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Postoperative Respiratory Complications in SARS-CoV-2 Positive Pediatric Patients across 20 United States Hospitals: A Cohort Study

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Highlights:

- SARS-CoV-2 positivity has led to cancelation and delay of elective pediatric surgical procedures without understanding how it affects outcomes.
- When making guidelines related to asymptomatic SARS-CoV-2 positive patients, the low rate of postoperative respiratory complications seen in our study can be considered and weighed against the morbidity of delaying surgery.

ABSTRACT

Introduction: Data examining rates of postoperative complications among SARS-CoV-2 positive children are limited. The purpose of this study was to evaluate the impact of symptomatic and asymptomatic SARS-CoV-2 positive status on postoperative respiratory outcomes for children.

Methods: This retrospective cohort study included SARS-CoV-2 positive pediatric patients across 20 hospitals who underwent general anesthesia from March to October 2020. The primary outcome was frequency of postoperative respiratory complications, including: high-flow nasal cannula/non-invasive ventilation, reintubation, pneumonia, Extracorporeal Membrane Oxygenation (ECMO), and 30-day respiratory-related readmissions or emergency department (ED) visits. Univariate analyses were used to evaluate associations between patient and procedure characteristics and stratified analyses by symptoms were performed examining incidence of complications.

Results: Of 266 SARS-CoV-2 positive patients, 163 (61.7%) were male, and the median age was 10 years (interquartile range 4-14). The majority of procedures were emergent or urgent (n=214, 80.5%). The most common procedures were appendectomies (n=78, 29.3%) and fracture repairs (n=40, 15.0%). 13 patients (4.9%) had preoperative symptoms including cough or dyspnea. 26 patients (9.8%) had postoperative respiratory complications, including 15 requiring high-flow oxygen, 8 with pneumonia, 4 requiring non-invasive ventilation, 3 respiratory ED visits, and 2 respiratory readmissions. Respiratory complications were more

common among symptomatic patients than asymptomatic patients (30.8% vs. 8.7%, $p=0.01$). Higher ASA class and comorbidities were also associated with postoperative respiratory complications.

Conclusions: Postoperative respiratory complications are less common in asymptomatic versus symptomatic SARS-COV-2 positive children. Relaxation of COVID-19-related restrictions for time-sensitive, non-urgent procedures in selected asymptomatic patients may be reasonably considered. Additionally, further research is needed to evaluate the costs and benefits of routine testing for asymptomatic patients.

Keywords: pediatric surgery, COVID-19, respiratory complications

Level of Evidence: III, retrospective study

Abbreviations:

ECMO: Extracorporeal Membrane Oxygenation

PedSRC: Pediatric Surgical Research Collaborative

REDCap: Research Electronic Data Capture

HFNC: high flow nasal cannula

PE: pulmonary embolus

ED: emergency department

ASA: American Society of Anesthesia

BMI: body mass index

US: United States

URI: upper respiratory infections

Introduction:

Since the start of the COVID-19 pandemic, hospitals have had to determine whether operations on SARS-CoV-2 positive children are safe to perform or should be postponed. Prior reports have noted the development of postoperative hypoxia following orthopedic surgery¹ and the risk of increased mortality² for previously asymptomatic SARS-CoV-2 positive adults. However, little is known regarding the risk of surgery in SARS-CoV-2 positive children, and children have been found less likely to experience severe COVID-19 symptoms compared to adults.^{1,2}

With access to preoperative testing, many hospitals are performing routine SARS-CoV-2 PCR tests prior to elective surgery.³ While most surgical practices will postpone elective surgery for SARS-CoV-2 positive patients due to concerns about postoperative morbidity and staff exposure, variations in managing positive test results in children have been reported.⁴⁻⁶ There are some preliminary data to suggest that SARS-CoV-2 positive pediatric patients do not carry the same risk of increased postoperative morbidity and mortality as adult patients.³⁻⁵ In some cases, delay of operation may confer additional risk to patients. For example, there could be an increased risk of incarceration due to delay in hernia repair or recurrent pilonidal abscess while waiting for definitive treatment. A more complete understanding of the impact of SARS-CoV-2 positive status on postoperative outcomes for pediatric patients may inform policymaking around the scheduling of semi-elective, non-urgent procedures. The aim of this study is to describe the rate of unanticipated respiratory

complications among symptomatic and asymptomatic SARS-CoV-2 positive pediatric patients undergoing general anesthesia.

Methods:

Patient Selection

We conducted a multi-center retrospective cohort study of SARS-CoV-2 positive children who underwent general anesthesia in 20 hospitals across the United States. We included patients 18 years of age or younger undergoing general anesthesia from March 13, 2020 to October 31, 2020, who had a positive SARS-CoV-2 test within the 10 days before their general anesthesia exposure. Patients undergoing Extracorporeal Membrane Oxygenation (ECMO) cannulation for COVID-related respiratory failure as their primary operation were excluded.

Sites were recruited through the Pediatric Surgical Research Collaborative (PedSRC)⁶, the American Pediatric Surgical Association Quality and Safety Committee, and through email correspondences with individual providers who had previously contributed to an online open-access data-sharing document.^{3,4}

Eligible patients were identified locally at each institution through one or more of the following mechanisms: electronic medical record queries, utilization of hospital data resource centers to identify encounters that met inclusion criteria, and/or review of operating room logs during the study period to identify cases with a positive SARS-CoV-2 test result associated with the encounter (within 10 days before).

Variable Development, Data Entry, and Outcomes Observed

Independent retrospective chart reviews were conducted at each institution, with data abstraction into a common Research Electronic Data Capture (REDCap) database through the University of Texas Health Science at Houston. Data collection instruments were created in REDCap, based from the existing literature on COVID-19 positivity and complications after anesthesia.⁷⁻¹¹ The final set of variables and their definitions were adjudicated by discussions within the PedSRC. Variables captured included patient demographics, comorbidities, absence or presence of preoperative COVID-19 symptoms, procedure-related details, and postoperative respiratory complications within 30 days of the procedure. A specified data dictionary and details on data collection processes were provided to each site. A copy of the data dictionary is provided in

Supplemental File 1. Cases were categorized as emergent (to occur within one hour of case request), urgent (to occur within 2 to 24 hours), or elective (non-urgent, non-emergent). All center identifiers were encrypted with unique four-digit pin IDs. The final de-identified cohort of all participating sites was evaluated in aggregate. All data collection forms and processes were overseen and approved by local IRBs at each participating site.

Statistical Analysis:

We performed descriptive analyses to evaluate the characteristics of patients undergoing surgery while SARS-CoV-2 positive and what types of procedures were being performed. We tested associations between patient characteristics, including COVID-19 symptoms and the likelihood of experiencing postoperative respiratory complications within 30 days (defined as the need for high flow nasal cannula (HFNC), non-invasive ventilation, reintubation, pneumonia, ECMO, pulmonary embolus (PE), thromboembolic complications, death, or 30-day readmission or emergency department (ED) revisit for a respiratory-related complaint). Covariates that were evaluated include case status (emergent, urgent, elective), patient comorbidities (obesity, asthma, cancer, immunosuppressive disease, prior pulmonary comorbidities/oxygen dependence), ASA (American Society of Anesthesia) class (I, II, III, IV) and age.

Missing data were included in flowcharts and descriptive analyses, allowing denominators to remain consistent in calculations. Estimates of medians with interquartile ranges were presented where appropriate. Chi-square tests, Fisher's Exact, and Wilcoxon Rank-Sum with a significant p-value set at $p < 0.05$ were conducted where appropriate to test associations between patient and procedure characteristics and the presence of respiratory complications after surgery. Stratified analyses were performed for symptomatic and asymptomatic patients, and Fisher's Exact test was used to compare differences between groups. All analyses were conducted using Stata version 17.0 (College Station, TX).

Results:

During the specified time frame, 281 patients underwent general anesthesia and were SARS-CoV-2 positive within 10 days before their procedure. Fifteen patients were missing data on respiratory complications and were excluded from the analysis, leaving 266 patients in total (**Figure 1**). The majority of patients were male (163 patients, 61.7%), and the median age was 10 years (interquartile range 4-14) (**Table 1**). SARS-CoV-

2 positivity was determined either the day before or the day of the procedure in the vast majority of patients (**Figure 1**). Patient and procedure characteristics of children with and without respiratory complications are shown in **Table 1**. Most cases were emergent (13.6%) or urgent (67.2%), but there were 51 patients (19.3%) who had elective surgery while SARS-CoV-2 positive. The majority of procedures were performed by general pediatric or orthopedic surgeons, with several other subspecialties represented (**Table 1**). Notable patient and procedure characteristics associated with respiratory complications included urgent surgery, higher ASA class, and preoperative dyspnea or need for HFNC or ventilator support (**Table 1**). The two most common procedures were appendectomies (29.3%) and fracture repairs (15.0%). Other procedures included vascular access, gastrostomy, hernia repair, craniotomy, and sternotomy, in addition to diagnostic studies such as MRI (**Supplemental Tables 1-2**).

There were 13 (4.9%) patients who had preoperative respiratory symptoms, most commonly cough or dyspnea, thought to be related to COVID-19 infection. Preoperative respiratory symptoms were seen in 1 (0.4%) patient who underwent emergent surgery, 10 (3.8%) patients who underwent urgent surgery, and 2 (0.8%) patients who underwent elective surgery. Additional documented preoperative “possible COVID-related symptoms” included abdominal pain (n=53, 19.9%) and fever (n=32, 12.0%).

Postoperative respiratory complications were seen in 26 (9.8%) patients. Patients with preoperative respiratory symptoms attributable to SARS-CoV-2 had significantly higher postoperative respiratory complication rates compared with asymptomatic patients (overall 30.8% vs. 8.7%, p=0.01). Patient and procedure characteristics of children with and without respiratory complications are shown in **Table 1**. Notable procedure-related risk factors for respiratory complications included urgent surgery, open surgery, and orthopedic surgery. Patients with comorbidities, higher ASA class, and preoperative dyspnea or need for HFNC or ventilator support were also more likely to have respiratory complications (**Table 1**).

Of the 26 patients who had postoperative respiratory complications, 15 (5.6%) patients required HFNC, 8 (3.0%) had pneumonia, 4 (1.5%) required non-invasive ventilation, 3 (1.1%) visited the emergency department for respiratory symptoms, and 2 (0.8%) were readmitted for respiratory symptoms. In the asymptomatic group, 22 patients had postoperative respiratory complications, 14 (5.5%) patients required HFNC, 6 (2.4%) had pneumonia, 3 (1.2%) required non-invasive ventilation, 2 (0.8%) visited the emergency

department for respiratory symptoms, and 2 (0.8%) were readmitted for respiratory symptoms. There was no reintubation, mortality, or progression to ECMO in our cohort.

Stratified analyses in symptomatic versus asymptomatic patients were performed to test associations between comorbidities, preoperative oxygen requirement, symptoms, ASA class, and body mass index (BMI) percentile in symptomatic versus asymptomatic patients (**Table 2**). Higher ASA class and comorbidities were also associated with postoperative respiratory complications in asymptomatic but not symptomatic patients. Being overweight or obese was not associated with respiratory complications in either symptomatic or asymptomatic patients.

Discussion:

In this multicenter retrospective review of a large pediatric cohort evaluating the association between SARS-CoV-2 positive status and postoperative outcomes, we found that the overall rate of postoperative respiratory complications in SARS-CoV-2 positive children undergoing anesthesia/surgery is lower than expected. Symptomatic patients were more likely to experience respiratory complications than asymptomatic patients. The most common complications were the use of HFNC and pneumonia. Patients who did experience respiratory complications were more likely to have higher ASA class and/or other comorbidities that would increase baseline risk.

Proceeding with elective surgery and anesthesia in asymptomatic patients may benefit both patients/families as well the healthcare system. Delays in surgical procedures due to COVID-19 have been cited for causing increased emotional distress for patients awaiting previously scheduled orthopedic procedures and/or oncologic procedures.^{12,13} Additionally, the financial impact of delaying procedures on the United States (US) healthcare system has been significant. The estimated net income from elective surgical procedures to the US hospital system is \$48-\$65 billion per year. Cancellation of elective surgical procedures due to COVID-19 leads to estimated losses of \$4-\$5.4 billion per month in net income to US hospitals during the time they were not being performed.¹⁴ Further, the backlog created by the deferred cases dramatically decreased access in many systems where access was already limited.

It is known that obesity is associated with more severe disease and poor outcomes in adult patients with COVID-19.¹⁵ It has also been shown that adolescents aged 13-20 years have an increased risk of severe disease relative to children aged 0-12 years.¹⁶ Our study had 83 (30.4%) patients classified as overweight or obese but did not find an association with postoperative respiratory complications for the obese/overweight patients. Similarly, we did not find that older patients were more likely to experience respiratory complications.

Similar findings to our study were recently published in a retrospective pediatric series of 66 SARS-CoV-2 positive patients who had undergone surgery (elective and urgent).¹⁰ They also found no incidence of mortality or progression to ECMO. In their cohort, 8% of patients required postoperative oxygen support ranging from nasal cannula to intubation.¹⁰ A second retrospective matched cohort study of 51 SARS-CoV-2 positive pediatric patients undergoing general anesthesia reported that having a non-severe (asymptomatic) SARS-CoV-2 infection was associated with an 11.8% risk of respiratory complication, but this group also did not observe any incidence of acute respiratory distress syndrome, pneumonia, or perioperative mortality.¹⁷ The risk of perioperative respiratory events in the general pediatric population has been cited to be around 0.1-3% for serious events such as aspiration, reintubation, respiratory failure, apnea, or laryngospasm and up to 10% for milder events such as transient desaturation.¹⁸ These event rates are comparable to those experienced by our asymptomatic patients, as the 8.7% who had respiratory complications was largely driven by HFNC requirement in 5.5%.

Postoperative respiratory complications in children who are symptomatic with upper respiratory infections (URI) other than SARS-CoV-2 appear to be more common, ranging from 24-30%.¹⁹⁻²² As COVID-19 is now an endemic problem, moving forward it may be prudent to develop policies where symptomatic patients are treated the same as symptomatic patients with other URIs. Pediatric patients who develop URI symptoms prior to a scheduled procedure are not routinely tested with a respiratory viral panel, but their case may be delayed until they recover from their URI. In the future, we might consider allowing the presence or absence of symptoms to determine whether surgery should be delayed, so the risks and benefits of delaying surgery versus proceeding with surgery can be considered. It may not be necessary to test every patient prior to a procedure as is currently the standard in many hospitals. Urgent or emergent procedures in patients who are symptomatic and test positive for SARS-CoV-2 should not be delayed, but it should be understood there is a

higher risk of respiratory complications in this population. Elective procedures in symptomatic SARS-CoV-2 positive patients should be rescheduled to decrease the risks of postoperative respiratory complications. It may be reasonable to consider relaxation of COVID-19-related restrictions for time-sensitive, non-urgent procedures in asymptomatic patients who are at risk of morbidity if surgery is delayed.

In addition to the operative risks patients face when undergoing surgery while for SARS-CoV-2, the risks to the clinicians taking care of these patients must be considered. COVID-19 infection is transmitted by respiratory droplets, so aerosol-generating procedures pose a higher risk of transmission to healthcare providers.²³ Transmission is a concern particularly when it comes to the need for intubation to provide general anesthesia. Existing policies to protect healthcare workers perioperatively have included adding isolation protocols or necessitating use of negative pressure rooms for intubation; however, data proving significant benefit of this in reducing transmission rates is limited, particularly in the asymptomatic patient. While the risk of COVID-19 transmission to healthcare workers is real, reported transmissions from index cases through studies on contact tracing and mass surveillance have been low,^{17,24} and are likely to be even lower with widespread vaccine mandates among healthcare workers.^{12,13} Additionally, properly donned personal protective equipment further decreases the risk of SARS-CoV-2 transmission.²⁴ These protective measures, along with existing data on lower than expected transmission from patient to provider, and findings from this study may support relaxing COVID restrictions in operative planning for children.

There are some limitations to this study that are important to mention. First, this is a retrospective cohort study with data collection occurring at 20 different centers, and since all data were not collected by the same person, this makes the study design more vulnerable to data collection errors. To reduce information bias due to data collection errors, there was a standardized REDCap database and data dictionary. Second, we did not include a comparison group of children who tested negative for COVID-19 as a control. Without a control group, we cannot definitively conclude that the observed respiratory complications were due to SARS-CoV-2 positive status. Third, there was no standardized protocol for laboratory testing for SARS-CoV-2 across all 20 centers. To decrease variability and selection bias without a standardized protocol, we only included patients who had a positive SARS-CoV-2 PCR test. The limitations of laboratory testing mean that there were likely some patients excluded from this study based on false-negative results. Future studies should be

performed to make recommendations on standardized preoperative testing protocols, especially now in the setting of vaccine availability. Fourth, while our cohort of patients is relatively large for pediatric patients who underwent general anesthesia while SARS-CoV-2 positive, we recognize that it is underpowered for detecting a statistically significant increased risk of death or severe morbidity. Additionally, the number of patients who were symptomatic from their COVID-19 infection were small, which limits the stratified analysis we performed for the asymptomatic and symptomatic populations. Fifth, this study was performed prior to the Delta and Omicron variants of COVID-19. This may have led to an increase in the number of children with COVID-19, but there was no apparent increase in disease severity in children with the Delta variant.^{25,26} Finally, this study was conducted prior to widespread vaccine availability. Now that the Pfizer vaccine has been approved for children 5 years and older²⁶, more studies will need to be performed to inform policies regarding whether there is any role for preoperative SARS-CoV-2 testing in vaccinated children.

Conclusions:

Post-procedural respiratory complications in asymptomatic SARS-CoV-2 positive children undergoing general anesthesia occurred in 8.7% of cases in this cohort. Moving forward, hospitals should consider these data when making policies regarding case cancellation and rescheduling. Before proceeding with anesthetic exposure and surgical procedures, providers should also consider risks of delaying the procedure for a time-sensitive but non-urgent problem, the COVID vaccination status of the patient, exposure risks for hospital staff and other patients, and features of the prevailing COVID variant.

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Table and Figure Legends:

Figure 1: Data flow to demonstrate sources of missing data

Figure 2: Number of days between positive test and surgery for cohort

Table 1: Rate of Postoperative Respiratory Complications by Patient/Procedure Characteristics, Univariate Analysis

Table 2: Incidence of Postoperative Respiratory Complications in Symptomatic vs Asymptomatic SARS-CoV-2 positive Patients

Supplemental File 1: Data Collected at Each Institution

Supplemental Table 1: List of Included Elective Procedures

Supplemental Table 2: List of all Included Procedures

Journal Pre-proof

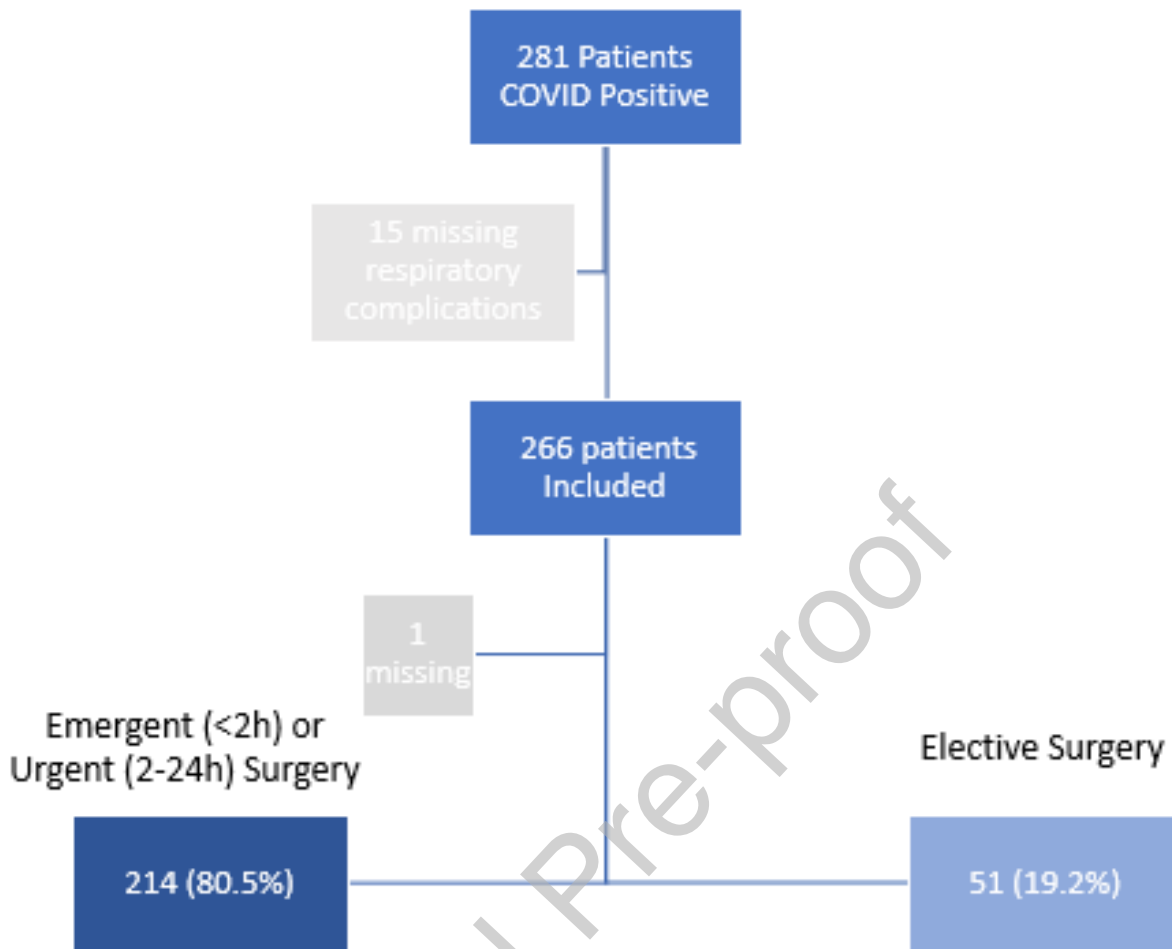
Figure 1: Data Flow to demonstrate exclusion of patients.

Figure 2: Number of days between positive SARS-CoV-2 test and procedure among children undergoing general anesthesia

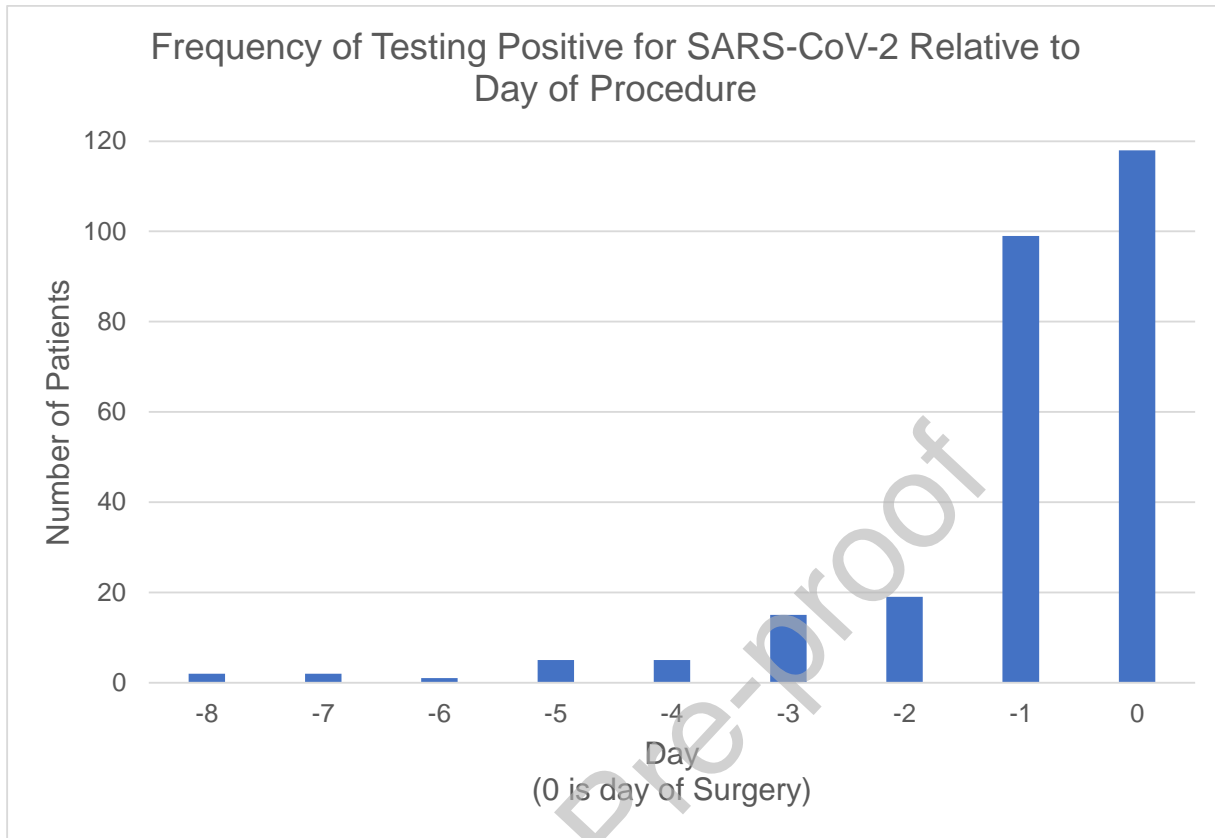


Table 1: Rate of postoperative respiratory complications by patient and procedure characteristics

Patient/Procedure Characteristic	Respiratory Complications				
	No		Yes		P-value
	N	%	N	%	
Surgery Type					
Emergent	28	77.8	8	22.2	0.007
Urgent	167	93.8	11	6.2	
Elective	44	86.3	7	13.7	
Surgical Approach					
Open	95	87.2	14	12.8	0.009
Laparoscopic	89	95.7	4	4.3	
Laparoscopic assist	3	60	2	40	
Endoscopic	21	100	0	0	
Other	30	83.3	6	16.7	
Surgical Specialty					
Neurosurgery	13	92	1	7.1	0.001
General Surgery	115	92.7	9	7.3	
Trauma	1	50	1	50	
Cardiac	1	50	1	50	
ENT	17	85	3	15	
Urology	10	100	0	0	
Plastic	4	50	4	50	
Orthopedic	47	95.9	2	4.1	
Other	31	86.1	5	13.9	
Comorbidities Present*					
No	165	94.3	10	5.7	0.003
Yes	74	83.2	15	16.9	
Body Mass Index					
Underweight	14	93.3	1	6.7	0.81
Healthy	82	90.1	9	9.9	
Overweight	30	93.8	2	6.3	
Obese	43	87.8	6	12.2	
ASA Class					
1	56	100	0	0	<0.001
2	126	92.7	10	7.4	
3	51	79.7	13	20.3	
4	5	62.5	3	37.5	
5	1	100	0	0	
Age (median, Interquartile Range)					
	9.4	4-14	12.7	5-14	0.415
Race					
					0.333
White	158	91.9	14	8.1	
Black	29	78.4	8	21.6	

Asian	4	100	0	0	
Mixed	6	100	0	0	
Other	22	91.7	2	8.3	
Unknown	17	89.5	2	10.5	
Sex					
Female	90	89.1	11	10.9	0.654
Male	148	90.8	15	9.2	
Preop Symptoms					
Loss of Smell/Taste					
No	238	90.2	26	9.9	0.64
Yes	2	100	0	0	
Abdominal Pain					
No	189	88.7	24	11.3	0.1
Yes	51	96.2	2	3.8	
Fevers					
No	211	90.2	23	9.8	0.935
Yes	29	90.6	3	9.4	
Cough					
No	231	90.6	24	9.4	0.338
Yes	9	81.8	2	18.2	
Dyspnea					
No	240	90.9	24	9.1	<0.001
Yes	0	0	2	100	
Respiratory Requirement Preop					
None					
No	17	73.9	6	26.1	0.006
Yes	223	91.8	20	8.2	
Nasal Cannula					
No	235	90.7	24	9.3	0.09
Yes	5	71.4	2	28.6	
Non-invasive Ventilation					
No	236	90.8	24	9.2	0.049
Yes	4	66.7	2	33.3	
Vent Support					
No	233	91	23	9	0.003
Yes	7	70	3	30	

* Comorbidities include cancer, being immunocompromised, presence of asthma, cancer, obesity;
ASA=American Society of Anesthesia

Table 2: Incidence of Postoperative Respiratory Complications in Symptomatic vs Asymptomatic SARS-CoV-2 positive Patients

Patient and Procedure Characteristics	Respiratory Complications		
	Symptomatic (n=13)	p-value	Asymptomatic (n=253)
Case class			
Elective	0 (0%)	0.46	7 (14.3%)
Emergent/Urgent	4 (36.4%)		15 (7.4%)
Comorbidity status			
No Comorbidities	1 (16.7%)	0.34	9 (5.3%)
Comorbidities	3 (42.9%)		12 (14.6%)
ASA Class			
ASA 1-2	1 (16.7%)	0.34	9 (4.8%)
ASA 3-5	3 (42.9%)		13 (19.7%)
BMI			
Underweight/Healthy BMI	3 (37.5%)	0.49	15 (8.5%)
Overweight/Obese BMI	1 (20.0%)		7 (9.1%)
Age (median, Interquartile Range)	14 (5-17)	0.14	11.9 (5-14)