

Case Series

Cardiac Surgery for Treatment of COVID-19–Associated Infectious Endocarditis

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Abstract

Background: Significant uncertainty exists about the optimal timing of surgery for infectious endocarditis (IE) surgery in patients with active SARS-CoV-2 infection. This case series and a systematic review of the literature were carried out to evaluate the timing of surgery and postsurgical outcomes for patients with COVID-19–associated IE.

Methods: The PubMed database was searched for reports published from June 20, 2020, to June 24, 2021, that contained the terms *infective endocarditis* and *COVID-19*. A case series of 8 patients from the authors' facility was also added.

Results: A total of 12 cases were included, including 4 case reports that met inclusion criteria in addition to a case series of 8 patients from the authors' facility. Mean (SD) patient age was 61.9 (17.1) years, and patients were predominantly male (91.7%). Being overweight was the main comorbidity among patients studied (7/8 [87.5%]). Among all patients evaluated in this study, dyspnea (n = 8 [66.7%]) was the leading symptom, followed by fever (n = 7 [58.3%]). *Enterococcus faecalis* and *Staphylococcus aureus* caused 75.0% of COVID-19–associated IE. The mean (SD) time to surgery was 14.5 (15.6) days (median, 13 days). In-hospital and 30-day mortality for all evaluated patients was 16.7% (n = 2).

Conclusion: Clinicians must carefully assess patients diagnosed with COVID-19 to prevent missing underlying diseases such as IE. If IE is suspected, clinicians should avoid postponement of crucial diagnostic and treatment steps.

Keywords: COVID-19; endocarditis; cardiac surgery

Introduction

In late December 2019, Chinese health authorities reported a sudden emergence of patient clusters experiencing an acute respiratory syndrome of unknown cause in Wuhan City. Later, a new human pathogen, SARS-CoV-2, was identified.¹ The subsequent pandemic has had an overwhelming impact on the health care landscape.

Particularly in cardiac surgery, procedures were restricted to urgent and emergency indications. Among these urgent and emergency cardiac procedures, the surgical treatment of infectious endocarditis (IE) is unique. Under regular, nonpandemic circumstances, determining the optimal timing of surgery for IE is challenging, but in patients with COVID-19, it was even more difficult.

The coincidence of IE in patients with recent or concomitant COVID-19 and the impact of 2 such potentially deadly entities on each other are unclear. The information available to clinicians is limited, making it difficult to develop an adequate treatment strategy. To bridge this data gap, an analysis of this challenging patient cohort was needed. The objective of this study was to investigate the time to surgery and outcomes for patients with IE and recent

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or concomitant COVID-19. To that end, the authors systematically reviewed the recent scientific literature and included patients from their facility to assess and describe this specific patient cohort’s demographic data, clinical course, and outcomes.

Patients and Methods

The following groups of patients with IE were included in this study: (1) those who had recovered from COVID-19 and who had had a positive COVID-19 test no earlier than 12 months before IE diagnosis (referred to as *patients with IE and recent COVID-19*) and (2) those with ongoing COVID-19 and positive COVID-19 test results concurrent with an IE diagnosis (referred to as *patients with IE and concomitant COVID-19*).

Study Selection Criteria

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline-conforming review was conducted to critically appraise the presently available data on IE in patients infected with SARS-CoV-2 for study selection.² Separate PubMed and Google Scholar searches were conducted by 2 independent reviewers (A.P. and A.T.W.). The databases were electronically retrieved with no language restriction using the search terms *COVID-19* and *infective endocarditis*, and results included studies published from June 20, 2020, to June 24, 2021. To expand the search options, the PubMed function “related articles” was applied. The database search results were evaluated by scrutinizing titles, reviewing full text to determine relevance, and analyzing the articles discovered. All selected articles were imported into Zotero reference management software. Subsequently, a manual search was performed to identify patients with positive COVID-19 test results who underwent a cardiac surgical intervention for IE. Accordingly, the inclusion criteria for the literature review were as follows: (1) case reports and respective case series, (2) reports of patients whose COVID-19 diagnosis was confirmed by reverse transcriptase–polymerase chain reaction (RT-PCR) or an antigen test, (3) reports of all patients whose IE diagnosis could be extracted from a full-text search according to the modified Duke criteria, and (4) reports of subsequently performed cardiac surgical treatment. Cohort studies that included patients with COVID-19 and IE but provided no discernible differentiated depiction of the patients’ clinical

Abbreviations and Acronyms

BMI	body mass index
EuroSCORE II	European System for Cardiac Operative Risk Evaluation
IE	infectious endocarditis
LVEF	left ventricular ejection fraction
RT-PCR	reverse transcriptase–polymerase chain reaction
TEE	transesophageal echocardiography

course or outcome were omitted. Also excluded were case reports and case series that reported a false-positive COVID-19 swab test result.

Eligibility Criteria and Data Extraction From Individual Cases

Individual case data were included if they (1) reported the clinical course, (2) stated the postsurgical outcome, (3) included the echocardiographic verification of IE vegetation, and (4) indicated the microbiological results of the IE cases. Data from each eligible study were extracted by 2 independent reviewers (A.P. and A.T.W.) and transmitted in an electronic health record. The extracted data consisted of the first author’s surname, year of publication, country in which the study was conducted, dates of the study, type of study (case report or case series), sample size, data about comorbidities (if reported), clinical presentation, the IE-affected heart valves, treatment, and patients’ postsurgical outcome. Consensus was reached regarding any differences that arose during this process. The process of study selection and data extraction is shown in Figure 1.

Case Series

A retrospective chart review of 8 patients with IE and recent or concomitant COVID-19 who had undergone a cardiac surgical treatment in the authors’ facility between November 1, 2020, and June 30, 2021, was performed. Within the scope of this study, patient demographic data (age, sex, height, and weight), date of IE and COVID-19 diagnosis, heart valves affected by IE, causative organism isolated from blood cultures, comorbidities (cardiovascular risk factors, coronary artery disease, renal insufficiency, pulmonary diseases, and neurologic impairments, among others), surgical procedures, duration of postoperative hospital stay, and postsurgical outcome (with a focus on in-hospital 30-day mortality) were assessed.

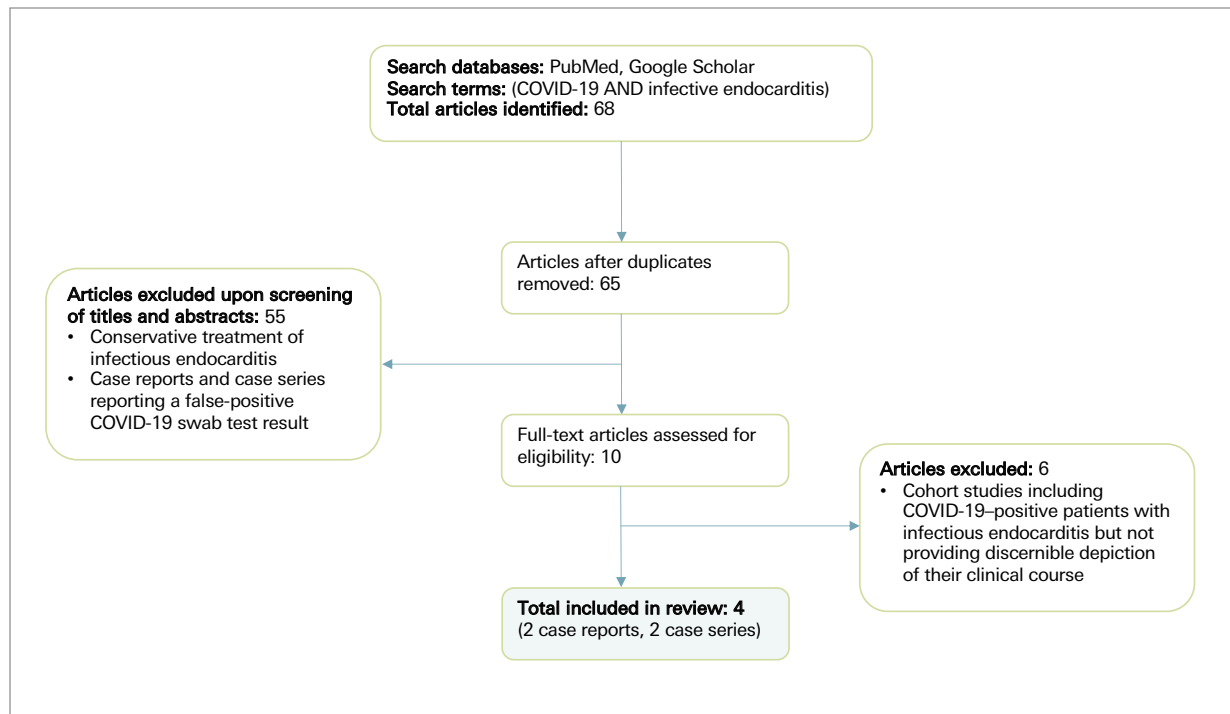


Fig. 1 Flow diagram depicts the process and data collection for this study.

Statistical Analysis

The data were insufficient for analytic comparison because of the low number of patients, the heterogeneous reports, and the nonrandom selection of patient cohorts; therefore, only a descriptive analysis was conducted. The categorical variables were expressed as numbers and percentages; continuous variables were expressed as means and SDs. Data for missing values were not imputed. R, version 4.0.3 (R Foundation for Statistical Computing) was used to conduct all analyses.

Results

Overview of Included Patients

A systematic search of PubMed and Google Scholar resulted in a total of 68 studies. After screening titles and abstracts, the authors isolated 13 studies eligible for full-text review. Nine studies were then excluded for not meeting the inclusion criteria. The remaining 4 articles matched the inclusion criteria and were included in this systematic review.³⁻⁶ Two articles were case series, and 2 were case studies that included a total of 7 patients. Thus, the literature review consisted of a total of

4 articles. Three patients in 1 case series were excluded after a full-text review revealed that they did not have endocarditis. Thus, this study analyzed the data from 12 patients, of whom 4 were from the literature review reports and 8 were from the authors' retrospective facility chart review. All patients examined in the literature review had IE concomitant with COVID-19. Two of the 8 chart review patients had IE and COVID-19 concomitantly. Table I summarizes the main data from all patients included in this study associated with endocarditis and COVID-19.

Patient Characteristics

Data on medical history and previous preoperative comorbidities were scarce in the 4 patients from the literature review (see Table II for unavailable data).³⁻⁶ The patients' mean (SD) age was 61.9 (17.1) years (median, 67.5 years; range, 36-82 years). Patients were mostly male (11/12 [91.7%]). The mean (SD) European System for Cardiac Operative Risk Evaluation (EuroSCORE II) mortality index was 21.0% (18.0%) (median, 19.1%; range, 1.24%-50.7%). The mean (SD) left ventricular ejection fraction (LVEF) was 51.9% (7.25%). The LVEF was mildly reduced (40%-55%) in 30% of cases (3/10 [patients 3, 4, and 8]) and moderately reduced (30%-

TABLE I. Data From All Study Patients in This Study With COVID-19–Associated Infectious Endocarditis

No.	Study	Sample size, No.	Patients who met inclusion criteria	COVID-19 status at the time of IE diagnosis	Identified pathogen	Affected heart valve	Time interval from COVID-19 diagnosis to IE diagnosis, d	Time to surgery, d	Urgency of the indication	Implanted valve type
Literature review										
1	Hussain et al ³ (2020) ^a	3	1	Concomitant	<i>Enterococcus faecalis</i>	NAV	NA	NA	Urgent	MAV
2	Sanders et al ⁴ (2020) ^b	1	1	Concomitant	<i>E faecalis</i>	NAV	NA	NA	Urgent	MAV
3	Hayes et al ⁵ (2021) ^a	2	1	Concomitant	<i>Streptococcus mitis</i>	NAV	NA	NA	Urgent	BAV
4	Varvodic et al ⁶ (2021) ^b	1	1	Concomitant	<i>Streptococcus pneumoniae</i>	NAV	18	1	Urgent	BAV
Chart review										
5	Current case series	8	8	Recent	<i>E faecalis</i>	NAV	25	2	Urgent	BAV
6				Concomitant	MSSA	NMV	3	26	Urgent	BAV
7				Recent	MSSA	NMV	20	10	Urgent	BAV
8				Recent	MSSA	NAV	35	46	Urgent	BAV
9				Recent	MSSA	MMV	142	4	Urgent	BAV
10				Recent	<i>E faecalis</i>	NAV	53	16	Urgent	BAV
11				Concomitant	<i>E faecalis</i>	BAV	1	26	Urgent	BAV
12				Recent	<i>Granulicatella elegans</i>	NAV	197	0	Elective	MAV

BAV, bioprosthetic aortic valve; IE, infectious endocarditis; MAV, mechanical aortic valve; MMV, mechanical mitral valve; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not available; NAV, native aortic valve; NMV, native mitral valve.

^a Case series.

^b Case report.

40%) in just 1 case (patient 10). Two patients (16.7% [patients 5 and 7]) had undergone previous cardiac surgery. Table II shows the baseline characteristics and comorbidities of all included patients.

Preoperative Comorbidities

Notably, 7 of 8 patients (87.5%) for whom a body mass index (BMI) could be calculated had a BMI of 25 or higher and thus could be classified as overweight; 4 of 8 patients (50%) were obese (defined as BMI ≥ 30). The mean (SD) BMI was 31.3 (6.8). Preoperative renal insufficiency was identified in 2 of 4 patients from the evaluated literature review; no data on preoperative kidney function was available for the other 2 patients. Patient 2 had kidney failure resulting from hypertensive nephropathy and required regular dialysis preoperatively, while patient 4 had acute kidney damage following antibiotic therapy with vancomycin and required temporary preoperative dialysis. Kidney function recovered

after the antibiotic regimen was changed. In the chart review, 5 of 8 patients (62.5%) had preoperative renal insufficiency, with 2 (25.0%) of them requiring dialysis before surgery. Hence, 7 of 10 (70%) study patients had preoperative renal insufficiency. The medical history regarding the presence of arterial hypertension could be obtained only from the patients listed in the chart review (5/8 [62.5%]). Patient 5 had a history of alcohol abuse and smoking. Patient 3 had HIV. Further comorbidities of the studied patient group are summarized in Table II.

Clinical Presentation of IE in Patients With COVID-19–Associated IE

Among all patients evaluated in this study, dyspnea (n = 8 [66.7%]) was the leading symptom, followed by fever (n = 7 [58.3%]). Heart murmur was present in 41.7% (n = 5) of all patients. Sepsis was manifest in 75% (n = 9) of all patients. Septic shock and the use of a preoperative vasopressor were not explicitly mentioned

TABLE II. Baseline Characteristics and Comorbidities of All Included Patients

Study	Age, y	Sex	EuroSCORE II, %	CAD	AHT	Diabetes	BMI	DLP	LVEF, %	PAOD	COPD	Renal insufficiency	History of disease
Literature review													
Hussain et al ³ (2020)	68	M	NA	NA	NA	Yes	NA	NA	NA	NA	NA	NA	1
Sanders et al ⁴ (2020)	38	M	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes ^a	NA
Hayes et al ⁵ (2021)	38	M	NA	NA	NA	NA	NA	NA	45	NA	NA	NA	NA
Varvodic et al ⁶ (2021)	36	M	NA	NA	NA	NA	NA	NA	45	NA	NA	Yes ^b	NA
Chart review													
Current case series	70	M	50.73	No	Yes	No	45.7	Yes	54	No	No	Yes	No
	77	M	26.71	No	Yes	No	27.8	No	55	Yes	No	Yes	No
	64	M	1.9	No	No	Yes	26.8	No	60	No	No	No	Yes
	76	M	36.2	No	Yes	No	30.9	No	50	No	No	Yes ^a	No
	67	M	31.66	No	Yes	No	34.4	No	55	No	No	Yes ^a	No
	82	F	11.55	Yes	No	Yes	29.2	No	38	No	No	No	Yes
	78	M	8.13	Yes	No	No	32.3	Yes	60	No	Yes	Yes	No
	49	M	1.24	No	Yes	No	23.1	No	57	No	No	No	No
Mean (SD)	61.9 (17.1)	–	21.0 (18.0)	–	–	–	31.3 (6.8)	–	51.9 (7.2)	–	–	–	–
Median, % (No./total No.)	–	91.7 M (11/12)	–	25.0 (2/8)	62.5 (5/8)	33.3 (3/9)	–	25.0 (2/8)	–	12.5 (1/8)	12.5 (1/8)	70.0 (7/10)	33.3 (3/9)

AHT, arterial hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DLP, dyslipidemia; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; F, female; LVEF, left ventricular ejection fraction; NA, not available; M, male; PAOD, peripheral arterial occlusion disease.

^a Preoperative terminal dialysis–dependent renal insufficiency.

^b Preoperative temporary dialysis.

in any of the evaluated cases in the literature review. In the chart review, 2 of 8 patients (25%) had septic shock following consecutive preoperative use of a vasopressor. Preoperative ventilation was indicated in 16.7% (n=2) of all patients. Two patients (16.7%) were affected by septic embolization, with consecutive neurologic deficits. Table III summarizes these data.

Time Interval From COVID-19 Diagnosis to IE Diagnosis

In the literature review, Varvodic et al⁶ indicated as the case report for patient 4 a precise clinical time course from initial COVID-19 diagnosis to conclusive IE diagnosis by transesophageal echocardiography (TEE). The exact data were missing from the rest of the studies in the literature review and so did not permit reconstruction of exact infection timelines. The mean (SD)

interval from COVID-19 diagnosis (as detected by RT-PCR or antigen test) to a definitive diagnosis of IE by detection of vegetations on TEE was 59.9 (68.2) days (median, 30; minimum [min], 1; maximum [max], 197 days) in patients with IE and either concomitant or recent COVID-19. The mean (SD) interval, calculated separately, was 7.3 (9.3) days in patients with IE and concomitant COVID-19 (n=3) and 78.7 (73.3) days in patients with IE and recent COVID-19 (n=6).

Endocarditis and Microbiological Profile

Infectious endocarditis of the native valves was present in 83.3% (n=10) of the total cases. In all cases involving native aortic and mitral valves (n=10 [83.3%]), 20.0% (n=2) had mitral valve IE, and the rest had aortic valve IE (n=8 [80.0%]). Prosthetic valve endocarditis was identified in 16.7% (n=2) of all cases. Infectious en-

TABLE III. Clinical Presentation of Infectious Endocarditis in Patients With COVID-19–Associated Infectious Endocarditis

Reference	Dyspnea	Fever	Heart murmur	Sepsis	Septic shock	Preoperative vasopressor use	Preoperative ventilation	Septic embolization	Postoperative death
Literature review									
Hussain et al ³ (2020)	No	Yes	Yes	Yes	NA	NA	No	No	No
Sanders et al ⁴ (2020)	Yes	Yes	Yes	Yes	NA	NA	No	No	No
Hayes et al ⁵ (2021)	Yes	Yes	No	Yes	NA	NA	No	No	No
Varvodic et al ⁶ (2021)	Yes	No	No	No	NA	NA	Yes	No	No
Chart review									
Current case series	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes
	No	Yes	No	Yes	No	No	No	No	Yes
	Yes	Yes	No	Yes	No	No	No	No	No
	No	No	No	Yes	No	No	Yes	Yes	No
	No	Yes	No	Yes	Yes	Yes	No	Yes	No
	Yes	No	Yes	Yes	No	No	No	No	No
	Yes	No	Yes	No	No	No	No	No	No
	Yes	Yes	No	No	No	No	No	No	No
Mean (No./total No.)	66.7 (8/12)	58.3 (7/12)	41.7 (5/12)	75.0 (9/12)	25.0 (2/8)	25.0 (2/8)	16.7 (2/12)	16.7 (2/12)	16.7 (2/12)

NA, not available.

docarditis affected a biological mitral valve prosthesis in 1 case (patient 9); in another, it affected a sutureless biological aortic valve prosthesis (patient 11). Perivalvular abscess formation was found in 41.7% (n=5) of all evaluated patients. Of the 12 patients reviewed in this series, the culture-positive rate was 100%. The most common isolated pathogen was *Enterococcus faecalis* (n=5 [41.7%]), followed by methicillin-susceptible *Staphylococcus aureus* (n=4 [33%]). *Granulicatella elegans*, *Streptococcus mitis*, and *S pneumoniae* were the other pathogens identified (1 case each). Therefore, *E faecalis* and *S aureus* caused 75.0% (n=9) of IE cases associated with concomitant or recent COVID-19 (Table I).

Surgical Urgency, Time to Surgery, and Surgical Procedures Performed

Urgent surgical treatment was needed in 91.7% (n=11) of patients, and 1 patient (8.3%) underwent surgery electively. For patient 4 from the literature review, the

timeline data were sufficiently precise to reconstruct the time to surgery from the initial diagnosis of IE by TEE. The mean (SD) time to surgery was 14.5 (15.6) days (median, 13; min, 0; max, 46 days) in patients with IE and concomitant or recent COVID-19. The mean (SD) time to surgery was 17.7 (14.4) days in patients with IE and concomitant COVID-19 (n=3) and 13.0 (20.6) days in patients with IE and recent COVID-19 (n=6).

A biological aortic valve prosthesis was implanted in 66.7% (n=6) of patients with aortic valve endocarditis (including native and prosthetic aortic valve endocarditis); in the remaining 33.3% (n=3), a mechanical valve prosthesis was used. One of the biological aortic valve prostheses implanted was sutureless (patient 4). In patients with mitral valve IE (n=3, including native and prosthetic mitral valve endocarditis), only biological prostheses were used. Thus, aortic valve replacement constituted 75.0% (n=9) of all surgical procedures using biological valves, followed by mitral valve replacements with biological valves.

Postoperative Clinical Course, Outcome, and Survival

In-hospital and 30-day mortality for all evaluated patients was 16.7% ($n=2$). The mean (SD) duration of postoperative hospital stay in surviving patients was 10.1 (3.6) days (median, 10; min, 4; max, 15 days); the duration was not indicated in 2 patients from the literature review. Complications were not reported in detail in the literature review. Patient 5 experienced a perioperative cerebral ischemic event. All patients from the chart review were dependent on the postoperative use of vasopressors with norepinephrine, with 3 patients (37.5%) requiring inotropic circulatory support with adrenaline. The mean (SD) mechanical ventilation time among patients from the chart review was 32 (47.4) hours (median, 7; min, 4; max, 120 hours). No cases of reintubation were reported, and there was no need for postoperative tracheotomy. Two patients from the chart review (25.0% [patients 5 and 6]) had acute-on-chronic kidney failure requiring postsurgical dialysis. Patient 12 underwent surgical implantation of a permanent dual-chamber pacemaker after aortic valve replacement with a mechanical valve prosthesis. Two patients (16.7% [patients 5 and 6]) died postoperatively. All patients from the chart review who were postoperatively discharged ($n=6$ [75.0%]) were still alive at the first 6-month follow-up.

Discussion

Despite the dramatic increase in publications related to COVID-19, as this study illustrates, IE requiring surgical treatment in patients with concomitant or recent COVID-19 is a relatively underreported aspect of the global pandemic. The COVID-19 pandemic has challenged the current diagnostic and treatment strategies for cardiovascular diseases in general. Because patients with COVID-19 frequently present with fever and dyspnea, which overlap IE symptoms, clinicians must carefully assess patients diagnosed with COVID-19 to avoid missing underlying diseases. Such misses are particularly concerning considering the hypothesis that an excessive inflammatory response caused by SARS-CoV-2 infection may result in damage to the endocardium of native heart valves, a convenient site for pathogen attachment, which in turn may lead to a rise in COVID-19–associated endocarditis cases.⁷

Most patients with COVID-19–associated endocarditis were older men who had mainly dyspnea and fever. Thus, in a time of pandemic, diagnosis of IE may well be more difficult because COVID-19 and IE share similar major symptoms. The clinical sign of a heart murmur, which was detected by auscultation in more than 40% of patients in the investigated group, may provide the decisive clue for diagnosing IE. Obesity was the main comorbidity in the case series studied. The mean (SD) time to surgery was 14.5 (15.6) days (median, 13 days) for all patients. The mean (SD) time to surgery was longer in patients with IE and concurrent COVID-19 than in patients with IE and recent COVID-19 (17.7 [14.4] vs 13.0 [20.6] days).

Varvodic et al⁶ indicated that postponement of TEE in an effort to minimize the risk of SARS-CoV-2 spread to medical personnel led to severe IE complications. Thus, when urgent IE is suspected, implementing diagnostic steps for IE diagnosis according to current guidelines is critical to avoid delays in diagnosis and subsequent treatment strategies as well as to decrease mortality in patients with IE.⁸

The small sample of patients and the heterogeneity of the sample data are the major limitations of this study. Because of the defined inclusion criteria, many other case reports or case series reporting conservative antibiotic treatment of IE or false-positive COVID-19 swab test results had to be excluded, which resulted in a small number of cases for the systematic review. Furthermore, because this review analyzed only patients with COVID-19–associated IE who underwent surgical treatment, selection bias may have occurred. It stands to reason that only those patients who were in a suitable condition for surgery were operated on. The quality of studies was variable and limited to case reports and small case series in which data were sometimes poorly reported or incomplete.

Conclusion

During the COVID-19 pandemic, misguided diagnosis, undiagnosed underlying IE, and prolongation of surgical treatment have posed risks for patients with COVID-19–associated diagnoses. When IE has been diagnosed, clinicians must determine an appropriate diagnostic and treatment pathway to avoid high mortality rates in these patients. Further, there appears to have

been a substantial delay in diagnosis of IE, presumably because the care team was understandably focused on the management of COVID-19.

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