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Factors Associated With Surgical Mortality and Complications Among Patients With and Without Coronavirus Disease 2019 (COVID-19) in Italy

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IMPORTANCE There are limited data on mortality and complications rates in patients with coronavirus disease 2019 (COVID-19) who undergo surgery.

OBJECTIVE To evaluate early surgical outcomes of patients with COVID-19 in different subspecialties.

DESIGN, SETTING, AND PARTICIPANTS This matched cohort study conducted in the general, vascular and thoracic surgery, orthopedic, and neurosurgery units of Spedali Civili Hospital (Brescia, Italy) included patients who underwent surgical treatment from February 23 to April 1, 2020, and had positive test results for COVID-19 either before or within 1 week after surgery. Gynecological and minor surgical procedures were excluded. Patients with COVID-19 were matched with patients without COVID-19 with a 1:2 ratio for sex, age group, American Society of Anesthesiologists score, and comorbidities recorded in the surgical risk calculator of the American College of Surgeons National Surgical Quality Improvement Program. Patients older than 65 years were also matched for the Clinical Frailty Scale score.

EXPOSURES Patients with positive results for COVID-19 and undergoing surgery vs matched surgical patients without infection. Screening for COVID-19 was performed with reverse transcriptase–polymerase chain reaction assay in nasopharyngeal swabs, chest radiography, and/or computed tomography. Diagnosis of COVID-19 was based on positivity of at least 1 of these investigations.

MAIN OUTCOMES AND MEASURES The primary end point was early surgical mortality and complications in patients with COVID-19; secondary end points were the modeling of complications to determine the importance of COVID-19 compared with other surgical risk factors.

RESULTS Of 41 patients (of 333 who underwent operation during the same period) who underwent mainly urgent surgery, 33 (80.5%) had positive results for COVID-19 preoperatively and 8 (19.5%) had positive results within 5 days from surgery. Of the 123 patients of the combined cohorts (78 women [63.4%]; mean [SD] age, 76.6 [14.4] years), 30-day mortality was significantly higher for those with COVID-19 compared with control patients without COVID-19 (odds ratio [OR], 9.5; 95% CI, 1.77-96.53). Complications were also significantly higher (OR, 4.98; 95% CI, 1.81-16.07); pulmonary complications were the most common (OR, 35.62; 95% CI, 9.34-205.55), but thrombotic complications were also significantly associated with COVID-19 (OR, 13.2; 95% CI, 1.48-∞). Different models (cumulative link model and classification tree) identified COVID-19 as the main variable associated with complications.

CONCLUSIONS AND RELEVANCE In this matched cohort study, surgical mortality and complications were higher in patients with COVID-19 compared with patients without COVID-19. These data suggest that, whenever possible, surgery should be postponed in patients with COVID-19.

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Video and Supplemental content

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We are in the midst of the novel coronavirus disease 2019 (COVID-19) outbreak worldwide, but limited data are available regarding patients who undergo surgical treatment and either have positive results for COVID-19 or, soon after surgery, develop it.[1] Brescia is located in Lombardy, the region in Italy most affected by the current pandemic; it experienced its first official case on February 23, 2020.[2,3] Spedali Civili Hospital became 1 of 3 regional referral centers for major trauma, neurosurgery, and orthopedics, with a catchment area of more than 3 million people.[4]

The hospital urgently changed its organization, creating dedicated in-hospital routes and an operating room for patients with COVID-19. While most elective surgeries were stopped, some patients with COVID-19 had to undergo emergent or urgent surgery, while others became symptomatic within 1 week from elective surgery. Because of the limited available data on these patients and the outbreak of the pandemic worldwide, we felt the urgency to share the experience of treating these patients.

In this retrospective cohort study, surgical patients with COVID-19 were matched to patients treated by the same surgical teams in Spedali Civili Hospital. Our primary objective was to examine early surgical mortality and complication rates in surgical patients with COVID-19 compared with a tightly matched control group. The secondary objective included the investigation of how COVID-19 compares with other well-known surgical risk factors.

Key Points

Question Is coronavirus disease 2019 (COVID-19) associated with early surgical mortality and complications?

Findings In this cohort study of 41 surgical patients with COVID-19 and 82 tightly matched control patients without COVID-19, significant differences were documented regarding rates of early mortality and complications, pneumonia and thrombotic complications were significantly associated with COVID-19, and different models identified COVID-19 as the first variable associated with surgical complications.

Meaning Whenever possible, surgery should be postponed in patients with COVID-19 because it is an additional surgical risk factor that overweighs traditional ones.

Methods

Study Population

Patients who underwent surgical treatment from February 23 to April 1, 2020, at Spedali Civili Hospital and either had positive results for COVID-19 preoperatively or developed it within 1 week after surgery were included in the study. Patients who underwent minor procedures, such as suturing of a superficial wound, tracheostomy, and lumbar puncture, were excluded; because of the specificity of the population (eg, only women, mainly during pregnancy), gynecological procedures were also excluded.

Patients were generally screened for COVID-19 before surgery and systematically after March 8, 2020. Screening for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was performed with reverse transcriptase–polymerase chain reaction assay in nasopharyngeal swabs; chest radiography and/or computed tomography were performed to investigate lung abnormalities. Diagnosis of COVID-19 was based on positivity of at least 1 of these investigations.

Patients with COVID-19 were matched in a 1:2 ratio to those not affected but with the same surgical pathology who had undergone the identical treatment by the same team. When possible, they were chosen during the same study period; otherwise, the first historical match was selected.

The study was approved by the local ethics committee (COVID-SURG-BS; NP 4059). Written or oral informed patient consent was obtained either at the time of surgery for the use of data for scientific purposes or at follow-up when possible.

Outcomes

The primary end points of the study were 30-day surgical mortality and complications in patients with COVID-19 compared with a tightly matched control group. The secondary objective included investigation of how COVID-19 compares with other well-known risk factors.

Data Collection

The following data were recorded for all surgical patients with COVID-19 and matched controls (**Table 1**): sex, age, comorbidities, and scores that are taken into account by the American College of Surgeons National Surgical Quality Improvement Program[5] surgical risk calculator,[6] including American Society of Anesthesiologists (ASA) class as well as pathology and type of surgery; patients older than 65 years were also classified and matched according to the Clinical Frailty Scale[7,8] (Table 1).

These preoperative data were recorded for all patients (**Table 2**): chest radiography (Brixia score for COVID-19 pneumonia[9,10] was recorded for pre- and postoperative examinations performed during the study period), respiratory function at admission, platelet counts, white blood cell and lymphocyte counts, and C-reactive protein (CRP), D-dimer, and fibrinogen levels. Type and duration of anesthesia as well as operative time (Table 2) were also collected. Complications were recorded according to Clavien-Dindo classification[11,12] and its continuous version, the Comprehensive Complication Index (CCI).[13,14] They were subdivided into thrombotic, hemorrhagic, pulmonary, cardiac, neurological, and local. The length of hospital admission (subdivided in the intensive care unit [ICU], sub-ICU, and ward) was also recorded.

Statistical Analysis

The data set included 123 patients (41 with COVID-19 [33.3%] and 82 controls [66.7%]) for 53 variables. Odds ratios were computed using the Fisher exact test for count data (95% CIs); in the case of thrombotic complications vs COVID-19, the exact logistic regression based on Markov Chain Monte Carlo with 20000 iterations and 2000 burn-ins (95% CIs) was computed. Descriptive statistics were computed for the entire data set, which was stratified by group (COVID-19/control) (Table 1 and Table 2).

Table 1. Descriptive Statistics[a] on Baseline Characteristics Used for Matching

Variable	No. (%)			*P* value
	Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	
Age, y				
Mean (SD)	76.93 (14.08)	75.95 (15.17)	76.60 (14.40)	.73[b]
Median (IQR) [range]	81.00 (69.00-87.75) [36.00-96.00]	78.00 (69.00-86.00) [35.00-98.00]	81.00 (69.00-86.50) [35.00-98.00]	
Age group, y				
<65	17 (20.73)	10 (24.39)	27 (21.95)	.96[c]
65-74	10 (12.20)	4 (9.76)	14 (11.38)	
75-84	26 (31.71)	13 (31.71)	39 (31.71)	
>85	29 (35.37)	14 (34.15)	43 (34.96)	
Sex				
Female	55 (67.07)	23 (56.10)	78 (63.41)	.23[d]
Male	27 (32.93)	18 (43.90)	45 (36.59)	
Functional status				
No. of any missing values	3	1	4	.99[c]
Independent	30 (37.97)	15 (37.50)	45 (37.82)	
Dependent				
Partially	35 (44.30)	18 (45.00)	53 (44.54)	
Totally	14 (17.72)	7 (17.50)	21 (17.65)	
Emergency case				
No	19 (23.17)	7 (17.07)	26 (21.14)	.44[d]
Yes	63 (76.83)	34 (82.93)	97 (78.86)	
ASA class				
I	2 (2.44)	1 (2.44)	3 (2.44)	.28[c]
II	7 (8.54)	3 (7.32)	10 (8.13)	
III	48 (58.54)	19 (46.34)	67 (54.47)	
IV-V	25 (30.49)	18 (43.90)	43 (34.96)	
Steroid use for chronic condition				
No	80 (97.56)	40 (97.56)	120 (97.56)	>.99[d]
Yes	2 (2.44)	1 (2.44)	3 (2.44)	
Ascites within 30 d prior to surgery				
No	81 (98.78)	41 (100.00)	122 (99.19)	.48[d]
Yes	1 (1.22)	0 (0.00)	1 (0.81)	
Systemic sepsis within 48 h before surgery				
No	76 (92.68)	33 (80.49)	109 (88.62)	.03[d]
Sepsis	6 (7.32)	4 (9.76)	10 (8.13)	
Septic shock	0 (0.00)	3 (7.32)	3 (2.44)	
SIRS	0 (0.00)	1 (2.44)	1 (0.81)	
Ventilator dependency				
No	82 (100.00)	38 (92.68)	120 (97.56)	.01[d]
Yes	0 (0.00)	3 (7.32)	3 (2.44)	
Disseminated cancer				
No	80 (97.56)	39 (95.12)	119 (96.75)	.47[d]
Yes	2 (2.44)	2 (4.88)	4 (3.25)	
Diabetes				
No	70 (85.37)	35 (85.37)	105 (85.37)	>.99[d]
Yes				
Exogenous parenteral insulin	2 (2.44)	1 (2.44)	3 (2.44)	
Oral hypoglycemic agent	10 (12.20)	5 (12.20)	15 (12.20)	
Hypertension requiring medication				
No	20 (24.39)	12 (29.27)	32 (26.02)	.56[d]
Yes	62 (75.61)	29 (70.73)	91 (73.98)	

(continued)

Table 1. Descriptive Statistics[a] on Baseline Characteristics Used for Matching (continued)

Variable	No. (%) Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	*P* value
Congestive heart failure in 30 d before surgery				
No	74 (90.24)	38 (92.68)	112 (91.06)	.66[d]
Yes	8 (9.76)	3 (7.32)	11 (8.94)	
Dyspnea				
No	73 (89.02)	35 (85.37)	108 (87.80)	.19[c]
Moderate exertion	8 (9.76)	3 (7.32)	11 (8.94)	
At rest	1 (1.22)	3 (7.32)	4 (3.25)	
Current smoker within 1 y				
No	74 (90.24)	36 (87.80)	110 (89.43)	.68[d]
Yes	8 (9.76)	5 (12.20)	13 (10.57)	
History of severe COPD				
No	79 (96.34)	40 (97.56)	119 (96.75)	.72[d]
Yes	3 (3.66)	1 (2.44)	4 (3.25)	
Dialysis				
No	81 (98.78)	41 (100.00)	122 (99.19)	.48[d]
Yes	1 (1.22)	0 (0.00)	1 (0.81)	
Acute renal failure				
No	82 (100.00)	41 (100.00)	123 (100.00)	NA
BMI				
No. of any missing values	1	0	1	.78[c]
<18.5	4 (4.94)	0 (0.00)	4 (3.28)	
18.5-24.9	51 (62.96)	26 (63.41)	77 (63.11)	
25.0-29.9	21 (25.93)	15 (36.59)	36 (29.51)	
30-34.9	5 (6.17)	0 (0.00)	5 (4.10)	
Clinical Frailty Scale				
Mean (SD)	4.23 (1.78)	4.10 (1.87)	4.19 (1.80)	.69[b]
Median (IQR) [range]	4.00 (3.00-6.00) [1.00-8.00]	4.00 (3.00-5.00) [1.00-8.00]	4.00 (3.00-6.00) [1.00-8.00]	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; SIRS, systemic inflammatory response syndrome.

[a] Descriptive statistics on baseline characteristics used for matching were computed for the entire data set (123 observations) and stratifying with respect to the group variable, COVID-19 (41 observations), and controls (82 observations). Specifically these were: (1) number of any missing values; mean (SD), first quartile (Q1); median, third quartile (Q3); and range (minimum-maximum) for quantitative variables; and (2) the number of any missing values, absolute, and percentage frequencies for qualitative variables (nominal and ordinal). Matching was satisfactory for all features reported, except systemic sepsis and ventilator dependency, which were associated with the group variable (χ^2 test: $P = .03$ and $P = .01$, respectively), as expected. Patients were also matched for type of pathology and surgery (see eTable in the Supplement for further details).

[b] Wilcoxon test.

[c] Trend test.

[d] χ^2 Goodness of fit test.

Because all quantitative variables had a nonnormal distribution (Shapiro test *P* value, <.001), the Wilcoxon test was used. A χ^2 goodness of fit test was used for nominal variables and the trend test for ordered ones.

The CCI was translated into an ordinal variable with 3 categories (CCI_ord):

1. CCI = 0: none
2. 0 < CCI ≤ 20.9: mild
3. CCI > 20.9: severe

Descriptive statistics were computed again, stratifying with respect to CCI_ord (eTable in the Supplement); the Kruskal-Wallis rank test was used for quantitative variables. Using this stratification, a subsample of 10 variables (group, age, sex, ASA class, systemic sepsis, ventilator dependency, dyspnea, respiratory function at admission, CRP, and fibrinogen) associated with CCI_ord was identified (eTable in the Supplement). These were the 10 covariates of the cumulative link models (CLMs) used to explain CCI_ord.[15] In fact, in our preliminary analysis using a matching like grouping variable, the between-participant variance was 0. Convergence of the model was achieved with a few covariates, one being the group (COVID-19/control). To investigate its importance in the association with complications, the likelihood ratio test (LRT) was used to compare the model obtained with the nested one, for which the group variable was excluded. The best model was chosen observing the *P* value, also controlling for the smaller Akaike information criterion (AIC).

To overcome the convergence problems encountered in CLMs, a nonparametric approach belonging to the supervised machine learning methods was used, namely the classification tree.[16] This approach is able to deal with variables of different nature (quantitative and qualitative) containing missing values and with problems of multicollinearity. The algorithm partitions the covariate space into regions that are as homogenous as possible with respect to the outcome. The partition is based on a splitting criterion that allows selecting the best covariate and its cutoff point at each tree node.[16] The classification tree was run using CCI_ord as an outcome and the variables associated with it as covariates (eTable in the Supplement). The resulting tree structure provides paths from the root node to the leaves, which represent rules of thumb that are useful to identify the most important variables associated with complications and the interactions between covariates. An interesting feature of the classification tree is the possibility of extracting the variable importance (VI), which measures a variable ability to classify the outcome. The VI of each variable is calculated as the sum of the decrease in impurity considering in which level the variable is chosen by the algorithm. These measures are normalized within the range of 0 to 100. The vari-

Table 2. Descriptive Statistics[a] of Preoperative Features and Outcomes of the Study Cohort

Variable	No. (%)			*P* value
	Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	
Respiratory function at admission				
No. of any missing values	2	3	5	<.001[b]
Poor	1 (1.25)	6 (15.79)	7 (5.93)	
Good	17 (21.25)	12 (31.58)	29 (24.58)	
Excellent	62 (77.50)	20 (52.63)	82 (69.49)	
PLT, $\times 10^3/\mu L$				
Mean (SD)	232.28 (93.76)	246.46 (121.78)	237.01 (103.65)	.94[c]
Median (IQR) [range]	215.00 (182.75-269.00) [39.00-619.00]	213.00 (160.00-269.00) [96.00-601.00]	214.00 (176.50-269.00) [39.00-619.00]	
WBC, µL				
Mean (SD)	4.65 (5.09)	4.82 (8.07)	4.70 (6.21)	.23[c]
Median (IQR) [range]	0.92 (0.35-8.50) [0.14-20.95]	0.41 (0.32-6.70) [0.12-36.70]	0.61 (0.33-8.20) [0.12-36.70]	
Lymphocyte, µL				
No. of any missing values	10	4	14	.20[c]
Mean (SD)	1.48 (0.72)	1.32 (0.78)	1.43 (0.74)	
Median (IQR) [range]	1.29 (1.09-2.04) [0.10-3.90]	1.24 (0.80-1.83) [0.29-3.92]	1.24 (1.04-2.01) [0.10-3.92]	
CRP, mg/dL				
No. of any missing values	12	2	14	<.001[c]
Mean (SD)	27.76 (38.71)	89.25 (77.43)	49.76 (62.80)	
Median (IQR) [range]	11.05 (3.40-38.42) [0.00-215.00]	64.70 (24.15-139.60) [1.20-258.00]	20.70 (4.90-63.60) [0.00-258.00]	
D-dimer, µg/mL				
No. of any missing values	73	14	87	.05[c]
Mean (SD)	1144.56 (1685.17)	1850.00 (1453.70)	1673.64 (1521.49)	
Median (IQR) [range]	375.00 (228.00-1023.00) [178.00-5250.00]	1577.00 (764.50-2490.00) [126.00-5250.00]	1036.50 (497.75-2465.00) [126.00-5250.00]	
Fibrinogen, mg/dL				
No. of any missing values	14	3	17	<.001[c]
Mean (SD)	315.53 (94.37)	481.18 (162.76)	374.92 (146.25)	
Median (IQR) [range]	307.00 (254.75-367.25) [18.00-654.00]	486.50 (332.75-622.50) [230.00-800.00]	333.00 (271.25-454.75) [18.00-800.00]	
Type of surgery				
Elective	9 (11.0)	4 (9.8)	13 (10.6)	.84[b]
Urgent	73 (89.0)	37 (90.2)	110 (89.4)	
Anesthesia				
General	43 (52.44)	20 (48.78)	63 (51.22)	.70[d]
Local	39 (47.56)	21 (51.22)	60 (48.78)	
Anesthesia duration, min				
Mean (SD)	130.13 (82.71)	145.73 (87.96)	135.33 (84.46)	.25[c]
Median (IQR) [range]	117.50 (71.25-148.75) [40.00-440.00]	120.00 (90.00-177.00) [40.00-450.00]	120.00 (80.00-159.50) [40.00-450.00]	
Surgery duration, min				
Mean (SD)	93.30 (71.66)	100.54 (75.60)	95.72 (72.77)	.46[c]
Median (IQR) [range]	70.00 (45.00-100.00) [20.00-350.00]	70.00 (55.00-125.00) [15.00-333.00]	70.00 (50.00-107.50) [15.00-350.00]	

(continued)

Table 2. Descriptive Statistics[a] of Preoperative Features and Outcomes of the Study Cohort (continued)

Variable	No. (%)			*P* value
	Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	
Pathology				
Abdominal aortic aneurysm	2 (2.44)	1 (2.44)	3 (2.44)	.99[d]
Acute				
Ischemia of lower limb	1 (1.22)	0 (0.00)	1 (0.81)	
Thrombosis of the abdominal aorta	2 (2.44)	1 (2.44)	3 (2.44)	
Chest wall cancer	2 (2.44)	1 (2.44)	3 (2.44)	
Chronic				
Mesenteric ischemia	1 (1.22)	0 (0.00)	1 (0.81)	
Subdural hematoma	8 (9.76)	4 (9.76)	12 (9.76)	
Femoral fracture	38 (46.34)	19 (46.34)	57 (46.34)	
Humeral fracture	2 (2.44)	1 (2.44)	3 (2.44)	
Intracerebral hematoma	4 (4.88)	2 (4.88)	6 (4.88)	
Intestinal occlusion	2 (2.44)	1 (2.44)	3 (2.44)	
Lower limb				
Acute ischemia	5 (6.10)	4 (9.76)	9 (7.32)	
Gangrene	2 (2.44)	1 (2.44)	3 (2.44)	
Melanoma	0 (0.00)	1 (2.44)	1 (0.81)	
Mesenteric ischemia postaortic dissection	1 (1.22)	0 (0.00)	1 (0.81)	
Node metastasis	2 (2.44)	0 (0.00)	2 (1.63)	
Pelvic tumor recurrence	0 (0.00)	1 (2.44)	1 (0.81)	
Perforated				
Appendix peritonitis	2 (2.44)	1 (2.44)	3 (2.44)	
Diverticulitis	2 (2.44)	1 (2.44)	3 (2.44)	
Rectal cancer	2 (2.44)	0 (0.00)	2 (1.63)	
Tibia fibula fracture	4 (4.88)	2 (4.88)	6 (4.88)	
Type of operation				
Adhesiolysis	2 (2.44)	1 (2.44)	3 (2.44)	>.99[d]
Aortomesenteric bypass	1 (1.22)	0 (0.00)	1 (0.81)	
Aortic replacement	2 (2.44)	1 (2.44)	3 (2.44)	
Axillary lymphadenectomy	0 (0.00)	1 (2.44)	1 (0.81)	
Chest wall resection	2 (2.44)	1 (2.44)	3 (2.44)	
Endarterectomy	1 (1.22)	0 (0.00)	1 (0.81)	
Evacuation of intracranial hemorrhage	12 (14.63)	6 (14.63)	18 (14.63)	
Femur fixation with nail	23 (28.05)	12 (29.27)	35 (28.46)	
Hartmann procedure	2 (2.44)	1 (2.44)	3 (2.44)	
Hip hemiarthroplasty	15 (18.29)	7 (17.07)	22 (17.89)	
Humerus fixation	2 (2.44)	1 (2.44)	3 (2.44)	
Laparoscopic appendectomy	2 (2.44)	1 (2.44)	3 (2.44)	
Low anterior resection	2 (2.44)	1 (2.44)	3 (2.44)	
Major amputation	2 (2.44)	1 (2.44)	3 (2.44)	
Radical node dissection	2 (2.44)	0 (0.00)	2 (1.63)	
Thromboembolectomy	8 (9.76)	5 (12.20)	13 (10.57)	
Tibia and fibula fixation	4 (4.88)	2 (4.88)	6 (4.88)	

(continued)

Table 2. Descriptive Statistics[a] of Preoperative Features and Outcomes of the Study Cohort (continued)

Variable	No. (%)			*P* value
	Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	
Thrombotic complications				
No	82 (100.00)	37 (90.24)	119 (96.75)	.004[d]
Yes	0 (0.00)	4 (9.76)	4 (3.25)	
Hemorrhagic complications				
No	50 (60.98)	26 (63.41)	76 (61.79)	.79[d]
Yes	32 (39.02)	15 (36.59)	47 (38.21)	
Pulmonary complications				
No	79 (96.34)	17 (41.46)	96 (78.05)	<.001[d]
Pneumonia	2 (2.44)	18 (43.90)	20 (16.26)	
ARF	1 (1.22)	6 (14.63)	7 (5.69)	
Cardiac complications				
No	81 (98.78)	39 (95.12)	120 (97.56)	.10[d]
Atrial fibrillation	1 (1.22)	0 (0.00)	1 (0.81)	
Shock	0 (0.00)	2 (4.88)	2 (1.63)	
Neurological complications				
No. of any missing values	8	2	10	.69[d]
No	72 (97.30)	38 (97.44)	110 (97.35)	
Delirium	1 (1.35)	1 (2.56)	2 (1.77)	
TIA	1 (1.35)	0 (0.00)	1 (0.88)	
Local complications				
No	76 (92.68)	38 (92.68)	114 (92.68)	.61[d]
Yes	6 (7.32)	3 (7.32)	9 (7.32)	
Clavien Dindo classification				
None	38 (46.34)	6 (14.63)	44 (35.77)	<.001[b]
I	3 (3.66)	1 (2.44)	4 (3.25)	
II	33 (40.24)	7 (17.07)	40 (32.52)	
I-II	0 (0.00)	1 (2.44)	1 (0.81)	
II-II	1 (1.22)	9 (21.95)	10 (8.13)	
IIIA	0 (0.00)	2 (4.88)	2 (1.63)	
IIIB	2 (2.44)	0 (0.00)	2 (1.63)	
I-IIIB	1 (1.22)	0 (0.00)	1 (0.81)	
II-IIIB	1 (1.22)	0 (0.00)	1 (0.81)	
IVA	0 (0.00)	2 (4.88)	2 (1.63)	
I-IVA	1 (1.22)	0 (0.00)	1 (0.81)	
II-IVA	0 (0.00)	2 (4.88)	2 (1.63)	
IIIA-IVB	0 (0.00)	2 (4.88)	2 (1.63)	
II-IVA-IVA	0 (0.00)	1 (2.44)	1 (0.81)	
V	2 (2.44)	8 (19.51)	10 (8.13)	
CCI				
Mean (SD)	13.79 (18.21)	40.14 (33.39)	22.57 (27.23)	<.001[c]
Median (IQR) [range]	14.80 (0.00-20.90) [0.00-100.00]	29.60 (20.90-53.20) [0.00-100.00]	20.90 (0.00-29.60) [0.00-100.00]	
Days in the ICU				
Mean (SD)	0.39 (1.59)	0.90 (2.89)	0.56 (2.11)	.52[c]
Median (IQR) [range]	0.00 (0.00-0.00) [0.00-13.00]	0.00 (0.00-0.00) [0.00-14.00]	0.00 (0.00-0.00) [0.00-14.00]	
Days in sub-ICU				
No. of any missing values	40	20	60	.20[c]
Mean (SD)	1.36 (2.73)	3.95 (6.55)	2.22 (4.50)	
Median (IQR) [range]	0.00 (0.00-1.50) [0.00-10.00]	0.00 (0.00-5.00) [0.00-20.00]	0.00 (0.00-2.00) [0.00-20.00]	

(continued)

Table 2. Descriptive Statistics[a] of Preoperative Features and Outcomes of the Study Cohort (continued)

Variable	No. (%)			P value
	Control (n = 82)	COVID-19 (n = 41)	Total (N = 123)	
Days in hospital				
Mean (SD)	13.13 (9.27)	13.34 (7.63)	13.20 (8.73)	.53[c]
Median (IQR) [range]	11.50 (7.00-17.75) [1.00-60.00]	12.00 (8.00-15.00) [3.00-45.00]	12.00 (7.50-17.00) [1.00-60.00]	
Death				
No	80 (97.56)	33 (80.49)	113 (91.87)	.001[d]
Yes	2 (2.44)	8 (19.51)	10 (8.13)	

Abbreviations: ARF, acute respiratory failure; CCI, comprehensive complication index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; PLT, platelets; WBC, white blood cell count.

SI conversion factors: To convert CRP to mg/L, multiply by 10; for D-dimer to nmol/L, multiply by 5.476; for fibrinogen to g/L, multiply by 0.01; for PLT to $\times 10^9$/L, multiply by 1; for lymphocytes and WBC to $\times 10^9$/L, multiply by 0.001.

[a] Poor respiratory function at admission was more frequent in patients with COVID-19 (χ^2 test: $P < .001$). Moreover, median values of CRP and fibrinogen were significantly higher ($P < .001$). The type of surgery and anesthesia, as well as operative and anesthesia times, did not differ between the study group and controls. The CCI score (which summarized complications [see the Methods for further details]) was significantly higher in COVID-19 ($P < .001$); in particular, thrombotic and pulmonary complications were associated with patients with COVID-19 (χ^2 test: $P = .004$ and $P = <.001$, respectively). Death rates were also significantly higher ($P = .001$).

[b] Trend test.

[c] Wilcoxon test.

[d] χ^2 Goodness of fit test.

able with the highest decrease of impurity was scored 100, with the remaining ones having lower scores. The obtained ranking was from the most to the least important variable. All analyses were performed with R, version 4.0.0 (R Foundation). Statistical significance was set at $P < .05$ for the data in this article's Tables and $P < .01$ for the model.

Results

Baseline Characteristics

Forty-one patients with COVID-19 (of 333 patients who underwent an operation during the study period by the surgical units involved in the study) and 82 controls were included in the study (78 women [63.4%]; mean [SD] age, 76.6 [14.4]) (Table 1 and Table 2). Of the 41 patients who underwent mainly emergent/urgent surgery (37 [90%]), 33 were positive for SARS-CoV-2 preoperatively (80.5%) and 8 (19.5%) had positive results for COVID-19 within 5 days from surgery.

Patients with COVID-19 were matched mainly with historical controls, as only 11 were found during the same study period. No significant differences were evident between the COVID-19 and control groups considering baseline features used for matching except for systemic sepsis (although odds ratio [OR], 3.04; 95% CI, 0.85-11.54; $P = .06$) and intubation status (although OR, ∞; 95% CI, 0.85-∞; $P = .04$) (Table 1).

Screening for SARS-CoV-2

Table 3[9,10] reports data on the 52 patients screened for COVID-19 during the study period with a nasopharyngeal swab and/or chest radiograph (a few patients were investigated with computed tomography only and excluded from the analysis), investigating the association between these 2 variables and complications (CCI_ord). Swab testing (at admission or discharge) was not associated with CCI_ord (OR, 1.68; 95% CI, 0.25-13.00; $P = .69$ and OR, 2.07; 95% CI, 0.30-24.51; $P = 0.68$, respectively; Table 3), while CXR Brixia scores[9,10] (at admission and discharge) showed a significantly higher median in the correspondence of high complications (Kruskal-Wallis test: $P = .01$ and $P = .003$, respectively; Table 3).

Surgical Treatment and Anesthesia in Patients With COVID-19

Among patients with COVID-19, 22 of 41 (53.65%) underwent orthopedic procedures, while the remaining were treated by vascular (7 [17.1%]), neurological (6 [14.6%]), general (5 [12.2%]), and thoracic (1 [2.4%]) surgeons (Table 2). The mean (SD) operative time was 101 (76) minutes (median, 70.00 minutes; range, 15-333 minutes) (Table 2).

Procedures were performed under general anesthesia for 20 patients (49%); regional anesthesia was used in 16 of 21 cases (76%) and was mainly spinal. The mean (SD) duration of anesthesia was 146 (88) minutes (median, 120 minutes; range, 40-450 minutes) (Table 2). None of these features were different in patients with COVID-19 vs controls (Table 2).

Deaths and Complication Rates

Mortality was significantly higher in the COVID-19 group (8 patients [19.51%] vs 2 patients in control group [2.44%]; OR, 9.5; 95% CI, 1.77-96.53) (Table 2). Complications (if CCI score = 0, 0; otherwise, 1) were also significantly more frequent (OR, 4.98; 95% CI, 1.81-16.07) (Table 2 and eTable in the Supplement).

Pulmonary complications (if pulmonary complications, no, 0; otherwise, 1) were the most frequent and significantly higher in patients with COVID-19 (OR, 35.63; 95% CI, 9.34-205.55) (Table 2). Of the patients who had pulmonary complications before surgery, only the ones with worsening pneumonia after surgery (ie, worsening of Brixia CRX score) were considered, while the ones whose pulmonary complications were unchanged or improved were not considered.

Hemorrhagic complications, mainly represented by the need for a blood transfusion, were the second most frequent postoperative adverse event, but no significant difference was

recorded compared with the control group (OR, 0.90; 95% CI, 0.38-2.09). When blood transfusion was excluded, 2 major hemorrhagic complications were seen in the COVID-19 group (after thromboembolectomy for acute thrombosis of the abdominal aorta in postoperative day [POD] 3; after chronic subdural hematoma in POD 2) but no significant difference was evident.

Four thrombotic complications were recorded in the COVID-19 group; these included 1 peripheral thrombosis in POD 4 and 3 arterial thromboses on POD 1 after thromboembolectomy for acute lower limb ischemia. The exact logistic regression based on Markov Chain Monte Carlo (20000 iterations and 2000 burn-in) confirmed the association (Table 2) between COVID-19 and thrombotic complications (P = .01; OR, 13.2; 95% CI, 1.48-∞).

Cardiac complications were relatively rare and associated with severe pulmonary complications. Neurological complications were also rare and transient (eg, delirium) if neurosurgical patients were excluded; in the latter subpopulation, neurological worsening was caused by postoperative rebleeding. Local complications (eg, surgical site infection and dehiscence) were relatively rare and did not differ from the control group.

Modeling of Complications

Because death was an extremely unbalanced variable (death, 8.1%, vs discharged, 91.9%), it was not possible to model it. Consequently, attention was focused on complications (CCI_ord), which were used as an outcome in a CLM with link function logit.

Ten variables associated with CCI_ord (group, age, sex, ASA class, systemic sepsis, ventilator dependency, dyspnea, respiratory function at admission, CRP, and fibrinogen; eTable in the Supplement) were used as covariates in the CLM. Because of convergence problems (parameters are not uniquely determined), the model is based on the covariates (group, age, and respiratory function at admission) that allow the convergence of the model.

Patients with COVID-19 were approximately 13 times more likely to have complications than controls (**Table 4**). Age was a significant factor for complications; for each additional year, there was a 1.04 higher OR for complications (Table 4).

To understand the importance of COVID-19 in this model, a LRT was applied that generated a nested model without the group variable. Because the P value for the likelihood ratio test was less than .001, the larger model (group + age + respiratory function at admission) was preferred over the nested one, thereby confirming the importance of COVID-19 (AIC = 224.23 for the full model vs AIC = 255.11 for the nested one).

To overcome the convergence problems encountered in CLM, the classification tree was used, with CCI_ord as an outcome and the 10 preoperative features associated with it (Table 2) as covariates (**Figure**). The algorithm automatically chose at first split the group variable, thus dividing controls from patients with COVID-19 (Figure). The VI extracted from the classification tree (**Video**) confirmed that COVID-19 (VI = 100) and age (VI = 42.96) were the most important variables for surgical complications.

Table 4. Cumulative Link Model[a]

Variables	OR (95% CI)	*P* value
Outcome CCI_ord ~ group + age + respiratory function at admission		
Group (COVID-19)	13.29 (5.09-34.68)	<.001
Age	1.04 (1.01-1.07)	.01
Respiratory function at admission		
Poor	3.35 (0.36-31.62)	.29
Good	0.38 (0.16-0.94)	.04
R^2 Nagelkerke = 0.43	NA	

Abbreviations: CCI, comprehensive complication; COVID-19, coronavirus disease 2019; NA, not applicable; OR, odds ratio.

[a] Convergence of the model was achieved with only 3 covariates (group, age, and respiratory function at admission). The model identified COVID-19 as the strongest variable associated with complications (they are 13 times more likely in patients with COVID-19) while age retained its relevance but with less strength.

Discussion

SARS-CoV-2 was first detected in Wuhan, China, in December 2019 and then spread worldwide, with the World Health Organization certifying the pandemic on March 11, 2020. Significant data are accumulating on COVID-19, the disease caused by it, from many different perspectives (eg, epidemiological, diagnostic, and therapeutic). There are still limited data on surgical patients who either have positive results for COVID-19 or soon develop it after surgery. Aminian et al[17] reported that 2 of 3 patients died as a consequence of postoperative fever and pulmonary complications after uneventful elective general surgery at the beginning of the COVID-19 outbreak in Iran. Lei et al[1] reported on 34 patients who underwent elective surgery during the incubation period of COVID-19 in 4 hospitals located in Wuhan from January 1 to February 5, 2020. All patients developed pneumonia shortly after surgery, 15 (44.1%) required admission to the ICU, and 7 (20.5%) ultimately died. Li et al[18] reported on 13 patients who underwent elective thoracic surgery with a 38.5% mortality rate.

In this series, patients were treated by different subspecialties (neurosurgery, orthopedics, general, thoracic, and vascular surgery) in a single hospital, Spedali Civili, located in Brescia, Lombardy, the region in Italy most affected by COVID-19. Minor procedures and gynecological surgeries were excluded. Within these strict criteria, 41 patients were identified and included in the study. They were matched with a 1:2 ratio for age, sex, comorbidities included in the American College of Surgeons National Surgical Quality Improvement Program surgical risk calculator,[5,6] Clinical Frailty Scale score,[7,8] type of pathology, and surgery (Table 1 and Table 2). Matching was satisfactory, as the only differences at baseline were strictly associated with COVID-19, causing sepsis and/or respiratory insufficiency requiring intubation in 3 patients during the preoperative period (Table 1). At admission, respiratory function was worse in patients with COVID-19 (Table 2).

During routine preoperative testing, CRP and fibrinogen were significantly associated with COVID-19 (Table 2), as reported by others.[19-23] When the 52 surgical patients included

Table 3. Chest Brixia Radiography Score[9,10] and Nasopharyngeal Swab in Association With Complications[a]

COVID-19 screening test	No. (%) None (n = 9)	Mild (n = 17)	Severe (n = 26)	*P* value
COVID-19 swab admission				
No. of any missing values	2	1	1	.13[b]
Negative	4 (57.14)	10 (62.50)	8 (32.00)	
Positive	3 (42.86)	6 (37.50)	17 (68.00)	
COVID-19 swab at discharge				
No. of any missing values	1	4	10	.13[b]
Negative	6 (75.00)	10 (76.92)	7 (43.75)	
Positive	2 (25.00)	3 (23.08)	9 (56.25)	
CXR score at admission				
No. of any missing values	0	3	1	.01[c]
Mean (SD)	2.11 (3.52)	1.21 (2.19)	4.44 (3.84)	
Median (IQR) [range]	0.00 (0.00-3.00) [0.00-9.00]	0.00 (0.00-1.75) [0.00-7.00]	3.00 (1.00-8.00) [0.00-14.00]	
CXR score postoperative d 3				
No. of any missing values	3	10	4	.003[c]
Mean (SD)	2.17 (3.49)	2.57 (2.82)	7.77 (4.50)	
Median (IQR) [range]	1.00 (0.00-2.00) [0.00-9.00]	2.00 (0.00-4.50) [0.00-7.00]	8.00 (4.00-10.00) [1.00-17.00]	

Abbreviations: CCI, comprehensive complication index; COVID-19, coronavirus disease 2019; CXR, chest radiography; IQR, interquartile range.

[a] Fifty-two patients who underwent screening for severe acute respiratory syndrome coronavirus 2 and surgery during the study period (COVID-19: 41; matched controls during the same study period: 11) were investigated by descriptive statistics stratified with respect to the categorized complications, namely none (CCI = 0), mild ($8.7 \leq CCI \leq 20.9$), and severe (CCI>20.9). The Kruskal-Wallis test highlighted significantly different medians in all 3 categories in the preoperative CXR Brescia score; in the postoperative CXR score, the median was significantly higher in severe complications vs the remaining categories.

[b] χ^2 Goodness of fit test.

[c] Kruskal-Wallis test.

in the cohort and screened for SARS-CoV-2 infection during the study period were evaluated, positive findings from preoperative chest radiography (Brixia score[9,10]) were significantly worse in patients with COVID-19 (Table 3).

The mortality of patients with COVID-19 in this series was lower than in some previous reports[17,18] but still high (19.5%). This difference might be explained by the high index of suspicion, which led to early diagnosis of many cases of mild postoperative interstitial pneumonia. Patients were immediately screened for COVID-19 during the postoperative period if any sign suggestive of disease was evident. Of the 8 patients who had positive results after surgery, all received a diagnosis within POD 5. We believe surgical stress might have led to COVID-19, possibly in patients harboring SARS-CoV-2 preoperatively. In this small subsample, complications were still significantly higher than controls and there was no statistical difference with the patients who had COVID-19 before surgery (eAppendix 1 in the Supplement), although severe complications were more frequent in the latter group.

Mortality and complications were significantly more frequent in patients with COVID-19 (Table 2 and Table 4) even excluding patients with sepsis, or who had ventilator dependency before surgery (eAppendix 2 in the Supplement). In particular, pulmonary complications were the most frequent, as reported by others,[1,17,18] and led to postoperative acute respiratory insufficiency in 6 of 41 patients with COVID-19 (14.6%) (Table 2). Interestingly, thrombotic complications were also significantly associated with COVID-19 (Table 2). Three of 4 patients with COVID-19 presented arterial thromboses on POD 1 after thromboembolectomy for acute lower limb ischemia, with only 1 having a technical issue (partial intimal flap), which might have partially justified the complication. Recent articles have highlighted the possible prothrombotic state of patients with COVID-19.[24-26]

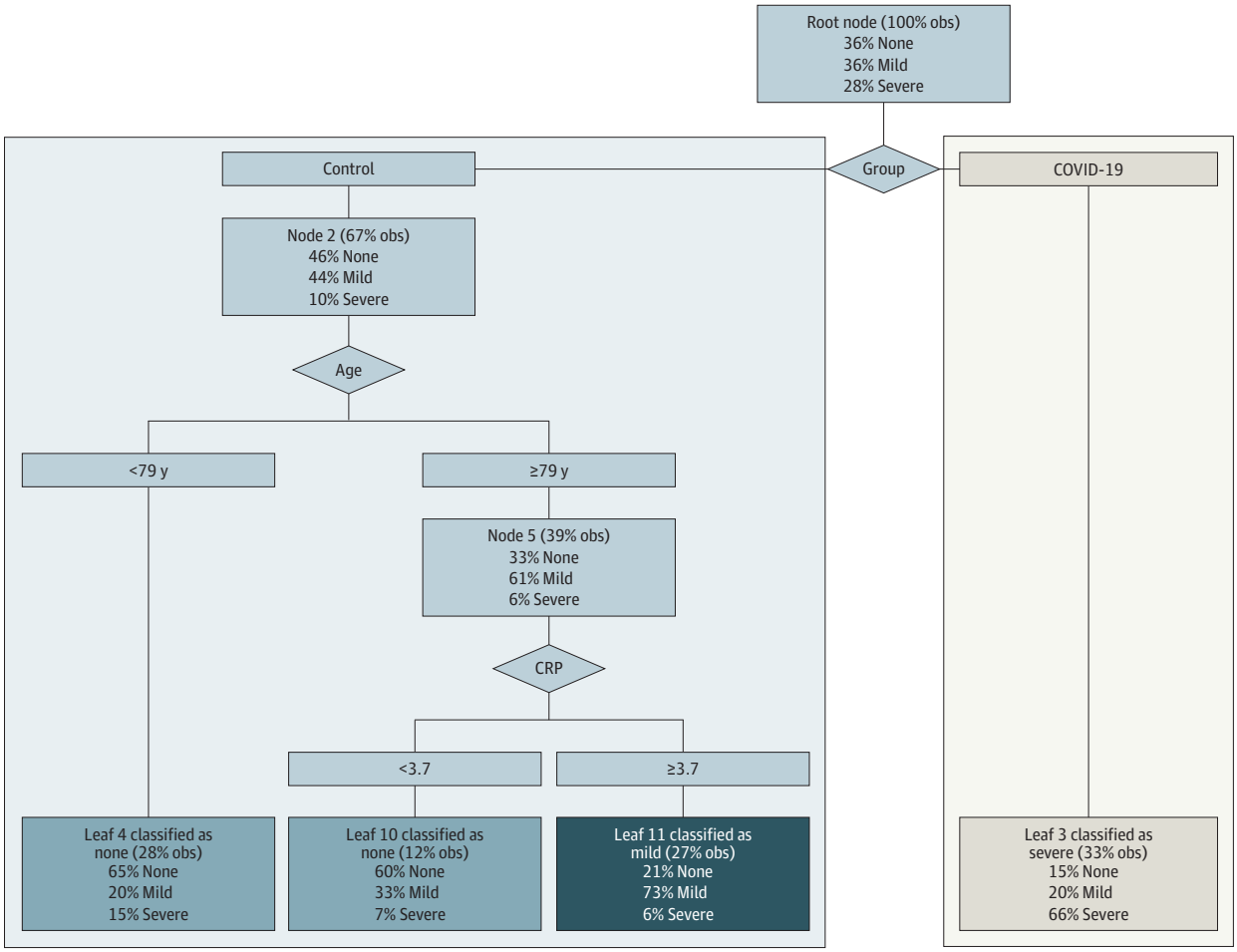
Different models confirmed that COVID-19 is strongly associated with complications. The CLM-identified group (COVID-19 vs control) and age as significantly associated with complications, but the model was not able to estimate the parameter of the remaining variables (convergence problems) (Table 4). The problem was overcome by the nonparametric classification tree, which is being increasingly used in medicine[27]; this tool confirmed the primary importance of COVID-19, highlighting differences between controls and patients with SARS-CoV-2 infection (Figure). The ranking obtained by the VI, extracted from the classification tree, identified COVID-19 as the main variable associated with surgical outcome (Video). Thus, COVID-19 masks the importance of well-known surgical risk factors usually considered during surgical decision-making. These data support the recommendation to postpone surgery, whenever possible, in patients with COVID-19.[28-35]

Limitations

This study has several limitations. The follow-up period is limited (mean [SD], 36 [17] days), and only early outcomes could be investigated. The matched controls were mainly historical, as it was possible to match only a few patients from the same study period. Although not evident retrospectively, we cannot theoretically exclude that some patients might have died as a consequence of collateral damage during the COVID-19 outbreak.

Data were collected from different subspecialties, using classifications (Clavien-Dindo[11,12] and its continuous version[13,14]) that have not been validated in all of them. Finally, the main limit is represented by a cohort of patients that is small and does not allow detailed subpopulation analyses. However, this study focused on the association of COVID-19 with surgical outcomes, with the advantage of a single-center study and a tightly matched control population. Future studies with larger cohorts are needed to determine the effect of COVID-19 in different surgical subspecialties and clinical scenarios (eg, sepsis).

Figure. Classification Tree for Complications and Their Associated Variables



Each leaf of the tree (in color) is classified according to the most frequent class in it (majority vote rule); blue, dark blue, and gray are for none, mild, and severe complications, respectively. The root node (containing all observations) is automatically divided by the algorithm with respect to the group variable: control patients are positioned on the left of the tree and coronavirus disease 2019 (COVID-19) on the right. The control branches lead to blue or dark blue leaves. In contrast, the COVID-19 branch leads to a unique gray leaf classified as severe complications. CRP indicates C-reactive protein; obs, observed.

Conclusions

This matched cohort study documents that surgical mortality and complications are significantly higher in patients with COVID-19. Pulmonary and thrombotic complications are significantly associated with it. Different models (CLM and classification tree) associated COVID-19 with complications, demonstrating that it is the primary factor to be considered in surgical decision-making.

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