Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Coronavirus Disease 2019 (COVID-19) and Severe Pericardial Effusion: From Pathogenesis to Management: A Case Report Based Systematic Review

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Abstract: The Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) created a global pandemic that continues to this day. In addition to pulmonary symptoms, the virus can have destructive effects on other organs, especially the heart. For example, large pericardial effusion has been observed as a critical and life-threatening finding in Coronavirus disease of 2019 (COVID-19) patients. In this case report based systematic review, we review the reports of moderate to severe pericardial effusion associated with tamponade physiology. Direct cardiomyocyte and pericardium invasion, inflammation and cytokine storms and oxidative stress due to acute respiratory distress syndrome, are the pathogenesis of this phenomenon. The results showed that the manifestations of this finding are variable. Pericardial effusion can be seen as a delayed complication, accompanied by myocarditis or pericarditis, isolated, or with acute respiratory distress syndrome. In most patients, emergency percutaneous

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pericardiocentesis was performed, and fluid analysis was often exudative in 3 pattern of hemorrhagic, serous, and serosanguinous. Medical treatment and follow-up are recommended, especially in cases of pericarditis. (Curr Probl Cardiol 2022;47:100933.)

Introduction

Since December 2019, the first infected case of Coronavirus Disease of 2019 (COVID-19) was reported in Wuhan by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] Based on current statistics, as of 21 April 2021, there have been 142,557,268 confirmed cases of COVID-19, including 3,037,398 deaths, reported to World Health Organization (WHO). Most of the patients with COVID-19 are asymptomatic or with very mild symptoms, and only 30% of them have coughs and high fever and may need intensive care unit (ICU) ingress. Also, it can result in extra-pulmonary manifestations such as renal complications, gastrointestinal dysfunctions, endocrine system disorders, cardiovascular events, neurological dysfunctions, dermatological symptoms, hematological manifestations, and thromboinflammation.[2,3] Cardiovascular manifestations in COVID-19 patients are myocardial injury, acute coronary syndrome, heart failure, arrhythmias, thromboembolic events, and rarely pericardial disease, including pericarditis and pericardial effusion. According to past reports, COVID-19 can lead to pericardial effusion present in different clinical settings, such as pericardial effusion in patients with pericarditis and/or myocarditis, isolated or accompanied by the acute respiratory syndrome. Interestingly minimal to sizeable pericardial effusion can be manifested in COVID-19 patients. In this case report-based systematic review, we aim to discuss COVID-19 cases with moderate to large pericardial effusion with tamponade physiology as a dangerous and life-threatening presentation.

Method

We conducted a literature search using PubMed/Medline, Scopus, and Web of Sciences databases from their inception up to 16 April 2021 utilizing Boolean operators and combinations of word variants for ("coronavirus" OR "COVID-19" OR "severe acute respiratory syndrome" OR "SARS-CoV-2") AND ("Pericardial Effusion" OR "Cardiac Tamponade"). The duplicate reports were excluded from study and abstracts with English language restriction were used to identify relevant

articles. The reference lists of selected articles were also reviewed for additional relevant articles. The search was conducted by an author, selecting eligible studies independently performed by 2 authors. A third author was consulted in the case of disagreement between the initial 2 reviewers.

Results

We identified 30 suitable case reports for inclusion in this systematic review (Table 1). Three papers have been presented as case series and brief literature review.[4–6]

Review of Literature

Pericardial Effusion Pathogenesis in COVID-19 Patients

There are several mechanisms of cardiovascular injury in COVID-19 patients. First is the direct involvement of SARS-COV-2, and the second is the indirect effect of this virus through the cytokine hypothesis and oxidative stress process. Similar theories have been proposed for pericardial involvement in COVID-19 patients.[1] Angiotensin-converting enzyme 2 (ACE2) receptor is expressed in different cells like cardiomyocytes and vascular endothelium, vascular smooth muscle cells, and cardiac fibroblast. SARS-COV-2 binds to cells by ACE2 receptors and activates the ACE2 signaling pathway. Ultimately the signaling pathway induces myocardial injury and cardiomyopathy, and this process may lead to pericardial effusion as a final phenomenon. However, the direct mechanism of COVID-19 in pericardial effusion is still unclear. Farina et al. report the isolation of SARS-CoV-2 in the pericardial fluid by the reverse transcription-polymerase chain reaction (RT-PCR) method.[7–9,2] Activation of macrophage and endothelial cells cause cytokine storm and inflammation in severe cases with a massive release of TNF-α, IL-1, IL-6, and IL-8. A further level of these cytokines above the normal thresholds leads to adverse damage.[9,10] One of the repercussions of cytokine storms in COVID-19 patients is pericarditis. Interstitial mononuclear cell infiltration in the myocardium of autopsy cases shows over activation of the immune system and inflammatory damage, too.[11] Therefore, the sustained cytokine releasing causes myocarditis and perimyocarditis.[9] Pericardial effusion may occur as a secondary reaction to myocardial and pericardial inflammation.[3] Just as say initially, acute respiratory distress syndrome (ARDS) is one of the main symptoms of COVID-19. Severe

Table 1. Clinical, diagnostic, therapeutic features, and survival outcomes in COVID-19 patients with moderate to severe pericardial effusion and tamponade physiology

	References	Age	Sex	Primary clinical manifestation	Treatment approaches	Pericardial fluid pattern	Survival
1	Foster et al.[13]	44	F	• Positional chest pain radiated to left shoulder	• Pericardial window • Colchicine	Hemorrhagic	Improvement
2	Rajevac et al.[32]	53	M	• Fever • Diarrhea • Chills • Productive cough			Death
3	Torabi et al.[25]	42	F	• Worsening metal status • Fever • Hypoxia	• Percutaneous pericardiocentesis	Serous	Death
4	Tiwary et al.[17]	30	M	• Bilateral abdominal flank pain • Shortness of breath • Fatigue • Tiredness • Lightheadedness	• Surgical pericardial window		Improvement
5	Ejikeme et al.[27]	54	M	• Mild intermittent chest pain	• Interventional radiologic guided pericardiocentesis	Initial serosanguinous, subsequently serous/ Transudate	Improvement
6	Dabbagh et al.[26]	67	F	• Worsening dyspnea • Orthopnea	• Percutaneous •ericardiocentesis • Colchicine • Corticosteroid	Hemorrhagic/ Exudative	Improvement
7	Cruz et al.[14]	64	M	• Chest pain • Dry cough • Fever • Dyspnea	• Pericardial window	Hemorrhagic	

(*continued on next page*)

Table 1. (*continued*)

	References	Age	Sex	Primary clinical manifestation	Treatment approaches	Pericardial fluid pattern	Survival
8	Parsova et al.[16]	58	F	• Shortness of breath • Swelling in both legs	• Percutaneous pericardiocentesis	Serosanguinous/Exudative	Improvement
9	Gioia et al.[18]	57	F	• Trouble breathing	• Percutaneous pericardiocentesis	Serous	Death
10	Fox et al.[20]	43	M	• Progressive orthopnea • Conversational dyspnea • Chest pain radiating to the neck and left shoulder • Mild nonproductive cough	• Percutaneous pericardiocentesis • Colchicine • Ibuprofen	Serosanguinous	Improvement
11	Sollie et al.[12]	29	F	• Chest pain • Shortness of breath	• Percutaneous pericardiocentesis • Aspirin • Ibuprofen • Colchicine • Prednisone	Serosanguinous	Improvement
13	Hua et al.[41]	47	F	• Fever • Dry cough	• Percutaneous pericardiocentesis	Serosanguinous	
14	Gill et al.[24]	34	F	• Shortness of breath • Diffuse left-sided chest pain • Weakness	• Percutaneous pericardiocentesis • Colchicine • Pulse dose steroid	Serous	Improvement
15	Amoozgar et al.[17]	56	M	• Non-radiating exertional chest pain • Dyspnea	• Pericardial window • Ibuprofen	Bloody	Improvement
16	Mozumder et al.[7]	54	F	• Orthopnea • Dyspnea • Fever	• Surgical drainage	Serosanguinous	Improvement

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Table 1. (*continued*)

	References	Age	Sex	Primary clinical manifestation	Treatment approaches	Pericardial fluid pattern	Survival
				• Cough • Myalgia • Nausea • Anorexia			
17	Farina et al.[8]	59	M	• Acute chest pain	• Echo-guided pericardiocentesis	Sero-haemorragic	Improvement
18	Purohit et al.[15]	82	F	• Dyspnea • Diarrhea • Cough • Fever	• Percutaneous pericardiocentesis	Serous straw-colored/ Exudative	
19	Heidari et al.[29]	28	M	• Pleuritic chest pain • Gradual-onset shortness of breath	• Fluoroscopic-guided catheter pericardiocentesis	Hemorrhagic	Improvement
20	Singh et al.[28]	62	M	• Progressive shortness of breath • Altered mental status	• Pericardiocentesis from an anterior approach	Sanguinous	Improvement
21	Sauer et al.[4]	51	M	• Chest pain suggestive of pericarditis • Dyspnea on exertion • Deterioration of the general condition	• Percutaneous pericardiocentesis • Colchicine	Serosanguinous/Exudative	Improvement
22	Sauer et al.[4]	84	M	• Dyspnea • Fever • Severe asthenia	• Percutaneous pericardiocentesis • Colchicine	Serous/Exudative	Improvement
23	Walker et al.[22]	30	M	• Worsening chest pain • Shortness of breath	• Pericardial window • Colchicine • Aspirin		Improvement

(*continued on next page*)

Table 1. (*continued*)

	References	Age	Sex	Primary clinical manifestation	Treatment approaches	Pericardial fluid pattern	Survival
24	Allam et al.[42]	41	F	• Sore throat • Cough • Shortness of breath	• Percutaneous pericardial aspiration	Serous/Exudative	Improvement
25	Reddy et al.[23]	63	F	• Severe, central, sharp chest pain	• Percutaneous Pericardiocentesis • NSAID • Colchicine	Serosanguinous/Exudative	Improvement
26	Khatri et al.[6]	50	M	• Fevers • Chills • Generalized malaise • Non-productive cough, • Dyspnea • Near syncope	• Percutaneous pericardiocentesis	Serosanguinous	Death
27	Cairns et al.[19]	58	F	• Fever • Diarrhea • Vomiting • Poor oral intake	• Percutaneous pericardiocentesis	Serous	Improvement
28	Derveni et al.[43]	89	M	• COPD exacerbation • Fever • Hypoxemia	• Echo-guided pericardiocentesis	Serous	Death
29	Raymond et al.[30]	7	F	• Cough • Chest pain • Orthopnea	• Surgical pericardiocentesis and pericardiectomy • Ibuprofen • Colchicine	Serosanguinous/Transudate	Improvement
30	Asif et al.[44]	70	F	• Chest pain • Worsening dyspnea • Myalgia	• Percutaneous pericardiocentesis • Colchicine	Serosanguinous	Improvement

hypoxia from acute respiratory damage entails oxidative stress and myocardial injury from increased myocardial oxygen demand. On the other hand, last hypoxia results in pulmonary hypertension due to persistent spasm of pulmonary capillaries. This process may lead to left ventricular ejection dysfunction and pericardial effusion[9] (Fig 1).

COVID-19 and Clinical Presentation of Large Pericardial Effusion

With rising numbers of COVID-19 cases, various manifestations of coronavirus have appeared. As mentioned above, significant pericardial effusion can be presented in various forms, from isolated form to cases of concomitant with pericarditis, myocarditis, and even respiratory symptoms (Fig 1).

Significant Pericardial Effusion as a Late Complication. Pericardial effusion can be presented as a late finding in COVID-19 positive patients. Farina et al. reported a 59- year old man that has undergone coronary artery bypass surgery. Twenty-three days after confirmation of COVID-19 disease, he developed pericardial effusion.[8] Similarly, Sollie et al. documented a case of pericardial effusion as the post-viral-sequelae. In this case, pericardial effusion happened after 3 weeks when this patient tested negative for COVID-19.[12] Also, in Foster et al. study of a 44-year-old woman reveal a positive COVID-19 test 3 weeks before her large hemorrhagic pericardial effusion (with a 2-week isolation period).[13] Cruz et al. reported another hemorrhagic pericardial effusion and cardiac tamponade on the ninth day of the illness.[14] In addition to the above, Purohit et al. presented an 82-year-old woman with 5 days of productive cough, fever with chills, and intermittent diarrhea. Serial echocardiograms demonstrated the progression of small pericardial effusion to tamponade in this case.[15] Parsova et al. presented a patient with COVID-19 that displays pericardial effusion throughout the disease progression. This case was hospitalized 2 weeks before the onset of pericardial effusion because of an atypical pneumonia diagnosis.[16]

Severe Pericardial Effusion Along With Myopericarditis. According to case reports, pericardial effusion can be compatible with myopericarditis in COVID-19 positive patients. Tiwary et al. presented the young male with type 1 diabetes mellitus and chronic kidney disease, admitted with bilateral abdominal flank pain, shortness of breath, fatigue, tiredness, and lightheadedness. On day ten after the presentation, the patient developed

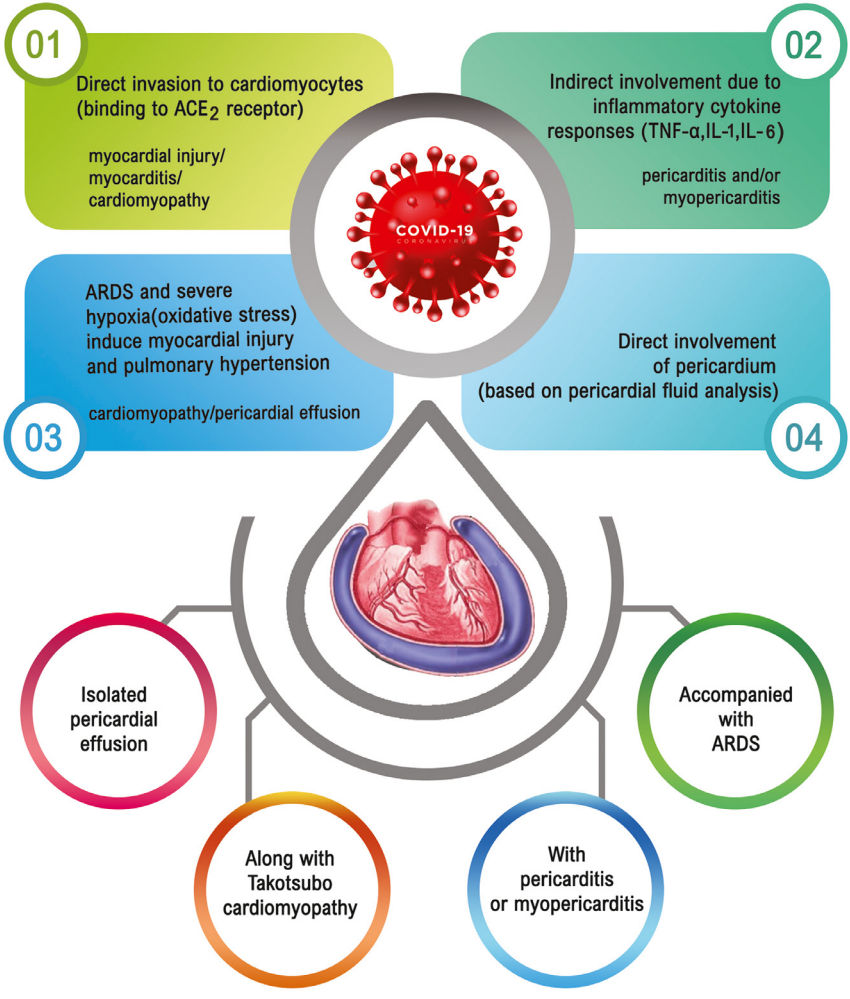

Fig 1. Pathogenesis and clinical presentation of severe pericardial effusion in COVID-19 infected patients.

myopericarditis and pericardial effusion with signs of tamponade.[17] A second case described a 57-year-old female who presented with severe respiratory distress. The patient had several cardiac arrests during hospitalization, and an echocardiogram showed severely reduced ejection fraction (EF) (15%-25%) and severe pericardial effusion. Their findings revealed myopericarditis and pericardial effusion in this COVID-19 patient.[18] Another myopericarditis case with large pericardial effusion and tamponade in patients with COVID-19 has been reported by Sauer et al. too.[4] However, in comparison, Cairns et al. reported an acute

myopericarditis and pericardial effusion case, even in the absence of respiratory symptoms.[19]

Isolated Pericarditis or Myocarditis and Large Pericardial Effusion. Rarely isolated myocarditis or pericarditis with pericardial effusion may be seen among patients with COVID-19. Fox et al. presented acute effusive pericarditis in a 43-year-old African American man with a history of progressive orthopnea, dyspnea in conversation, chest pain radiating to the neck and left shoulder, and friction rub was heard in his physical examination. Ultrasound revealed a large pericardial effusion with doubt for tamponade, and electrocardiogram (ECG) findings are consistent with acute pericarditis. This patient had not been evidenced of interstitial pulmonary disease, pneumonia, and myocardial injury.[20] Similar COVID-19 pericarditis and cardiac tamponade without respiratory symptoms have been reported by Naqvi et al., too.[21] Another similar condition was reported by Sauer et al. their patient presented with pleuritic chest pain, dyspnea, and large pericardial effusion. Magnetic resonance imaging (MRI) showed signs of pericarditis without myocarditis.[4] In this manner, Walker et al. presented the patient with a pericarditis diagnosis, with pericardial effusion resulting in cardiac tamponade secondary to COVID-19 infection.[22] In another scenario, a 63-year-old female with a history of severe pleuritic, positional chest pain, and positive SARS-CoV-2 was admitted to the hospital. Her ECG finding was compatible with large pericardial effusion as tachycardia, low-voltage, and electrical alternans in QRS complexes,[23] indicating rapid progression of dry pericarditis to tamponade.[23]

An example of isolated myocarditis and pericardial effusion in a COVID-19 patient, Gill et al. presented a 34-year-old woman with shortness of breath, diffuse left-sided chest pain, weakness, and normal O_2 saturation. Cardiac echocardiography showed a large pericardial effusion with tamponade physiology and left ventricle EF of 20%.[24]

Takotsubo Cardiomyopathy and Tamponade. To continue, we highlight a COVID-19 patient who developed Takotsubo cardiomyopathy following cardiac tamponade to be aware of these challenges. This case of COVID-19 reported by Torabi et al. indicates that the LV apex was dilated with systolic hypokinesis and basal segments had preserved contraction, supporting the diagnosis of the Takotsubo pattern.[25] Also, another similar case was reported by Dabbagh et al. they presented Takotsubo cardiomyopathy following large hemorrhagic pericardial effusion in a 67-year-old woman. She was hospitalized with the usual symptoms of COVID-19 and

left shoulder pain. One week later, the patient presented with progressing dyspnea and orthopnea. A sizeable pericardial effusion is shown in transthoracic echocardiography (TTE). After pericardiocentesis, this patient developed Takotsubo syndrome, as evident by TTE, ECG findings, and an increase in cardiac troponin I.[26]

ARDS and Concomitant Manifestation of Large Pericardial Effusion. There are several cases of respiratory failure due to COVID-19 and cardiac tamponade. Ejikeme et al. reported a 54 years old man with bilateral infiltration in initial chest x-ray and positive RNA qualitative nucleic acid amplification test (NAAT). This patient refers to the hospital with mild intermittent chest pain for weeks and low O2 saturation (50%). A 2-D echocardiogram revealed sizeable pericardial effusion in this patient.[27] Another similar case involved a 62-year-old man admitted to the emergency department with hypotension and hypoxic respiratory failure. TTE showed pericardial effusion and signs of tamponade.[28] A case report by Haidari et al. showed respiratory failure with concomitant large pericardial effusion, too.[29]

Pericardial Effusion and Pediatrics. Pericarditis presenting with acute pericardial tamponade can be accurate in children, such as, in a case reported by Raymond et al., A seven-year-old female presented with cough, chest pain, and orthopnea for 3 days. A chest X-ray revealed an enlarged cardiac silhouette. An electrocardiogram showed sinus tachycardia, T-wave inversion in inferior and lateral leads, low voltage QRS with electrical alternans, and echocardiogram findings suggest large circumferential pericardial effusion with tamponade physiology.[30]

Diagnostic Approaches for COVID-19 Patients With Severe Pericardial Effusion

History taking, physical examination, biomarkers, ECG, and imaging findings can be used to diagnose heart disease in patients with COVID-19 (Fig 2). In general, any finding to diagnose pericarditis or pericardial effusion can be substantial. The history of a patient with pleuritic chest pain radiating to the trapezius muscle is a pathognomonic sign of pericarditis which warns of the need for pericardial effusion. Shortness of breath and deterioration of symptoms, especially dyspnea and orthopnea, can be a warning sign for significant fluid in the pericardium.

On physical examination, raised JVP, tachycardia, tachypnea, hypotension, pulsus paradoxus, muffled heart sound, and pericardial friction rub

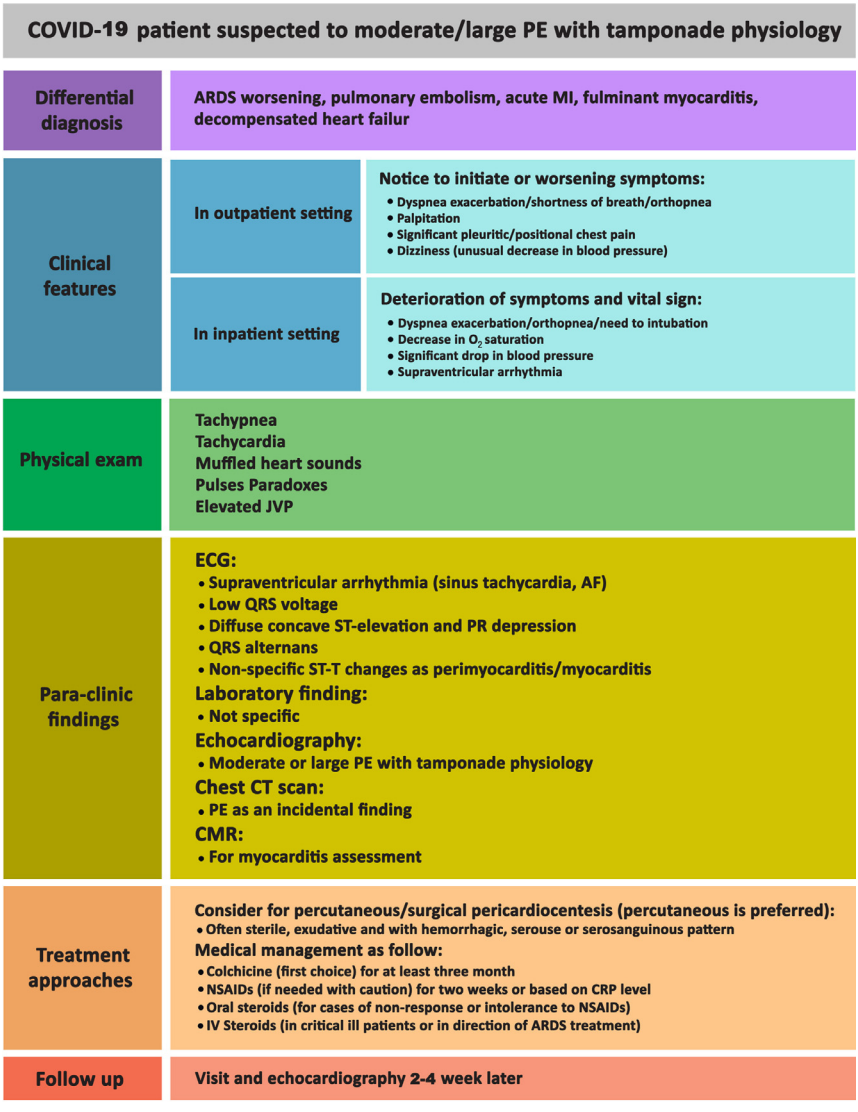

Fig 2. Diagnostic and therapeutic guidance for the COVID-19 patients suspected to moderate/large pericardial effusion with tamponade physiology.

can be the signs of significant pericardial effusion with or without pericarditis and myocarditis.[7,21,31]

No specific biomarkers have been identified for the diagnosis of large pericardial effusion. Inflammatory markers, D-Dimer,[31] and brain natriuretic peptide[26] have increased in most cases, especially in cases of severe pulmonary involvement. Troponin as a non-specific biomarker can be

negative,[12,20,26–29,31] slightly elevated,[8,13,15,24] or high. In cases with high troponin levels, suspicion of concomitant myocarditis increases.[18]

Chest x-rays are frequently used in COVID-19 patients. In very large effusions, the cardiac silhouette can appear Flask-liken. However, chest x-ray findings are not sensitive and specific enough. Clues to pericardial effusion in ECG are sinus tachycardia (especially without fever), low QRS voltage, and electrical alternant.[12] PR depression with concave diffuse ST elevation and nonspecific ST-T changes like invert T wave are signs of pericarditis and myocarditis, respectively. Pericardial effusion may be seen as an incidental finding during a chest CT scan. According to a recent meta-analysis, 4.5% of CT scans revealed pericardial effusion. Like what happened in the case report of Rajevac et al.,[32,33] echocardiography helps estimate the size and detect pericardial effusion. Some echocardiography findings help diagnose cardiac tamponades, such as the collapse of the right atrium at end-diastole and the right ventricle in early diastole, reciprocal changes in left and right ventricular volumes with respiration for diagnosing of pulsus paradoxus, dilation of the inferior vena cava, and increased respiratory variation of mitral and tricuspid valve inflow. Further imaging with MRI is rarely needed; however, it can be done in patients with indeterminate echocardiography findings or suspected of myocarditis.[34]

Treatment Strategies

Size can classify pericardial effusion in patients of COVID-19 as mild, moderate, and large. Medication is limited to mild and moderate pericardial effusion cases, especially those with pericarditis pathology. In general, we do not have a specific guideline for pericardial effusion in patients with COVID-19. However, it has been suggested that using colchicine alone or in combination with anti-inflammatory medications can be helpful[4]. The WHO disagrees with the order of Non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19 because NSAIDs facilitate virus invasion into cells by increasing ACE2 receptor expression.[23] However, The European Medicines Agency (EMA) said there is no scientific evidence for worsening the condition of COVID-19 patients about using NSAIDs.[35] The most commonly used NSAIDs reported was ibuprofen, which did not have any severe side effects. The recommended duration is 3 months for colchicine and 7-14 days for NSAIDs or C-Reactive Protein (CRP) level based.[20,29,36] As said beforehand, colchicine has been selected as the first drug for pericarditis, and pericardial effusion in COVID-19 patients, which can directly or indirectly reduce inflammation. Steroids can be also used especially in patients with the critical condition

and severe respiratory disease, like what was done in Gill et al. case report that managed with colchicine and intravenous steroids.[24] Oral steroids can be used instead of NSAIDs in patients who have not responded or are intolerant to NSAIDs. Therefore, preferably using steroids with colchicine be recommended to reduce recurrence.

Hemodynamically unstable patients with moderate and/or large effusion require urgent drainage.[27] There are 2 ways to treat large pericardial effusion: surgical drainage and percutaneous pericardiocentesis. Both techniques lead to rapid relief of cardiac effusion. Percutaneous pericardiocentesis is more common in most hospital settings and can be performed under echocardiographic or fluoroscopy guidance.[37] Surgical drainage is done when the patient has coagulopathy, or a biopsy is desired for diagnostic purposes. For instance, Cruz et al. using the surgical technique and then sending a pericardium sample to the pathology for their patient.[14]

Pericardial Effusion Assessment

Three types of serosanguinous, serous, and bloody pericardial effusion have been shown in patients with COVID-19. Hemorrhagic pericardial effusion needs intensive treatment due to developed recurrence or constrictive pericarditis as a complication.[38] Also, usually, it has not associated with a viral infection, except Coxsackievirus and now COVID-19.[39] Lactate dehydrogenase and albumin levels evaluations indicated that most of the pericardial effusions in COVID-19 are exudative;[4,15,16,23,26,40] however, in a few cases, a transudate pattern has been seen.[27,30] Findings suggested the fluid was sterile and viral, fungal, and acid-fast bacteria cultures were negative. Standard viral RNA can often detect the virus in the pericardial fluid and was negative in most cases. Although, reverse transcriptase-polymerase chain reaction and electron microscopy can be used for detecting COVID-19 in the pericardial fluid.[8,14]

Conclusion

Over time, we realized that the coronavirus is not limited to symptoms of the respiratory system. It can cause extra-pulmonary complications too. Severe pericardial effusion following a viral infection is generally a rare and delayed finding, but in this review, we saw its various and critical manifestations in patients with COVID-19. Pericardial effusion can be presented in COVID-19 cases from stable and outpatients to severely critical patients who needed ICU, which requires rapid invasive action in hemodynamically disruptive conditions. As a result, it should be noted that the presence of significant pericardial effusion in COVID-19 patients

indicates a poorer prognosis. However, the severity of inflammation, myocardial involvement, and pulmonary involvement is not always directly related to the severity of pericardial effusion.

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Authors' contribution

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2. Search and interpretation of data: MKA, FK, AP
3. Drafting of the manuscript and revising it: MKA, FK, AP
4. Final approval: All authors

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