Infective Endocarditis and Covid -19 Coinfection: An Updated Review

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Abstract. With the rising number of COVID-19 patients, there have been reports of patients presenting with concomitant infective endocarditis. In this retrospective review, we included all articles from Medline with COVID-19 and infective endocarditis coinfection. Ten articles were identified from eight different countries over the world over the past 11 months. All patients reported with the above coinfections were male with a mean age of 53 years. Clinical features of COVID-19 and the presence of ground-glass opacity in CT thorax were predominant among patients with positive RT-PCR for COVID-19. New-onset embolic infarct, pulmonary edema was a contributor to the diagnosis of endocarditis in most patients. Involvement of the aortic valve was most common. Delayed diagnosis and cardiac surgery were contributors to increased morbidity. (www.actabiomedica.it)

Key words: Infective endocarditis, COVID 19, Outcome

Introduction

Severe acute respiratory virus coronavirus 19 (COVID-19) continues to be a pandemic of global concern. The persistent worldwide spread of severe acute respiratory syndrome coronavirus two continues. Our understanding of the epidemiology, clinical course, significant organ involvement, risk populations, diagnosis, investigations, treatment modalities, and the outcome following COVID 19 is continually changing. With passing time, the complexities secondary to the presence of this infection continues to widen. Ten new Infective Endocarditis cases (IE) are reported for 100,000 population years in the western population (1). Large population-based studies have shown that the percentage of patients with newly diagnosed infective endocarditis continues to be the same as in the past two decades (2). Literature regarding the interaction of COVID-19 among patients with infective endocarditis is limited (3,4). This review aims to describe the epidemiological, clinical, management, and outcome details of patients with infective endocarditis and COVID-19 coinfection.

Methodology

In this retrospective review, we included all the articles published in Medline on COVID-19 and infective endocarditis. The terms "COVID-19", "SARS coronavirus 19" and "infective endocarditis," "endocarditis" were used in the Mesh database of PubMed. All the articles published before November 15th were eligible to be included in this review. To be included in this review, articles had to have evidence of confirmed COVID-19 infection and the presence of infective endocarditis as per the modified Dukes criteria. We only

included articles with clinical details and excluded opinions, reviews, and recommendations. Two trained physicians independently obtained data.

Results

We identified 28 articles on COVID-19 and infective endocarditis in the database. Among these ten articles reported coinfection of infected endocarditis with COVID-19. A total of 11 patients were reported in 8 different countries. Figure 1 shows the various countries from where the case of infective endocarditis and COVID-19 were reported. We included all the reported patients; however, clinical details were not available for the two patients reported by Garatti et al (4). Table 1 shows the demographic details, clinical features of patient's concerning COVID-19. Table 2 shows the details of infective endocarditis and treatment in these patients. Below we also summarize in short, all the cases reported in these articles.

Case 1

Hussain et al. describe an elderly male with COVID-19 presenting with fevers and back pain. In this scenario, they talk about COVID-19 delaying a potentially life-saving surgery due to uncertainties regarding the clinical course of COVID-19. The patient was diagnosed with infective endocarditis(IE) based on modified Duke's criteria - two blood cultures positive for Enterococcus and multiple vegetations visualized on the aortic valve using a transesophageal echocardiogram with the largest measuring 11 mm. His surgery was delayed as he tested positive for SARS-COV2 on admission. The patient did not have any respiratory symptoms or CT chest abnormalities concerning pulmonary involvement. Yet, the authors were faced with a dilemma about whether to take him for surgery when he remained positive for SARS-CoV2 or postpone the surgery until two SARS-CoV2 swabs resulted negative. Fortunately for the patient and the authors, the patient tested negative for COVID-19 twice in the next 48 hours, and he was taken to surgery. The patient

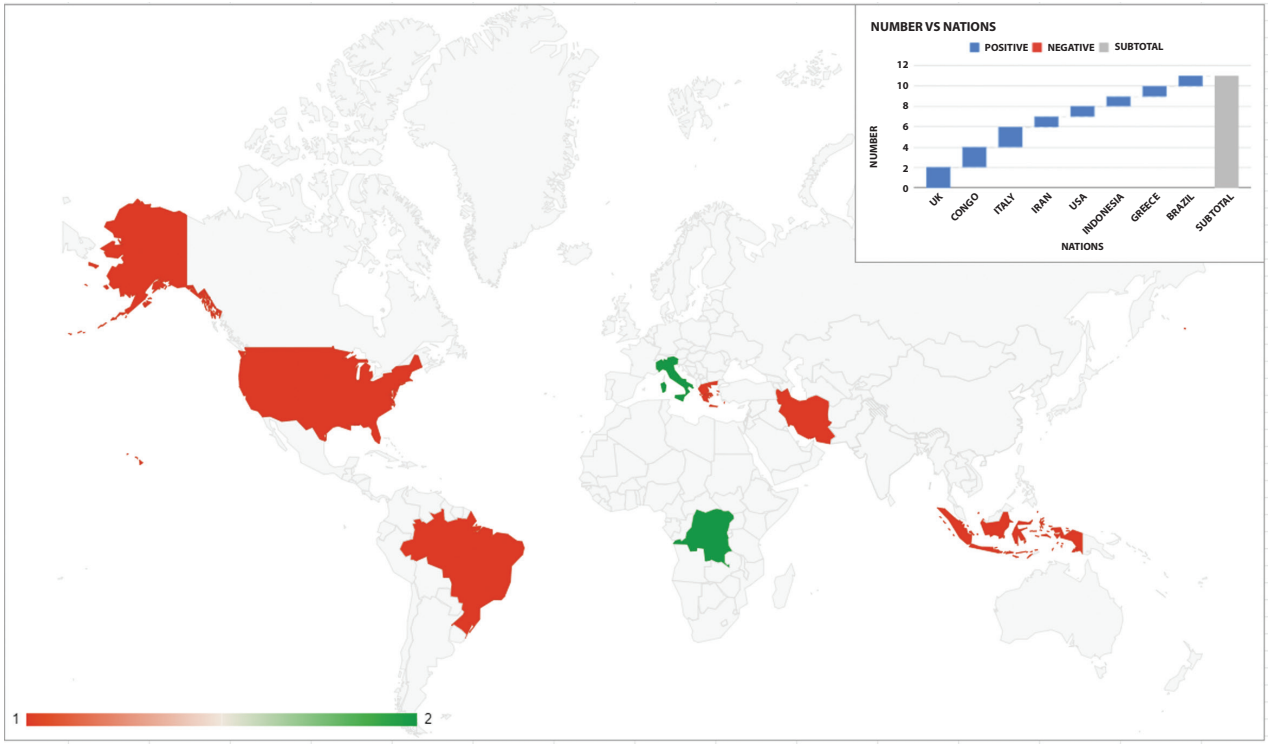

Figure 1. Showing countries reporting cases of COVID 19 and IE coinfection.

Table 1. Showing Demographic details, clinical features of patients with COVID 19 and IE.

Number	Report	Nation	Age	Sex	RF	COVID 19 diagnosis	Clinical features	Laboratory	Imaging
1	Schizas et al	Greece	59	M	HTN	RT- PCR positivity	Fever, Dyspnea	NA	CXR/ CT: Pulmonary edema
2	Regazzoni et al	Italy	70	M	None	Established	Pneumonia and Hypoxia	Elevated WBC, CRP	CT: Extensive GGO
3	Amir et al	Indonesia	61	M	HTN, Smoking, RHD	RT- PCR positivity	Fever, cough, dyspnea, chest discomfort Hypoxia Bibasilar rhonchi	Leukocytosis, lymphopenia, Elevated high sensitivity troponin I, AST, ALT Hyponatremia	CT: multilobar GGO affecting both superior, right medial, posterior, medial and lateral segments of both inferior lobes
4	Hussain et al	UK	68	M	T2DM, CA Prostrate	Established	Fever, back pain, diastolic murmur	NA	CT: No parenchymal changes, small aortic root abscess
5	Alizadehasl et al	Iran	24	M	RHD, Mechanical MV	RT- PCR positivity	Fever, Chills, Anorexia	Leukocytosis, Elevated CRP	CXR: Viral pneumonia
6	Yang et al	UK	60	M	HT, DM, COPD, A Fib, bladder CA	RT- PCR positivity	Fever, pedal edema, back pain, reduced appetite	Elevated ESR, CRP,	
7	Sanders et al	US	38	M	ESRD	RT- PCR positivity	Cough, Shortness of breath, fatigue	Leukocytosis, elevated CRP, elevated ferritin	CXR: pulmonary vascular congestion, retrocardiac opacity
8	Mantero et al	Italy	59	M	Prosthetic AV	CT chest	Fever, dry cough, aphasia, right facial deficit	Leukocytosis	CT chest: interstitial pneumopathy
9	Garatti et al	Congo	-	-	-	-	-	-	-
10	Garatti et al	Congo	-	-	-	-	-	-	-
11	Dias et al	Brazil	36	M			Fever, cough, myalgia	Leukocytosis, elevated CRP, elevated ferritin	CT chest: cavitary lesions in lung fields, bilateral GGO

M: Male, HTN: Hypertension, RHD: Rheumatic heart disease, T2DM: Type 2 diabetes mellitus, COPD: Chronic obstructive pulmonary disease, Afib: Atrial fibrillation, CA: cancer, ESRD: End stage renal disease, RT –PCR: Reverse transcriptase polymerase chain reaction, CXR: chest x ray, CT: Computed tomography, WBC: White blood count, CRP: C reactive protein, GGO: Ground glass opacities, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MV: Mitral valve, AV: Aortic valve.

Table 2. Showing details of IE and management in patients with COVID 19 and IE

Number	Report	IE diagnosis	Clinical features	Culture	ECHO	COVID 19 treatment	IE treatment	Morbidity	Outcome
1	Schizas et al	TTE	Acute pulmonary edema	Staphylococcus lugdunensis	Severe AR Right and non-coronary cusp vegetation	NA	NA	Mechanical ventilation Acute pulmonary edema Mechanical aortic valve placement	Discharged after 4 weeks
2	Regazzoni et al	TEE MRI Brain	Hyperpyrexia Confusion Elevated CRP, Procalcitonin, IL-6, fibrinogen, D- dimer Severe thrombocytopenia MRI brain: Multiple ischemic areas with hemorrhagic transformation	Methicillin sensitive Staphylococcos sureus	Severe AR Large AV vegetation	High flow Oxygen Corticosteroid Hydroxychloroquine	Antibiotics	Embolic infarcts Delayed cardiac surgery	NA
3	Amir et al	TTE	Apical pan systolic murmur Right upper sternal border diastolic murmur Osler nodes Splinter hemorrhages	Negative	Severe MR Flail mitral leaflet with vegetation Moderate AR	Oxygen supplementation Oseltamivir Azithromycin Moxifloxacin Ramipril N-Acetylcysteine Ascorbic acid	No prophylactic antibiotics for IE	Acute decompensated heart failure Acute liver failure Acute kidney injury Surgical treatment withheld	Discharged on day 10
4	Hussain et al	TEE	C5-C6 discitis	Enterococcus faecalis	Multiple AV vegetation and Aortic root abscess, multiple TV vegetation	NA	IV antibiotics	Delayed cardiac surgery Mechanical AV valve replacement	Discharged on the 7th post-operative day

Number	Report	IE diagnosis	Clinical features	Culture	ECHO	COVID 19 treatment	IE treatment	Morbidity	Outcome
5	Alizadehasl et al	TEE	Sinus tachycardia	Staphylococcus aureus	Vegetation's on posterior prosthetic MV leaflet	Azithromycin			
6	Yang et al	TTE	Fever	Streptococcus sanguinis	MV vegetations	Oxygen	IV antibiotics	Vertical diplopia, left paramedian midbrain infarct, right branch retinal artery occlusion	Good functional recovery
7	Sanders et al	TTE	Ejection systolic murmur, 1st degree AV block, left anterior fascicular block	Enterococcus faecalis	Mobile vegetation on AV	NA	IV antibiotics	Mechanical aortic valve placement, subaortic membrane resection	Discharged
8	Mantero et al	TTE	Fever	Enterococcus faecalis	Vegetations on biological prosthetic valve, periprosthetic abscess	Hydroxychloroquine, lopinavir/ ritonavir	IV antibiotics	IV thrombolysis for ischemic stroke	NA
9	Garatti et al				AV vegetations				
10	Garatti et al				AV vegetations				
11	Dias et al	TTE	Left lower sternal pansystolic murmur	Staphylococcus aureus	Mobile vegetation on TV, severe tricuspid regurgitation	Oxygen, mechanical ventilation	IV antibiotics	Hypoxic respiratory failure Severe TR Septic pulmonary emboli	Death

TTE: Transthoracic echocardiography, TEE: Transesophageal echocardiography, AR: Aortic regurgitation, MR: Mitral regurgitation, TR: tricuspid regurgitation, AV: Aortic valve, MV: Mitral valve, TV: Tricuspid valve, IE: Infective endocarditis, MRI: magnetic resonance imaging, IL-6: Interleukin 6, C5: Cervical disc 5, IV: Intravenous, AV block: Atrioventricular block.

had a mechanical aortic valve placed, his postoperative course was uncomplicated, and he was discharged home (5).

Case 2

Regazzoni et al. reported a case of an otherwise elderly male who was hospitalized for COVID-19. In this article, the authors discussed the possibility of the steroids, given for the treatment of COVID-19, predisposing patients to secondary infections, including IE. He was treated with methylprednisolone and hydroxychloroquine for COVID-19 pneumonia in addition to oxygen supplementation through high flow nasal cannula. He initially recovered, but later his hospitalization was complicated by fever and confusion. His labs showed worsening inflammatory markers, including an increase in white count from 11,680 cells/mm3 on admission to 19,580 cells/mm3, an increase in CRP from 86 mg/L to 222 mg/L. Another infectious process was suspected, given the fever and laboratory results. The workup resulted in him being diagnosed with IE with positive blood cultures and echocardiographic evidence of vegetations. His confusion resulted from an embolic ischemic stroke, which was attributed to the IE sequelae. He was treated with antibiotics, but his cardiac surgery was postponed (6).

Case 3

This report by Schizas et al. described a middle-aged hypertensive male admitted for fever and respiratory distress. In this case, the low sensitivity of the available polymerase chain reaction tests for SARS-CoV2 led to a possible positive COVID-19 diagnosis, which resulted in a delay in the real diagnosis. The chest imaging showing findings suggestive of heart failure and no characteristic changes associated with COVID-19. He was treated as a case of COVID-19 as the initial nasopharyngeal swab for SARS-CoV2 was positive. Given his clinical deterioration, alternative diagnoses were pursued. This led to the diagnosis of reduced cardiac function with severe acute aortic regurgitation, which was new for the patient. The patient ended up having emergent surgery for his aortic regurgitation, and vegetations were identified on the aortic valve. He satisfied the two major Duke's clinical criteria for IE, and his blood cultures also returned positive. Regardless of the delay in the confounding lab results and diagnosis, the patient improved with surgery and IV antibiotics (7).

Case 4

Amir et al. described a concomitant COVID-19 and IE with overlapping clinical symptoms. This case report discussed a smoker with undiagnosed rheumatic heart disease, and a recent international journey referred to a cardiac center with cardiac and respiratory complaints. The patient satisfied one major and three minor modified Duke's clinical criteria for IE. His chest imaging revealed findings consistent with COVID-19, and he was tested for SARS-CoV2. Laboratory abnormalities on admission were a white blood cell count of 17,400 cells/mm3, alanine aminotransferase of 2826 U/l, aspartate aminotransferase of 1808 U/l, estimated Glomerular Filtration Rate of 38.7 ml/min, sodium of 132, high sensitivity troponin I of 2736.7 ng/ml and a C-reactive protein of 0.12 ng/ml. Electrocardiogram revealed sinus rhythm with an ischemic anteroseptal wall, left axis deviation, and left ventricular hypertrophy. His nasopharyngeal swab was positive for SARS-CoV2, and he was treated for both COVID-19 and IE. When the authors managed the case, there were concerns that angiotensin-converting enzyme inhibitors could worsen mortality from COVID-19, so they elected to stop ramipril, which they had initiated on admission. The patient had a drop in his platelet count to 143,000/mm3 during the hospitalization. Despite having echocardiographic evidence of valvular vegetations, the patient's blood cultures were negative. The authors attributed this to the patient having received antibiotics for pneumonia before being referred to their center. He recovered from his illness and was planned to have surgery at a later time. The authors emphasize that COVID-19 can present with other clinical conditions, and a comprehensive physical can help diagnose those conditions (8).

Case 5

Dias et al. reported a 36-year-old man presenting with fever and severe respiratory distress. On clinical

examination, he had multiple purpuric macules over his extremities. Along with features of COVID 19, his CT chest also revealed cavitary lesions suggestive of septic emboli. He had leukocytosis, elevated inflammatory markers, and anemia. She was diagnosed and treated for tricuspid valve methicillin-resistant staphylococcus aureus endocarditis. She succumbed to his illness despite maximal medical treatment (9).

Case 6

Yang et al. talk about the devastating prothrombotic effects of combined IE and COVID-19. This patient was an elderly immunosuppressed male who was initially admitted for heart failure. The etiology of his heart failure was confirmed to be mitral valve IE caused by Streptococcus sanguinis. His hospital course was complicated by the development of COVID-19, non-ST segment elevation myocardial infarction, and stroke. The authors hypothesized that the patient went into a procoagulant state due to a combination of his underlying atrial fibrillation and systemic inflammation induced by COVID-19 and IE. This also led to the patient developing an acute paramedian midbrain infarct, embolic occlusion of the right retinal artery's inferior branch, and visual symptoms. The authors treated him with high dose aspirin followed by full-dose anticoagulation. His symptoms resolved, and he was discharged on antibiotics as well as anticoagulation (10).

Case 7

The publication by Alizadehasl et al. in the European Heart Journal is yet another case that questions corticosteroids' role in predisposing the patients to IE. The authors describe a young male with a mechanical mitral valve seen by them three weeks after being treated for COVID-19 pneumonia. This patient, who had a history of rheumatic heart disease, received corticosteroids as a part of the COVID-19 treatment cocktail during his previous admission. Given the presenting complaint of fever during this hospitalization, a diagnosis of IE was pursued. The diagnosis was confirmed by echocardiographic evidence of vegetations on the mitral valve and the growth of Staphylococcus aureus in blood cultures. The patient had a positive outcome after six weeks of antibiotics. A repeat echocardiogram showed resolution of the vegetations. The authors raised an assumption here that COVID-19 can cause damage to valves, predisposing to bacterial attachment, especially in patients with underlying risk factors (11).

Case 8

Sanders et al. reported a young man with end stage renal disease on hemodialysis catheter presenting with a febrile illness and symptoms of COVID 19 along with new-onset systolic murmur. He had an ECHO evidence of severe aortic regurgitation, > 10 mm aortic vegetation and paravalvular abscess secondary to enterococcus, warranting aortic valve replacement. He was discharged home in a stable condition with a six week course of antibiotics (12).

Case 9:

In their letter, Mantero et al. discussed a gentleman with a bioprosthetic aortic valve presenting with sudden onset aphasia and facial weakness in the background of being treated for COVID 19. He was treated with intravenous recombinant tissue plasminogen activator. Twenty-four hours later, the CT brain showed hemorrhagic transformation in multiple lobes. The patients' ECHO showed evidence of prosthetic valve endocarditis and paravalvular abscess. He was treated and had a resolution of his intracranial bleed by ten days. The authors discussed that presence of COVID-19 infection might lead to superimposed bacterial infection and a procoagulant state (13).

Discussion

Among the 11 patients, identified details were available for nine patients. All of these patients were male. The mean age of these patients was 53 years. Risk factors of prior valvular abnormality and hypertensive disorder were reported in 33% [3/9] of patients. Clinical features of fever, shortness of breath, and cough were reported in 78% [7/9], 67% [6/9], and 44% [4/9]

of patients, respectively. In 56% [5/9] of these patient's RT-PCR positivity was reported in the article, all the others reported as established COVID-19 patients. Evidence of leukocytosis was reported, and 66% [6/9] of patients and elevated C-reactive protein were reported in 55% [5/9]. Computed Tomography of the chest was reported in 66% [6/9] of patients. The most common finding in the CT chest was the presence of bilateral ground-glass opacity. The clinical picture for suspicion of infective endocarditis was new-onset embolic infarct and acute pulmonary edema in 33% [3/9] of patients, respectively.

Blood cultures were reported in all nine patients. The most common organisms identified were Staphylococcus and Enterococcus in 44% [4/9] and 33% [3/9] of patients. The culture was negative in one of the patients. Details of echocardiography were available in all nine patients, among which 55% [5/9] with transthoracic echocardiography and 33% [3/9] were transesophageal. The most commonly involved valve was the aortic valve in 78% [7/9] of patients. In 44% [4/9] of the patient requirement of oxygen was reported. Details of medications used for the management of COVID-19 was not uniformly reported. Details of the intravenous antibiotics used were available in 66% [6/9] patients. Mortality was reported in only 11% [1/9]. 55% of patients recovered and were discharged between 10 to 28 days. 55% [5/9] of patients underwent cardiac surgery, though 33% [3/9] had delayed surgical intervention.

With increasing numbers of patients with COVID-19, reports of other concomitant coinfections are on the rise (14,15). Over the past year, cases of COVID-19 patients presenting along with infective endocarditis has been increasingly reported (5,7,16). Availability of rapid RT-PCR-based COVID-19 testing facilitates diagnosis of COVID-19 (17,18). However, reports of delayed diagnosis and treatment of infective endocarditis continue to be a concern in these patients (7,19). The similarity between the clinical features of both the infections, including fever, shortness of breath, leukocytosis, and elevated inflammatory markers, could attribute to the delay in the diagnosis of infective endocarditis (7,8,20,21). Similarly, isolation methods, decreasing physical contact for meticulous physical examination, delayed echocardiography and deferring surgical intervention in IE patients with COVID-19 patients continue to be challenging (21-25). In this review, more than half of the patient's had either an embolic phenomenon or acute pulmonary edema at the time of presentation, which could be because of the delay in presentation, or diagnosis because of the factors discussed above (7,10,26). Despite these challenges, mortality has been reported in only one patient. A recent study compared the number of cases of IE diagnosed in Belgium and France and reported that cases of IE decreased by 33% with an increase in the number of COVID 19 cases (2). They also noted that patients diagnosed with IE during the pandemic had lesser TEE for diagnosis of IE and had the worst prognosis. The reported cerebral embolism and in-hospital mortality were 56% and 61% during the pandemic than 18.5% and 31% before it (2).

Limitation

This retrospective review has a small sample size of adult patients with IE and COVID 19 coinfection, as published in Medline in English. Details of clinical features, laboratory parameters, imaging, and echocardiography were not uniform across these articles (27,28). Similarly, details of various treatment regimens used, their dosages, and durations for treatment of COVID-19 were not available. Antibiotic susceptibility pattern, dosages, durations were not uniformly available for infective endocarditis either. Interactions of various medications, dosages modifications, and regimen modifications between both these infections were also not uniformly available (27-29). Most of these articles did not uniformly report outcomes, including hypotension, respiratory failure requiring invasive or noninvasive ventilation, worsening organ dysfunction, prolonged antibiotics requirement, and hospital stay. Early suspicion, rapid diagnosis, prompt initiation of treatment, including cardiac surgery in these patients, can improve outcomes (29-32). A multidisciplinary approach is crucial in managing these complex diagnostic challenges. Studies in the future should uniformly report clinical, laboratory parameters, details of management, complications, and outcome of patients with the above coinfection (32-34).

Future reports should include information on the impact of COVID-19 on infective endocarditis management and vice versa.

Conclusion

There has been an increase in reports of COVID-19 patients presenting with concomitant infective endocarditis. These reports have been mostly in older men. Clinical features of COVID-19 continue to predominate in these patients. Infective endocarditis is diagnosed in the presence of worsening pulmonary edema and embolic infarct. Staphylococcus and Enterococcus continue to be the predominant organism, with aortic valve involvement being the most common. Despite the delay in diagnosis, cardiac surgery, and increased morbidity, reported mortality continues to be less. Identifying the various barriers and contributors to poor outcomes in these patients is crucial in improving patient outcomes.

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Consent: Not required

Authors contribution: AAG, AKM planned and formulated the study. AAG, SA collected and analyzed the data. AAG, SA, AKM completed the manuscript. KJJ, AKM reviewed and approved the manuscript.

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