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A clinical profile of infective endocarditis in patients with recent COVID-19: A systematic review



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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) can progress to cardiovascular complications which are linked to higher in-hospital mortality rates. Infective endocarditis (IE) can develop in patients with recent COVID-19 infections, however, characterization of IE following COVID-19 infection has been lacking. To better characterize this disease, we performed a systematic review with descriptive analysis of the clinical features and outcomes of these patients.

Methods: Our search was conducted in 8 databases for all published reports of probable or definite IE in patients with a prior COVID-19 confirmed diagnosis. After ensuring an appropriate inclusion of the articles, we extracted data related to clinical characteristics, modified duke criteria, microbiology, outcomes, and procedures.

Results: Searches generated a total of 323 published reports, and 20 articles met our inclusion criteria. The mean age of patients was 52.2 ± 16.9 years and 76.2% were males. *Staphylococcus aureus* was isolated in 8 (38.1%) patients, *Enterococcus faecalis* in 3 patients (14.3%) and *Streptococcus mitis/oralis* in 2 (9.5%) patients. The mean time interval between COVID-19 and IE diagnoses was 16.7 ± 15 days. Six (28.6%) patients required critical care due to IE, 7 patients (33.3%) underwent IE-related cardiac surgery and 5 patients (23.8%) died during their IE hospitalization.

Conclusions: Our systematic review provides a profile of clinical features and outcomes of patients with a prior COVID-19 infection diagnosis who subsequently developed IE. Due to the ongoing COVID-19 pandemic, it is essential that clinicians appreciate the possibility of IE as a unique complication of COVID-19 infection.

Key Indexing Terms: Infective endocarditis; SARS-CoV-2; COVID-19; Outcomes. [Am J Med Sci 2022;364(1):16–22.]

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected over 220,000,000 individuals globally by September of 2021.¹ COVID-19 usually presents with signs and symptoms of upper and/or lower respiratory tract infection^{2–5} which may rapidly progress to severe respiratory failure. Cardiovascular complications have also been described in these patients and can develop either during or after the course of this illness.⁶ Cardiac complications include myocarditis^{7–12}, stress cardiomyopathy¹³, myocardial infarction¹⁴, heart failure exacerbations¹⁵ and arrhythmias¹⁶, all associated with a higher risk of in-hospital mortality.¹⁷ In addition, case reports of probable or definite infective endocarditis (IE) have also been reported in SARS-CoV-2 infected patients. Therefore, the current systematic review was conducted to provide a descriptive analysis of the clinical features and outcomes of patients with IE and recent COVID-19.

METHODS

Data sources and searches

The literature was searched by a medical librarian (DJG) for studies including both IE and COVID-19 infection. Search strategies were created using a combination of keywords and standardized index terms as well as run against COVID-19 database filters in Ovid Embase, Ovid Medline, and PubMed. Searches were conducted on August 30, 2021 in Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Embase (1974+), Latin American and Caribbean Health Sciences Literature (LILACS, 1982+), Ovid Medline (1946+ including epub ahead of print, in-process & other non-indexed citations), PubMed (1946+), Scientific Electronic Library Online (SciELO, 1997+), Scopus (1823+), and Web of Science Core Collection (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+). No limits were applied yielding a total of 323 citations. Deduplication was performed in Covidence¹⁸ leaving 178 citations (Table 1). Full search strategies are provided in the supplementary appendix.

Table 1. Literature search.

| Databases & Registers | # of initial hits |
|-----------------------------------|-------------------|
| Central (clinical trial register) | 0 |
| Embase | 138 |
| LILACS | 1 |
| Ovid Medline | 32 |
| PubMed | 63 |
| SciELO | 0 |
| Scopus | 49 |
| Web of Science | 40 |
| Totals | 323 |
| Duplicates Removed | 145 |
| Final total | 178 |

The search strategy and study protocol were developed following the PRISMA statement for systematic reviews. This study was registered with the international prospective register of systematic reviews (PROSPERO), registration number CRD42021275412.

Study selection

To capture all cases in pertinent studies, the inclusion criteria included: (1) positive COVID-19 diagnosis confirmed by reverse-transcription polymerase chain reaction or serologic antibiotic testing; and (2) modified Duke criteria¹⁹ for definite or possible infective endocarditis were used to define IE cases; case reports and series in English or Spanish language from September 1, 2019 through August 30, 2021 were selected. This date range was selected to include all case reports regarding the initiation of the SARS-CoV-2 pandemic.

Exclusion criteria included: (1) patients without a diagnosis of COVID-19 or definite/possible IE; (2) patients with non-bacterial thrombotic endocarditis; and (3) patients without laboratory confirmation that COVID-19 preceded an IE diagnosis.

We planned to exclude patients with a time interval greater than 3 months between COVID-19 and IE diagnosis, but no cases with this interval were detected in our systematic review.

Data extraction

Following the initial search in 8 databases, references were uploaded to the platform Covidence and shared with all investigators. Titles and abstracts screening were performed independently by two reviewers (JAQM, JRH) and then conflicts were addressed by more senior investigators (DCD, LMB). Full text of the remaining articles was evaluated independently by the same two reviewers to ensure appropriateness for inclusion, if a disagreement presented it was discussed and resolved among them. Finally, reviewers proceeded to data extraction from the selected articles. Thirteen of the corresponding authors from the selected studies were contacted via e-mail for missing information, seven responded back.

Data synthesis and analysis

A collection form was prepared and then used, it included geographical information, clinical characteristics, modified duke criteria, microbiology, outcomes, laboratories, and procedures. Categorical variables of interest were summarized by totaling across the different case reports and reported as proportions with percentages. Continuous variables were similarly averaged across all case reports and presented as mean \pm standard deviation and/or median with interquartile range (IQR). The pooled data were then presented in tables.

RESULTS

Twenty-one cases from 20 publications that satisfied inclusion criteria were identified^{20–39} (Fig. 1). There were 8 cases in the United States, 7 in Europe (Italy 3, Spain 2, United Kingdom 1 and Greece 1), 3 in the Middle East (Iran, Morocco, Tunisia), 2 in South America (Brazil and Ecuador), and 1 in Asia (Indonesia). Mean age of patients was 52.2 ± 16.9 years, median 77 within an (IQR) of 37 to 68.5, and 76.2% were males. *Staphylococcus aureus* was the most common pathogen and was isolated in 8 (38.1%) patients, 2 of which were methicillin resistant. *Enterococcus faecalis* was isolated in 3 patients (14.3%) and *Streptococcus mitis/oralis* was identified in 2 (9.5%) patients. The mean and median time interval between COVID-19 and IE diagnoses was 16.7 ± 15 days and 10 days (IQR: 7.75 to 20.75) respectively.

Six (28.6%) patients required critical care due to IE, 7 patients (33.3%) underwent IE-related cardiac surgery and 5 patients (23.8%) died during their IE hospitalization (Table 2).

Clinical characteristics are presented in Table 3. The most common symptoms were fever in 18 (85.7%) patients, cough in 10 (47.6%), dyspnea in 9 (42.9%) and

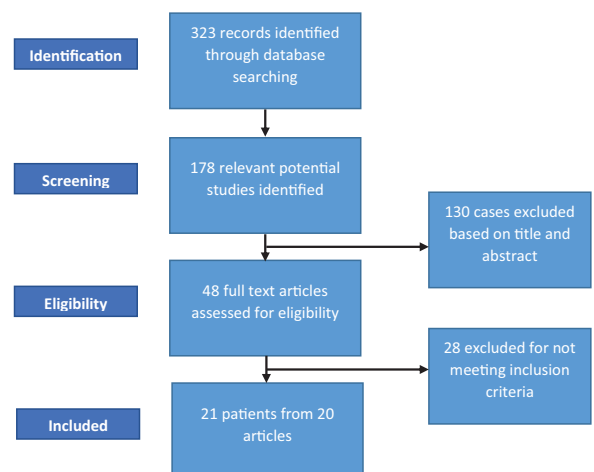


FIG. 1. Selection flow chart demonstrating abstract and article screening.

Table 2. Cases of patients with COVID-19 who developed IE.

| Author | Age | Gender | Location | Microorganism | IE-related ICU care | IE-related cardiac surgery | In-hospital mortality |
|------------------------------|-----|--------|----------------|-------------------------------------|---------------------|----------------------------|-----------------------|
| De Castro ²⁰ | 34 | Female | United States | <i>Haemophilus parainfluenzae</i> | | Yes | |
| Amir ²¹ | 61 | Male | Indonesia | Negative (recent prior antibiotics) | | | |
| Alizadeh ²² | 50 | Male | United Kingdom | MSSA | Yes | | |
| Alizadehasl ²³ | 24 | Male | Iran | MSSA | | | |
| Kumanayaka ²⁴ | 38 | Male | United States | <i>Streptococcus mitis/oralis</i> | | | |
| Regazzoni ²⁵ | 70 | Male | Italy | MSSA | | | |
| Lowell ²⁶ | 59 | Female | United States | <i>Streptococcus agalactiae</i> | | Yes | |
| Kraiem ²⁷ | 60 | Male | Tunisia | <i>Enterococcus faecalis</i> | | | |
| Benmalek ²⁸ | 76 | Female | Morocco | Coagulase-negative staphylococcus | Yes | | |
| Choudhury ²⁹ | 73 | Male | United States | MSSA | | | |
| Joshi ³⁰ | 28 | Male | United States | <i>Serratia marcescens</i> | Yes | | Yes |
| Hayes ³¹ | 38 | Male | United States | <i>Streptococcus mitis/oralis</i> | Yes | Yes | |
| Spinoni ³² | 57 | Male | Italy | MRSA | | | |
| Dias ³³ | 36 | N/A | Brazil | MRSA | | | Yes |
| De Vivo ³⁴ | 77 | Male | Italy | <i>Staphylococcus epidermidis</i> | | Yes | |
| Velez-Paez ³⁵ | 53 | Male | Ecuador | <i>Staphylococcus hominis</i> | | | Yes |
| Sanders ³⁶ | 38 | Male | United States | <i>Enterococcus faecalis</i> | | Yes | |
| Schizas ³⁷ | 59 | Male | Greece | <i>Staphylococcus lugdunensis</i> | Yes | Yes | |
| Ramos-Martinez ³⁸ | 68 | Female | Spain | <i>Enterococcus faecalis</i> | | Yes | Yes |
| Ramos-Martinez ³⁸ | 67 | Male | Spain | MSSA | Yes | | Yes |
| Brotherton ³⁹ | 31 | Male | United States | MSSA | | | |

Abbreviations: IE, infective endocarditis; ICU, intensive care unit; N/A, not available; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

fatigue in 6 (28.6%). Mean temperature (37.9 ± 1.2), and oxygen saturation (89.3 ± 10.2) were reported in 10 cases; mean heart rate (109 ± 21.6), systolic (109.4 ± 20.3) and diastolic (58.1 ± 14.5) blood pressures in 9 cases; and mean respiratory rate (23.4 ± 4.4) in 5 cases.

Cardiac auscultation detected 1 diastolic and 5 systolic murmurs (3 of them holosystolic). One patient presented with Osler nodes and splinter hemorrhages on the index finger and two others had embolic phenomena.

The most prevalent comorbidities were diabetes mellitus type 2 (5 [23.8%] patients), hypertension (3 [14.3%] patients), and atrial fibrillation (3, [14.3%] patients).

Among predisposing conditions of IE, 7 (33.3%) patients were receiving immunosuppressant medications for COVID-19 prior to their IE diagnosis, including methylprednisolone, dexamethasone, and tocilizumab; 5 (23.8%) patients had indwelling central venous catheters; 3 (14.3%) other patients were on chronic hemodialysis; one patient each had injection drug use, rheumatic heart disease, prosthetic valve, or cardiovascular implantable electronic device.

Echocardiographic findings

Seventeen (81.0%) of the 21 patients had a transthoracic echocardiogram (TTE) and 12 (57.1%) of them had a transesophageal echocardiogram (TEE) performed (Table 4). TTE findings included vegetations involving the mitral valve (4 patients, 23.5%), aortic valve (4 patients,

23.5%), tricuspid valve (3 patients, 17.6) and a cardiovascular implanted electronic device lead (1 patient, 5.9%). Out of the 12 reported vegetations, 6 (50%) had a dimension > 10 mm. Mitral regurgitation was present in 4 patients (23.5%), of which 2 were mild (11.8%), 1 moderate, and 1 severe. Tricuspid regurgitation was present in 3 patients (17.6%), of which 1 was moderate and 2 severe. Aortic regurgitation was diagnosed in 5 patients (29.4%), of which 3 were graded as moderate and 2 as severe.

TEE detected vegetations involving the aortic valve in 5 (41.7%) patients, mitral valve in 4 (33.3%) patients, tricuspid valve in 2 (16.7%) patients and the lead of a cardiac implanted electronic device in 1 patient (8.3%). A vegetation size > 10 mm was found in 2 patients. Severe mitral regurgitation was present in 4 (33.3%) patients. Tricuspid regurgitation was seen in 2 (16.7%) patients and was mild in one case and moderate the other. One patient had paravalvular abscess.

DISCUSSION

To our knowledge, this is the only registered systematic review published that provides a clinical profile of IE in patients with recent COVID-19. Such an analysis is critical recognizing the ongoing COVID-19 pandemic and its cardiovascular complications, infectious and non-infectious in nature.

Table 3. IE-related clinical characteristics of patients with previous COVID-19.

| Symptoms | N (%) | | |
|--|------------------|---------------------|--|
| Fever | 18 (85.7) | | |
| Cough | 10 (47.6) | | |
| Dyspnea | 9 (42.9) | | |
| Fatigue | 6 (28.6) | | |
| Chills | 4 (19.0) | | |
| Altered mental status | 4 (19.0) | | |
| Anorexia | 3 (14.3) | | |
| Abdominal pain | 3 (14.3) | | |
| Myalgia | 2 (9.5) | | |
| Urinary symptoms | 2 (9.5) | | |
| Arthritis | 2 (9.5) | | |
| Diarrhea | 1 (4.8) | | |
| Chest pain/ discomfort | 1 (4.8) | | |
| Nocturnal hyperhidrosis | 1 (4.8) | | |
| Nausea | 1 (4.8) | | |
| Headaches | 1 (4.8) | | |
| Postnasal drip | 1 (4.8) | | |
| Low back pain | 1 (4.8) | | |
| Hyperreflexia | 1 (4.8) | | |
| Weight loss | 1 (4.8) | | |
| Vital signs (# of cases reported) | Mean ± SD | Median (IQR) | |
| Temperature, Celsius (10) | 37.9 ± 1.2 | 38.0 (37.3–38.8) | |
| Saturation of oxygen, % (10) | 89.3 ± 10.2 | 92.5 (86.5–96.3) | |
| Heart rate (9) | 109.0 ± 21.6 | 100 (95.5–123.0) | |
| Systolic blood pressure, mmHg (9) | 109.4 ± 20.3 | 110 (90.0–129.0) | |
| Diastolic blood pressure, mmHg (9) | 58.1 ± 14.5 | 58.0 (46.0–69.5) | |
| Respiratory rate (5) | 23.4 ± 4.4 | 24.0 (19.0–27.5) | |
| Endocarditis clinical findings | N (%) | | |
| Systolic murmur | 5 (23.8) | | |
| Vascular phenomena | 2 (9.5) | | |
| Diastolic murmur | 1 (4.8) | | |
| Osler nodes | 1 (4.8) | | |
| Splinter hemorrhages | 1 (4.8) | | |
| Predisposing conditions | N (%) | | |
| Immunosuppression | 7 (33.3) | | |
| Intravenous catheter | 5 (23.8) | | |
| Chronic hemodialysis | 3 (14.3) | | |
| Urinary catheter | 2 (9.5) | | |
| Rheumatic heart disease | 2 (9.5) | | |
| Injection drug user | 1 (4.8) | | |
| Prosthetic valve | 1 (4.8) | | |
| Cardiovascular implanted electronic device | 1 (4.8) | | |
| Comorbidities | N (%) | | |
| Diabetes mellitus type 2 | 5 (23.8) | | |
| Hypertension | 3 (14.3) | | |
| Atrial fibrillation | 3 (14.3) | | |
| Chronic obstructive pulmonary disease | 1 (4.8) | | |
| Hypercholesterolemia | 1 (4.8) | | |
| Obesity | 1 (4.8) | | |
| Chronic osteomyelitis | 1 (4.8) | | |
| Human immunodeficiency virus infection | 1 (4.8) | | |
| Chronic kidney disease | 1 (4.8) | | |
| Gestation | 1 (4.8) | | |
| Smoking history | 1 (4.8) | | |

Abbreviations: IE, infective endocarditis; IQR, interquartile range.

Table 4. Echocardiographic findings in patients with COVID-19 who subsequently developed IE.

| Echocardiographic finding | Number of patients |
|-------------------------------|--------------------|
| TTE | 17 |
| Mitral vegetation | 4 |
| Aortic vegetation | 4 |
| Tricuspid vegetation | 3 |
| Mitral + tricuspid vegetation | 1 |
| Lead vegetation | 1 |
| Mitral regurgitation | 4 |
| Mild | 2 |
| Moderate | 1 |
| Severe | 1 |
| Tricuspid regurgitation | 3 |
| Moderate | 1 |
| Severe | 2 |
| Aortic regurgitation | 5 |
| Moderate | 3 |
| Severe | 2 |
| TEE | 12 |
| Mitral vegetation | 4 |
| Aortic vegetation | 5 |
| Tricuspid vegetation | 2 |
| Mitral + tricuspid vegetation | 1 |
| Lead vegetation | 1 |
| Mitral regurgitation | 2 |
| Mild | 1 |
| Moderate | 1 |
| Severe aortic regurgitation | 4 |
| Paravalvular aortic abscess | 1 |

Abbreviations: IE, infective endocarditis; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

Several unique clinical features have characterized IE following a COVID-19 infection diagnosis. First, the mean age of our cohort was 52.2 years, considerably younger than most patients with non-IDU-related IE in the US and Europe; in these cohorts, the age is usually > 60 years.^{40,41} Reported median age data also reflected a younger cohort in our systematic review as compared to that in North America; 57 years (IQR: 37 to 68.5) vs. 63 years (IQR: 48 to 75).⁴² Second, the predominance (76%) of males is more than expected in these other cohorts. Third, respiratory complaints were commonplace and were likely due to recent COVID-19 infection.

The time between COVID-19 infection and IE diagnoses deserves additional address for several reasons. First, IE is an uncommon syndrome⁴³, in contrast to COVID-19¹; thus, the likelihood that fever will trigger an early consideration of IE as a cause is low. Second, due to the infectivity of COVID-19, invasive diagnostic procedures, in particular TEE, have been avoided to reduce potential healthcare-associated spread of COVID-19.^{44,45} This concern was likely representative of the limited (57%) use of TEE in our cohort. *S. aureus*, as the predominant IE pathogen in our cohort, could have also

impacted the time interval between the two syndrome diagnoses. Due to its well-recognized virulence, IE due to this pathogen is likely to be acute in presentation.

Whether mechanisms involved in the pathogenesis of COVID-19 infection can predispose to IE remain undefined. It is tempting to speculate, however, that there may be at least two independent mechanisms that could be operative in the predilection of IE. Based on an animal model of infection⁴⁶, sentinel findings highlighted the possibility that not only damaged endothelium can predispose to IE caused by *S. aureus*, but a second independent mechanism may involve inflammation of the cardiac valve with expression of surface structures to enhance bacterial adhesion. It is clear from prior COVID-19-related investigations that vascular endothelial surfaces can be impacted by endotheliitis⁴⁷; whether the same is true for valvular endothelium seems plausible. Obviously, more work is needed to better define IE pathogenesis in the setting of recent COVID-19 infection. Moreover, some patients had predisposing conditions associated with the development of IE which could have been important in IE pathogenesis

Of note, only one blood culture-negative endocarditis case was included in our cohort and was likely due to recent antibiotic exposure. Antibiotic use in cases of COVID-19, particularly early in the pandemic, has secured extensive review and stewardship concerns regarding selection of antibiotic resistance, increased risk of drug adverse events, and financial costs. These concerns must be balanced, however, with the need to treat healthcare-related infections among COVID-19 patients, particularly those with prolonged hospital stays and critical care exposure.^{48–50}

Five (23.8%) patients died during their in-hospital stay for IE management, which is a rate reflected, based on previously published cohorts not related to recent COVID-19 infection.^{51–53} Considering the potential impact of recent COVID-19 infection on mortality, a higher mortality rate may have been expected. Of course, there is risk of publication bias among case reports included in the current systematic review with publication of only successfully treated patients.

Limitations

Despite performing a search which included multiple library databases in our systematic review, a limited number of cases were identified. As outlined above, several factors could limit the number of IE cases being detected. Also, the retrospective nature of the systematic review resulted in a lack of clinical data to confirm COVID-19 infection in some cases which were excluded. Moreover, the lack of detailed clinical data prevented inclusion of IE cases per modified Duke criteria. This study may have been limited by reporting bias; nevertheless, we contacted the corresponding authors from selected publications for missing information. Finally, due to the millions of COVID-19 cases that have

occurred globally, an argument that the small number of reported IE cases were not associated with COVID-19 infection. Based on factors including healthcare exposure, predominant pathogen, possible pathogenesis consideration, and immunosuppression therapy, it seems reasonable to consider a possible link of IE with recent COVID-19 infection.

CONCLUSIONS

This systematic review provides the first descriptive analysis of the clinical features and outcomes of 21 patients with IE and prior COVID-19. Due to the ongoing pandemic, it is expected that additional IE cases will occur, and clinicians should be aware of this life-threatening complication.

Addendum

We recently learned of an unregistered systematic review with fewer cases that was published in the journal entitled “*American Journal of Medical Case Reports*” (10.12691/ajmcr-9-7-11). We recognize that due to the unprecedented interest generated by the current pandemic, all aspects of COVID-19-related presentations are both more likely to be published and in a more rapid manner, therefore increasing the risk of publication overlap.

AUTHOR CONTRIBUTION

J.A.Q.M.: Conceptualization, data collection, data analysis, Writing - original draft, Writing - review & editing; J.R.H.: Conceptualization, data collection, Writing - review & editing; M.M.: Conceptualization, Writing - review & editing; D.J.G.: Conceptualization, literature search; D.C.D.: Conceptualization, Writing - review & editing; L.M.B.: Conceptualization, Writing - original draft, Writing - review & editing.

CONFLICTS OF INTEREST

Larry M. Baddour, M.D. reports UpToDate, royalty payments (authorship duties); Boston Scientific, consultant duties; Botanix Pharmaceuticals, consulting duties; Roivant Sciences Inc., consultant duties. None of the other authors had disclosures.

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PATIENT CONSENT STATEMENT

This study does not include factors necessitating patient consent.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjms.2022.02.005>.

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