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Association of preoperative COVID-19 and postoperative respiratory morbidity during the Omicron epidemic wave: the DROMIS-22 multicentre prospective observational cohort study



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Summary

Background Preoperative COVID-19 has been associated with excess postoperative morbi-mortality. Consequently, guidelines were developed that recommended the postponement of surgery for at least 7 weeks after the infection. We hypothesised that vaccination against the SARS-CoV-2 and the large predominance of the Omicron variant attenuated the effect of a preoperative COVID-19 on the occurrence of postoperative respiratory morbidity.

Methods We conducted a prospective cohort study in 41 French centres between 15 March and 30 May 2022 (ClinicalTrials NCT05336110), aimed at comparing the postoperative respiratory morbidity between patients with and without preoperative COVID-19 within 8 weeks prior to surgery. The primary outcome was a composite outcome combining the occurrence of pneumonia, acute respiratory failure, unexpected mechanical ventilation, and pulmonary embolism within the first 30 postoperative days. Secondary outcomes were 30-day mortality, hospital length-of-stay, readmissions, and non-respiratory infections. The sample size was determined to have 90% power to identify a doubling of the primary outcome rate. Adjusted analyses were performed using propensity score modelling and inverse probability weighting.

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Findings Of the 4928 patients assessed for the primary outcome, of whom 92.4% were vaccinated against the SARS-CoV-2, 705 had preoperative COVID-19. The primary outcome was reported in 140 (2.8%) patients. An 8-week preoperative COVID-19 was not associated with increased postoperative respiratory morbidity (odds ratio 1.08 [95% CI 0.48–2.13]; $p = 0.83$). None of the secondary outcomes differed between the two groups. Sensitivity analyses concerning the timing between COVID-19 and surgery, and the clinical presentations of preoperative COVID-19 did not show any association with the primary outcome, except for COVID-19 patients with ongoing symptoms the day of surgery (OR 4.29 [1.02–15.8]; $p = 0.04$).

Interpretation In our Omicron-predominant, highly immunised population undergoing general surgery, a preoperative COVID-19 was not associated with increased postoperative respiratory morbidity.

Funding The study was fully funded by the French Society of Anaesthesiology and Intensive Care Medicine (SFAR).

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Keywords: COVID-19; Anaesthesia; Surgery; Perioperative risk; Respiratory complications; Postoperative pneumonia; Acute respiratory failure; Prognosis

Research in context

Evidence before this study

We searched PubMed for studies assessing the effect of preoperative COVID-19 on the postoperative morbidity and/or mortality of surgical patients. The search used the terms “COVID-19”, “SARS-CoV-2”, “surgery”, “perioperative”, and “respiratory complications” with no language restrictions among articles published from 1 March 2020 (onset of the pandemic in western countries) up to 1 September 2022 and retrieved 192 results. After excluding paediatric studies, case reports, short case series with less than 50 patients with preoperative COVID-19, and non-comparative studies (*i.e.*, studies without a non-COVID-19 group to compare the incidence of postoperative respiratory morbidity), ten cohort studies, including three from the COVIDSurg Collaborative, were identified. All reported increased postoperative respiratory morbidity (and sometimes mortality) in patients with preoperative COVID-19. All ten studies included patients who had undergone surgery during the first epidemic waves in 2020 or early 2021 before the emergence of the SARS-CoV-2 Omicron variant and the use of vaccination.

Added value of this study

In our prospective cohort study assessing 4928 patients who underwent surgery between March and May 2022, we

reported, using propensity score modelling analysis, similar postoperative respiratory morbidity rates in patients with and without preoperative COVID-19. Similar results were found for patients with COVID-19 within the most recent period prior to surgery. A possible exception may be observed for patients with ongoing COVID-19 symptoms the day of surgery. Preoperative COVID-19 was also not associated with postoperative 30-day mortality, length of hospital stay, or non-respiratory infections.

Implications of all the available evidence

Previous studies reported an excess respiratory morbidity attributable to preoperative COVID-19, ranging mainly from 3 to 6 times. In contrast, for the first time, our results revealed no significant increase in postoperative respiratory morbidity. This difference is probably due, at least in part, to the spread of the Omicron variant, which is responsible for a less severe form of COVID-19, and to the large-scale vaccination programmes that decrease both the number of SARS-CoV-2 infections and their severity. Taken altogether, these findings may suggest a possible update of the current guidelines based on results from the first epidemic waves, in case of preoperative Omicron COVID-19, at least in vaccinated patients asymptomatic on the day of general surgery.

Introduction

Since its onset in 2020, the COVID-19 pandemic has been responsible for increased morbidity and mortality in perioperative patients. The international multicentre prospective cohort study by the COVIDSurg and GlobalSurg Collaborative demonstrated an excess of respiratory morbidity and mortality among patients undergoing surgery less than 7 weeks after a SARS-CoV-2 infection.¹ As a result, scientific societies and health

authorities recommended that scheduled surgeries be postponed for at least 7 weeks after the onset of infection. This contributed to reducing the risk associated with surgery but led to massive postponement of the surgical management of a large number of patients. In addition to the negative impacts of lockdowns that led to delayed healthcare,² these well-intentioned surgical postponements probably inadvertently increased the severity of many diseases that may have benefited

from prompt surgical management, resulting in another health crisis.

Other large cohorts have confirmed the COVIDSurg findings.^{3,4} Importantly, all these studies were performed during the first and second COVID-19 surges. Since then, the characteristics of the pandemic have evolved. Indeed, at least two major changes occurred during the last waves. First, the Omicron SARS-CoV-2 variant emerged and spread, becoming the predominant variant accounting for more than 95% of the strains sequenced in almost all countries in the world since the end of January 2022.⁵ Although it is approximately four times more transmissible than the alpha wild-type SARS-CoV-2,⁶ the Omicron variant is responsible for less severe forms of the COVID-19.^{7,8} Second, the massive programmes of COVID-19 vaccination reduced the rate of contamination and the incidence of severe disease in patients who contracted the infection.

The aim of this study was to provide an updated assessment of the impact of a preoperative SARS-CoV-2 infection on postoperative outcomes. We hypothesised that a preoperative COVID-19, predominantly due to Omicron variant, occurring in a largely immunised population may not be associated with increased postoperative respiratory morbidity.

Methods

Study design and ethics

In this prospective multicentre cohort study, we enrolled patients from 41 French tertiary care centres requiring any types of surgery between 15 March 2022 and 30 May 2022. The study was registered on ClinicalTrials (NCT05336110, full protocol in the [Online Supplementary Material](#), p. 20–36). The protocol was approved by the ethics committee *Comité de Protection des Personnes Sud-Ouest et Outre-Mer 1* on 10 March 2022 under number 22.00518.000091 – CPP 1-22-012. Due to the non-interventional design of the study and according to French law,⁹ the patients' written consent was waived by the ethical committee. Thus, before undergoing surgery, local co-investigators provided written information to patients who could then decline inclusion in the study. This manuscript adheres to the STROBE guidelines. The STROBE checklist is provided in the [Online Supplementary Material](#).

Patients

All participating centres were free to consecutively include patients undergoing either a single type of surgery, a few types of surgery, or all types of surgery performed in the hospital for a minimum of 1 week and a maximum of four consecutive weeks within the inclusion period, depending on the availability of research support. All adult patients (>18 years old) undergoing a surgical procedure in the operating rooms (excluding off-site procedures not performed in the operating theatre)

under general and/or regional anaesthesia, for whom a result of a preoperative SARS-CoV-2 diagnostic test was available the day of the surgery (or during the 48 h following the surgery in case of emergency), were eligible. All surgical disciplines (*i.e.*, orthopaedic, digestive, thoracic, etc.) and grades of surgery (*i.e.*, major or non-major surgery, see the [Online Supplementary Material](#) p. 8 for definition) were eligible, as were all indications and levels of urgency, except for some minor procedures listed for each investigator ([Online Supplementary Material](#), p. 2–3). These procedures have been excluded in order to homogenise the population included, as they could be managed in the operating theatre or not, and/or under general or locoregional anaesthesia or not, depending on the organisation of each centre and the types of patients. The non-inclusion criteria were pregnancy, surgery performed under sedation and/or local anaesthesia alone, patient under guardianship or curatorship, patients without social protection, patients already included once in the study, and patients whose immediate postoperative follow-up was planned in a non-participating hospital.

Definitions and outcomes

Patients were classified as having pre-operative COVID-19 if they had a positive SARS-CoV-2 RT-PCR and/or a positive rapid antigen test performed from a nasopharyngeal swab during 8 weeks preceding the surgical intervention. The timing between the diagnosis of COVID-19 and the surgical procedure was defined as the timing between the first symptoms and the day of surgery for symptomatic patients and between the date of the first preoperative positive test and the day of surgery for asymptomatic patients.

The primary outcome was a composite respiratory morbidity outcome consisting of the occurrence within the first 30 postoperative days of: *i.* pneumonia; and/or *ii.* acute respiratory failure (hypoxia with PaO₂ <60 mmHg and/or SpO₂ ≤90% on room air with at least one related clinical sign); and/or *iii.* unplanned use or prolongation of postoperative mechanical ventilation (requirement for invasive or non-invasive mechanical ventilation not planned or for longer than planned before surgery); and/or *iv.* new symptomatic pulmonary embolism (see the full definition of each component of the primary outcome and of secondary outcomes in the [Online Supplementary Material](#), p. 4–7).

The secondary outcomes were a 30-day mortality rate, postoperative hospital length-of-stay, need for hospital readmission during the 30 days following surgery, and occurrence of a non-respiratory infection.

Data collection

The following information was collected prospectively by local investigators for each patient, using REDCap electronic data capture tools¹⁰ provided by the French Society of Anaesthesiology and Intensive Care Medicine

(SFAR); age; sex; American Society of Anaesthesiology (ASA) class; revised cardiac risk index; presence of significant respiratory comorbidities, hypertension, or diabetes; COVID-19 vaccination status; type and result of COVID-19 preoperative test; indication for surgery (cancer, functional, trauma, and sepsis), type (abdominal, vascular, bones, etc.) and grade (major/non major) of surgery and surgical urgency (elective or emergency) (definitions in [Online Supplementary Material](#), p. 8); type of anaesthesia (general and/or regional); and duration of surgery and mechanical ventilation (if required). The postoperative outcomes were retrieved from the patients' medical files and a follow-up phone call at day 30. If the patient did not respond, two supplementary calls were made between day 30 and day 40, after which, in the case of persistent non-response, criteria at hospital discharge were considered instead of criteria at day 30.

Statistical analysis

Estimation of reported COVID-19 within 8 weeks

The incidence of respiratory morbidity outcome and secondary outcomes were compared between patients with and without reported COVID-19 within 8 weeks prior to surgery. The number of events was expected to be low for some of the assessed endpoints, which did not allow for controlling confounding by multiple adjusting for a sufficient number of variables, as at least 10–15 events per variable are usually required, with authors recommending an even higher number of events. Among alternative methods recommended to control confounding, propensity score (PS) modelling with inverse probability weighting (IPW) is a valid option.^{11,12} We therefore adjusted for confounding by PS analysis using IPW. Propensity scores, which reflect the probability of being tested positive on preoperative COVID-19 screening, were calculated using random-intercept logistic regression models accounting for the multicentre design.¹³ All the following variables collected *a priori* were forced into this non-parsimonious PS model: age class, chronic respiratory diseases, grade of surgery (*i.e.*, major vs. non-major surgery), emergency surgery, ASA class ≥ 3 , hypertension, type of anaesthesia, vaccination against COVID-19, and surgery for cancer. Inverse probability weights were trimmed at the 99th percentile and stabilized. The relevancy of PS modelling was assessed by graphically overlapping PS distributions and evaluating the positivity hypothesis, as well as comparing standardized mean differences before and after weighing patient data by IPW. The effect of COVID-19 was then estimated using random-effect univariate logistic regression with inverse probability weighting (IPW) and cluster resampling across 5000 bootstrap replications to account for the multicentre design for binary outcomes,¹⁴ and linear regression for the continuous postoperative hospital length-of-stay output. Sensitivity analyses were conducted by defining reported COVID-19 within 3

weeks and within 6 weeks (instead of 8 weeks) prior to surgery, and considering the different clinical presentations of preoperative COVID-19. Results are provided as odds ratios (OR) for binary outcomes (and days differences for hospital length-of-stay) with their 95% confidence intervals (95% CI).

Factors associated with postoperative respiratory complications

To determine pre- and intra-operative factors associated with the composite respiratory morbidity outcome we performed a multiple logistic regression. The following baseline covariates deemed clinically relevant were included in the model without univariate screening: preoperative COVID-19, age class, sex, revised cardiac risk index, ASA class ≥ 3 , chronic respiratory disease, hypertension, grade of surgery (*i.e.*, major vs. non-major surgery), emergency surgery, type of anaesthesia and surgery for cancer.

Power calculation

Assuming a 3% incidence of the composite respiratory morbidity outcome in patients without COVID-19 within 8 weeks prior to surgery,¹ sample sizes of 700 and 4000 patients with and without COVID-19 would permit the determination of a 2.0 OR for the association between COVID-19 within 8 weeks and the respiratory morbidity outcome with a 90% power.

Analyses and reporting of data

Categorical variables were reported as “frequency (percentage)”. All analyses were performed with R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed at the $p < 0.05$ significance threshold.

Role of the funding source

The study was fully funded by the French Society of Anaesthesiology and Intensive Care Medicine (SFAR).

Results

Patients and characteristics

During the study period, 5536 patients were screened, of which 5189 were included and 4928 were assessed for the primary outcome ([Fig. 1](#)). The patients and surgery features are shown in [Table 1](#). Of note, 4388 (92.4%) patients were vaccinated against the SARS-CoV-2, including 4091 (86.1%) patients with a complete scheme and 297 (6.3%) patients having received a single dose. Seven hundred and five (14.3%) patients had a preoperative COVID-19. The time from COVID-19 diagnosis to surgery was <1 week in 96 (13.6%) patients, between 1 and 2 weeks for 33 (4.7%) patients, 2 and 3 weeks for 51 (7.2%) patients, 3 and 4 weeks for 51 (7.2%) patients, 4 and 6 weeks for 168 (23.9%) patients, and 6 and 8 weeks for 305 (43.3%) patients. Mild

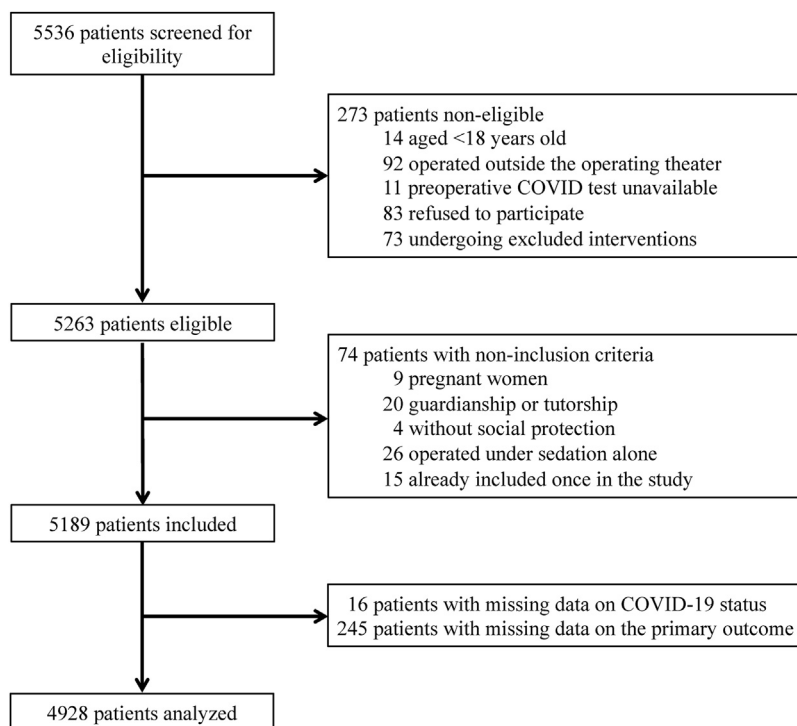


Fig. 1: Flow chart for cohort recruitment including details on inclusion and non-inclusion criteria.

symptoms of COVID-19 were found in 45.6% of patients; however, 21.4% had lower respiratory symptoms. At the time of surgery, 94.7% of patients with preoperative COVID-19 were asymptomatic. Patients with preoperative COVID-19 were younger, less likely to have hypertension and diabetes, and more likely to require emergent surgery than those without preoperative COVID-19 (Table 1).

Primary outcome

The primary outcome rate was 2.8% ($n = 140$), including pneumonia in 56 (1.1%) patients, acute respiratory failure in 51 (1.0%) patients, unexpected requirement for postoperative mechanical ventilation in 70 (1.4%) patients, and symptomatic pulmonary embolism in 20 (0.4%) patients. This outcome occurred in 24 (3.4%) patients with preoperative COVID-19 and 116 (2.75%) patients without preoperative COVID-19, respectively. After inverse PS weighting, the occurrence of a preoperative COVID-19 in the 2 months before surgery was not associated with an increased rate of postoperative respiratory morbidity (OR 1.08 95% CI [0.48–2.13]; $p = 0.83$) (Table 2 and Supplementary Fig. S1).

Considering the at-risk period reported in the COV-IDSurg Collaborative cohort,¹ a sensitivity analysis was performed to assess the potential impact of preoperative COVID-19 in the 6 weeks before surgery. After

adjustment, this event was not associated with an increased rate of postoperative respiratory morbidity (OR 0.96 [0.32–2.22]; $p = 0.94$) (Supplementary Table and Fig. S8 in the Online Supplementary Material). In addition, due to the observed variations in raw incidence of postoperative respiratory morbidity with time since COVID-19 diagnosis (Fig. 2), a sensitivity analysis was performed on patients with COVID-19 in the 3 weeks before surgery. This was also not associated with an increased rate of postoperative respiratory morbidity (OR 0.60 [0.27–2.07]; $p = 0.33$) (Table 2 and Supplementary Fig. S7 in the Online Supplementary Material).

Sensitivity analyses on the presence of symptoms (*i.e.*, symptomatic or asymptomatic COVID-19) and their severity (*i.e.*, mild symptoms or respiratory signs) at the time of COVID-19 diagnosis, and the grade of surgery (*i.e.*, major or non-major surgery) did not show significant associations with the primary outcome (Supplementary Table and Figs. S2–S6 in the Online Supplementary Material). Finally, patients with preoperative COVID-19 within 8 weeks prior to surgery and ongoing symptoms on the day of surgery had an increased risk of respiratory morbidity compared to non-COVID-19 patients (OR 4.29 [1.02–15.8]; $p = 0.04$) and COVID-19 patients symptom-free on the day of surgery (OR 7.05 [1.07–82.1]; $p = 0.04$) (Supplementary Table, Figs. S9 and S10 in the Online Supplementary Material).

	N ^a	All patients (N = 4928)	Patients with COVID-19 in the 8 weeks before surgery (N = 705)	Patients without COVID-19 in the 8 weeks before surgery (N = 4223)
Age (years old)	4928			
18–29		566 (11.5%)	87 (12.3%)	479 (11.3%)
30–49		1355 (27.5%)	270 (38.3%)	1085 (25.7%)
50–69		1906 (38.7%)	214 (30.4%)	1692 (40.1%)
70–79		829 (16.8%)	99 (14.0%)	730 (17.3%)
≥80		272 (5.5%)	35 (5.0%)	237 (5.6%)
Sex	4923			
Male		2398 (48.7%)	318 (45.1%)	2080 (49.3%)
Female		2525 (51.3%)	386 (54.9%)	2139 (50.7%)
ASA class	4923			
1–2		3843 (78.1%)	563 (80.0%)	3280 (77.7%)
3–5		1080 (21.9%)	141 (20.0%)	939 (22.3%)
Revised Cardiac Risk Index	4824			
0		3621 (75.1%)	543 (78.5%)	3078 (74.5%)
1		837 (17.4%)	103 (14.9%)	734 (17.8%)
2		268 (5.6%)	33 (4.8%)	235 (5.7%)
≥3		98 (2.0%)	13 (1.8%)	85 (2.0%)
Respiratory comorbidity	4928			
COPD		237 (4.8%)	28 (4.0%)	209 (4.9%)
Asthma		236 (4.8%)	28 (4.0%)	208 (4.9%)
Other ^b		46 (0.9%)	5 (0.7%)	41 (1.0%)
Hypertension	4928	1485 (30.1%)	170 (24.1%)	1315 (31.1%)
Diabetes	4928	536 (10.9%)	51 (7.2%)	485 (11.5%)
Vaccination against COVID-19	4751			
First vaccination alone		297 (6.3%)	59 (8.7%)	238 (5.9%)
Complete scheme		4091 (86.1%)	563 (83.0%)	3528 (86.6%)
No vaccination		363 (7.6%)	56 (8.3%)	307 (7.5%)
COVID-19 in the 8 weeks prior to surgery				
Delay before surgery	704	NA		NA
<1 week			96 (13.6%)	
1–2 weeks			33 (4.7%)	
2–3 weeks			51 (7.2%)	
3–4 weeks			51 (7.2%)	
4–6 weeks			168 (23.9%)	
6–8 weeks			305 (43.3%)	
Symptoms and severity at diagnosis	676	NA		NA
Asymptomatic			220 (32.5%)	
Mild symptoms without respiratory signs			308 (45.6%)	
Respiratory signs (cough, dyspnoea, etc.)			145 (21.4%)	
Hospitalization			3 (0.4%)	
Symptoms at surgery	695	NA		NA
Asymptomatic or resolved			658 (94.7%)	
Still symptomatic			37 (5.3%)	
Type of surgery	4926			
Orthopaedic		1560 (31.7%)	248 (35.2%)	1312 (31.1%)
Digestive		733 (14.9%)	92 (13.1%)	641 (15.2%)
Gynaecologic		515 (10.5%)	86 (12.2%)	429 (10.2%)
Urologic		450 (9.1%)	57 (8.1%)	393 (9.3%)
Thoracic		127 (2.6%)	15 (2.1%)	112 (2.7%)
Cardio-vascular		328 (6.7%)	34 (4.8%)	294 (7.0%)
Plastic		146 (3.0%)	27 (3.8%)	119 (2.8%)
Head and neck		814 (16.5%)	107 (15.2%)	707 (16.7%)
Other		253 (5.1%)	38 (5.4%)	215 (5.1%)

(Table 1 continues on next page)

	N ^a	All patients (N = 4928)	Patients with COVID-19 in the 8 weeks before surgery (N = 705)	Patients without COVID-19 in the 8 weeks before surgery (N = 4223)
(Continued from previous page)				
Grade of surgery	4922			
Major		1035 (21.0%)	147 (20.9%)	888 (21.1%)
Non-major		3887 (79.0%)	557 (79.1%)	3330 (78.9%)
Indication of surgery	4924			
Cancer		976 (19.8%)	131 (18.6%)	845 (20.0%)
Functional		2860 (58.1%)	394 (56.0%)	2466 (58.4%)
Trauma		456 (9.3%)	73 (10.4%)	383 (9.1%)
Septic		251 (5.1%)	55 (7.8%)	196 (4.6%)
Other		381 (7.7%)	51 (7.2%)	330 (7.8%)
Urgency of surgery	4927			
Elective		4133 (83.9%)	544 (77.3%)	3589 (85.0%)
Emergency		794 (16.1%)	160 (22.7%)	634 (15.0%)
Type of anaesthesia	4925			
General anaesthesia		4155 (84.4%)	567 (80.4%)	3588 (85.0%)
Regional anaesthesia alone		770 (15.6%)	137 (19.6%)	633 (15.0%)
Duration of surgery	4919			
< 30 min		633 (12.9%)	99 (14.0%)	535 (12.7%)
30–60 min		1291 (26.2%)	197 (27.9%)	1094 (26.0%)
60–120 min		1614 (32.8%)	229 (32.5%)	1385 (32.9%)
120–240 min		1049 (21.3%)	142 (20.1%)	907 (21.5%)
>240 min		332 (6.7%)	38 (5.4%)	294 (7.0%)
Duration of mechanical ventilation	4148			
<30 min		140 (3.4%)	12 (2.1%)	128 (3.6%)
30–60 min		718 (17.3%)	96 (17.0%)	622 (17.4%)
60–120 min		1588 (38.3%)	228 (40.4%)	1360 (38.0%)
120–240 min		1140 (27.5%)	161 (28.5%)	979 (27.3%)
>240 min		562 (13.5%)	68 (12.0%)	494 (13.8%)

NA: not applicable. ^aN = number of available data. ^bOther significant respiratory diseases were bronchiectasis, diffuse emphysema, pulmonary fibrosis, lung transplantation, and chronic respiratory insufficiency requiring long-term oxygen.

Table 1: Characteristics of patients at inclusion.

Secondary outcomes

The mortality rate at day 30 was 0.7% in the patients with preoperative COVID-19 and 0.3% in those without preoperative COVID-19 (OR 1.38 [0.40–3.23]; $p = 0.54$) (Table 2). The postoperative length-of-stay did not differ between the two groups (median 2, interquartile range [1–5] days in both groups; $p = 0.66$) (Table 2). The readmission rate during the first 30 postoperative days was 5.8%, without any difference between the two groups (4.5% vs. 5.9%; OR 0.71 [0.43–1.09]; $p = 0.14$) (Table 2). Finally, non-respiratory infections occurred in 5.7% of patients with preoperative COVID-19 and in 6.1% of patients without preoperative COVID-19 (OR 0.77 [0.47–1.09]; $p = 0.23$) (Table 2).

Factors associated with postoperative respiratory morbidity

The multivariable analysis aiming to determine pre- and intra-operative variables associated with postoperative respiratory morbidity identified the following factors:

ASA class ≥ 3 (OR 2.75 [1.74–4.36]; $p < 0.001$), revised cardiac risk index ≥ 3 (OR 2.64 [1.18–5.62]; $p = 0.01$), preoperative respiratory comorbidity (OR 1.75 [1.08–2.75]; $p = 0.02$), major surgery (OR 1.96 [1.28–2.98]; $p = 0.002$), cancer surgery (OR 1.63 [1.05–2.50]; $p = 0.03$), and emergency surgery (OR 2.41 [1.54–3.71]; $p < 0.001$). According to the PS results, 8-week preoperative COVID-19 was not associated with the primary outcome (OR 1.28 [0.77–2.05]; $p = 0.32$) (Table 3).

Discussion

In contrast to previous studies performed in the pre-Omicron and pre-vaccination era, this well-powered, more contemporary multicentre prospective study showed no significant association between 8-week preoperative COVID-19 and postoperative respiratory morbidity. A similar result was found for the sensitivity analyses focusing on patients with COVID-19 in the last 6 or 3 weeks before surgery. Regarding secondary

Preoperative COVID-19 within 8 weeks prior to surgery					
	No COVID-19 (N = 4223)	COVID-19 (N = 705)	Weighted OR or weighted difference	95% Confidence interval	p value
Primary outcome					
Respiratory morbidity, n (%)	116 (2.75%)	24 (3.4%)	1.08	0.48-2.13	0.83
Secondary outcomes					
30-day mortality, n (%)	14 (0.3%)	5 (0.7%)	1.38	0.40-3.23	0.54
Non-respiratory infections, n (%)	257 (6.1%)	40 (5.7%)	0.77	0.47-1.09	0.23
Readmissions, n (%)	250 (5.9%)	32 (4.5%)	0.71	0.43-1.09	0.14
Hospital length-of-stay, days	2 [1-5]	2 [1-5]	-0.08 (day)	-0.40 to 0.30	0.66
Preoperative COVID-19 within 3 weeks prior to surgery					
	No COVID-19 (N = 4747)	COVID-19 (N = 180)	Weighted OR or weighted difference	95% Confidence interval	p value
Primary outcome					
Respiratory morbidity, n (%)	132 (2.8%)	8 (4.4%)	0.60	0.27-2.07	0.33
Secondary outcomes					
30-day mortality, n (%)	16 (0.3%)	3 (1.7%)	1.66	0.83-4.08	0.21
Non-respiratory infections, n (%)	286 (6.0%)	11 (6.1%)	0.66	0.12-1.81	0.55
Readmissions, n (%)	269 (5.7%)	13 (7.2%)	0.73	0.14-1.87	0.64
Hospital length-of-stay, days	2 [1-5]	3 [1-7]	-0.18 (day)	-0.44 to 0.97	0.62

Table 2: Association between preoperative COVID-19 and primary and secondary outcomes.

outcomes, there were likewise no associations between preoperative COVID-19 and 30-day mortality rate, length-of-hospital stay, readmission rate, or non-respiratory infections between the two groups. The difference with previous results, including those from the COVIDSurg cohort,¹ can probably be explained, at least in part, by the high rate of immunisation in our cohort and the high prevalence of the SARs-CoV-2 Omicron variant at the time of the study.

The 14.3% rate of patients with a preoperative COVID-19 in our study, lower than the 24% incidence of COVID-19 within the previous 8 weeks in the whole

population during the same period,¹⁵ may reflect compliance with national guidelines recommending a timing of at least 7 weeks between a SARS-CoV-2 infection and rescheduling the surgical procedure. However, one key difference from other studies is the lower incidence of postoperative respiratory morbidity in patients with preoperative COVID19, raising a concern that we were underpowered to detect smaller differences than the two-fold excess respiratory morbidity excluded by our results. In the COVIDSurg Collaborative study, the respiratory morbidity in patients with preoperative COVID-19 was 3.4–3.9 times higher

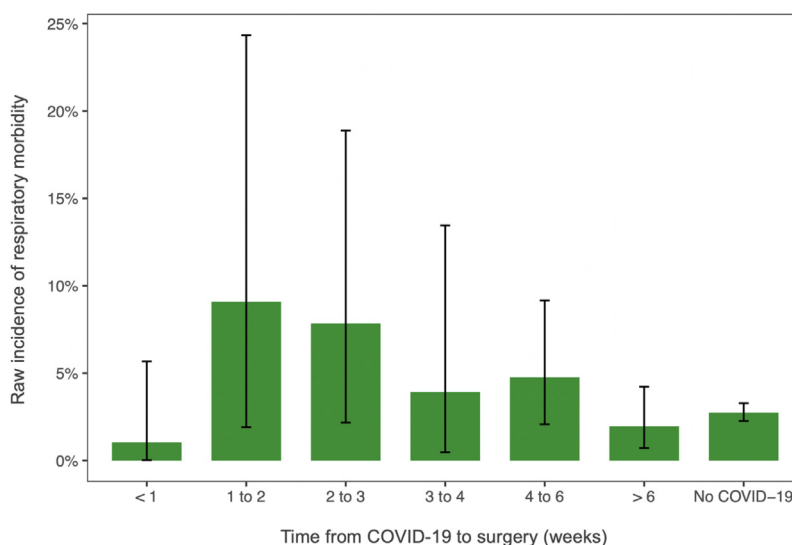


Fig. 2: Raw incidence of the respiratory morbidity outcome depending on the time between preoperative COVID-19 and surgery. Histograms represent the raw incidence and error bars the 95% confidence interval of the proportion.

Factors	Odds ratio	95% Confidence interval	p value
Preoperative COVID-19 within 8 weeks prior to surgery	1.28	0.77–2.05	0.32
Age			
18–29 years old	1 (ref)		
30–49 years old	1.38	0.55–4.18	0.53
50–69 years old	1.16	0.47–3.51	0.77
70–79 years old	1.66	0.64–5.18	0.33
≥80 years old	2.71	0.97–8.82	0.07
Male sex	0.90	0.61–1.32	0.58
ASA class ≥3	2.75	1.74–4.36	<0.001
Revised Cardiac Risk Index			
RCRI 0	1 (ref)		
RCRI 1–2	1.40	0.89–2.21	0.15
RCRI ≥3	2.64	1.18–5.62	0.01
Chronic respiratory disease	1.75	1.08–2.75	0.02
Hypertension	1.05	0.68–1.62	0.83
Emergency surgery	2.41	1.54–3.71	<0.001
Major surgery	1.96	1.28–2.98	<0.01
Cancer surgery	1.63	1.05–2.50	0.03
Type of anaesthesia			
Regional anaesthesia alone	1 (ref)		
General anaesthesia	1.17	0.64–2.31	0.64

Table 3: Factors associated with the primary respiratory morbidity outcome (multiple regression analysis).

than in non-COVID-19 patients.¹ Similarly, Deng *et al.*⁴ reported a higher risk of postoperative pneumonia (adjusted OR 6.5 95% CI [4.1–10.3]) and respiratory failure (aOR 3.4 [2.2–5.1]) in patients with preoperative COVID-19 in the 4 weeks before surgery. Kiyatkin *et al.*³ also reported a risk of postoperative respiratory failure 2.8 times higher in patients with COVID-19 in the 4 weeks before surgery. Thus, considering our results and those from previous studies, it could be observed that the postoperative respiratory risk related to preoperative COVID-19 have decreased and if an excess risk still exists with the Omicron SARS-CoV-2 variant in immunised patients, it is less than two-fold following general surgery.

While increasing study power to detect a smaller than two-fold risk increase may be feasible, the clinical relevance of such a study has to be balanced against the increase in complications that surgical delay invariably causes, particularly in the oncologic context. Indeed, several studies have suggested worsened outcomes when cancer treatment is delayed, notably for surgical treatment. For instance, postponing surgery for colorectal cancer by 4 weeks was associated with poorer overall survival (hazard ratio for death 1.13 95% CI [1.02–1.26]).¹⁶ Similarly, Hanna *et al.*¹⁷ reported a mortality risk for each 4-week delay of surgical treatment increased by 1.06 [1.01–1.12], 1.08 [1.03–1.13], and 1.06 [1.04–1.08] for bladder, breast, and head and neck cancer, respectively. Thus, if guidelines recommended to postpone these surgeries for at least 4–6 completed weeks, based on reports of excess postoperative

morbidity-mortality after preoperative COVID-19 exceeding that associated with delaying cancer surgical treatment, this strategy should probably be re-discussed in the light of our results. A note of caution may be needed for patients with COVID-19 symptoms on the day of surgery, as we observed a higher primary outcome rate in this subgroup. However, this result should be considered preliminary and needs to be confirmed by further studies due to the small number of such patients in our cohort.

Our study has several limitations. First, the assessment of COVID-19 in the 8 weeks before surgery was based on the truthfulness of patients' statements. Thus, several patients could have been misclassified as having no preoperative COVID-19 due to oversights or misrepresentations for fear of not being operated on, or due to asymptomatic patients who did not know that they were infected with SARS-CoV-2. Second, we included patients with preoperative COVID-19 from 6 to 8 weeks before surgery as "COVID-19" patients in the principal analysis, while the COVIDSurg Collaborative cohort study previously reported a respiratory morbidity risk similar to that of non-COVID-19 patients if surgery was performed at least 7 weeks after infection. However, other studies reported a postoperative respiratory risk for a COVID-19 up to 8 weeks before surgery.⁴ In addition, we could not exclude *a priori* that the Omicron variant would lead to different consequences than the historical strain in patients with later COVID-19. Nevertheless, the relevance of the analysis on the whole cohort is reinforced by the sensitivity analyses

performed on patients with a more recent COVID-19 (*i.e.*, within 6 and 3 weeks prior to surgery). Third, due to the design of the study, we cannot assert with certainty that all preoperative COVID-19 were due to the Omicron variant. Nevertheless, from 8 to 6 weeks before the onset of the inclusions, Omicron represented 97.3% of the SARS-CoV-2 variants circulating in France, and then it represented up to more than 99.7% from 6 weeks before the beginning of the inclusions to the closing date for inclusions.¹⁵ Fourth, it could be argued that the actual immunisation rate, *i.e.*, including both the vaccinated patients and those who had been infected in the preceding months, was not collected in our study. However, a large majority (92.1%) of the patients had received at least one dose of COVID-19 vaccine at the time of surgery. Adding that some of the non-vaccinated patients may have been infected more than two months prior to surgery, it could be concluded that our cohort was overwhelmingly immunised against SARS-CoV-2. Fifth, despite the valid methods we used to control confounders, residual confounding factors cannot be ruled out, which is inherent in any observational design. Finally, as each centre included patients undergoing from one to all types of surgeries that were performed in their operating theatre during 1–4 weeks, one could question the representativeness of this cohort and the external validity of our results. However, several criteria contribute to showing that these results can be extrapolated to a large surgical population. Indeed, the incidence of postoperative respiratory morbidity observed in our patients without preoperative COVID-19 (2.75%) was close to that reported by the COVIDSurg Collaborative (2.7%). Similarly, the incidence of postoperative pneumonia in our cohort was in line with that of large pre-COVID datasets.¹⁸ In addition, the identification of six factors associated with postoperative respiratory morbidity in our multivariable analysis, which had also been identified in previous retrospective studies,^{19–21} reinforces the consistency of our findings.

In conclusion, in the Omicron variant era, a preoperative COVID-19 in the 8 weeks prior to surgery was not associated with an increased incidence of postoperative respiratory morbidity in a general surgical population of patients largely immunised against the SARS-CoV-2. Further studies are required to confirm these results and draw definitive conclusions about the potential increase in respiratory risk in the subgroup of COVID-19 patients with ongoing symptoms on the day of surgery.

Contributors

M.G., M.L., and J.-M.C. conceived and designed the study. M.G., M.L., J.-M.C., and N.L. analysed and interpreted the data. N.L. did the statistical analysis. C.D. administered the project and was responsible for data curation. M.G., M.L., J.-M.C., and N.L. drafted the original manuscript. M.G. and N.L. performed reviews of the manuscript. All the other authors acquired the data, reviewed the manuscript, and vouch for the accuracy and completeness of the data and for the adherence of the

study to the protocol. All authors were responsible for the final decision to submit for publication. All authors have seen and approved the manuscript. M.G., M.L., J.-M.C., N.L., and C.D. had full access to all of the data in the study.

Data sharing statement

Data collected for the study will be made available from the corresponding author upon reasonable request.

Declaration of interests

M.G. declares past honoraria from Medtronic France SAS for a presentation on the topic of surgery postponement in the case of preoperative COVID-19. All the other authors declare that they do not have any conflict of interest related to this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2023.101881>.

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