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Original Contribution

Increased incidence of post-operative respiratory failure in patients with pre-operative SARS-CoV-2 infection

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ABSTRACT

Objective: While studies have reported increased post-operative pulmonary complications with SARS-CoV-2 infection, many are limited by use of historical controls or focus on less severe respiratory complications. We characterized the association between pre-operative SARS-CoV-2 infection and post-operative respiratory failure (PORF).

Design and setting: This was a single center retrospective cohort study in New York City between March 14–June 14, 2020.

Patients: Exclusion criteria were age < 18-years, obstetric procedures, absence of SARS-CoV-2 PCR testing, and pre-operative respiratory failure. A total of 778 patients met criteria, of which 87 had SARS-CoV-2.

Measurements: The primary outcome, PORF, included inability to extubate for ≥24 h or unplanned re-intubation within 5 days. Multiple exposures were measured including SARS-CoV-2 infection 4 weeks before or 5 days after surgery. Multivariable logistic regression was performed to adjust for pre-operative hypoxemia, oxygen use, and pneumonia as well as tachycardia, gender, Charlson Comorbidity Index (CCI), Surgical Mortality Probability Model (S-MPM) index, and peri-operative blood transfusion.

Main results: SARS-CoV patients had higher CCI (P = 0.007) and S-MPM scores (P = 0.02). The incidence of PORF was 16% versus 7% in uninfected comparators (P = 0.001). Amongst infected individuals, 39% exhibited symptoms of COVID-19 and PORF was more common in these patients compared to asymptomatic individuals (26% vs. 9%, P = 0.04). Adjusted analysis revealed increased odds of PORF with infection (OR 2.8, 95% CI 1.2–6.2). This persisted even when adjusting for probable mediators such as pre-operative hypoxemia. Infected patients also demonstrated increased adjusted odds of 30-day mortality (OR 3.5, 95% CI 1.4–9.1).

Conclusions: Detection of SARS-CoV-2 infection within 4 weeks before or 5 days after surgery is associated with increased odds of 5-day PORF and 30-day mortality. This supports delaying elective surgery, but questions remain regarding the applicability of this recommendation for asymptomatic patients needing urgent or semi-urgent procedures such as oncologic surgery.

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic continues to plague the world and its impact on peri-operative care remains a major concern. This is particularly relevant for post-surgical pulmonary complications including post-operative respiratory failure (PORF). PORF is variably defined as severe hypoxemia on room air, ≥24-h of continued invasive mechanical ventilation (IMV) post-operatively, and/or unplanned reintubation or need for non-invasive ventilation (NIV) within 3–30 days after surgery. Historically, the incidence of these aforementioned adverse events was 0.5–4% after non-cardiac surgery [1,2]. One major risk factor for PORF is respiratory infection within the previous month, which has been reported to increase the odds of post-operative hypoxemia and other pulmonary complications by nearly 5 times

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[3,4]. This may be due to exacerbation of pre-existing infection by surgical immunomodulation and violation of the innate immune barrier during tracheal intubation for general anesthesia [5,6]. Given the independent 4–17% risk of respiratory failure in COVID-19 [7–9], surgery during SARS-CoV-2 infection may constitute a perfect storm for PORF and lead to a high incidence of post-surgical respiratory failure. Moreover, because of the ongoing global [10] and inpatient burden of COVID-19 [11] as well as the importance of reviewing outcomes from resolved outbreaks to prepare for any future surges or similar respiratory pandemics, characterizing in detail SARS-CoV-2 infection-related PORF in both surge and non-surge conditions is an important goal for perioperative research.

The association between SARS-CoV-2 infection and PORF has been preliminarily explored and there is suggestion of heightened risk. For example, a single-center study from Wuhan, China at the start of the pandemic reported an approximately 30% incidence of re-intubation of post-operative patients for non-surgical reasons [12] while a subsequent multicenter, primarily British study during surge conditions reported a 51% incidence of 30-day post-operative pulmonary complications, which included respiratory failure and post-operative pneumonia (PNA) [13]. This was consistent with an Italian study around this same time demonstrating a 15% incidence of 30-day acute respiratory failure [14] as well as a concurrent US study in hip surgery patients that reported a 14% incidence of post-operative mechanical ventilation [15]. A recently published study in non-surge conditions demonstrated an approximately 3 times increased risk of post-operative pulmonary complications in patients with pre-operative SARS-CoV-2 infection as far as 6 weeks preoperatively [16].

While these and other studies have contributed to a nearly universal cautionary approach to surgery in these patients, including a recommendation by the American Society of Anesthesiology and the Anesthesia Patient Safety Foundation to delay elective surgery for 4 weeks regardless of symptoms [17,18], there remain gaps in our understanding of this important problem. For example, most existing studies did not exclude patients with pre-operative respiratory failure or adjust for those with pre-operative symptomatic PNA. In one key study [13], infection was considered present if viral RNA was detected up to 30-days after surgery. Because this may include iatrogenic post-operative exposure, this complicates the applicability of this study's findings for pre-operative screening and risk stratification. Many studies also lacked a time-matched comparator group, which is key for interpreting observations during a pandemic when standard healthcare practices are necessarily modified. Additionally, some studies were limited to patients with SARS-CoV-2 detection within 1 week of surgery, which is not consistent with current 30-day pre-operative screening recommendations [18]. Finally, only one study differentiated between symptomatic and asymptomatic infection [16].

To address these knowledge gaps and explore any modifiable anesthetic, surgical, or disease-specific interventions that could improve outcomes in this high-risk surgical population, we aimed to characterize in detail the association between pre-operative SARS-CoV-2 infection and severe PORF necessitating mechanical ventilation and ICU admission relative to a time-matched non-infected comparison group during the peak infection period in New York City. We hypothesized that pre-operative infection was indeed associated with PORF even when adjusting for clinically-evident pre-operative pulmonary dysfunction.

2. Materials and methods

2.1. Ethical approval and study design

This single-center retrospective cohort study was approved by the Albert Einstein College of Medicine Institutional Review Board. Given its retrospective nature, informed consent was waived. This manuscript adheres to all STROBE guidelines.

2.2. Study subjects

The sole inclusion criterion was for patients to have undergone surgery at one of three academic hospitals within Montefiore Medical Center between March 14 to June 14, 2020. Importantly, elective surgery was suspended on March 19th due to an exponential surge in COVID-19 hospitalization. Subsequently, only urgent, semi-urgent, and emergent surgeries occurred until June 10th when completely elective surgeries formally resumed. It became our practice to delay surgery for 30 days after the last positive PCR test around this time, hence termination of patient recruitment several days later in mid-June. Exclusion criteria were age $<$ 18-years-old, labor and delivery procedures performed in the operating room, and absence of any SARS-CoV-2 PCR test results within either 4 weeks before or 5 days after surgery. Other exclusion criteria were pre-operative respiratory failure defined as IMV for $\geq$24-h pre-operatively and repeat instances of surgery for the same patient within the study period.

2.3. Outcomes, exposures, and risk factors

The primary outcome was PORF, which was defined a priori as a composite of inability to extubate for $\geq$24 h after surgical conclusion or unplanned re-intubation, high-flow nasal canula (HFNC), or non-invasive ventilation (NIV) within 5 days post-operatively. This definition and timeframe are consistent with recent studies of PORF as well as the timing of peak hypoxemia post-operatively [19–23]. Secondary outcomes included: 30-day post-operative mortality; new onset, intensivist-adjudicated PNA diagnosed by respiratory symptoms, imaging findings, and/or signs of systemic inflammation; acute kidney injury (AKI) as defined by a post-operative increase in serum creatine of $\geq$0.3 mg/dl; deep vein thrombosis (DVT) or pulmonary embolus (PE) detected by ultrasound or CT imaging; post-operative hospital and intensive care unit (ICU) length of stay (LOS); and 30-day re-operation need.

The exposure of interest was a positive SARS-CoV-2 nasal swab PCR test result within 4 weeks before or 5 days after surgery. The 5-day post-operative period was chosen to reflect the mean incubation period of SARS-CoV-2 infection and the assumption that a positive PCR test within this period likely reflected pre-operative viral exposure [24]. These patients were labeled as SARS-CoV-2 infected. We also noted any signs or symptoms of COVID-19 including intensivist-adjudicated respiratory or flu-like illness or consistent imaging findings. A large number of well-established pre- and intra-operative risk factors for PORF and COVID-19 were measured for each patient. Pre-operative variables included: age; sex; SARS-CoV-2 PCR results; IgG antibody test results; intensivist adjudicated symptoms and signs of COVID-19; presence of comorbidities including coronary artery disease (CAD), peripheral artery disease (PAD), congestive heart failure (CHF), stroke or transient ischemic attack (TIA), stage 3 or greater chronic kidney disease (CKD), hypertension (HTN), diabetes mellitus (DM), a composite of chronic obstructive or respiratory lung disease, history of cancer (CA), dementia, and smoking status. To simplify multivariable analysis, most of these comorbidities were aggregated into the Charlson Comorbidity Index (CCI). Pre-operative physiologic parameters included routine vital signs, supplemental oxygen utilization, and 30-day pre-operative PNA adjudicated by an intensivist. Other peri-operative parameters included: ASA Physical Status (ASA-PS) classification; surgery type; 48-h perioperative blood transfusion (i.e., any exogenous blood 24-h before, during, or after surgery); and surgical risk and mortality prediction as estimated by the Surgical Mortality Probability Model (S-MPM) index. This latter index is composed of a patient's ASA-PS category, surgical emergency classification as defined by the attending anesthesiologist, and risk grade of surgery [25,26]. Like CCI, S-MPM was used to consolidate variables and reduce collinearity in multivariable analysis.

2.4. Statistical analysis

Data were obtained with manual chart review combined with automated electronic health record extraction for surgical details and blood transfusion information. All statistical analyses were performed on Stata version SE 16.1 (StataCorp; College Station, TX, USA). Alpha was set at 0.05 for bivariate association testing. Continuous variables were tested for normality with histograms and normally distributed data were evaluated for their associations with either SARS-CoV-2 infection or PORF using two-tailed unpaired Student's *t*-tests and reported as mean (SD). Non-normal data were compared with Mann-Whitney rank-sum tests and reported as median (IQR 25–75%). Categorical data were compared using Chi-square and Fisher exact tests, where appropriate, and reported as proportions and odds ratios with 95% confidence intervals. The Breslow-Day test was used to compare odds ratios between stratified cohort subgroups and evaluate for confounding versus effect modification. To adjust for independent predictors, confounders, and mediators of PORF, two separate multivariable logistic regression models were derived using backwards elimination and beginning with all variables that demonstrated significant bivariate associations with either PORF or infection status based on a permissive alpha of 0.2. Variables were eliminated if their regression coefficients were non-significant with a stricter alpha of 0.05 and the model was reduced until the number of covariables was approximately one-tenth the number of outcomes. Clinically important variables were forced into the models to account for important mediators and confounders. All assumptions of logistic regression were evaluated including collinearity of covariables and linearity of continuous predictors. The first model was reduced to the following variables: SARS-CoV-2 infection; pre-operative PNA, SpO2, and dichotomous supplemental oxygen utilization; S-MPM; and peri-operative blood transfusion. The second model was similarly derived except we excluded all probable mediators of the association between SARS-CoV-2 infection and PORF, namely pre-operative PNA, SpO2, and oxygen utilization, and replaced these variables with the gender, CCI, and HR. Multivariable regression was likewise performed for the secondary outcome 30-day post-operative mortality.

3. Results

3.1. Characteristics of study population differentiated by SARS-CoV-2 infection status

Of the 1020 patients who met inclusion criteria and had surgery between March 14 and June 14, 2020, 242 were excluded (Fig. 1). Of the 778 remaining patients, 87 had up to 4 week pre- or 5 day post-operative SARS-CoV-2 positive nasopharyngeal PCR tests and these patients are hereon classified as SARS-CoV-2 infected.

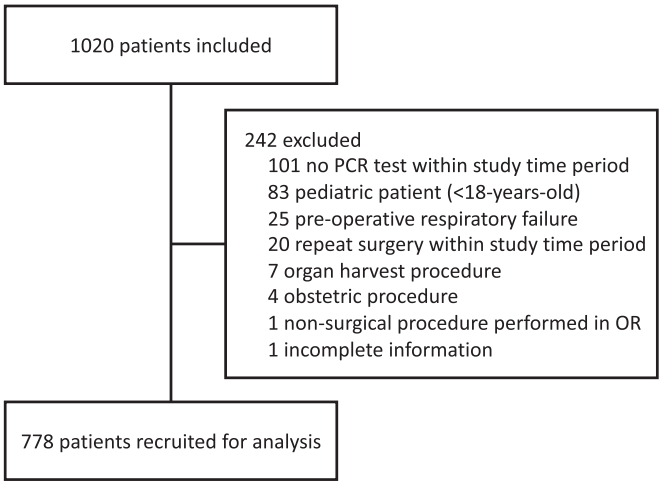

Fig. 1. Study population inclusion and exclusion criteria with details about the number of patients excluded for each particular exclusion criterion. Abbreviations: OR, operating room.

As summarized in Table 1, patients with SARS-CoV-2 infection were older (median 61- vs. 57-years-old; P = 0.02) and generally sicker. Specifically, they had a greater prevalence of PAD (22% vs. 13%; P = 0.03), HTN (67% vs. 53%; P = 0.02), and stroke or TIA (16% vs. 8%; P = 0.01) as well as dementia (10% vs. 5%, P = 0.04). Neither race nor gender were associated with SARS-CoV-2 infection. Likewise, there was no associations between viral infection and chronic lung diseases or recent, ≤2 months tobacco use. Combining these and other comorbidities, patients with SARS-CoV-2 infection had a higher median Charlson Comorbidity Index (4 vs. 3; P = 0.007).

With respect to SARS-CoV-2 infection, 19 out of 87 patients, or 22%, had a positive nasopharyngeal PCR test first detected within 3–4 weeks pre-operatively compared to 55/87 (63%) within 1–2 weeks pre-operatively and 13/87 (15%) within 5 days post-operatively. The median time between surgery and first PCR positivity was 5 days pre-operatively (IQR 12 to 1 days pre-operatively). Nearly half (34 out of 87, 39%) of infected patients had clinically symptomatic COVID-19 diagnosed by respiratory symptoms (30/34, 88%) or extrapulmonary symptoms such as fever, myalgias, or gastrointestinal symptoms (25/34, 75%). Of these 34 symptomatic patients, 24/34 (71%) had chest x-ray findings consistent with COVID-19 PNA. Importantly, infected patients with suspicious x-ray findings but no symptoms whatsoever were labeled as asymptomatic given the possibility of false positive, non-specific findings.

Patients with SARS-CoV-2 infection also tended to have pre-operative vital signs consistent with sepsis (Table 1). Specifically, infected patients had slightly higher mean HR (89 vs. 82 bpm; P = 0.001) and RR (18.8 vs. 18.2 breaths per minute; P = 0.01) compared to uninfected patients. They also had a greater likelihood of requiring supplemental oxygen pre-operatively (20% vs. 10%; P = 0.005). Specifically, nasal canula oxygen use was more frequent in infected patients (17% vs. 8%) while need for brief IMV, NIV, or HFNC for <24-h before surgery was similar in both groups (3% vs. 2%). Consistent with their nearly 40% symptomatic presentation, SARS-CoV-2 infected patients were more likely to have pre-operative PNA (28% vs. 3%; P < 0.001). Neither fever, MAP, nor individual systolic or diastolic blood pressures (data not shown) had any associations with viral infection.

Regarding surgical and anesthetic details, patients with SARS-CoV-2 infection tended to have higher risk indices (Table 1). For example, compared to uninfected patients, viral infection was associated with higher ASA-PS scores (20% vs. 34% with ASA 1–2, 61% vs. 50% ASA 3, and 20% vs. 16% ASA 4–5; P = 0.02) as well as higher median S-MPM scores (5 vs. 4; P = 0.02). Regarding these greater S-MPM scores, they appeared to be driven primarily by higher ASA-PS scores as there were no associations between SARS-CoV-2 infection and emergency surgery classification (26% in infected vs. 20% in uninfected individuals) or the proportions of low-, intermediate-, and high-risk procedures according to S-MPM categorization (P = 0.28). Use of general anesthesia as opposed to non-general anesthesia was slightly less frequent in SARS-CoV-2 infected patients (76% vs. 84%; P = 0.04). There were no significant differences between groups with respect to the proportions of cardiothoracic or upper abdominal, lower abdominal or pelvic or cranial, or peripheral surgery. While surgery duration was similar between groups, use of exogenous blood products within 24-h before or after surgery was more common in SARS-CoV-2 infected patients (26% vs. 16%; P = 0.007).

3.2. Associations between post-operative respiratory failure and perioperative risk factors

As detailed in Table 2, the incidence of PORF in this cohort was 59 out of 778 patients or 8%. Those who experienced PORF were older (median age 60- vs. 57-years; P = 0.003) and had more comorbidities

Table 1
Demographic, comorbidity, and perioperative characteristics of study cohort and their associations with SARS-CoV-2 infection.

	SARS-CoV-2 infected (n = 87)	SARS-CoV-2 uninfected (n = 691)	Difference between groups, P
Demographics			
Age, yr	60 (52, 70)	57 (40, 67)	0.02
Sex, n			0.75
Female	44 (51%)	362 (52%)	
Male	43 (49%)	329 (48%)	
Race and ethnicity, n			0.36
Hispanic	37 (42%)	288 (42%)	
Black	29 (33%)	188 (27%)	
White	11 (13%)	99 (14%)	
Asian	3 (3%)	17 (3%)	
Other	6 (7%)	53 (8%)	
Unidentified	1 (1%)	46 (7%)	
Comorbidities			
CAD, n	16 (18%)	123 (18%)	0.89
PAD, n	19 (22%)	91 (13%)	0.03
CHF, n	10 (11%)	79 (11%)	0.99
HTN, n	58 (67%)	265 (53%)	0.02
Stroke or TIA, n	14 (16%)	56 (8%)	0.01
CKD, n	24 (25%)	128 (19%)	0.12
DM, n	39 (45%)	240 (35%)	0.06
Chronic lung disease, n	11 (12%)	128 (19%)	0.18
Dementia, n	9 (10%)	33 (5%)	0.04
Cancer active or in remission, n	22 (25%)	140 (20%)	0.27
BMI $\geq$ 30, n	26 (30%)	243 (35%)	0.35
Tobacco use within 2 months, n	10 (12%)	123 (18%)	0.14
CCI	4 (2, 6)	3 (0, 5)	0.007
Pre-operative vital signs and pneumonia			
Temperature $\geq$ 38.0 °C, n	2 (2%)	17 (2%)	0.92
HR, beats per minute	89 (18)	82 (17)	0.001
RR, breaths per minute	18.8 (2.3)	18.2 (2.2)	0.01
MAP, mmHg	92 (14)	93 (13)	0.85
SpO2, %	99 (98, 100)	99 (97, 100)	0.69
Supplemental oxygen requirement, n[1]	17 (20%)	67 (10%)	0.005
Nasal canula oxygen	15 (17%)	56 (8%)	
HFNC, NIV, or IMV	2 (3%)	11 (2%)	
Pre-operative PNA, n	24 (28%)	24 (3%)	<0.001
Surgical and anesthetic details and risk factors			
ASA-PS score, n			0.02
1–2	17 (20%)	238 (34%)	
3	53 (61%)	344 (50%)	
4–5	19 (20%)	109 (16%)	
Emergency surgery, n	23 (26%)	139 (20%)	0.17
Surgery type, n[2]			0.52
CTS, esophageal, or gastrectomy surgery	4 (5%)	51 (7%)	
Abdominal, pelvic, vascular, or cranial neurosurgery	61 (70%)	490 (71%)	
General abdominal	23 (25%)	212 (31%)	
Transplant	1 (1%)	17 (2%)	
Urologic, gynecologic	4 (5%)	106 (15%)	
Vascular	28 (32%)	120 (17%)	
Cranial surgery	7 (8%)	35 (5%)	
Peripheral non-vascular surgery	22 (25%)	150 (22%)	
Orthopedics or spine	18 (21%)	88 (13%)	
ENT or OMFS	1 (1%)	27 (4%)	
Plastic or breast surgery	0	21 (3%)	
Other	3 (3%)	14 (2%)	
S-MPM procedure risk			0.28
Low risk	41 (60%)	441 (64%)	
Intermediate risk	26 (30%)	157 (23%)	
High risk	9 (10%)	93 (14%)	
Anesthesia type			0.04
MAC, neuraxial, or regional	21 (24%)	108 (16%)	
General anesthesia	66 (76%)	583 (84%)	
Surgical duration, min	137 (97, 204)	120 (74, 220)	0.23
S-MPM composite score	5 (4, 5)	4 (2, 5)	0.02
Blood transfusion within 24-h before or after surgery, n	24 (26%)	110 (16%)	0.007

Normally distributed continuous data are presented as mean (SD) while non-normal data are presented as median (IQR). Proportion data are presented as number (percent of total) of SARS-CoV-2 infected or non-infected patients. Associations were evaluated between variables and SARS-CoV-2 infection relative to non-infection. Abbreviations: NA, not applicable; CAD, coronary artery disease; PAD, peripheral artery disease; CHF, congestive heart failure; TIA, transient ischemic attack; CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; CA, cancer; BMI, body mass index; CCI, Charlson Comorbidity Index; PNA, pneumonia either viral or bacterial; CTS, cardiothoracic surgery; OMFS, oral and maxillofacial surgery; MAC, monitored anesthesia care; S-MPM, Surgical Mortality Probability Model.

[1] The association between infection and pre-operative supplemental oxygen need was evaluated using a dichotomized variable coding any or no oxygen. Percents of the different types of oxygen are relative to the total number of patients needing oxygen.

[2] The association between infection and surgery type was evaluated using three broad groups of surgical procedures organized by respiratory failure risk.

(median CCI 4 vs. 3; $P < 0.0001$). Neither race, sex, nor chronic lung disease, obesity, nor smoking were associated with post-surgical respiratory failure. With respect to pre-operative clinical parameters, patients who experienced PORF had higher HR (median 86 vs. 80 bpm; $P = 0.001$) and RR (median 18 in both groups but higher 75th percentile in SARS-CoV-2 patients; $P = 0.02$). Moreover, pre-operative oxygen saturation was lower (median SpO2 97% vs. 99%; $P < 0.0001$) and supplemental oxygen need pre-operatively was greater in those who developed PORF compared to patients who did not (46% vs. 8%; $P < 0.001$). Pre-operative PNA was also more common in those who went on to develop PORF (24% vs. 5%; $P < 0.001$).

Patients with SARS-CoV-2 infection had a greater incidence of PORF than did uninfected patients. Specifically, infection was present in 14 of 59 or 24% of all patients with PORF compared to 73 of 719 or 10% of those without PORF ($P = 0.001$). Put another way, 14/87 or 16% of patients with SARS-CoV-2 infection had PORF compared to 45/691 or 7% of uninfected individuals. PORF was more common in those with clinically symptomatic COVID-19 compared to asymptomatic infection (9/34 or 26% in symptomatic vs. 5/53 or 9% in asymptomatic infected patients; $P = 0.04$). When limiting analysis to only asymptomatic infected patients compared to uninfected patients, PORF was equally likely in both groups (5/53 or 9% vs. 45/691 or 7%; $P = 0.41$). When examining in detail different timings of PCR diagnosis, detection of SARS-CoV-2 infection within 1–2 weeks pre-operatively was significantly associated with PORF compared to no infection within the perioperative period (9/55 or 16% PORF incidence in 1–2 weeks pre-operative infection group vs. 45/691 or 7% in never infected patients; $P = 0.007$). PORF was likewise significantly associated with SARS-CoV-2 detection within 5 days post-operatively relative to no infection (3/13 or 23% vs. 45/691 or 7%, $P = 0.02$). However, further out first detection of infection 3–4 weeks pre-operatively was not associated with PORF (2/19 or 11% vs. 45/691 or 7%; $P = 0.36$). Evaluating pre-operative PNA, a key confounder, for effect modification revealed were no significant differences in the odds of PORF with SARS-CoV-2 infection when stratifying by presence or absence of PNA (OR 1.7 [95% CI 0.6–4.3] vs. OR 1.5 [95% CI 0.4–6.5]; $P = 0.88$).

With respect to surgical and anesthetic factors, PORF was more common in those with higher ASA-PS classification (ASA 4–5 in 59% of patients who developed PORF vs. 13% in patients who did not

Table 2
Associations between post-operative respiratory failure and peri-operative risk factors including SARS-CoV-2 infection.

	Post-operative respiratory failure		
	Yes (n = 59, 8%)	No (n = 719, 92%)	P
Demographics and comorbidities			
Age, yr	63 (55, 70)	57 (40, 67)	0.003
Male sex, n	31 (53%)	341 (47%)	0.45
Race and ethnicity, n			0.65
Hispanic	25 (42%)	300 (42%)	
Black	18 (31%)	199 (28%)	
White	10 (17%)	100 (14%)	
Asian or other	6 (10%)	73 (10%)	
Unidentified	0	47 (7%)	
Chronic lung disease, n	16 (27%)	123 (17%)	0.054
BMI ≥ 30, n	19 (32%)	250 (35%)	0.69
Tobacco use within 2 months, n	12 (21%)	121 (17%)	0.47
CCI	4 (3, 7)	3 (0, 5)	<0.0001
SARS-CoV-2 infection status			
SARS-CoV-2 status, n			0.001
Uninfected (n = 691)	45/59 (76%)	646/719 (90%)	
Infected (n = 87)	14/59 (24%)	73/719 (10%)	
Symptomatic (n = 34)[1]	9/14 (66%)	25/73 (36%)	0.04[1]
Asymptomatic (n = 53)[1]	5/14 (34%)	48/73 (64%)	
Preoperative parameters			
Temperature ≥ 38.0 °C, n	1 (2%)	21 (3%)	0.58
HR, beats per minute	86 (74, 108)	80 (70, 92)	0.001
RR, breaths per minute	18 (17, 20)	18 (18, 19)	0.02
MAP, mmHg	91 (15)	93 (13)	0.35
SpO2, %	97 (98, 100)	99 (98, 100)	<0.0001
Supplemental oxygen need, n	27 (46%)	57 (8%)	<0.001
Pre-operative PNA, n	14 (24%)	34 (5%)	<0.001
Surgical and anesthetic risk factors			
ASA-PS score			<0.001
1–2	0	255 (35%)	
3	24 (41%)	373 (52%)	
4–5	35 (59%)	91 (13%)	
Emergency surgery, n	31 (52%)	131 (18%)	<0.001
Surgery type, n			0.0001
CTS, esophageal, or gastrectomy	12 (20%)	43 (6%)	
Abdominal, pelvic, vascular, or cranial	40 (67%)	511 (71%)	
Peripheral	7 (12%)	165 (23%)	
S-MPM procedure risk, n			<0.0001
Low-risk	13 (22%)	480 (67%)	
Intermediate-risk	20 (34%)	162 (23%)	
High-risk	26 (44%)	76 (11%)	
S-MPM	7 (5,8)	4 (2, 5)	<0.001
General anesthesia	59 (100%)	590 (82%)	<0.001
Surgery duration, min	206 (118, 387)	119 (75, 205)	<0.0001
Transfusion 24-h pre- or post-operative, n	35 (59%)	99 (14%)	<0.001

Normally distributed continuous data are presented as mean ± SD while non-normal data are presented as median (IQR). Proportion data are presented as number (percent) of patients with or without the composite respiratory failure outcome. Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; DSI, diastolic shock index; PNA, pneumonia either viral or bacterial; LMA, laryngeal mask airway; S-MPM, Surgical Mortality Probability Model.

[1] Infected patients were subdivided into those with and without symptoms of COVID-19, their proportions were reported relative to the total number of infected patients, and their associations with PORF were evaluated separately from analysis of the all infected versus non-infected patients.

experience PORF; P < 0.001). Emergency surgery was likewise associated with PORF (P < 0.001) as was surgery type categorized by respiratory failure risk (P = 0.0001) and S-MPM procedure risk (P < 0.0001). Related to this, the composite S-MPM risk index was higher in those with PORF (median 7 vs. 4; P < 0.001). When stratifying patients by S-MPM procedure risk, SARS-CoV-2 infection was equally associated with PORF regardless of surgical risk (OR 4.0 [95% CI 1.2–13.6] for low-risk procedures vs. OR 2.4 [95% CI 1.1–5.4] for intermediate- or high-risk procedures; P = 0.48). Likewise, when stratifying by emergency surgery status, infection was similarly associated with PORF regardless of emergency status (OR 2.7 [95% CI 1.2–7.2] for emergency surgery vs. OR 2.5 [95% CI 1.0–6.4] for non-emergency surgery; P = 0.91). There was zero incidence of PORF in patients who had non-general anesthesia. PORF was also associated with longer surgical duration (median 206 vs. 119 min; P < 0.001) and exogenous blood component transfusions (59% vs. 14%; P < 0.001).

To adjust for important confounders, mediators, and independent risk factors for PORF, for example pre-operative PNA, and better estimate the association between viral infection and respiratory failure, we generated two different logistic regression models (Table 3). In model A, all significant bivariate associations noted previously were tested and this yielded a 6 variable logistic regression model consisting of SARS-CoV-2 infection, pre-operative PNA, oxygen saturation, and supplemental oxygen use as well as S-MPM risk index and peri-operative blood transfusion. All variables except for pre-operative PNA were significant predictors of PORF in this adjusted model, including SARS-CoV-2 infection (OR 2.6, 95% CI 1.1–6.5). In model B, similar multivariable logistic regression was performed except probable mediators of the association between SARS-CoV-2 and PORF were intentionally excluded, namely pre-operative SpO2, oxygen use, and PNA. These variables were replaced with gender, HR, and CCI, the next most significant predictors of PORF in multivariable modeling. This second model likewise demonstrated a significant association between viral infection and PORF (OR 2.8, 95% CI 1.2–6.4).

3.3. Risk factors for other post-operative complications

In addition to the primary composite outcome, we also evaluated the unadjusted associations between SARS-CoV-2 infection and various other post-operative outcomes (Table 4). Examining the individual subcomponents of the primary outcome revealed that SARS-CoV-2

Table 3
Two models describing adjusted associations between post-operative respiratory failure, SARS-CoV-2 infection, and five other key peri-operative risk factors.

Risk factors	Model A – Adjustment includes mediators	P	Model B – Excludes mediators	P
	Adjusted OR for PORF (95% CI)		Adjusted OR for PORF (95% CI)	
SARS-CoV-2 infection	2.6 (1.1–6.5)	0.04	2.8 (1.2–6.4)	0.02
Pre-operative HR, bpm	NA		1.03 (1.01–1.04)	0.004
Pre-operative SpO2, %	0.75 (0.65–0.86)	<0.001	NA	
Pre-operative supplemental oxygen need	5.7 (2.6–12.6)	<0.001	NA	
Pre-operative PNA	1.3 (0.5–3.4)	0.62	NA	
Male gender	NA		0.8 (0.4–1.5)	0.40
CCI	NA		1.02 (0.89–1.16)	0.76
Pre-operative S-MPM risk index	2.6 (1.9–3.4)	<0.001	2.7 (2.1–3.5)	<0.001
Peri-operative blood transfusion	5.8 (2.8–12.1)	0.012	4.2 (2.1–8.1)	<0.001

Model A was adjusted for statistically significant variables noted during bivariate testing with no exclusion of probable mediators of SARS-CoV-2's association with PORF. Model B was adjusted for all variables not felt to be mediators but rather only confounders or independent predictors of PORF (i.e., pre-operative SpO2 and oxygen need were excluded and substituted with gender and CCI). Analysis was limited to patients who had surgery under general anesthesia because no PORF occurred with other types of anesthesia. Abbreviations: NA, not applicable and not included in the multivariable model; PORF, post-operative respiratory failure; PNA, pneumonia; CCI, Charlson Comorbidity Index; S-MPM, Surgical Mortality Probability Model.

Table 4
Unadjusted associations between SARS-CoV-2 infection and secondary post-operative adverse outcomes.

	SARS-CoV-2 infected (n = 87)	SARS-CoV-2 uninfected (n = 691)	Difference between group, P
Secondary post-operative respiratory outcomes			
Unplanned reintubation, n	4 (5%)	7 (1%)	0.03
Inability to extubate for ≥24 h, n	10 (11%)	28 (4%)	0.006
Duration of intubation, days[1]	2 (1.5, 7)	3.5 (2,10)	0.11
HFNC or NIV within 5 days, n	1 (1%)	16 (2%)	0.48
New 30-day post-operative PNA, n	9 (11%)	37 (5%)	0.06
Secondary post-operative non-respiratory outcomes			
30-day mortality, n	9 (10%)	18 (3%)	<0.001
Days between surgery and death[2]	7 (4, 8)	14.5 (4, 28)	0.11
In-hospital mortality[2]	6/9 (67%)	13/18 (72%)	0.77
Incidence of PORF before death[2]	6/9 (67%)	10/18 (56%)	0.58
New post-operative DVT or PE, n	5 (6%)	19 (3%)	0.12
Re-operation need, n	14 (16%)	85 (12%)	0.32
New post-operative AKI, n	18 (21%)	100 (14%)	0.12
Post-operative ICU admission, n	21 (24%)	148 (21%)	0.56
Post-operative hospital LOS, days[3]	6 (2,11)	3 (1, 6)	0.0001

Non-normal continuous data are presented as median (IQR) while proportion data are presented as number (percent) of patients with or without the SARS-CoV-2 infection. Abbreviations: PORF, post-operative respiratory failure; HFNC, high-flow nasal canula; NIV, non-invasive ventilation; PNA, pneumonia; DVT, deep vein thrombosis; PE, pulmonary embolus; AKI, acute kidney injury; LOS, length of stay.

[1] Total days of intubation were measured only for those patients who were intubated.

[2] Days until death and in-hospital mortality were evaluated only in patients with 30-day post-operative mortality.

[3] Post-operative hospital LOS was measured as the time until either hospital discharge alive or in-hospital death.

infection was associated with unplanned reintubation within 5 days post-operatively (5% incidence in infected individuals vs. 1% in uninfected patients; P = 0.03) as well as inability to extubate intra-operatively (11% vs. 4%; P = 0.006). We also noted a greater incidence of new post-operative PNA in patients with SARS-CoV-2 infection, although this association was not statistically significant (11% vs. 5%; P = 0.06). In unadjusted analyses, 30-day post-operative mortality occurred in 10% of SARS-CoV-2 patients compared to 3% of uninfected individuals (P < 0.001). The median time from surgery to death was shorter in infected patients (7 vs. 14.5 days) and the incidence of PORF preceding death was greater in infected patients (67% vs. 56%), although these differences were not statistically significant. Post-operative hospital LOS until discharge alive or in-hospital death was longer in infected patients (median 6 vs. 3 days; P = 0.0001). Regarding 30-day mortality, we performed multivariable logistic regression and, after adjusting for CCI, pre-operative HR, and pre-operative S-MPM risk index, SARS-CoV-2 infection remained significantly associated with mortality (OR 3.5, 95% CI 1.4–9.1) as detailed in Table 5.

Table 5
Adjusted associations between 30-day post-operative mortality, SARS-CoV-2 infection, and three other peri-operative risk factors.

Perioperative risk factors	Adjusted OR for 30-day post-operative mortality (95% CI)	P
SARS-CoV-2 infection	3.5 (1.4–9.1)	0.01
CCI	1.2 (1.01–1.41)	0.03
Pre-operative HR, bpm	1.03 (1.01–1.05)	0.02
Pre-operative S-MPM risk index	1.9 (1.4–2.6)	<0.001

The covariables in this multivariable logistic regression model are all those that were significantly associated with 30-day mortality during model building. Abbreviations: CCI, Charlson Comorbidity Index; S-MPM, Surgical Mortality Probability Model.

4. Discussion

As hypothesized and supporting existing evidence, pre-operative SARS-CoV-2 infection as diagnosed with positive nasal PCR detection within 4 weeks before or 5 days after surgery was associated with a nearly 3 times increased adjusted odds of post-operative respiratory failure (PORF) relative to time-matched, uninfected comparator patients. Interestingly, this increased risk was present even after adjusting for probable mediators of this association, namely pre-operative hypoxemia, supplemental oxygen need, and pre-operative pneumonia, suggesting an important causal mechanism beyond clinically evident pre-operative pulmonary dysfunction. This association with respiratory failure may have been driven by the roughly 40% incidence of symptomatic COVID-19 as only symptomatic infection was significantly associated with PORF in unadjusted, exploratory analyses. Because nearly half of the cases of SARS-CoV-2 infection are asymptomatic [13,14,27] and surgical guidelines currently recommend a 30-day postponement of surgery irrespective of symptoms [18], we feel this latter finding is particularly intriguing and hypothesis generating. It may be that if a patient is asymptomatic and has the same comorbidity and surgical characteristics as our study cohort, she or he may have no greater risk for post-operative respiratory failure compared to a patient who is not infected. Likewise, unadjusted analysis suggests the greatest risk with more acute 1–2 week pre-operative infection as opposed to less acute 3–4 week pre-operative infection. With regard to other surgical outcomes, SARS-CoV-2 infection was associated with a 3.5-fold adjusted increased 30-day post-operative mortality.

Although the incidence of PORF in SARS-CoV-2 infected patients in our cohort was on the lower end of the 14–51% range reported in previous studies during surge conditions [12–15], it is challenging to make comparisons due to different definitions and recruitment criteria. The substantially higher 51% incidence reported by the COVIDSurg Collaborative study may have been due to their screening of patients for infection only 7 days before and up to 30 days after surgery, which may have biased their cohort towards more acutely ill patients who may have had less time to heal before undergoing surgery. Additionally, the COVIDSurg Collaborative group screened for respiratory failure out to 30-days post-operatively compared to 5-days in this study, they did not exclude patients with pre-operative respiratory failure, and they included peri-operative PNA as part of the composite post-operative pulmonary complication outcome. Because nearly one-quarter of patients had PNA going into surgery, adding this to the composite outcome could inflate its incidence possibly up to the 51% incidence reported by the COVIDSurg Collaborative. Supporting this, Doglietto et al. reported a 14% incidence of PORF in their COVID-19 cohort and a substantially higher, 59% incidence when factoring in peri-operative PNA [14]. Regarding this latter study, although the incidence of PORF in the present study was similar, Doglietto et al. reported a substantially higher 13 times increased odds of PORF. However, their comparator group was a historical matched cohort that had surgery performed under normal, pre-pandemic circumstances. Our use of a time-matched, uninfected

comparator group therefore highlights the unique value of our study for characterization of PORF in SARS-CoV-2 infected patients.

Our data hint at an important synergy between COVID-19- and surgery-related immune dysfunction that may contribute to multiorgan injury including respiratory failure. It is well established that both surgery and anesthesia elicit widespread inflammatory changes including an immunomodulatory component that may facilitate infection. For example, IL-6 levels are higher in surgical patients who experience post-operative complications, there is evidence that elevated IL-6 levels contribute to lymphopenia, and IL-6 levels are coincidently higher in COVID-19 patients who experience severe disease [28,29]. Not only did we observe a higher incidence of PORF in SARS-CoV-2 infected patients compared to non-infected controls, we identified a 4–6 times greater adjusted odds of PORF in patients who received blood component either 24-h before or after surgery. Pre-pandemic studies have highlighted an increased incidence of both post-operative infection and respiratory complications in patients receiving transfusions [30]. Moreover, inflammation itself is a well-established contributor to multiorgan dysfunction including acute kidney injury [31] and SARS-CoV-2 infection is associated with a proinflammatory state [32]. This complex inflammatory injury mechanism may account for our observation of a persistent association between SARS-CoV-2 infection and PORF despite adjusting for clear clinical markers of pre-operative pulmonary dysfunction including hypoxemia, pneumonia, and supplemental oxygen need.

There are several limitations to our study. First, this is a single-center retrospective study in a predominantly non-Caucasian cohort. Nevertheless, the comorbidity and outcome patterns are similar to those reported in previous studies with different demographics. Specifically, most patients with SARS-CoV-2 infection were elderly and had a high incidence of cardiovascular co-morbidities [8,9,13,33–35]. Likewise, infected patients were overall less healthy than uninfected individuals as indicated by their higher CCI, ASA-PS, and S-MPM scores. Moreover, this unique cohort is a valuable addition to the less diverse cohorts used in other studies, particularly as COVID-19 continues to ravage large parts of the developing world. Second, there is limited sample size and we must interpret with caution our intriguing observaitons of significantly increased odds of PORF with acute 1–2 week versus less acute 3–4 week pre-operative infection as well as increased PORF with symptomatic versus asymptomatic disease. However, this is the only study we are aware of that focuses on severe post-operative respiratory failure in a relatively unhealthy population needing urgent surgery, for which the risk of PORF is high and options for surgical delay are limited. Third, this study describes findings from the first COVID-19 surge in New York City when elective surgery was suspended and patients may have had delayed hospital presentation for fear of iatrogenic infection, consequently confounding associations between infection and post-operative complications relative to subsequent surges or in the periods in-between, during which mortality was generally lower [36]. We chose this unique time period because it was not yet universal to postpone surgery for 30-days after infection, there was a high prevalence of infection, and all findings in SARS-CoV-2 infected patients could be compared against non-infected patients as well as adjusted for emergency surgerical status and surgical risk, thereby ameliorating some of the latent confounding caused by epidemic-restrictive surgical practices. This latter aspect of our work is a key strength compared to other studies performed during this time evaluating risk relative to historical, uninfected controls. Moreover, the proportion of emergency surgeries was in fact lower in our cohort than in other studies [13,14]. Nevertheless, it is difficult to apply these findings to patients with COVID-19 needing elective surgery or minor surgery with general anesthesia. However, a recent study did not demonstrate any reduced risk of post-operative pulmonary complications in infected individuals having elective or minor surgery [16]. Fourth, although we were interested in pre-operative SARS-CoV-2 infection as a risk factor for PORF, 15% of patients defined as SARS-CoV-2 infected were in fact diagnosed within 5 days post-operatively. This post-operative inclusion was permitted because SARS-CoV-2 pre-operative screening was not universal during this time, especially early in the surge, and it was necessary to extend screening for several days post-operatively to capture all infected patients. Moreover, as previously explained, given a median incubation time of 5–6 days, we felt that a positive nasopharyngeal screen within 5 days after surgery likely reflected pre-operative infection with subclinical disease on the day of surgery [24]. Lastly, we are assuming that nasopharyngeal detection of viral RNA reflects active SARS-CoV-2 infection. There is substantial evidence of false negative and positive tests [37] but this uncertainty is inherent in most COVID-19 studies.

There are several future directions for this work. As part of an effort to validate our findings in a later cohort that includes purely elective surgery, it will be important to further explore the association between PORF and symptomatic versus asymptomatic COVID-19 as well as acute versus less acute infection. It may also be interesting to compare incidence of respiratory failure in time-matched medical and surgical patients to explore further the role of various surgical and anesthetic factors in exacerbating infection, for example general compared to neuraxial or regional anesthesia. Finally, it will be important to characterize how long after initial infection this increased risk of post-operative respiratory failure persists to better establish the perioperative impact of so-called “Long Covid Syndrome” [7,38].

In conclusion, SARS-CoV-2 infection was found to be associated with increased odds of post-surgical respiratory failure after adjustment for confounders, mediators, and independent predictors of respiratory failure. This supports current surgical guidelines in the USA that recommend delaying non-urgent surgery for $\geq$4 weeks [18] and it suggests an important synergistic inflammatory mechanism driving PORF that may be modifiable with pharmacotherapy or alternative anesthetic or surgical techniques. Importantly, our observation of no association between asymptomatic infection and PORF in this non-elective surgery patient cohort highlights the continued uncertainty of this recommendation to delay surgery for asymptomatic patients needing higher risk, urgent or semi-urgent surgery that cannot be delayed for >4–6 weeks (e.g., oncologic surgery). If this latter finding is validated in future work, this may suggest greater flexibility and personalization by the peri-operative team is warranted. Whether or not the COVID-19 pandemic subsides in the near future, this work adds to our knowledge of post-operative respiratory failure and may inform risk evaluation for future respiratory viral epidemics.

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Declarations of interest

None.

Author contributions

Michael E. Kiyatkin: This author helped with all aspects of this study including study conceptualization, data curation, validation, and analysis as well as supervision of the research team and preparation of this manuscript.

Samantha P. Levine: This author helped with data collection and manuscript preparation and editing.

Atsumi Kimura: This author helped with data collection and manuscript editing.

Ryan W. Linzer: This author helped with data collection and manuscript editing.

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Aryeh Gurvich: This author helped with data collection and manuscript editing.

Michelle N. Gong: This author helped with study conceptualization, analysis of results, and manuscript review.

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