

# Is perioperative COVID-19 really associated with worse surgical outcomes? A nationwide COVIDSurg propensity-matched analysis

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<b>BACKGROUND:</b>	Patients undergoing surgery with perioperative COVID-19 are suggested to have worse outcomes, but whether this is COVID-related or due to selection bias remains unclear. We aimed to compare the postoperative outcomes of patients with and without perioperative COVID-19.
<b>METHODS:</b>	Patients with perioperative COVID-19 diagnosed within 7 days before or 30 days after surgery between February and July 2020 from 68 US hospitals in COVIDSurg, an international multicenter database, were 1:1 propensity score matched to patients without COVID-19 undergoing similar procedures in the 2012 American College of Surgeons National Surgical Quality Improvement Program database. The matching criteria included demographics (e.g., age, sex), comorbidities (e.g., diabetes, chronic obstructive pulmonary disease, chronic kidney disease), and operation characteristics (e.g., type, urgency, complexity). The primary outcome was 30-day hospital mortality. Secondary outcomes included hospital length of stay and 13 postoperative complications (e.g., pneumonia, renal failure, surgical site infection).
<b>RESULTS:</b>	A total of 97,936 patients were included, 1,054 with and 96,882 without COVID-19. Prematching, COVID-19 patients more often underwent emergency surgery (76.1% vs. 10.3%, $p < 0.001$ ). A total of 843 COVID-19 and 843 non-COVID-19 patients were successfully matched based on demographics, comorbidities, and operative characteristics. Postmatching, COVID-19 patients had a higher mortality (12.0% vs. 8.1%, $p = 0.007$ ), longer length of stay (6 [2–15] vs. 5 [1–12] days), and higher rates of acute renal failure (19.3% vs. 3.0%, $p < 0.001$ ), sepsis (13.5% vs. 9.0%, $p = 0.003$ ), and septic shock (11.8% vs. 6.0%, $p < 0.001$ ). They also had higher rates of thromboembolic complications such as deep vein thrombosis (4.4% vs. 1.5%, $p < 0.001$ ) and pulmonary embolism (2.5% vs. 0.4%, $p < 0.001$ ) but lower rates of bleeding (11.6% vs. 26.1%, $p < 0.001$ ).
<b>CONCLUSION:</b>	Patients undergoing surgery with perioperative COVID-19 have higher rates of 30-day mortality and postoperative complications, especially thromboembolic, compared with similar patients without COVID-19 undergoing similar surgeries. Such information is crucial for the complex surgical decision making and counseling of these patients. ( <i>J Trauma Acute Care Surg.</i> 2023;94: 513–524. Copyright © 2023 American Association for the Surgery of Trauma.)
<b>LEVEL OF EVIDENCE:</b>	Prognostic and Epidemiologic; Level IV.
<b>KEY WORDS:</b>	COVID-19; COVIDSurg; mortality; postoperative complications.

The COVID-19 pandemic has caused significant disruptions in health care systems globally. Reallocation of vital medical resources to provide critical care to a rapidly increasing number of patients afflicted by SARS-CoV-2 infection resulted in many surgeries getting canceled or postponed.<sup>1</sup> However, emergency surgery and some elective surgery (e.g., cancer surgery) services

continued to operate, providing care for patients whose surgical disease required immediate or timely intervention.<sup>2</sup> Perioperative infection with SARS-CoV-2 could increase the risk of adverse outcomes due to a synergistic effect of dysregulated systemic inflammation and hypercoagulability associated with SARS-CoV-2.<sup>3,4</sup> In addition, a broad spectrum of concomitant pulmonary and extrapulmonary manifestations of SARS-CoV-2 in surgical patients could make them particularly prone to serious postoperative complications.<sup>5–8</sup>

Earlier reports of surgical patients infected with SARS-CoV-2 revealed high postoperative mortality and morbidity rates.<sup>2,9–11</sup> However, these results should be cautiously interpreted, as these studies did not have control patients without SARS-CoV-2 infection to estimate the additive effect of SARS-CoV-2 infection on postoperative outcomes. Specifically, many suggest that the majority of the patients with SARS-CoV-2 infection that underwent surgery had a larger number of comorbid conditions and a poorer clinical condition at presentation. It remained unclear whether the increased morbidity and mortality in surgical patients with SARS-CoV-2 infection are attributable to the viral disease and its surrounding system challenges or are a selection bias of whom we operated on during the pandemic. To provide careful

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benchmarking, several recent studies compared risk-adjusted postoperative outcomes between patients with and without SARS-CoV-2 infection during the pandemic and pre-pandemic periods.<sup>12–14</sup> These studies suggested that the presence of SARS-CoV-2 in the perioperative period may be associated with worse surgical outcomes, although the data remains nondefinite. Despite the current guidelines regarding the timing of elective surgery following SARS-CoV-2 infection,<sup>15</sup> many surgeons worldwide continue to face the challenging dilemma of whether to pursue surgery or opt for often less effective but potentially safer nonoperative alternatives in emergency surgery patients with SARS-CoV-2 and to balance safety and negative impact of delayed elective surgery.<sup>10,16,17</sup>

To further address selection bias associated with the COVID-19 pandemic, our study aimed to compare postoperative mortality and major complications between patients with perioperative SARS-CoV-2 infection and propensity score–matched historical controls without SARS-CoV-2 infection undergoing elective and emergency surgeries of similar complexity.

## PATIENTS AND METHODS

### Study Population and Setting

The data for this study were collected as a part of the international multicenter COVIDSurg Collaborative. We included all patients 17 years or older undergoing any type of surgery with a perioperative SARS-CoV-2 infection (diagnosed within 7 days before or 30 days after surgery) in 1 of the 68 US hospitals between February and July 2020. Only US patients from the COVIDSurg database were used to minimize any country-level variation of care, as they were propensity score matched to patients from the 2012 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) registry. To maximize matching success, the year 2012 was chosen because of the availability of a broader spectrum of variables that were omitted in the subsequent years of NSQIP registries but were present in the COVIDSurg database (e.g., history of myocardial infarction, history of transient ischemic attack or stroke, peripheral vascular disease, coronary artery disease).

The ACS-NSQIP methodology of systematic data collection has been well established and validated.<sup>18,19</sup> The NSQIP Participant Use Data File details the full list of variables provided by the NSQIP.<sup>20</sup> The following variables were used in the current study to perform propensity score matching: demographics (age, sex), body mass index (BMI), American Society of Anesthesiologists (ASA) classification, comorbidities (e.g., diabetes, chronic obstructive pulmonary disease, cancer), the preoperative requirement of ventilator-assisted respiration, and hemoglobin and white blood cell count. In addition, the NSQIP variables of “EMERGENCY” or “ELECTSURG” were used to categorize a principal operative procedure as emergent or elective, respectively. All operative procedures were further categorized based on a surgical specialty defined by the NSQIP variable “SURGSPEC” (e.g., general surgery, orthopedics, vascular).

### Study Variables and Outcomes

#### COVIDSurg Database

Patient characteristics included age, sex, BMI, and ASA physical status classification grade. Comorbidity variables included the following: smoking status, cancer, chronic kidney disease,

chronic obstructive pulmonary disease, congestive heart failure, diabetes, coronary artery disease, peripheral vascular disease, history of stroke, or transient ischemic attack. Operative variables included urgency of surgery (elective vs. emergency surgery), the principal anesthesia mode (local, regional, and general), a primary procedure performed (grouped by surgical specialty), and grade of surgery (minor vs. major) based on the Bupa schedule of procedures.

Patients with SARS-CoV-2 infection were diagnosed by one of the following criteria: (1) laboratory confirmation of SARS-CoV-2 infection based on the presence of viral RNA using quantitative reverse-transcription polymerase chain reaction, (2) pathognomonic radiographic findings based on chest computed tomography or chest x-ray, or (3) clinical diagnosis made by a treatment team following constellation of symptoms that were consistent with SARS-CoV-2 infection (cough, dyspnea, fever, and myalgia). The timing of SARS-CoV-2 infection was categorized as preoperative or postoperative. A corresponding local principal investigator of each participating hospital was asked to verify the completeness of the records and that all eligible patients were appropriately entered into the database.

### Assigning a Grade of Surgery Complexity to CPT Codes

The COVIDSurg Database includes a variable defining the complexity of each operation as “minor” or “major”, based on the Bupa schedule of procedures.<sup>21</sup> The NSQIP database defines the principal and most complex operative procedure among all the procedures performed during the index hospitalization, with the “PRNCPTX” variable, using Current Procedural Terminology (CPT) codes. Still, a classification of operative complexity is not readily available. To measure (and match for) the equivalent grade (minor vs. major) of surgery in NSQIP, the following methodology was applied: (1) we identified all CPT codes that correspond to operative procedures listed in the COVIDSurg database, and (2) we linked these CPT codes with the complexity value (minor vs. major) of the corresponding procedure in the COVIDSurg database. The list of CPT codes corresponding to surgical procedures from the COVIDSurg Database and the associated procedural complexity values is provided in Supplementary Table 1S, <http://links.lww.com/TA/C844>.

### Outcomes

The primary outcome was 30-day mortality. Secondary outcomes were hospital length of stay (LOS) and 13 postoperative complications such as pneumonia, sepsis, septic shock, acute kidney injury, myocardial infarction, stroke or transient ischemic attack, cardiac arrest requiring cardiopulmonary resuscitation, thromboembolic outcomes (deep vein thrombosis, pulmonary embolism), surgical site infections (SSIs) (superficial, deep and organ space SSIs), and bleeding necessitating transfusion.

### Statistical Analyses

Descriptive statistics were computed for patient characteristics and postoperative outcomes. Categorical and continuous variables were compared using the  $\chi^2$  test and Wilcoxon rank-sum test, respectively. Patients with SARS-CoV-2 infection were propensity score matched (1:1) to the nearest neighbor without SARS-CoV-2, with a caliper width of 0.2 of the standard deviation of the probit of the propensity score.<sup>22</sup> Propensity scores

for each patient were derived from a multivariable logistic regression model based on patient characteristics (age, sex, BMI, ASA physical status), SARS-CoV-2 exposure, comorbidities (smoking status, cancer, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, diabetes, coronary artery disease, peripheral vascular disease, history of stroke or transient ischemic attack), preoperative invasive ventilation, hemoglobin and white blood cell count, anesthesia type, urgency (emergent vs. elective), and the complexity of surgery (major vs. minor). To assess the overall distribution of propensity score before and after matching, kernel densities were plotted. Matched patients were compared using the  $\chi^2$  test for categorical variables and Wilcoxon rank-sum test for continuous outcomes.

Patients who had missing data related to inclusion and exclusion criteria, assigned grade of surgery, and mortality were excluded. The remaining missing data were handled using multiple imputations by chained equations, computing 10 imputations for each missing data point. Descriptive statistics were calculated based on unimputed data.

Four sensitivity analyses were performed, each with a new and separate propensity score match. The first one included only patients with SARS-CoV-2 infection with preoperative respiratory findings (defined by the presence of dyspnea, cough, hemoptysis, or sputum) and/or radiologic evidence associated with SARS-CoV2 infection. The second sensitivity analysis included only asymptomatic patients with SARS-CoV-2 infection. The third sensitivity analysis only included patients who underwent emergency surgery. The last sensitivity analysis included only patients who underwent elective surgery. Categorical variables and outcomes were reported as the number of patients (percentage), whereas continuous variables and outcomes were reported as median (interquartile range [IQR]). Clinical outcomes were adjusted for multiple comparisons using the Benjamini-Hochberg method to control for false discovery rate.<sup>23</sup> The level of statistical significance was set at a two-sided  $p$  value of  $<0.05$ . All analyses were performed using STATA v.17 (StataCorp 2021, College Station, TX).

## Ethical Oversight and Reporting

This study was submitted to and exempted from approval by the local institutional review board. The results of this study are reported following the Strengthening the Reporting of Observational Studies in Epidemiology and Reporting of Studies Conducted Using Observational Routinely Collected Health Data recommendations (Supplementary Data 1, <http://links.lww.com/TA/C843>).<sup>24,25</sup>

## RESULTS

### Patient Characteristics Pre-Matching

We identified 1,054 patients with SARS-CoV-2 infection from the COVIDSurg database and 96,882 patients from the 2012 NSQIP database undergoing similar surgeries based on the corresponding CPT codes and assigned grade of surgery definition. Baseline demographic and clinical characteristics of the patients before propensity score matching are shown in Table 1. The two cohorts of patients with and without perioperative SARS-CoV-2 infection were significantly different in baseline characteristics. Patients with SARS-CoV-2 infection more often

underwent emergency surgery (76.1% vs. 10.3%,  $p < 0.001$ ) but less often underwent complex operations (54.7% vs. 73.4%,  $p < 0.001$ ).

Among patients with SARS-CoV-2 infection, 569 of 1,054 patients (53.98%) were diagnosed preoperatively, whereas 395 patients (37.48%) were diagnosed postoperatively; 90 patients (8.54%) had a missing time of diagnosis. Among patients with a preoperative diagnosis of SARS-CoV-2 infection, 372 patients (65.38%) did not have any constellation of symptoms associated with SARS-CoV-2 infection.

### Patient Characteristics Post-Matching

After 1:1 propensity score matching, a total of 843 SARS-CoV-2 positive and 843 SARS-CoV-2 negative patients were included in the analysis (Table 2). In brief, the two cohorts were similar in all preoperative characteristics, including demographics, ASA, comorbidities, grade of surgery, and type of surgery. Figure 1 shows the prematching and postmatching kernel density plots, demonstrating a similar distribution of propensity scores postmatching.

### Outcomes of Matched COVID-19 Versus Non-COVID-19 Patients

After propensity score matching, patients with SARS-CoV-2 infection had a higher rate of 30-day mortality (12.0% vs. 8.1%,  $p = 0.012$ ) and longer hospital LOS (median [IQR], 6 [2–15] vs. 5 [1–12] days;  $p = 0.035$ ) compared with patients without SARS-CoV-2 (Fig. 2 and Table 3). In addition, patients with perioperative SARS-CoV-2 infection had higher rates of acute renal failure (19.3% vs. 3.0%,  $p < 0.001$ ), pneumonia (24.2% vs. 4.6%,  $p < 0.001$ ), sepsis (13.5% vs. 9.0%,  $p = 0.006$ ), septic shock (11.8% vs. 6.0%,  $p < 0.001$ ), wound dehiscence (2.1% vs. 0.7,  $p = 0.019$ ), and cardiac arrest (4.4% vs. 1.4%,  $p < 0.001$ ) but similar rates of superficial/deep (4.6% vs. 3.8,  $p = 0.4$ ) and organ space SSIs (1.4% vs. 2.3,  $p = 0.214$ ). The presence of SARS-CoV-2 in the perioperative period was also associated with higher rates of postoperative thromboembolic complications such as deep vein thrombosis (4.4% vs. 1.5%,  $p < 0.001$ ), pulmonary embolism (2.5% vs. 0.4%,  $p < 0.001$ ), and stroke (1.8% vs. 0.5%,  $p = 0.017$ ) but lower rate of bleeding requiring transfusions (11.6% vs. 26.1%,  $p < 0.001$ ).

### Sensitivity Analyses: Patients With and Without Preoperative Respiratory/Radiologic Findings of SARS-CoV-2 Infection

In a sensitivity analysis including only patients with preoperative respiratory or radiologic findings, 408 patients with SARS-CoV-2 infection and 408 patients without SARS-CoV-2 infection were de novo propensity score matched in a similar fashion (Supplementary Table 2S, <http://links.lww.com/TA/C844>). The overall 30-day mortality rate in symptomatic patients with SARS-CoV2 infection was significantly higher than in a matched cohort of patients without SARS-CoV-2 infection (19.1% vs. 11.3%,  $p = 0.004$ ). Similar to the overall cohort, the preoperative diagnosis of SARS-CoV2 infection, along with the presence of respiratory or radiologic findings of COVID-19 disease, was associated with a longer hospital LOS (median [IQR], 9 [4–23] vs. 8 [3–15] days;  $p = 0.035$ ) and higher rates of eight postoperative complications shown in Figure 3A and

**TABLE 1.** Demographic and Clinical Characteristics of Patients Without SARS-CoV-2 Infection (NSQIP) and Patients With SARS-CoV-2 Infection (COVIDSurg)

Characteristics	Patients Without SARS-CoV-2 (n = 96,882)	Patients With SARS-CoV-2 (n = 1,054)	p
Age group, n (%)			0.62
17–49 y	32,608 (33.7)	374 (35.5)	
50–59 y	21,327 (22.0)	226 (21.4)	
60–69 y	21,556 (22.2)	217 (20.6)	
70–79 y	14,341 (14.8)	157 (14.9)	
80+ y	7,050 (7.3)	80 (7.6)	
Sex, n (%)			<0.001
Female	53,951 (55.7)	454 (43.1)	
Male	42,931 (44.3)	600 (56.9)	
BMI, n (%)			0.096
Underweight	1,486 (1.5)	23 (2.4)	
Normal	23,232 (24.0)	247 (25.4)	
Overweight	30,584 (31.6)	288 (29.7)	
Obese	41,580 (42.9)	413 (42.5)	
ASA status, n (%)			<0.001
1	10,170 (10.5)	41 (3.9)	
2	46,805 (48.3)	214 (20.3)	
3	35,229 (36.4)	450 (42.7)	
4	4,542 (4.7)	322 (30.6)	
5	136 (0.1)	27 (2.6)	
Comorbidities, n (%)			
Current smoker	17,258 (17.8)	98 (9.3)	<0.001
Cancer	1,888 (1.9)	88 (8.3)	<0.001
Chronic kidney disease	778 (0.8)	184 (17.5)	<0.001
COPD	3,874 (4.0)	61 (5.8)	0.003
Congestive heart failure	487 (0.5)	102 (9.7)	<0.001
Diabetes	13,659 (14.1)	380 (36.1)	<0.001
Coronary artery disease	967 (1.0)	83 (7.9)	<0.001
Peripheral vascular disease	2,033 (2.1)	106 (10.1)	<0.001
Stroke or transient ischemic attack	1,902 (2.0)	87 (8.3)	<0.001
Preoperative invasive ventilation, n (%)	312 (0.3)	165 (15.7)	<0.001
Hemoglobin, median (IQR), g/L	13.3 (12.3–14.3)	11.1 (8.7–13.1)	<0.001
WBC count, median (IQR), $\times 10^9/L$	7.1 (5.8–9)	9 (6.6–13.2)	<0.001
Urgency of surgery, n (%)			<0.001
Elective	86,890 (89.7)	252 (23.9)	
Emergency	9,992 (10.3)	802 (76.1)	
Anesthesia, n (%)			0.68
Local	40 (4.7)	43 (5.1)	
Regional	54 (6.4)	46 (5.5)	
General	749 (88.8)	754 (89.4)	
Grade of surgery, n (%)			<0.001
Minor	25,811 (26.6)	477 (45.3)	
Major	71,071 (73.4)	577 (54.7)	
Surgical specialty, n (%)			<0.001
Neurosurgery	4,972 (5.1)	82 (7.8)	
General surgery	53,170 (54.9)	355 (33.7)	
Thoracic	984 (1.0)	22 (2.1)	
Plastics	1,571 (1.6)	5 (0.5)	
Gynecology	7,466 (7.7)	59 (5.6)	

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TABLE 1. (Continued)

Characteristics	Patients Without SARS-CoV-2 (n = 96,882)	Patients With SARS-CoV-2 (n = 1,054)	p
ENT surgery	877 (0.9)	171 (16.2)	
Cardiac surgery	1,388 (1.4)	24 (2.3)	
Urology	5,047 (5.2)	65 (6.2)	
Orthopedics	17,946 (18.5)	105 (10.0)	
Vascular surgery	3,461 (3.6)	153 (14.5)	

COPD, chronic obstructive pulmonary disease; ENT, ear, nose, and throat surgery; WBC, white blood cell.

Supplementary Table 3S, <http://links.lww.com/TA/C844>. In contrast, the rate of postoperative bleeding events that required transfusions was still higher in patients without SARS-CoV-2 infection.

An additional sensitivity analysis considering only asymptomatic patients with SARS-CoV-2 infection resulted in 458 patients with SARS-CoV-2 infection propensity score matched with 458 patients without SARS-CoV-2 infection (Supplementary Table 4S, <http://links.lww.com/TA/C844>). Overall, 30-day mortality among asymptomatic patients was still significantly higher when compared with matched patients without SARS-CoV-2 infection (6.6% vs. 3.1%,  $p = 0.033$ ). Similarly, when compared with patients without SARS-CoV-2 infection, the rates of acute kidney injury, cardiac arrest, pneumonia, and septic shock were higher in patients with SARS-CoV-2 infection despite the absence of preoperative symptoms and radiologic findings associated with COVID-19 infection upon admission (Fig. 3B and Supplementary Table 5S, <http://links.lww.com/TA/C844>).

### Sensitivity Analyses: Emergency Versus Elective Surgery

In the sensitivity analysis of patients who underwent emergency surgery, patients with SARS-CoV-2 infection had a significantly higher 30-day mortality rate (13.9% vs. 9.0%,  $p = 0.012$ ) compared with propensity score–matched patients undergoing emergency surgeries of similar complexity but without SARS-CoV-2 infection (Supplementary Table 6S, <http://links.lww.com/TA/C844>). Despite no significant difference in hospital LOS between the two cohorts of patients undergoing emergency surgeries (7 days [IQR, 2–17 days] vs. 6 days [IQR, 3–12.5 days],  $p = 0.18$ ), perioperative diagnosis of SARS-CoV-2 infection was associated with higher rates of pneumonia (23.7% vs. 4.6%,  $p < 0.001$ ), septic shock (12.9% vs. 7.0%,  $p < 0.001$ ), acute kidney injury (21.7% vs. 5.7%,  $p < 0.001$ ), cardiac arrest (4.2% vs. 1.5%,  $p = 0.009$ ), deep venous thrombosis (5.1% vs. 1.6%,  $p < 0.001$ ) and pulmonary embolism (2.8% vs. 0.2%,  $p < 0.001$ ), and SSIs (6.0% vs. 2.8%,  $p = 0.009$ ) (Fig. 3C and Supplementary Table 7S, <http://links.lww.com/TA/C844>). In contrast, patients without SARS-CoV-2 infection experienced a higher rate of postoperative bleeding that required transfusion (25.3% vs. 13.6%,  $p < 0.001$ ).

In the sensitivity analysis, including only patients undergoing elective surgery, patients with SARS-CoV-2 infection were similarly matched to patients without SARS-CoV-2 infection (Supplementary Table 8S, <http://links.lww.com/TA/C844>). Figure 3D and Supplementary Table 9S, <http://links.lww.com/TA/C844>,

show the postoperative outcomes of these two cohorts of patients. Perioperative SARS-CoV-2 infection in elective procedures was not associated with a statistically different 30-day mortality rate (6.3% vs. 1.9%,  $p = 0.06$ ) and hospital LOS (3 days [IQR, 1–9 days] vs. 2 days [IQR, 0–5 days];  $p = 0.06$ ). In contrast, patients undergoing elective surgeries with perioperative SARS-CoV-2 infection had higher rates of pneumonia (22.3% vs. 1.0%,  $p < 0.001$ ), sepsis (7.3% vs. 1.5%,  $p = 0.014$ ), septic shock (6.8% vs. 0.5%,  $p < 0.001$ ), acute kidney injury (13.1% vs. 2.4%,  $p < 0.001$ ), and deep venous thrombosis (2.9% vs. 0.0%,  $p = 0.04$ ). All missing data values were imputed using multiple imputation by chained equations (Supplementary Table 10S, <http://links.lww.com/TA/C844>).

### DISCUSSION

This nationwide study compares the rates of mortality and 13 postoperative complications between patients with SARS-CoV-2 infection from the COVIDSurg database and propensity score matched non-SARS-CoV-2 patients from the ACS-NSQIP database undergoing surgeries of similar urgency and complexity. Our study found that perioperative SARS-CoV-2 infection is associated with a significantly higher rate of 30-day mortality, longer hospital LOS, and a higher risk of severe postoperative complications when compared with matched patients without SARS-CoV-2 infection. The increased risk was observed even in asymptomatic patients who did not exhibit signs and symptoms of SARS-CoV-2.

While comparing patients with SARS-CoV-2 infection with the prepandemic historical controls, our findings provide further insight into the combined effect of SARS-CoV-2 infection and the impact caused by stressed health care systems on surgical patients operated during the first wave of the COVID-19 pandemic in the United States. Lal et al.<sup>26</sup> used the Veterans Affairs database and similarly reported increased rates of pulmonary, septic, and ischemic complications but did not find increased 30-day mortality in propensity score–matched patients with SARS-CoV-2 infection. In contrast, a more recent study using the same database but examining midterm surgical outcomes in matched patients with and without SARS-CoV-2 found a significantly higher risk of mortality, pulmonary, thrombotic, and septic complications in patients, particularly during the first 4 weeks following SARS-CoV-2 infection.<sup>13</sup> However, despite the decent sample size and the use of propensity score matching, both studies have limited generalizability because of the inherent patient characteristics specific to the Veterans Affairs population. Nevertheless, the elevated risk of postoperative

**TABLE 2.** Postmatching Demographic and Clinical Characteristics of Patients Without SARS-CoV-2 Infection (NSQIP) and Patients With SARS-CoV-2 Infection (COVIDSurg)

Characteristics	Patients Without SARS-CoV-2 (n = 843)	Patients With SARS-CoV-2 (n = 843)	p
Age group, n (%)			0.54
17–49 y	298 (35.3)	317 (37.6)	
50–59 y	177 (21.0)	181 (21.5)	
60–69 y	169 (20.0)	165 (19.6)	
70–79 y	115 (13.6)	115 (13.6)	
80+ y	84 (10.0)	65 (7.7)	
Sex, n (%)			1
Female	378 (44.8)	378 (44.8)	
Male	465 (55.2)	465 (55.2)	
BMI, n (%)			0.83
Underweight	18 (2.1)	20 (2.6)	
Normal	234 (27.8)	204 (26.3)	
Overweight	246 (29.2)	224 (28.8)	
Obese	345 (40.9)	329 (42.3)	
ASA status, n (%)			0.38
1	53 (6.3)	41 (4.9)	
2	167 (19.8)	191 (22.7)	
3	369 (43.8)	375 (44.5)	
4	223 (26.5)	211 (25.0)	
5	31 (3.7)	25 (3.0)	
Comorbidities, n (%)			
Current smoker	86 (10.2)	83 (9.8)	0.81
Cancer	80 (9.5)	71 (8.4)	0.44
Chronic kidney disease	115 (13.6)	106 (12.6)	0.52
COPD	51 (6.0)	42 (5.0)	0.34
Congestive heart failure	71 (8.4)	54 (6.4)	0.11
Diabetes	263 (31.2)	270 (32.0)	0.71
Coronary artery disease	55 (6.5)	53 (6.3)	0.84
Peripheral vascular disease	77 (9.1)	76 (9.0)	0.93
Stroke or transient ischemic attack	63 (7.5)	55 (6.5)	0.45
Preoperative invasive ventilation, n (%)	78 (9.3%)	78 (9.3%)	1
Hemoglobin, median (IQR), g/L	11.7 (9.9–13.3)	11.7 (9.25–13.4)	0.7
WBC count, median (IQR), $\times 10^9/L$	9.4 (6.9–13.1)	8.8 (6.4–12.9)	0.054
Urgency of surgery, n (%)			0.17
Elective	213 (25.3)	238 (28.2)	
Emergency	630 (74.7)	605 (71.8)	
Anesthesia, n (%)			0.68
Local	40 (4.7)	43 (5.1)	
Regional	54 (6.4)	46 (5.5)	
General	749 (88.8)	754 (89.4)	
Grade of surgery, n (%)			0.92
Minor	310 (36.8)	312 (37.0)	
Major	533 (63.2)	531 (63.0)	
Surgical specialty, n (%)			0.6
Neurosurgery	65 (7.7)	76 (9.0)	
General surgery	377 (44.7)	346 (41.0)	
Thoracic	22 (2.6)	20 (2.4)	
Plastics	4 (0.5)	5 (0.6)	
Gynecology	42 (5.0)	54 (6.4)	

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TABLE 2. (Continued)

Characteristics	Patients Without SARS-CoV-2 (n = 843)	Patients With SARS-CoV-2 (n = 843)	p
ENT surgery	42 (5.0)	53 (6.3)	
Cardiac surgery	29 (3.4)	23 (2.7)	
Urology	39 (4.6)	50 (5.9)	
Orthopedics	104 (12.3)	98 (11.6)	
Vascular surgery	119 (14.1)	118 (14.0)	

COPD, chronic obstructive pulmonary disease; ENT, ear, nose, and throat surgery; WBC, white blood cell.

mortality and morbidity also supports the findings from another large international study, which reported increased rates of 30-day mortality up to 7 weeks following SARS-CoV-2 infection.<sup>14</sup> Although data collection was done in October 2020, the results provided early evidence for the subsequent recommendation regarding the timing of surgery in unvaccinated patients. To address this gap, a recent study examining the role of COVID-19 vaccination in elective surgery did not find an increased risk of perioperative complications in vaccinated patients compared with prepandemic controls.<sup>27</sup>

In our study, the SARS-CoV-2 positive cohort consisted of both symptomatic and asymptomatic patients. Both groups had a significantly higher 30-day mortality when compared as separate cohorts with matched non-SARS-CoV-2 patients in the sensitivity analyses. Early studies reported no difference in mortality among symptomatic and asymptomatic SARS-CoV-2-infected patients, which might be attributed to limited testing capacity at the beginning of the pandemic.<sup>28,29</sup> In contrast, another study focusing on patients undergoing select emergency general surgery procedures found that the higher risk of 30-day mortality and pulmonary complications is only notable in patients who had preoperative respiratory clinical or radiological findings of SARS-CoV-2 infection.<sup>30</sup>

One particular finding of our study also worth discussing is the markedly higher proportion of postoperative thromboembolic complications among patients with perioperative SARS-CoV-2 infection compared with matched controls. This is consistent with early evidence suggesting that an inflammatory coagulopathy plays a role in the development of thromboembolic events in SARS-CoV-2-infected patients.<sup>4,31</sup> Perioperative or recent SARS-CoV-2 infection was similarly found to be an independent risk factor for postoperative venous thromboembolism in a recent large, international COVIDSurg study.<sup>32</sup> As interestingly, the matched cohort of patients without SARS-CoV-2 infection in

our study even experienced a higher rate of postoperative bleeding that required transfusion compared with patients with SARS-CoV-2 infection, a finding that might also indicate the potential hypercoagulable state associated with COVID-19.<sup>33,34</sup>

The majority of our SARS-CoV-2 patients underwent emergent operations, which was not surprising given that many academic and government organizations recommended limiting or postponing elective surgeries during pandemic peaks.<sup>2,35,36</sup> Considering that most patients in the NSQIP registry had elective procedures, we performed two additional sensitivity analyses comparing separately elective cases in SARS-CoV-2-positive patients with historical controls undergoing surgeries of similar complexity. Patients with SARS-CoV-2 who had elective procedures compared with historical controls had a tendency toward a higher rate of 30-day mortality, but this did not reach statistical significance. In our opinion, the failure of finding a difference in the outcome should be evaluated with caution, as it is possibly due to a lower sample size (type II error), the fact that elective procedures performed during the COVID-19 pandemic might not be representative of elective surgery done before the pandemic because of prioritization of more critical elective procedures, and considering the prior findings reported in the first COVIDSurg study. That study demonstrated a substantially high risk of postoperative mortality (23.8%) and pulmonary complications (51.2%) in patients with perioperative COVID-19 and that increase was also notable in elective surgery patients.<sup>9</sup> In addition, a recent study examining postoperative complications in 5,479 patients undergoing elective surgeries in the United States compared SARS-CoV-2-positive patients with the prepandemic cohort of surgical patients undergoing similar surgeries. Although Deng et al.<sup>12</sup> reported a markedly elevated risk of 30-day postoperative complications associated with SARS-CoV-2 infection, the study lacked mortality information and information on whether patients with a confirmed SARS-CoV-2

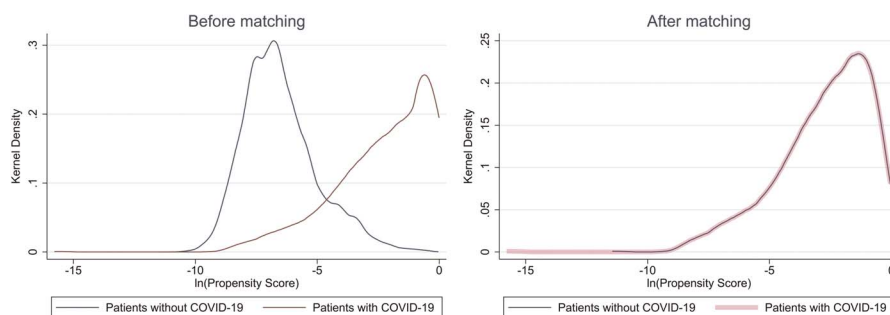
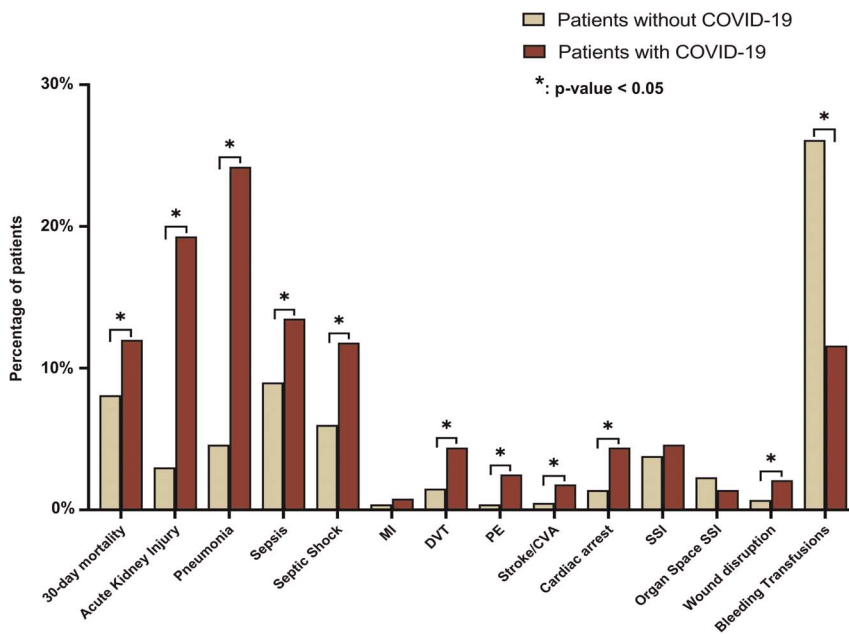


Figure 1. Prematching and postmatching kernel density plots of the natural logarithm of propensity scores.



**Figure 2.** Thirty-day mortality and postoperative complications of propensity score–matched patients with and without SARS-CoV-2 infections. CVA, cerebrovascular accident; DVT, deep venous thrombosis; MI, myocardial infarction; PE, pulmonary embolism.

infection were symptomatic or asymptomatic. One study with a pre-pandemic control group was performed by the Dutch Surgical COVID-19 Research Collaborative and similarly aimed to dissect the independent role of perioperative SARS-CoV-2 infection in amplifying the surgical risk of postoperative outcomes. Their matched-cohort analysis of 123 SARS-CoV-2–positive and 196 SARS-CoV-2–negative control patients similarly showed increased risks of 30-day mortality (12.2%) and postoperative complications (20.3%).<sup>29</sup> Interestingly, the mortality rate of 4.6% in the control SARS-CoV-2 negative group was twice as high compared with the pre-pandemic rate of 2% reported in a

Dutch national surgical registry. A prospective cohort study focusing on surgical patients with a perioperative SARS-CoV-2 infection in the United States, performed as a part of the COVIDSurg collaborative, found the rates of mortality and pulmonary complications to be 11.0% and 39.5%, respectively.<sup>37</sup> Although the mortality rate in the United States was lower compared with the initial international COVIDSurg data, it was still higher when compared with the pre-pandemic rates of mortality.<sup>38</sup> Those studies lacked control comparison groups.

Another multicenter study that included 2,132 patients from 25 Spanish hospitals found similar rates of 30-day

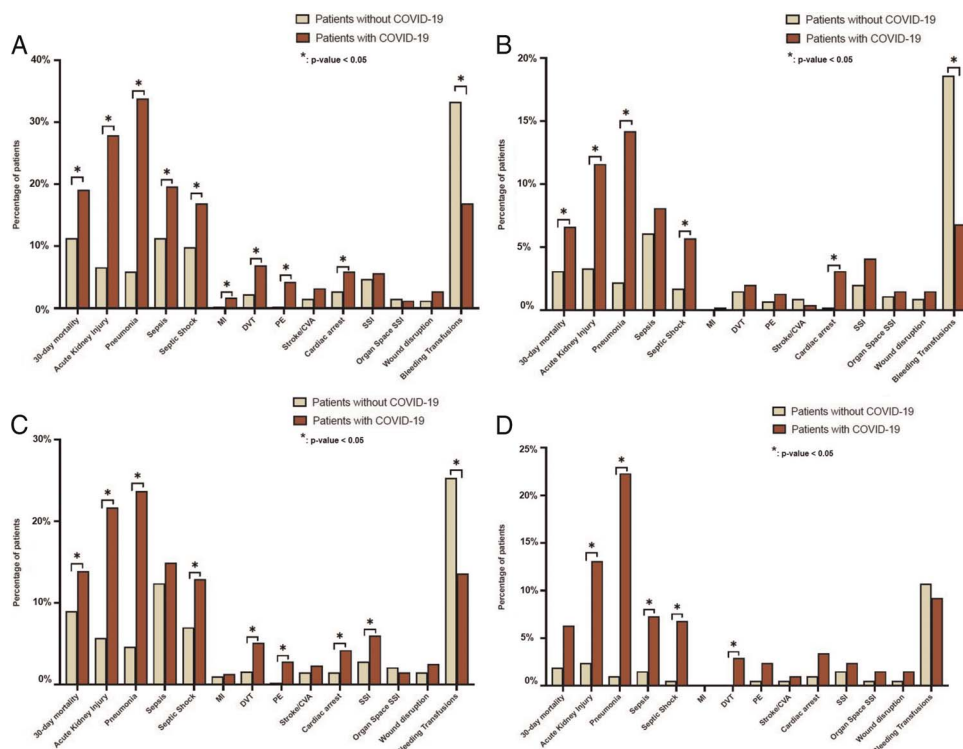
**TABLE 3.** 30-Day Mortality and Postoperative Complications of Propensity Score–Matched Patients With and Without SARS-CoV-2 Infections

Outcome	Patients Without SARS-CoV-2 (n = 843)	Patients With SARS-CoV-2 (n = 843)	p	Risk Difference (CI 95%)
30-d Mortality	68 (8.1%)	101 (12.0%)	0.012	0.04 (0.01–0.07)
Hospital LOS, median (IQR)	5 (1–12)	6 (2–15)	0.035	—
Pneumonia	39 (4.6%)	204 (24.2%)	<0.001	0.20 (0.16–0.23)
Sepsis	76 (9.0%)	114 (13.5%)	0.006	0.05 (0.01–0.08)
Septic shock	51 (6.0%)	99 (11.8%)	<0.001	0.06 (0.03–0.08)
Acute kidney injury	25 (3.0%)	163 (19.3%)	<0.001	0.16 (0.13–0.19)
Myocardial infarction	3 (0.4%)	7 (0.8%)	0.214	0.00 (–0.00 to 0.01)
Cardiac arrest	12 (1.4%)	37 (4.4%)	<0.001	0.03 (0.01–0.05)
Deep venous thrombosis	13 (1.5%)	37 (4.4%)	<0.001	0.03 (0.01–0.04)
Pulmonary embolism	3 (0.4%)	21 (2.5%)	<0.001	0.02 (0.01–0.03)
Stroke/CVA	4 (0.5%)	15 (1.8%)	0.017	0.01 (0.00–0.02)
SSI	32 (3.8%)	39 (4.6%)	0.4	0.01 (–0.01 to 0.03)
Organ space SSI	19 (2.3%)	12 (1.4%)	0.214	–0.01 (–0.02 to 0.00)
Wound disruption	6 (0.7%)	18 (2.1%)	0.019	0.01 (0.00–0.03)
Bleeding transfusions	220 (26.1%)	98 (11.6%)	<0.001	–0.14 (0.00 to 0.03)

p Values were adjusted for multiple comparisons using the Benjamini-Hochberg correction.

CI, confidence interval; CVA, cerebrovascular accident; DVT, deep venous thrombosis; MI, myocardial infarction; PE, pulmonary embolism.





**Figure 3.** Sensitivity analyses (A–D) for 30-day mortality and postoperative complications of propensity score–matched patients without SARS-CoV-2 infection and (A, upper left corner) symptomatic patients with SARS-CoV-2 infection and preoperative respiratory/radiologic findings, (B, upper right corner) asymptomatic patients with SARS-CoV-2 infection, (C, lower left corner) patients with SARS-CoV-2 infection who had emergency surgery, and (D, lower right corner) patients with SARS-CoV-2 infection who had elective surgery. CVA, cerebrovascular accident; DVT, deep venous thrombosis, MI, myocardial infarction; PE, pulmonary embolism.

mortality among surgical patients with and without SARS-CoV-2 infection (12.6% vs. 4.6%).<sup>39</sup> However, despite their propensity score–matched analysis not revealing a statistically significant difference in 30-day mortality (12.0% vs. 8.1%;  $p = 0.163$ ), SARS-CoV-2 infection was still associated with higher rates of 90-day mortality and 30-day postoperative complications. Several factors potentially limit the generalizability of their findings, including a small number of patients with SARS-CoV-2 infection (175 patients) and considering only emergency cases confined to a single surgical specialty. In view of our findings, as well as those in the aforementioned US, Spanish, and Dutch studies, we suggest that the increased morbidity and mortality of patients with COVID-19 are potentially inherent to the disease and its systemic and pulmonary complications as discussed previously. Nevertheless, we cannot exclude system-related factors during the pandemic (e.g., staff shortage, bed capacity issues) that could have contributed.

Our study still has a few limitations. First, the study included patients from the 2012 ACS-NSQIP registry as historical matched controls, and surgical practice and definitions of specific postoperative outcomes may have changed over time. Second, our propensity score–matched analysis might have residual confounding bias because of unaccounted confounders not being available in the databases used in this study. Specifically, there was no information about reasons for surgery, which could contribute to residual confounding by indication, especially because the patient population included those diagnosed preoperatively and postoperatively. Similarly, the COVIDSurg database

did not have data regarding COVID-19 severity. Third, since the data were collected during the first wave of the pandemic, our analysis did not include patients who received vaccination or COVID-19 therapeutics and those who could have been infected by a different variant of SARS-CoV-2 (Delta, Omicron), thereby limiting the generalizability of our findings. A recently launched international, multicenter study, COVIDSurg-3 by the COVIDSurg Collaborative, aims to examine postoperative surgical outcomes in the era of vaccination and Omicron. Fourth, the low sample size in subgroups might have limited ability to detect a statistically significant difference in outcomes between the groups. In addition, the grade of surgery was defined based on the Bupa Schedule, which might not entirely reflect a surgical procedure's complexity when mapped onto the NSQIP-defined principal procedure variable. Nevertheless, using CPT codes corresponding to procedures performed in the COVIDSurg database provided consistency and minimized variation in labeling the grade of surgery in the NSQIP dataset.

## CONCLUSION

Using a nationwide propensity score–matched cohort, we demonstrated significantly higher rates of mortality and postoperative complications, especially thromboembolic events, among patients with perioperative SARS-CoV-2 infection compared with a matched cohort of patients without SARS-CoV-2 infection. Moreover, matched SARS-CoV-2–infected patients had a higher risk of mortality even if they were asymptomatic

at presentation. Such information is crucial for the complex surgical decision making and counseling of patients presenting with positive SARS-CoV-2 infection status. Further studies are required to understand the impact of new variants, large-scale vaccination, and new therapeutics on the postoperative outcomes of COVID-19 patients.

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#### DISCLOSURE

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