/Valsartan	≥ 45%
Solomon *et al*[34]	PARAGON HF	Sacubitril/Valsartan	≥ 45%
Pieske *et al*[35]	SOCRATES-PRESERVED	Vericiguat	≥ 45%
Armstrong *et al*[36]	VITALITY-HFpEF	Vericiguat	≥ 45%
Anker *et al*[15]	EMPEROR-PRESERVED	Empagliflozin	> 40%
Solomon *et al*[37]	DELIVER trial	Dapagliflozin	> 40%
Meta-analysis			
Meta-analysis Global Group in Chronic Heart Failure[38]	MAGGIC	-	≥ 50
Zheng *et al*[39]	Systematic review and meta-analysis	Neurohormonal inhibitors	≥ 40%

LVEF: Left ventricular ejection fraction.

empagliflozin (compared with placebo) in HFpEF defined by an LVEF > 40%[15,16] which is different from the 50% cutoff recommended in the Universal Definition and Classification of Heart Failure[7]. It is noteworthy that in the EMPEROR-preserved trial, ~90% of the patients suffered from hypertension, ~49% from diabetes, and ~51% from atrial fibrillation. By contrast, in a study by Lupon *et al*[17], which was used as evidence supporting phenotypic persistence in HFpEF[18], an LVEF cutoff of 50% was used and the patient characteristics were entirely different from those in the EMPEROR-preserved trial with approximately 12% of the participants suffering from hypertrophic cardiomyopathy and 36% from valvular heart disease. Thus, when interpreting these two HFpEF studies, it would be challenging to extrapolate the findings of one to the other. Therefore, no firm conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF.

LVEF-based classification of HF phenotypes has served well over the years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as longitudinal strain[19] and cardiac power[20] outperform the LVEF. The incorporation of artificial intelligence (AI) in diagnostic modalities, outcome predictions, and management of HF (individualized precision medicine) constitutes a major development in the field of cardiovascular medicine. In this regard, developing and validating universally accepted scoring systems based on AI would be a fruitful area of research. The LVEF has been considered the holy grail for HF classification treatment guidance for years. The time for change has come, unless one wants to justify those claiming that most published research findings are false[21].

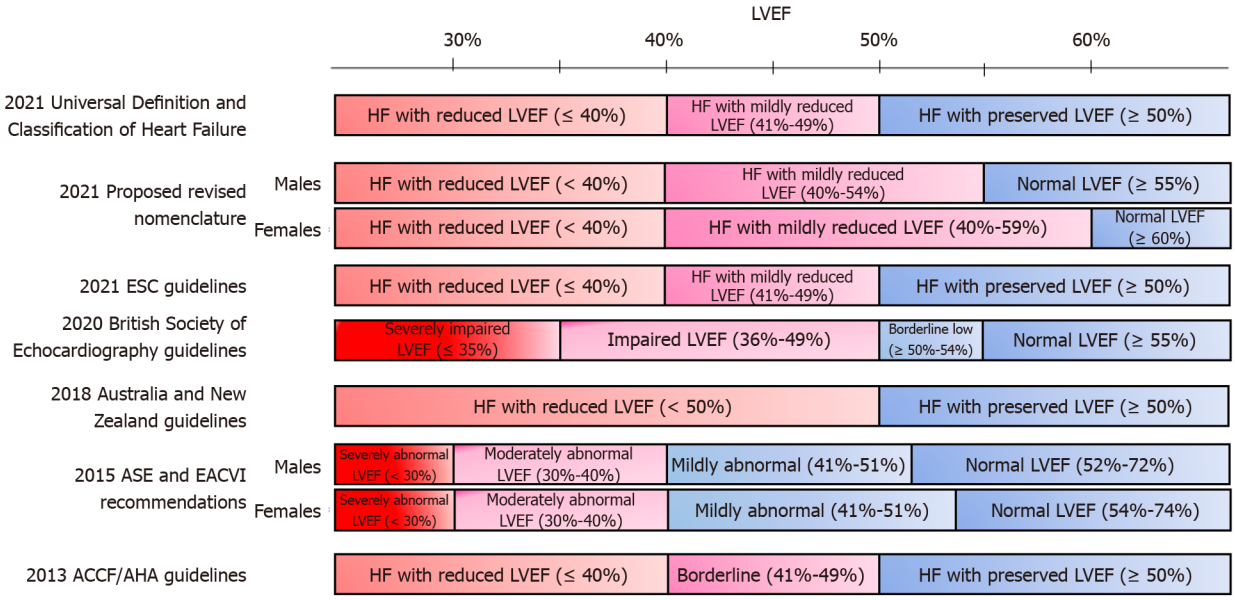

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Figure 1 There is significant discordance in the normal values of left ventricular ejection fraction reported by several major scientific societies and associations. This makes the classification of heart failure based on the left ventricular ejection fraction problematic. ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ASE: American Society of Echocardiography; EACVI: European Association of Cardiovascular Imaging; ESC: European Society of Cardiology.

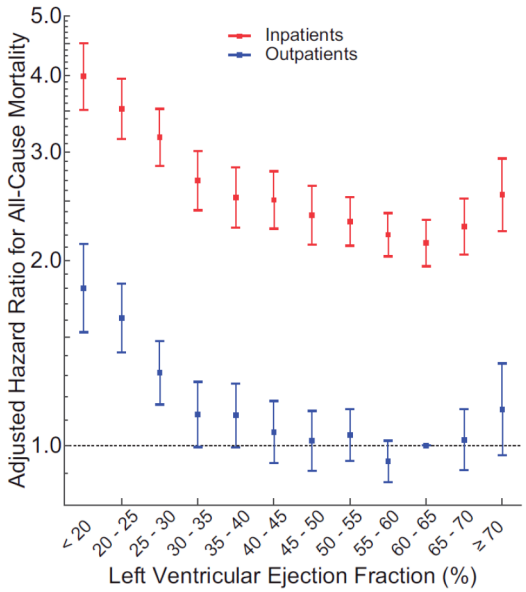

Figure 2 Left ventricular ejection fraction adjusted hazard ratios in patients with heart failure (number of echocardiograms = 40616). Left ventricular ejection fraction (LVEF) intervals are inclusive of the lower threshold. Error bars represent the 95%CI. The referent group was outpatients with an LVEF of 60%-65%. While 51192 echocardiograms were performed on patients with heart failure in the primary analysis, only 40616 echocardiograms are represented in this figure due to excluding echocardiograms missing measurements of end-diastolic volume index or wall thicknesses, for which adjustments were made in the analysis. Citation: Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020; 41(12): 1249-1257. Copyright ©The Author(s) 2019. Published by the European Society of Cardiology.

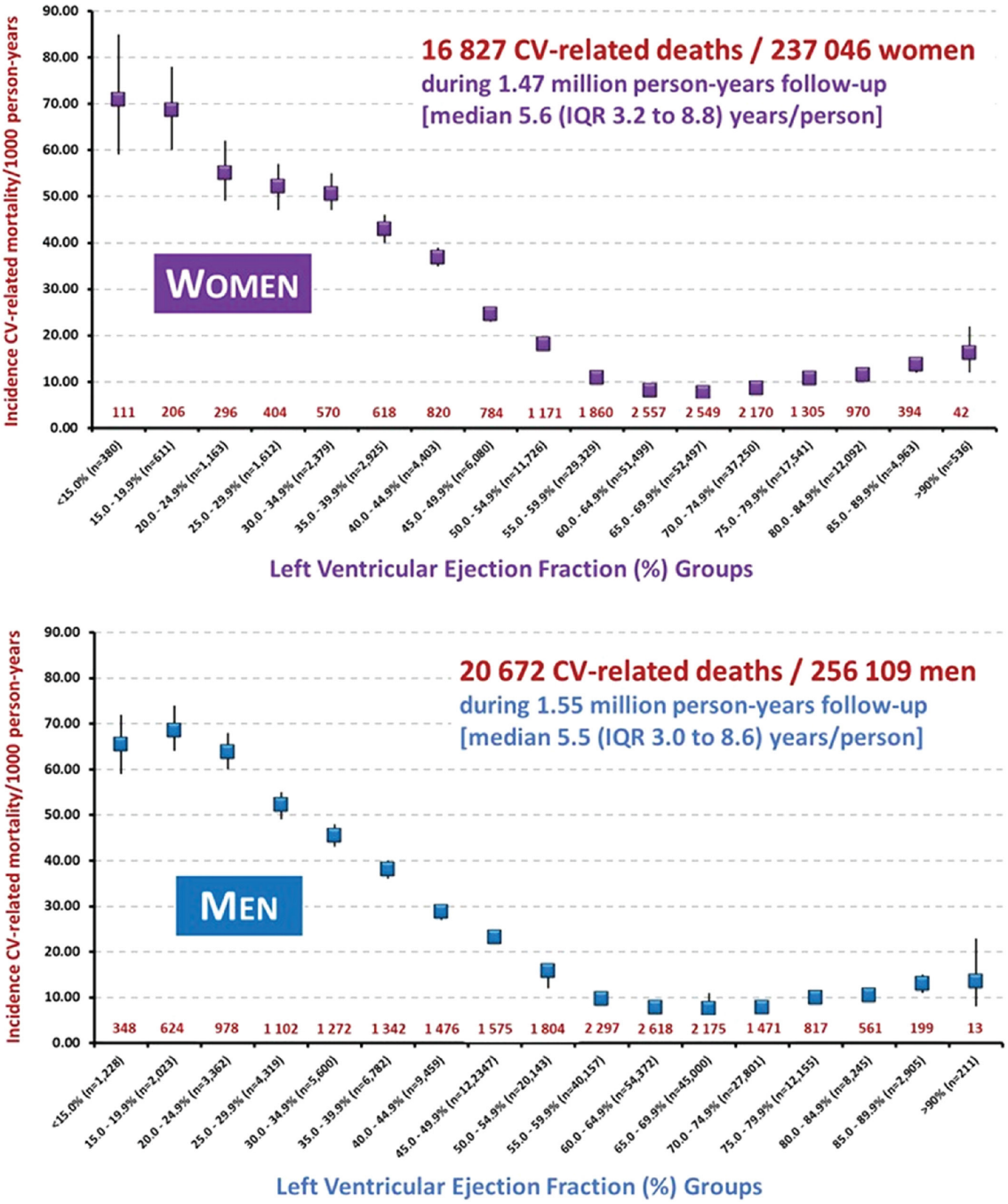

Figure 3 Incident rate of cardiovascular-related mortality. The rate of cardiovascular (CV)-related mortality per 1000 person-years is presented separately for women (top graph) and men (bottom) according to 5-unit increments in the left ventricular ejection fraction. The total number of deaths contributing to the rate of mortality in each group (red numerals) is provided above the horizontal axis. IQR: Interquartile range. Citation: Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G; NEDA Investigators. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. *Eur J Heart Fail* 2021; 23(3): 406-416. Copyright ©The Author(s) 2020. Published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

FOOTNOTES

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