Journal of Advances in Medicine and Medical Research

Volume 36, Issue 6, Page 160-176, 2024; Article no.JAMMR.117343
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Unraveling the Complex Interplay: COVID-19 and Heart Failure: A Comprehensive Review

Dharani Swarna Deiveegan [a], Atinder Singh [b], Muhammad Ilyas Shazi [c], Wajeeh Ur Rehman [d#], Muhammad Rizwan Akram [e], Saliha Tauqeer [f], Darshankumar Raval [g++], Ruqiya Bibi [h], Muhammad Subhan [i*] and Advaith Manoharasetty [j]

[a] K.A.P. Viswanatham Government Medical College, affiliated to the Tamil Nadu Dr. M.G.R. Medical University, India.
[b] Wcmsrh, Pt. BD Sharma University of Health Sciences, Rohtak, India.
[c] Ministry of Health, Saudi Arabia.
[d] Saidu Group of Teaching Hospital, Pakistan.
[e] Bronxcare Health System, Bronx, New York, USA.
[f] Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan.
[g] Mayo Clinic, Jacksonville Florida, USA.
[h] Jinnah Hospital Lahore/Allama Iqbal Medical College, Lahore, Pakistan.
[i] Department of Internal Medicine (Gastroenterology), Jinnah Hospital Lahore/Allama Iqbal Medical College, Lahore, Pakistan.
[j] Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i65461

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/117343

Review Article

Received: 23/03/2024
Accepted: 27/05/2024
Published: 02/06/2024

[++]Research Fellow;
[#] Resident Physician;
**Corresponding author: E-mail: muhammadsubhan1998@gmail.com;*

Cite as: *Deiveegan, D. S., Singh, A., Shazi, M. I., Rehman, W. U., Akram, M. R., Tauqeer, S., Raval, D., Bibi, R., Subhan, M., & Manoharasetty, A. (2024). Unraveling the Complex Interplay: COVID-19 and Heart Failure: A Comprehensive Review. Journal of Advances in Medicine and Medical Research, 36(6), 160–176. https://doi.org/10.9734/jammr/2024/v36i65461*

ABSTRACT

The association between COVID-19 and heart failure (HF) presents multifaceted challenges and implications for clinical management. This comprehensive review explores the epidemiological, clinical, and mechanistic associations between COVID-19 and HF, emphasizing the bidirectional impact of these conditions on patient outcomes. COVID-19 can precipitate or exacerbate HF through myocardial injury, inflammation, thrombosis, and immune dysregulation, while pre-existing HF increases the severity and complications of COVID-19. Diagnostic challenges arise from overlapping symptoms and the need to differentiate between COVID-19-related lung pathology and HF manifestations. Understanding the underlying pathophysiological mechanisms, including ACE2 dysregulation, cytokine release syndrome, and hypercoagulability, is crucial for optimizing management strategies. Early identification, multidisciplinary collaboration, personalized treatment, and patient education are essential to managing COVID-19 and HF. Insights from this review inform clinical practice, highlighting the importance of tailored interventions and ongoing research to mitigate the impact of these complex interactions on patient outcomes and public health initiatives.

Keywords: Heart failure; COVID-19; myocardial injury; societal norms; historical context; health risk.

1. INTRODUCTION

The extensive ramifications of the global COVID-19 pandemic caused by SARS-CoV-2 have been extensive [1]. This has resulted in substantial changes to healthcare systems, economies, and societal norms on a global scale [1]. Within the context of this crisis, an emerging area of concern is the relationship between COVID-19 and cardiovascular health [1,2]. The association between COVID-19 and heart Failure (HF) is fascinating, necessitating a comprehensive review to explore its multifaceted dimensions [2]. COVID-19 constitutes a highly transmissible respiratory ailment from SARS-CoV-2 [2]. While its primary target is the respiratory system, the virus has increasingly been associated with a broad spectrum of systemic manifestations, including cardiovascular complications [3]. Among these concerns is the development of HF, characterized by the heart's inability to pump blood and meet the body's metabolic demands effectively [4]. The historical context of the COVID-19 pandemic, originating in late 2019, has brought forth a continuously evolving global health crisis characterized by challenges, innovations, and adaptations in healthcare strategies [5]. The initial instances of COVID-19 surfaced in Wuhan, China, in December 2019 [6]. Subsequently, recognizing the severity of the situation, the World Health Organization officially designated it a health emergency on 30th January 2020, marking a critical milestone in the global response to the unfolding crisis [6]. The virus has since infected over 300 million individuals and caused over 6 million deaths worldwide as of February 2024 [5-7]. The first reports of cardiac complications in COVID-19 patients emerged in early 2020, and several studies have since documented the prevalence, risk factors, mechanisms, and outcomes of COVID-19-related HF [6-8]. COVID-19 can damage cardiovascular systems in several ways, such as causing direct myocardial injury, myocarditis, arrhythmias, thromboembolism, stress cardiomyopathy, and exacerbating pre-existing cardiovascular diseases [7-9]. HF is one of the most common and severe cardiac complications of COVID-19, affecting up to 30% of hospitalized patients and increasing the risk of death by 2-3 times [6-9]. The risk of HF is higher in older patients, those with comorbidities such as hypertension, diabetes, obesity, and chronic kidney disease, and those with severe COVID-19 infection [8-10]. COVID-19 patients with HF may manifest with typical clinical features of HF, such as dyspnea, orthopnea, edema, and fatigue, or with atypical manifestations, such as chest pain, palpitations, syncope, or cardiac arrest [11]. Some patients may develop HF as a late complication of COVID-19, even after recovery from the acute infection [12]. Diagnosing HF in COVID-19 patients requires a combination of clinical, laboratory, electrocardiographic, echocardiographic, and imaging criteria.[13]. The primary investigations for COVID-19 patients with suspected or confirmed HF include Nasopharyngeal swabs to detect SARS-CoV-2 RNA via PCR, Troponin, B-type natriuretic peptide (BNP), Liver Function Tests(LFTs), Renal Function Tests (RFTs), Electrocardiogram (ECG), Chest X-ray (CXR), Echocardiography, Cardiac magnetic resonance imaging (CMR), and Coronary angiography [14]. The management plan for COVID-19 patients with heart-related diseases is based on the severity of

the infection, the type and stage of HF, and other comorbidities [15]. The general principles include supportive care for respiratory failure, hypoxemia, shock, and multiorgan dysfunction, such as oxygen therapy, mechanical ventilation, antiviral therapy, such as remdesivir, anti-inflammatory treatment for cytokine storm, such as corticosteroids, tocilizumab, or other immunomodulators, antithrombotic therapy for thromboprophylaxis, HF therapy for cardiac dysfunction, monitoring and follow-up for clinical and laboratory parameters, cardiac function, and complications, such as arrhythmias, cardiac tamponade, or cardiogenic shock [14-16]. This review explores COVID-19's impact on heart failure across demographic groups, investigating related risk factors and disparities to inform targeted prevention strategies. Understanding the mechanisms and contributors to heart failure in COVID-19 patients is essential for improving outcomes and delving into etiological factors, pathogenic pathways, and therapeutic approaches, including multidisciplinary care.

2. METHODOLOGY

A thorough literature review was conducted across multiple databases, including Google Scholar and PubMed, to identify articles related to COVID-19 and HF published between January 2020 and March 2024. The search utilized keywords relevant to the epidemiology, pathophysiology, diagnosis, treatment, and outcomes of COVID-19 and HF. Eligible studies encompassed original research, systematic reviews, and human subject studies. Exclusion criteria were applied to exclude case reports, animal studies, and articles with a high risk of bias. Quality assessment tools appropriate for each study type were employed to evaluate the methodological soundness of included studies, with preference given to high-quality studies meeting predetermined criteria. Because of substantial heterogeneity among the data contained in the collected data, data synthesis was performed narratively rather than through meta-analysis. This approach involved summarizing findings qualitatively to provide a comprehensive overview of the current evidence on the relationship between COVID-19 and HF.

2.1 Epidemiology and Clinical Significance and Diagnostic Challenges

COVID-19 and HF are familiar and severe conditions with complex and bidirectional relationships [17,18]. This section will explore the epidemiological and clinical association between COVID-19 and HF and the challenges healthcare professionals face when diagnosing these conditions. COVID-19 can cause or worsen HF by damaging the heart muscle, triggering inflammation, reducing oxygen supply, forming blood clots, or inducing stress [19]. HF can increase the risk and severity of COVID-19 by weakening the immune system, enhancing the entry of the virus into the cells, or interfering with the treatment of COVID-19 [20]. The prevalence of HF among COVID-19 patients varies depending on the study design, population characteristics, and diagnostic criteria [21]. Some studies have reported a prevalence of up to 30% in severe cases of COVID-19 [19-22]. This indicates that HF is a significant concern among COVID-19 patients and requires careful monitoring and intervention [21,22]. COVID-19 and HF have a poor prognosis on the clinical course and outcome of patients [23]. Patients with both conditions have a higher risk of respiratory distress, acute decompensation, intensive care unit admission, mechanical ventilation, extracorporeal membrane oxygenation, or advanced therapies [24]. They also have a higher risk of mortality, morbidity, hospitalization, readmission, and long-term health sequelae [25].The epidemiological relationship between HF and COVID-19 is complex and multifaceted [26]. Studies have shown that patients with pre-existing HF are at a higher risk for a severe clinical course if they contract COVID-19, and HF is an independent predictor of in-hospital mortality [24-26]. Conversely, COVID-19 can lead to both acute decompensation of chronic HF and de-novo HF due to myocardial injury and cardiovascular complications [24-26]. For instance, myocardial injury was reported in at least 10% of unselected COVID-19 cases and up to 41% in critically ill patients or those with concomitant cardiovascular comorbidities [27]. Li et al. synthesized findings from 10 studies focusing on the impact of cardiovascular disease (CVD), hypertension, and acute cardiac injury on in-hospital mortality among COVID-19 patients [1,28]. Their analysis depicted a strong statistical association between the presence of CVD and hypertension and increased odds of in-hospital mortality, with unadjusted odds ratios of 4.85 for CVD and 3.67 for hypertension [1,28]. Furthermore, acute cardiac injury was strongly associated with elevated odds of in-hospital mortality, with an unadjusted odds ratio of 21.15 [1,28]. These findings underscore the critical role of cardiovascular comorbidities and cardiac injury in

the prognosis of COVID-19 patients, emphasizing the need for early identification and management of these conditions to enhance clinical outcomes [1,28]. Further, the Philippine CORONA study highlighted that patients with COVID-19 and coronary artery disease or HF had significantly worse outcomes, including increased all-cause mortality, death from cardiac causes, respiratory failure, and prolonged hospitalization [29]. Even after adjusting for confounders, the presence of CAD/HF was associated with death from a cardiac cause with OR 2.22, 95% CI 1.49–3.3, and $p < 0.01$ [29]. These findings underscore the bidirectional relationship between HF and COVID-19, where each condition can exacerbate the other [26-29]. The pandemic has also reduced HF hospitalizations, which has been linked to a subsequent increase in HF mortality, indicating that the secondary impacts of the pandemic on healthcare systems have also impacted HF management and outcomes [30]. This intricate interplay highlights the need for careful management of HF patients during the pandemic and a deeper understanding of the long-term cardiovascular consequences of COVID-19 [28-30]. Diagnosing heart failure (HF) in patients with COVID-19 presents unique challenges [31]. The overlapping symptoms of HF and COVID-19, such as shortness of breath, dry cough, chest discomfort, and fatigue, can complicate the clinical picture [32]. For example, chest imaging can show lung changes that could be due to either pulmonary edema from HF or COVID-19-related lung damage [35]. Other times, patients may have atypical presentations of COVID-19, such as having cardiovascular symptoms without respiratory symptoms [32]. Another challenge involves differentiating COVID-19 and HF from other conditions with similar symptoms, such as respiratory infections, pulmonary embolisms, and chronic obstructive pulmonary disease (COPD) exacerbations [33]. These conditions necessitate distinct treatments and must be ruled out by healthcare providers before confirming a diagnosis of COVID-19 or HF [33]. Additionally, patients with COVID-19 and HF often exhibit complex multimorbidity, with various medical conditions and histories that can complicate their diagnosis and management [33]. Additionally, abnormal cardiac biomarkers, common in COVID-19 due to mechanisms like direct cardiac injury or increased thrombotic activity, may not always indicate underlying HF [32]. The pandemic has also impacted the management of HF, with changes in healthcare provision leading to a reliance on remote consultations and self-monitoring by patients [32]. This shift has made it difficult to perform standard diagnostic procedures like echocardiography, which are crucial for HF diagnosis [32,33]. Moreover, the fear of contracting the virus has led to patients with HF symptoms avoiding hospital visits, potentially resulting in underdiagnosis or delayed treatment [33]. In cases where COVID-19 leads to new-onset HF, clinicians face distinguishing between HF symptoms and those caused by the acute viral infection [34]. This is especially challenging in patients without previous underlying disease or risk factors, where new HF diagnoses following COVID-19 are rare but concerning [34]. These diagnostic challenges highlight the need for heightened clinical vigilance and innovative approaches to HF management [32-34]. Clinicians must balance the risks of exposure with the necessity of accurate HF diagnosis and timely treatment to mitigate the adverse outcomes associated with both conditions [36-40]. To overcome these challenges, healthcare professionals must adopt a multidisciplinary approach that entails collaboration among specialists, such as cardiologists, pulmonologists, infectious disease experts, and primary care physicians [41-43]. They also need to use a combination of clinical evaluation and diagnostic testing to assess the patient's condition and determine the cause of their symptoms [41-43]. They should also consider the patient's comorbidities and medical history when diagnosing and planning a treatment strategy [41-43].

2.2 Prognosis and Outcomes

The prognosis and outcomes of HF in COVID-19 patients have been the subject of extensive research [41,42]. Studies have shown that patients with pre-existing HF are at an elevated risk of excruciating ailment from COVID-19, with nearly one-third of such patients dying during hospitalization [43]. COVID-19 can exacerbate heart failure through several mechanisms, including inflammation, direct cardiac injury, and increased thrombotic activity [43-46]. A multicenter prospective study highlighted the role of NT-proBNP levels in predicting mortality in critically ill COVID-19 patients, with a 30-day mortality rate of 27.4% among the study participants [45]. Patients with a high probability of HF experienced a notably elevated mortality and morbidity rate in comparison to those with a lower likelihood (40.8% vs. 16.5%, respectively) [44]. A study conducted by Saikun Wang highlights the substantial impact of pre-existing

coronary heart disease (CHD) on COVID-19 outcomes [45]. Individuals with pre-existing CHD are at significantly higher risk of mortality from COVID-19, with an odds ratio (OR) of 2.45 with a 95% CI: 2.04 - 2.94 and P < 0.001 [45]. In addition, these patients are at a more elevated risk of acquiring severe or critical COVID-19, as evidenced by an OR of 2.57 with a 95%CI: 1.98 - 3.33 and P < 0.001, and have increased odds of requiring admission to Intensive Care Units (ICU) or Coronary Care Units (CCU) (OR = 2.75, 95%CI: 1.61 - 4.72, P = 0.002). Conversely, individuals with pre-existing CHD have reduced odds of discharge or recovery from COVID-19 (OR = 0.43, 95%CI: 0.28 - 0.66, P < 0.001) [45]. Subgroup analyses revealed that factors such as publication year, follow-up duration, gender, and hypertension significantly influence the prognosis of COVID-19 patients with pre-existing coronary heart disease (CHD), particularly among male or hypertensive patients [45]. Husam M Salah conducted research related to post-COVID-19 heart failure (HF) incidence was approximately 1.1% (95% CI: 0.7–1.6) over a mean follow-up period of 9.2 months [46]. Recovered COVID-19 patients exhibited a significantly increased risk of incident HF compared to non-COVID-19 patients, with a hazard ratio (HR) of 1.90 with 95% CI: 1.54–3.24 and p < 0.0001 [46]. Meta-regression analysis revealed a direct relationship between the risk of incident HF and age (p = 0.001) and hypertension (p = 0.02), while a negative association was observed with more extended follow-up periods (p = 0.01) [46]. These findings highlight that individuals who have recovered from COVID-19 face nearly double the risk of developing heart failure in the long term, particularly among older individuals or those with a history of hypertension [46]. This underscores the importance of closely monitoring cardiovascular health in COVID-19 survivors and integrating these findings into post-recovery care protocols [46]. These findings underscore the bidirectional relationship between HF and COVID-19, where each condition can significantly worsen the prognosis of the other [46]. Healthcare providers must recognize the increased risks and manage these patients with careful consideration of their cardiac function and the potential impacts of COVID-19 on their cardiovascular health [45,46]. The prognosis and outcomes of HF and cardiovascular disease in COVID-19 patients have become significant areas of interest in recent research [44]. Recent studies have shed light on the prevalence and impact of cardiac arrhythmias in patients with COVID-19 infection [45-48]. The multicenter cohort study by Hayek et al. sheds light on the outcomes of critically ill COVID-19 patients who experienced in-hospital cardiac arrest [47]. Among 5,019 critically ill COVID-19 patients, a substantial 14% experienced in-hospital cardiac arrest [47]. Alarmingly, only 57% of these individuals received cardiopulmonary resuscitation (CPR) [47]. The overall survival rate (SR) to hospital discharge following cardiopulmonary resuscitation (CPR) was 12%, with age playing a significant role; 21% of patients under 45 years survived compared to only 3% of those aged 80 years and above [47]. Patients who experienced in-hospital cardiac arrest were often older, had several complications, and were more likely to be admitted to hospitals with limited ICU bed capacity [47]. These findings underscore the high incidence and poor prognosis associated with in-hospital cardiac arrest in critically ill COVID-19 patients [47]. The study highlights the critical importance of advanced care planning and strategic resource allocation to optimize outcomes in this vulnerable patient population [47]. These may include prolonged hospitalization, increased severity of respiratory symptoms, and a higher likelihood of mortality compared to those without underlying cardiac conditions [45-48]. Individuals with pre-existing cardiac conditions, such as HF, face a 10% to 20% higher likelihood of experiencing severe illness due to COVID-19, in contrast to those with healthy cardiac profiles [45,46]. Approximately 30% of adults with a previous history of HF faced mortality during hospitalization for COVID-19 [45-47]. The in-hospital mortality rate for individuals with a history of HF is nearly twice that of adults without such a history [45-47]. COVID-19 can exacerbate cardiovascular complications in patients with pre-existing heart conditions [47,48]. Studies from the past year emphasize an increased incidence of myocardial injury, arrhythmias, and acute coronary syndromes in this specific population, contributing to a poorer prognosis [45-49].

The management of COVID-19 in patients with HF poses unique therapeutic challenges [51,52]. Recent studies indicate the necessity for personalized treatment strategies, considering the delicate balance between antiviral interventions and cardiac medications to optimize patient outcomes [50-53]. Emerging evidence points to potential long-term effects on cardiovascular health in COVID-19 survivors with a history of HF [53,54]. Persistent symptoms, such as fatigue and dyspnea, warrant continued

monitoring and rehabilitation efforts to mitigate the long-term impact on cardiac function [11,52,53]. Identifying high-risk individuals early allows for targeted interventions, potentially altering the disease trajectory and improving overall outcomes [54]. The burden of COVID-19-related heart complications extends to healthcare systems, with increased demand for specialized care and resources [54]. Insights from recent studies emphasize the importance of preparedness and resource allocation to manage the unique challenges posed by this subset of patients [50-55]. As research on the prognosis and outcomes of HF and cardiovascular disease in COVID-19 patients continues to evolve, there is a growing need for collaborative, interdisciplinary studies. Future directions should focus on refining risk prediction models, optimizing treatment strategies, and exploring innovative approaches to enhance patient care and outcomes. In conclusion, synthesizing recent studies underscores the intricate relationship between COVID-19, pre-existing heart conditions, and patient outcomes. Ongoing research will further shape our understanding, guiding clinical practice and public health initiatives.

2.3 Mechanisms Underlying Association

COVID-19 and HF are two conditions that can affect the heart and lungs, but these elements can engage in intricate interactions with one another [2,3-5]. The precise pathophysiological mechanisms governing this interaction remain incomplete but may involve several factors [3,4]. Several studies have explored the role of ACE2 in SARS-CoV-2 infection, identifying it as a crucial receptor for viral entry into cells and noting its downregulation post-infection to limit further viral access [56-59]. The renal angiotensin Aldosterone System (RAAS) regulates blood pressure and electrolyte balance [57]. It involves the conversion of angiotensinogen to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) [58]. The SARS-CoV-2 virus enters human cells via the angiotensin-converting enzyme 2 (ACE2) receptor, prominently present in cardiac tissues [58]. The binding of the virus to ACE2 downregulates its expression, leading to dysregulation of the RAAS. Dysregulated RAAS activation can result in vasoconstriction, inflammation, oxidative stress, and fibrosis, contributing to myocardial injury, hypertension, and heart failure in COVID-19 patients [58]. Although direct cardiomyocyte infection by SARS-CoV-2 is rare, cardiovascular complications in COVID-19 often arise from indirect mechanisms or pre-existing cardiac dysfunction [56]. Recent findings of elevated ACE2 expression in heart pericytes suggest a potential route for SARS-CoV-2 infection, contributing to local microvascular dysfunction and coagulopathy, a common cardiovascular complication in hospitalized COVID-19 patients [57]. The viral spike protein and ACE2 receptor binding is crucial in SARS-CoV-2 entry into target cells, facilitated by Ser proteases TMPRSS2 and furin [57,58]. While initial infection primarily affects upper respiratory tract cells, ACE2 expression in various tissues, including cardiomyocytes and coronary pericytes, suggests a potential role in myocardial vulnerability to SARS-CoV-2 [57,58]. Local ACE2 gene polymorphisms have been associated with hypertension and cardiovascular disease, with evidence suggesting a lower risk of fatal cardiovascular events in females due to ACE2's location on the X chromosome [58]. Women may be less susceptible to severe SARS-CoV-2 infection due to protective mechanisms related to ACE2 and hormonal influences [58]. Despite limited data, hypotheses suggest that older COVID-19 patients may experience worse outcomes due to dysregulated Ang II pathways and decreased ACE2 levels, particularly in organs with high ACE2 expression, such as the lungs, kidneys, heart, and endothelium [58,59]. Cytokine Release Syndrome (CRS) is a severe immune reaction characterized by the overproduction of cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin-1 (IL-1), among others [57,59]. In COVID-19 patients, CRS is triggered by the virus's ability to activate immune cells, leading to an exaggerated immune response [57]. Increased cytokines release can lead to systemic inflammation and endothelial dysfunction, impairing blood vessel function and promoting thrombosis [57,58].CRS-induced endothelial dysfunction may contribute to myocardial injury and myocarditis, leading to cardiac complications such as arrhythmias, HF, and cardiogenic shock [59,60]. Atherosclerotic plaques in the coronary arteries can destabilize due to systemic inflammation and endothelial dysfunction associated with COVID-19 [59]. Inflammation within the plaque, induced by cytokines and other inflammatory mediators, can weaken the fibrous cap, making it prone to rupture [57-59]. Plaque rupture can trigger the formation of thrombi, causing acute coronary syndromes (ACS) such as myocardial infarction (MI) [60]. COVID-19-

related plaque destabilization and subsequent thrombosis can result in acute coronary events and contribute to the development of myocardial injury and cardiac complications [60]. COVID-19 is linked to a prothrombotic condition depicted by increased thrombotic events, including venous thromboembolism (VTE), pulmonary embolism (PE), and arterial thrombosis [58]. Several factors contribute to this prothrombotic state, including endothelial dysfunction, platelet activation, coagulation cascade activation, and fibrinolysis inhibition [58]. Dysregulated cytokine production, endothelial injury, and coagulation system activation contribute to thrombus formation in the microvasculature and larger vessels [59-60]. Thrombotic events can lead to ischemic injury in various organs, including the heart, resulting in myocardial infarction, myocardial ischemia, or myocarditis, and subsequent cardiac complications [58-60]. Severe COVID-19 often leads to respiratory distress and hypoxia, depriving the heart of necessary oxygen and causing damage to cardiac tissues [58]. COVID-19 can worsen pre-existing cardiovascular risk factors like hypertension and diabetes, which in turn can accelerate the onset and progression of HF [61]. The virus can disrupt the immune system, potentially leading to autoimmune reactions where the body's immune system attacks its heart tissues [62]. COVID-19 can cause microvascular dysfunction and impaired endothelial function, affecting blood flow regulation and leading to ischemic heart damage [63,64]. Fig. 1 depicts the pathophysiological mechanisms causing arrhythmia and HF insulted by COVID-19.

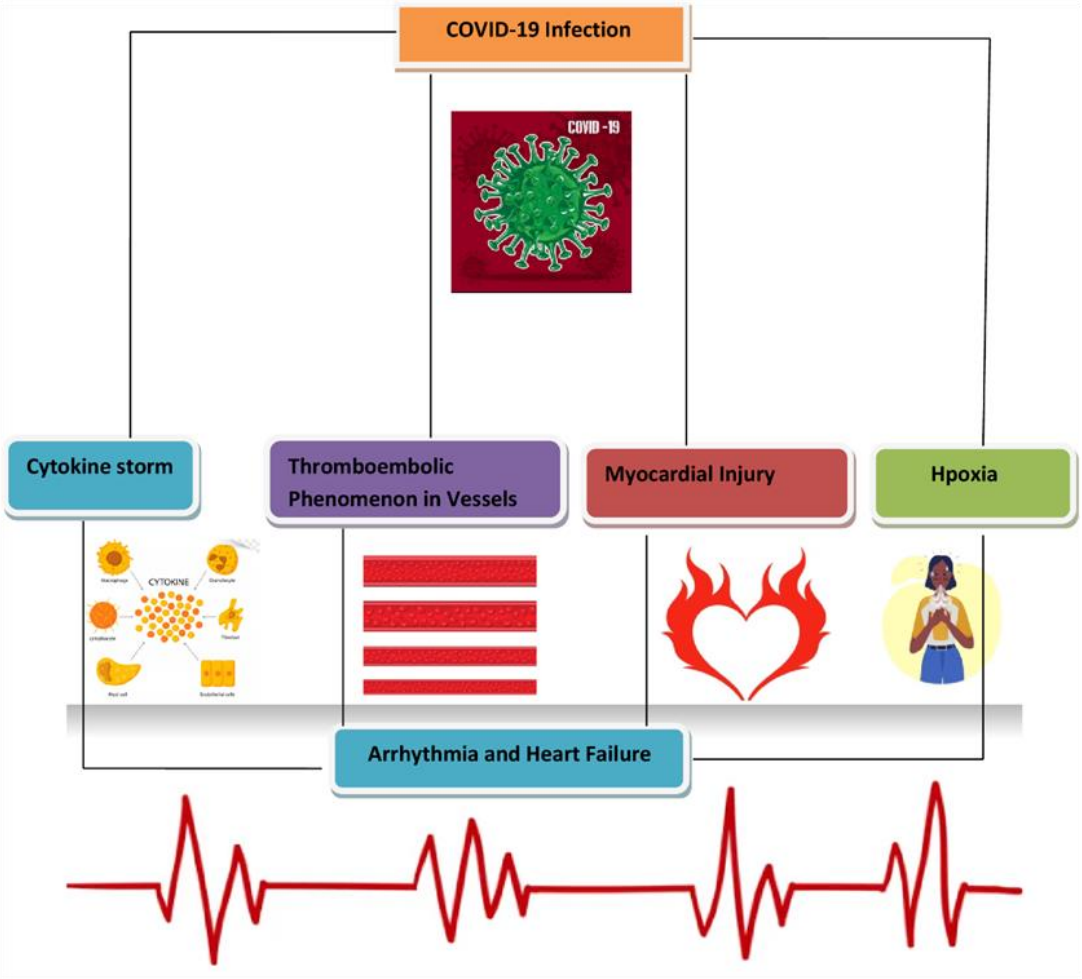

Fig. 1. Pathophysiological mechanisms causing arrhythmia and HF insulted by COVID-19

"Exploring the Intersection: COVID-19 and Heart Failure - Understanding the Dual Burden for Comprehensive Care and Public Health Resilience".

Specific individuals may have a genetic predisposition that renders them more vulnerable to COVID-19-induced heart failure [65]. Certain medications used to treat COVID-19 may have cardiotoxic effects, which could harm the heart tissues [66]. The long-term impact of COVID-19, known as "long COVID," can include persistent cardiac symptoms that affect the heart's function and prognosis long after the initial infection has resolved [67]. These processes collectively increase the risk of adverse cardiovascular events, including arrhythmias, heart failure, myocardial infarction, and cardiogenic shock [67]. Comprehending these factors is essential for effectively managing and treating COVID-19 patients at risk of heart failure [67,68]. It's important to note that ongoing research continues to shed light on these mechanisms, and treatments are being developed and refined to address these multifaceted challenges.

3. COVID-19 AND CARDIOVASCULAR COMPLICATIONS: CONSIDERATIONS FOR CLINICAL MANAGEMENT

COVID-19 and HF are interrelated conditions that pose significant challenges for managing affected patients [15,68]. Managing these conditions involves several aspects: prevention, diagnosis, treatment, monitoring, follow-up, collaboration, education, and support [16,17]. One of the most critical aspects of management is preventing COVID-19 infection and transmission [68]. Individuals with HF face an increased susceptibility to severe COVID-19 outcomes and should be prioritized for vaccination and boosted against COVID-19 [69]. They should also adhere to preventive measures, such as masking, social distancing, hand hygiene, and isolation, to reduce their exposure to the virus [69]. They should also avoid nonessential travel and crowded places, especially in areas with high infection rates [69]. Another management aspect is the early detection and diagnosis of COVID-19 and HF [70]. Healthcare providers should sustain a heightened suspicion of HF in individuals with COVID-19, particularly those with known cardiovascular risk factors [70]. Diagnostic investigations, including CXR, echocardiography, and biomarker assays, are crucial in identifying HF in COVID-19 patients [70]. Managing COVID-19 and HF together requires a multidisciplinary approach that involves collaboration among various medical specialities, such as cardiologists, pulmonologists, infectious disease specialists, and critical care teams [71]. Coordinated efforts among these specialists can provide comprehensive care, improve outcomes, and reduce mortality [71]. Under existing guidelines and recommendations, individuals diagnosed with COVID-19 and HF should receive optimal treatment for both conditions [72]. The treatment may include anti-inflammatory drugs, anticoagulants, diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and antiviral agents [72]. The treatment should be individualized and tailored to the patient's clinical status, comorbidities, drug interactions, and contraindications [72,73]. The treatment should also be monitored and adjusted to achieve the best possible outcomes [72]. In severe cases of COVID-19 and HF, mechanical circulatory support devices like ventricular assist devices (VADs) may be necessary to provide temporary cardiac support [73]. These devices can help maintain adequate blood flow and oxygenation while the heart recovers or is awaiting heart transplantation [73]. COVID-19 patients often experience respiratory distress, which can be exacerbated by the presence of HF [74]. Oxygen and ventilation may be required to support respiratory function [74]. Careful monitoring is essential to prevent complications associated with oxygen therapy [74]. Achieving and maintaining optimal fluid balance and electrolyte levels are vital in HF management [75]. Monitoring fluid intake, output, and electrolyte levels is essential to prevent complications and optimize cardiac function [75]. Cardiac rehabilitation and exercise programs tailored to the individual's condition can play a significant role in the long-term management of HF [76]. These programs focus on improving physical fitness, decreasing symptoms, and improving patients' overall mental health and quality of life [76]. Educating patients about their conditions and involving them in their care is essential [77]. Patients should be informed about medication management, dietary restrictions, symptom recognition, and the importance of adhering to treatment plans [77]. Empowering patients to self-manage their conditions can lead to better long-term outcomes [77]. Managing two complex conditions simultaneously can have a significant impact on a patient's mental health [78]. Enabling access to mental health resources and support is imperative for fostering holistic well-being and

addressing psychological challenges [78]. Continued research and innovation are fundamental for advancing the management of COVID-19 and HF [78]. Ongoing studies aim to uncover more effective therapies, diagnostic tools, and treatment strategies [70-78]. Healthcare professionals must prioritize staying informed about the latest research findings to ensure the delivery of optimal care to patients [78]. The implications for management extend to public health strategies that address the needs of affected individuals and healthcare systems [78]. Strategies for managing and preventing HF in COVID-19 have broader implications for mitigating the pandemic's impact on healthcare systems and population health [77,78]. This extensive review thoroughly examines the cardiovascular complications associated with COVID-19 from numerous studies and provides a comprehensive understanding of the cardiovascular implications of COVID-19 [77,78]. Current evidence suggests that severe COVID-19 outcomes, including mortality, are more prevalent among older individuals with chronic health conditions such as hypertension, diabetes, cardiac issues, and chronic obstructive pulmonary disease (COPD) [78]. Notably, significant cardiac complications, including myocardial injury and fatal arrhythmias, have been identified in early studies of COVID-19 patient populations [78-80]. The data presented emphasizes the considerable impact of COVID-19 on the cardiovascular system, with reports indicating a broad spectrum of complications ranging from myocarditis, acute myocardial infarction, acute HF, arrhythmia to thrombotic events, and disseminated intravascular coagulation (DIC) [78,79]. Notably, individuals with pre-existing cardiovascular conditions face a heightened risk of mortality when infected with SARS-CoV-2 [78,79]. Age and sex differences are also highlighted, with older individuals and those with comorbidities, especially cardiovascular diseases, being at a higher risk of adverse outcomes [80]. An initial study by Michael Worobey examined 41 COVID-19-affected patients, predominantly male with a median age of 49, many of whom had contact with the Huanan seafood market, the initial COVID-19 epicentre [81]. Approximately one-third of these patients had comorbidities like diabetes, cardiovascular disease, and hypertension [81]. Elevated levels of cardiac troponin I were observed in a subset of patients, hinting at potential acute ischemic heart damage [81]. However, such troponin levels should be corroborated with an electrocardiogram or imaging evidence of myocardial ischemia for accurate diagnosis [81]. Interestingly, elevated troponin levels have also been linked to higher mortality rates in patients with severe pneumonia, even in the absence of acute coronary syndrome (ACS) [81]. The possibility of transient myopericarditis, resembling a heart attack in severe COVID-19 cases due to a cytokine storm, cannot be ruled out, as seen in SARS cases [81]. Pro-inflammatory cytokines have been elevated in ICU and non-ICU patients, consistent with cytokine release syndrome (CRS) noted in prior coronavirus infections [81]. Another study involving 99 COVID-19-affected patients, with a median age of 55.5 years and a significant number also linked to the Huanan market, found that cardiovascular and cerebrovascular diseases were common among them [82]. Cardiac injury in this group was assessed using myocardial zymogram analysis, which measures metalloproteinase activity [82]. However, this method's results can be misinterpreted due to the deficiency of metalloproteinases (tissue inhibitors) in the assay environment [82]. Therefore, other established cardiac biomarkers are recommended for acute cardiac injury diagnosis [82]. The study also noted elevated creatine kinase levels and lactate dehydrogenase, typically used for early acute myocardial infarction diagnosis [82]. However, these enzymes are not exclusive to the heart, limiting their diagnostic specificity and sensitivity [82]. In a comprehensive analysis, researchers examined 138 patients affected by COVID-19, with a median age of 56 years [83]. This study, conducted during the pandemic, shed light on the prevalence of comorbidities among COVID-19 patients and their impact on clinical outcomes [83]. Among the most prevalent comorbidities observed were hypertension, cardiovascular disease, diabetes, and cancer, highlighting the importance of understanding the underlying health conditions that may exacerbate COVID-19 severity [83]. Notably, patients with these comorbidities experienced significantly higher rates of ICU admission, underscoring the heightened risk faced by individuals with pre-existing health issues [83]. Among ICU patients, arrhythmias and acute cardiac injury were identified as the most common complications [83]. Acute cardiac injury was defined by increased levels of hypersensitive cardiac troponin I, indicating myocardial damage [83]. This finding emphasizes the impact of COVID-19 on the cardiovascular system, with cardiac complications posing significant challenges in managing critically ill patients [83]. Zhao et al.

investigated the role of HF and N-terminal pro-brain natriuretic peptide (NT-proBNP) in predicting outcomes for critically ill COVID-19 patients [84]. The study included 402 laboratory-confirmed critically ill patients [84]. Within a 30-day follow-up, 27.4% of patients died, and patients with HF likely had a significantly higher mortality rate with ICU admission as compared to those with grey zone or unlikely HF (40.8% vs 25% and 16.5%, respectively) [84]. Independent risk factors associated with COVID-19 mortality included HF likely, age, lymphocyte count, albumin levels, and total bilirubin level [84]. A predictive nomogram was developed, achieving a C-index of 0.8, which can aid in risk stratification and clinical decision-making for critically ill COVID-19 patients [84,85]. In a multicenter cohort study of 191 adult COVID-19 patients, nearly half had pre-existing conditions such as hypertension, diabetes, and coronary heart disease [86]. Non-survivors had a higher prevalence of comorbidities compared to survivors [86]. Secondary outcomes and complications included acute kidney injury (AKI), sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS), with acute HF and cardiac injury being widespread [86]. Laboratory findings highlighted elevated nonspecific biomarkers and pro-inflammatory markers [86]. Since biomarker measurements alone are insufficient for a definitive diagnosis of cardiac injury due to SARS-CoV-2, further clinical investigations using a multimodal approach are advocated [86]. The link between SARS-CoV-2 infection and cardiovascular disease has been supported by a descriptive analysis of all COVID-19 cases in China, confirming that a significant portion of patients had cardiovascular disease, including hypertension [87]. While retrospective studies cannot establish causality, they have shown an increased mortality rate associated with cardiovascular disease, diabetes, chronic respiratory disease, and hypertension [87]. The impact of cardiovascular diseases on the prognosis of COVID-19 patients remains a critical question. Italy, with a high percentage of older individuals and one of the highest death rates from COVID-19 worldwide, presents a unique case for study [88]. Recent data from Italy indicates that the majority of deceased patients had multiple comorbidities, suggesting that the clinical outcomes of COVID-19 may be exacerbated by the cumulative effect of various chronic conditions and overall frailty in the elderly population [88]. COVID-19 is recognized for its capacity to induce diverse end-organ dysfunctions, extending beyond its initial impact on the respiratory system [76]. Fig. 2 illustrates the intricate web of complications triggered by COVID-19, involving vital organs such as the heart, kidneys, liver, and neurological system [77,78].

The above visual representation underscores the systemic nature of the virus, showcasing its potential to affect multiple physiological systems [77,78]. Understanding these complications is imperative for healthcare professionals in comprehensively addressing the complexities associated with COVID-19 and guiding diagnostic and therapeutic strategies for optimal patient care [77,78]. Cardiovascular complications in COVID-19 extend beyond respiratory manifestations [12]. Notably, myocardial injury has emerged as a significant concern in affected individuals, warranting in-depth exploration [16]. Understanding the interplay between the virus and cardiac cells is crucial for unravelling the pathophysiology of this complication [79]. Identifying myocardial injury poses diagnostic challenges, and recent studies have delved into the spectrum of severity [78-80].

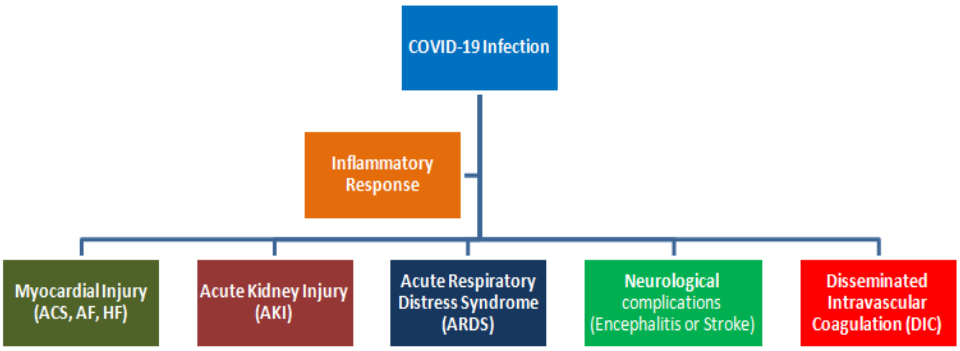

Fig. 2. End organ dysfunctions or complications caused by COVID-19

Table 1. Comprehensive Overview of Studies on HF in COVID-19

Publisher	Year of Publication	Cases and Control	Result
Italia L et al. [1]	2021	1,401 patients with COVID-19 and HF from 11 studies	The mortality rate of patients with COVID-19 and HF was 50%, compared with 10% in patients without HF.
Milton Packer [87]	2021	Randomized, double-anonymized, placebo-controlled trial	In a study involving 3730 patients with chronic HF and reduced ejection fraction, empagliflozin demonstrated a 25% reduction in the risk of the combined outcome of cardiovascular death or worsening HF hospitalization, compared to a placebo. The treatment also showed positive effects on renal outcomes and improved the quality of life for participants.
Zahra Raisi-Estabragh [88]	2023	17,871 COVID-19 cases from UK Biobank with 35,742 matched controls	This cohort study revealed that individuals hospitalized with COVID-19 face an elevated risk of incident cardiovascular events and mortality across various outcomes. In contrast, individuals not requiring hospitalization exhibited an increased risk of venous thromboembolism and death.
Wan EYF et al. [89]	2023	87,478 participants from the UK Biobank cohort who had COVID-19 tests	In the sample, 1.1% of participants with COVID-19 were observed to experience HF, categorizing it as a rare complication. The researchers concluded that the risk of HF escalated by 90% among individuals within the nine months following the onset of COVID-19.
Sheng Wang et al. [90]	2023	Systematic review and meta-analysis	In a recent systematic review and meta-analysis encompassing 17 studies with 12,497 COVID-19 cases and 1,401 controls, the presence of pre-existing coronary heart disease (CHD) was linked to a substantial increase in the risks of mortality, ICU admission, and mechanical ventilation in individuals afflicted with COVID-19. Additionally, the study observed a correlation between CHD and elevated levels of inflammatory markers and cardiac injury biomarkers among COVID-19 patients. These findings underscore the pivotal role of CHD as a significant risk factor contributing to adverse outcomes in COVID-19 and underscore the imperative for intensified monitoring and tailored treatment approaches for individuals concurrently dealing with both conditions.

Biomarkers play a pivotal role in assessing the extent of myocardial involvement in COVID-19 patients [79,81]. The systematic review and meta-analysis provide critical insights into the prevalence of cardiac complications among COVID-19 patients and their impact on mortality rates [88]. The study revealed that acute cardiac injury was prevalent in 19.46% with a 95% CI of 18.23–20.72 of COVID-19 patients, while HF was observed in 19.07% with a 95% CI of 15.38–23.04 [88].

Additionally, cardiac arrest occurred in 3.44% with a 95% CI of 3.08–3.82 of cases, and an abnormal serum troponin level was noted in 22.86% with a 95% CI of 21.19–24.56 of COVID-19 patients [88]. Patients who developed acute cardiac injury had an overall odds ratio of mortality that was 14.24 times higher (OR = 14.24; 95% CI: 8.67–23.38). Similarly, among patients with abnormal serum troponin levels, the pooled odds ratio of mortality was 19.03 (OR = 19.03; 95% CI: 11.85–30.56). Another study by Tobler DL et al. showed that COVID-19 increases the long-term risk of ischemic and non-ischemic cardiovascular disease, such as atrial fibrillation (AF), HF, CAD, and heart attacks [89]. They analyzed the data from a large cohort of COVID-19 patients [89]. The study revealed increased cardiovascular events among the participants compared to the matched controls, even after adjusting for traditional risk factors [89]. They also found that COVID-19 patients with pre-existing cardiac disease or risk factors were more likely to develop acute HF and shock, requiring advanced therapies such as extracorporeal membrane oxygenation or VADs [82]. A growing body of literature underscores the prevalence and varied types of arrhythmias in COVID-19 patients [87]. Understanding their impact on disease severity is crucial for comprehensive patient management [87]. The intricate mechanisms by which SARS-CoV-2 induces arrhythmias are a focal point of recent research [87]. Electrophysiological effects on the heart contribute to understanding arrhythmogenesis in the context of COVID-19 [87]. Exploring the incidence and patterns of ACS in COVID-19 patients is essential for recognizing the association between COVID-19 severity and ACS [84]. Identifying high-risk individuals prone to ACS is equally significant [83,84]. In recent literature, efforts to stratify risk and identify individuals prone to arrhythmias have gained prominence [83,84]. Challenges in recognizing and diagnosing ACS in the presence of COVID-19 are central to discussions on patient care [84]. Managing arrhythmias and ACS in COVID-19 requires a multifaceted approach [84]. Overcoming challenges in treating these conditions concurrently is pivotal for optimizing patient outcomes [84,85]. Understanding the impact of arrhythmias on COVID-19 outcomes and the prognostic significance of ACS in COVID-19 patients provides valuable insights for clinicians managing individuals with these dual conditions [83-85]. A multidisciplinary approach that seamlessly integrates cardiology and infectious disease expertise is essential for managing arrhythmias and ACS in COVID-19 [83-85]. Coordination between these specialties contributes to holistic patient care [83-85]. Current trends in research shed light on emerging developments in the field of arrhythmias and ACS associated with COVID-19. Outlining future research directions ensures continued advancements in knowledge and treatment strategies. Different comprehensive overviews of studies on HF in COVID-19 with their brief results are summarized in Table 1.

4. CONCLUSION

COVID-19 and heart failure (HF) present intricate and bidirectional relationships that significantly impact patient outcomes. The epidemiological and clinical association between COVID-19 and HF underscores healthcare professionals' complex challenges in diagnosing and managing these conditions. COVID-19 can precipitate or worsen HF through various mechanisms, while pre-existing HF can exacerbate the severity and course of COVID-19. This interplay contributes to heightened risks of respiratory distress, acute decompensation, and adverse outcomes, including mortality and morbidity. The diagnostic challenges in differentiating COVID-19 and HF symptoms underscore the importance of a multidisciplinary approach and advanced diagnostic tools. Despite these challenges, early identification and targeted interventions are crucial for improving clinical outcomes.

Moreover, studies highlight the long-term cardiovascular consequences of COVID-19, with survivors facing increased risks of incident HF and adverse cardiovascular events. Understanding the underlying pathophysiological mechanisms, including ACE2 dysregulation, cytokine release syndrome, and hypercoagulability, is pivotal for optimizing management strategies. Management of COVID-19 and HF requires a comprehensive approach encompassing prevention, early diagnosis, personalized treatment, multidisciplinary

collaboration, and patient education. Continued research and innovation are essential to refine risk prediction models and develop tailored therapies, ultimately improving care and outcomes for individuals affected by these complex conditions. In summary, integrating insights from diverse studies enhances our understanding of COVID-19's cardiovascular implications, guiding clinical practice and public health endeavors targeting challenges posed by this evolving pandemic.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Italia L, Tomasoni D, Bisegna S, Pancaldi E, Stretti L, Adamo M, et al. COVID-19 and heart failure: from epidemiology during the pandemic to myocardial injury, myocarditis, and heart failure sequelae. Front Cardiovasc Med. 2021;8:713560.
2. Palazzuoli A, Metra M, Collins SP, Adamo M, Ambrosy AP, Antohi LE, et al. Heart failure during the COVID-19 pandemic: clinical, diagnostic, management, and organizational dilemmas. ESC Heart Fail. 2022;9(6):3713-36.
3. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;5(7):831-40.
4. Brogi E, Marino F, Bertini P, Tavazzi G, Corradi F, Forfori F. Cardiac complications in patients with COVID-19: a systematic review. J Anesth Analg Crit Care. 2022;2(1):18.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
6. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-8.
7. Dong E, Ratcliff J, Goyea TD, Katz A, Lau R, Ng TK, et al. The Johns Hopkins University Center for Systems Science and Engineering COVID-19 Dashboard: data collection process, challenges faced, and lessons learned. Lancet Infect Dis. 2022;22(12):e370-e376.
8. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10.
9. Ruge M, Gomez JMD, du Fay de Lavallaz J, Hlepas A, Rahman A, Patel P, et al. The prognostic value of cardiac troponin for 60 day mortality and major adverse events in COVID-19 patients. Cardiovasc Pathol. 2021;55:107374.
10. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81(2):e16-e25.
11. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020;141(20):1648-55.
12. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(11):1265-73.
13. Al-Wahaibi K, Al-Wahshi Y, Mohamed Elfadil O. Myocardial Injury Is Associated with Higher Morbidity and Mortality in Patients with 2019 Novel Coronavirus Disease (COVID-19). SN Compr Clin Med. 2020;2(12):2514-20.
14. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. Intensive Care Med. 2020;46(6):1111-3.
15. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020;382(17):1653-9.
16. Alhogbani T. Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus. Ann Saudi Med. 2016;36(1):78-80.
17. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
18. Kochav SM, Coromilas E, Nalbandian A, Ranard LS, Gupta A, Chung MK, et al. Cardiac arrhythmias in COVID-19

infection. Circ Arrhythm Electrophysiol. 2020 Jun;13(6):e008719.
19. Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldbarg S, et al. Worldwide survey of COVID-19–associated arrhythmias. Circ Arrhythm Electrophysiol. 2021;14(3):e009458.
20. Peltzer B, Manocha KK, Ying X, Kirzner J, Ip JE, Thomas G, et al. Arrhythmic complications of patients hospitalized with COVID-19: incidence, risk factors, and outcomes. Circ Arrhythm Electrophysiol. 2020;13(10):e009121.
21. Rattanawong P, Shen W, El Masry H, Sorajja D, Srivathsan K, Valverde A, Scott LR. Guidance on short-term management of atrial fibrillation in coronavirus disease 2019. J Am Heart Assoc. 2020;9(14):e017529.
22. Mountantonakis SE, Saleh M, Fishbein J, Gandomi A, Lesser M, Chelico J, Gabriels J, Qiu M, Epstein LM, Northwell COVID-19 Research Consortium. Atrial fibrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection. Heart Rhythm. 2021;18(4):501-7.
23. Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, Ntinopoulou M, Sertaridou E, Tsironidou V, Tsigalou C, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest. 2020;130(11):6151-7.
24. Katkat F, Kalyoncuoğlu M, Karahan S, Abanus H, Turhan Çağlar FN, Karabulut D, et al. Does coexistence of fragmented QRS and cardiovascular disease have the ability to predict the mortality in hospitalized, critically ill patients with COVID-19? Anatol J Cardiol. 2021; 25(11):803-10.
25. Ruparelia N, Panoulas V. The missing acute coronary syndromes in the COVID-19 era. Ther Adv Cardiovasc Dis. 2020;14:1753944720977732.
26. Teixeira DO Amaral V, Viana AA, Heubel AD, Linares SN, Martinelli B, Witzler PHC, et al. Cardiovascular, Respiratory, and Functional Effects of Home-Based Exercise Training after COVID-19 Hospitalization. Med Sci Sports Exerc. 2022;54(11):1795-1803.
27. Xu J, Xiao W, Liang X, et al. A meta-analysis on the risk factors adjusted association between cardiovascular disease and COVID-19 severity. BMC Public Health. 2021;21:1533.
28. Espiritu AI, Pilapil JCA, Aherrera JAM, et al. Outcomes of patients with COVID-19 and coronary artery disease and heart failure: findings from the Philippine CORONA study. BMC Res Notes. 2024;17:14.
29. Schuster M, Müller J, Schwarz EI, Saxer S, Schneider SR, Ulrich S, et al. Oxygen therapy in pulmonary vascular disease: a systematic review, meta-analysis, and comment. Heart Fail Clin. 2023;19(1S):e1-e11.
30. Bauer A, Schreinlechner M, Sappler N, Dolejsi T, Tilg H, Aulinger BA, et al; ACEI-COVID investigators. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. Lancet Respir Med. 2021;9(8):863-872.
31. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, et al; Writing Committee for the REMAP-CAP Investigators. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-1329.
32. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
33. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
34. Bouadma L, Mekontso-Dessap A, Burdet C, Merdji H, Poissy J, Dupuis C, et al; COVIDICUS Study Group. High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. JAMA Intern Med. 2022;182(9):906-916.

35. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491-1502.
36. Morrow A, Gray SR, Bayes HK, Sykes R, McGarry E, Anderson D, et al. Prevention and early treatment of the long-term physical effects of COVID-19 in adults: design of a randomised controlled trial of resistance exercise-CISCO-21. Trials. 2022;23(1):660.
37. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500.
38. Jimeno-Almazán A, Franco-López F, Buendía-Romero Á, Martínez-Cava A, Sánchez-Agar JA, Sánchez-Alcaraz Martínez BJ, et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. Scand J Med Sci Sports. 2022;32(12):1791-801.
39. Nie X, Qian L, Sun R, Huang B, Dong X, Xiao Q, Zhang Q, Lu T, Yue L, Chen S, et al. Multi-organ proteomic landscape of COVID-19 autopsies. Cell. 202;184(3):775-791.e14.
40. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, et al; HEP-COVID Investigators. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med. 2021;181(12):1612-1620.
41. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, et al; PROVENT Study Group. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. N Engl J Med. 2022;386(23):2188-2200.
42. Zimlich R. What to Know About Heart Failure and COVID-19. Verywell Health. 2023 Jan 5. Available:https://www.verywellhealth.com/heart-failure-and-covid-19-5115262.
43. Gao W, Fan J, Sun D, Yang M, Guo W, Tao L, Zheng J, Zhu J, Wang T, Ren J. Heart Failure Probability and Early Outcomes of Critically Ill Patients With COVID-19: A Prospective, Multicenter Study. Front Cardiovasc Med. 2021;8:738814.
44. Wang S, Zhu R, Zhang C, Guo Y, Lv M, Zhang C, Bian C, Jiang R, Zhou W, Guo L. Effects of the pre-existing coronary heart disease on the prognosis of COVID-19 patients: A systematic review and meta-analysis. PLoS One. 2023;18(10): e0292021.
45. Salah HM, Fudim M, O'Neil ST, Manna A, Chute CG, Caughey MC. Post-recovery COVID-19 and incident heart failure in the National COVID Cohort Collaborative (N3).
46. Hayek SS, Brenner SK, Azam TU, Shadid HR, Anderson E, Berlin H, Pan M, Meloche C, Feroz R, O'Hayer P, Kaakati R, Bitar A, Padalia K, Perry D, Blakely P, Gupta S, Shaefi S, Srivastava A, Charytan DM, Bansal A, Mallappallil M, Melamed ML, Shehata AM, Sunderram J, Mathews KS, Sutherland AK, Nallamothu BK, Leaf DE; STOP-COVID Investigators. In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study. BMJ. 2020;371:m3513.
47. Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldbarg S, Kim JH, Yeo I, Tracy C, Ayanian S, Akar J. Worldwide survey of COVID-19–associated arrhythmias. Circ Arrhythm Electrophysiol. 2021;14(3):e009458.
48. Kohli U, Meinert E, Chong G, Tesher M, Jani P. Fulminant myocarditis and atrial fibrillation in child with acute COVID-19. J Electrocardiol. 2022;73:150-2.
49. Mann DL, Givertz MM, Vader JM, Starling RC, Shah P, McNulty SE, et al; LIFE Investigators. Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA Cardiol. 2022;7(1):17-25.
50. Xie Y, You Q, Wu C, Cao S, Qu G, Yan X, et al. Impact of cardiovascular disease on clinical characteristics and outcomes of coronavirus disease 2019 (COVID-19). Circ J. 2020;84(8):1277-83.
51. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324(11):1048-57.

52. Bergami M, Manfrini O, Nava S, Caramori G, Yoon J, Badimon L, et al. Relationship between azithromycin and cardiovascular outcomes in unvaccinated patients with COVID-19 and preexisting cardiovascular disease. J Am Heart Assoc. 2023;12(14):e028939.
53. Lawler PR, Derde LPG, van de Veerdonk FL, McVerry BJ, Huang DT, et al; Writing Committee for the REMAP-CAP Investigators. Effect of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker initiation on organ support-free days in patients hospitalized with COVID-19: a randomized clinical trial. JAMA. 2023;329(14):1183-96.
54. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation. 2021;143(2):135-44.
55. Pouremamali A, Babaei A, Malekshahi SS, Abbasi A, Rafiee N. Understanding the pivotal roles of ACE2 in SARS-CoV-2 infection: from structure/function to therapeutic implication. Egypt J Med Hum Genet. 2022;23(1):103.
56. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543-558. doi: 10.1038/s41569-020-0413-9. Epub 2020 Jul 20. PMID: 32690910; PMCID: PMC7370876.
57. Qu L, Chen C, Yin T, Fang Q, Hong Z, Zhou R, Tang H, Dong H. ACE2 and Innate Immunity in the Regulation of SARS-CoV-2-Induced Acute Lung Injury: A Review. Int J Mol Sci. 2021;22(21):11483.
58. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020;116(6):1097–1100.
59. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol. 2020;318(5):H1084-H1090.
60. 10. Huang D, Yang H, Yu H, Wang T, Chen Z, Yao R, et al. A prediction model for major adverse cardiovascular events (MACE) in patients with coronavirus disease 2019 (COVID-19). BMC Pulm Med. 2022;22(1):343.
61. Bansal M. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):247-250. DOI:10.1016/j.dsx.2020.03.013.
62. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *European Heart Journal*. 2020;41(32):3038-3044. doi: 10.1093/eurheartj/ehaa623.
63. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation. 2020;141(23):1903-14.
64. Ashton R, Ansdell P, Hume E, Maden-Wilkinson T, Ryan D, Tuttiett E, et al. COVID-19 and the long-term cardio-respiratory and metabolic health complications. Rev Cardiovasc Med. 2022;23(2):53-9.
65. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020;38(7):1504-7.
66. Zakynthinos GE, Tsolaki V, Oikonomou E, Vavouranakis M, Siasos G, Zakynthinos E. New-Onset Atrial Fibrillation in the Critically Ill COVID-19 Patients Hospitalized in the Intensive Care Unit. J Clin Med. 2023;12(22):6989.
67. Morrow AJ, Sykes R, McIntosh A, Kamdar A, Bagot C, Bayes HK, et al. A multisystem, cardio-renal investigation of post-COVID-19 illness. Nat Med. 2022;28(6):1303-13.
68. Tomasoni D, Inciardi RM, Lombardi CM, Tedino C, Agostoni P, Ameri P, et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. Eur J Heart Fail. 2020;22(12):2238-47.
69. Asokan I, Rabadia SV, Yang EH. The COVID-19 pandemic and its impact on the cardio-oncology population. Curr Oncol Rep. 2020;22(6):53.
70. Bonow RO, O'Gara PT, Yancy CW. Cardiology and COVID-19. JAMA. 2020;324(12):1131-2.
71. Magadum A, Kishore R. Cardiovascular manifestations of COVID-19 infection. Cells. 2020;9(11):2508.
72. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, et al. Cardiovascular manifestations and

treatment considerations in COVID-19. Heart. 2020;106(15):1132-41.
73. Paris S, Inciardi RM, Lombardi CM, Tomasoni D, Ameri P, Carubelli V, et al. Implications of atrial fibrillation on the clinical course and outcomes of hospitalized COVID-19 patients: results of the Cardio-COVID-Italy multicentre study. Europace. 2021;23(10):1603-11.
74. Adu-Amankwaah J, Mprah R, Adekunle AO, Ndzie Noah ML, Adzika GK, Machuki JO, et al. The cardiovascular aspect of COVID-19. Ann Med. 2021;53(1):227-36.
75. Addison D, Campbell CM, Guha A, Ghosh AK, Dent SF, Jneid H. Cardio-Oncology in the era of the COVID-19 pandemic and beyond. J Am Heart Assoc. 2020;9(19):e017787.
76. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-90.
77. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543-58.
78. Worobey M, Levy JI, Malpica Serrano L, Crits-Christoph A, Pekar JE, Goldstein SA, Rasmussen AL, Kraemer MUG, Newman C, Koopmans MPG, Suchard MA, Wertheim JO, Lemey P, Robertson DL, Garry RF, Holmes EC, Rambaut A, Andersen KG. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. Science. 2022;377(6609):951-959.
79. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
80. Zhao Z, Chen A, Hou W, Graham JM, Li H, Richman PS, Thode HC, Singer AJ, Duong TQ. Prediction model and risk scores of ICU admission and mortality in COVID-19. PLoS One. 2020;15(7):e0236618.
81. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802–810.
82. Fersia O, Bryant S, Nicholson R, McMeeken K, Brown C, Donaldson B, et al. The impact of the COVID-19 pandemic on cardiology services. Open Heart. 2020;7(2):e001359.
83. Packer M, Anker SD, Butler J, Filippatos G, Pieske B, Rosano G, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2021;384(1):41-51.
84. Raisi-Estabragh Z, Cooper J, Salih A, Raman B, Lee AM, Neubauer S, Harvey NC, Petersen SE. Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank. Heart. 2022;109(2):119-126.
85. Wan EYF, Mathur S, Zhang R, Yan VKC, Lai FTT, Chui CSL, Li X, Wong CKH, Chan EWY, Yiu KH, Wong ICK. Association of COVID-19 with short- and long-term risk of cardiovascular disease and mortality: a prospective cohort in UK Biobank. Cardiovasc Res. 2023;119(8):1718–1727.
86. Franco JVA, Garegnani LI, Metzendorf MI, et al. Post-covid-19 conditions in adults: systematic review and meta-analysis of health outcomes in controlled studies. BMJ Med. 2024;3:e000723.
87. Chen A, Zhao Z, Hou W, Singer AJ, Li H, Duong TQ. Time-to-Death Longitudinal Characterization of Clinical Variables and Longitudinal Prediction of Mortality in COVID-19 Patients: A Two-Center Study. Frontiers in Medicine. 2021;8:661940. DOI:10.3389/fmed.2021.661940.
88. Wan EYF, Mathur S, Zhang R, Yan VKC, Lai FTT, Chui CSL, Li X, Wong CKH, Chan EWY, Yiu KH, Wong ICK. Association of COVID-19 with short- and long-term risk of cardiovascular disease and mortality: a prospective cohort in UK Biobank. Cardiovascular Research. 2023;119 (8):1718–1727
89. Mercadé-Besora N, Li X, Kolde R, et al. The role of COVID-19 vaccines in preventing post-COVID-19 thromboembolic and cardiovascular complications. Heart. 2024;109(2):119-126. DOI:10.1136/heartjnl-2023-323483.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/117343