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Perioperative SARS-CoV-2 infection and postoperative complications: A retrospective cohort study

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Perioperative SARS-CoV-2 infection and postoperative complications: A retrospective cohort study

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ABSTRACT

Objective To explore the association between perioperative SARS-CoV-2 infection and the postoperative complications during the breakout of Omicron epidemic wave.

Design Observational retrospective cohort study. Multivariable logistic regression was performed to explore the association between the duration from surgery to COVID-19 diagnosis and the likelihood of postoperative complications.

Setting A general hospital in China.

Participants 7927 patients aged 18 years and older who underwent surgical treatment between December 1, 2022, and February 28, 2023.

Primary outcome measures The outcome was a composite of postoperative adverse events occurred within the initial 30 postoperative days.

Results Of all patients, 420 (11.76%) experienced postoperative complications. Compared to No COVID-19, Preoperative COVID-19 within one week (Pre-1w) exhibited a high risk of postoperative complications (adjusted odds ratio (aOR), 2.67; 95% CI, 1.50-4.78), followed by patients with Pre-2w (aOR, 2.14; 95% CI, 1.20-3.80). For patients with Postoperative COVID-19 within one week (Post-1w), the aOR was 2.48 (95% CI, 1.48-4.13), followed by patients with Post-2w (aOR, 1.95;

95% CI, 1.10-3.45), and those with Post-3w (aOR, 2.25; 95% CI, 1.27-3.98). The risks of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection. Stratification analyses suggested that perioperative COVID-19 increased risk of postoperative complications in older patients, smokers, those with comorbidities, or experiencing moderate or severe COVID-19 symptoms.

Conclusions Our findings reveal a significant time-dependent relationship between perioperative COVID-19 and postoperative complications, highlighting the importance of tailored preoperative risk evaluations, enhanced postoperative surveillance, and the implementation of effective postoperative COVID-19 prevention measures.

Data availability statement

Data will be available from the corresponding author upon reasonable request.

Strengths and limitations of this study

This study captured both preoperative and postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management.

A broad range of surgical complications were considered, enabling physicians to gain a comprehensive understanding of the overall perioperative risk.

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Both infected and uninfected patients have a COVID-19 PCR or antigen testing result, ensuring the reliability of the findings.

A single-centre retrospective observational design of the study limited the generalizability of the results.

Keywords COVID-19; COVID-19 severity; Postoperative complications; Prognosis; Surgery.

Introduction

Since the first reports of a novel severe acute respiratory syndrome (SARS)-like coronavirus in December 2019 in Wuhan, China, the SARS-CoV-2 virus has evolved five variants from Alpha to Omicron.¹⁻³ This had led to a rapid spread, both regionally and globally, resulting in over 760 million cases and 6.9 million deaths worldwide.⁴ Perioperative COVID-19 has been demonstrated to have an adverse impact on perioperative mortality and morbidity.⁵⁻⁹ Approximately 50% of SARS-CoV-2-infected individuals experience postoperative pulmonary complications and the overall 30-day mortality was up to 23.8%.⁹ To mitigate the postoperative risks, a large number of surgeries had been postponed, while this may delay the treatment of their primary diseases and decrease survival.¹⁰⁻¹³ Hence, there is a crucial need for a comprehensive assessment of the health advantages associated with the postponement of surgical management and the potential adverse repercussions of delayed treatment.

Emerging in November 2021, SARS-CoV-2 Omicron variant became the dominant variant and exhibited increased transmissibility while inducing less severe disease compared with previous variants.¹⁴⁻¹⁸ In addition, massive vaccination programs and the use of antiviral treatments have changed the clinical characteristics of patients with COVID-19.¹⁹⁻²³ The current evidence regarding postoperative outcomes in patients undergoing surgery during the Omicron wave was inconsistent. Two studies found an increased postoperative risk when surgeries were performed within one week after contracting COVID-19.^{24,25} On the contrary, other studies found no significant difference in postoperative outcomes comparing patients with

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SARS-CoV-2 Omicron infection with those who were not infected.^{26,27} Furthermore, few studies focused on the risk of postoperative complications associated with SARS-CoV-2 infection after surgery.

In this study, we aimed to investigate the associations between pre- or post-operative SARS-CoV-2 infection and postoperative outcomes, respectively. We further analysed the risk of postoperative outcomes at various time intervals between SARS-CoV-2 infection and the surgery date, providing updated evidence for guiding optimal surgery timing and minimizing adverse postoperative outcomes

Methods

Study design and participants

The protocol of this study was approved by the Institutional Review Board of Guangdong Provincial People's Hospital (No. KY2023-031-02), and the study was registered on Chictr.org.cn (ChiCTR2300072473). Informed consent was obtained from all included patients. The study adhered to the principles of the Declaration of Helsinki.

In this retrospective cohort study, we recruited 7927 patients who aged ≥ 18 years and requiring surgery at Guangdong Provincial People's Hospital in China between December 1, 2022, and February 28, 2023. Data of patient information, surgery, SARS-CoV-2 infection, and postoperative complications within the first 30 days after surgery were collected from medical records and telephone follow-up. Excluded from the study were individuals who underwent surgery with local anaesthesia alone (n=824), those without reverse transcription-polymerase chain reaction (PCR) or rapid antigen test results (n=1151), those with infection time beyond the observation period (n=729), those who refused to participate (n=298), and those lost to follow-up (n=1354). Thus, a total of 3571 individuals were finally included for the study analysis (**Figure 1**).

Assessment of SARS-CoV-2 infection

Confirmation of SARS-CoV-2 infection was established based on a positive outcome from either PCR testing or rapid antigen tests. The duration from surgery to the

diagnosis of COVID-19 was defined as the period between the day of surgery and the date of the initial positive test result. In instances where patients underwent multiple surgeries, the surgical date closest to the time of infection was utilized for analysis. Consequently, patients were categorized into three groups as follows: those infected before surgery (Preoperative COVID-19), those infected within 30 days after surgery (Postoperative COVID-19), and those with no positive SARS-CoV-2 test results during the study period (No COVID-19). The severity of COVID-19 was assessed and classified as either mild (WHO Severity 1-3) or moderate/severe (WHO Severity 4-9) based on the WHO Clinical Progression Scale.²⁸

Definitions of postoperative complications

The outcome was defined as a composite of postoperative adverse events occurring within the initial 30 days following surgery (**Supplementary Table 1**). This encompassed acute kidney injury (AKI), postoperative respiratory complications (including pneumonia, respiratory failure, and pulmonary embolism), postoperative cardiovascular complications (including arrhythmia, myocardial infarction, acute heart failure, acute ischemic heart disease, cardiac arrest, cardiogenic shock, cerebral haemorrhage, cerebral infarction, hypoxic-ischemic encephalopathy, deep vein thrombosis, limb artery thrombosis, splenic infarction, and hepatic infarction), unplanned secondary surgery, sepsis, and mortality.

Covariates

The covariates encompassed age, sex, body mass index (BMI), smoking status, COVID-19 vaccination status, number of comorbidities (see the definition in

Supplementary Table 2), history of cancer, American Society of Anesthesiologists (ASA) grade classification (see the definition in **Supplementary Table 3**), grade of surgery (see the definition in **Supplementary Table 4**), urgency of surgery (see the definition in **Supplementary Table 5**), duration of surgery, type of anaesthesia, and type of surgery. We gathered such data from a variety of sources including Electronic Health Records, laboratory data, anaesthesia information management systems, and questionnaires. The proportions of missing data for key variables such as height, weight, smoking status, and COVID-19 vaccination status were 2.30%, 0.25%, 11.12%, and 5.58% respectively. Median and mode imputation were employed to replace missing data for continuous and categorical variables, respectively.

Statistical analysis

Logistic regression was employed to estimate Odds ratios (OR) with 95% confidence intervals (CIs) to examine the associations between the duration from surgery to COVID-19 diagnosis and the risk of postoperative complications, with No COVID-19 group as the reference category. We initially incorporated a restricted cubic spline term for the duration from surgery to the diagnosis of SARS-CoV-2 infection, utilizing 3 knots at the 10th, 50th, and 90th centiles into the model to explore the nonlinear relationship between the timeframe and the risk of postoperative complications. The assessment of nonlinearity was conducted using a likelihood ratio test to determine the associated P value. Following this, we categorized the time from COVID-19 diagnostic into discrete intervals, stratifying patients into four groups based on Preoperative and Postoperative COVID-19 statuses: within one week (Pre-1w and Post-1w), one to two weeks (Pre-2w and Post-2w), two to three weeks

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(Pre-3w and Post-3w), and beyond three weeks (Pre-4w or more and Post-4w or more).

The analysis was further divided to independently evaluate the associations between Preoperative COVID-19 diagnostic time and postoperative complications, as well as those between Postoperative COVID-19 diagnostic time and postoperative complications. Risks of postoperative complications were examined by stratifying the analysis based on age (younger elderly [<50 years] and older elderly [≥ 50 years]), smoking status (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), and severity of COVID-19 (mild or moderate/severe).

We conducted sensitivity analysis to ensure the reliability of our results. We utilized a subset of the sample with complete data to replicate our main findings, examining any potential impact of missing value of sociodemographic factors. Furthermore, in light of the varying health statuses of patients undergoing emergency surgery and the surgeon's accurate judgment of the patient's condition, we conducted sensitivity analyses specifically focusing on patients undergoing elective surgery.

All analyses were performed using R v4.3.0, with a two-tailed significance level of 0.05.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or

dissemination plans of this research.

Role of the funding source

The funders were not involved in study design, data collection, data analysis, data interpretation, and writing of the report. JZ, FZ, LD, HS, and JL had full access to all the data in the study. All authors accepted responsibility for the decision to submit for publication.

Results

Characteristics of patients

During the study period, 3571 patients were included in the study analysis (**Table 1**). The median age of patients was 52 years (Interquartile Range [IQR] 40-63 years), 45.42% were men, and 92.92% were vaccinated against COVID-19. Of all individuals, 93.50% underwent elective surgery, 62.22% underwent major surgery, and 85.69% had surgeries lasting no more than four hours. Patients were categorized into three groups based on the timing of COVID-19 diagnosis relative to surgery: No COVID-19 (n=959, 26.86%), Preoperative COVID-19 (n=1871, 52.39%), and Postoperative COVID-19 (n=741, 20.75%). Among patients with COVID-19, the majority experienced mild symptoms (94.22%), with only 5.45% and 6.61% exhibiting moderate or severe symptoms in Preoperative and Postoperative COVID-19 respectively. When compared with those with No COVID-19, patients with both Preoperative and Postoperative COVID-19 had lower rates of smoking, with 11.17% versus 14.29% for Preoperative COVID-19 and 12.69% versus 14.29% for Postoperative COVID-19, respectively. Patients with No COVID-19 had a higher ASA classification than those with Preoperative or Postoperative COVID-19. The baseline characteristics of patients with and without postoperative complications were presented in **Supplementary Table 6**.

Time-dependent association between duration from surgery to the diagnosis of COVID-19 and risk of postoperative complications

During the study period, 420 (11.76%) patients experienced postoperative complications. A higher rate (13.90%) of postoperative complications was observed

in patients with Postoperative COVID-19 compared to those with Preoperative COVID-19 (11.44%). Among these postoperative complications, 217 (6.08%) cases were AKI, 135 (3.78%) were respiratory complications, 132 (3.70%) were cardiovascular complications, 51 (1.43%) were unplanned secondary surgeries, 23 (0.64%) resulted in mortality, and 21 cases (0.59%) were sepsis (**Supplementary Figure 1**).

We initially examined the nonlinear trend in the association between the duration from surgery to the diagnosis of COVID-19 and the risk of postoperative complications (**Figure 2**). Using the time interval between the surgery date and COVID-19 diagnosis as the axis of symmetry (dividing preoperative and postoperative by week), the risk curve exhibited a bell-shaped pattern, peaking approximately at the surgery date. The risk of postoperative complications was higher when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it was preoperative or postoperative COVID-19. The risk diminished gradually as the time interval between the surgery date and COVID-19 diagnosis increased (p for nonlinearity = 0.005). However, in cases of preoperative COVID-19, the risk did not decrease further beyond a four-week interval, whereas in cases of postoperative COVID-19, it gradually diminished until four weeks after surgery.

Association between Preoperative COVID-19 and risk of postoperative complications

The risk of postoperative complications gradually decreased with an increase in the time interval between SARS-CoV-2 infection and surgery date (**Table 2**). Compared

to patients with No COVID-19, those with Pre-1w exhibited the highest risk of postoperative complications (aOR 2.67 [95% CI 1.50-4.78], $p=0.001$), followed by patients with Pre-2w (aOR 2.14 [95% CI 1.20-3.80], $p=0.010$). Compared to patients with No COVID-19, there was no statistically significant increase in risk observed in patients with Pre-3w (aOR 1.27 [95% CI 0.67-2.39], $p=0.46$) or those with Pre-4w or more (aOR 1.24 [95% CI 0.92-1.68], $p=0.15$).

Stratification analysis by the severity of COVID-19 revealed a higher risk of postoperative complications in patients with moderate or severe symptoms compared to those with mild symptoms (aOR 5.92 vs. 2.04 with Pre-1w, 5.12 vs. 1.88 with Pre-2w) (**Table 3**). Stratification analysis by smoking status revealed an exceptionally high risk in smoking patients with Pre-1w (aOR 17.22 [95% CI 3.87-76.70], $p<0.001$), while the aOR for non-smoking patients with Pre-1w was 2.06 (95% CI 1.07-3.97, $p=0.032$). In summary, patients aged ≥ 50 years, smokers, those with comorbidities, or those with moderate or severe symptoms were associated with a higher risk of postoperative complications in cases of preoperative COVID-19 within two weeks.

Association between Postoperative COVID-19 and risk of postoperative complications

The risk of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection (**Figure 2**). Compared to patients with No COVID-19, those with Post-1w exhibited the highest risk of postoperative complications (aOR 2.48 [95% CI 1.48-4.13], $p=0.001$),

followed by patients with Post-3w (aOR 2.25 [95% CI 1.27-3.98], p=0.006), and those with Post-2w (aOR 1.95 [95% CI 1.10-3.45], p=0.023) (**Table 2**). Compared to patients with No COVID-19, the increased risk was not statistically significant in patients with Post-4w or more (aOR 1.24 [95% CI 0.72-2.14], p=0.44).

Stratification analysis by the severity of COVID-19 revealed extremely high risks of postoperative complications in patients with Post-1w with moderate or severe symptoms (aOR 11.52 [95% CI 4.36-30.45], p<0.001), as well as in patients with Post-2w (aOR 14.96 [95% CI 3.69-60.60], p<0.001), and in patients with Post-3w (aOR 29.42 [95% CI 4.47-193.81], p<0.001) (**Table 4**). Conversely, no significant risk was observed among patients with mild symptoms. Stratification analysis by smoking status revealed consistently high risks in smoking patients, with aOR being 3.69 in Post-1w, 5.05 in Post-2w, 6.33 in Post-3w, and 7.35 in Post-4w or more, whereas the aOR for non-smoking patients with Post-1w was 2.35 (95% CI 1.34-4.11], p=0.003). In summary, patients aged ≥ 50 years, smokers, those without COVID-19 vaccination, with comorbidities, or with moderate or severe symptoms were associated with a higher risk of postoperative complications in cases of postoperative COVID-19 occurring within three weeks.

Considering potential health status differences between patients who underwent emergency and elective surgery, a sensitivity analysis was conducted solely on patients who underwent elective surgery, and the findings remained consistent with the main results (**Supplementary Table 7**). Additionally, to investigate the potential impact of missing value of sociodemographic factors, a sensitivity analysis was

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carried out on a subset of the sample without imputed data, revealing similar findings and trends to the main results (**Supplementary Table 8**).

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Discussion

Our study underscored the importance of timing in the association between perioperative COVID-19 and the risk of postoperative complications. The risk significantly escalated when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it's preoperative or postoperative. Besides, perioperative COVID-19 increased the risk of postoperative complications in specific subgroups, including older patients, smokers, those with comorbidities, or those experiencing moderate or severe COVID-19 symptoms.

While there are existing recommendations regarding surgical decision-making following SARS-CoV-2 infection, a consensus has not yet been achieved in this regard. Study from the COVIDSurg and GlobalSurg Collaborative reported a significant increase in mortality when surgery was performed within seven weeks after COVID-19 diagnosis during the pre-vaccine phase.²⁸ Additionally, the Covid-19 Research Database found that surgery performed 4 to 8 weeks after confirmed SARS-CoV-2 infection continues to carry an elevated risk of developing postoperative pneumonia.²⁹ However, emerging studies presented differing perspectives. A study conducted across 37 American centres revealed that the time span from a positive test to the actual surgery significantly impacted both mortality and pulmonary risk, with the risk subsiding after two weeks.⁷ Conversely, research from 41 French centres found no significant association between surgery within three weeks of COVID-19 diagnosis and postoperative respiratory comorbidities.²⁷ Our

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research findings revealed a heightened risk of composite postoperative complications, encompassing respiratory, cardiovascular, and other complications, when surgery was conducted within two weeks of a preoperative COVID-19 diagnosis. Therefore, conducting preoperative individualized risk assessments is imperative, and scheduling elective surgeries within two weeks after a SARS-CoV-2 diagnosis should be avoided. Our findings lend support to global endeavours aimed at updating restrictions on the timing of scheduled surgeries.

Furthermore, the risks of postoperative complications after SARS-CoV-2 infection varied across distinct subgroups. Our study revealed that older patients, smokers, and those with comorbidities faced an increased risk of adverse postoperative outcomes following SARS-CoV-2 infection. In a cohort of 3027 COVID-19-positive individuals, several risk factors were identified for mortality, including increased age, current smoking, presence of comorbidity, and undergoing emergency surgery.³⁰ However, this study only considered patients with perioperative COVID-19 and did not compare them to those without infection. Moreover, our study also revealed that individuals with moderate or severe symptoms faced a markedly elevated risk of postoperative complications up to two weeks preceding their surgery, whereas those with mild symptoms exhibited a modest increase in complications. A study from the National COVID Cohort Collaborative (N3C) found that the impact of COVID-19 on postoperative outcomes is dependent on severity of illness, with only moderate and severe disease leading to higher risk of adverse outcomes.³¹ Another study from N3C found that postoperative cardiovascular risk remained high even 8 weeks after infection with moderate or severe SARS-CoV-2, but did not increase among those

undergoing surgery within 4 weeks following mild infection.³² These studies failed to find an association between postoperative complications and mild COVID-19. Overall, it is essential for patients to undergo thorough evaluation before surgery, with a specific focus on assessing individual risk factors, to determine the optimal timing for surgical interventions.

There is limited research available on the risk of postoperative complications in patients who contract SARS-CoV-2 after surgery, with most prior studies focusing on series of Total Joint Arthroplasty (TJA) patients and overlooking the impact of other surgical procedures.^{33,34} Another study of only 22 patients with COVID-19 occurring in the recovery period after open-heart surgery showed a higher pneumonia and mortality rates in unvaccinated patients.³⁵ Our study revealed that individuals who tested positive for SARS-CoV-2 up to three weeks after surgery were at a higher risk of complications compared to those without the infection. Hence, robust postoperative management strategies to mitigate SARS-CoV-2 transmission risk are vital, with protective measures recommended for at least three weeks post-surgery. Our study highlighted the significance of monitoring a patient's SARS-CoV-2 infection status not only before but also after surgery.

The stratified analysis of patients with postoperative COVID-19 revealed that unvaccinated individuals, who were older, smokers, or had comorbidities, faced a higher risk of complications. Furthermore, patients with moderate or severe symptoms of COVID-19 posed a significantly heightened risk of postoperative complications. Previous studies have shown that vaccination is effective in reducing the risk of

severe illness, hospitalization, and death from COVID-19.^{36,37} Recent work by the COVIDSurg Collaborative and GlobalSurg Collaborative reported that preoperative vaccination could prevent nearly 60,000 deaths per year on average among patients requiring elective surgery.³⁸ However, these studies did not account for postoperative SARS-CoV-2 infections. Our findings underscore the importance of reinforcing postoperative protective strategies for these vulnerable patients.

This study had several strengths. Firstly, unlike previous research, our study not only focused on preoperative SARS-CoV-2 infections but also examined postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management. Secondly, we investigated the interaction between various risk factors to gain further insight into the factors influencing postoperative complications. Thirdly, we considered a broad range of surgical complications, including respiratory and cardiovascular morbidity, acute kidney injury, unplanned secondary surgery, sepsis, and mortality, thereby enabling physicians to gain a comprehensive understanding of the overall perioperative risk. Fourthly, patients were diagnosed with COVID-19 through PCR or antigen testing. Even uninfected patients were confirmed to have negative results, ensuring the reliability of the findings.

This study also had some limitations. Firstly, the sample size was limited. Conducting further research with a larger sample size would provide a more comprehensive understanding of the interaction among various influencing factors. Secondly, the retrospective observational nature of the study made it challenging to completely rule

out the influence of unmeasured residual confounding factors, despite efforts to retrieve as many covariates as possible. Thirdly, the single-centre design of the study had limited the generalizability of the results and made it difficult to conduct a detailed subpopulation analysis. Despite the mentioned limitations, our study provided original and reliable evidence to support the relaxation of restrictions on the timing of scheduled surgery, as well as the importance of emphasizing postoperative management to prevent postoperative infection.

In summary, our study has uncovered a critical time-dependent relationship between perioperative COVID-19 infection and the likelihood of postoperative complications, revealing an increased risk when the SARS-CoV-2 infection was closer to the date of surgery. Additionally, advanced age, the existence of comorbid conditions, absence of COVID-19 vaccination, and symptom severity significantly influenced the risk of postoperative complications. Our findings not only contribute to the development of precise individual preoperative risk assessments, but also offer evidence-based guidelines for postoperative care.

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Declaration of interests

The authors have no conflicts of interest to declare.

Data sharing statement

Data will be available from the corresponding author upon reasonable request.

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Author Contributions

Jue Ma, HaiHua Shu, Yong Li, and Jie Li conceived and designed the study. HaiHua Shu and Jie Li administered the project and was responsible for data curation. Jia Zhan, Fei Zhong, LingYan Dai, and Jie Li analysed and interpreted the data. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, and XiRui Zhao wrote the first draft of manuscript. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, XiRui Zhao, HaiHua Shu and Jie Li contributed to the interpretation of the results and revision of the manuscript. Jia Zhan, Jue Ma, YunFei Chai, Lu Chang, JunJiang Wang, Yong Tang, WenZhao Zhong, GuangYan Zhang, Le Li, Qiang Zhu, ZhiHao Chen, Xin Xia, LiShan Peng, Jing Wu, RuiYun Li, DanYang Li, Yan Zhu, Xin Zhou, YiChun Wu, RuiRong Chen got involved in data collection. All the authors approved the final version of the manuscript. HaiHua Shu is the guarantor; he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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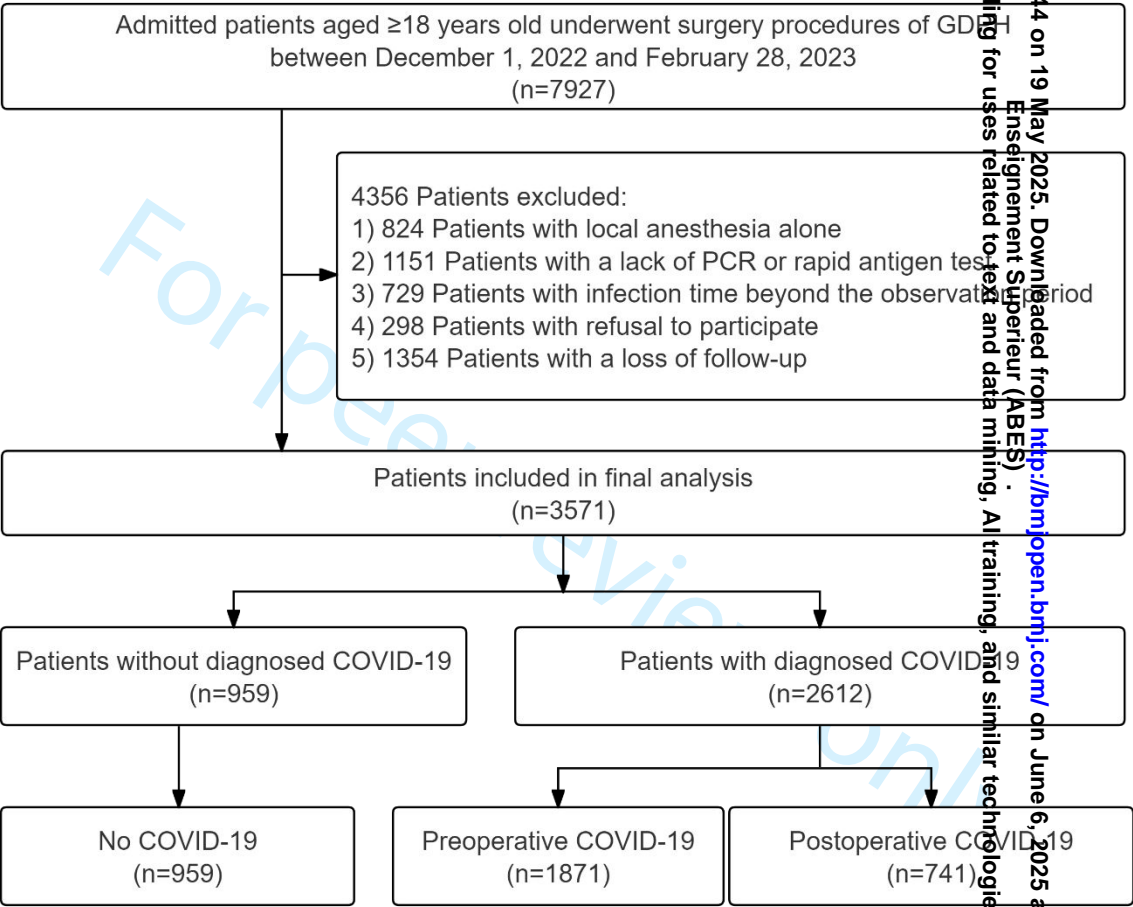


Figure 1. Flow chart of study design

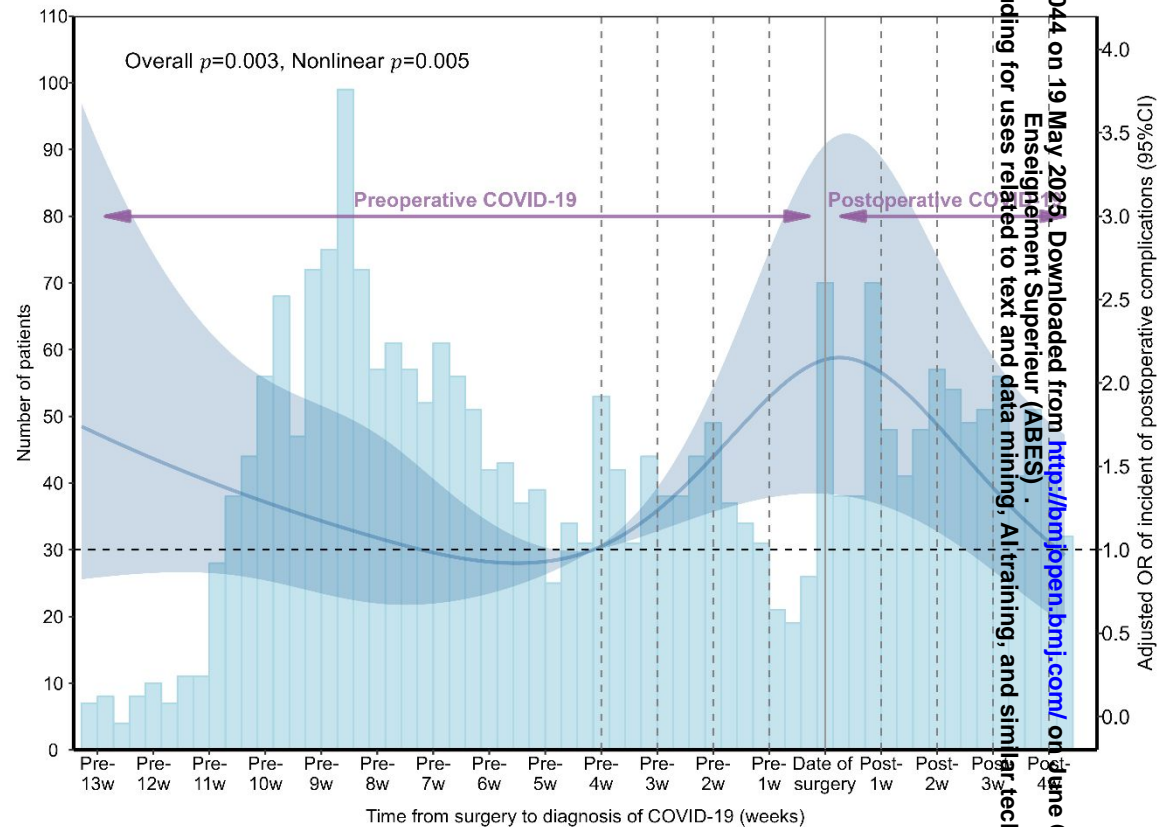


Figure 2. Relationship between time from surgery to diagnosis of COVID-19 and adjusted OR for incident of postoperative complications

Included 2612 patients with perioperative COVID-19. On the X-axis, Pre means patients with Preoperative COVID-19 and Post means patients with Postoperative COVID-19.

Table 1. Characteristics of patients based on the time of diagnosis of COVID-19 relative to surgery

	Overall (n=3571)	No COVID-19 (n=959)	Preoperative COVID-19 (n=1871)	Postoperative COVID-19 (n=741)
Men, n (%)	1622 (45.42)	432 (45.05)	859 (45.90)	331 (44.67)
Age, years, IQR	52 [40, 63]	55 [44, 65]	50 [38, 61]	51 [39, 61]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.05 [20.70, 24.97]	23.15 [20.93, 25.39]	23.21 [21.02, 25.15]
Smoking, n (%)	440 (12.32)	137 (14.29)	209 (11.17)	94 (12.69)
Diagnosis of COVID-19, n (%)				
No COVID-19	959 (26.86)	959 (100.00)	0 (0.00)	0 (0.00)
Preoperative COVID-19	1871 (52.39)	0 (0.00)	1871 (100.00)	0 (0.00)
Postoperative COVID-19	741 (20.75)	0 (0.00)	0 (0.00)	741 (100.00)
COVID-19 vaccination status, n (%)	3318 (92.92)	854 (89.05)	1755 (93.80)	709 (95.68)
Severity of COVID-19 [#] , n (%)				
Mild	2461 (94.22)	NA	1769 (94.55)	692 (93.39)
Moderate/Severe	151 (5.78)	NA	102 (5.45)	49 (6.61)
Number of comorbidities*, n (%)				
0	2323 (65.05)	564 (58.81)	1261 (67.40)	498 (67.21)

1				
2				
3				
4	1	112 (3.14)	36 (3.75)	53 (2.33)
5	2	519 (14.53)	171 (17.83)	260 (11.96)
6	3	364 (10.19)	111 (11.57)	174 (7.57)
7	≥4	253 (7.08)	77 (8.03)	123 (5.37)
8	History of cancer, n (%)	1296 (36.29)	370 (38.58)	642 (33.00)
9	ASA classification, n (%)			
10	Grade 1-2	3048 (85.35)	792 (82.59)	1615 (86.50)
11	Grade 3-5	523 (14.65)	167 (17.41)	256 (13.50)
12	Grade of surgery, n (%)			
13	Minor	1349 (37.78)	337 (35.14)	743 (39.70)
14	Major	2222 (62.22)	622 (64.86)	1128 (60.30)
15	Urgent of surgery, n (%)			
16	Elective	3339 (93.50)	903 (94.16)	1741 (95.50)
17	Emergency	232 (6.50)	56 (5.84)	130 (6.95)
18	Duration of surgery, n (%)			
19	≤240 minutes	3060 (85.69)	811 (84.57)	1612 (86.10)
20	>240 minutes	511 (14.31)	148 (15.43)	259 (13.84)
21	General anaesthesia, n (%)	3402 (95.27)	929 (96.87)	1765 (94.33)
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Type of surgery, n (%)				
Thoracic	821 (22.99)	179 (18.67)	454 (25.22)	188 (25.37)
Head and Neck	518 (14.51)	154 (16.06)	263 (14.76)	101 (13.63)
Cardio-vascular	336 (9.41)	103 (10.74)	154 (8.53)	79 (10.66)
Digestive	444 (12.43)	160 (16.68)	208 (11.56)	76 (10.26)
Breast	371 (10.39)	84 (8.76)	190 (10.61)	97 (13.09)
Gynaecologic and Obstetrics	317 (8.88)	63 (6.57)	193 (10.73)	61 (8.23)
Orthopaedic	276 (7.73)	78 (8.13)	134 (7.46)	64 (8.64)
Other surgeries‡	488 (13.67)	138 (14.39)	275 (15.29)	75 (10.12)
Postoperative complications, n (%)	420 (11.76)	103 (10.74)	214 (11.84)	103 (13.90)

Continuous variables are described as median (Interquartile Range, IQR) and categorical variables are described as number (percent).

#Due to 959 of the patients was NO COVID-19, the total of Severity of COVID-19 may not sum up to the overall study population size.

*Comorbidity included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, arrhythmia, myopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification=American Society of Anesthesiologists Physical Status Classification. COVID-19=Coronavirus disease 2019. BMI=body mass index.

Table 2. Association between preoperative and postoperative COVID-19 and risk of postoperative complications

Cases/total (%)		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Pre-1w	24/126 (19.05)	2.21 (1.34, 3.64)	0.002	2.42 (1.41, 4.15)	0.001	2.67 (1.50, 4.78)	0.001
Pre-2w	24/135 (17.78)	2.03 (1.23, 3.33)	0.005	2.26 (1.32, 3.87)	0.003	2.14 (1.20, 3.80)	0.010
Pre-3w	15/143 (10.49)	1.09 (0.61, 1.96)	0.76	1.14 (0.62, 2.09)	0.68	1.27 (0.67, 2.39)	0.46
Pre-4w or more	151/1467 (10.29)	1.06 (0.81, 1.38)	0.69	1.15 (0.86, 1.53)	0.34	1.24 (0.92, 1.68)	0.15
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Post-1w	33/172 (19.19)	2.22 (1.43, 3.47)	<0.001	2.29 (1.41, 3.72)	0.001	2.48 (1.48, 4.13)	0.001
Post-2w	22/168 (13.10)	1.42 (0.86, 2.34)	0.17	1.61 (0.93, 2.78)	0.09	1.95 (1.10, 3.45)	0.023
Post-3w	22/180 (12.22)	1.44 (0.87, 2.39)	0.15	1.93 (1.12, 3.32)	0.018	2.25 (1.27, 3.98)	0.006

Post-4w or more	26/221 (11.76)	1.24 (0.77, 1.97)	0.38	1.34 (0.81, 2.23)	0.21	1.24 (0.72, 2.14)	0.44
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Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, ≥4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedic, and Other surgeries).

Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.

Table 3. Stratification analysis of association between preoperative COVID-19 and risk of postoperative complications

Subgroup	Case/total (%)	OR (95%CI)*	p value	Case/total (%)	OR (95%CI)*	p value
Age						
<50 (n=1247)				≥50 (n=1583)		
No COVID-19	26/351 (7.41)	Ref.		77/608 (12.66)	Ref.	
Pre-1w	5/59 (8.47)	1.78 (0.59, 5.32)	0.30	19/67 (28.36)	3.34 (1.67, 6.70)	0.001
Pre-2w	5/63 (7.94)	0.99 (0.31, 3.23)	0.99	19/72 (26.39)	2.65 (1.36, 5.16)	0.004

Pre-3w	5/76 (6.58)	0.90 (0.29, 2.73)	0.85	10/67 (14.93)	1.46 (0.67, 3.18)	0.34
Pre-4w or more	42/698 (6.02)	0.82 (0.46, 1.47)	0.51	109/769 (14.17)	1.43 (1.00, 2.03)	0.05
Smoking						
No (n=2484)				Yes (n=346)		
No COVID-19	90/822 (10.95)	Ref.		13/137 (9.49)	Ref.	
Pre-1w	18/108 (16.67)	2.06 (1.07, 3.97)	0.032	6/18 (33.33)	17.22 (3.87, 76.70)	<0.001
Pre-2w	22/117 (18.8)	2.31 (1.25, 4.25)	0.007	2/18 (11.11)	1.65 (0.27, 10.03)	0.58
Pre-3w	12/125 (9.6)	1.20 (0.60, 2.42)	0.60	3/18 (16.67)	2.52 (0.51, 12.53)	0.26
Pre-4w or more	127/1312 (9.68)	1.12 (0.81, 1.55)	0.49	24/155 (15.48)	2.54 (1.05, 6.15)	0.04
COVID-19 vaccination status						
No (n=221)				Yes (n=2609)		
No COVID-19	17/105 (16.19)	Ref.		86/854 (10.07)	Ref.	
Pre-1w	1/7 (14.29)	2.97 (0.20, 44.55)	0.43	23/119 (19.33)	2.68 (1.47, 4.88)	0.001
Pre-2w	1/6 (16.67)	1.66 (0.08, 33.08)	0.74	23/129 (17.83)	2.14 (1.18, 3.89)	0.013
Pre-3w	2/5 (40)	1.94 (0.20, 18.96)	0.57	13/138 (9.42)	1.21 (0.62, 2.38)	0.57
Pre-4w or more	13/98 (13.27)	1.31 (0.51, 3.38)	0.58	138/1369 (10.08)	1.24 (0.90, 1.71)	0.18
Comorbidity						

0 (n=1825)				≥1 (n=1005)			
No COVID-19	19/564 (3.37)	Ref.		84/395 (21.27)	Ref.		
Pre-1w	4/79 (5.06)	1.48 (0.46, 4.71)	0.51	20/47 (42.55)	3.66 (1.80, 7.42)	<0.001	
Pre-2w	9/97 (9.28)	2.60 (1.10, 6.12)	0.029	15/38 (39.47)	2.03 (0.92, 4.47)	0.08	
Pre-3w	5/95 (5.26)	1.72 (0.60, 4.90)	0.31	10/48 (20.83)	1.06 (0.48, 2.36)	0.89	
Pre-4w or more	43/990 (4.34)	1.47 (0.83, 2.59)	0.19	108/477 (22.64)	1.17 (0.82, 1.66)	0.38	
Severity of COVID-19							
Mild (n= 2728)				Moderate/severe (n=1061)			
No COVID-19	103/959 (10.74)	Ref.		103/959 (10.74)	Ref.		
Pre-1w	14/104 (13.46)	2.04 (1.02, 4.07)	0.044	10/22 (45.45)	5.92 (2.04, 17.18)	0.001	
Pre-2w	19/124 (15.32)	1.88 (1.01, 3.50)	0.047	5/11 (45.45)	5.12 (1.11, 23.67)	0.036	
Pre-3w	12/135 (8.89)	1.18 (0.59, 2.34)	0.65	3/8 (37.5)	2.40 (0.48, 12.09)	0.29	
Pre-4w or more	143/1406 (10.17)	1.29 (0.95, 1.77)	0.09	8/61 (13.11)	0.68 (0.29, 1.61)	0.38	

*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedic, and Other surgeries).

Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

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Table 4. Stratification analysis of association between postoperative COVID-19 and risk of postoperative complications

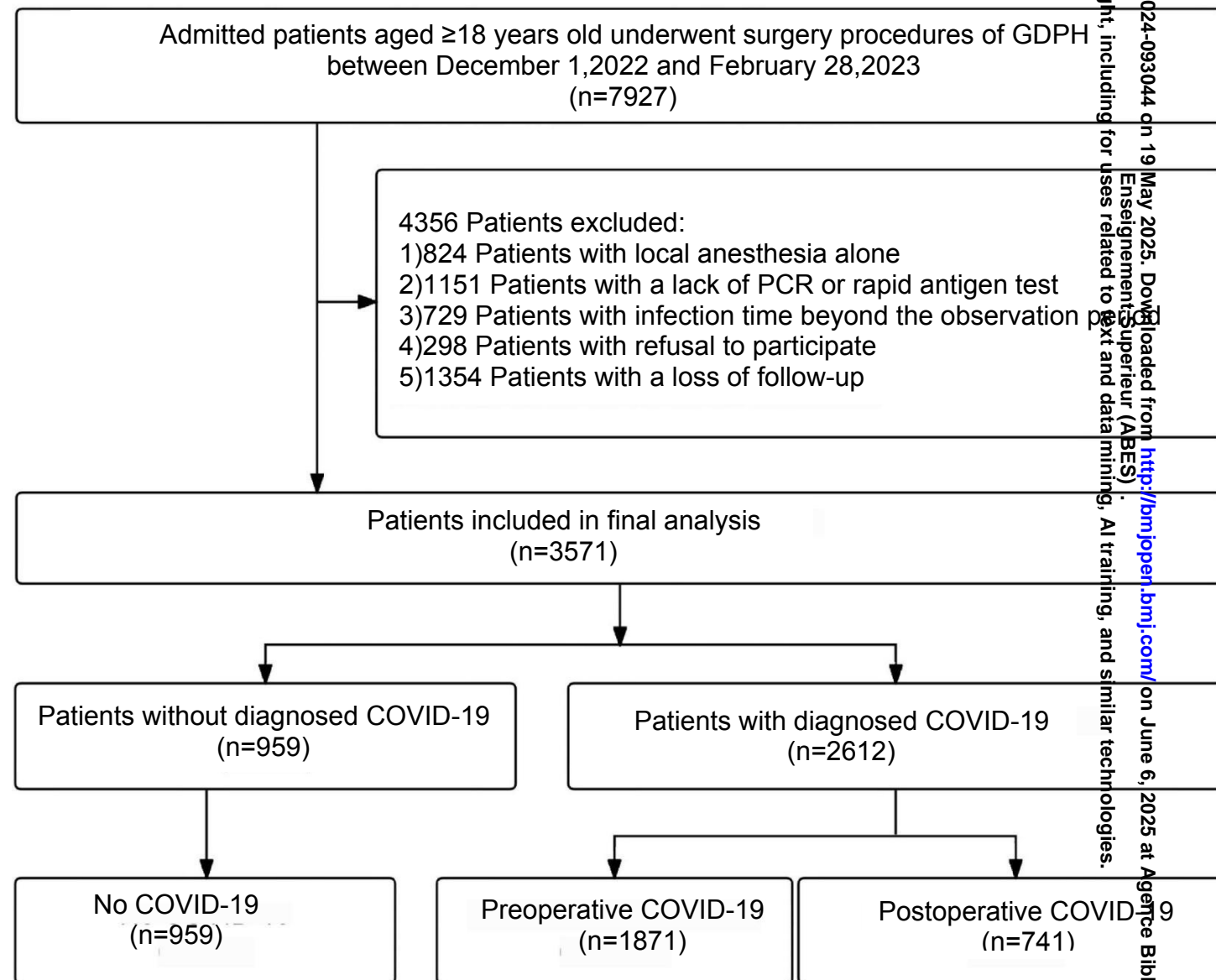
Subgroup	Case/total (%)	OR (95%CI) *	p value	Case/total (%)	OR (95%CI) *	p value
Age						
<50 (n=688)				≥50 (n=1012)		
No COVID-19	26/351 (7.41)	Ref.		77/608 (12.66)	Ref.	
Post-1w	4/72 (5.56)	0.38 (0.10, 1.48)	0.16	29/100 (29)	3.80 (2.13, 6.77)	<0.001
Post-2w	6/70 (8.57)	1.58 (0.49, 5.10)	0.44	16/98 (16.33)	2.01 (1.02, 3.95)	0.042
Post-3w	6/87 (6.9)	1.34 (0.43, 4.15)	0.61	16/93 (17.2)	2.45 (1.25, 4.81)	0.009
Post-4w or more	5/108 (4.63)	0.41 (0.12, 1.42)	0.16	21/113 (18.58)	1.74 (0.94, 3.23)	0.08
Smoking						
No (n=1469)				Yes (n=231)		
No COVID-19	90/822 (10.95)	Ref.		13/137 (9.49)	Ref.	
Post-1w	28/150 (18.67)	2.35 (1.34, 4.11)	0.003	5/22 (22.73)	3.69 (0.86, 15.81)	0.08
Post-2w	19/147 (12.93)	1.73 (0.92, 3.24)	0.09	3/21 (14.29)	5.05 (0.99, 25.61)	0.05
Post-3w	17/156 (10.9)	1.82 (0.96, 3.47)	0.07	5/24 (20.83)	6.33 (1.40, 28.59)	0.016
Post-4w or more	16/194 (8.25)	0.79 (0.41, 1.51)	0.47	10/27 (37.04)	7.35 (1.84, 29.29)	0.005
Vaccination against COVID-19						
No (n=137)				Yes (n=1563)		

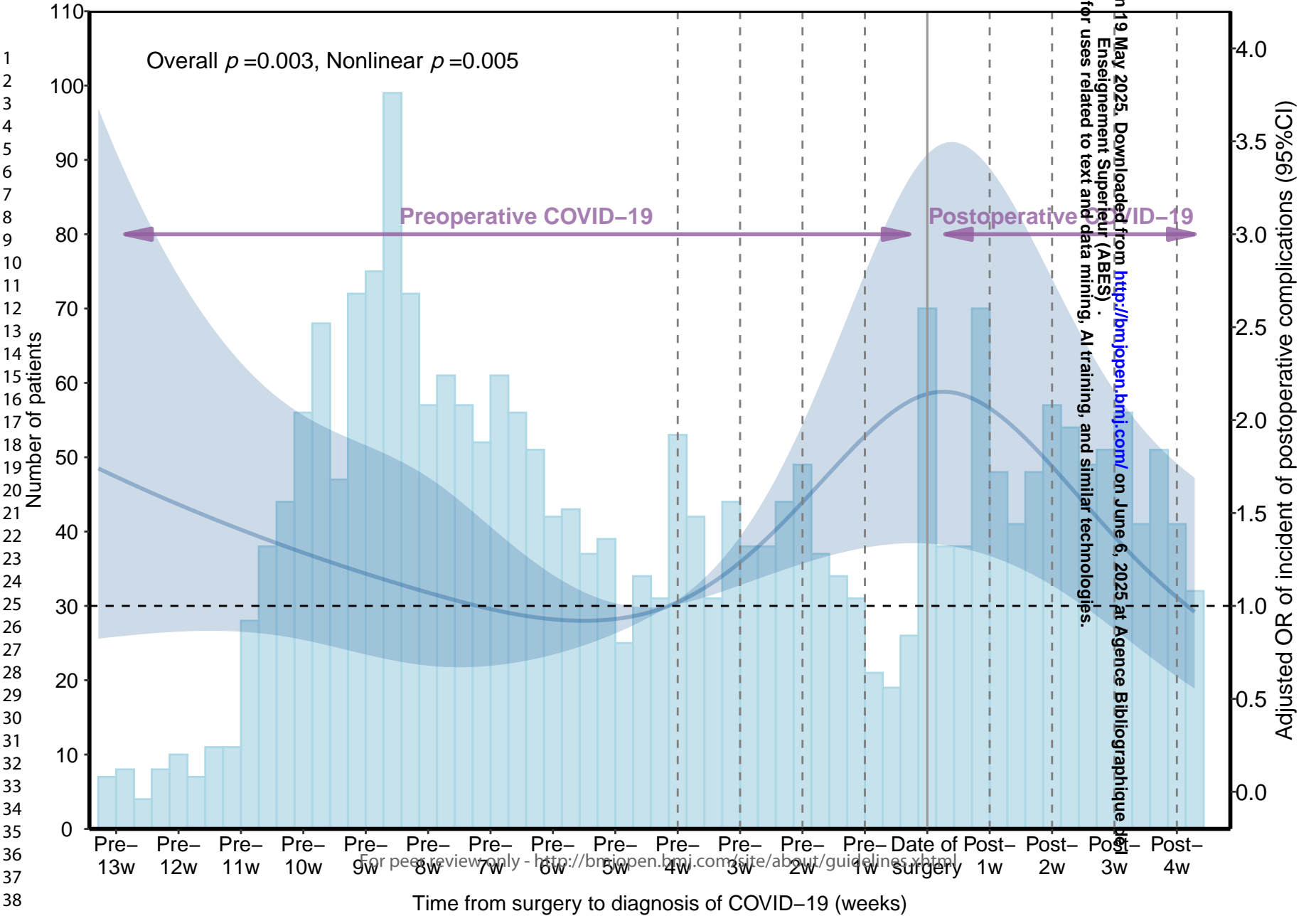
No COVID-19	17/105 (16.19)	Ref.		86/854 (10.07)	Ref.	
Post-1w	5/8 (62.5)	6.64 (0.78, 56.58)	0.08	28/164 (17.07)	2.19 (1.26, 3.80)	0.006
Post-2w	3/9 (33.33)	2.64 (0.36, 19.27)	0.34	19/159 (11.95)	1.86 (1.01, 3.44)	0.048
Post-3w	1/7 (14.29)	3.64 (0.29, 45.31)	0.32	21/173 (12.14)	2.27 (1.25, 4.14)	0.007
Post-4w or more	2/8 (25)	0.54 (0.06, 4.74)	0.58	24/213 (11.27)	1.20 (0.68, 2.14)	0.53
Comorbidity						
0 (n=1062)				≥1 (n=638)		
No COVID-19	19/564 (3.37)	Ref.		84/395 (21.27)	Ref.	
Post-1w	8/104 (7.69)	2.73 (1.04, 7.18)	0.042	25/68 (36.76)	2.42 (1.32, 4.44)	0.004
Post-2w	5/116 (4.31)	2.13 (0.72, 6.32)	0.17	17/52 (32.69)	2.13 (1.07, 4.23)	0.031
Post-3w	7/130 (5.38)	2.48 (0.90, 6.78)	0.08	15/50 (30)	1.95 (0.95, 4.01)	0.07
Post-4w or more	2/148 (1.35)	0.51 (0.10, 2.46)	0.40	24/73 (32.88)	1.64 (0.90, 2.98)	0.11
Severity of COVID-19						
Mild (n= 1651)				Moderate/severe (n= 1008)		
No COVID-19	103/959 (10.74)	Ref.		103/959 (10.74)	Ref.	
Post-1w	19/149 (12.75)	1.44 (0.77, 2.68)	0.25	14/23 (60.87)	11.52 (4.36, 30.45)	<0.001
Post-2w	14/156 (8.97)	1.26 (0.64, 2.45)	0.50	8/12 (66.67)	14.96 (3.69, 60.60)	<0.001
Post-3w	18/174 (10.34)	1.74 (0.94, 3.21)	0.08	4/6 (66.67)	29.42 (4.47, 193.81)	<0.001

Post-4w or more	22/213 (10.33)	1.11 (0.63, 1.98)	0.71	4/8 (50)	3.02 (0.60, 15.29)	0.18
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*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedic and Other surgeries).

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.



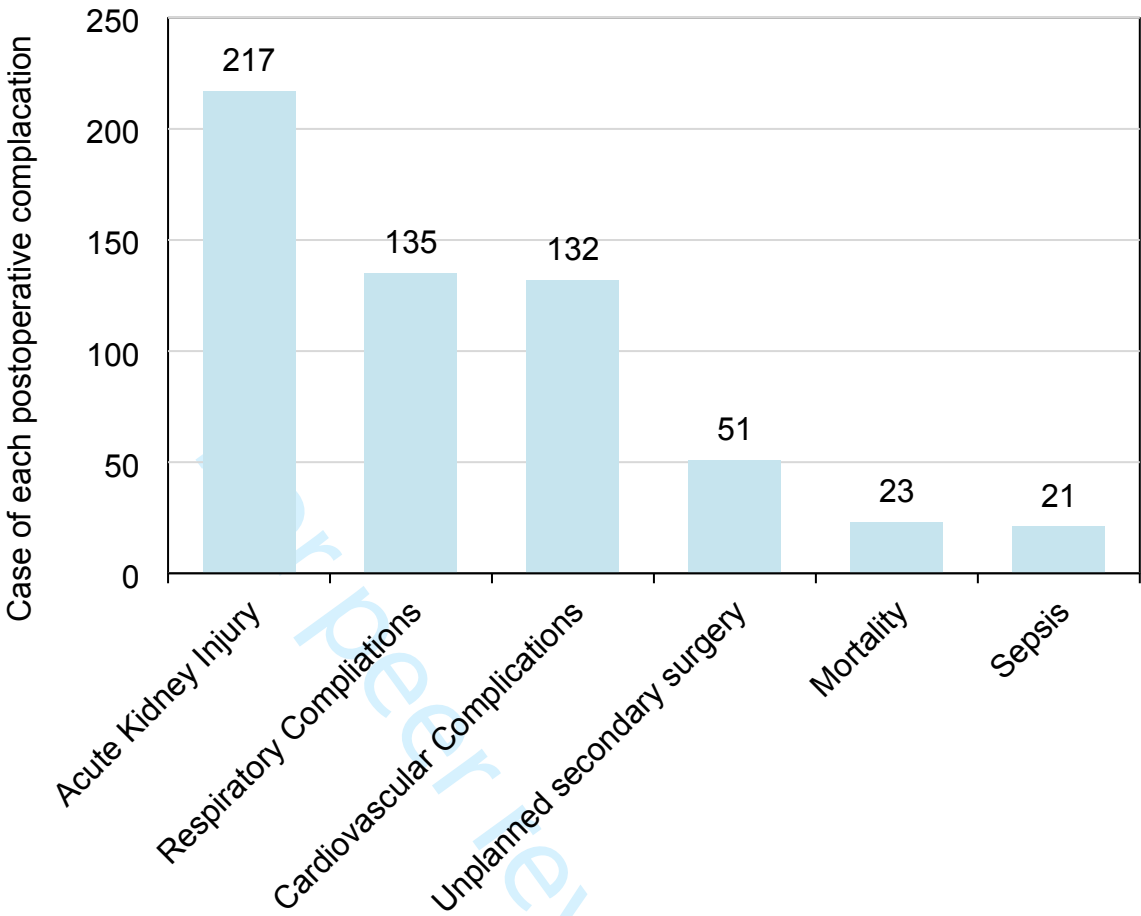


Supplementary material

Perioperative SARS-CoV-2 infection and postoperative complications: a retrospective cohort study

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Supplementary Figure 1. Distribution of composites of postoperative complications

Data were presented as the number of cases. It should be noted that multiple postoperative complications may occur in a single patient.

Supplementary Table 1. Postoperative complications: details and corresponding ICD-10 codes

Postoperative complications	Details	ICD-10 Codes
Respiratory complications	Pneumonia	J12, J13, J14, J15, J16, J17, J18, J80, J85.802, J96, I26
	Respiratory failure	
	Pulmonary embolism	
Cardiovascular complications	Deep vein thrombosis	I82, I74, R09.2, I21, I49, I50, I60, I61, I62, I63, I64
	Limb artery thrombosis	
	Splenic infarction	
	Hepatic infarction	
	Cerebral hemorrhage	
	Cerebral infarction	
	Hypoxic-ischemic encephalopathy	
	Arrhythmia	
	Myocardial infarction	
	Acute heart failure	
	Acute ischemic heart disease	
	Cardiac arrest	
	Cardiogenic shock	
Acute kidney injury		N17
Sepsis		A41
Unplanned secondary surgery		
Mortality		

Supplementary Table 2. Preoperative comorbidities: details and corresponding ICD-10 codes

Preoperative comorbidities	ICD-10 Codes
Diabetes	E10, E11, E13, E14
Chronic obstructive pulmonary disease	J44
Diffuse emphysema	J43
Bronchiectasis	J47
Asthma	J45
Pulmonary fibrosis	J84
Lung transplantation status	Z94
Respiratory failure	J96
Hypertension	I10, I15
Chronic heart failure	I50
Coronary artery disease	I25
Cardiomyopathy	I42
Ventricular aneurysm	I25
Pericardial disease	I30, I31
Cerebrovascular disease	I63, I65, I66, I67, I68, I69
Chronic kidney disease	N18

Supplementary Table 3. Definition of American Society of Anaesthesiologists (ASA) Physical Status Classification

ASA Classification*	Details
ASA 1	A normal healthy patient.
ASA 2	A patient with mild systemic disease.
ASA 3	A patient with a severe systemic disease that is not life-threatening.
ASA 4	A patient with a severe systemic disease that is a constant threat to life.
ASA 5	A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery.
ASA 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

*Statement on ASA Physical Status Classification System. December 13, 2020. <https://www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system> (accessed January 24, 2024).

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Supplementary Table 4. Details of grade of surgery

Surgery	Minor	Major
Thoracic surgery	Endoscopic thoracic; Sympathectomy; Chest-wall procedures; Biopsy; Removal of the thoracic internal fixator.	Lung resection; Lung transplant; Esophagectomy; Mediastinal procedures; Chondrosternoplasty; Correction of pectus carinatum.
Head and neck surgery	Reduction of nasal bone; Electrocoagulation of epistaxis; Laryngoscopy; Biospy; Tracheotomy.	Neck dissection; Thyroidectomy; Parathyroidectomy and transplant; Sinusotomy; Cochlear implant reconstruction; Ossicular chain reconstruction; Stapes implantation; Laryngectomy and reconstruction; Myringoplasty; Parotidectomy; Tympanoplasty; Mastoidectomy; Adenoidectomy; Tonsillectomy; Palatopharyngoplasty; Branchial fistula resection; Deviated septum surgery; Septoplasty;

		Nasal polypectomy; Excision of turbinates.
Cardio-vascular surgery		Valve procedures; Coronary artery bypass graft; Coronary artery transplant; Artificial vessel replacement; Atrial tumor resection; Aortic aneurysm procedures; Left ventricular outflow tract dredging; Carotid endarterectomy; Auricular or/and ventricular septal defect repair.
Digestive surgery	Gastroscopy (diagnostic or biopsy); Stoma closure procedures; Appendicectomy; Biopsy; Anal fistula procedures; Procedure for prolapse and hemorrhoids.	Gastroscopy (therapy); Enterostomy; Gastrectomy; Small intestine resection; Hemicolectomy or colectomy; Cholecystectomy; Pancreaticoduodenectomy; Hepatectomy; Liver transplant; Biliary procedures; Oesophagectomy; Splenectomy; Radiofrequency ablation of liver or Pancreatic.
Breast surgery	Biopsy;	Mastectomy

	Removal of breast implants; Mammoplasty; Quadrantectomy of the breast.	
Gynaecology and obstetrics surgery	Hysteroscopy (diagnostic); Repair of obstetric lacerations; Colposcopic procedures.	Hysterectomy; Salpingo-oophorectomy; Hysteroscopy (therapeutic); Caesarean section.
Orthopaedics surgery	Amputation of toe or finger; Tendon procedures; Arthroscopy (diagnostic); Removal of fracture; fixation; Biopsy; Debridement.	Amputation of limb; Spinal procedures; Arthroscopy (therapeutic); Knee replacement; Hip replacement; Revision of hip or knee replacement; Shoulder replacement; Reduction of the fracture.
Other surgeries	Ureteroscopic procedures; Cystoscopic (diagnostic); Biopsy; Ureteric stent insertion; Orchiopexy; Resection of hydrocele of testis; Posthectomy; Scrotal procedures; Ureteral stenting; Excision of skin lesion; Great saphenous vein procedures;	Nephrectomy; Adrenalectomy; Prostatectomy; Partial penectomy; Pyeloureteroplasty; Ureterocystostomy; Nephrectomy; Cystectomy; Transurethral resection of bladder tumour; Kidney transplant; Cystoscopic (therapeutic);

	Hernia repair.	Procedures for kidney stones; Renal cyst procedures; Hypophysectomy; Aneurysm procedures; Spinal cord procedures; Intracranial procedure.
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Supplementary Table 5. Details of urgency of surgery

Category	Details
Elective surgery	whose indication and scheduling have been conjointly decided by the patient and the surgeon, then followed by a consultation with an anaesthesiologist occurring at least 48h prior to the date of surgery, and then definitively scheduled in the operating theatre programme.
Emergency surgery	unplanned urgent interventions performed in the 48 hours after the surgical indication has been set ("relative emergency"), or in the four hours after the surgical indication has been set "absolute emergency").

Supplementary Table 6. Patient characteristics based on absence or presence of postoperative complications

	Overall (n=3571)	Absence of postoperative complications (n=3151)	Presence of postoperative complications (n=420)
Men, n (%)	1622 (45.42)	1401 (44.46)	221 (52.62)
Age, years, IQR	52.00 [40.00, 63.00]	51.00 [39.00, 61.00]	59.00 [50.00, 69.00]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.12 [20.93, 25.20]	23.21 [20.87, 25.04]
Smoking, n (%)	440 (12.32)	369 (11.71)	71 (16.90)
Diagnosis of COVID-19, n (%)			
No COVID-19	959 (26.86)	856 (27.17)	103 (24.52)
Preoperative COVID-19	1871 (52.39)	1657 (52.59)	214 (50.95)
Postoperative COVID-19	741 (20.75)	638 (20.25)	103 (24.52)
COVID-19 vaccination status, n (%)	3318 (92.92)	2943 (93.40)	375 (89.29)
Severity of COVID-19, n (%)			
Mild	2461 (94.22)	2200 (95.86)	261 (82.33)
Moderate/Severe	151 (5.78)	95 (4.14)	56 (17.67)

Number of comorbidities*, n (%)			
0	2323 (65.05)	2221 (70.49)	102 (24.29)
1	112 (3.14)	97 (3.08)	15 (3.57)
2	519 (14.53)	414 (13.14)	105 (25.00)
3	364 (10.19)	260 (8.25)	104 (24.76)
≥4	253 (7.08)	159 (5.05)	94 (22.38)
History of cancer, n (%)			
	1296 (36.29)	1200 (38.08)	96 (22.86)
ASA classification, n (%)			
Grade 1-2	3048 (85.35)	2843 (90.23)	205 (48.81)
Grade 3-5	523 (14.65)	308 (9.77)	215 (51.19)
Grade of surgery, n (%)			
Minor	1349 (37.78)	1250 (39.67)	99 (23.57)
Major	2222 (62.22)	1901 (60.33)	321 (76.43)
Urgent of surgery, n (%)			
Elective	3339 (93.50)	2979 (94.54)	360 (85.71)
Emergency	232 (6.50)	172 (5.46)	60 (14.29)

Duration of surgery, n (%)			
≤240 minutes	3060 (85.69)	2800 (88.86)	260 (61.90)
>240 minutes	511 (14.31)	351 (11.14)	160 (38.10)
General anesthesia, n (%)			
	3402 (95.27)	2998 (95.14)	404 (96.19)
Type of surgery, n (%)			
Thoracic	821 (22.99)	762 (24.18)	59 (14.05)
Head and Neck	518 (14.51)	496 (15.74)	22 (5.24)
Cardio-vascular	336 (9.41)	172 (5.46)	164 (39.05)
Digestive	444 (12.43)	385 (12.22)	59 (14.05)
Breast	371 (10.39)	366 (11.62)	5 (1.19)
Gynaecologic and Obstetrics	317 (8.88)	305 (9.68)	12 (2.86)
Orthopadic	276 (7.73)	256 (8.12)	20 (4.76)
Other surgeries‡	488 (13.67)	409 (12.98)	79 (18.81)

Continuous variables are described as median (Interquartile Range, IQR) and categorical variables are described as number (percent).

*Comorbidity included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, cardiomyopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification=American Society of Anaesthesiologists Physical Status Classification. COVID-19=Coronavirus disease 2019. BMI=body mass index.

Supplementary Table 7. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications in patients undergoing elective surgery

Cases/total		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	
Pre-1w	17/100 (17.00)	2.11 (1.19, 3.75)	0.011	2.22 (1.20, 4.12)	0.012	2.84 (1.48, 5.46)	0.002
Pre-2w	22/122 (18.03)	2.25 (1.34, 3.78)	0.002	2.67 (1.53, 4.69)	0.000	2.62 (1.43, 4.77)	0.002
Pre-3w	15/137 (10.95)	1.26 (0.70, 2.27)	0.43	1.28 (0.69, 2.37)	0.43	1.39 (0.73, 2.66)	0.32
Pre-4w or more	132/1382 (9.55)	1.06 (0.80, 1.42)	0.68	1.13 (0.84, 1.53)	0.41	1.23 (0.89, 1.69)	0.20
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	
Post-1w	24/157 (15.29)	1.90 (1.15, 3.12)	0.012	1.73 (1.00, 2.99)	0.04	1.95 (1.09, 3.50)	0.026

Post-2w	21/162 (12.96)	1.54 (0.92, 2.59)	0.10	1.65 (0.94, 2.92)	2.02 (1.11, 3.67)	0.021
Post-3w	21/170 (12.35)	1.63 (0.97, 2.74)	0.07	2.19 (1.24, 3.85)	2.51 (1.37, 4.59)	0.003
Post-4w or more	20/206 (9.71)	1.11 (0.66, 1.87)	0.69	1.19 (0.68, 2.09)	1.19 (0.65, 2.18)	0.57

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥ 4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopaedic, and Other surgeries).

Supplementary Table 8. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications excluding imputed data

		Postoperative complications					
		Model 1		Model 2		Model 3	
						OR (95% CI)	p value
Cases/total		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No-COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.	
Pre-1w	13/82 (15.85)	1.84 (0.97, 3.51)	0.06	2.15 (1.07, 4.31)	0.03	2.54 (1.22, 5.25)	0.012
Pre-2w	14/97 (14.43)	1.69 (0.91, 3.14)	0.10	2.08 (1.07, 4.03)	0.03	2.40 (1.20, 4.79)	0.013
Pre-3w	11/114 (9.65)	1.01 (0.52, 1.97)	0.98	1.03 (0.51, 2.07)	0.94	1.17 (0.57, 2.40)	0.67
Pre-4w or more	121/1226 (9.87)	1.05 (0.78, 1.42)	0.74	1.13 (0.82, 1.54)	0.46	1.25 (0.90, 1.75)	0.19
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.	
Post-1w	20/131 (15.27)	1.77 (1.04, 3.04)	0.037	1.84 (1.03, 3.30)	0.04	1.93 (1.04, 3.58)	0.036

Post-2w	16/142 (11.27)	1.26 (0.71, 2.25)	0.42	1.42 (0.76, 2.66)	1.58 (0.82, 3.05)	0.17
Post-3w	16/156 (10.26)	1.22 (0.69, 2.16)	0.50	1.69 (0.91, 3.12)	1.89 (0.99, 3.59)	0.05
Post-4w or more	21/189 (11.11)	1.25 (0.75, 2.10)	0.40	1.29 (0.74, 2.27)	1.17 (0.64, 2.15)	0.60

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥ 4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or > 240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopaedic, and Other surgeries).

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1 Perioperative SARS-CoV-2 infection and postoperative complications: A single-
2 center retrospective cohort study in China

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49 ABSTRACT

50 **Objective** To explore the association between perioperative SARS-CoV-2 infection
51 and the postoperative complications during the breakout of Omicron epidemic wave.

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53 **Design** Observational retrospective cohort study. Multivariable logistic regression
54 was performed to explore the association between the duration from surgery to
55 COVID-19 diagnosis and the likelihood of postoperative complications.

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57 **Setting** A general hospital in China.

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59 **Participants** 7927 patients aged 18 years and older who underwent surgical treatment
60 between December 1, 2022, and February 28, 2023.

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62 **Primary outcome measures** The outcome was a composite of postoperative adverse
63 events occurred within the initial 30 postoperative days.

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65 **Results** Of all patients, 420 (11.76%) experienced postoperative complications.
66 Compared to No COVID-19, Preoperative COVID-19 within one week (Pre-1w)
67 exhibited a high risk of postoperative complications (adjusted odds ratio (aOR), 2.67;
68 95% CI, 1.50-4.78), followed by patients with Pre-2w (aOR, 2.14; 95% CI,
69 1.20-3.80). For patients with Postoperative COVID-19 within one week (Post-1w),
70 the aOR was 2.48 (95% CI, 1.48-4.13), followed by patients with Post-2w (aOR, 1.95;

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95% CI, 1.10-3.45), and those with Post-3w (aOR, 2.25; 95% CI, 1.27-3.98). The risks of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection. Stratification analyses suggested that perioperative COVID-19 increased risk of postoperative complications in older patients, smokers, those with comorbidities, or experiencing moderate or severe COVID-19 symptoms.

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Conclusions Our findings reveal a significant time-dependent relationship between perioperative COVID-19 and postoperative complications, highlighting the importance of tailored preoperative risk evaluations, enhanced postoperative surveillance, and the implementation of effective postoperative COVID-19 prevention measures.

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Data availability statement

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Data will be available from the corresponding author upon reasonable request.

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Strengths and limitations of this study

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This study captured both preoperative and postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management.

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A broad range of surgical complications were considered, enabling physicians to gain a comprehensive understanding of the overall perioperative risk.

Both infected and uninfected patients have a COVID-19 PCR or antigen testing result, ensuring the reliability of the findings.

A single-center retrospective observational design of the study limited the generalizability of the results.

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Keywords COVID-19; COVID-19 severity; Postoperative complications; Prognosis; Surgery.

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100 **Introduction**

101 Since the first reports of a novel severe acute respiratory syndrome (SARS)-like
102 coronavirus in December 2019 in Wuhan, China, the SARS-CoV-2 virus has evolved
103 five variants from Alpha to Omicron.¹⁻³ This had led to a rapid spread, both regionally
104 and globally, resulting in over 760 million cases and 6.9 million deaths worldwide.⁴
105 Perioperative COVID-19 has been demonstrated to have an adverse impact on
106 perioperative mortality and morbidity.⁵⁻⁹ Approximately 50% of
107 SARS-CoV-2-infected individuals experience postoperative pulmonary complications
108 and the overall 30-day mortality was up to 23.8%.⁹ To mitigate the postoperative
109 risks, a large number of surgeries had been postponed, while this may delay the
110 treatment of their primary diseases and decrease survival.¹⁰⁻¹³ Hence, there is a crucial
111 need for a comprehensive assessment of the health advantages associated with the
112 postponement of surgical management and the potential adverse repercussions of
113 delayed treatment.

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115 Emerging in November 2021, SARS-CoV-2 Omicron variant became the dominant
116 variant and exhibited increased transmissibility while inducing less severe disease
117 compared with previous variants.¹⁴⁻¹⁸ In addition, massive vaccination programs and
118 the use of antiviral treatments have changed the clinical characteristics of patients
119 with COVID-19.¹⁹⁻²³ The current evidence regarding postoperative outcomes in
120 patients undergoing surgery during the Omicron wave was inconsistent. Two studies
121 found an increased postoperative risk when surgeries were performed within one
122 week after contracting COVID-19.^{24,25} On the contrary, other studies found no
123 significant difference in postoperative outcomes comparing patients with

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124 SARS-CoV-2 Omicron infection with those who were not infected.^{26,27} Furthermore,
125 few studies focused on the risk of postoperative complications associated with
126 SARS-CoV-2 infection after surgery.

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128 Given the rapid global spread and significant impact of COVID-19, coupled with its
129 high mutation rate, current research findings on postoperative complications
130 associated with COVID-19 infection remain inconsistent. In this study, we aimed to
131 investigate the associations between pre- or post-operative SARS-CoV-2 infection
132 and postoperative outcomes, respectively. We further analysed the risk of
133 postoperative outcomes at various time intervals between SARS-CoV-2 infection and
134 the surgery date, providing updated evidence for guiding optimal surgery timing and
135 minimizing adverse postoperative outcomes

Methods

Study design and participants

The protocol of this study was approved by the Institutional Review Board of Guangdong Provincial People's Hospital (No. KY2023-031-02), and the study was registered on Chictr.org.cn (ChiCTR2300072473). Informed consent was obtained from all included patients in a text message or written way. The study adhered to the principles of the Declaration of Helsinki.

In this retrospective cohort study, we initially recruited 7927 patients who aged ≥ 18 years who underwent and requiring surgery at Guangdong Provincial People's Hospital in China between December 1, 2022, and February 28, 2023. Patients were excluded based on the following criteria: 1) those who underwent surgery with local anaesthesia alone (n=824); 2) those without reverse transcription-polymerase chain reaction (PCR) or rapid antigen test results for COVID-19 (n=1151); 3) those with infection time beyond the observation period (n=729); 4) those who refused to participate (n=298); and 5) those lost to follow-up (n=1354). After applying these exclusion criteria, a final cohort of 3571 individuals remained for analysis (**Figure 1**). Data on patient demographics, surgical procedures, SARS-CoV-2 infection status, and postoperative complications within the first 30 days after surgery were collected from medical records and telephone follow-ups.

Assessment of SARS-CoV-2 infection

Confirmation of SARS-CoV-2 infection was established based on a positive outcome

from either PCR testing or rapid antigen tests. The duration from surgery to the diagnosis of COVID-19 was defined as the period between the day of surgery and the date of the initial positive test result. In instances where patients underwent multiple surgeries, the surgical date closest to the time of infection was utilized for analysis. Consequently, patients were categorized into three groups as follows: those infected before surgery (Preoperative COVID-19), those infected within 30 days after surgery (Postoperative COVID-19), and those with no positive SARS-CoV-2 test results during the study period (No COVID-19). The severity of COVID-19 was assessed and classified as either mild (WHO Severity 1-3) or moderate/severe (WHO Severity 4-9) based on the WHO Clinical Progression Scale (see the definition in **Supplementary Table 1**).²⁸

Definitions of postoperative complications

The outcome was defined as a composite of postoperative adverse events occurring within the initial 30 days following surgery (**Supplementary Table 2**). This encompassed acute kidney injury (AKI), postoperative respiratory complications (including pneumonia, respiratory failure, and pulmonary embolism), postoperative cardiovascular complications (including arrhythmia, myocardial infarction, acute heart failure, acute ischemic heart disease, cardiac arrest, cardiogenic shock, cerebral haemorrhage, cerebral infarction, hypoxic-ischemic encephalopathy, deep vein thrombosis, limb artery thrombosis, splenic infarction, and hepatic infarction), unplanned secondary surgery, sepsis, and mortality.

Covariates

The covariates encompassed age, sex, body mass index (BMI), smoking status, COVID-19 vaccination status, number of comorbidities (see the definition in **Supplementary Table 3**), history of cancer, American Society of Anesthesiologists (ASA) grade classification (see the definition in **Supplementary Table 4**), grade of surgery (see the definition in **Supplementary Table 5**), urgency of surgery (see the definition in **Supplementary Table 6**), duration of surgery, type of anaesthesia, and type of surgery. We gathered such data from a variety of sources including Electronic Health Records, laboratory data, anaesthesia information management systems, and questionnaires. The proportions of missing data for key variables such as height, weight, smoking status, and COVID-19 vaccination status were 2.30%, 0.25%, 11.12%, and 5.58% respectively. Median and mode imputation were employed to replace missing data for continuous and categorical variables, respectively.

Statistical analysis

Logistic regression was employed to estimate Odds ratios (OR) with 95% confidence intervals (CIs) to examine the associations between the duration from surgery to COVID-19 diagnosis and the risk of postoperative complications, with No COVID-19 group as the reference category. We initially incorporated a restricted cubic spline term for the duration from surgery to the diagnosis of SARS-CoV-2 infection, utilizing 3 knots at the 10th, 50th, and 90th centiles into the model to explore the nonlinear relationship between the timeframe and the risk of postoperative complications. We performed a subgroup analysis to explore whether trends in the risk of outcomes were consistent across surgical types. The assessment of nonlinearity was conducted using a likelihood ratio test to determine the associated P value.

Following this, we categorized the time from COVID-19 diagnostic into discrete intervals, stratifying patients into four groups based on Preoperative and Postoperative COVID-19 statuses: within one week (Pre-1w and Post-1w), one to two weeks (Pre-2w and Post-2w), two to three weeks (Pre-3w and Post-3w), and beyond three weeks (Pre-4w or more and Post-4w or more).

The analysis was further divided to independently evaluate the associations between Preoperative COVID-19 diagnostic time and postoperative complications, as well as those between Postoperative COVID-19 diagnostic time and postoperative complications. Risks of postoperative complications were examined by stratifying the analysis based on age (younger elderly [<50 years] and older elderly [≥ 50 years]), smoking status (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), and severity of COVID-19 (mild or moderate/severe).

We conducted sensitivity analysis to ensure the reliability of our results. We utilized a subset of the sample with complete data to replicate our main findings, examining any potential impact of missing value of sociodemographic factors. Furthermore, in light of the varying health statuses of patients undergoing emergency surgery and the surgeon's accurate judgment of the patient's condition, we conducted sensitivity analyses specifically focusing on patients undergoing elective surgery.

All analyses were performed using R v4.3.0, with a two-tailed significance level of 0.05.

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231 **Patient and public involvement**

232 Patients and/or the public were not involved in the design, or conduct, or reporting or
233 dissemination plans of this research.

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235 **Role of the funding source**

236 The funders were not involved in study design, data collection, data analysis, data
237 interpretation, and writing of the report. JZ, FZ, LD, HS, and JL had full access to all
238 the data in the study. All authors accepted responsibility for the decision to submit for
239 publication.

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240 Results

241 Characteristics of patients

242 During the study period, 3571 patients were included in the study analysis (**Table 1**).
243 The median age of patients was 52 years (Interquartile Range [IQR] 40-63 years),
244 45.42% were men, and 92.92% were vaccinated against COVID-19. Of all
245 individuals, 93.50% underwent elective surgery, 62.22% underwent major surgery,
246 and 85.69% had surgeries lasting no more than four hours. Patients were categorized
247 into three groups based on the timing of COVID-19 diagnosis relative to surgery: No
248 COVID-19 (n=959, 26.86%), Preoperative COVID-19 (n=1871, 52.39%), and
249 Postoperative COVID-19 (n=741, 20.75%). Among patients with COVID-19, the
250 majority experienced mild symptoms (94.22%), with only 5.45% and 6.61%
251 exhibiting moderate or severe symptoms in Preoperative and Postoperative
252 COVID-19 respectively. When compared with those with No COVID-19, patients
253 with both Preoperative and Postoperative COVID-19 had lower rates of smoking,
254 with 11.17% versus 14.29% for Preoperative COVID-19 and 12.69% versus 14.29%
255 for Postoperative COVID-19, respectively. Patients with No COVID-19 had a higher
256 ASA classification than those with Preoperative or Postoperative COVID-19. The
257 baseline characteristics of patients with and without postoperative complications were
258 presented in **Supplementary Table 7**.

259

260 Time-dependent association between duration from surgery to the diagnosis of 261 COVID-19 and risk of postoperative complications

262 During the study period, 420 (11.76%) patients experienced postoperative
263 complications. A higher rate (13.90%) of postoperative complications was observed

in patients with Postoperative COVID-19 compared to those with Preoperative COVID-19 (11.44%). Among these postoperative complications, 217 (6.08%) cases were AKI, 135 (3.78%) were respiratory complications, 132 (3.70%) were cardiovascular complications, 51 (1.43%) were unplanned secondary surgeries, 23 (0.64%) resulted in mortality, and 21 cases (0.59%) were sepsis (**Supplementary Figure 1**).

We initially examined the nonlinear trend in the association between the duration from surgery to the diagnosis of COVID-19 and the risk of postoperative complications (**Figure 2**). Using the time interval between the surgery date and COVID-19 diagnosis as the axis of symmetry (dividing preoperative and postoperative by week), the risk curve exhibited a bell-shaped pattern, peaking approximately at the surgery date. The risk of postoperative complications was higher when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it was preoperative or postoperative COVID-19. The risk diminished gradually as the time interval between the surgery date and COVID-19 diagnosis increased (p for nonlinearity = 0.005). However, in cases of preoperative COVID-19, the risk did not decrease further beyond a four-week interval, whereas in cases of postoperative COVID-19, it gradually diminished until four weeks after surgery.

Association between Preoperative COVID-19 and risk of postoperative complications

The risk of postoperative complications gradually decreased with an increase in the time interval between SARS-CoV-2 infection and surgery date (**Table 2**). Compared

to patients with No COVID-19, those with Pre-1w exhibited the highest risk of postoperative complications (aOR 2.67 [95% CI 1.50-4.78], $p=0.001$), followed by patients with Pre-2w (aOR 2.14 [95% CI 1.20-3.80], $p=0.010$). Compared to patients with No COVID-19, there was no statistically significant increase in risk observed in patients with Pre-3w (aOR 1.27 [95% CI 0.67-2.39], $p=0.46$) or those with Pre-4w or more (aOR 1.24 [95% CI 0.92-1.68], $p=0.15$).

Stratification analysis by the severity of COVID-19 revealed a higher risk of postoperative complications in patients with moderate or severe symptoms compared to those with mild symptoms (aOR 5.92 vs. 2.04 with Pre-1w, 5.12 vs. 1.88 with Pre-2w) (**Table 3**). Stratification analysis by smoking status revealed an exceptionally high risk in smoking patients with Pre-1w (aOR 17.22 [95% CI 3.87-76.70], $p<0.001$), while the aOR for non-smoking patients with Pre-1w was 2.06 (95% CI 1.07-3.97, $p=0.032$). In summary, patients aged ≥ 50 years, smokers, those with comorbidities, or those with moderate or severe symptoms were associated with a higher risk of postoperative complications in cases of preoperative COVID-19 within two weeks.

Association between Postoperative COVID-19 and risk of postoperative complications

The risk of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection (**Figure 2**). Compared to patients with No COVID-19, those with Post-1w exhibited the highest risk of postoperative complications (aOR 2.48 [95% CI 1.48-4.13], $p=0.001$),

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312 followed by patients with Post-3w (aOR 2.25 [95% CI 1.27-3.98], p=0.006), and
313 those with Post-2w (aOR 1.95 [95% CI 1.10-3.45], p=0.023) (**Table 2**). Compared to
314 patients with No COVID-19, the increased risk was not statistically significant in
315 patients with Post-4w or more (aOR 1.24 [95% CI 0.72-2.14], p=0.44).

317 Stratification analysis by the severity of COVID-19 revealed extremely high risks of
318 postoperative complications in patients with Post-1w with moderate or severe
319 symptoms (aOR 11.52 [95% CI 4.36-30.45], p<0.001), as well as in patients with
320 Post-2w (aOR 14.96 [95% CI 3.69-60.60], p<0.001), and in patients with Post-3w
321 (aOR 29.42 [95% CI 4.47-193.81], p<0.001) (**Table 4**). Conversely, no significant
322 risk was observed among patients with mild symptoms. Stratification analysis by
323 smoking status revealed consistently high risks in smoking patients, with aOR being
324 3.69 in Post-1w, 5.05 in Post-2w, 6.33 in Post-3w, and 7.35 in Post-4w or more,
325 whereas the aOR for non-smoking patients with Post-1w was 2.35 (95% CI
326 1.34-4.11], p=0.003). In summary, patients aged ≥50 years, smokers, those without
327 COVID-19 vaccination, with comorbidities, or with moderate or severe symptoms
328 were associated with a higher risk of postoperative complications in cases of
329 postoperative COVID-19 occurring within three weeks.

331 Considering potential health status differences between patients who underwent
332 emergency and elective surgery, a sensitivity analysis was conducted solely on
333 patients who underwent elective surgery, and the findings remained consistent with
334 the main results (**Supplementary Table 8**). Additionally, to investigate the potential
335 impact of missing value of sociodemographic factors, a sensitivity analysis was

336 carried out on a subset of the sample without imputed data, revealing similar findings
337 and trends to the main results (**Supplementary Table 9**).

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Discussion

Our study underscored the importance of timing in the association between perioperative COVID-19 and the risk of postoperative complications. The risk significantly escalated when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it's preoperative or postoperative. Besides, perioperative COVID-19 increased the risk of postoperative complications in specific subgroups, including older patients, smokers, those with comorbidities, or those experiencing moderate or severe COVID-19 symptoms.

While there are existing recommendations regarding surgical decision-making following SARS-CoV-2 infection, a consensus has not yet been achieved in this regard. Study from the COVIDSurg and GlobalSurg Collaborative reported a significant increase in mortality when surgery was performed within seven weeks after COVID-19 diagnosis during the pre-vaccine phase.²⁹ Additionally, the Covid-19 Research Database found that surgery performed 4 to 8 weeks after confirmed SARS-CoV-2 infection continues to carry an elevated risk of developing postoperative pneumonia.³⁰ However, emerging studies presented differing perspectives. A study conducted across 37 American centres revealed that the time span from a positive test to the actual surgery significantly impacted both mortality and pulmonary risk, with the risk subsiding after two weeks.⁷ Conversely, research from 41 French centres found no significant association between surgery within three weeks of COVID-19 diagnosis and postoperative respiratory comorbidities.²⁷ Our

research findings revealed a heightened risk of composite postoperative complications, encompassing respiratory, cardiovascular, and other complications, when surgery was conducted within two weeks of a preoperative COVID-19 diagnosis. Therefore, conducting preoperative individualized risk assessments is imperative, and scheduling elective surgeries within two weeks after a SARS-CoV-2 diagnosis should be avoided. Our findings lend support to global endeavours aimed at updating restrictions on the timing of scheduled surgeries.

Furthermore, the risks of postoperative complications after SARS-CoV-2 infection varied across distinct subgroups. Our study revealed that older patients, smokers, and those with comorbidities faced an increased risk of adverse postoperative outcomes following SARS-CoV-2 infection. In a cohort of 3027 COVID-19-positive individuals, several risk factors were identified for mortality, including increased age, current smoking, presence of comorbidity, and undergoing emergency surgery.³¹ However, this study only considered patients with perioperative COVID-19 and did not compare them to those without infection. Moreover, our study also revealed that individuals with moderate or severe symptoms faced a markedly elevated risk of postoperative complications up to two weeks preceding their surgery, whereas those with mild symptoms exhibited a modest increase in complications. A study from the National COVID Cohort Collaborative (N3C) found that the impact of COVID-19 on postoperative outcomes is dependent on severity of illness, with only moderate and severe disease leading to higher risk of adverse outcomes.³² Another study from N3C found that postoperative cardiovascular risk remained high even 8 weeks after infection with moderate or severe SARS-CoV-2, but did not increase among those

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384 undergoing surgery within 4 weeks following mild infection.³³ These studies failed to
385 find an association between postoperative complications and mild COVID-19.
386 Overall, it is essential for patients to undergo thorough evaluation before surgery, with
387 a specific focus on assessing individual risk factors, to determine the optimal timing
388 for surgical interventions.

389

390 There is limited research available on the risk of postoperative complications in
391 patients who contract SARS-CoV-2 after surgery, with most prior studies focusing on
392 series of Total Joint Arthroplasty (TJA) patients and overlooking the impact of other
393 surgical procedures.^{34,35} Another study of only 22 patients with COVID-19 occurring
394 in the recovery period after open-heart surgery showed a higher pneumonia and
395 mortality rates in unvaccinated patients.³⁶ Our study revealed that individuals who
396 tested positive for SARS-CoV-2 up to three weeks after surgery were at a higher risk
397 of complications compared to those without the infection. Hence, robust postoperative
398 management strategies to mitigate SARS-CoV-2 transmission risk are vital, with
399 protective measures recommended for at least three weeks post-surgery. Our study
400 highlighted the significance of monitoring a patient's SARS-CoV-2 infection status
401 not only before but also after surgery.

402

403 The stratified analysis of patients with postoperative COVID-19 revealed that
404 unvaccinated individuals, who were older, smokers, or had comorbidities, faced a
405 higher risk of complications. Furthermore, patients with moderate or severe symptoms
406 of COVID-19 posed a significantly heightened risk of postoperative complications.
407 Patients undergoing cardiovascular surgery have a higher risk of postoperative

complications when infected with COVID-19 than those undergoing other types of surgery (**Supplementary Figure 2**). Previous studies have shown that vaccination is effective in reducing the risk of severe illness, hospitalization, and death from COVID-19.^{37,38} Recent work by the COVIDSurg Collaborative and GlobalSurg Collaborative reported that preoperative vaccination could prevent nearly 60,000 deaths per year on average among patients requiring elective surgery.³⁹ However, these studies did not account for postoperative SARS-CoV-2 infections. Our findings underscore the importance of reinforcing postoperative protective strategies for these vulnerable patients.

This study had several strengths. Firstly, unlike previous research, our study not only focused on preoperative SARS-CoV-2 infections but also examined postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management. Secondly, we investigated the interaction between various risk factors to gain further insight into the factors influencing postoperative complications. Thirdly, we considered a broad range of surgical complications, including respiratory and cardiovascular morbidity, acute kidney injury, unplanned secondary surgery, sepsis, and mortality, thereby enabling physicians to gain a comprehensive understanding of the overall perioperative risk. Fourthly, patients were diagnosed with COVID-19 through PCR or antigen testing. Even uninfected patients were confirmed to have negative results, ensuring the reliability of the findings.

This study also had some limitations. Firstly, the sample size was limited. Conducting

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432 further research with a larger sample size would provide a more comprehensive
433 understanding of the interaction among various influencing factors. Secondly, the
434 retrospective observational nature of the study made it challenging to completely rule
435 out the influence of unmeasured residual confounding factors, despite efforts to
436 retrieve as many covariates as possible. Thirdly, the single-centre design of the study
437 had limited the generalizability of the results and made it difficult to conduct a
438 detailed subpopulation analysis. Forthly, patients with relative symptoms were more
439 likely to be tested for COVID-19. We excluded patients who did not undergo testing,
440 which may explain the particularly high proportion of COVID-19 positive patients in
441 the population. Despite the mentioned limitations, our study provided original and
442 reliable evidence to support the relaxation of restrictions on the timing of scheduled
443 surgery, as well as the importance of emphasizing postoperative management to
444 prevent postoperative infection.

445

446 In summary, our study has uncovered a critical time-dependent relationship between
447 perioperative COVID-19 infection and the likelihood of postoperative complications,
448 revealing an increased risk when the SARS-CoV-2 infection was closer to the date of
449 surgery. Additionally, advanced age, the existence of comorbid conditions, absence of
450 COVID-19 vaccination, and symptom severity significantly influenced the risk of
451 postoperative complications. Our findings not only contribute to the development of
452 precise individual preoperative risk assessments, but also offer evidence-based
453 guidelines for postoperative care.

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Declaration of interests

The authors have no conflicts of interest to declare.

Data sharing statement

Data will be available from the corresponding author upon reasonable request.

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Author Contributions

Jue Ma, HaiHua Shu, Yong Li, and Jie Li conceived and designed the study. HaiHua Shu and Jie Li administered the project and was responsible for data curation. Jia Zhan, Fei Zhong, LingYan Dai, and Jie Li analysed and interpreted the data. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, and XiRui Zhao wrote the first draft of manuscript. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, XiRui Zhao, HaiHua Shu and Jie Li contributed to the interpretation of the results and revision of the manuscript. Jia Zhan, Jue Ma, YunFei Chai, Lu Chang, JunJiang Wang, Yong Tang, WenZhao Zhong, GuangYan Zhang, Le Li, Qiang Zhu, ZhiHao Chen, Xin Xia, LiShan Peng, Jing Wu, RuiYun Li, DanYang Li, Yan Zhu, Xin Zhou, YiChun Wu, RuiRong Chen got involved in data collection. All the authors approved the final version of the manuscript. HaiHua Shu is the guarantor; he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure 1. Flow chart of study design

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Figure 2. Relationship between time from surgery to diagnosis of COVID-19 and adjusted OR for incident of postoperative complications

Included 2612 patients with perioperative COVID-19. On the X-axis, Pre means patients with Preoperative COVID-19 and Post means patients with Postoperative COVID-19.

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Table 1. Characteristics of patients based on the time of diagnosis of COVID-19 relative to surgery

	Overall (n=3571)	No COVID-19 (n=959)	Preoperative COVID-19 (n=1871)	Postoperative COVID-19 (n=741)
Men, n (%)	1622 (45.42)	432 (45.05)	859 (45.91)	331 (44.67)
Age, years, IQR	52 [40, 63]	55 [44, 65]	50 [38, 61]	51 [39, 61]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.05 [20.70, 24.97]	23.15 [20.95, 25.39]	23.21 [21.02, 25.15]
Smoking, n (%)	440 (12.32)	137 (14.29)	209 (11.17)	94 (12.69)
COVID-19 vaccination status, n (%)	3318 (92.92)	854 (89.05)	1755 (93.80)	709 (95.68)
Severity of COVID-19 [#] , n (%)				
Mild	2461 (94.22)	NA	1769 (94.55)	692 (93.39)
Moderate/Severe	151 (5.78)	NA	102 (5.45)	49 (6.61)
Number of comorbidities*, n (%)				
0	2323 (65.05)	564 (58.81)	1261 (67.40)	498 (67.21)
1	112 (3.14)	36 (3.75)	53 (2.83)	23 (3.10)
2	519 (14.53)	171 (17.83)	260 (13.90)	88 (11.88)
3	364 (10.19)	111 (11.57)	174 (9.30)	79 (10.66)
≥4	253 (7.08)	77 (8.03)	123 (6.57)	53 (7.15)
History of cancer, n (%)	1296 (36.29)	370 (38.58)	642 (34.31)	284 (38.33)
ASA classification, n (%)				
Grade 1-2	3048 (85.35)	792 (82.59)	1615 (86.32)	641 (86.50)
Grade 3-5	523 (14.65)	167 (17.41)	256 (13.68)	100 (13.50)
Grade of surgery, n (%)				
Minor	1349 (37.78)	337 (35.14)	743 (39.71)	269 (36.30)
Major	2222 (62.22)	622 (64.86)	1128 (60.29)	472 (63.70)
Urgent of surgery, n (%)				

Elective	3339 (93.50)	903 (94.16)	1741 (93.05)	695 (93.79)
Emergency	232 (6.50)	56 (5.84)	130 (6.95)	46 (6.21)
Duration of surgery, n (%)				
≤240 minutes	3060 (85.69)	811 (84.57)	1612 (86.16)	637 (85.96)
>240 minutes	511 (14.31)	148 (15.43)	259 (13.84)	104 (14.04)
General anaesthesia, n (%)	3402 (95.27)	929 (96.87)	1765 (94.33)	708 (95.55)
Type of surgery, n (%)				
Thoracic	821 (22.99)	179 (18.67)	454 (24.27)	188 (25.37)
Head and Neck	518 (14.51)	154 (16.06)	263 (14.06)	101 (13.63)
Cardio-vascular	336 (9.41)	103 (10.74)	154 (8.23)	79 (10.66)
Digestive	444 (12.43)	160 (16.68)	208 (11.12)	76 (10.26)
Breast	371 (10.39)	84 (8.76)	190 (10.15)	97 (13.09)
Gynaecologic and Obstetrics	317 (8.88)	63 (6.57)	193 (10.32)	61 (8.23)
Orthopaedic	276 (7.73)	78 (8.13)	134 (7.16)	64 (8.64)
Other surgeries [‡]	488 (13.67)	138 (14.39)	275 (14.70)	75 (10.12)
Postoperative complications, n (%)	420 (11.76)	103 (10.74)	214 (11.44)	103 (13.90)

Continuous variables are described as median (Interquartile Range, IQR) and categorical variables are described as number (percent).

#Due to 959 of the patients was NO COVID-19, the total of Severity of COVID-19 may not sum up to the overall study population size.

*Comorbidity included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, cardiomyopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡ Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification=American Society of Anesthesiologists Physical Status Classification.
COVID-19=Coronavirus disease 2019. BMI=body mass index.

Table 2. Association between preoperative and postoperative COVID-19 and risk of postoperative complications

Cases/total (%)		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Pre-1w	24/126 (19.05)	2.21 (1.34, 3.64)	0.002	2.42 (1.41, 4.15)	0.001	2.67 (1.50, 4.78)	0.001
Pre-2w	24/135 (17.78)	2.03 (1.23, 3.33)	0.005	2.26 (1.32, 3.87)	0.003	2.14 (1.20, 3.80)	0.010
Pre-3w	15/143 (10.49)	1.09 (0.61, 1.96)	0.76	1.14 (0.62, 2.09)	0.68	1.27 (0.67, 2.39)	0.46
Pre-4w or more	151/1467 (10.29)	1.06 (0.81, 1.38)	0.69	1.15 (0.86, 1.53)	0.34	1.24 (0.92, 1.68)	0.15
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Post-1w	33/172 (19.19)	2.22 (1.43, 3.47)	<0.001	2.29 (1.41, 3.72)	0.001	2.48 (1.48, 4.13)	0.001
Post-2w	22/168 (13.10)	1.42 (0.86, 2.34)	0.17	1.61 (0.93, 2.78)	0.09	1.95 (1.10, 3.45)	0.023
Post-3w	22/180 (12.22)	1.44 (0.87, 2.39)	0.15	1.93 (1.12, 3.32)	0.018	2.25 (1.27, 3.98)	0.006

Post-4w or more	26/221 (11.76)	1.24 (0.77, 1.97)	0.38	1.34 (0.81, 2.23)	0.25	1.24 (0.72, 2.14)	0.44
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Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, ≥ 4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedic, and Other surgeries).

Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.

Table 3. Stratification analysis of association between preoperative COVID-19 and risk of postoperative complications

Subgroup	No COVID-19	Pre-1w	Pre-2w	Pre-3w	Pre-4w or more
Age					
<50 (n=1247)	Ref.	1.78 (0.59, 5.32)	0.99 (0.31, 3.23)	0.90 (0.27, 2.73)	0.82 (0.46, 1.47)
≥50 (n=1583)	Ref.	3.34 (1.67, 6.70)	2.65 (1.36, 5.16)	1.46 (0.67, 3.18)	1.43 (1.00, 2.03)
Smoking					
No (n=2484)	Ref.	2.06 (1.07, 3.97)	2.31 (1.25, 4.25)	1.20 (0.50, 2.42)	1.12 (0.81, 1.55)
Yes (n=346)	Ref.	17.22 (3.87, 76.70)	1.65 (0.27, 10.03)	2.52 (0.61, 12.53)	2.54 (1.05, 6.15)
COVID-19 vaccination status					
No (n=221)	Ref.	2.97 (0.20, 44.55)	1.66 (0.08, 33.08)	1.94 (0.20, 18.96)	1.31 (0.51, 3.38)
Yes (n=2609)	Ref.	2.68 (1.47, 4.88)	2.14 (1.18, 3.89)	1.21 (0.62, 2.38)	1.24 (0.90, 1.71)
Comorbidity					
0 (n=1825)	Ref.	1.48 (0.46, 4.71)	2.60 (1.10, 6.12)	1.72 (0.60, 4.90)	1.47 (0.83, 2.59)
≥1 (n=1005)	Ref.	3.66 (1.80, 7.42)	2.03 (0.92, 4.47)	1.06 (0.48, 2.36)	1.17 (0.82, 1.66)
Severity of COVID-19					
Mild (n= 2728)	Ref.	2.04 (1.02, 4.07)	1.88 (1.01, 3.50)	1.18 (0.49, 2.34)	1.29 (0.95, 1.77)
Moderate/severe (n= 1061)	Ref.	5.92 (2.04, 17.18)	5.12 (1.11, 23.67)	2.40 (0.47, 12.09)	0.68 (0.29, 1.61)

*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedics and Other surgeries).

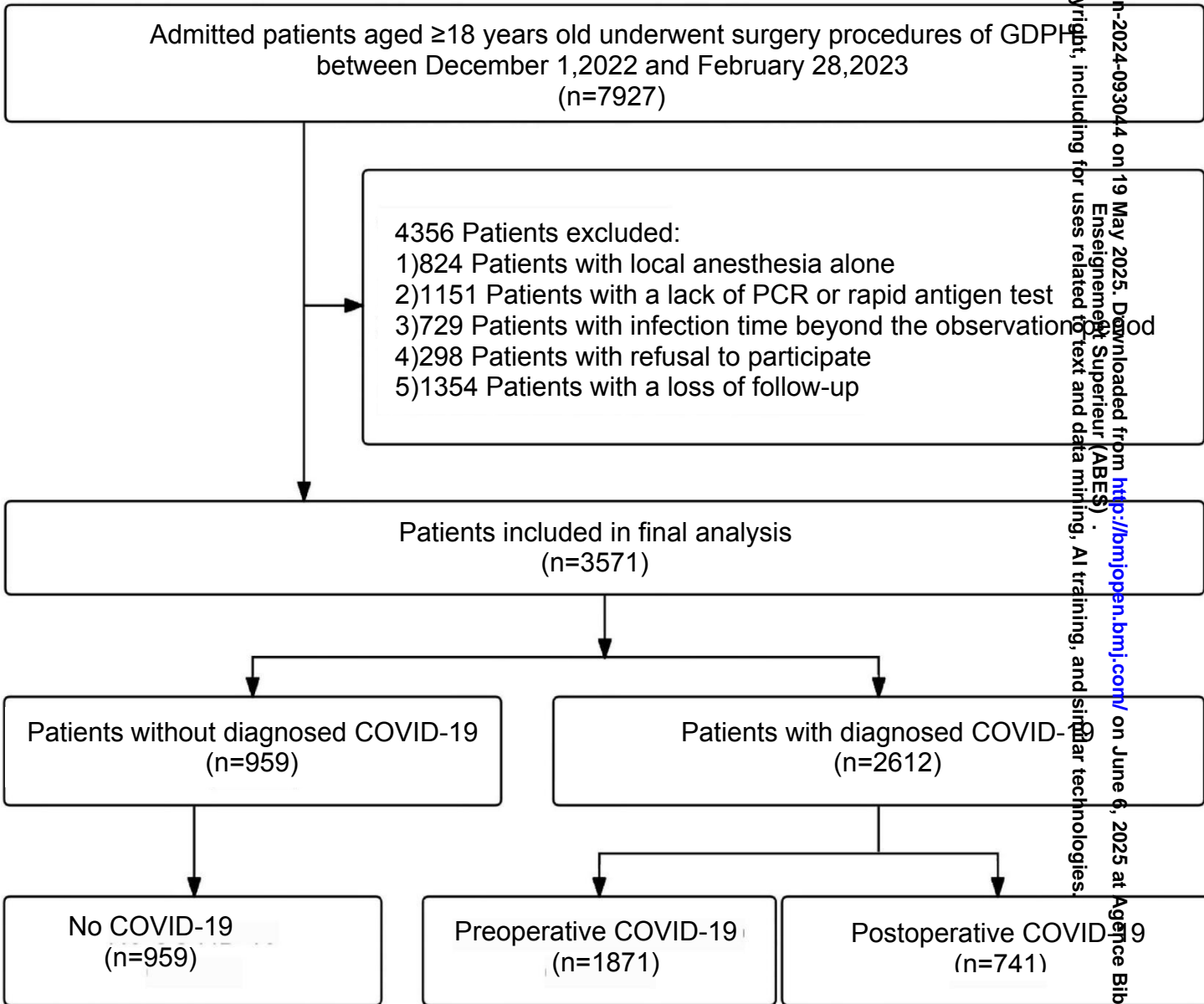
Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

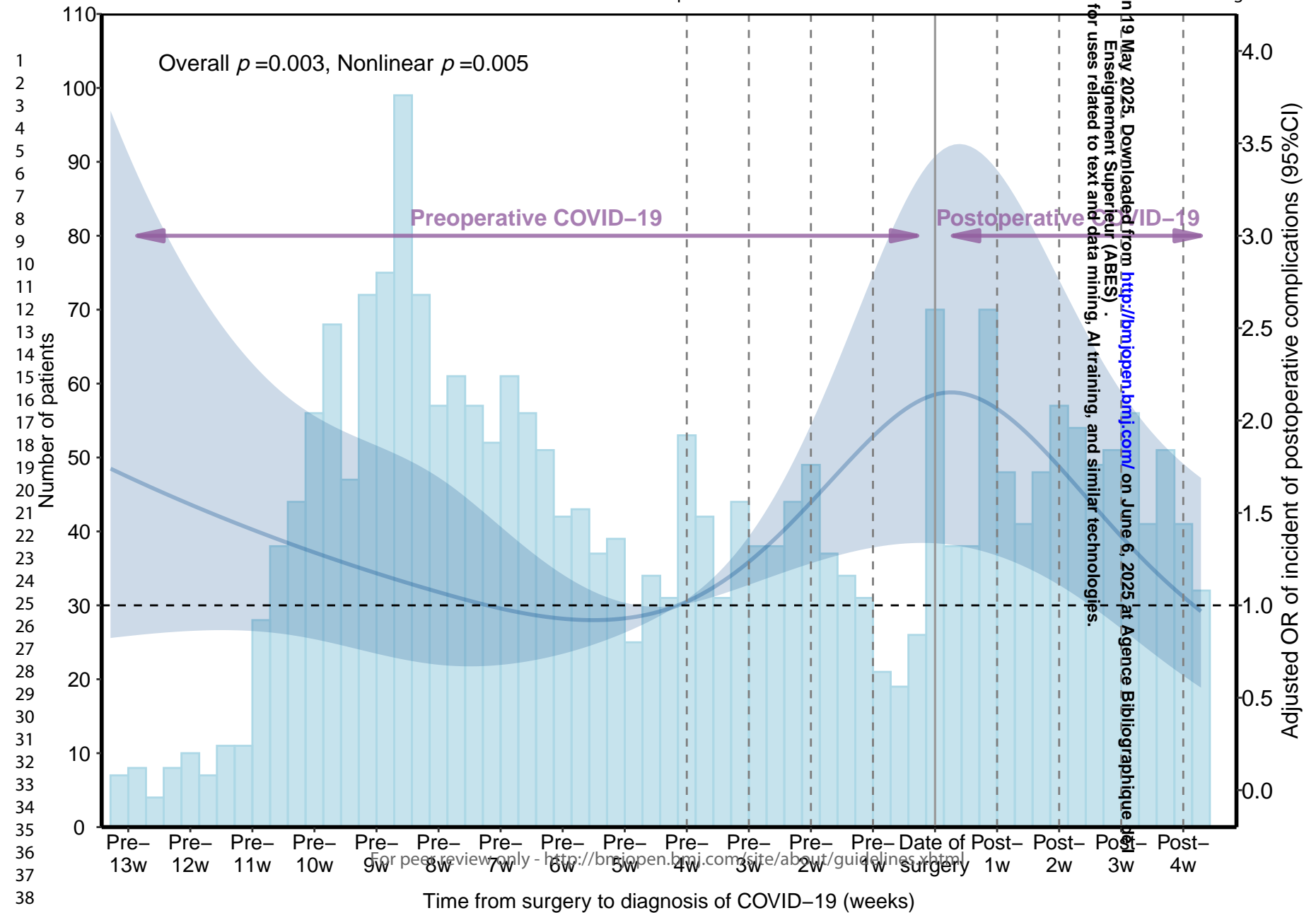
Table 4. Stratification analysis of association between postoperative COVID-19 and risk of postoperative complications

Subgroup	No COVID-19	Post-1w	Post-2w	Post-3w	Post-4w or more
Age					
<50 (n=688)	Ref.	0.38 (0.10, 1.48)	1.58 (0.49, 5.10)	1.34 (0.45, 4.15)	0.41 (0.12, 1.42)
≥50 (n=1012)	Ref.	3.80 (2.13, 6.77)	2.01 (1.02, 3.95)	2.45 (1.05, 4.81)	1.74 (0.94, 3.23)
Smoking					
No (n=1469)	Ref.	2.35 (1.34, 4.11)	1.73 (0.92, 3.24)	1.82 (0.66, 3.47)	0.79 (0.41, 1.51)
Yes (n=231)	Ref.	3.69 (0.86, 15.81)	5.05 (0.99, 25.61)	6.33 (1.02, 28.59)	7.35 (1.84, 29.29)
COVID-19 vaccination status					
No (n=137)	Ref.	6.64 (0.78, 56.58)	2.64 (0.36, 19.27)	3.64 (0.29, 45.31)	0.54 (0.06, 4.74)
Yes (n=1563)	Ref.	2.19 (1.26, 3.80)	1.86 (1.01, 3.44)	2.27 (1.15, 4.14)	1.20 (0.68, 2.14)
Comorbidity					
0 (n=1062)	Ref.	2.73 (1.04, 7.18)	2.13 (0.72, 6.32)	2.48 (0.40, 6.78)	0.51 (0.10, 2.46)
≥1 (n=638)	Ref.	2.42 (1.32, 4.44)	2.13 (1.07, 4.23)	1.95 (0.65, 4.01)	1.64 (0.90, 2.98)
Severity of COVID-19					
Mild (n= 1651)	Ref.	1.44 (0.77, 2.68)	1.26 (0.64, 2.45)	1.74 (0.44, 3.21)	1.11 (0.63, 1.98)
Moderate/severe (n= 1008)	Ref.	11.52 (4.36, 30.45)	14.96 (3.69, 60.60)	29.42 (4.41, 193.81)	3.02 (0.60, 15.29)

*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedics and Other surgeries).

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.





Supplementary material

Perioperative SARS-CoV-2 infection and postoperative complications: a retrospective cohort study

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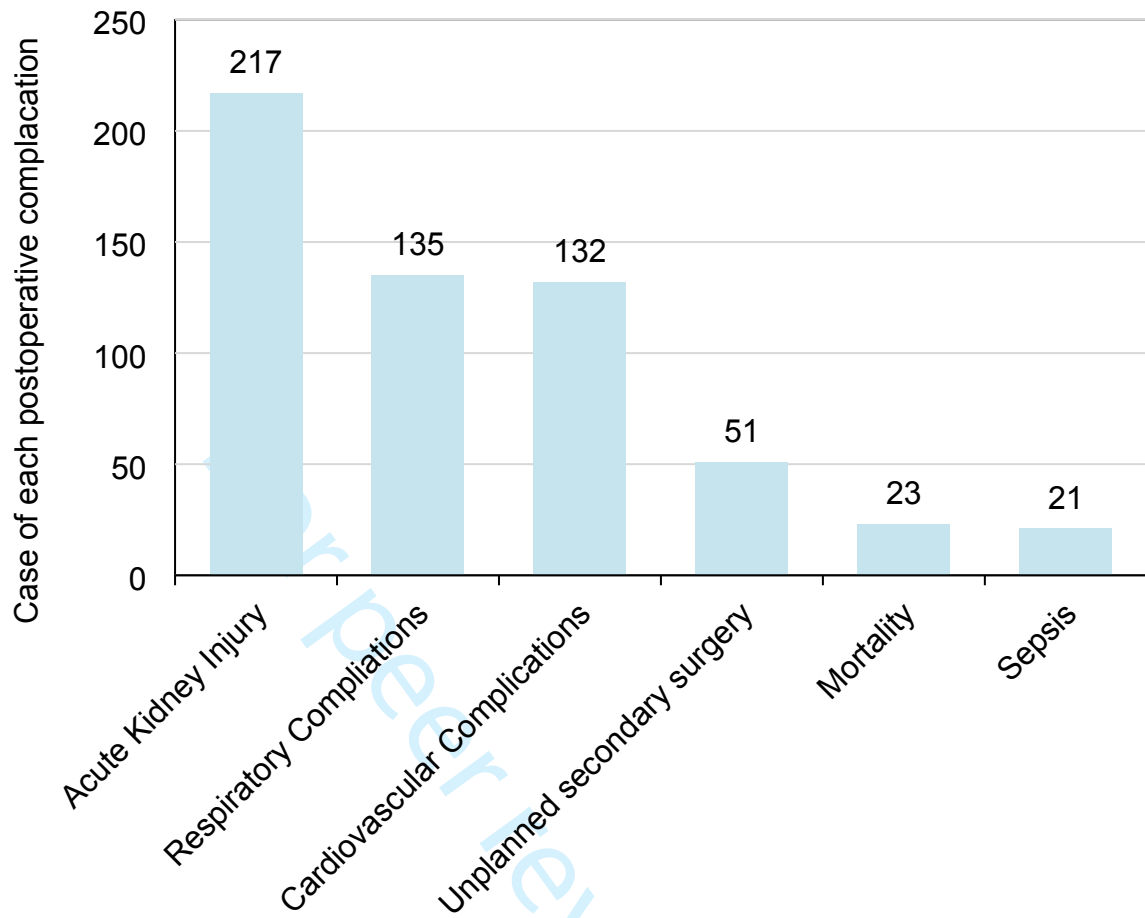
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Supplementary Figure 1. Distribution of composites of postoperative complications

Data were presented as the number of cases. It should be noted that multiple postoperative complications may occur in a single patient.

Supplementary Table 1. WHO clinical progression scale of COVID-19

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO ₂ /FiO ₂ ≥150 or SpO ₂ /FiO ₂ ≥200	7
	Mechanical ventilation pO ₂ /FiO ₂ <150 (SpO ₂ /FiO ₂ <200) or vasopressors	8
	Mechanical ventilation pO ₂ /FiO ₂ <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Supplementary Table 2. Postoperative complications: details and corresponding ICD-10 codes

Postoperative complications	Details	ICD-10 Codes
Respiratory complications	Pneumonia	J12, J13, J14, J15, J16, J17, J18, J80, J85.802, J96, I26
	Respiratory failure	
	Pulmonary embolism	
Cardiovascular complications	Deep vein thrombosis	I82, I74, R09.2, I21, I49, I50, I60, I61, I62, I63, I64
	Limb artery thrombosis	
	Splenic infarction	
	Hepatic infarction	
	Cerebral hemorrhage	
	Cerebral infarction	
	Hypoxic-ischemic encephalopathy	
	Arrhythmia	
	Myocardial infarction	
	Acute heart failure	
	Acute ischemic heart disease	
Acute kidney injury	Cardiac arrest	N17
	Cardiogenic shock	
Sepsis		A41
Unplanned secondary surgery		
Mortality		

Supplementary Table 3. Preoperative comorbidities: details and corresponding ICD-10 codes

Preoperative comorbidities	ICD-10 Codes
Diabetes	E10, E11, E13, E14
Chronic obstructive pulmonary disease	J44
Diffuse emphysema	J43
Bronchiectasis	J47
Asthma	J45
Pulmonary fibrosis	J84
Lung transplantation status	Z94
Respiratory failure	J96
Hypertension	I10, I15
Chronic heart failure	I50
Coronary artery disease	I25
Cardiomyopathy	I42
Ventricular aneurysm	I25
Pericardial disease	I30, I31
Cerebrovascular disease	I63, I65, I66, I67, I68, I69
Chronic kidney disease	N18

Supplementary Table 4. Definition of American Society of Anaesthesiologists (ASA) Physical Status Classification

ASA Classification*	Details
ASA 1	A normal healthy patient.
ASA 2	A patient with mild systemic disease.
ASA 3	A patient with a severe systemic disease that is not life-threatening.
ASA 4	A patient with a severe systemic disease that is a constant threat to life.
ASA 5	A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery.
ASA 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

*Statement on ASA Physical Status Classification System. December 13, 2020. <https://www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system> (accessed January 24, 2024).

Supplementary Table 5. Details of grade of surgery

Surgery	Minor	Major
Thoracic surgery	Endoscopic thoracic; Sympathectomy; Chest-wall procedures; Biopsy; Removal of the thoracic internal fixator.	Lung resection; Lung transplant; Esophagectomy; Mediastinal procedures; Chondrosternoplasty; Correction of pectus carinatum.
Head and neck surgery	Reduction of nasal bone; Electrocoagulation of epistaxis; Laryngoscopy; Biospy; Tracheotomy.	Neck dissection; Thyroidectomy; Parathyroidectomy and transplant; Sinusotomy; Cochlear implant reconstruction; Ossicular chain reconstruction; Stapes implantation; Laryngectomy and reconstruction; Myringoplasty; Parotidectomy; Tympanoplasty; Mastoidectomy; Adenoidectomy; Tonsillectomy; Palatopharyngoplasty; Branchial fistula resection; Deviated septum surgery; Septoplasty;

		Nasal polypectomy; Excision of turbinates.
Cardio-vascular surgery		Valve procedures; Coronary artery bypass graft; Coronary artery transplant; Artificial vessel replacement; Atrial tumor resection; Aortic aneurysm procedures; Left ventricular outflow tract dredging; Carotid endarterectomy; Auricular or/and ventricular septal defect repair.
Digestive surgery	Gastroscopy (diagnostic or biopsy); Stoma closure procedures; Appendicectomy; Biopsy; Anal fistula procedures; Procedure for prolapse and hemorrhoids.	Gastroscopy (therapy); Enterostomy; Gastrectomy; Small intestine resection; Hemicolectomy or colectomy; Cholecystectomy; Pancreaticoduodenectomy; Hepatectomy; Liver transplant; Biliary procedures; Oesophagectomy; Splenectomy; Radiofrequency ablation of liver or Pancreatic.
Breast surgery	Biopsy;	Mastectomy

	Removal of breast implants; Mammoplasty; Quadrantectomy of the breast.	
Gynaecology and obstetrics surgery	Hysteroscopy (diagnostic); Repair of obstetric lacerations; Colposcopic procedures.	Hysterectomy; Salpingo-oophorectomy; Hysteroscopy (therapeutic); Caesarean section.
Orthopaedics surgery	Amputation of toe or finger; Tendon procedures; Arthroscopy (diagnostic); Removal of fracture; fixation; Biopsy; Debridement.	Amputation of limb; Spinal procedures; Arthroscopy (therapeutic); Knee replacement; Hip replacement; Revision of hip or knee replacement; Shoulder replacement; Reduction of the fracture.
Other surgeries	Ureteroscopic procedures; Cystoscopic (diagnostic); Biopsy; Ureteric stent insertion; Orchiopexy; Resection of hydrocele of testis; Posthectomy; Scrotal procedures; Ureteral stenting; Excision of skin lesion; Great saphenous vein procedures;	Nephrectomy; Adrenalectomy; Prostatectomy; Partial penectomy; Pyeloureteroplasty; Ureterocystostomy; Nephrectomy; Cystectomy; Transurethral resection of bladder tumour; Kidney transplant; Cystoscopic (therapeutic);

	Hernia repair.	Procedures for kidney stones; Renal cyst procedures; Hypophysectomy; Aneurysm procedures; Spinal cord procedures; Intracranial procedure.
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Supplementary Table 6. Details of urgency of surgery

Category	Details
Elective surgery	whose indication and scheduling have been conjointly decided by the patient and the surgeon, then followed by a consultation with an anaesthesiologist occurring at least 48h prior to the date of surgery, and then definitively scheduled in the operating theatre programme.
Emergency surgery	unplanned urgent interventions performed in the 48 hours after the surgical indication has been set (“relative emergency”), or in the four hours after the surgical indication has been set “absolute emergency”).

Supplementary Table 7. Patient characteristics based on absence or presence of postoperative complications

	Overall (n=3571)	Absence of postoperative complications (n=3151)	Presence of postoperative complications (n=420)
Men, n (%)	1622 (45.42)	1401 (44.46)	221 (52.62)
Age, years, IQR	52.00 [40.00, 63.00]	51.00 [39.00, 61.00]	59.00 [50.00, 69.00]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.12 [20.93, 25.20]	23.21 [20.87, 25.04]
Smoking, n (%)	440 (12.32)	369 (11.71)	71 (16.90)
Diagnosis of COVID-19, n (%)			
No COVID-19	959 (26.86)	856 (27.17)	103 (24.52)
Preoperative COVID-19	1871 (52.39)	1657 (52.59)	214 (50.95)
Postoperative COVID-19	741 (20.75)	638 (20.25)	103 (24.52)
COVID-19 vaccination status, n (%)	3318 (92.92)	2943 (93.40)	375 (89.29)
Severity of COVID-19, n (%)			
Mild	2461 (94.22)	2200 (95.86)	261 (82.33)
Moderate/Severe	151 (5.78)	95 (4.14)	56 (17.67)

Number of comorbidities*, n (%)			
0	2323 (65.05)	2221 (70.49)	102 (24.29)
1	112 (3.14)	97 (3.08)	15 (3.57)
2	519 (14.53)	414 (13.14)	105 (25.00)
3	364 (10.19)	260 (8.25)	104 (24.76)
≥4	253 (7.08)	159 (5.05)	94 (22.38)
History of cancer, n (%)			
	1296 (36.29)	1200 (38.08)	96 (22.86)
ASA classification, n (%)			
Grade 1-2	3048 (85.35)	2843 (90.23)	205 (48.81)
Grade 3-5	523 (14.65)	308 (9.77)	215 (51.19)
Grade of surgery, n (%)			
Minor	1349 (37.78)	1250 (39.67)	99 (23.57)
Major	2222 (62.22)	1901 (60.33)	321 (76.43)
Urgent of surgery, n (%)			
Elective	3339 (93.50)	2979 (94.54)	360 (85.71)
Emergency	232 (6.50)	172 (5.46)	60 (14.29)

Duration of surgery, n (%)			
≤240 minutes	3060 (85.69)	2800 (88.86)	260 (61.90)
>240 minutes	511 (14.31)	351 (11.14)	160 (38.10)
General anesthesia, n (%)			
	3402 (95.27)	2998 (95.14)	404 (96.19)
Type of surgery, n (%)			
Thoracic	821 (22.99)	762 (24.18)	59 (14.05)
Head and Neck	518 (14.51)	496 (15.74)	22 (5.24)
Cardio-vascular	336 (9.41)	172 (5.46)	164 (39.05)
Digestive	444 (12.43)	385 (12.22)	59 (14.05)
Breast	371 (10.39)	366 (11.62)	5 (1.19)
Gynaecologic and Obstetrics	317 (8.88)	305 (9.68)	12 (2.86)
Orthopadic	276 (7.73)	256 (8.12)	20 (4.76)
Other surgeries‡	488 (13.67)	409 (12.98)	79 (18.81)

Continuous variables are described as median (Interquartile Range, IQR) and categorical variables are described as number (percent).

*Comorbidity included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, cardiomyopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification=American Society of Anaesthesiologists Physical Status Classification. COVID-19=Coronavirus disease 2019. BMI=body mass index.

Supplementary Table 8. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications in patients undergoing elective surgery

Cases/total		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	
Pre-1w	17/100 (17.00)	2.11 (1.19, 3.75)	0.011	2.22 (1.20, 4.12)	0.012	2.84 (1.48, 5.46)	0.002
Pre-2w	22/122 (18.03)	2.25 (1.34, 3.78)	0.002	2.67 (1.53, 4.69)	0.000	2.62 (1.43, 4.77)	0.002
Pre-3w	15/137 (10.95)	1.26 (0.70, 2.27)	0.43	1.28 (0.69, 2.37)	0.43	1.39 (0.73, 2.66)	0.32
Pre-4w or more	132/1382 (9.55)	1.06 (0.80, 1.42)	0.68	1.13 (0.84, 1.53)	0.41	1.23 (0.89, 1.69)	0.20
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	
Post-1w	24/157 (15.29)	1.90 (1.15, 3.12)	0.012	1.73 (1.00, 2.99)	0.04	1.95 (1.09, 3.50)	0.026

Post-2w	21/162 (12.96)	1.54 (0.92, 2.59)	0.10	1.65 (0.94, 2.92)	0.08	2.02 (1.11, 3.67)	0.021
Post-3w	21/170 (12.35)	1.63 (0.97, 2.74)	0.07	2.19 (1.24, 3.85)	0.00	2.51 (1.37, 4.59)	0.003
Post-4w or more	20/206 (9.71)	1.11 (0.66, 1.87)	0.69	1.19 (0.68, 2.09)		1.19 (0.65, 2.18)	0.57

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤240 minutes or >240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopadic, and Other surgeries).

Supplementary Table 9. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications excluding imputed data

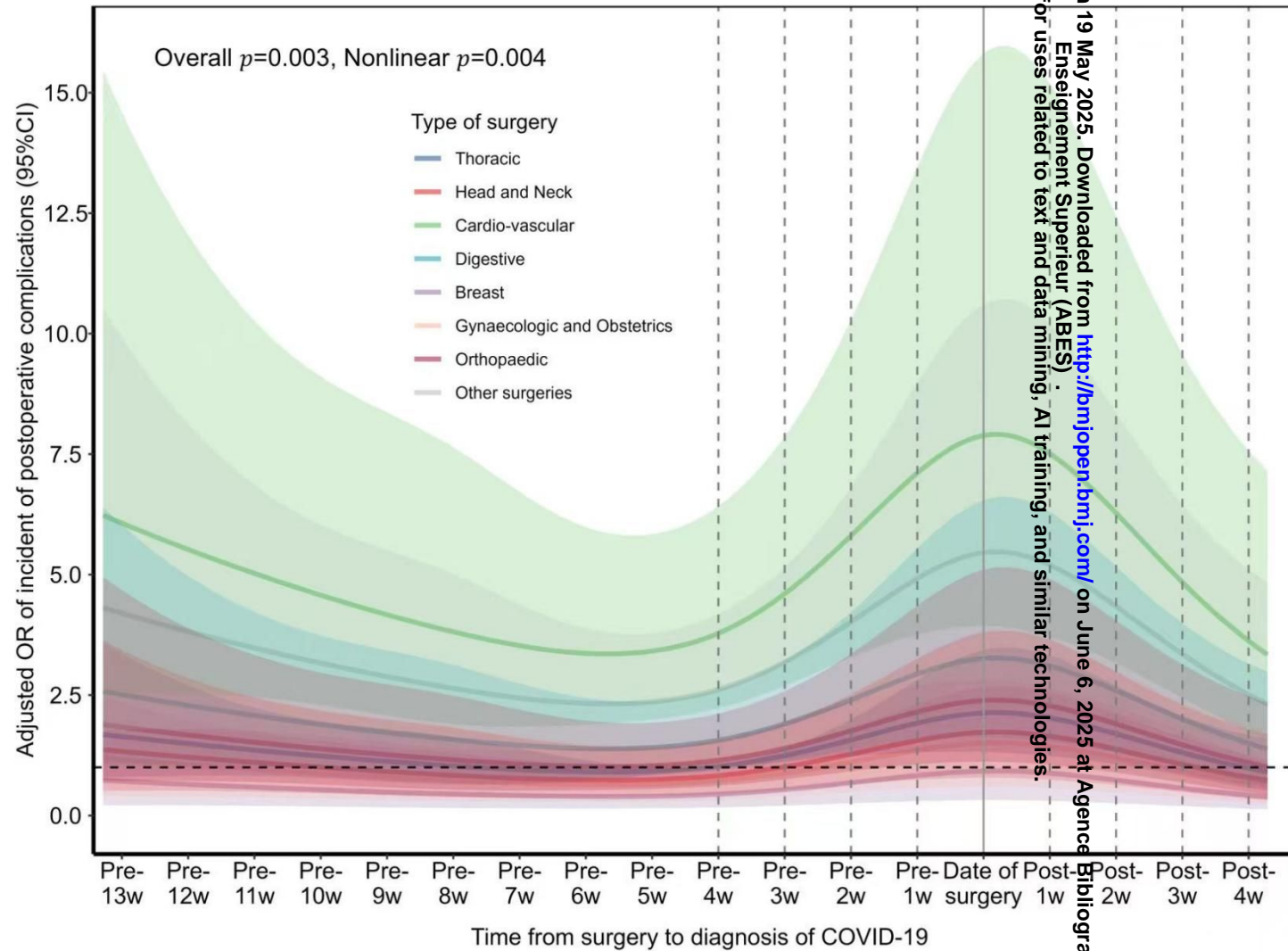
		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No-COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.	
Pre-1w	13/82 (15.85)	1.84 (0.97, 3.51)	0.06	2.15 (1.07, 4.31)	0.03	2.54 (1.22, 5.25)	0.012
Pre-2w	14/97 (14.43)	1.69 (0.91, 3.14)	0.10	2.08 (1.07, 4.03)	0.036	2.40 (1.20, 4.79)	0.013
Pre-3w	11/114 (9.65)	1.01 (0.52, 1.97)	0.98	1.03 (0.51, 2.07)	0.94	1.17 (0.57, 2.40)	0.67
Pre-4w or more	121/1226 (9.87)	1.05 (0.78, 1.42)	0.74	1.13 (0.82, 1.54)	0.46	1.25 (0.90, 1.75)	0.19
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.	
Post-1w	20/131 (15.27)	1.77 (1.04, 3.04)	0.037	1.84 (1.03, 3.30)	0.04	1.93 (1.04, 3.58)	0.036

Post-2w	16/142 (11.27)	1.26 (0.71, 2.25)	0.42	1.42 (0.76, 2.66)	1.58 (0.82, 3.05)	0.17
Post-3w	16/156 (10.26)	1.22 (0.69, 2.16)	0.50	1.69 (0.91, 3.12)	1.89 (0.99, 3.59)	0.05
Post-4w or more	21/189 (11.11)	1.25 (0.75, 2.10)	0.40	1.29 (0.74, 2.27)	1.17 (0.64, 2.15)	0.60

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥ 4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or > 240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopadic, and Other surgeries).



Supplementary Figure 2. Relationship between time from surgery to diagnosis of COVID-19 and adjusted OR for incident of postoperative complications with different surgical types.

Included 2612 patients with perioperative COVID-19. On the X-axis, Pre means patients with Preoperative COVID-19 and Post means patients with Postoperative COVID-19.

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Perioperative SARS-CoV-2 infection and postoperative complications: A single-center retrospective cohort study in China

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49 ABSTRACT

50 **Objective** To explore the association between perioperative SARS-CoV-2 infection
51 and the postoperative complications during the breakout of Omicron epidemic wave.

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53 **Design** Observational retrospective cohort study. Multivariable logistic regression
54 was performed to explore the association between the duration from surgery to
55 COVID-19 diagnosis and the likelihood of postoperative complications.

56
57 **Setting** A general hospital in China.

58
59 **Participants** 7927 patients aged 18 years and older who underwent surgical treatment
60 between December 1, 2022, and February 28, 2023.

61
62 **Primary outcome measures** The outcome was a composite of postoperative adverse
63 events occurred within the initial 30 postoperative days.

64
65 **Results** Of all patients, 420 (11.76%) experienced postoperative complications.
66 Compared to No COVID-19, Preoperative COVID-19 within one week (Pre-1w)
67 exhibited a high risk of postoperative complications (adjusted odds ratio (aOR), 2.67;
68 95% CI, 1.50-4.78), followed by patients with Pre-2w (aOR, 2.14; 95% CI,
69 1.20-3.80). For patients with Postoperative COVID-19 within one week (Post-1w),
70 the aOR was 2.48 (95% CI, 1.48-4.13), followed by patients with Post-2w (aOR, 1.95;

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95% CI, 1.10-3.45), and those with Post-3w (aOR, 2.25; 95% CI, 1.27-3.98). The risks of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection. Stratification analyses suggested that perioperative COVID-19 increased risk of postoperative complications in older patients, smokers, those with comorbidities, or experiencing moderate or severe COVID-19 symptoms.

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Conclusions Our findings reveal a significant time-dependent relationship between perioperative COVID-19 and postoperative complications, highlighting the importance of tailored preoperative risk evaluations, enhanced postoperative surveillance, and the implementation of effective postoperative COVID-19 prevention measures.

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Data availability statement

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Data will be available from the corresponding author upon reasonable request.

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Strengths and limitations of this study

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This study captured both preoperative and postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management.

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A broad range of surgical complications were considered, enabling physicians to gain a comprehensive understanding of the overall perioperative risk.

Both infected and uninfected patients have a COVID-19 PCR or antigen testing result, ensuring the reliability of the findings.

A single-center retrospective observational design of the study limited the generalizability of the results.

Keywords COVID-19; COVID-19 severity; Postoperative complications; Prognosis; Surgery.

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100 **Introduction**

101 Since the first reports of a novel severe acute respiratory syndrome (SARS)-like
102 coronavirus in December 2019 in Wuhan, China, the SARS-CoV-2 virus has evolved
103 five variants from Alpha to Omicron.¹⁻³ This had led to a rapid spread, both regionally
104 and globally, resulting in over 760 million cases and 6.9 million deaths worldwide.⁴
105 Perioperative COVID-19 has been demonstrated to have an adverse impact on
106 perioperative mortality and morbidity.⁵⁻⁹ Approximately 50% of
107 SARS-CoV-2-infected individuals experience postoperative pulmonary complications
108 and the overall 30-day mortality was up to 23.8%.⁹ To mitigate the postoperative
109 risks, a large number of surgeries had been postponed, while this may delay the
110 treatment of their primary diseases and decrease survival.¹⁰⁻¹³ Hence, there is a crucial
111 need for a comprehensive assessment of the health advantages associated with the
112 postponement of surgical management and the potential adverse repercussions of
113 delayed treatment.

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115 Emerging in November 2021, SARS-CoV-2 Omicron variant became the dominant
116 variant and exhibited increased transmissibility while inducing less severe disease
117 compared with previous variants.¹⁴⁻¹⁸ In addition, massive vaccination programs and
118 the use of antiviral treatments have changed the clinical characteristics of patients
119 with COVID-19.¹⁹⁻²³ The current evidence regarding postoperative outcomes in
120 patients undergoing surgery during the Omicron wave was inconsistent. Two studies
121 found an increased postoperative risk when surgeries were performed within one
122 week after contracting COVID-19.^{24,25} On the contrary, other studies found no
123 significant difference in postoperative outcomes comparing patients with

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124 SARS-CoV-2 Omicron infection with those who were not infected.^{26,27} Furthermore,
125 few studies focused on the risk of postoperative complications associated with
126 SARS-CoV-2 infection after surgery.

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128 Given the rapid global spread and significant impact of COVID-19, coupled with its
129 high mutation rate, current research findings on postoperative complications
130 associated with COVID-19 infection remain inconsistent. In this study, we aimed to
131 investigate the associations between pre- or post-operative SARS-CoV-2 infection
132 and postoperative outcomes, respectively. We further analysed the risk of
133 postoperative outcomes at various time intervals between SARS-CoV-2 infection and
134 the surgery date, providing updated evidence for guiding optimal surgery timing and
135 minimizing adverse postoperative outcomes

Methods

Study design and participants

The protocol of this study was approved by the Institutional Review Board of Guangdong Provincial People's Hospital (No. KY2023-031-02), and the study was registered on Chictr.org.cn (ChiCTR2300072473). Informed consent was obtained from all included patients in a text message or written way. The study adhered to the principles of the Declaration of Helsinki.

In this retrospective cohort study, we initially recruited 7927 patients who aged ≥ 18 years who underwent and requiring surgery at Guangdong Provincial People's Hospital in China between December 1, 2022, and February 28, 2023. Patients were excluded based on the following criteria: 1) those who underwent surgery with local anaesthesia alone (n=824); 2) those without reverse transcription-polymerase chain reaction (PCR) or rapid antigen test results for COVID-19 (n=1151); 3) those with infection time beyond the observation period (n=729); 4) those who refused to participate (n=298); and 5) those lost to follow-up (n=1354). After applying these exclusion criteria, a final cohort of 3571 individuals remained for analysis (**Figure 1**). Data on patient demographics, surgical procedures, SARS-CoV-2 infection status, and postoperative complications within the first 30 days after surgery were collected from medical records and telephone follow-ups.

Assessment of SARS-CoV-2 infection

Confirmation of SARS-CoV-2 infection was established based on a positive outcome

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from either PCR testing or rapid antigen tests. The duration from surgery to the diagnosis of COVID-19 was defined as the period between the day of surgery and the date of the initial positive test result. In instances where patients underwent multiple surgeries, the surgical date closest to the time of infection was utilized for analysis. Consequently, patients were categorized into three groups as follows: those infected before surgery (Preoperative COVID-19), those infected within 30 days after surgery (Postoperative COVID-19), and those with no positive SARS-CoV-2 test results during the study period (No COVID-19). The severity of COVID-19 was assessed and classified as either mild (WHO Severity 1-3) or moderate/severe (WHO Severity 4-9) based on the WHO Clinical Progression Scale (see the definition in **Supplementary Table 1**).²⁸

Definitions of postoperative complications

The outcome was defined as a composite of postoperative adverse events occurring within the initial 30 days following surgery (**Supplementary Table 2**). This encompassed acute kidney injury (AKI), postoperative respiratory complications (including pneumonia, respiratory failure, and pulmonary embolism), postoperative cardiovascular complications (including arrhythmia, myocardial infarction, acute heart failure, acute ischemic heart disease, cardiac arrest, cardiogenic shock, cerebral haemorrhage, cerebral infarction, hypoxic-ischemic encephalopathy, deep vein thrombosis, limb artery thrombosis, splenic infarction, and hepatic infarction), unplanned secondary surgery, sepsis, and mortality.

Covariates

The covariates encompassed age, sex, body mass index (BMI), smoking status, COVID-19 vaccination status, number of comorbidities (see the definition in **Supplementary Table 3**), history of cancer, American Society of Anesthesiologists (ASA) grade classification (see the definition in **Supplementary Table 4**), grade of surgery (see the definition in **Supplementary Table 5**), urgency of surgery (see the definition in **Supplementary Table 6**), duration of surgery, type of anaesthesia, and type of surgery. We gathered such data from a variety of sources including Electronic Health Records, laboratory data, anaesthesia information management systems, and questionnaires. The proportions of missing data for key variables such as height, weight, smoking status, and COVID-19 vaccination status were 2.30%, 0.25%, 11.12%, and 5.58% respectively. Median and mode imputation were employed to replace missing data for continuous and categorical variables, respectively.

Statistical analysis

Logistic regression was employed to estimate Odds ratios (OR) with 95% confidence intervals (CIs) to examine the associations between the duration from surgery to COVID-19 diagnosis and the risk of postoperative complications, with No COVID-19 group as the reference category. We initially incorporated a restricted cubic spline term for the duration from surgery to the diagnosis of SARS-CoV-2 infection, utilizing 3 knots at the 10th, 50th, and 90th centiles into the model to explore the nonlinear relationship between the timeframe and the risk of postoperative complications. We performed a subgroup analysis to explore whether trends in the risk of outcomes were consistent across surgical types. The assessment of nonlinearity was conducted using a likelihood ratio test to determine the associated P value.

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Following this, we categorized the time from COVID-19 diagnostic into discrete intervals, stratifying patients into four groups based on Preoperative and Postoperative COVID-19 statuses: within one week (Pre-1w and Post-1w), one to two weeks (Pre-2w and Post-2w), two to three weeks (Pre-3w and Post-3w), and beyond three weeks (Pre-4w or more and Post-4w or more).

The analysis was further divided to independently evaluate the associations between Preoperative COVID-19 diagnostic time and postoperative complications, as well as those between Postoperative COVID-19 diagnostic time and postoperative complications. Risks of postoperative complications were examined by stratifying the analysis based on age (younger elderly [<50 years] and older elderly [≥ 50 years]), smoking status (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), and severity of COVID-19 (mild or moderate/severe).

We conducted sensitivity analysis to ensure the reliability of our results. We utilized a subset of the sample with complete data to replicate our main findings, examining any potential impact of missing value of sociodemographic factors. Furthermore, in light of the varying health statuses of patients undergoing emergency surgery and the surgeon's accurate judgment of the patient's condition, we conducted sensitivity analyses specifically focusing on patients undergoing elective surgery.

All analyses were performed using R v4.3.0, with a two-tailed significance level of 0.05.

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231 **Patient and public involvement**

232 Patients and/or the public were not involved in the design, or conduct, or reporting or
233 dissemination plans of this research.

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235 **Role of the funding source**

236 The funders were not involved in study design, data collection, data analysis, data
237 interpretation, and writing of the report. JZ, FZ, LD, HS, and JL had full access to all
238 the data in the study. All authors accepted responsibility for the decision to submit for
239 publication.

240 Results

241 Characteristics of patients

242 During the study period, 3571 patients were included in the study analysis (**Table 1**).
243 The median age of patients was 52 years (Interquartile Range [IQR] 40-63 years),
244 45.42% were men, and 92.92% were vaccinated against COVID-19. Of all
245 individuals, 93.50% underwent elective surgery, 62.22% underwent major surgery,
246 and 85.69% had surgeries lasting no more than four hours. Patients were categorized
247 into three groups based on the timing of COVID-19 diagnosis relative to surgery: No
248 COVID-19 (n=959, 26.86%), Preoperative COVID-19 (n=1871, 52.39%), and
249 Postoperative COVID-19 (n=741, 20.75%). Among patients with COVID-19, the
250 majority experienced mild symptoms (94.22%), with only 5.45% and 6.61%
251 exhibiting moderate or severe symptoms in Preoperative and Postoperative
252 COVID-19 respectively. When compared with those with No COVID-19, patients
253 with both Preoperative and Postoperative COVID-19 had lower rates of smoking,
254 with 11.17% versus 14.29% for Preoperative COVID-19 and 12.69% versus 14.29%
255 for Postoperative COVID-19, respectively. Patients with No COVID-19 had a higher
256 ASA classification than those with Preoperative or Postoperative COVID-19. The
257 baseline characteristics of patients with and without postoperative complications were
258 presented in **Supplementary Table 7**.

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260 Time-dependent association between duration from surgery to the diagnosis of 261 COVID-19 and risk of postoperative complications

262 During the study period, 420 (11.76%) patients experienced postoperative
263 complications. A higher rate (13.90%) of postoperative complications was observed

in patients with Postoperative COVID-19 compared to those with Preoperative COVID-19 (11.44%). Among these postoperative complications, 217 (6.08%) cases were AKI, 135 (3.78%) were respiratory complications, 132 (3.70%) were cardiovascular complications, 51 (1.43%) were unplanned secondary surgeries, 23 (0.64%) resulted in mortality, and 21 cases (0.59%) were sepsis (**Supplementary Figure 1**).

We initially examined the nonlinear trend in the association between the duration from surgery to the diagnosis of COVID-19 and the risk of postoperative complications (**Figure 2**). Using the time interval between the surgery date and COVID-19 diagnosis as the axis of symmetry (dividing preoperative and postoperative by week), the risk curve exhibited a bell-shaped pattern, peaking approximately at the surgery date. The risk of postoperative complications was higher when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it was preoperative or postoperative COVID-19. The risk diminished gradually as the time interval between the surgery date and COVID-19 diagnosis increased (p for nonlinearity = 0.005). However, in cases of preoperative COVID-19, the risk did not decrease further beyond a four-week interval, whereas in cases of postoperative COVID-19, it gradually diminished until four weeks after surgery. Further analysis across surgical categories revealed that cardiovascular procedures carried the highest perioperative infection risk, whereas no statistically significant difference was observed among head and neck, gynecological and obstetric, and breast surgeries (**Supplementary Figure 2**).

288 Association between Preoperative COVID-19 and risk of postoperative 289 complications

290 The risk of postoperative complications gradually decreased with an increase in the
291 time interval between SARS-CoV-2 infection and surgery date (**Table 2**). Compared
292 to patients with No COVID-19, those with Pre-1w exhibited the highest risk of
293 postoperative complications (aOR 2.67 [95% CI 1.50-4.78], p=0.001), followed by
294 patients with Pre-2w (aOR 2.14 [95% CI 1.20-3.80], p=0.010). Compared to patients
295 with No COVID-19, there was no statistically significant increase in risk observed in
296 patients with Pre-3w (aOR 1.27 [95% CI 0.67-2.39], p=0.46) or those with Pre-4w or
297 more (aOR 1.24 [95% CI 0.92-1.68], p=0.15).

298

299 Stratification analysis by the severity of COVID-19 revealed a higher risk of
300 postoperative complications in patients with moderate or severe symptoms compared
301 to those with mild symptoms (aOR 5.92 vs. 2.04 with Pre-1w, 5.12 vs. 1.88 with
302 Pre-2w) (**Table 3**). Stratification analysis by smoking status revealed an exceptionally
303 high risk in smoking patients with Pre-1w (aOR 17.22 [95% CI 3.87-76.70],
304 p<0.001), while the aOR for non-smoking patients with Pre-1w was 2.06 (95% CI
305 1.07-3.97, p=0.032). In summary, patients aged ≥ 50 years, smokers, those with
306 comorbidities, or those with moderate or severe symptoms were associated with a
307 higher risk of postoperative complications in cases of preoperative COVID-19 within
308 two weeks.

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310 Association between Postoperative COVID-19 and risk of postoperative 311 complications

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The risk of postoperative complications decreased roughly with the increase of the time interval between the surgery date and SARS-CoV-2 infection (**Figure 2**). Compared to patients with No COVID-19, those with Post-1w exhibited the highest risk of postoperative complications (aOR 2.48 [95% CI 1.48-4.13], p=0.001), followed by patients with Post-3w (aOR 2.25 [95% CI 1.27-3.98], p=0.006), and those with Post-2w (aOR 1.95 [95% CI 1.10-3.45], p=0.023) (**Table 2**). Compared to patients with No COVID-19, the increased risk was not statistically significant in patients with Post-4w or more (aOR 1.24 [95% CI 0.72-2.14], p=0.44).

Stratification analysis by the severity of COVID-19 revealed extremely high risks of postoperative complications in patients with Post-1w with moderate or severe symptoms (aOR 11.52 [95% CI 4.36-30.45], p<0.001), as well as in patients with Post-2w (aOR 14.96 [95% CI 3.69-60.60], p<0.001), and in patients with Post-3w (aOR 29.42 [95% CI 4.47-193.81], p<0.001) (**Table 4**). Conversely, no significant risk was observed among patients with mild symptoms. Stratification analysis by smoking status revealed consistently high risks in smoking patients, with aOR being 3.69 in Post-1w, 5.05 in Post-2w, 6.33 in Post-3w, and 7.35 in Post-4w or more, whereas the aOR for non-smoking patients with Post-1w was 2.35 (95% CI 1.34-4.11], p=0.003). In summary, patients aged ≥50 years, smokers, those without COVID-19 vaccination, with comorbidities, or with moderate or severe symptoms were associated with a higher risk of postoperative complications in cases of postoperative COVID-19 occurring within three weeks.

Considering potential health status differences between patients who underwent

emergency and elective surgery, a sensitivity analysis was conducted solely on patients who underwent elective surgery, and the findings remained consistent with the main results (**Supplementary Table 8**). Additionally, to investigate the potential impact of missing value of sociodemographic factors, a sensitivity analysis was carried out on a subset of the sample without imputed data, revealing similar findings and trends to the main results (**Supplementary Table 9**).

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Discussion

Our study underscored the importance of timing in the association between perioperative COVID-19 and the risk of postoperative complications. The risk significantly escalated when SARS-CoV-2 infection occurred closer to the surgery date, regardless of whether it's preoperative or postoperative. Besides, perioperative COVID-19 increased the risk of postoperative complications in specific subgroups, including older patients, smokers, those with comorbidities, or those experiencing moderate or severe COVID-19 symptoms.

While there are existing recommendations regarding surgical decision-making following SARS-CoV-2 infection, a consensus has not yet been achieved in this regard. Study from the COVIDSurg and GlobalSurg Collaborative reported a significant increase in mortality when surgery was performed within seven weeks after COVID-19 diagnosis during the pre-vaccine phase.²⁹ Additionally, the Covid-19 Research Database found that surgery performed 4 to 8 weeks after confirmed SARS-CoV-2 infection continues to carry an elevated risk of developing postoperative pneumonia.³⁰ However, emerging studies presented differing perspectives. A study conducted across 37 American centres revealed that the time span from a positive test to the actual surgery significantly impacted both mortality and pulmonary risk, with the risk subsiding after two weeks.⁷ Conversely, research from 41 French centres found no significant association between surgery within three weeks of COVID-19 diagnosis and postoperative respiratory comorbidities.²⁷ Our

research findings revealed a heightened risk of composite postoperative complications, encompassing respiratory, cardiovascular, and other complications, when surgery was conducted within two weeks of a preoperative COVID-19 diagnosis. Therefore, conducting preoperative individualized risk assessments is imperative, and scheduling elective surgeries within two weeks after a SARS-CoV-2 diagnosis should be avoided. Our findings lend support to global endeavours aimed at updating restrictions on the timing of scheduled surgeries.

Furthermore, the risks of postoperative complications after SARS-CoV-2 infection varied across distinct subgroups. Our study revealed that older patients, smokers, and those with comorbidities faced an increased risk of adverse postoperative outcomes following SARS-CoV-2 infection. In a cohort of 3027 COVID-19-positive individuals, several risk factors were identified for mortality, including increased age, current smoking, presence of comorbidity, and undergoing emergency surgery.³¹ However, this study only considered patients with perioperative COVID-19 and did not compare them to those without infection. Moreover, our study also revealed that individuals with moderate or severe symptoms faced a markedly elevated risk of postoperative complications up to two weeks preceding their surgery, whereas those with mild symptoms exhibited a modest increase in complications. A study from the National COVID Cohort Collaborative (N3C) found that the impact of COVID-19 on postoperative outcomes is dependent on severity of illness, with only moderate and severe disease leading to higher risk of adverse outcomes.³² Another study from N3C found that postoperative cardiovascular risk remained high even 8 weeks after infection with moderate or severe SARS-CoV-2, but did not increase among those

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388 undergoing surgery within 4 weeks following mild infection.³³ These studies failed to
389 find an association between postoperative complications and mild COVID-19.
390 Overall, it is essential for patients to undergo thorough evaluation before surgery, with
391 a specific focus on assessing individual risk factors, to determine the optimal timing
392 for surgical interventions.

393

394 There is limited research available on the risk of postoperative complications in
395 patients who contract SARS-CoV-2 after surgery, with most prior studies focusing on
396 series of Total Joint Arthroplasty (TJA) patients and overlooking the impact of other
397 surgical procedures.^{34,35} Another study of only 22 patients with COVID-19 occurring
398 in the recovery period after open-heart surgery showed a higher pneumonia and
399 mortality rates in unvaccinated patients.³⁶ Our study revealed that individuals who
400 tested positive for SARS-CoV-2 up to three weeks after surgery were at a higher risk
401 of complications compared to those without the infection. Hence, robust postoperative
402 management strategies to mitigate SARS-CoV-2 transmission risk are vital, with
403 protective measures recommended for at least three weeks post-surgery. Our study
404 highlighted the significance of monitoring a patient's SARS-CoV-2 infection status
405 not only before but also after surgery.

406

407 The stratified analysis of patients with postoperative COVID-19 revealed that
408 unvaccinated individuals, who were older, smokers, or had comorbidities, faced a
409 higher risk of complications. Furthermore, patients with moderate or severe symptoms
410 of COVID-19 posed a significantly heightened risk of postoperative complications.
411 Cardiovascular procedures demonstrated the highest perioperative infection risk

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among surgical categories. Previous studies have shown that vaccination is effective in reducing the risk of severe illness, hospitalization, and death from COVID-19.^{37,38} Recent work by the COVIDSurg Collaborative and GlobalSurg Collaborative reported that preoperative vaccination could prevent nearly 60,000 deaths per year on average among patients requiring elective surgery.³⁹ However, these studies did not account for postoperative SARS-CoV-2 infections. Our findings underscore the importance of reinforcing postoperative protective strategies for these vulnerable patients.

This study had several strengths. Firstly, unlike previous research, our study not only focused on preoperative SARS-CoV-2 infections but also examined postoperative SARS-CoV-2 infections, providing recommendations for optimizing surgical timing and improving postoperative management. Secondly, we investigated the interaction between various risk factors to gain further insight into the factors influencing postoperative complications. Thirdly, we considered a broad range of surgical complications, including respiratory and cardiovascular morbidity, acute kidney injury, unplanned secondary surgery, sepsis, and mortality, thereby enabling physicians to gain a comprehensive understanding of the overall perioperative risk. Fourthly, patients were diagnosed with COVID-19 through PCR or antigen testing. Even uninfected patients were confirmed to have negative results, ensuring the reliability of the findings.

This study also had some limitations. Firstly, the sample size was limited. Conducting further research with a larger sample size would provide a more comprehensive

understanding of the interaction among various influencing factors. Secondly, the retrospective observational nature of the study made it challenging to completely rule out the influence of unmeasured residual confounding factors, despite efforts to retrieve as many covariates as possible. Thirdly, the single-centre design of the study had limited the generalizability of the results and made it difficult to conduct a detailed subpopulation analysis. Forthly, patients with relative symptoms were more likely to be tested for COVID-19. We excluded patients who did not undergo testing, which may explain the particularly high proportion of COVID-19 positive patients in the population. Despite the mentioned limitations, our study provided original and reliable evidence to support the relaxation of restrictions on the timing of scheduled surgery, as well as the importance of emphasizing postoperative management to prevent postoperative infection.

In summary, our study has uncovered a critical time-dependent relationship between perioperative COVID-19 infection and the likelihood of postoperative complications, revealing an increased risk when the SARS-CoV-2 infection was closer to the date of surgery. Additionally, advanced age, the existence of comorbid conditions, absence of COVID-19 vaccination, and symptom severity significantly influenced the risk of postoperative complications. Our findings not only contribute to the development of precise individual preoperative risk assessments, but also offer evidence-based guidelines for postoperative care.

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Declaration of interests

The authors have no conflicts of interest to declare.

Data sharing statement

Data will be available from the corresponding author upon reasonable request.

Funding

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Author Contributions

Jue Ma, HaiHua Shu, Yong Li, and Jie Li conceived and designed the study. HaiHua Shu and Jie Li administered the project and was responsible for data curation. Jia Zhan, Fei Zhong, LingYan Dai, and Jie Li analysed and interpreted the data. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, and XiRui Zhao wrote the first draft of manuscript. Jia Zhan, Fei Zhong, LingYan Dai, YiDan Zhang, XiRui Zhao, HaiHua Shu and Jie Li contributed to the interpretation of the results and revision of the manuscript. Jia Zhan, Jue Ma, YunFei Chai, Lu Chang, JunJiang Wang, Yong Tang, WenZhao Zhong, GuangYan Zhang, Le Li, Qiang Zhu, ZhiHao Chen, Xin Xia, LiShan Peng, Jing Wu, RuiYun Li, DanYang Li, Yan Zhu, Xin Zhou, YiChun Wu, RuiRong Chen got involved in data collection. All the authors approved the final version of the manuscript. HaiHua Shu is the guarantor; he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure 1. Flow chart of study design

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Figure 2. Relationship between time from surgery to diagnosis of COVID-19 and adjusted OR for incident of postoperative complications

Included 2612 patients with perioperative COVID-19. On the X-axis, Pre means patients with Preoperative COVID-19 and Post means patients with Postoperative COVID-19.

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Table 1. Characteristics of patients based on the time of diagnosis of COVID-19 relative to surgery

	Overall (n=3571)	No COVID-19 (n=959)	Preoperative COVID-19 (n=1871)	Postoperative COVID-19 (n=741)
Men, n (%)	1622 (45.42)	432 (45.05)	859 (45.91)	331 (44.67)
Age, years, IQR	52 [40, 63]	55 [44, 65]	50 [38, 61]	51 [39, 61]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.05 [20.70, 24.97]	23.15 [20.95, 25.39]	23.21 [21.02, 25.15]
Smoking, n (%)	440 (12.32)	137 (14.29)	209 (11.17)	94 (12.69)
COVID-19 vaccination status, n (%)	3318 (92.92)	854 (89.05)	1755 (93.80)	709 (95.68)
Severity of COVID-19 [#] , n (%)				
Mild	2461 (94.22)	NA	1769 (94.55)	692 (93.39)
Moderate/Severe	151 (5.78)	NA	102 (5.45)	49 (6.61)
Number of comorbidities*, n (%)				
0	2323 (65.05)	564 (58.81)	1261 (67.40)	498 (67.21)
1	112 (3.14)	36 (3.75)	53 (2.83)	23 (3.10)
2	519 (14.53)	171 (17.83)	260 (13.90)	88 (11.88)
3	364 (10.19)	111 (11.57)	174 (9.30)	79 (10.66)
≥4	253 (7.08)	77 (8.03)	123 (6.57)	53 (7.15)
History of cancer, n (%)	1296 (36.29)	370 (38.58)	642 (34.31)	284 (38.33)
ASA classification, n (%)				
Grade 1-2	3048 (85.35)	792 (82.59)	1615 (86.32)	641 (86.50)
Grade 3-5	523 (14.65)	167 (17.41)	256 (13.68)	100 (13.50)
Grade of surgery, n (%)				
Minor	1349 (37.78)	337 (35.14)	743 (39.71)	269 (36.30)
Major	2222 (62.22)	622 (64.86)	1128 (60.29)	472 (63.70)
Urgent of surgery, n (%)				

Elective	3339 (93.50)	903 (94.16)	1741 (93.05)	695 (93.79)
Emergency	232 (6.50)	56 (5.84)	130 (6.95)	46 (6.21)
Duration of surgery, n (%)				
≤240 minutes	3060 (85.69)	811 (84.57)	1612 (86.16)	637 (85.96)
>240 minutes	511 (14.31)	148 (15.43)	259 (13.84)	104 (14.04)
General anaesthesia, n (%)	3402 (95.27)	929 (96.87)	1765 (94.33)	708 (95.55)
Type of surgery, n (%)				
Thoracic	821 (22.99)	179 (18.67)	454 (24.27)	188 (25.37)
Head and Neck	518 (14.51)	154 (16.06)	263 (14.06)	101 (13.63)
Cardio-vascular	336 (9.41)	103 (10.74)	154 (8.23)	79 (10.66)
Digestive	444 (12.43)	160 (16.68)	208 (11.12)	76 (10.26)
Breast	371 (10.39)	84 (8.76)	190 (10.15)	97 (13.09)
Gynaecologic and Obstetrics	317 (8.88)	63 (6.57)	193 (10.32)	61 (8.23)
Orthopaedic	276 (7.73)	78 (8.13)	134 (7.16)	64 (8.64)
Other surgeries [‡]	488 (13.67)	138 (14.39)	275 (14.70)	75 (10.12)
Postoperative complications, n (%)	420 (11.76)	103 (10.74)	214 (11.44)	103 (13.90)

Continuous variables are described as median (Interquartile Range, IQR) and categorical variables are described as number (percent).

#Due to 959 of the patients was NO COVID-19, the total of Severity of COVID-19 may not sum up to the overall study population size.

*Comorbidity included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, cardiomyopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡ Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification=American Society of Anesthesiologists Physical Status Classification.
COVID-19=Coronavirus disease 2019. BMI=body mass index.

Table 2. Association between preoperative and postoperative COVID-19 and risk of postoperative complications

Cases/total (%)		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Pre-1w	24/126 (19.05)	2.21 (1.34, 3.64)	0.002	2.42 (1.41, 4.15)	0.001	2.67 (1.50, 4.78)	0.001
Pre-2w	24/135 (17.78)	2.03 (1.23, 3.33)	0.005	2.26 (1.32, 3.87)	0.003	2.14 (1.20, 3.80)	0.010
Pre-3w	15/143 (10.49)	1.09 (0.61, 1.96)	0.76	1.14 (0.62, 2.09)	0.68	1.27 (0.67, 2.39)	0.46
Pre-4w or more	151/1467 (10.29)	1.06 (0.81, 1.38)	0.69	1.15 (0.86, 1.53)	0.34	1.24 (0.92, 1.68)	0.15
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	103/959 (10.74)	Ref.		Ref.		Ref.	
Post-1w	33/172 (19.19)	2.22 (1.43, 3.47)	<0.001	2.29 (1.41, 3.72)	0.001	2.48 (1.48, 4.13)	0.001
Post-2w	22/168 (13.10)	1.42 (0.86, 2.34)	0.17	1.61 (0.93, 2.78)	0.09	1.95 (1.10, 3.45)	0.023
Post-3w	22/180 (12.22)	1.44 (0.87, 2.39)	0.15	1.93 (1.12, 3.32)	0.018	2.25 (1.27, 3.98)	0.006

Post-4w or more	26/221 (11.76)	1.24 (0.77, 1.97)	0.38	1.34 (0.81, 2.23)	0.25	1.24 (0.72, 2.14)	0.44
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Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, ≥ 4) and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedic, and Other surgeries).

Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.

Table 3. Stratification analysis of association between preoperative COVID-19 and risk of postoperative complications

Subgroup	No COVID-19	Pre-1w	Pre-2w	Pre-3w	Pre-4w or more
Age					
<50 (n=1247)	Ref.	1.78 (0.59, 5.32)	0.99 (0.31, 3.23)	0.90 (0.27, 2.73)	0.82 (0.46, 1.47)
≥50 (n=1583)	Ref.	3.34 (1.67, 6.70)	2.65 (1.36, 5.16)	1.46 (0.67, 3.18)	1.43 (1.00, 2.03)
Smoking					
No (n=2484)	Ref.	2.06 (1.07, 3.97)	2.31 (1.25, 4.25)	1.20 (0.50, 2.42)	1.12 (0.81, 1.55)
Yes (n=346)	Ref.	17.22 (3.87, 76.70)	1.65 (0.27, 10.03)	2.52 (0.61, 12.53)	2.54 (1.05, 6.15)
COVID-19 vaccination status					
No (n=221)	Ref.	2.97 (0.20, 44.55)	1.66 (0.08, 33.08)	1.94 (0.20, 18.96)	1.31 (0.51, 3.38)
Yes (n=2609)	Ref.	2.68 (1.47, 4.88)	2.14 (1.18, 3.89)	1.21 (0.62, 2.38)	1.24 (0.90, 1.71)
Comorbidity					
0 (n=1825)	Ref.	1.48 (0.46, 4.71)	2.60 (1.10, 6.12)	1.72 (0.60, 4.90)	1.47 (0.83, 2.59)
≥1 (n=1005)	Ref.	3.66 (1.80, 7.42)	2.03 (0.92, 4.47)	1.06 (0.48, 2.36)	1.17 (0.82, 1.66)
Severity of COVID-19					
Mild (n= 2728)	Ref.	2.04 (1.02, 4.07)	1.88 (1.01, 3.50)	1.18 (0.49, 2.34)	1.29 (0.95, 1.77)
Moderate/severe (n= 1061)	Ref.	5.92 (2.04, 17.18)	5.12 (1.11, 23.67)	2.40 (0.47, 12.09)	0.68 (0.29, 1.61)

*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedics and Other surgeries).

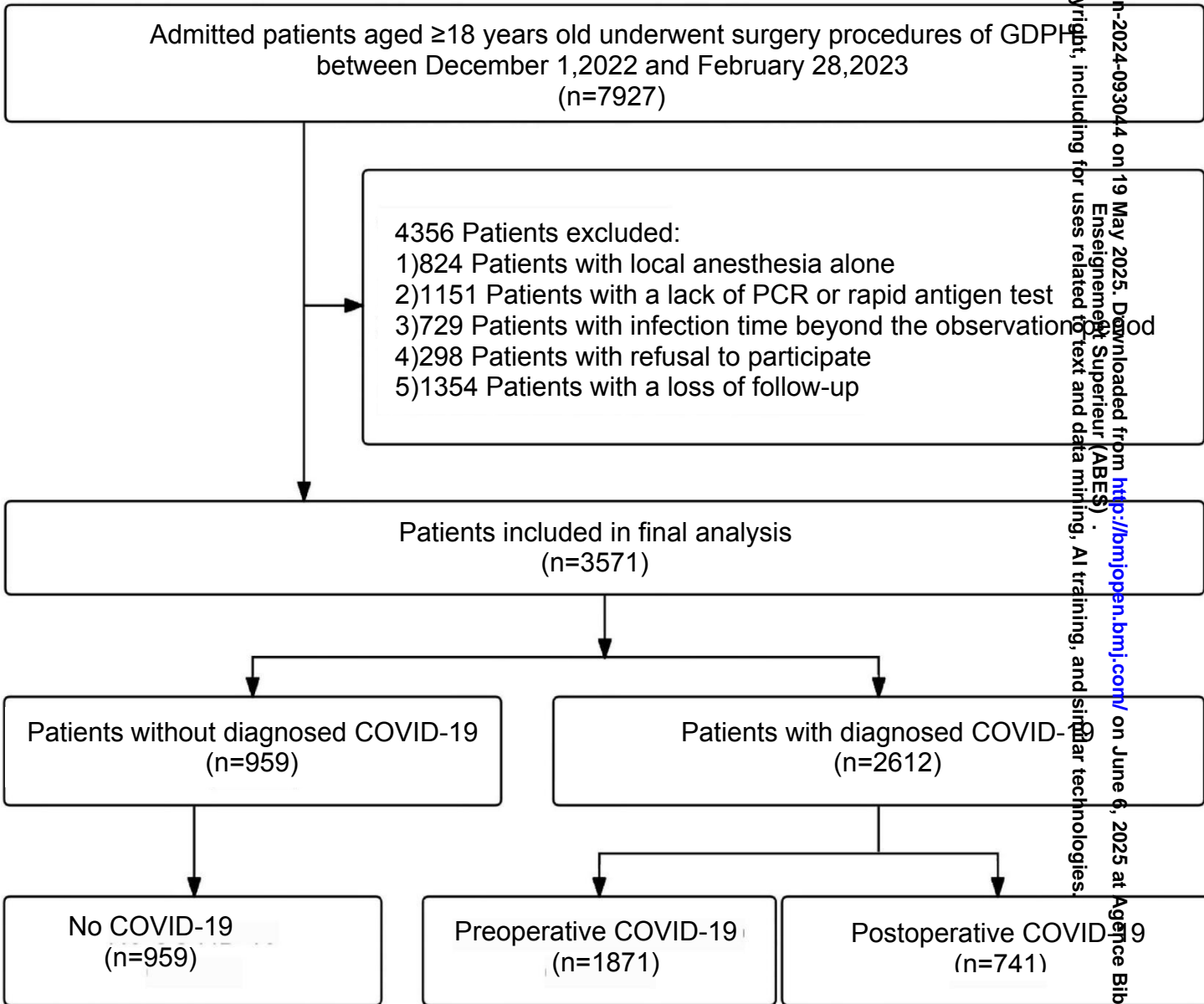
Pre-1w = Preoperative COVID-19 within one week; Pre-2w = Preoperative COVID-19 within one to two weeks; Pre-3w = Preoperative COVID-19 within two to three weeks; Pre-4w or more = Preoperative COVID-19 beyond three weeks.

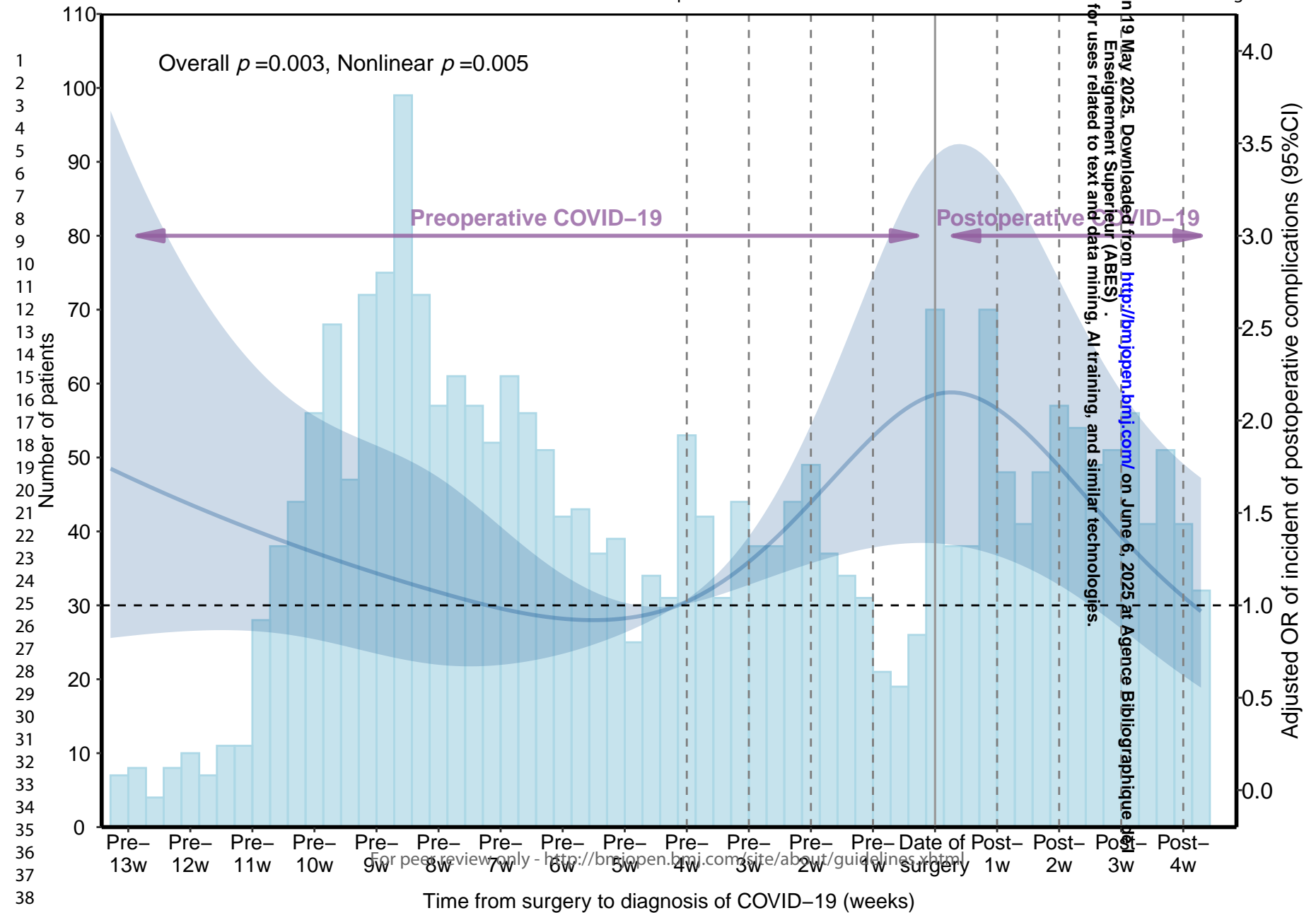
Table 4. Stratification analysis of association between postoperative COVID-19 and risk of postoperative complications

Subgroup	No COVID-19	Post-1w	Post-2w	Post-3w	Post-4w or more
Age					
<50 (n=688)	Ref.	0.38 (0.10, 1.48)	1.58 (0.49, 5.10)	1.34 (0.45, 4.15)	0.41 (0.12, 1.42)
≥50 (n=1012)	Ref.	3.80 (2.13, 6.77)	2.01 (1.02, 3.95)	2.45 (1.15, 4.81)	1.74 (0.94, 3.23)
Smoking					
No (n=1469)	Ref.	2.35 (1.34, 4.11)	1.73 (0.92, 3.24)	1.82 (0.66, 3.47)	0.79 (0.41, 1.51)
Yes (n=231)	Ref.	3.69 (0.86, 15.81)	5.05 (0.99, 25.61)	6.33 (1.22, 28.59)	7.35 (1.84, 29.29)
COVID-19 vaccination status					
No (n=137)	Ref.	6.64 (0.78, 56.58)	2.64 (0.36, 19.27)	3.64 (0.29, 45.31)	0.54 (0.06, 4.74)
Yes (n=1563)	Ref.	2.19 (1.26, 3.80)	1.86 (1.01, 3.44)	2.27 (1.15, 4.14)	1.20 (0.68, 2.14)
Comorbidity					
0 (n=1062)	Ref.	2.73 (1.04, 7.18)	2.13 (0.72, 6.32)	2.48 (0.40, 6.78)	0.51 (0.10, 2.46)
≥1 (n=638)	Ref.	2.42 (1.32, 4.44)	2.13 (1.07, 4.23)	1.95 (0.65, 4.01)	1.64 (0.90, 2.98)
Severity of COVID-19					
Mild (n= 1651)	Ref.	1.44 (0.77, 2.68)	1.26 (0.64, 2.45)	1.74 (0.44, 3.21)	1.11 (0.63, 1.98)
Moderate/severe (n= 1008)	Ref.	11.52 (4.36, 30.45)	14.96 (3.69, 60.60)	29.42 (4.41, 193.81)	3.02 (0.60, 15.29)

*Adjusted for age (continuous) and sex (men and women), BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), comorbidities (yes or no), history of cancer (yes or no), ASA classification (grade 1-2 and grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anaesthesia (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and Obstetrics, Orthopaedics and Other surgeries).

Post-1w = Postoperative COVID-19 within one week; Post-2w = Postoperative COVID-19 within one to two weeks; Post-3w = Postoperative COVID-19 within two to three weeks; Post-4w or more = Postoperative COVID-19 beyond three weeks.





Supplementary material

Perioperative SARS-CoV-2 infection and postoperative complications: a retrospective cohort study

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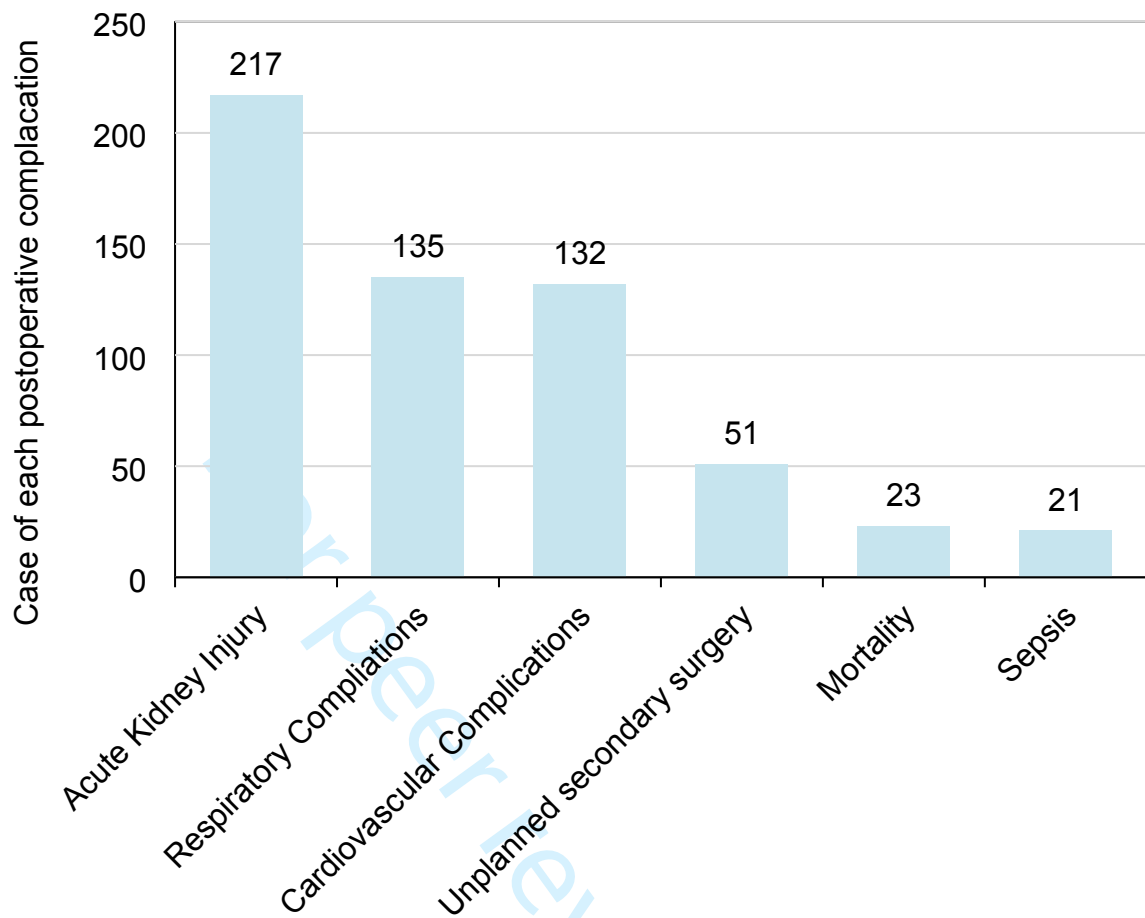
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Supplementary Figure 1. Distribution of composites of postoperative complications

Data were presented as the number of cases. It should be noted that multiple postoperative complications may occur in a single patient.

Supplementary Table 1. WHO clinical progression scale of COVID-19

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO ₂ /FiO ₂ ≥150 or SpO ₂ /FiO ₂ ≥200	7
	Mechanical ventilation pO ₂ /FIO ₂ <150 (SpO ₂ /FiO ₂ <200) or vasopressors	8
	Mechanical ventilation pO ₂ /FiO ₂ <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Supplementary Table 2. Postoperative complications: details and corresponding ICD-10 codes

Postoperative complications	Details	ICD-10 Codes
Respiratory complications	Pneumonia	J12, J13, J14, J15, J16, J17, J18, J80, J85.802, J96, I26
	Respiratory failure	
	Pulmonary embolism	
Cardiovascular complications	Deep vein thrombosis	I82, I74, R09.2, I21, I49, I50, I60, I61, I62, I63, I64
	Limb artery thrombosis	
	Splenic infarction	
	Hepatic infarction	
	Cerebral hemorrhage	
	Cerebral infarction	
	Hypoxic-ischemic encephalopathy	
	Arrhythmia	
	Myocardial infarction	
	Acute heart failure	
	Acute ischemic heart disease	
Acute kidney injury	Cardiac arrest	N17
	Cardiogenic shock	
Sepsis		A41
Unplanned secondary surgery		
Mortality		

Supplementary Table 3. Preoperative comorbidities: details and corresponding ICD-10 codes

Preoperative comorbidities	ICD-10 Codes
Diabetes	E10, E11, E13, E14
Chronic obstructive pulmonary disease	J44
Diffuse emphysema	J43
Bronchiectasis	J47
Asthma	J45
Pulmonary fibrosis	J84
Lung transplantation status	Z94
Respiratory failure	J96
Hypertension	I10, I15
Chronic heart failure	I50
Coronary artery disease	I25
Cardiomyopathy	I42
Ventricular aneurysm	I25
Pericardial disease	I30, I31
Cerebrovascular disease	I63, I65, I66, I67, I68, I69
Chronic kidney disease	N18

Supplementary Table 4. Definition of American Society of Anaesthesiologists (ASA) Physical Status Classification

ASA Classification*	Details
ASA 1	A normal healthy patient.
ASA 2	A patient with mild systemic disease.
ASA 3	A patient with a severe systemic disease that is not life-threatening.
ASA 4	A patient with a severe systemic disease that is a constant threat to life.
ASA 5	A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery.
ASA 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

*Statement on ASA Physical Status Classification System. December 13, 2020.

<https://www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system> (accessed January 24, 2024).

Supplementary Table 5. Details of grade of surgery

Surgery	Minor	Major
Thoracic surgery	Endoscopic thoracic; Sympathectomy; Chest-wall procedures; Biopsy; Removal of the thoracic internal fixator.	Lung resection; Lung transplant; Esophagectomy; Mediastinal procedures; Chondrosternoplasty; Correction of pectus carinatum.
Head and neck surgery	Reduction of nasal bone; Electrocoagulation of epistaxis; Laryngoscopy; Biopsy; Tracheotomy.	Neck dissection; Thyroidectomy; Parathyroidectomy and transplant; Sinusotomy; Cochlear implant reconstruction; Ossicular chain reconstruction; Stapes implantation; Laryngectomy and reconstruction; Myringoplasty; Parotidectomy; Tympanoplasty; Mastoidectomy; Adenoidectomy; Tonsillectomy; Palatopharyngoplasty; Branchial fistula resection;

		Deviated septum surgery; Septoplasty; Nasal polypectomy; Excision of turbinates.
Cardio-vascular surgery		Valve procedures; Coronary artery bypass graft; Coronary artery transplant; Artificial vessel replacement; Atrial tumor resection; Aortic aneurysm procedures; Left ventricular outflow tract dredging; Carotid endarterectomy; Auricular or/and ventricular septal defect repair.
Digestive surgery	Gastroscopy (diagnostic or biopsy); Stoma closure procedures; Appendicectomy; Biopsy; Anal fistula procedures; Procedure for prolapse and hemorrhoids.	Gastroscopy (therapy); Enterostomy; Gastrectomy; Small intestine resection; Hemicolectomy or colectomy; Cholecystectomy; Pancreaticoduodenectomy; Hepatectomy; Liver transplant; Biliary procedures; Oesophagectomy;

		Splenectomy; Radiofrequency ablation of liver or pancreatic.
Breast surgery	Biopsy; Removal of breast implants; Mammoplasty; Quadrantectomy of the breast.	Mastectomy
Gynaecology and obstetrics surgery	Hysteroscopy (diagnostic); Repair of obstetric lacerations; Colposcopic procedures.	Hysterectomy; Salpingo-oophorectomy; Hysteroscopy (therapeutic); Caesarean section.
Orthopaedics surgery	Amputation of toe or finger; Tendon procedures; Arthroscopy (diagnostic); Removal of fracture; fixation; Biopsy; Debridement.	Amputation of limb; Spinal procedures; Arthroscopy (therapeutic); Knee replacement; Hip replacement; Revision of hip or knee replacement; Shoulder replacement; Reduction of the fracture.
Other surgeries	Ureteroscopic procedures; Cystoscopy (diagnostic); Biopsy; Ureteric stent insertion; Orchiopexy; Resection of hydrocele of testis;	Nephrectomy; Adrenalectomy; Prostatectomy; Partial penectomy; Pyeloureteroplasty; Ureterocystostomy; Nephrectomy;

	Posthectomy; Scrotal procedures; Ureteral stenting; Excision of skin lesion; Great saphenous vein procedures; Hernia repair.	Cystectomy; Transurethral resection of bladder tumour; Kidney transplant; Cystoscopic (therapeutic); Procedures for kidney stones; Renal cyst procedures; Hypophysectomy; Aneurysm procedures; Spinal cord procedures; Intracranial procedure.
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Supplementary Table 6. Details of urgency of surgery

Category	Details
Elective surgery	whose indication and scheduling have been conjointly decided by the patient and the surgeon, then followed by a consultation with an anaesthesiologist occurring at least 48h prior to the date of surgery, and then definitively scheduled in the operating theatre programme.
Emergency surgery	unplanned urgent interventions performed in the 48 hours after the surgical indication has been set (“relative emergency”), or in the four hours after the surgical indication has been set “absolute emergency”).

Supplementary Table 7. Patient characteristics based on absence or presence of postoperative complications

	Overall (n=3571)	Absence of postoperative complications (n=3151)	Presence of postoperative complications (n=420)
Men, n (%)	1622 (45.42)	1401 (44.46)	221 (52.62)
Age, years, IQR	52.00 [40.00, 63.00]	51.00 [39.00, 61.00]	59.00 [50.00, 69.00]
BMI, kg/m ² , IQR	23.15 [20.93, 25.19]	23.12 [20.93, 25.20]	23.21 [20.87, 25.04]
Smoking, n (%)	440 (12.32)	369 (11.71)	71 (16.90)
Diagnosis of COVID-19, n (%)			
No COVID-19	959 (26.86)	856 (27.17)	103 (24.52)
Preoperative COVID-19	1871 (52.39)	1657 (52.59)	214 (50.95)
Postoperative COVID-19	741 (20.75)	638 (20.25)	103 (24.52)
COVID-19 vaccination status, n (%)	3318 (92.92)	2943 (93.40)	375 (89.29)
Severity of COVID-19, n (%)			
Mild	2461 (94.22)	2200 (95.86)	261 (82.33)

Moderate/Severe	151 (5.78)	95 (4.14)	56 (17.67)
Number of comorbidities*, n (%)			
0	2323 (65.05)	2221 (70.49)	102 (24.29)
1	112 (3.14)	97 (3.08)	15 (3.57)
2	519 (14.53)	414 (13.14)	105 (25.00)
3	364 (10.19)	260 (8.25)	104 (24.76)
≥4	253 (7.08)	159 (5.05)	94 (22.38)
History of cancer, n (%)	1296 (36.29)	1200 (38.08)	96 (22.86)
ASA classification, n (%)			
Grade 1-2	3048 (85.35)	2843 (90.23)	205 (48.81)
Grade 3-5	523 (14.65)	308 (9.77)	215 (51.19)
Grade of surgery, n (%)			
Minor	1349 (37.78)	1250 (39.67)	99 (23.57)
Major	2222 (62.22)	1901 (60.33)	321 (76.43)
Urgent of surgery, n (%)			

Elective	3339 (93.50)	2979 (94.54)	360 (85.71)
Emergency	232 (6.50)	172 (5.46)	60 (14.29)
Duration of surgery, n (%)			
≤240 minutes	3060 (85.69)	2800 (88.86)	260 (61.90)
>240 minutes	511 (14.31)	351 (11.14)	160 (38.10)
General anesthesia, n (%)	3402 (95.27)	2998 (95.14)	404 (96.19)
Type of surgery, n (%)			
Thoracic	821 (22.99)	762 (24.18)	59 (14.05)
Head and Neck	518 (14.51)	496 (15.74)	22 (5.24)
Cardio-vascular	336 (9.41)	172 (5.46)	164 (39.05)
Digestive	444 (12.43)	385 (12.22)	59 (14.05)
Breast	371 (10.39)	366 (11.62)	5 (1.19)
Gynaecologic and Obstetrics	317 (8.88)	305 (9.68)	12 (2.86)
Orthopadic	276 (7.73)	256 (8.12)	20 (4.76)
Other surgeries‡	488 (13.67)	409 (12.98)	79 (18.81)

Continuous variables are described as median (Interquartile Range, IQR), and categorical variables are described as number (percent).

*Comorbidities included diabetes, chronic obstructive pulmonary disease, diffuse emphysema, bronchiectasis, asthma, pulmonary fibrosis, lung transplantation status, respiratory failure, hypertension, coronary artery disease, chronic heart failure, cardiomyopathy, ventricular aneurysm, pericardial disease, cerebrovascular disease, and chronic kidney disease.

‡Other surgeries included urologic surgery, interventional surgery, plastic surgery, hernia surgery, and neurosurgery.

ASA Classification = American Society of Anaesthesiologists Physical Status Classification. COVID-19 = coronavirus disease 2019. BMI = body mass index.

Supplementary Table 8. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications in patients undergoing elective surgery

Cases/total		Postoperative complications					
		Model 1		Model 2		Model 3	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Preoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	
Pre-1w	17/100 (17.00)	2.11 (1.19, 3.75)	0.011	2.22 (1.20, 4.12)	0.012	2.84 (1.48, 5.46)	0.002
Pre-2w	22/122 (18.03)	2.25 (1.34, 3.78)	0.002	2.67 (1.53, 4.69)	0.000	2.62 (1.43, 4.77)	0.002
Pre-3w	15/137 (10.95)	1.26 (0.70, 2.27)	0.43	1.28 (0.69, 2.37)	0.43	1.39 (0.73, 2.66)	0.32
Pre-4w or more	132/1382 (9.55)	1.06 (0.80, 1.42)	0.68	1.13 (0.84, 1.53)	0.41	1.23 (0.89, 1.69)	0.20
Postoperative COVID-19 vs No COVID-19							
Time from surgery to diagnosis of COVID-19							
No COVID-19	88/903 (9.75)	Ref.		Ref.		Ref.	

Post-1w	24/157 (15.29)	1.90 (1.15, 3.12)	0.012	1.73 (1.00, 2.99)	0.048	1.95 (1.09, 3.50)	0.026
Post-2w	21/162 (12.96)	1.54 (0.92, 2.59)	0.10	1.65 (0.94, 2.92)	0.09	2.02 (1.11, 3.67)	0.021
Post-3w	21/170 (12.35)	1.63 (0.97, 2.74)	0.07	2.19 (1.24, 3.85)	0.003	2.51 (1.37, 4.59)	0.003
Post-4w or more	20/206 (9.71)	1.11 (0.66, 1.87)	0.69	1.19 (0.68, 2.09)	0.57	1.19 (0.65, 2.18)	0.57

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥ 4), and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopadic, and Other surgeries).

Supplementary Table 9. Sensitivity analysis of association between preoperative and postoperative COVID-19 and risk of postoperative complications excluding imputed data

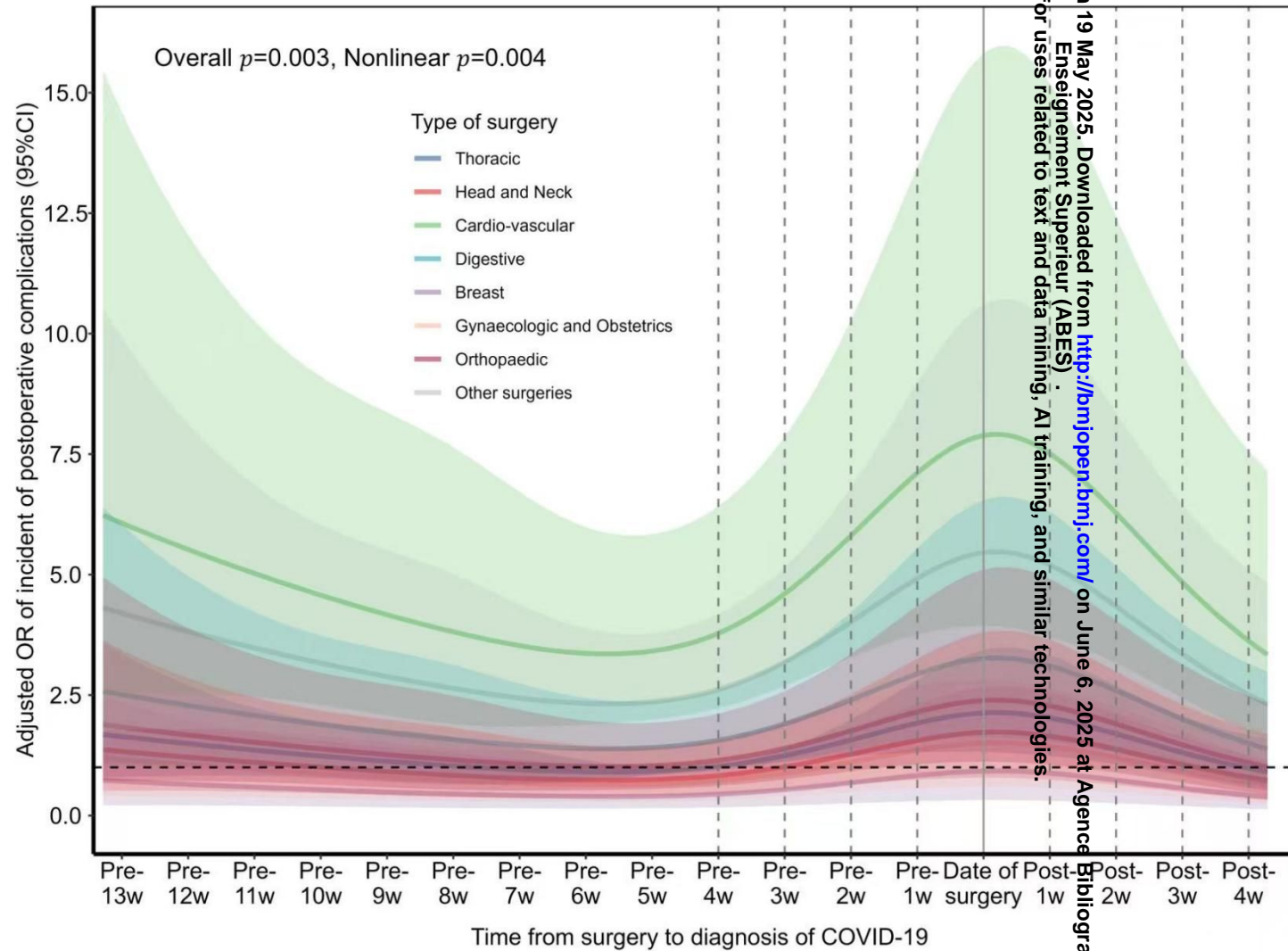
		Postoperative complications							
		Cases/total		Model 1		Model 2		Model 3	
				OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Preoperative COVID-19 vs No COVID-19									
Time from surgery to diagnosis of COVID-19									
No-COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.			
Pre-1w	13/82 (15.85)	1.84 (0.97, 3.51)	0.06	2.15 (1.07, 4.31)	0.03	2.54 (1.22, 5.25)	0.012		
Pre-2w	14/97 (14.43)	1.69 (0.91, 3.14)	0.10	2.08 (1.07, 4.03)	0.036	2.40 (1.20, 4.79)	0.013		
Pre-3w	11/114 (9.65)	1.01 (0.52, 1.97)	0.98	1.03 (0.51, 2.07)	0.94	1.17 (0.57, 2.40)	0.67		
Pre-4w or more	121/1226 (9.87)	1.05 (0.78, 1.42)	0.74	1.13 (0.82, 1.54)	0.46	1.25 (0.90, 1.75)	0.19		
Postoperative COVID-19 vs No COVID-19									
Time from surgery to diagnosis of COVID-19									
No COVID-19	82/815 (10.06)	Ref.		Ref.		Ref.			

Post-1w	20/131 (15.27)	1.77 (1.04, 3.04)	0.037	1.84 (1.03, 3.30)	0.04	1.93 (1.04, 3.58)	0.036
Post-2w	16/142 (11.27)	1.26 (0.71, 2.25)	0.42	1.42 (0.76, 2.66)	0.04	1.58 (0.82, 3.05)	0.17
Post-3w	16/156 (10.26)	1.22 (0.69, 2.16)	0.50	1.69 (0.91, 3.12)	0.04	1.89 (0.99, 3.59)	0.05
Post-4w or more	21/189 (11.11)	1.25 (0.75, 2.10)	0.40	1.29 (0.74, 2.27)	0.04	1.17 (0.64, 2.15)	0.60

Model 1: Adjusted for age (continuous) and sex (men or women).

Model 2: Additionally adjusted for BMI (continuous), smoking (yes or no), COVID-19 vaccination status (yes or no), number of comorbidities (0, 1, 2, 3, and ≥ 4), and history of cancer (yes or no).

Model 3: Further adjusted for ASA classification (grade 1-2 or grade 3-5), grade of surgery (minor or major), urgency of surgery (elective or emergency), duration of surgery (≤ 240 minutes or >240 minutes), general anesthetic (yes or no) and type of surgery (Thoracic, Head and neck, Cardio-vascular, Digestive, Breast, Gynaecologic and obstetrics, Orthopadic, and Other surgeries).



Supplementary Figure 2. Relationship between time from surgery to diagnosis of COVID-19 and adjusted OR for incident of postoperative complications with different surgical types.

Included 2612 patients with perioperative COVID-19. On the X-axis, Pre means patients with Preoperative COVID-19, and Post means patients with Postoperative COVID-19.