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PERICARDIAL COMPLICATIONS IN PATIENTS WITH COVID-19: A REVIEW OF RECENT EVIDENCE

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ABSTRACT
The novel coronavirus disease (COVID-19) essentially affects the lungs causing pneumonia in addition to various other clinical manifestations. The latest evidence is in favor of the deleterious effects of COVID-19 on the cardiovascular system, with symptomatology including pulmonary embolism, acute coronary syndrome, and stroke. Limited attention has been placed on the cardiovascular sequelae of the disease, including pericardial tamponade, pericarditis, or pericardial effusion. A few cases have shed light on the involvement of pericardial disease in patients with COVID-19. With this review, we aim to collate updated evidence of COVID-19 associated with pericardial disease, while also making links to treatment strategies and highlighting the pathophysiology. On the whole, it is recommended the cardiac monitoring in infected and recovered patients is key to prevent pericardial damage and promoting the long-term rehabilitation of patients. Furthermore, primary clinical studies in the future ought to establish the role of post-COVID-19 pericardial ailments while making recommendations for patients.

KEYWORDS: Pericardial complications; COVID-19; SARS-CoV-2; Heart; Review.

1. BACKGROUND
Since the outbreak of the novel coronavirus (severe acute respiratory syndrome 2 or SARS-CoV-2) in Wuhan, China in December 2019, coronavirus disease 2019 (COVID-19) had spread worldwide leading to around 3.8 million deaths as of 12 May 2021.[1,2] COVID-19 is known to primarily infect the lungs causing pneumonia, and has led to a myriad of other clinical manifestations.[3] Recent evidence supports that COVID-19 affects the cardiovascular system leading to pulmonary embolism, stroke, and acute coronary syndrome.[4] Reports also associated arrhythmias, Takotsubo cardiomyopathies, and cardiac arrest to COVID-19.[5,6] Little attention has been paid to the pericardial complications of the disease, which include pericardial effusion, pericarditis, and pericardial tamponade. While a few cases have highlighted the involvement of pericardial disease in patients infected with COVID-19,[7] this review aims to synthesize the latest evidence of COVID-19 associated pericardial disease and make associations to the pathophysiology and treatment strategies.

2. An Overview of Reported Findings

We present findings for the area of involvement, age/gender, presentations, cardiac enzymes, management, and outcomes in Table 1. In total, 22 case reports, 3 cohorts, and 1 cross-sectional study was included in the analysis (Figure 1). The most common symptoms on presentation were chest pain (14), fever (10), cough/shortness of breath (8), and myalgia (2). The majority of the patients survived, with various management options used across all studies such as pericardiocentesis, mechanical ventilation, and pharmacological treatment.

Table 1: Characteristics of COVID-19 studies addressing pericardial complications.

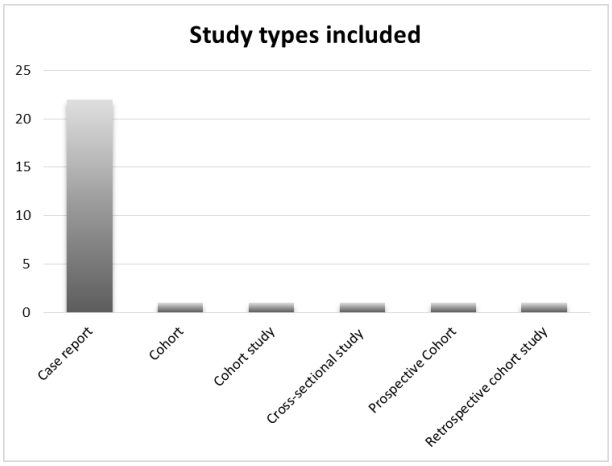
No	Author, year	Study type	Area of involvement	Age/gender	Presentation	Cardiac enzymes	Management	Outcome
1.	Purohit et al., 2021[8]	Case report	Myopericardial and tamponade	82 years, F	Productive cough, fever with chills, and intermittent diarrhea	Mildly raised troponin	Pericardiocentesis	Survived
2.	Asif et al., 2020[9]	Case report	Acute Pericardial and Cardiac Tamponade	70 years, F	Chest pain, worsening dyspnea, and myalgias	NA	Pericardiocentesis, norepinephrine	Survived
3.	Giustino et al., 2020[10]	Cohort study	Myocardial Injury	63 years, 62.7% M (N=305)	60.1% Shortness of breath, 58.9% cough, 53.1% fever, 17.4% chest pain, 22% myalgia	Median (IQR)* Cardiac troponin I peak: 0.09 (0.02–0.86), Cardiac troponin T peak: 0.11 (0.01–0.61), CK-MB peak: 4.1 (1.9–18.6)	73.6% hydroxychloroquine, 58.8% azithromycin, 45.5% glucocorticoids, 55.6% anticoagulation, 49.8% LMWH, 87.5% Percutaneous coronary intervention	57 (18.7%) patients died
4.	Allam et al., 2020[11]	Case report	Pericardial fluid	43 years, F	Sore throat, cough, and shortness of breath	Troponin I 0.000 µg/l (0.020–0.060)	Pericardial aspiration	Survived
5.	Amoozgar et al., 2020[12]	Case report	Pericardial effusion	56 years, M	Chest pain and dyspnea	NA	Pericardial window placement and ibuprofen	Survived
6.	Kumar et al., 2020[13]	Case report	Acute pericardial	66 years, M	Acute-onset severe pleuritic chest pain	hs-cTnT normal	Symptomatic treatment and oral colchicine	Survived
7.	Zeng et al., 2020[14]	Retrospective cohort study	10% (right heart enlargement, right ventricular wall thickening, pericardial effusion), 2 (0.5%) with fulminant myocarditis	64 years for ICU (N = 35) vs. 45 years for non-ICU (N= 381); 66% M vs. 46% M	Hypoxia, multiple organ failure	ICU vs non-ICU: troponin I (0.029 ng/mL [0.007–0.063] vs 0.006 ng/mL [0.006–0.006]); myoglobin (65.45 µg/L [39.77–130.57] vs 37.00 µg/L [26.40–53.54])	----------	3 (9%) died
8.	Dabbagh et al., 2020[15]	Case report	Large hemorrhagic pericardial effusion, tamponade	57 years, M	Cough, shortness of breath, left shoulder pain	Normal	Pericardiocentesis and medications including hydroxychloroquine, colchicine, glucocorticoids	Survived
9.	Walker et al., 2020[16]	Case report	Pericardial effusion, acute pericardial, and cardiac tamponade	30 years, F	Chest pain, cough, fever, shortness of breath	Normal	Pericardial window colchicine, aspirin	
10.	Barman et al., 2020[17]	Cross-sectional study	Pericardial effusions (12.2%)	63.3 years in severe (n = 44) vs 49.7 years in non-severe (n = 46); 54% M	Fever (n=45), cough (n=57), shortness of breath (n=27)	Hs-TnI: 20 (5–86) in severe vs 9 (3–16) in non-severe	Mechanically ventilated (n=24), ICU admission (n=29)	NA

				vs 47% M				
11.	Ejikeme et al., 2020[18]	Case report	Pericardial Effusion	54 years, M	Mild intermittent chest pain	Normal	Pericardiocentesis	Survived
12.	Finn et al., 2021[19]	Cohort	Myocardial (46.3%), pericardial (12.2%), cardiomyopathy (29.3%)	66 years (N=66), 77.2% M	Cardiovascular risk factors present (n=29), Cardiogenic shock (n=21)	Troponin mean 17 ng/ml	Pericardiocentesis, cardiac catheterization, corticosteroids, remdesivir	25 (61%) died
13.	Fox et al., 2020[20]	Case report	Pericardial, cardiac tamponade	43 years, M	Chest pain, orthopnea, dyspnea	Normal	Pericardiocentesis, ibuprofen, colchicine	Survived
14.	Parato et al., 2021[21]	Case report	Pericardial	75 years, M; 68 years, M	Fever and dyspnea; severe dyspnea and hypoxia	Elevated high-sensitivity cardiac troponin-I	Enoxaparin, lopinavir/ritonavir, hydroxychloroquine, methylprednisolone	Both patients survived
15.	Parsova et al., 2020[22]	Case report	Cardiac tamponade	58 years, F	Shortness of breath and swelling in both legs	Raised troponin T level (0.07 pg/mL)	Pericardiocentesis	Survived
16.	Doyen et al., 2021[23]	Prospective Cohort	Pericardial effusion (43%),	60 years, 84% M (N=43)	49% with cardiac injury at baseline*	HS troponin I (n=17): 29 (16-366); HS troponin T (n=26): 23 (14-69)	Vasopressor/inotrope use (n=33)	4 (9%) died
17.	Heidari et al., 2020[24]	Case Report	Hemorrhagic pericardial, cardiac tamponade	28, M	Pleuritic chest pain, shortness of breath	Normal	Fluoroscopic-guided catheter pericardiocentesis, lopinavir-ritonavir, Ibuprofen, colchicine	Survived
18.	Dalen et al., 2020[25]	Case report	Acute perimyocardial cardiac tamponade	55, F	Fatigue and near-syncope	Troponin T elevated 108 ng/L	Pericardiocentesis, supportive care	Survived
19.	Gokalp et al., 2021[26]	Case report	Pericardial effusion	17, M	Upper respiratory tract symptoms	NA	Pericardiocentesis, ibuprofen, and hydroxychloroquine	Survived
20.	Blagojevic et al., 2020[27]	Case report	Acute pericardial	51, M	Chest pain	NA	Aspirin, beta-blocker, ceftriaxone, lopinavir/ritonavir	Survived
21.	Messina et al., 2021[28]	Case report	Pericardial and pleural effusion	90, F	Chest pain, shortness of breath, and fever	NA	In-hospital treatment, not otherwise specified	Survived
22.	Gioia et al., 2021[29]	Case report	Myopericarditis and Cardiac Tamponade	57, F	Dyspnea	Troponin I 64.0 ng/mL	Vasopressor, resuscitative efforts, ultimately death	Died
23.	Cairns et al., 2021[30]	Case report	Myopericarditis with cardiac tamponade	58, F	Fever, diarrhea, and vomiting	Troponin high on admission= 388.8 ng/L, increasing to 3532.9 ng/L the next day	Pericardial drain, antibiotics	Survived
24.	Faraj et al., 2021[31]	Case report	Acute pericarditis	36, M	Chest pain	Normal	Colchicine	Survived
25.	Dimopoulou et	Case report	Acute effusive	14.5 M, 15.5 F	Chest pain, low-	Normal	Colchicine and ibuprofen	Survived

	al., 2021[32]		pericarditis		grade fever			
26.	Patel et al., 2021[33]	Case report	Acute pericarditis	63, M	Fever, cough, and chest pain	Normal	hydroxychloroquine, colchicine, lopinavir/ritonavir	Discharged
27.	Diaconu et al., 2021[34]	Case report	Subacute effusive-constrictive pericarditis	27, F	Fever, dry cough, chest pain, and breathlessness	Normal	Ventilatory and supportive treatments, ultimately death	Died

*Pericardial effusion (43%)

Abbreviations: NA= Not available, hs-cTnT= High sensitivity cardiac troponin T, Hs-TnI= High sensitive troponin I



3. PATHOPHYSIOLOGY

Under normal conditions, the pericardium along with the fluid lubricates the moving surfaces of the heart, isolates the heart from other thoracic structures, and holds the heart in a fixed geometric position.[35] The pericardium is a relatively avascular structure, where an increased vascularity is the hallmark of inflammation.[35] COVID-19 is essentially a disease of the respiratory epithelium and the endothelial cells play a role in other organs, including the heart. The vascular endothelium plays the role of being a crucial interface between the tissues and the blood compartment, maintaining homeostasis.[36] The tightly regulated functions include control of fibrinolysis, vasomotion, homeostasis, oxidative stress, inflammation, vascular structure, and permeability.[36] SARS-CoV-2 produces a myriad of manifestations not limited to the lungs, heart, kidney, brain, and vasculature.[36] Libby and colleagues hypothesize that COVID-19 notably in the later stages represents an endothelial disease.[36] The authors propose that pro-inflammatory protein mediators, namely cytokines, play a central role in shifting endothelial functions from promoting homeostasis to playing defense.[36] The well-known phlogistic phenomenon of the cytokine storm is understood for the positive feedback look where cytokine production leads to overwhelmed counter-regulatory mechanisms.[37] However, while SARS-CoV-2 has shown to be associated with cardiotropic properties, the direct damage to cardiac structures is a rare occurrence.[37] Esfandiarei et al. posited that the pathophysiology of viral combination may be attributed to a variety of direct cell injury and T-lymphocyte mediated cytotoxicity.[38] This may further be aggravated due to cytokine storm syndrome.

4. COVID-19 Associated Pericardial Complications

The true incidence of pericarditis in patients with COVID-19 is unknown, however, the risk of pericardial involvement is higher in patients with confirmed disease as compared to the general population.[39] Post-mortem studies show that pericarditis is found in 1 out of 5 patients.[40] Recently recovered COVID-19 patients who underwent cardiac magnetic resonance imaging (CMRI) showed pericardial late gadolinium enhancement (LGE) involvement in 22% of patients. Further, 40% of athletes who were recovering from COVID-19 infections showed LGE involvement, whereas 58% had pericardial effusions identified on CMRI.[41] Chest pain is an important clinical sign, which was present in only 29% healthcare workers who were infected with COVID-19 at baseline.[42] These workers were followed post 10 weeks of infection and only 14% of the total participants fulfilled the criteria for pericarditis.[42] Pericarditis typically presents with viral symptoms and chest pain. While some patients with pericarditis may not have myocarditis, many acute cases accompany large pericardial effusions requiring drainage.[43] Recent reports suggest that acute pericarditis due to COVID-19 without myocardial involvement is a common occurrence. Furqan et al. states that pericardial effusion is found in around 5% of COVID-19 patients on chest tomography findings; the complication develops due to insults to the pericardium or myocardium and has various presentations on the clinical onset.[39] The first case of pericardial tamponade was identified in COVID-19 patients who had deteriorating renal function. In cases where pericardial tamponade is associated with acute pericarditis in COVID-19 patients, acute care is required.[39] In such occurrences, pericardiocentesis is required, or a pericardial window may be used.[39]

Singh et al. located 11 COVID-19 positive cases by a systematic search strategy to isolate patients presenting with pericardial effusion, cardiac tamponade, or pericarditis.[7] In total, 5 males and 6 females were identified with pericardial complications. While all subjects were tested positive at presentation, around 80% confirmed findings such as chest pain, cough, and dyspnea.[7] The median time and interquartile range (IQR) of the onset of the first symptom to pericardial effusion was around 7 days (1-26 days; IQR).[7] Five of the 11 patients reported heart failure and reduced ejection fraction on echocardiography.[7] Of the eight cases who underwent echocardiographic, two reported positive findings for pericardial tamponade, two reported inferolateral and inferior walls hypokinesia, and four reported signs of diffuse hypokinesia.[7] Moreover, comorbidities such as hypertension, diabetes, or obesity were present in five of 11 patients.[7] Overall, 1 patient developed takotsubo syndrome, 3 died, and 4 developed cardiac tamponade.

5. Treatment of Pericardial Complications associated with COVID-19

It is important to consider the various treatment options for pericardial complications due to COVID-19. Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically the first choice in all recurring and acute cases of pericarditis if there are no other contraindications.[44] Other medications include acetylsalicylic acid and colchicine. There are concerns about the safety of ibuprofen in patients with COVID-19. A case series originating from France published data where ibuprofen increased the expression of ACE2 receptors. Moreover,

the Food and Drug Administration (FDA) does not recommend the use of ibuprofen in symptomatic cases.[44] As shown in table 1, colchicine has been used in addition to NSAIDs to treat acute or recurring pericarditis, with good results. Corticosteroids are also being widely used to improve inflammatory symptoms, however, there are limitations due to failure of treatment, contraindications, and intolerance.[45] Table 1 also shows that patients were treated with hydroxychloroquine to overcome pericarditis, however, there are no clear guidelines on the safety and efficacy of the drug. As discussed earlier, some severe forms of COVID-19 may lead to endothelial damage in addition to microvascular thrombosis. To overcome thromboembolic events, anticoagulant drugs may be used, which may, in turn, increase the risk of tamponade or hemopericardium.[45] Overall, cardiac monitoring is the key to preventing pericardial impairments and promoting the long-term improvement in pericardial complications.

6. Recommendations for the Care of Pericardial Diseases Post-COVID-19

It is pertinent to implement a multi-disciplinary approach in identifying and preventing the long-term impacts that pericardial diseases may have on COVID-19 positive individuals. To ensure that post-COVID-19 negative outcomes are minimalized, diagnostic testing within 2 weeks of discharge must be commenced among patients that have high D-dimer or inflammatory marker levels.[45] Data suggests that cardiovascular complications such as arrhythmias and cardiomyopathies may present 2 months post-recovery.[45] Patients must be assessed by cardiologists (using transthoracic echocardiography and cardiopulmonary exercise testing) within 1-2 months post-recovery.[45] Furthermore, pulmonologists must conduct regular chest CT scans and pulmonary function tests to establish any adverse outcomes post-acute infection.[45] While these tests may not be conducted in resource-limited settings, routine testing of cardiac sequelae (i.e., pericardial complications) in previously hospitalized patients with confirmed COVID-19 diagnosis must be conducted within 30-90 days post-discharge.

7. CONCLUSION

The true long-term manifestations of COVID-19 infection are unknown. However, as with other entities, pericardial diseases due to COVID-19 can be overcome by addressing host factors, the severity of acute illness, the severity of pericardial injury, therapies delivered, post-recovery care, and the standard timings of follow-up. Based on studies reviewed, some patients who have compounded cardiovascular abnormalities such as the history of myocardial infarction, myocarditis, or other cardiac injuries, may be more prone to pericardial complications. While the current paradigms of treatment tend to focus on acute recovery, the treatment given during the acute illness phase may lead to long-term cardiovascular outcomes post 1-2 months of recovery. It is essential to determine whether anti-inflammatory and antifibrotic acute therapies may lead to any added adverse effects. It is also important to screen for residual disease in the convalescent phase to establish the long-term burden of pericardial disease due to COVID-19. If a high burden of disease is found, prophylactic therapies may be used to prevent long-term complications. In this paper, we make recommendations for testing within 1-2 months post-recovery by cardiologists using transthoracic echocardiography and cardiopulmonary exercise testing. Future clinical studies in this area may help establish the nature of post-COVID-19 pericardial diseases and the best management plan for patients recovering from or currently battling morbid cardiac involvements.

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