Effect of Hospital-associated SARS-CoV-2 Infections in Cardiac Surgery. A Multicenter Study

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ABSTRACT

BACKGROUND The effect of hospital-associated SARS-CoV-2 infections in cardiac surgery patients remains poorly investigated, and current data are limited to small case series with conflicting results.

METHODS A multicenter European collaboration was organized to analyze the outcomes of patients who tested positive with hospital-associated SARS-CoV-2 infection after cardiac surgery. The study investigators hypothesized that early infection could be associated with worse postoperative outcomes; hence 2 groups were considered: (1) an early hospital-associated SARS-CoV-2 infection group comprising patients who had a positive molecular test result ≤7 days after surgery, with or without symptoms; and (2) a late hospital-associated SARS-CoV-2 infection group comprising patients whose test positivity occurred >7 days after surgery, with or without symptoms. The primary outcome was 30-day mortality. Secondary outcomes included all-cause mortality or morbidity at early follow-up and SARS-CoV-2–related hospital readmission.

RESULTS A total of 87 patients were included in the study. Of those, 30 were in the early group and 57 in the late group. Overall, 30-day mortality was 8%, and in-hospital mortality was 11.5%. The reintubation rate was 11.4%. Early infection was significantly associated with higher mortality (adjusted OR, 26.6; 95% CI, 2, 352.6; $P < .01$) when compared with the late group. At 6-month follow-up, survival probability was also significantly higher in the late infection group: 91% (95% CI, 83%, 98%) vs 75% (95% CI, 61%, 93%) in the early infection group ($P = .036$). Two patients experienced COVID-19–related rehospitalization.

CONCLUSIONS In this multicenter analysis, hospital-associated SARS-CoV-2 infection resulted in higher than expected postoperative mortality after cardiac surgery, especially in the early infection group.

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The outbreak of the novel coronavirus disease (SARS-CoV-2 infection, COVID-19) pandemic has posed a significant burden on the clinical outcomes and logistics of cardiac surgery and has contributed to an unprecedented disruption of the service worldwide, with a dramatic reduction in the number of procedures performed.[1]

Considering the variability of the incubation period and the potential inadvertent widespread contagion between patients and health workers within the same health care environment, the possibility of SARS-CoV-2 seroconversion or infections acquired in hospital settings is increasingly being reported.[2] The effect of these

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perioperative SARS-CoV-2 infections in cardiac surgery patients is poorly understood, and current data are limited to anecdotal reports or small case series with nonunivocal results.[3-9]

In this scenario, a multicenter European collaboration was organized to analyze the outcomes of patients in whom hospital-associated SARS-CoV-2 infection developed perioperatively in cardiac surgery.

The main aim of the study was to investigate the effect of SARS-CoV-2 seroconversion or infection developed in hospital environments on the perioperative and short-term mortality and morbidity after cardiac surgery. We also hypothesized that early infection (diagnosis or SARS-CoV-2 positivity detected close to the index surgery) could be associated with worse outcomes.

PATIENTS AND METHODS

STUDY DESIGN. This study was a multicenter retrospective analysis of prospectively collected data on the basis of a predefined and anonymized extraction sheet and clinical or telephone follow-up. The study period was from January 2020 to February 2021, thus including all 3 waves of the COVID-19 pandemic.

Patients from 6 European cardiac units who had no previous history of SARS-CoV-2 infection and who underwent elective, urgent, or emergency surgery were included if they had a negative molecular or antigenic COVID-19 test result 24 to 72 hours preoperatively (or were considered not infected according to the epidemiologic criteria in effect during the pandemic period in which tests were not still available) (Supplemental Material) and then had test positivity, with or without symptoms of infection, after the index procedure. Patients who underwent transcatheter procedures or salvage surgery were excluded. Center specification and inclusion or exclusion criteria are given in the Supplemental Material. SARS-CoV-2 testing was performed postoperatively as part of a routine intensive care screening measure to prevent and monitor ventilator-associated pneumonia that was implemented during the pandemic in all the centers. The aim was to include and analyze outcomes of patients who were incubating infection or having SARS-CoV-2 seroconversion within hospital environments. For this reason, patients admitted to non–cardiac surgery departments for different reasons and who had a diagnosis of cardiac surgical disease or patients who were preoperatively admitted in cardiology environments for further diagnostic workup before surgery were also included. However, patients in whom documented SARS-CoV-2 positivity developed during their pathway before surgery were excluded.

On the basis of previous studies showing an incubation period generally ranging between 3 and 7 days, with a mean incubation period estimated to be 6.4 days,[10] 2 groups were considered: (1) patients with early hospital-associated SARS-CoV-2 seroconversion and a positive molecular test result ≤7 days after surgery, with or without symptoms (early group); and (2) patients with late hospital-associated SARS-CoV-2 seroconversion whose test positivity occurred >7 days after surgery, with or without symptoms (late group).

The primary outcome was 30-day mortality. Secondary outcomes included all-cause mortality or morbidity at early follow-up and COVID-19–related hospital readmission. National electronical databases, clinic visits, and follow-up telephone calls were used to follow up patients.

STATISTICAL ANALYSIS. Distribution of data was also checked for normality before further analysis with the Shapiro-Wilk test. Continuous data are presented as mean ± SD or median and IQ). An unpaired t test or the Wilcoxon rank-sum test was used for statistical comparison. Categoric data are presented as proportions and compared using the χ^2 test.

A stepwise binary logistic regression was used to assess the effect of multiple variables on 30-day mortality. Candidate explanatory variables (n = 8) included were early or late infection, age, sex, body mass index, diabetes, left ventricular ejection fraction, baseline creatinine, and chronic obstructive pulmonary disease. Linearity assumptions were checked. The model was also tested for multicollinearity with variance inflation factor, and explanatory variables with a variance inflation factor higher than 5 were excluded because they were considered poor regression estimates. The goodness of fit was assessed with the Hosmer-Lemeshow goodness of fit test. Results were presented as adjusted ORs and 95% CIs.

Survival was analyzed using the Kaplan-Meier method, and corresponding survival curves (hazard function) were built by plotting all observations. Comparisons of survival estimates for different patient strata were performed with the log-rank statistic. A Cox proportional hazard regression model was constructed to identify factors associated with mortality, and results were presented as adjusted HRs and 95% CIs. The proportional hazard assumption was checked using the statistical test on the basis of the Schoenfeld residual for each of the covariates and global test.

Between-center mortality variability was also evaluated, and pooled mortality proportion (early vs late infection) was plotted along with the prediction interval by using a random effects model. Statistical analysis was performed with R Studio Team software)R Studio).

ETHICAL APPROVAL. Ethical approval was obtained from participating institutions through their Institutional Review Boards according to the internal policy of each center. In some instances, consent was also obtained through the chairperson of the ethics committee, who waived the need for patient consent, considering the retrospective design of the study and the anonymization of the individual patients in the database.

RESULTS

PATIENTS. From January 14, 2020 to February 22, 2021, 87 patients underwent elective, urgent, or emergency cardiac surgery among 6 European cardiac units (Anthea Hospital, Bari, Italy; Blackpool Victoria Hospital, Blackpool United Kingdom; St Bartholomew's Hospital, London, United Kingdom; Careggi University Hospital, Florence, Italy; Villa Torri Hospital, Bologna, Italy; Maria Eleonora Hospital, Palermo, Italy) and tested positive for SARSs-CoV-2 at a certain point after the index surgery. Of those patients, 30 were in the early infection group, and 57were in the late infection group.

Demographic and operative characteristics for both the groups are reported in Table 1. Mean age was 67 ± 12 years, with a 60% proportion of male patients, and a mean European System for Cardiac Operative Risk Evaluation II score (EuroSCORE II) of 3.6 ± 2.9.

More than 50% of the operations were performed as urgent surgery, with coronary artery revascularization representing 34% of the total procedures performed.

Notably, patients in the early group were at lower risk for surgery than patients in the late group (EuroSCORE II, 2.02 ± 1.4 vs 4.4 ± 3.2, respectively; $P = .03$); there were also more patients with chronic obstructive pulmonary disease and in need of urgent surgery in the late hospital-acquired condition group (Table 1).

EARLY POSTOPERATIVE OUTCOMES. Out of the entire cohort, almost 50% had symptoms of COVID-19 along with molecular test positivity.

Corticosteroids were used in approximately 30% of the patients, with a similar use rate among the early and late and groups. Therapeutic low-molecular-weight heparin was used in 35% of the patients, with a significantly higher rate in the early group (60% in the early group vs 22.8% in the late group; $P = .02$) (Table 2).

Overall, in-hospital mortality was 11.5% and 30-day mortality was 8%. The reintubation rate was 11.4%, and the total length of stay was 21.9 ± 13.8 days (Table 2).

Early infection was significantly associated with higher 30-day mortality (adjusted OR, 26.6; 95% CI, 2, 352.6; $P <$ .01) when compared with the late group (Figure 1, Supplemental Table 1). The early group also had a higher need for antibiotic therapy in comparison with the late group (50% vs 19.2%, respectively; $P = .03$).

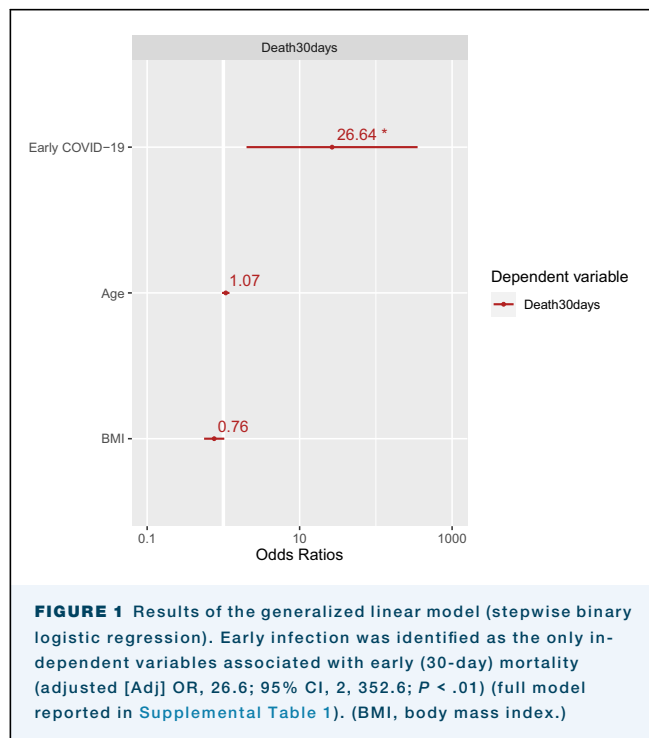**TABLE 1 Baseline Patients' Characteristics and Operative Details**

Characteristics and Operative Details	Overall N = 87	Early Positivity (≤7 d) n = 30	Late Positivity (>7 d) n = 57	P
Age, y, mean (SD)	67 (12.6)	66 (11.7)	67.5 (13.2)	.6
BMI, kg/m², mean (SD)	27.2 (4.3)	27.8 (4.5)	26.9 (4.2)	.45
Sex, male	61 (70.1)	25 (83.3)	36 (63.2)	.08
LVEF, %, mean (SD)	53.6 (9.6)	55.2 (6.6)	52.7 (10.9)	.27
Immunosuppression	5 (5.7)	1 (3.3)	4 (7)	.82
EuroSCORE II, mean (SD)	3.6 (2.9)	2.02 (1.4)	4.4 (3.2)	.03
Current smokers	10 (11.5)	1 (3.3)	9 (15.8)	.01
COPD	8 (10)	0	8 (15.7)	.06
Asthma	4 (5)	0	4 (7.8)	.94
Sleep apnea	2 (2.5)	0	2 (3.9)	.73
Previous pneumonia	1 (1.2)	0	1 (2)	.99
Diabetes	16 (20)	6 (20.7)	10 (19.6)	.99
Previous stroke	1 (1.1)	0	1 (1.8)	.37
Preoperative dialysis	1 (1.2)	1 (3.4)	0	.99
Procedure status				.03
Elective	34 (39.1)	17 (56.7)	17 (29.8)	
Urgent	45 (51.7)	13 (43.3)	32 (56.1)	
Emergency	6 (6.9)	0	6 (10.5)	
Operation type				.07
AAR isolated	7 (8)	1 (3.3)	6 (10.5)	
AAR combined	4 (4.6)	1 (3.3)	3 (5.3)	
AF ablation	1 (1.1)	0	1 (1.8)	
AVR isolated	12 (13.8)	4 (13.3)	8 (14)	
AVR combined	7 (8)	1 (3.3)	6 (10.5)	
CABG isolated	30 (34.4)	16 (53.3)	14 (24.5)	
CABG combined	2 (2.3)	2 (6.7)	0	
MVR isolated, n (%)	16 (18.4)	4 (13.3)	12 (21.1)	
MVR combined	7 (8)	1 (3.3)	6 (10.5)	
Tricuspid valve isolated	1 (1.1)	0	1 (1.8)	
Redo	5 (5.7)	2 (6.7)	3 (5.3)	.56

Data are reported as number or frequency (%) unless otherwise indicated. AAR, ascending aorta replacement; AF, atrial fibrillation; AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF, left ventricular ejection function; MVR, mitral valve repair/replacement.

TABLE 2 Postoperative Details

Details	Overall N = 87	Early Positivity (≤7 d) n = 30	Late Positivity (>7 d) n = 57	P
COVID-19 diagnosis, days from surgery, mean (SD)	14.7 (9.2)	3.5 (1.8)	19.9 (11.4)	<.01
COVID-19 symptoms	42 (48.3)	18 (60)	24 (42.1)	.35
Use of corticosteroid)	24 (27.5)	10 (33.3)	14 (24.5)	.51
Therapeutic dose heparin	31 (35.6)	18 (60)	13 (22.8)	.02
Antibiotics	26 (29.8)	15 (50)	11 (19.2)	.03
Reintubation	10 (11.4)	6 (20)	4 (7)	.11
LOS ICU, d, mean (SD)	5.1 (7.5)	4.8 (6.7)	5.2 (8)	.80
LOS, total, d, mean (SD)	21.9 (13.8)	16.8 (10.8)	25.4 (14.4)	.01
30-day mortality	7 (8)	5 (16.7)	2 (3.5)	.05
In-hospital death	10 (11.5)	6 (20)	4 (7)	.11

Data are reported as number or frequency (%) unless otherwise indicated. ICU, intensive care unit; LOS, length of stay.

FIGURE 1 Results of the generalized linear model (stepwise binary logistic regression). Early infection was identified as the only independent variables associated with early (30-day) mortality (adjusted [Adj] OR, 26.6; 95% CI, 2, 352.6; *P* < .01) (full model reported in Supplemental Table 1). (BMI, body mass index.)

Major postoperative complications according to The Society of Thoracic Surgeons and stratified by early and late groups are provided in the Supplemental Material.

FOLLOW-UP. Follow-up was 100% completed. At the short-term analysis (mean follow-up, 6.7 ± 4.7 months; median 6 months; maximum 14 months), 6-month survival probability (all causes of death) was significantly higher in the late group than in the early group: 91% (95% CI, 83%, 98%) vs 75% (95% CI, 61%, 93%) (log-rank = .036) (Figure 2).

FIGURE 2 Early (n = 30) and late (n = 57) hospital-acquired SARS-CoV-2 infection, hazard estimate, (adjusted HR, 18.72; 95% CI, 1.72,203.89; *P* < .01); 6-month survival probability (all causes of death) was significantly higher in the late than in the early infection group: 91% (95% CI, 83%, 98%) vs 75% (95% CI, 61%, 93%) (log-rank = .036).
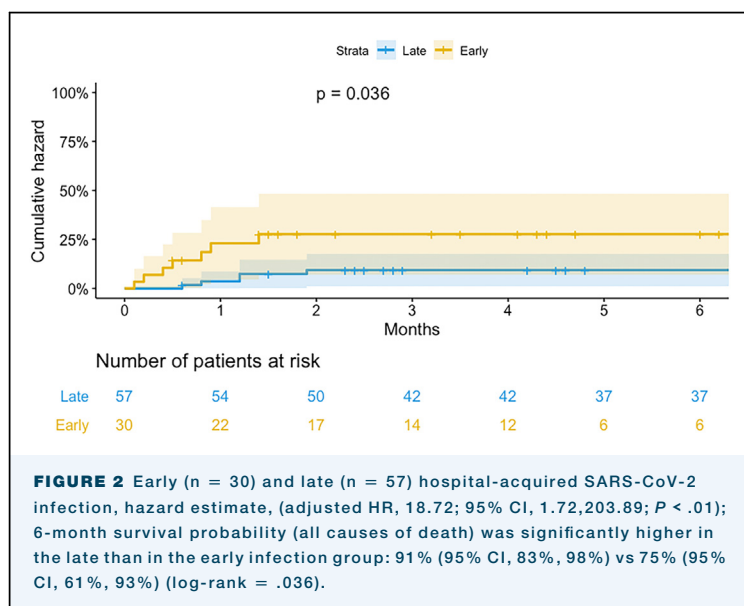
Only 2 patients experienced COVID-19-related rehospitalization. Early infection was the only independent predictor of mortality at follow-up (adjusted HR, 18.72; 95% CI, 1.72, 203.89; *P* < .01) (full model described in Supplemental Table 2, and Schoenfeld residual test given in the Supplemental Material).

BETWEEN-CENTER MORTALITY VARIABILITY FOR EARLY AND LATE HOSPITAL-ACQUIRED CONDITIONS. Figure 3 depicts the pooled mortality proportion for early infection (0.25; 95% CI, 0.12, 0.45) and late infection (0.11; (95% CI, 0.04, 0.26), as well as the between-center variability (effect size magnitude and direction), along with the mortality prediction interval for both early and late infection. Very low statistical heterogeneity was observed in the early and late infection groups and in the overall population.
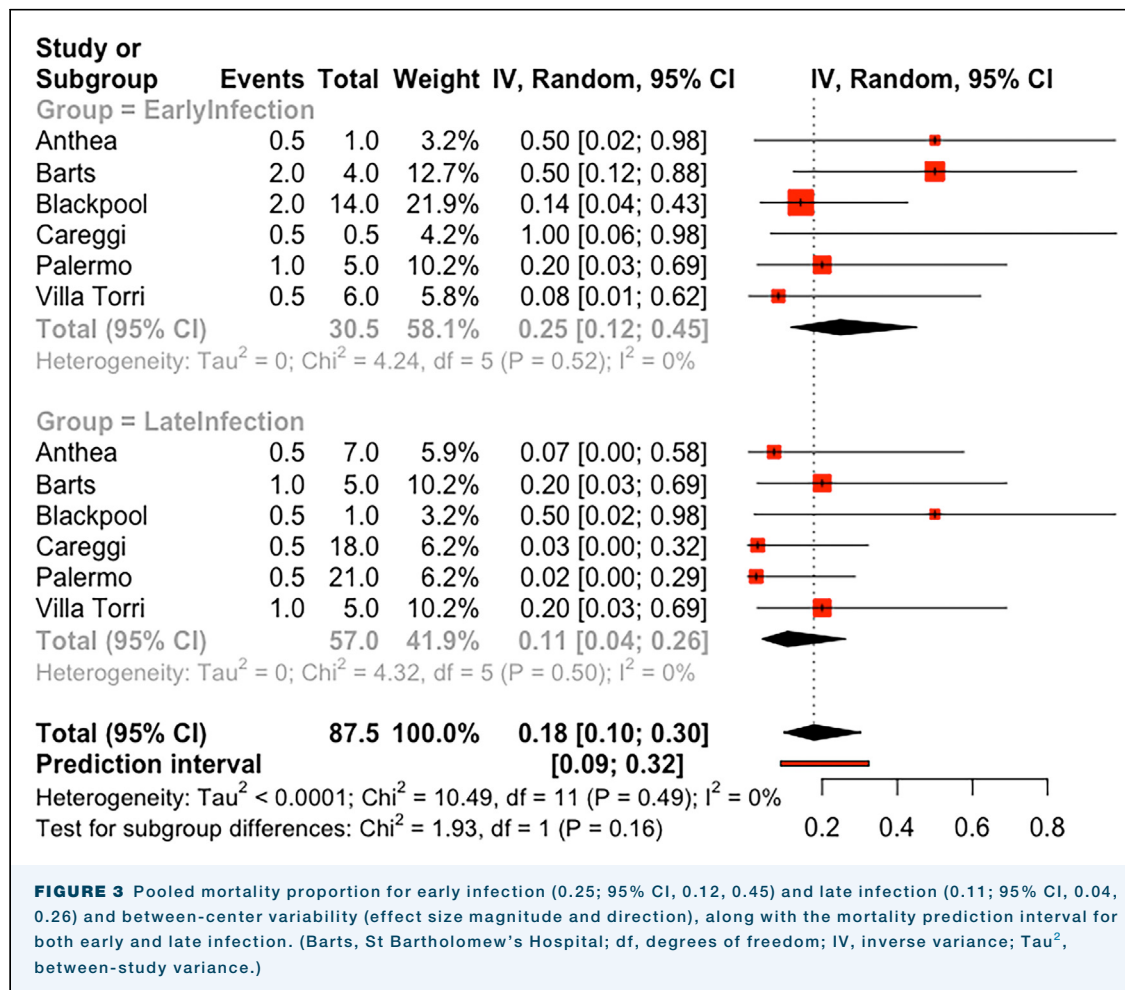
COMMENT

The biologic characteristics of SARS-CoV-2 and the known potential for viral shedding from asymptomatic individuals contributed to the increasingly reported contagion of health care workers and to the circulation of the virus within health care environments.[2]

The overwhelming demand for critical care beds, the conversion of cardiac units into COVID-19 centers,[11] and the often inadequate supply of therapeutic and personal protective equipment further augmented the risks of cross-infection between patients and health care workers,[1] thus paving the way to the potential for nosocomial infections.

In this multicenter analysis, perioperative in-hospital-associated COVID-19 or seroconversion resulted in higher than expected postoperative mortality after cardiac surgery.

Patients in whom SARS-CoV-2 positivity was detected early after surgery had a higher risk of in-hospital mortality and short-term mortality compared with patients who received their diagnosis at a later stage.

According to the inclusion criteria, and within the limitations of SARS-CoV-2 testing sensibility and specificity, we evaluated all patients with a negative SARS-CoV-2 status within the hospital before surgery in an attempt to distinguish infection derived from the community. Despite this evaluation, patients who could have potentially had undetectable seroconversion or silent infection during their in-hospital pathway to surgery could have hypothetically been included. For these reasons, the results described in this analysis can be considered as referring to incubation or seroconversion during the perioperative phase. In fact, most of the cases of early seroconversion are probably attributable to infections incubating while in the in-hospital pathway. Interestingly, the main finding of the study is that

FIGURE 3 Pooled mortality proportion for early infection (0.25; 95% CI, 0.12, 0.45) and late infection (0.11; 95% CI, 0.04, 0.26) and between-center variability (effect size magnitude and direction), along with the mortality prediction interval for both early and late infection. (Barts, St Bartholomew's Hospital; df, degrees of freedom; IV, inverse variance; Tau², between-study variance.)

seroconversion early after surgery is associated with worse clinical outcomes.

Besides the known limitations inherent in the retrospective design of this study, the results can be considered hypothesis generating. It is noteworthy that the mortality rate in seroconverted cardiothoracic patients after surgery has been reported as higher than 20%.[5,12,13] The higher than expected mortality rate in this study, independent of the time of onset, could have several explanations. First is the unusually large proportion of urgent cases in this cohort. The restricted access to health care facilities during the pandemic and the reported fear of patients to seek medical attention[4] may have contributed to the delayed presentation of many patients in more advanced stages of both coronary and valve diseases. In support of this hypothesis, a recent review of the literature showed a significant delay in the presentation of patients with myocardial infarction and a reduction in primary percutaneous coronary intervention during the COVID-19 era, when compared with historical control subjects.[14] Second, the results of the multivariable analysis

showed that early infection could be a risk factor for mortality in cardiac surgery. Considering the multicenter design of the current study, it is difficult to control for the effects of different treatment and management protocols in patients with COVID-19 across the units, and this difficulty may have had an effect on the results. Third, staffing issues and other logistic and organizational problems in intensive care or operating environments could also have played a role in the worse outcomes, but the effect of these variables is difficult to compute.

Another important finding of this study was that early seroconversion was a significant risk factor for mortality, unlike late diagnosis. This finding suggests, within the limitations of this study, that hospital-associated COVID-19 could have represented one of the main drivers of the high mortality in this cohort. Importantly, the baseline EuroSCORE was significantly lower in the early group than in the late, thereby indicating that the deleterious effect of the hospital-associated infection in these patients was not attributable to an increased preoperative risk.

Nevertheless, it is possible to hypothesize a synergistic effect of the early inflammatory syndrome normally associated with cardiopulmonary bypass[15] and the known inflammatory response associated with COVID-19.[16] The 2 intertwined inflammatory triggers may have been responsible for a cytokine storm aggravating the cardiocirculatory, respiratory, and hematologic conditions of the patients, thus leading to nefarious outcomes. The close timing of the deleterious biologic effects elicited by both cardiopulmonary bypass and COVID-19 could support the findings of the worse outcomes in the early group. Conversely, the finding that seasonal viral respiratory infections with epidemic features, such as influenza, can have an impact on cardiac surgery perioperative mortality and respiratory complications has been established in recent large retrospective analyses.[17] These data would at least indirectly corroborate our results and open the way to further research.

Nosocomial SARS-CoV-2 infections in general medical environments are rare, however, as reported in a large US registry, and the risk of transmission from health care workers to patients is generally low.[18,19] Conversely, besides their inherent limitations, the data reported here portray a different scenario that is pertinent to high-risk surgical environments and could suggest that in specialties such as cardiac surgery, additional preventive measures or stricter policies should be applied. However, wider studies focusing on different surgical specialties should be performed to confirm and validate these hypotheses.

STUDY LIMITATIONS. A major limitation of this study is related to the potential inaccuracy of the tests used to detect SARS-CoV-2 before surgery. Even though in the majority of the patients in the cohort a negative SARS-CoV-2 status was confirmed before the procedure by molecular assay, it is possible that false negative test results led to the inclusion of patients with a still silent or undetectable community-acquired SARS-CoV-2 infection, rather than a true hospital-acquired infection. However, considering the viral incubation times and the sensitivity of the current available tests, we could reliably speculate that the late infection group, in which infection was detected >7 days after the index procedure, was populated by patients with actual hospital-associated infections.

Additionally, we were unable to delineate the full pathway of the hospitalized patients before their operation for all the participating centers to individuate the specific moment of potential infection. The heterogeneity of both the type of hospital environments and department in which patients transited and their relative time durations surely is also considered a major confounder. Moreover, despite infection containment, it was difficult to control for heterogeneity in the time from culture diagnosis to surgery, and this could have influenced definitions of hospital-associated infections.

Importantly, given the multicenter design of this study and the differences in preventive policies adopted by each separate country in the world during the pandemic, the protocols for patient management and infection control (also in the postoperative period) could have varied, thus implying different impacts in outcomes. This variability could have constituted another significant bias in interpretation of the results.

In addition, the data here reported belong to a timeframe that includes different COVID-19 waves of infections with significant differences in the knowledge and response of health care environments to the pandemic. Specifically, this study was conducted during a timeframe where vaccinations were not available. Moreover, in that period the different viral variants (eg, Omicron, Delta) were not known, and identification techniques were not readily available.

The correlation between the severity of symptoms and clinical outcomes was not explored, and we were unable to evaluate the impact of standardized COVID-19 treatment protocols (eg, heparin, steroids, ventilation) on the hospital course, considering the relatively small numbers and the risk of model overfitting when introducing several perioperative variables.

Details of mechanical ventilation protocols and use of renal replacement therapy were not included. Because the study captures very early stages of the pandemic, no targeted antiviral agents were used across the units.

In the attempt to balance the risk of overfitting, the regression model in this study included limited variables. It is plausible that many other well-known factors recognized in the literature to influence the prognosis of cardiac surgery patients could have been included to improve reliability of the independent prognostic role of the variables. A larger sample size could have provided scope to include more variables and still obtain a meaningful analysis.

In view of the foregoing limitations, we could not demonstrate an actual pathophysiologic link allowing us to consider these cases definitely as hospital-acquired infections. However, in light of the selection criteria and the timeframes of diagnosis, we could reliably associate these infections with hospital environments, thereby adding new reflections on the significance of SARS-CoV-2 infections in cardiac surgical environments and new knowledge to the mosaic of the COVID-19 pandemic. The advent and widespread use of SARS-CoV-2 vaccinations could exert a different impact on the patients' immune response, but this study was performed during the prevaccination era. Understanding of these aspects and mechanisms would merit further ad hoc investigation.

CONCLUSION. SARS-CoV-2 infection (COVID-19) has caused an unprecedented disruption in cardiac surgery services. The possibility of hospital-associated infection surely represents a concern with potentially impactful consequences. This study evaluated this problem, and although the data should be interpreted in light of the previously mentioned biases, the results suggest the hypothesis that SARS-CoV-2 infections diagnosed in the hospital in the immediate perioperative period can lead to worse clinical outcomes in cardiac surgery. Conversely, infections that developed at a later stage during the hospital stay had a more benign course. The study reinforces the importance of implementing measures to prevent postoperative SARS-CoV-2 infection. The timing from the index procedure to SARS-CoV-2 positivity seems important from a prognostic standpoint. Further clinical studies on hospital-acquired SARS-CoV-2 infection (COVID-19) are warranted to confirm this hypothesis.

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