Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study

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ECDC, European Centre for Disease Prevention and Control; PBM, patient blood management; RBC, red blood cell; WHO, World Health Organization. **References: 1.** Drabinski T *et al. Adv Ther.* 2020;37:3515–36. **2.** Trentino KM *et al. Anaesthesia.* 2021;76(3):357–65. **3.** Wan S *et al. J Arthroplasty.* 2020;35:3084–88. **4.** Kaserer A *et al. Anaesthesia.* 2019;74(12):1534–41. **5.** Shander A *et al. Anesth Analg.* 2020;131(1):75–85. **6.** WHO interim guidance: Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19), March 2020. **7.** ECDC rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – sixth update, March 2020. **8.** Leahy MF *et al. Transfusion.* 2017;57(6):1347–58. **9.** Keding V *et al. World J Surg Oncol.* 2018;16:159. **10.** Khalafallah AA *et al. Lancet Haematol.* 2016;3(9):e415–25. **11.** Deppe AC *et al. J Surg Res.* 2016;203(2):424–33. **12.** Althoff FC *et al. Ann Surg.* 2019;269(5):794–804. **13.** Gani F *et al. Ann Surg.* 2019;269(6):1073–79. **14.** Spahn DR *et al. Lancet.* 2019;393(10187):2201–12. **15.** Froessler B *et al. Ann Surg.* 2016;264(1):41–6. HQ-FCM-2100014 February 2021

Original Article

Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study

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Summary

Peri-operative SARS-CoV-2 infection increases postoperative mortality. The aim of this study was to determine the optimal duration of planned delay before surgery in patients who have had SARS-CoV-2 infection. This international, multicentre, prospective cohort study included patients undergoing elective or emergency surgery during October 2020. Surgical patients with pre-operative SARS-CoV-2 infection were compared with those without previous SARS-CoV-2 infection. The primary outcome measure was 30-day postoperative mortality. Logistic regression models were used to calculate adjusted 30-day mortality rates stratified by time from diagnosis of SARS-CoV-2 infection to surgery. Among 140,231 patients (116 countries), 3127 patients (2.2%) had a pre-operative SARS-CoV-2 diagnosis. Adjusted 30-day mortality in patients without SARS-CoV-2 infection was 1.5% (95%CI 1.4–1.5). In patients with a pre-operative SARS-CoV-2 diagnosis, mortality was increased in patients having surgery within 0–2 weeks, 3–4 weeks and 5–6 weeks of the diagnosis (odds ratio (95%CI) 4.1 (3.3–4.8), 3.9 (2.6–5.1) and 3.6 (2.0–5.2), respectively). Surgery performed ≥ 7 weeks after SARS-CoV-2 diagnosis was associated with a similar mortality risk to baseline (odds ratio (95%CI) 1.5 (0.9–2.1)). After a ≥ 7 week delay in undertaking surgery following SARS-CoV-2 infection, patients with ongoing symptoms had a higher mortality than patients whose symptoms had resolved or who had been asymptomatic (6.0% (95%CI 3.2–8.7) vs. 2.4% (95%CI 1.4–3.4) vs. 1.3% (95%CI 0.6–2.0), respectively). Where possible, surgery should be delayed for at least 7 weeks following SARS-CoV-2 infection. Patients with ongoing symptoms ≥ 7 weeks from diagnosis may benefit from further delay.

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Introduction

Patients with peri-operative SARS-CoV-2 infection are at increased risk of death and pulmonary complications following surgery [1–3]. As the cumulative number of people who have had SARS-CoV-2 infection rises, it will be increasingly common for patients needing surgery to have previously had SARS-CoV-2 infection. High-income countries that are already implementing vaccination programmes are likely to experience reductions in new SARS-CoV-2 case infection rates, but these countries already have tens of millions of SARS-CoV-2 infection survivors. Most low- and middle-income countries (LMICs) are likely to have limited access to SARS-CoV-2 vaccines until at least 2023 [4, 5]. Thus, pre-operative SARS-CoV-2 infection will remain a challenge for the foreseeable future.

Pre-pandemic studies suggest delaying surgery in patients who have experienced respiratory infection in the 4 weeks preceding surgery [6–8]. However, there is only

limited evidence regarding the optimal timing of surgery following SARS-CoV-2 infection. A prospective cohort study including 122 patients having surgical for cancer, found that surgery ≥ 4 weeks after a positive SARS-CoV-2 swab result was associated with a lower risk of postoperative mortality than earlier surgery [9]. A study in Brazil included 49 patients whose elective surgery was delayed following the pre-operative diagnosis of asymptomatic SARS-CoV-2 infection [10]. These patients subsequently underwent surgery following confirmation of a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab result. The postoperative complication rates were comparable to patients without SARS-CoV-2 infection. However, the study did not assess the optimal duration of delay following SARS-CoV-2 diagnosis. Clinical guidelines support postponing non-emergency surgery for patients with pre-operative SARS-CoV-2 infection, but specific recommendations are conflicting, recommending delays ranging from 1 to 12 weeks [11–15].

More granular data are needed urgently to inform clinical practice, especially regarding the significance of symptomatic vs. asymptomatic pre-operative SARS-CoV-2 infection. The aim of this study was to determine the optimal timing of surgery following SARS-CoV-2 infection.

Methods

This was an international, multicentre, prospective cohort study that included patients undergoing any type of surgery. The study was registered at each participating hospital in accordance with local and national regulations. Informed patient consent was taken if required by local or national regulations. In the UK, this study was registered as either a clinical audit or service evaluation at each recruiting institution. Co-investigators were required to confirm that applicable local and national approvals were in place before uploading data to the online database. The study was compliant with guidelines for the reporting of observational studies [16]. In the conduct of this study, no changes were made to usual patient care. Routine, anonymised data were collected using a secure online database (REDCap, Vanderbilt University, Nashville, TN, USA).

Participating hospitals included consecutive patients undergoing elective or emergency surgery for any indication in October 2020. Surgery was defined as any procedure that is routinely performed in an operating theatre by a surgeon. A list of excluded procedures was provided to investigators and is available in online Supporting Information, Appendix S1. Before commencing data collection, hospitals defined which surgical specialties would be participating. Hospitals could choose to collect data in one or multiple surgical specialties, depending on local resources. Data could be collected over up to four blocks of 7 consecutive days (5 October 2020 – 1 November 2020).

Patients were classified as having pre-operative SARS-CoV-2 infection based on any one of the following criteria: (a) positive RT-PCR nasopharyngeal swab taken before surgery (even if the result became available after surgery); (b) positive rapid antigen test performed before surgery; (c) chest computed tomography (CT) scan performed before surgery showing changes consistent with pneumonitis secondary to SARS-CoV-2 infection; (d) positive pre-operative immunoglobulin G or immunoglobulin M antibody test; or (e) clinical diagnosis made before surgery (in the absence of negative RT-PCR swab results). Patients who were diagnosed with SARS-CoV-2 in the period between postoperative days 0 and 30 were not studied. Data were captured on whether patients had experienced SARS-CoV-2 symptoms, and if so, whether these symptoms had resolved by the time of surgery. Both respiratory and non-respiratory symptoms were considered. These were classified as follows: asymptomatic; symptomatic but symptoms now resolved; or symptomatic with ongoing symptoms. Time from the diagnosis of SARS-CoV-2 infection to day of surgery was collected as a categorical factor and pre-determined to be analysed in the following categories: 0–2 weeks; 3–4 weeks; 5–6 weeks; and ≥ 7 weeks.

The primary outcome measure was 30-day postoperative mortality. Patients were followed-up either in-person or by telephone, as soon after postoperative day 30 as possible. If it was not possible to complete 30-day follow-up, in-patient mortality status was recorded. The secondary outcome measure was the incidence of 30-day postoperative pulmonary complications. This was a composite of pneumonia, acute respiratory distress syndrome (ARDS) and/or unexpected postoperative ventilation. Full definitions are available in online Supporting Information, Appendix S1.

The following information was collected for each patient: age; sex; ASA physical status; revised cardiac risk index (RCRI); presence of respiratory comorbidities; indication for surgery; grade of surgery (major/minor); and surgical urgency (elective/emergency). For data protection purposes, age was collected as a categorical variable. Consistent with previous analyses, age was categorised as < 70 years or ≥ 70 years [1, 2]. American Society of Anesthesiologists physical status was classified as grades 1–2 or grades 3–5. Patients were recorded as having respiratory comorbidities if they had a diagnosis of asthma or chronic obstructive pulmonary disease (COPD).

Indications for surgery were classified as: benign disease; cancer; obstetrics; or trauma. Emergency surgery was defined as surgery on an unplanned admission, and elective surgery was defined as surgery on a planned admission. The RCRI calculation and grade of surgery classification are available in online Supporting Information, Appendix S1. National income was recorded for each participating country, based on the World Bank's classification [17].

To ensure consistent denominators, missing data were included in the descriptive analyses. Imputation for missing data was not planned as, based on previous studies, a < 2% rate of missing data was anticipated [1, 2]. For categorical variables, a chi-squared test was used to test for differences between groups.

To adjust time from SARS-CoV-2 diagnosis to surgery for confounding factors, logistic regression models were fitted with variables selected a priori. These were variables that have previously been identified as independent predictors of mortality in patients with peri-operative SARS-CoV-2 infection [1] and included: age; sex; ASA physical status; RCRI; indication for surgery; grade of surgery; urgency of surgery; presence of respiratory comorbidities; and national income. Average marginal effects were used to produce adjusted mortality estimates stratified by time from SARS-CoV-2 diagnosis to surgery. The main model included all patients.

Since delayed surgery is more likely for elective rather than emergency cases, a sensitivity analysis was performed including only elective patients. A further sensitivity analysis was performed including only patients who either had RT-PCR nasopharyngeal swab-proven pre-operative SARS-CoV-2 infection or who were not infected. To address further possible bias, average marginal effects were used to produce adjusted mortality rates by time from SARS-CoV-2 diagnosis to surgery, stratified by the following pre-selected variables: age; ASA physical status; urgency of surgery; and grade of surgery. In order to explore the association of pre-operative COVID-19 symptoms, a further logistic regression model was fitted. This included only those patients who had a pre-operative SARS-CoV-2 diagnosis, since COVID-19 symptom status was not applicable to patients who did not have pre-operative SARS-CoV-2. These models were fitted with a primary outcome of 30-day postoperative mortality. Further models were fitted for the secondary outcome of the incidence of 30-day postoperative pulmonary complications. Analyses were completed in Stata, version 15.1 (StataCorp, College Station, TX, USA).

Results

A total of 140,231 patients were included across 1674 hospitals in 116 countries (see online Supporting Information, Figure S1). Patient and surgical characteristics are shown in Table 1. Baseline characteristic data for patients having elective surgery are available in online Supporting Information (Table S1). In total, 3127 (2.2%) patients had a pre-operative SARS-CoV-2 diagnosis. The time from SARS-CoV-2 diagnosis to surgery was 0–2 weeks in 1138 patients (36.4%), 3–4 weeks in 461 patients (14.7%), 5–6 weeks in 326 patients (10.4%) and ≥ 7 weeks in 1202 patients (38.4%) (Table 1). The majority of patients were asymptomatic at the time of surgery (either having

Table 1 Baseline characteristics and outcomes for patients undergoing surgery stratified by time from diagnosis of SARS-CoV-2 infection. Values are number (proportion).

	No pre-operative SARS-CoV-2 infection (n = 137,104)	Pre-operative SARS-CoV-2 infection (by timing of diagnosis prior to surgery)			
		0–2 weeks (n = 1138)	3–4 weeks (n = 461)	5–6 weeks (n = 326)	≥ 7 weeks (n = 1202)
Age; years					
0–29	31,456 (22.9%)	331 (29.1%)	84 (18.2%)	62 (19.0%)	169 (14.1%)
30–49	37,673 (27.5%)	355 (31.2%)	149 (32.3%)	101 (31.0%)	364 (30.3%)
50–69	41,649 (30.4%)	265 (23.3%)	162 (35.1%)	109 (33.4%)	471 (39.2%)
70–79	17,577 (12.8%)	93 (8.2%)	52 (11.3%)	41 (12.6%)	121 (10.1%)
≥ 80	8747 (6.4%)	94 (8.3%)	14 (3.0%)	13 (4.0%)	77 (6.4%)
Missing	2 (0%)	–	–	–	–
Sex					
Female	71,375 (52.1%)	610 (53.6%)	220 (47.7%)	177 (54.3%)	634 (52.7%)
Missing	5 (0.0%)	–	–	–	–

(continued)

Table 1 (*continued*)

	No pre-operative SARS-CoV-2 infection (n = 137,104)	Pre-operative SARS-CoV-2 infection (by timing of diagnosis prior to surgery)			
		0–2 weeks (n = 1138)	3–4 weeks (n = 461)	5–6 weeks (n = 326)	≥ 7 weeks (n = 1202)
ASA physical status					
1–2	103,503 (75.5%)	779 (68.5%)	316 (68.5%)	227 (69.6%)	805 (67.0%)
3–5	33,553 (24.5%)	359 (31.5%)	145 (31.5%)	99 (30.4%)	397 (33.0%)
Missing	48 (0.0%)	–	–	–	–
Revised cardiac risk index					
0	61,379 (44.8%)	433 (38.0%)	176 (38.2%)	123 (37.7%)	446 (37.1%)
1	60,722 (44.3%)	512 (45.0%)	211 (45.8%)	145 (44.5%)	564 (46.9%)
2	11,116 (8.1%)	134 (11.8%)	50 (10.8%)	41 (12.6%)	129 (10.7%)
≥ 3	3818 (2.8%)	59 (5.2%)	24 (5.2%)	17 (5.2%)	62 (5.2%)
Missing	69 (0.1%)	–	–	–	1 (0.1%)
Respiratory comorbidities					
Yes	12,190 (8.9%)	114 (10.0%)	45 (9.8%)	31 (9.5%)	123 (10.2%)
Missing	111 (0.1%)	–	–	–	–
Indication for surgery					
Benign	86,764 (63.3%)	629 (55.3%)	273 (59.2%)	208 (63.8%)	822 (68.4%)
Cancer	23,612 (17.2%)	100 (8.8%)	117 (25.4%)	73 (22.4%)	234 (19.5%)
Trauma	17,048 (12.4%)	193 (17.0%)	48 (10.4%)	27 (8.3%)	96 (8.0%)
Obstetrics	9673 (7.1%)	216 (19.0%)	23 (5.0%)	18 (5.5%)	50 (4.2%)
Missing	7 (0.0%)	–	–	–	–
Grade of surgery					
Minor	55,301 (40.3%)	400 (35.1%)	131 (28.4%)	122 (37.4%)	462 (38.4%)
Major	81,771 (59.6%)	738 (64.9%)	330 (71.6%)	204 (62.6%)	739 (61.5%)
Missing	32 (0.0%)	–	–	–	1 (0.1%)
Urgency of surgery					
Elective	95,680 (69.8%)	338 (29.7%)	300 (65.1%)	232 (71.2%)	892 (74.2%)
Emergency	41,413 (30.2%)	800 (70.3%)	161 (34.9%)	94 (28.8%)	310 (25.8%)
Missing	11 (0.0%)	–	–	–	–
COVID-19 symptoms					
Asymptomatic	–	731 (64.2%)	203 (44.0%)	133 (40.8%)	317 (26.4%)
Symptomatic – resolved	–	124 (10.9%)	193 (41.9%)	163 (50.0%)	820 (68.2%)
Symptomatic – ongoing	–	277 (24.3%)	65 (14.1%)	28 (8.6%)	56 (4.7%)
Missing	–	6 (0.5%)	-	2 (0.6%)	9 (0.7%)
Country income					
High	90,024 (65.7%)	461 (40.5%)	159 (34.5%)	135 (41.4%)	696 (57.9%)
Low/middle	47,080 (34.3%)	677 (59.5%)	302 (65.5%)	191 (58.6%)	506 (42.1%)
30-day postoperative mortality					
Yes	1973 (1.4%)	104 (9.1%)	32 (6.9%)	18 (5.5%)	24 (2.0%)
Missing	92 (0.1%)	0 (0.0%)	–	–	2 (0.2%)
30-day postoperative pulmonary complications					
Yes	3654 (2.7%)	149 (13.1%)	60 (13.0%)	33 (10.1%)	42 (3.5%)
Missing	105 (0.1%)	–	–	–	3 (0.2%)

ASA, American Society of Anaesthesiologists.

Table 2 Unadjusted and adjusted model for 30-day postoperative mortality in all patients. Values are odds ratio (OR) (95%CI).

	Unadjusted		Adjusted	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Age; years				
0–69	Reference	–	Reference	–
≥ 70	3.12 (2.86–3.40)	< 0.001	1.72 (1.56–1.90)	< 0.001
Sex				
Female	Reference	–	Reference	–
Male	1.41 (1.29–1.53)	< 0.001	1.09 (0.99–1.19)	0.068
ASA physical status				
1–2	Reference	–	Reference	–
3–5	8.96 (8.13–9.87)	< 0.001	5.32 (4.75–5.96)	< 0.001
Revised cardiac risk index				
0	Reference	–	Reference	–
1	2.33 (2.07–2.61)	< 0.001	1.43 (1.26–1.63)	< 0.001
2	6.50 (5.69–7.42)	< 0.001	1.82 (1.56–2.13)	< 0.001
≥ 3	12.81 (11.02–14.89)	< 0.001	2.78 (2.32–3.32)	< 0.001
Respiratory comorbidities				
No	Reference	–	Reference	–
Yes	1.71 (1.51–1.94)	< 0.001	1.02 (0.89–1.16)	0.767
Indication for surgery				
Benign	Reference	–	Reference	–
Cancer	1.62 (1.46–1.80)	< 0.001	1.98 (1.76–2.23)	< 0.001
Trauma	1.60 (1.43–1.80)	< 0.001	0.91 (0.79–1.04)	0.173
Obstetrics	0.27 (0.19–0.37)	< 0.001	0.23 (0.16–0.33)	< 0.001
Grade of surgery				
Minor	Reference	–	Reference	–
Major	3.25 (2.90–3.63)	< 0.001	2.37 (2.11–2.67)	< 0.001
Urgency of surgery				
Elective	Reference	–	Reference	–
Emergency	5.60 (5.10–6.15)	< 0.001	6.48 (5.83–7.21)	< 0.001
Country income				
High	Reference	–	Reference	–
Low/middle	1.76 (1.61–1.92)	< 0.001	2.96 (2.69–3.26)	< 0.001
Pre-operative SARS-CoV-2 by timing of pre-operative diagnosis				
No diagnosis	Reference	–	Reference	–
0–2 weeks	6.88 (5.60–8.46)	< 0.001	3.22 (2.55–4.07)	< 0.001
3–4 weeks	5.11 (3.56–7.33)	< 0.001	3.03 (2.03–4.52)	< 0.001
5–6 weeks	4.00 (2.48–6.45)	< 0.001	2.78 (1.64–4.71)	< 0.001
≥ 7 weeks	1.40 (0.93–2.10)	0.107	1.02 (0.66–1.56)	0.940

ASA, American Society of Anesthesiologists.

never had symptoms or symptoms having resolved) (Table 1).

Compared with patients who did not have SARS-CoV-2 infection, patients with pre-operative SARS-CoV-2 infection were more likely to be ASA physical status 3–5 (24.5% vs. 32.0%; $p < 0.001$), to undergo major surgery (59.6% vs. 64.2%; $p < 0.001$) and to undergo emergency surgery (30.2% vs. 43.7%; $p < 0.001$). However, there was lower proportion of patients aged ≥ 70 years in the cohort with SARS-CoV-2 infection (16.1% vs. 19.2%; $p < 0.001$).

The overall 30-day postoperative mortality rate was 1.5% (2151/140,231). When stratified by time from

SARS-CoV-2 diagnosis to surgery, 30-day postoperative mortality rates were as follows: 9.1% (104/1138) 0–2 weeks; 6.9% (32/461) 3–4 weeks; 5.5% (18/326) 5–6 weeks; and 2.0% (24/1202) at ≥ 7 weeks. The 30-day mortality rate in patients who did not have a pre-operative SARS-CoV-2 infection was 1.4% (1973/137,104).

In the adjusted model, there was a significantly higher risk of 30-day mortality in patients with pre-operative SARS-CoV-2 infection diagnosed 0–2 weeks, 3–4 weeks and 5–6 weeks before surgery compared with patients who did not have a pre-operative SARS-CoV-2 infection (Table 2). However, there was no significant difference in 30-day postoperative mortality rate in those patients diagnosed with SARS-CoV-2 infection ≥ 7 weeks before surgery (Table 2).

Adjusted 30-day mortality rate in patients who did not have SARS-CoV-2 infection was 1.5% (95%CI 1.4–1.5). This was increased in patients who had surgery at 0–2 weeks, 3–4 weeks and at 5–6 weeks after SARS-CoV-2 diagnosis (Fig. 1). In patients who had surgery ≥ 7 weeks after SARS-CoV-2 diagnosis, the 30-day mortality rate was similar to patients who did not have SARS-CoV-2 infection (Fig. 1).

Sensitivity analyses including only patients having elective surgery (available in online Supporting Information, Tables S1–S3) and only patients with RT-PCR nasopharyngeal swab-proven SARS-CoV-2 infection (available in online Supporting Information, Tables S4–S5) showed that patients having surgery 0–2 weeks, 3–4 weeks and 5–6 weeks after SARS-CoV-2 diagnosis had significantly higher adjusted 30-day postoperative mortality rates compared with patients who did not have SARS-CoV-2 infection (Fig. 1). Patients operated ≥ 7 weeks after SARS-CoV-2 infection had a similar mortality as patients without SARS-CoV-2 infection. These findings were also consistent across sub-groups stratified by age, ASA physical status, and grade and urgency of surgery (Fig. 2).

In the analysis restricted to patients who had experienced pre-operative SARS-CoV-2 infection, patients with ongoing COVID-19 symptoms had a higher adjusted 30-day mortality rate than patients whose

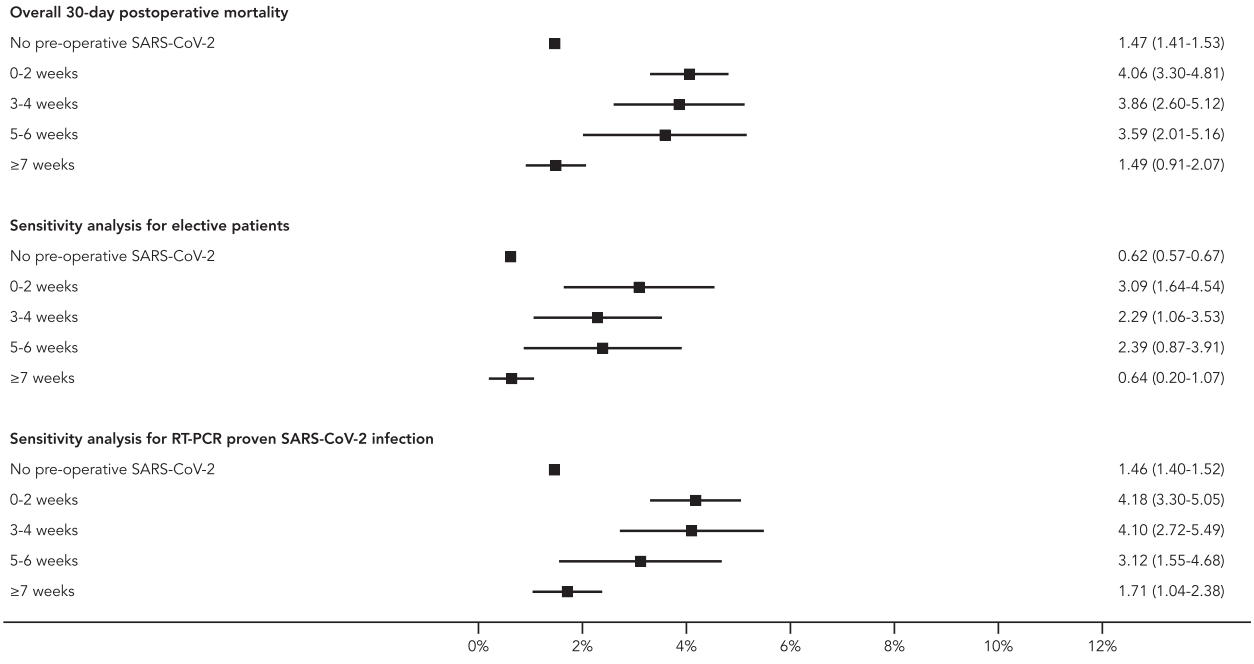

Figure 1 Overall adjusted 30-day postoperative mortality from main analysis and sensitivity analyses for patients having elective surgery and those patients with a reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab positive result for SARS-CoV-2. 'No pre-operative SARS-CoV-2' refers to patients without a diagnosis of SARS-CoV-2 infection. The time-periods relate to the timing of surgery following the diagnosis of SARS-CoV-2 infection. Sensitivity analysis for RT-PCR nasopharyngeal swab proven SARS-CoV-2 includes patients who either had RT-PCR nasopharyngeal swab proven SARS-CoV-2 or did not have a SARS-CoV-2 diagnosis; patients with a SARS-CoV-2 diagnosis which was not supported by a RT-PCR nasopharyngeal swab were not analysed. Full models and results are available in online Supporting Information (Appendix S1, Tables S3–S4 (elective patients), Tables S5–S6 (swab-proven SARS-CoV-2 infection)).

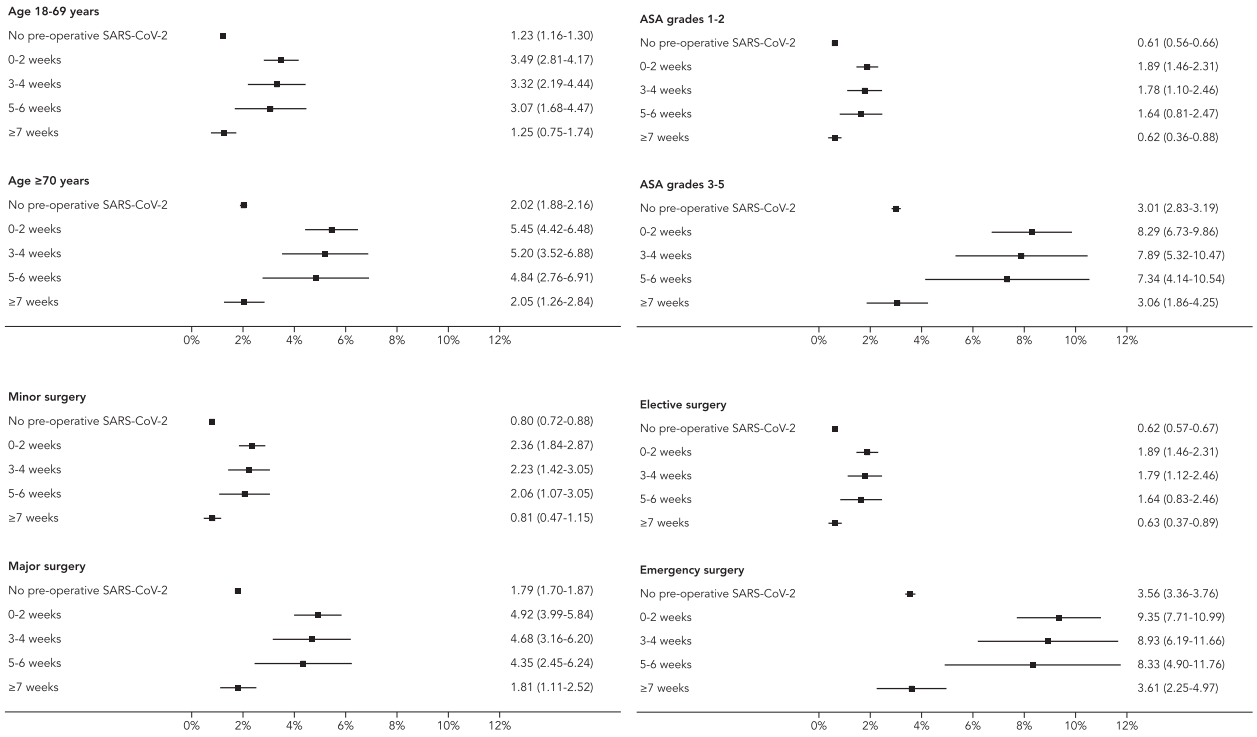

Figure 2 Adjusted 30-day postoperative mortality rates from main analysis, stratified by pre-defined sub-groups. 'No pre-operative SARS-CoV-2' refers to patients without a diagnosis of SARS-CoV-2 infection. The time-periods relate to the timing of surgery following the diagnosis of SARS-CoV-2 infection. Full models and results are available in online Supporting Information (Appendix S1, Table S2).

symptoms had resolved or who had been asymptomatic (Fig. 3). Following a ≥ 7-week delay between SARS-CoV-2 infection and surgery, patients with ongoing COVID-19 symptoms had a higher mortality rate than patients whose symptoms had resolved or who had been asymptomatic (Fig. 3).

Overall, 2.8% (3938/140,231) of patients developed a postoperative pulmonary complication within 30 days, including 1.7% (2387/140,231) who developed pneumonia, 0.8% (1100/140,231) who developed ARDS, and 0.8% (1137/140,231) who had an unexpected requirement for mechanical ventilation. In both the overall analysis and the sensitivity analysis for elective surgery, patients who had surgery 0–2 weeks, 3–4 weeks and 5–6 weeks after SARS-CoV-2 diagnosis had significantly higher adjusted 30-day postoperative pulmonary complication rates compared with patients who did not have SARS-CoV-2 infection. However, patients who had surgery ≥ 7 weeks after SARS-CoV-2 infection had similar rates of postoperative pulmonary complications as patients without SARS-CoV-2 infection (Fig. 4). Among patients operated ≥ 7 following SARS-CoV-2 diagnosis, those with ongoing COVID-19 symptoms were at greatest risk of 30-day postoperative pulmonary complications (Fig. 5).

Discussion

This study found that patients operated within 6 weeks of SARS-CoV-2 diagnosis were at an increased risk of 30-day postoperative mortality and 30-day postoperative pulmonary complications. These risks decreased to baseline in patients who underwent surgery ≥ 7 weeks after SARS-CoV-2 diagnosis. These findings were consistent across both low-risk (age < 70 years, ASA physical status 1–2, minor surgery) and high-risk (age ≥ 70 years, ASA physical status 3–5, major surgery) sub-groups. Therefore, surgery should be delayed for at least 7 weeks following SARS-CoV-2 infection to reduce the risk of postoperative mortality and pulmonary complications. In addition, we have shown that patients who are still symptomatic ≥ 7 weeks after SARS-CoV-2 infection and undergo surgery also have an increased mortality rate. As such, these patients may benefit from a further delay until their symptoms resolve.

Our findings that pre-operative SARS-CoV-2 infection increases the risk of postoperative mortality and pulmonary

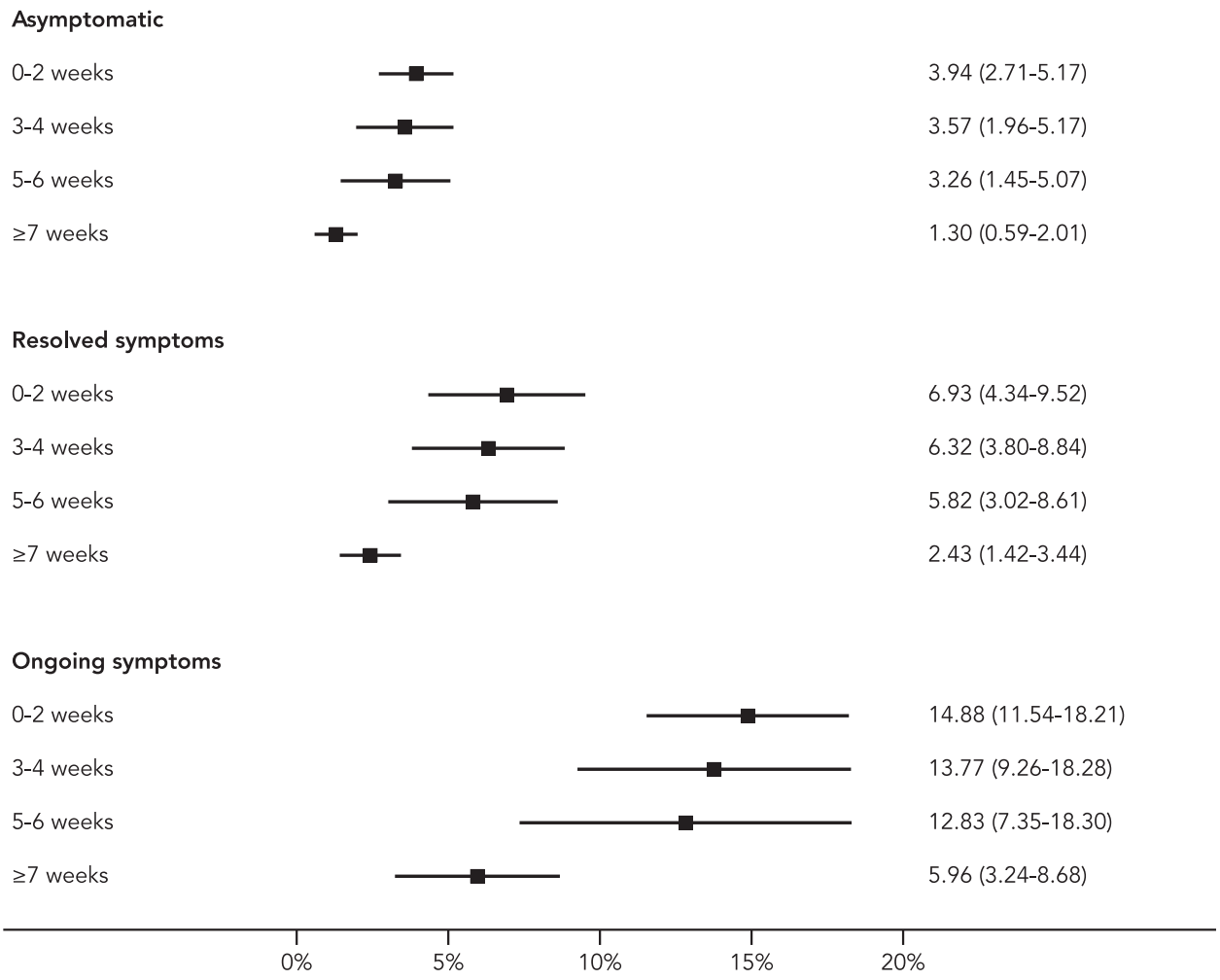

Figure 3 Adjusted 30-day postoperative mortality rates in patients with pre-operative SARS-CoV-2 infection stratified by COVID-19 symptoms. The time-periods relate to the timing of surgery following the diagnosis of SARS-CoV-2 infection. Full models and results are available in online Supporting Information (Appendix S1, Tables S7–S8).

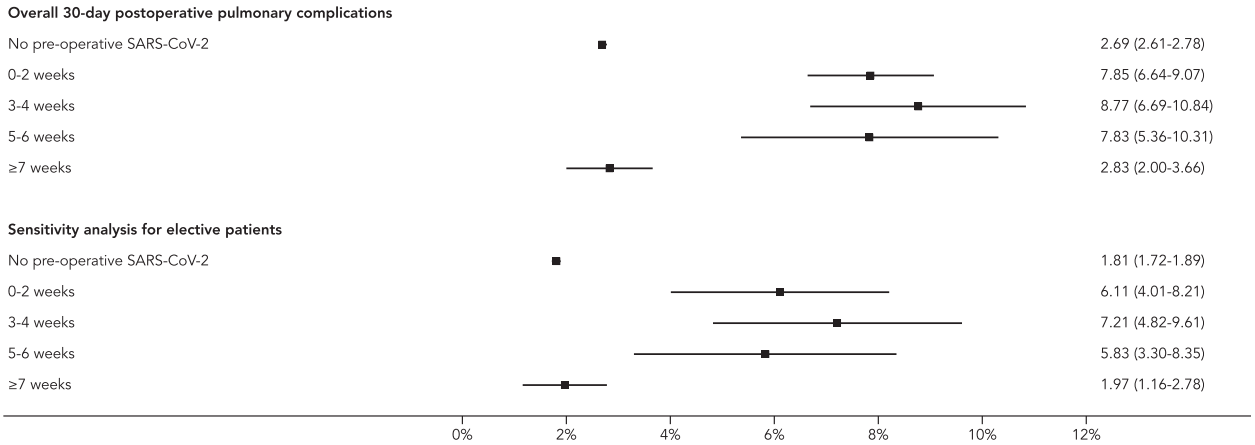

Figure 4 Overall adjusted 30-day postoperative pulmonary complications (PPC) rate from main analysis and sensitivity analysis for patients having elective surgery. 'No pre-operative SARS-CoV-2' refers to patients without a diagnosis of SARS-CoV-2 infection. The time-periods relate to the timing of surgery following the diagnosis of SARS-CoV-2 infection. Full models and results are shown in online Supporting Information (Appendix S1, Tables S9–S10).

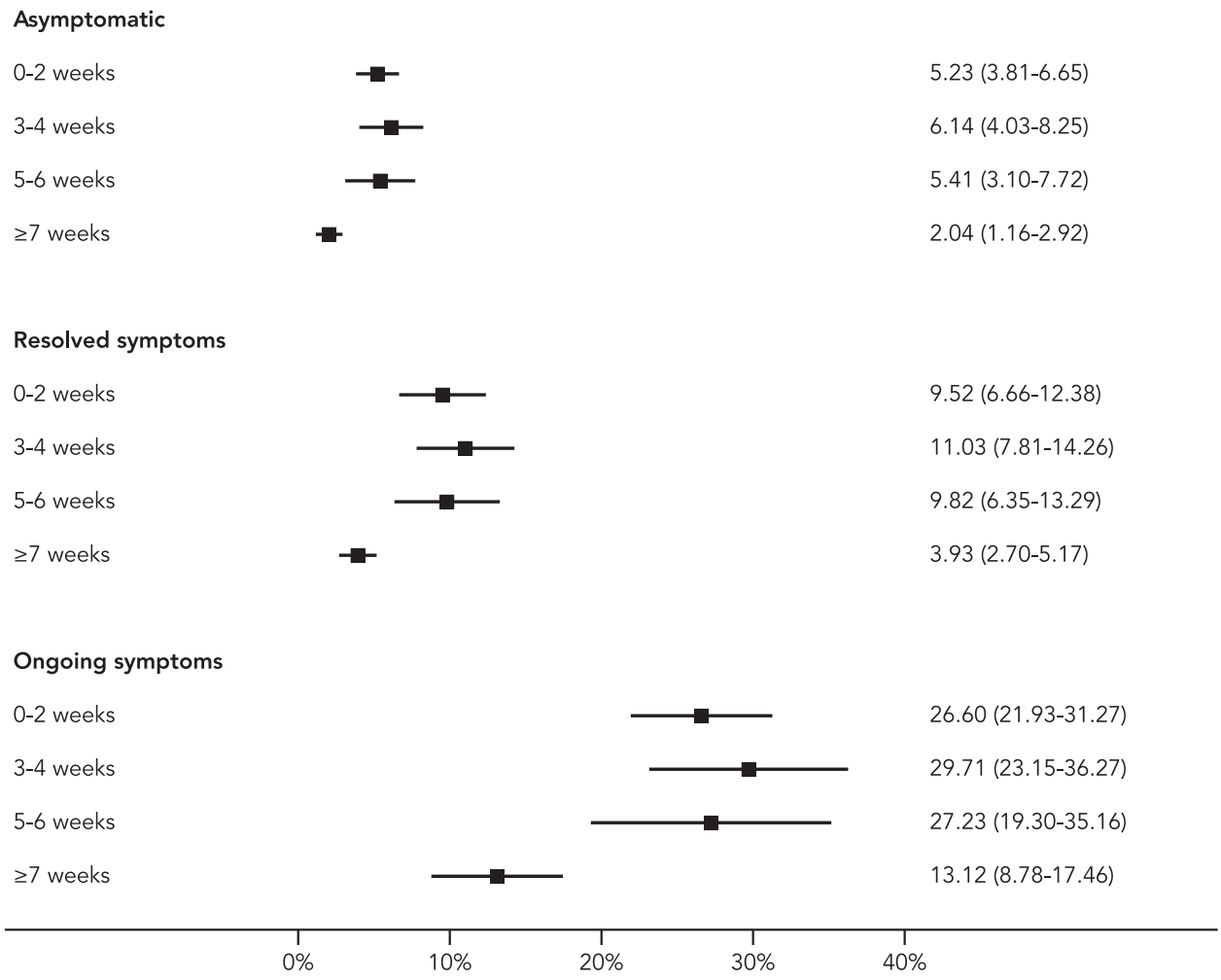

Figure 5 Adjusted 30-day postoperative pulmonary complications (PPC) rate in patients with pre-operative SARS-CoV-2 infection stratified by COVID-19 symptoms. The time-periods relate to the timing of surgery following the diagnosis of SARS-CoV-2 infection. Full model and results are available in online Supporting Information (Appendix S1, Tables S13–S14).

complications is line with previous work [1–3]. However, this is the first study to provide robust data regarding the optimal timing for surgery following SARS-CoV-2 infection. The greater granularity in this analysis compared with previous studies [9, 10] has enabled ≥ 7 weeks to be determined as the optimal cut-off. Whilst cut-offs beyond 7 weeks were not formally tested, they are unlikely to offer a significant advantage, since adjusted mortality rates for delay intervals ≥ 7 weeks were broadly stable (see online Supporting Information, Appendix S1). Moreover, overall mortality following a delay of ≥ 7 weeks was similar to mortality in patients who did not have pre-operative SARS-CoV-2 infection.

There is a backlog of tens of millions of elective operations that were cancelled during the early phase of the COVID-19 pandemic [18]. This study offers evidence to support the safe restarting of surgery in the context of a rapidly increasing number of people who have survived SARS-CoV-2. This study's findings should support informed shared decision-making by anaesthetists, surgeons and patients. Decisions should be tailored for each patient, since the possible advantages of delaying surgery for at least 7 weeks following SARS-CoV-2 diagnosis must be balanced against the potential risks of delay. For some urgent surgical procedures, such as resection of advanced tumours [19, 20], surgeons and patients may decide that the risks of delay are not justified.

This study has some limitations. Firstly, ascertainment of SARS-CoV-2 status was based on routine pre-operative tests. Therefore, it is possible that some patients who had previously experienced SARS-CoV-2 infection may have been misclassified as never having been infected. This

could be particularly likely for patients with asymptomatic infection who may be less likely to get tested. However, it is re-assuring that a high proportion of patients in this cohort were recorded as having had asymptomatic infection, suggesting that many such cases were detected. Secondly, this study was based on time from SARS-CoV-2 diagnosis to surgery, but it is possible that diagnosis was delayed in some patients, underestimating the true delay from when patients were infected to the date of surgery. This was addressed by a sensitivity analysis restricting SARS-CoV-2 diagnosis to those patients who had positive RT-PCR nasopharyngeal swab results, since swab-based diagnosis is likely to give the best approximation of date of infection. The results of this sensitivity analysis were consistent with the main analyses. Thirdly, it was not possible to conduct procedure-specific analyses, although exploration of results stratified by grade (minor vs. major) and urgency of surgery (elective vs. urgency) demonstrates that the overall findings were consistent across these groups. Finally, whilst both subgroup analyses by age, ASA physical status, urgency and grade of surgery, and sensitivity analyses for elective surgery were all consistent with the main analysis, there is a possibility of residual bias.

In conclusion, we performed an international, multicentre, prospective cohort study of 140,231 patients undergoing surgery in 116 countries, in order to determine the optimal timing of surgery after SARS-CoV-2 infection. We found that risks of postoperative morbidity and mortality are greatest if patients are operated within 6 weeks of diagnosis of SARS-CoV-2 infection. Our results suggest that, where possible, surgery should be delayed for at least 7 weeks following SARS-CoV-2 infection. Patients with ongoing symptoms at $\geq$ 7 weeks from diagnosis may benefit from further delay.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Supporting information.

Table S1. Baseline characteristics and outcomes in elective patients.

Table S2. Unadjusted and adjusted 30-day postoperative mortality (95%CI) in key sub-groups from main analysis.

Table S3. Sensitivity analysis for elective patients with unadjusted and adjusted models for 30-day postoperative mortality.

Table S4. Sensitivity analysis for elective patients with unadjusted and adjusted 30-day postoperative mortality (95%CI) in key sub-groups.

Table S5. Sensitivity analysis for RT-PCR nasopharyngeal swab proven SARS-CoV-2 infection, with unadjusted and adjusted models for 30-day postoperative mortality.

Table S6. Sensitivity analysis for RT-PCR nasopharyngeal swab proven SARS-CoV-2 infection with unadjusted and adjusted 30-day postoperative mortality in key sub-groups.

Table S7. Unadjusted and adjusted models for 30-day postoperative mortality in patients with pre-operative SARS-CoV-2 infection.

Table S8. Unadjusted and adjusted 30-day postoperative mortality in patients with pre-operative SARS-CoV-2 infection in key sub-groups.

Table S9. Unadjusted and adjusted model for 30-day postoperative pulmonary complications in all patients.

Table S10. Unadjusted and adjusted 30-day postoperative pulmonary complications in key sub-groups from main analysis.

Table S11. Sensitivity analysis for elective patients with unadjusted and adjusted model for 30-day postoperative pulmonary complications.

Table S12. Sensitivity analysis for elective patients with unadjusted and adjusted 30-day postoperative pulmonary complications in key sub-groups.

Table S13. Unadjusted and adjusted models for 30-day postoperative pulmonary complications in patients with pre-operative SARS-CoV-2 infection.

Table S14. Unadjusted and adjusted 30-day postoperative pulmonary complications in patients with pre-operative SARS-CoV-2 infection in key sub-groups.

Table S15. List of excluded procedures.

Table S16. 30-day postoperative mortality and postoperative pulmonary complication rates stratified by timing of surgery after SARS-CoV-2 diagnosis.

Table S17. 30-day postoperative mortality and postoperative pulmonary complication rates in patients operated $\geq$ 3 weeks after SARS-CoV-2 diagnosis, stratified by results of most recent repeat RT-PCR nasopharyngeal swab.

Figure S1. Study flowchart.

Figure S2. Adjusted 30-day postoperative mortality rates from sensitivity analysis for elective patients, stratified by pre-defined sub-groups.

Appendix S2. COVIDSurg Collaborative and GlobalSurg Collaborative authors (all PubMed indexed co-authors).