

ANESTHESIOLOGY

Perioperative Mortality of the COVID-19 Recovered Patient Compared to a Matched Control: A Multicenter Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Surgical procedures performed on patients with recent exposure to COVID-19 infection have been associated with increased mortality risk

What This Article Tells Us That Is New

- In a retrospective observational cohort study in patients presenting for elective inpatient surgery between April 2020 and April 2021, patients with a previous positive test for COVID-19 before the surgery had an elevated risk of perioperative mortality and pulmonary complications but not kidney injury
- The risk was less if the positive test was more than 2 weeks before surgery

ABSTRACT

Background: Surgical procedures performed on patients with recent exposure to COVID-19 infection have been associated with increased mortality risk in previous studies. Accordingly, elective surgery is often delayed after infection. The study aimed to compare 30-day hospital mortality and postoperative complications (acute kidney injury, pulmonary complications) of surgical patients with a previous COVID-19 infection to a matched cohort of patients without known previous COVID-19. The authors hypothesized that COVID-19 exposure would be associated with an increased mortality risk.

Methods: In this retrospective observational cohort study, patients presenting for elective inpatient surgery across a multicenter cohort of academic and community hospitals from April 2020 to April 2021 who had previously tested positive for COVID-19 were compared to controls who had received at least one previous COVID-19 test but without a known previous COVID-19–positive test. The cases were matched based on anthropometric data, institution, and comorbidities. Further, the outcomes were analyzed stratified by timing of a positive test result in relation to surgery.

Results: Thirty-day mortality occurred in 229 of 4,951 (4.6%) COVID-19–exposed patients and 122 of 4,951 (2.5%) controls. Acute kidney injury was observed in 172 of 1,814 (9.5%) exposed patients and 156 of 1,814 (8.6%) controls. Pulmonary complications were observed in 237 of 1,637 (14%) exposed patients and 164 of 1,637 (10%) controls. COVID-19 exposure was associated with an increased 30-day mortality risk (adjusted odds ratio, 1.63; 95% CI, 1.38 to 1.91) and an increased risk of pulmonary complications (1.60; 1.36 to 1.88), but was not associated with an increased risk of acute kidney injury (1.03; 0.87 to 1.22). Surgery within 2 weeks of infection was associated with a significantly increased risk of mortality and pulmonary complications, but that effect was nonsignificant after 2 weeks.

Conclusions: Patients with a positive test for COVID-19 before elective surgery early in the pandemic have an elevated risk of perioperative mortality and pulmonary complications but not acute kidney injury as compared to matched controls. The span of time from positive test to time of surgery affected the mortality and pulmonary risk, which subsided after 2 weeks.

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Global surgical and perioperative impacts should be considered as part of the enormous toll exacted by the COVID-19 pandemic. Early reports illustrated a high mortality rate of up to 24% in surgical patients with a perioperative COVID-19 infection,¹⁻⁷ and ongoing research continues to indicate an elevated risk of COVID-19-associated perioperative morbidity and mortality.⁸⁻¹² The majority of previous research did not differentiate elective care from urgent surgery. Furthermore, previous studies are limited by ascertainment bias whereby symptomatic patients were more likely to be tested for COVID-19.¹³ Outcomes data for the growing cohort of patients who have recovered from COVID-19 and subsequently undergo elective surgery remain scarce. Given the potential emergence of vaccine-avoidant strains of COVID-19 and the need for some patients to undergo surgery while acutely ill or recovering, it is crucial to understand when a patient can safely undergo surgery after COVID-19 and the risks attendant to earlier *versus* delayed surgery.

The ability of COVID-19 to impact a variety of organ systems could impart elevated perioperative risk even among patients with overtly mild disease.¹⁴ We have also gained further understanding of the inflammatory component and vascular endothelial damage or dysfunction precipitated by COVID-19,¹⁵ which may increase perioperative risk. Studies to date have included all surgical patients without refining a cohort to include those for whom surgical care may be reasonably delayed, thus providing little guidance for the more common situation of a patient who could delay surgery after a COVID-19 exposure if necessary. To accurately weigh the risks and benefits of proceeding with a surgical intervention, an understanding of the perioperative risk associated with undergoing surgery and anesthesia after COVID-19 is necessary. This would allow clinicians to plan the time between disease convalescence and surgical intervention. Understanding the relative risk of proceeding with surgery in patients with a previous confirmed COVID-19 exposure *versus* those in a negative COVID-19 matched cohort would assist perioperative clinicians in making decisions to proceed with surgery or delay. In addition, this information will facilitate accurate risk stratification, consent discussions, and postoperative care planning.

Therefore, we performed a multicenter observational cohort study of COVID-19-exposed patients undergoing elective surgery and compared them to a matched cohort of patients tested for COVID-19 but without a positive result for COVID-19. In order to reduce confounding from the possibility that patients who received a COVID-19 test are systematically different from those who did not receive a test, we limited our comparison to the group of patients who had at least one valid COVID-19 test result during the study period. Within this cohort, we aimed to compare the 30-day hospital mortality and immediate perioperative complications (acute kidney injury [AKI] at 48h, pulmonary complications within 90 days) of surgical patients with a previous

COVID-19-positive infection, presenting for surgery not directly attributable to COVID-19, to a matched cohort of patients without a known previous diagnosis of COVID-19. We hypothesized that patients with a history of previous COVID-19 infection will have an increased perioperative mortality and complication rate when compared to patients without known previous COVID-19, and that this rate would decrease with extended time of infection to time of surgery.

Materials and Methods

Study Design and Database

This was a retrospective cohort study utilizing propensity-matched observational data collected as part of an established research consortium, the Multicenter Perioperative Outcomes Group (Ann Arbor, Michigan). Institutional review board approval was obtained by all participating sites to contribute deidentified data to the Multicenter Perioperative Outcomes Group with a waiver of written informed consent, and the primary study center (Oregon Health & Science University, Portland, Oregon) obtained institutional review board approval to study this limited dataset. Our report adhered to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement extension of the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies as well as extension of STROBE for reporting of propensity-matched studies.^{16,17} Before the data were accessed, the study proposal including the data analysis and statistical plan was presented to the Multicenter Perioperative Outcomes Group perioperative clinical research committee, and underwent revision and final approval with study registration and posting on May 10, 2021.¹⁸ After study approval and registration, data were extracted from the Multicenter Perioperative Outcomes Group dataset. Methods for local electronic health record data acquisition, validation, mapping to semantically interoperable universal Multicenter Perioperative Outcomes Group concepts, and secure transfer to the coordinating center have been previously described.¹⁹

Study Population

The study period for the exposure cohort was from April 2020 until April 2021 and included Multicenter Perioperative Outcomes Group participating centers that had (1) reported outcome and exposure variables without gaps in the study period; (2) submitted laboratory findings with mapped variables to the COVID-19 polymerase chain reaction, nucleic acid, or antigen tests; (3) contributed more than 20 exposure cases to the dataset; and (4) reported mortality outcomes.

We included patients age greater than 18 yr with at least one laboratory COVID-19 test (positive or negative result) undergoing inpatient surgical procedures. We

excluded cases with American Society of Anesthesiologists (ASA; Schaumburg, Illinois) emergency classification, ASA Physical Status V or VI, ambulatory procedures, vascular surgery, liver transplant surgery, lung transplant surgery, nonoperative procedures, magnetic resonance imaging, cardiac surgery, and cases started between the hours of 8:00 PM and 6:00 AM. These exclusions were aimed at targeting an elective inpatient population undergoing surgery not directly attributable to sequelae from a potential COVID-19 diagnosis.

The primary analysis compared all outcomes to patients in the same time period who had negative COVID-19 tests before surgery. A preplanned sensitivity analysis was performed, comparing COVID-19–exposed patients to matched patients having surgery during the year before the pandemic (April 2019 to March 2020).

The exposure cohort time period occurred during the first identified COVID-19 strains as well as the alpha variant. The delta variant did not appear in the United States during this study period. By the end of the observation period (April 2021), many Americans had received some COVID-19 vaccination.

COVID-19 Diagnosis Exposure

The primary exposure variable studied was COVID-19 diagnosis ascertained by preoperative laboratory polymerase chain reaction, nucleic acid, or antigen test any time before the surgical procedure. “Detected” or “positive” was considered positive while “not detected” or “negative” was considered negative. Cases with positive tests noted only after the surgical procedure were excluded.

Outcome Definitions

The primary outcome was all-cause 30-day mortality defined using a combination of recorded date of procedure and date of mortality. The secondary outcome of AKI was defined by the Kidney Disease: Improving Global Outcomes guidelines as serum creatinine of at least 0.4 mg/dl within 48 h after surgery or an increase of at least 50% from baseline within a 7-day period.²⁰ The secondary outcome of pulmonary complications is defined broadly by the presence of new pulmonary International Classification of Diseases, Tenth Revision codes within 90 days (pneumonia, respiratory failure, pneumothorax, pulmonary embolus) not present on admission.

Covariate Data

For descriptive purposes and confounder adjustment of variables potentially associated with the COVID-19 exposure and study outcomes, perioperative characteristics were included as covariates. These included patient demographic, anthropometric, medical history, anesthetic, surgical, and laboratory testing variables as available within

the Multicenter Perioperative Outcomes Group database (tables 1 to 3).

Statistical Analysis

We performed a descriptive analysis of patient and procedure characteristics, including the overall cohort and cohorts with and without the exposure variable. As part of our descriptive analysis, we assessed missingness in our variables, which informed the analytic approach: we conducted a complete case analysis if less than 5% of the data was missing in all the variables; otherwise, we implemented multiple imputation by chained equations or omitted a variable if the rate of missingness was disproportionately greater than the other variables. A missing data report is included in the Supplemental Digital Content (<https://links.lww.com/ALN/D352>).

The timing between the positive test and procedure date and the 30-day postoperative mortality after elective surgery in patients with a previous COVID-19 diagnosis was described using descriptive statistics and data visualization (e.g., histograms and bar charts).

We compared the 30-day postoperative mortality and the perioperative complications of surgical patients who recovered from a previous COVID-19 infection, presenting for unrelated surgery, to a cohort that tested negative for COVID-19. For our primary analysis, we compared the exposed cohort to a contemporaneously matched control cohort with laboratory-confirmed negative tests during the same time period. We also conducted a sensitivity analysis with a matched control from the year before (April 2019 to March 2020). We expected patients who recovered from COVID-19 infection might differ from uninfected patients, and in order to compare outcomes in these two groups, we performed exact matching based on the institution, age, ASA classification, race, sex, and solid tumor (without metastasis). We then used inverse probability weighting to further reduce the potential bias and confounding in our comparisons. In this study, the propensity score was the conditional probability that a patient had a previous laboratory-confirmed COVID-19 infection, given a set of covariates. For each patient in our sample, we estimated the propensity for COVID-19 infection using a nonparametric gradient boosted model to account for possible nonlinear relationships between the covariates and propensity scores.^{21,22} The model was executed to estimate the propensity for COVID-19 in the entire cohort and to evaluate the quality of covariate balance between the two groups before and after weighting. The returned propensity scores were then transformed into inverse probability weights and used to construct a weighted cohort of patients who were diagnosed with COVID-19 who were similar to patients with a negative result, based on the observable characteristics. The variables listed in tables 1 to 3 were considered for estimating the propensity scores.

Table 1. Demographic Covariates Explored in Weighting and Balance across Cohorts

Covariate: Demographics	Unweighted				Weighted			
	COVID-19: N (%) 5,260	Control: N (%)	Effect Size	Chi-square P Value	COVID-19: N (%) 4,951	Control: N (%)	Effect Size*	Chi-square P Value†
Age: (18, 30)	923 (18%)	923 (18%)	0	> 0.999	884 (18%)	884 (18%)	-0.006	> 0.999
Age: (30, 36)	640 (12%)	640 (12%)	0	—	617 (12%)	617 (12%)	-0.003	—
Age: (36, 45)	537 (10%)	537 (10%)	0	—	510 (10%)	510 (10%)	-0.003	—
Age: (45, 54)	518 (9.8%)	518 (9.8%)	0	—	475 (9.6%)	475 (9.6%)	0.004	—
Age: (54, 60)	450 (8.6%)	450 (8.6%)	0	—	413 (8.3%)	413 (8.3%)	0.002	—
Age: (60, 65)	416 (7.9%)	416 (7.9%)	0	—	385 (7.8%)	385 (7.8%)	0	—
Age: (65, 69)	368 (7.0%)	368 (7.0%)	0	—	338 (6.8%)	338 (6.8%)	0.004	—
Age: (69, 74)	461 (8.8%)	461 (8.8%)	0	—	435 (8.8%)	435 (8.8%)	0.002	—
Age: (74, 80)	446 (8.5%)	446 (8.5%)	0	—	423 (8.5%)	423 (8.5%)	0.003	—
Age: (80, 90]	501 (9.5%)	501 (9.5%)	0	—	471 (9.5%)	471 (9.5%)	-0.001	—
ASA Physical Status: I	62 (1.2%)	62 (1.2%)	0	> 0.999	61 (1.2%)	61 (1.2%)	-0.002	0.999
ASA Physical Status: II	1,523 (29%)	1,523 (29%)	0	—	1,486 (30%)	1,486 (30%)	-0.002	—
ASA Physical Status: III	2,742 (52%)	2,742 (52%)	0	—	2,617 (53%)	2,617 (53%)	0.002	—
ASA Physical Status: IV	933 (18%)	933 (18%)	0	—	787 (16%)	787 (16%)	0.001	—
Body mass index: normal weight	1,090 (21%)	1,257 (24%)	-0.076	0	1,041 (21%)	1,167 (24%)	-0.009	0.873
Body mass index: obese class I	722 (14%)	652 (12%)	0.039	—	681 (14%)	624 (13%)	0.005	—
Body mass index: obese class II	1,217 (23%)	1,081 (21%)	0.063	—	1,133 (23%)	1,023 (21%)	0.011	—
Body mass index: obese class III	682 (13%)	598 (11%)	0.049	—	630 (13%)	576 (12%)	0.005	—
Body mass index: pre-obese	1,438 (27%)	1,490 (28%)	-0.022	—	1,360 (27%)	1,411 (28%)	-0.001	—
Body mass index: underweight	111 (2.1%)	182 (3.5%)	-0.082	—	106 (2.1%)	150 (3.0%)	-0.022	—
Sex: female	3,243 (62%)	3,243 (62%)	0	> 0.999	3,095 (63%)	3,095 (63%)	-0.008	0.685
Sex: male	2,017 (38%)	2,017 (38%)	0	—	1,856 (37%)	1,856 (37%)	0.008	—
Race: American Indian or Alaska Native	24 (0.5%)	24 (0.5%)	0	> 0.999	23 (0.5%)	23 (0.5%)	0.001	> 0.999
Race: Asian or Pacific Islander	122 (2.3%)	122 (2.3%)	0	—	114 (2.3%)	114 (2.3%)	0.001	—
Race: biracial or multiracial	12 (0.2%)	12 (0.2%)	0	—	11 (0.2%)	11 (0.2%)	-0.002	—
Race: Black, not of Hispanic origin	1,057 (20%)	1,057 (20%)	0	—	958 (19%)	958 (19%)	-0.004	—
Race: Hispanic, black	12 (0.2%)	12 (0.2%)	0	—	12 (0.2%)	12 (0.2%)	0	—
Race: Hispanic, white	156 (3.0%)	156 (3.0%)	0	—	145 (2.9%)	145 (2.9%)	0	—
Race: unknown race	690 (13%)	690 (13%)	0	—	647 (13%)	647 (13%)	0.003	—
Race: White, not of Hispanic origin	3,187 (61%)	3,187 (61%)	0	—	3,041 (61%)	3,041 (61%)	0.001	—

*Standardized effect size (or standardized bias), defined as the difference in proportions divided by the pooled SD. †P value of the chi-square test of independence. ASA, American Society of Anesthesiologists.

To evaluate balance across groups, we utilized plots and tables to compare the absolute standardized mean difference, defined as the difference between the group means divided by their pooled SD, as an effect size of covariate imbalance between groups. We adopt the position that a standardized difference of 0.1 represents a meaningful imbalance.²³ The P value of the two-sample chi-square test for covariates between the unweighted and weighted results was also calculated (Supplemental Digital Content, <https://links.lww.com/ALN/D352>). Briefly, the chi-square test examines whether two samples come from the same distribution by comparing observed counts with expected counts under the null hypothesis of a common distribution. A P value greater than 0.05 suggests that there is insufficient evidence of a difference and thus implies a similar covariate distribution between treatment groups.

Common support was examined with density plots to check for overlap across the groups' propensity score distributions, and then trimming was performed so that group propensities shared a common range.

To compare 30-day postoperative mortality and perioperative complications in recovered COVID-19 patients *versus* never diagnosed patients, we used a generalized linear mixed model with binomial family and logit link function. The cohort was weighted by the inverse probability weighting to balance the groups in terms of their likelihood of a COVID-19 infection and included a categorical variable for previous COVID-19 diagnosis, as described above. No additional covariates were added, as balance was adequately achieved between diagnosis groups. Two-tailed Wald tests of the categorical variable for previous COVID-19 diagnosis were used to formally test the effect of previous infection at a 5% significance level. The same modeling approach was implemented to compare the perioperative complication rates for AKI and pulmonary complications. We also conducted a sensitivity analysis comparing patients with a previous COVID-19 diagnosis to matched controls from the year before (April 2019 to March 2020) to assess the robustness of the conclusions and to ensure appropriate interpretation of the results. For this matched group,

Table 2. Comorbidity Covariates Explored in Weighting and Balance across Cohorts

Covariate: Comorbidities	Unweighted				Weighted			
	COVID-19: N (%)	Control: N (%)	Effect Size	Chi-square P Value	COVID-19: N (%)	Control: N (%)	Effect Size*	Chi-square P Value†
AIDS HIV	19 (0.4%)	26 (0.5%)	-0.02	0.296	18 (0.4%)	19 (0.4%)	-0.006	0.729
Alcohol abuse	61 (1.2%)	80 (1.5%)	-0.031	0.107	53 (1.1%)	59 (1.2%)	-0.012	0.487
Blood loss anemia	157 (3.0%)	152 (2.9%)	0.006	0.773	142 (2.9%)	134 (2.7%)	0.004	0.814
Cardiac arrhythmia	1,716 (33%)	1,622 (31%)	0.038	0.049	1,545 (31%)	1,465 (30%)	0.014	0.485
Chronic pulmonary disease	1,126 (21%)	1,243 (24%)	-0.053	0.006	1,056 (21%)	1,148 (23%)	-0.007	0.725
Coagulopathy	795 (15%)	616 (12%)	0.1	0	677 (14%)	539 (11%)	0.024	0.21
Congestive heart failure	841 (16%)	922 (18%)	-0.041	0.035	776 (16%)	796 (16%)	-0.01	0.608
Depression	918 (17%)	954 (18%)	-0.018	0.359	862 (17%)	886 (18%)	-0.003	0.884
Diabetes with complications	596 (11%)	528 (10%)	0.042	0.032	533 (11%)	481 (9.7%)	0.014	0.454
Diabetes without complications	846 (16%)	734 (14%)	0.06	0.002	766 (15%)	676 (14%)	0.013	0.519
Drug abuse	210 (4.0%)	299 (5.7%)	-0.079	0	193 (3.9%)	255 (5.2%)	-0.02	0.284
Fluid and electrolyte disorders	1,760 (33%)	1,458 (28%)	0.125	0	1,570 (32%)	1,309 (26%)	0.023	0.237
Hypertension with complications	1,190 (23%)	1,199 (23%)	-0.004	0.834	1,084 (22%)	1,068 (22%)	0.001	0.939
Hypertension without complications	1,981 (38%)	1,949 (37%)	0.013	0.519	1,833 (37%)	1,814 (37%)	0.001	0.954
Hypothyroidism	677 (13%)	695 (13%)	-0.01	0.602	637 (13%)	653 (13%)	0	0.988
Iron deficiency anemia	460 (8.7%)	400 (7.6%)	0.042	0.033	408 (8.2%)	354 (7.2%)	0.011	0.583
Liver disease	438 (8.3%)	464 (8.8%)	-0.018	0.365	389 (7.9%)	402 (8.1%)	-0.006	0.746
Lymphoma	71 (1.3%)	82 (1.6%)	-0.017	0.37	67 (1.4%)	68 (1.4%)	-0.008	0.617
Metastatic cancer	302 (5.7%)	296 (5.6%)	0.005	0.801	290 (5.9%)	285 (5.8%)	0.003	0.886
Obesity	1,604 (30%)	1,387 (26%)	0.091	0	1,470 (30%)	1,311 (26%)	0.019	0.337
Other neurologic disorders	765 (15%)	611 (12%)	0.087	0	666 (13%)	536 (11%)	0.019	0.319
Paralysis	88 (1.7%)	72 (1.4%)	0.025	0.202	76 (1.5%)	58 (1.2%)	0.009	0.602
Peptic ulcer disease excluding bleeding	141 (2.7%)	129 (2.5%)	0.014	0.459	130 (2.6%)	108 (2.2%)	0.003	0.871
Peripheral vascular disorders	552 (10%)	570 (11%)	-0.011	0.57	506 (10%)	508 (10%)	0	0.998
Psychoses	88 (1.7%)	72 (1.4%)	0.025	0.202	76 (1.5%)	58 (1.2%)	0.009	0.602
Pulmonary circulation disorders	316 (6.0%)	321 (6.1%)	-0.004	0.838	270 (5.5%)	278 (5.6%)	0	0.988
Renal failure	1,035 (20%)	995 (19%)	0.019	0.323	938 (19%)	889 (18%)	0.002	0.898
Rheumatoid arthritis collagen	165 (3.1%)	197 (3.7%)	-0.033	0.087	152 (3.1%)	177 (3.6%)	-0.006	0.771
Solid tumor without metastasis	605 (12%)	605 (12%)	0	1	578 (12%)	578 (12%)	0.005	0.801
Valvular disease	434 (8.3%)	583 (11%)	-0.096	0	397 (8.0%)	502 (10%)	-0.02	0.3
Weight loss	645 (12%)	525 (10.0%)	0.073	0	559 (11%)	451 (9.1%)	0.016	0.391

*Standardized effect size (or standardized bias), defined as the difference in proportions divided by the pooled SD. †P value of the chi-square test of independence. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

we similarly performed exact matching followed by inverse probability weighting.

To determine if the 30-day postoperative mortality rate was related to the length of time from COVID-19 diagnosis to surgery, we conducted an analysis of patients who took a COVID-19 test before their procedure date. We implemented a generalized linear mixed model with 30-day postoperative mortality as the outcome, regressed on COVID-19 diagnosis, length of time from diagnosis to surgery, and their interaction. Length of time from diagnosis to surgery was binned into 2-week segments: 0 to 2 weeks, 2 to 4 weeks, 4 to 6 weeks, 6 to 8 weeks, and greater than 8 weeks. We then formed comparisons of mortality rates between COVID-19 diagnosis levels within each week segment and used a Holm-Bonferroni correction to adjust for multiple comparisons. All analyses were performed utilizing R 4.2.1 and are available in the Supplemental Digital Content (<https://links.lww.com/ALN/D352>).

Power Analysis

Based on a cohort discovery tool in the Multicenter Perioperative Outcomes Group, there were 77,876 patients with a negative COVID-19 laboratory test and 2,116 confirmed positive patients. Including 2,000 cases in each arm would achieve power to detect a 2.4-fold difference in mortality between groups. This sample size calculation was computed from a two-proportion test with alpha set to 0.05. We did not *a priori* define a minimally significant difference in mortality rates.

Results

The final analysis included 37 medical centers, yielding 237,126 patients with a preoperative COVID-19 test, each undergoing one index surgery. COVID-19 was detected in 5,361 patients undergoing elective surgery (2.3%). After matching and propensity score trimming, 30-day in-hospital postoperative mortality occurred in 229 of 4,951 (4.6%).

Table 3. Procedure Covariates Explored in Weighting and Balance across Cohorts

Covariate: Body Region	Unweighted				Weighted			
	COVID-19: N (%)	Control: N (%)	Effect Size	Chi-square P Value	COVID-19: N (%)	Control: N (%)	Effect Size*	Chi-square P Value†
Burn	23 (0.4%)	21 (0.4%)	0.006	0	21 (0.4%)	20 (0.4%)	0.005	0.998
Cardiac	67 (1.3%)	120 (2.3%)	-0.076	—	60 (1.2%)	98 (2.0%)	-0.015	—
Gynecologic	44 (0.8%)	53 (1.0%)	-0.018	—	43 (0.9%)	51 (1.0%)	-0.006	—
Head	226 (4.3%)	259 (4.9%)	-0.03	—	217 (4.4%)	241 (4.9%)	-0.004	—
Hip/leg/foot	661 (13%)	655 (12%)	0.003	—	629 (13%)	619 (13%)	0.001	—
Lower abdomen	394 (7.5%)	460 (8.7%)	-0.046	—	385 (7.8%)	436 (8.8%)	-0.003	—
Male reproductive system	8 (0.2%)	5 (<0.1%)	0.016	—	5 (0.1%)	4 (<0.1%)	0.007	—
Neck	325 (6.2%)	187 (3.6%)	0.122	—	223 (4.5%)	171 (3.5%)	0.028	—
Obstetrics	1,292 (25%)	1,129 (21%)	0.074	—	1,258 (25%)	1,113 (22%)	0.003	—
Other procedures‡	3 (<0.1%)	10 (0.2%)	-0.038	—	3 (<0.1%)	3 (<0.1%)	-0.016	—
Pelvis	27 (0.5%)	19 (0.4%)	0.023	—	22 (0.4%)	18 (0.4%)	0.008	—
Radiologic	144 (2.7%)	219 (4.2%)	-0.078	—	138 (2.8%)	181 (3.7%)	-0.014	—
Shoulder/arm/hand	103 (2.0%)	122 (2.3%)	-0.025	—	100 (2.0%)	112 (2.3%)	-0.006	—
Spine and spinal cord	215 (4.1%)	300 (5.7%)	-0.075	—	205 (4.1%)	284 (5.7%)	-0.007	—
Thorax—extrathoracic	192 (3.7%)	161 (3.1%)	0.033	—	175 (3.5%)	146 (2.9%)	0.007	—
Thorax—intrathoracic	333 (6.3%)	343 (6.5%)	-0.008	—	311 (6.3%)	329 (6.6%)	0.004	—
Upper abdomen	955 (18%)	945 (18%)	0.005	—	919 (19%)	890 (18%)	-0.002	—
Urologic	238 (4.5%)	236 (4.5%)	0.002	—	227 (4.6%)	225 (4.5%)	-0.001	—

*Standardized effect size (or standardized bias), defined as the difference in proportions divided by the pooled SD. †P value of the chi-square test of independence. ‡“Other procedure” codes, covering services such as anesthesia for nerve blocks and daily hospital management of epidural continuous drug administration. <https://www.aapc.com/codes/cpt-codes-range/00100-01999/>

Among those reporting creatinine laboratory outcomes, AKI was observed in 172 of 1,814 (9.5%). Among those reporting diagnosis codes, pulmonary complications were observed in 237 of 1,637 (14%).

Patient Population: Baseline Characteristics

As described in table 1, our study population had a median age between 54 and 60 yr, was majority white race, was majority female, and majority had an ASA Physical Status score of III. The most common comorbidity was hypertension without complication.

Multivariable Analyses

Each positive case was exact-matched to both a contemporaneous and historical control on institution, age, ASA classification, race, sex, and solid tumor (without metastasis). After exact-matching, propensity score weights were constructed using observed presurgical covariates. The resulting covariate balances after weighting are displayed in tables 1 to 3.

After exact matching and inverse probability weighting, COVID-19 exposure was associated with an increased 30-day mortality risk compared to contemporaneous matches (odds ratio, 1.63; 95% CI, 1.38 to 1.91) and historical matches (odds ratio, 1.89; 95% CI, 1.49 to 2.39). COVID-19 exposure was associated with an increased risk of pulmonary complications in contemporaneous matches (odds ratio, 1.60; 95% CI, 1.36 to 1.88) and historical matches (odds ratio, 1.83; 95% CI, 1.53 to 2.18).

COVID-19 exposure was not associated with an increased risk of AKI in either contemporaneous matches (odds ratio, 1.03; 95% CI, 0.87 to 1.22) or historical matches (odds ratio, 0.97; 95% CI, 0.81 to 1.16).

The effect of time between COVID-19 infection and time of surgery is shown in figure 1. The 0- to 2-week time frame was associated with a significantly increased risk of mortality, but that effect became nonsignificant after 2 weeks. Figure 2 similarly demonstrates the effect of interval between infection and time of surgery on risk of pulmonary complications. The effect of pulmonary complications was increased in the 0- to 2-week period but also became nonsignificant after 2 weeks. Finally, figure 3 represents the effect of this interval on risk of AKI, demonstrating no increased risk from COVID-19 exposure at any interval.

Discussion

In this matched and weighted observational study of patients testing positive for COVID-19 before elective inpatient surgery, COVID-19 exposure early in the pandemic was associated with an increased 30-day mortality compared to a contemporaneous matched cohort as well as a historical cohort. Exposure was also associated with an increased risk of postoperative pulmonary complications but not postoperative AKI. Surgery performed within 2 weeks of a positive test was associated with elevated risk of mortality and pulmonary complications, but the effect was not observed beyond 2 weeks.

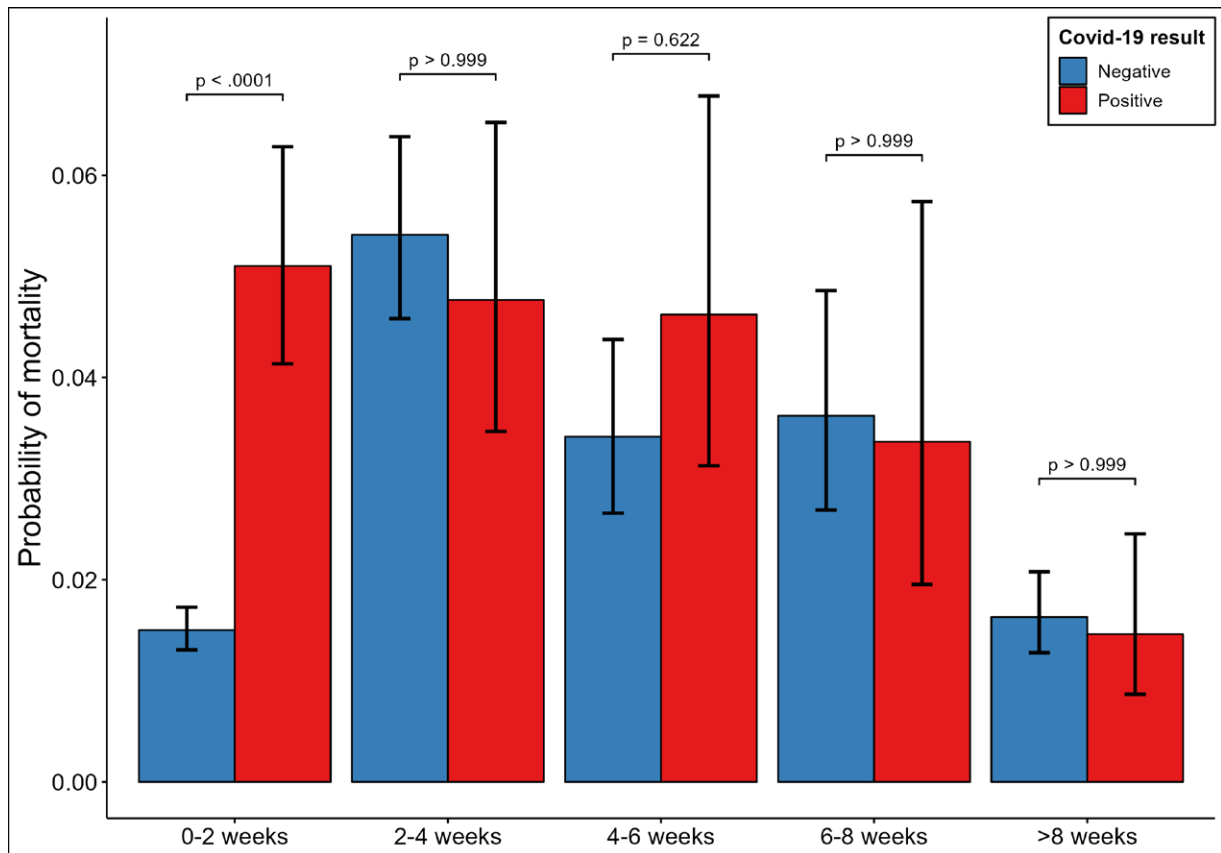


Fig. 1. Graph representing the probability of mortality after testing positive for COVID-19 in relation to surgical timing.

Previous studies have attempted to define the perioperative mortality of patients infected with COVID-19.^{1-3,7,9,10,24,25} Many of these studies encompass international surveys and the experience of countries with a different patient demographic than the United States. Most United States studies are limited to isolated surgical populations or do not investigate mortality. One large observational study from the American College of Surgeons (Chicago, Illinois) similarly identified a higher mortality rate, but most of the effect was observed in patients diagnosed with COVID-19 after surgery.²⁶ Our findings give more granular context to the United States experience. Our findings add to the existing literature by assessing risk in the elective surgery population, where there may be greater flexibility with respect to timing of the procedure. Our findings are novel as they compare patients to two sets of rigorously matched controls: contemporaneous controls and historical controls, with confounding further addressed *via* inverse probability weighting. As the COVID-19 pandemic has changed the healthcare landscape, both sets of controls were important to mitigate confounding due to secular trends as well as risk of occult or unreported infections in control subjects.

A major strength of the study is the use of data from multiple centers with shared reporting structure, mitigating reporting bias, and the inclusion in the contemporaneous cohort of only those patients with the presence of at least one COVID-19 test result. Other studies have included exposed patients who were tested for symptomatic reasons rather than a cohort that was tested as a routine.

The risks of surgery after COVID-19 infection must be balanced against the risks of delaying surgery; these data will help to guide the shared decision-making and discussions that should occur among the patient, the surgeon, and the anesthesiologist. In contrast to previous work indicating that the risk of mortality is significant up to 7 weeks,³ we observed that this risk tapered off after 2 weeks. Another study demonstrated that a composite risk of complications and death declined with time after infection.²⁷ This has important clinical practice implications as patients may be able to proceed with surgery after a brief waiting period. Current recommendations advise a waiting period up to 7 weeks for higher-risk patients. National organizations should consider these data when advising how long to delay elective surgery should COVID-19 variants become more lethal and for emerging viral respiratory infections.

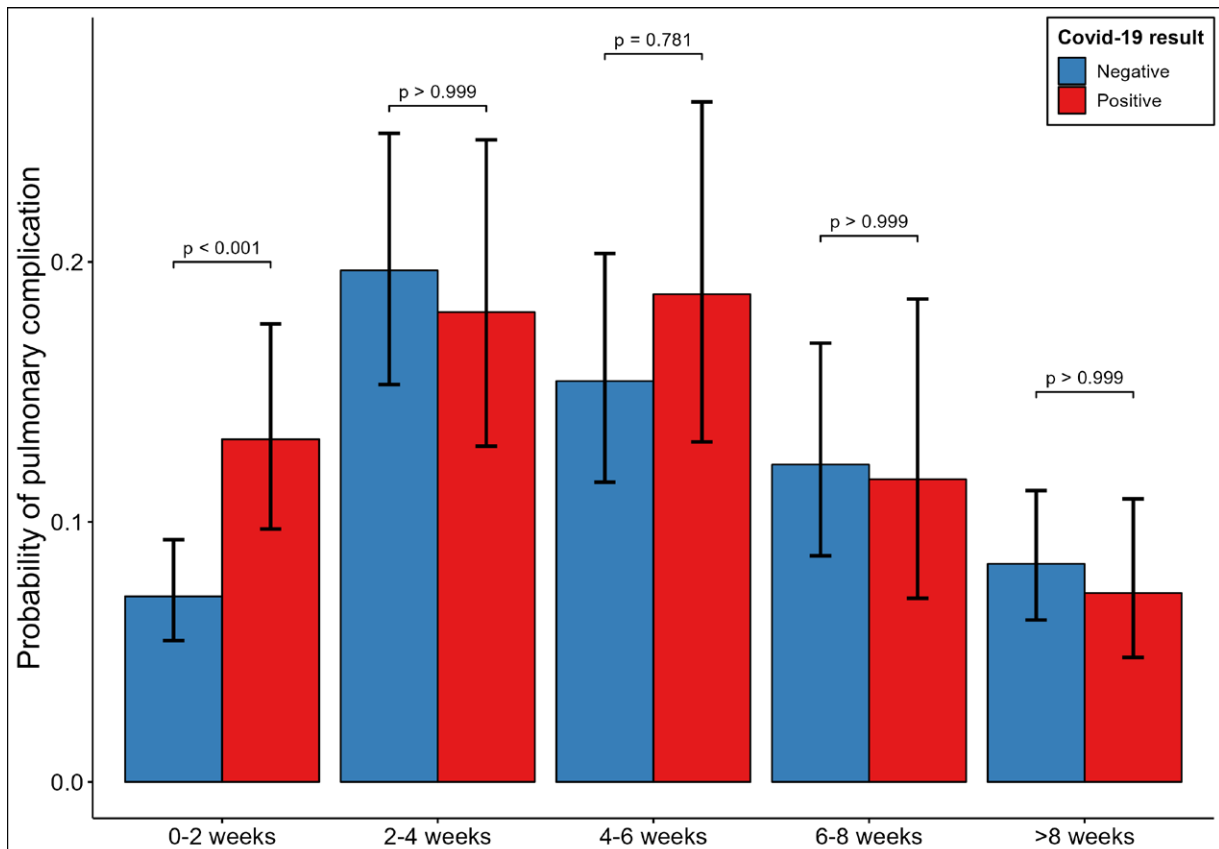


Fig. 2. Graph representing the probability of a pulmonary complication after testing positive for COVID-19 in relation to surgical timing.

Our finding of elevated risk of pulmonary complications carries significant biologic plausibility and is also consistent with previous work demonstrating increased risks both with non-COVID-19 respiratory infections²⁸ and with COVID-19.⁹ As these risks become nonsignificant after 2 weeks from time of test to surgery, our data again may offer guidance for key risk-benefit discussions regarding surgical delay.

The risk of perioperative AKI in the setting of antecedent COVID-19 infection has not been well-studied. AKI was frequently observed in hospitalized COVID-19 patients,²⁹ and an increased perioperative risk has been observed with urgent and emergent surgeries.²⁴ One survey-based study did find a higher rate of AKI in COVID-19 patients undergoing surgery early in the pandemic compared to a matched control 8 yr earlier.³⁰ It is reassuring that we did not identify an increased risk of AKI in the perioperative period among a population of patients undergoing elective surgery. In any event, this finding of the current study deserves further attention in future dedicated studies.

The cohort identified in this study was exposed to previous variants with a known higher risk of mortality compared

to more recent omicron variants.³¹ While vaccination data were not available in this study, the sample included a time frame up to April 2021 when most Americans had not yet been vaccinated, but vaccination had begun. Thus, our findings may not be generalizable to vaccinated patients or patients exposed to more recent variants. Indeed, vaccination does appear to confer a lower risk of perioperative mortality.³² Even so, our findings have important healthcare implications for understanding the risks associated with respiratory infections in general. Much of our guidance on how to manage COVID-19 came from previous work on severe acute respiratory syndrome and Middle Eastern respiratory syndrome. In the event of another respiratory pandemic or evolution of COVID-19, these findings will add to the understanding of perioperative risks to patients undergoing elective surgery.

Study Limitations

Our study has several important limitations to consider. First, there was variability in preoperative asymptomatic testing requirements across the United States. However, national standards recommended such practice, and we only included centers that provided robust exposure and

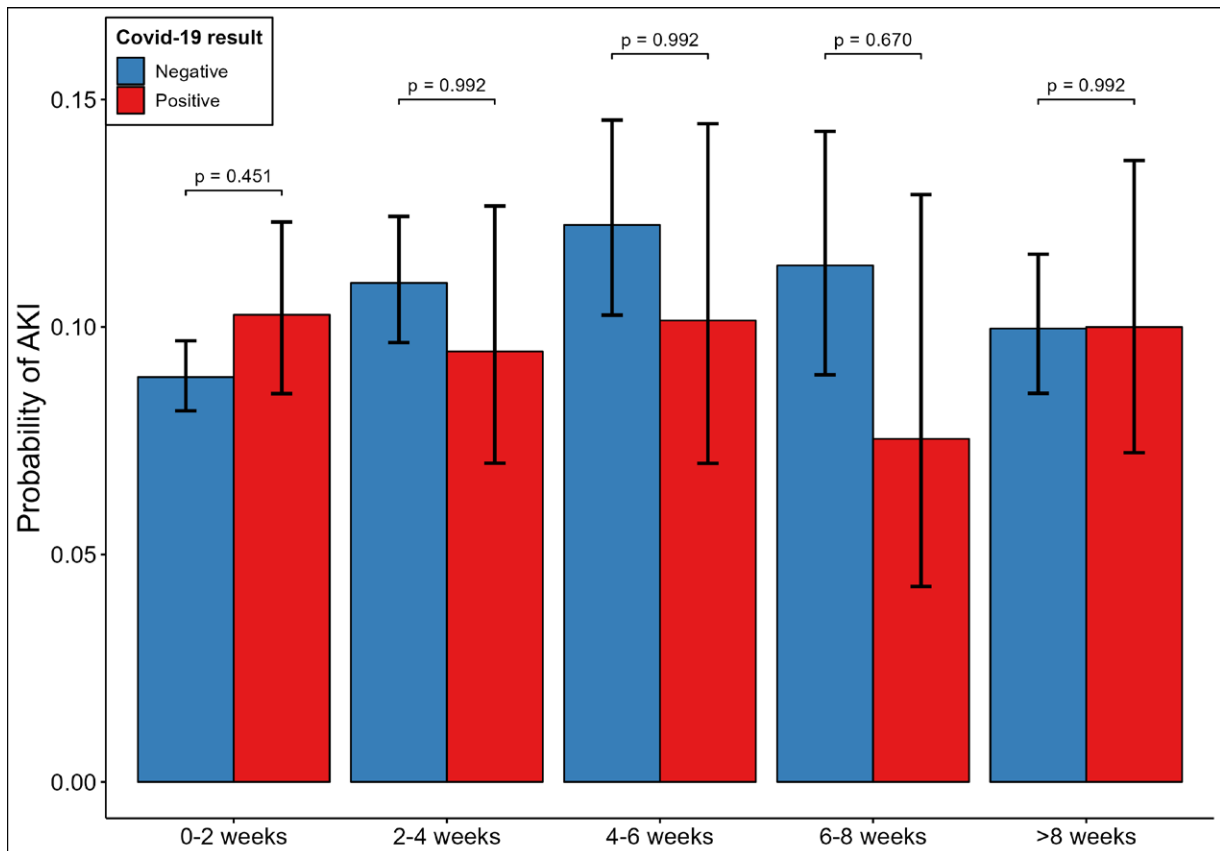


Fig. 3. Graph representing the probability of acute kidney injury (AKI) after testing positive for COVID-19 in relation to surgical timing.

outcome data for each covariate of interest. It is likely that the sampled cohort had routine preoperative testing and variable mapping that included the outcomes and exposures of interest. During the epoch sampled, most COVID-19 tests were polymerase chain reaction tests. As such, a proportion of patients with positive COVID-19 samples will represent patients with postinfectious remote viral shedding rather than acute infection. Conversely, antigen tests being less sensitive may have misclassified some infected patients as false negatives. Additionally, the preoperative symptom profiles of the COVID-19–positive patients were not available in this dataset, limiting our ability to discriminate between positivity due to symptomatic infections *versus* asymptomatic acute infections or remote postinfectious positivity. As discussed, these findings from an early cohort may not generalize to vaccinated patients, patients who have suffered from previous COVID-19 infection, or those exposed to more recent COVID-19 variants. It is also plausible that surgeries performed in a shorter interval from infection were simply more urgent, so there is likely residual confounding by indication. The exposure outcome of pulmonary complications is broad and includes diagnosis codes with disparate mechanistic sources. Finally, there may be

underreporting bias in the outcomes of interest due to lack of integration across American healthcare systems, such that patients undergoing surgery at one institution may present elsewhere for care related to, *e.g.*, postoperative pulmonary complications or AKI. Similarly, an institution may not have been made aware of postdischarge mortality events.

Conclusions

In summary, we found that patients with positive test for COVID-19 before surgery early in the pandemic have an elevated risk of perioperative mortality and pulmonary complications, as compared to both matched test-negative contemporaneous controls as well as matched historical controls presenting before the pandemic. We did not observe an effect of COVID-19 on postoperative AKI risk. The span of time from positive test to time of surgery affected the mortality and pulmonary risk, which subsided after 2 weeks and 6 weeks, respectively.

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Competing Interests

Dr. Mathis receives funding from the U.S. National Institutes of Health (Bethesda, Maryland; K01HL141701, R01DK133226) unrelated to the current work. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content, <https://links.lww.com/ALN/D352>

Supplemental Figure 1: Density plots of propensity scores unweighted (A) and weighted (B). The distribution of the propensity scores between patients diagnosed with COVID-19 (red) and those without known previous diagnosis (blue) were different in the unweighted sample, but more similar in the inverse probability weight-weighted sample.

Supplemental Table 1: Covariate Balance Mortality

Supplemental Figure 1.2: Balance of individual covariates in the primary analysis of mortality in the unweighted and weighted samples.

Supplemental Table 2: Covariate Balance Mortality Sensitivity Outcome

Supplemental Figure 2.2: Balance of individual covariates in the sensitivity (historical) analysis of mortality in the unweighted and weighted samples.

Supplemental Figure 3: Density plots of propensity scores unweighted (A) and weighted (B).

Supplemental Table 3: Covariate Balance: Pulmonary Outcome

Supplemental Figure 3.2: Balance of individual covariates in the primary analysis of pulmonary complications in the unweighted and weighted sample.

Supplemental Figure 4: Density plots of propensity scores unweighted (A) and weighted (B).

Supplemental Table 4: Covariate Balance Pulmonary Sensitivity Outcome

Supplemental Figure 4.2: Balance of individual covariates in the sensitivity (historical) analysis of pulmonary complications in the unweighted and weighted samples.

Supplemental Figure 5: Density plots of propensity scores unweighted (A) and weighted (B).

Supplemental Table 5: Covariate Balance Acute Kidney Injury

Supplemental Figure 5.2: Balance of individual covariates in the primary analysis of acute kidney injury in the unweighted and weighted samples.

Supplemental Figure 6: Density plots of propensity scores unweighted (A) and weighted (B).

Supplemental Table 6: Covariate Balance Acute Kidney Injury Sensitivity Outcome

Supplemental Figure 6.2: Balance of individual covariates in the sensitivity (historical) analysis of acute kidney injury in the unweighted and weighted samples.

Supplemental Table 7: Missing Data Analysis

Supplemental Table 8: Statistical Package Code for Weighting and Matching

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Appendix

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