Impact of SARS-CoV-2 infection on postoperative complications of patients undergoing surgery after general outbreak in China: a protocol for multicentre prospective cohort study

Ziyu Zheng, Baobao Gao, Gang Luo, Lini Wang, Chong Lei

ABSTRACT

Introduction There is currently limited evidence addressing perioperative prognosis of surgical patients during COVID-19 pandemic; especially targeting on the Chinese population since the wave in 2022. Considering a distinct feature from the rest of the world demonstrated and the fast mutation and spread of the virus, evidence most relevant to China is urgently in need. The objective of this study is to seek for supporting evidence via evidence-based risk evaluations for postoperative complications to accumulate experience for coming infection waves.

Methods and analysis This protocol proposes a multicentre, prospective, observational cohort study aiming to explore the link between SARS-CoV-2 infection and postoperative complications among surgical patients under general or regional anaesthesia between 16 January 2023 and 31 December 2023. A retrospective cohort covering the same period in 2019 is extracted for historic reference. Data are extracted from the health information system and anaesthesia information management system. The COVID-19 infection is collected via an online survey. Missing values in weight or height will be imputed by each other with age and gender via multiple imputation. Other missing values will not be handled specially. Standard descriptive statistics will be reported followed by statistical modelling. Binomial regression with logit link is used for binary outcome. The time-to-event outcome is analysed using Cox regression with discharge from hospital further treated as a competing state. Hierarchical models will be assessed to account for temporal or central random effects. Temporal trends will be displayed with future expectations.

Ethics and dissemination Ethical approval is obtained from the ethical committee in XiJing Hospital (No. KY20232002-C-1); approvals are expected for each participating institute. Verbal consent will be informed and obtained prior to online survey collection. Personal information remains confidential, and publications will be deidentified.

Trial registration number NCT05677815.

INTRODUCTION

The pandemic of COVID-19 spreads rapidly over the past 3 years causing huge concern to the global health and safety. Yet, SARS-CoV-2 is still mutating at a fast and to some extent unknown way, producing more contagious strains with high immune escaping abilities. Due to these features, the overwhelming breakthrough in the population means that the incidence of patients needing surgeries who are currently or previously infected has increased and will potentially keep increasing inevitably. Thus, how the perioperative management should adapt promptly to the infectious status and strains of viruses has become one of the prominent and passionately discussed issues.

By far, the largest clinical trial on the long-term outcomes of critically ill patients with SARS-CoV-2 infections revealed that not all standard treatment approaches are beneficial in the long run. Moreover, some conventional treatments which would have been successful even led to worse prognoses. Precise to perioperative fields, some studies have already reported that the history of SARS-CoV-2 infection elevates the risk of complications among surgical patients. There is currently limited evidence addressing perioperative prognosis of surgical patients during COVID-19 pandemic; especially targeting on the Chinese population since the wave in 2022. Considering a distinct feature from the rest of the world demonstrated and the fast mutation and spread of the virus, evidence most relevant to China is urgently in need. The objective of this study is to seek for supporting evidence via evidence-based risk evaluations for postoperative complications to accumulate experience for coming infection waves.

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postoperative complications. A negative association was found between the postoperative complications and the time lag of surgery since infection. To balance the trade-off between surgeries taken place too soon after infection and too late that the conditions requiring treatments aggravate, an updated recommendation suggested that the elective surgeries should be postpone for at least 7 weeks. Such postpone will decrease risks in both postoperative complication risks and 30-day mortality to the baseline level where no historic SARS-CoV-2 infections presented. Other studies have also implied that such delay for asymptomatic or less severe patients could be presented. However, all of the recommendations and consensus have their own limitations; they were mostly derived from the early stage observation of the ancestral variant infections using scarce data in the European and the US populations. Simple generalisation and adaption to other circumstances may be inappropriate. Being the country with the largest population density in the world, the first wave of outbreak in China captured different features from any other countries in the world; the vast majority (both in proportions and raw figures) was infected within a month. This could potentially be explained by the genetic and cultural differences of the population; it is thus unlikely that the upcoming waves still present distinctions. Inferred from previous studies, increased potentials of postoperative complications will bring further challenges to both surgeons and anaesthesiologists as a chain effect. Such situation will not phase out in the short term according to the assessment of early virus strain; 6.2% of patients in the early pandemic period still bear persistent post COVID-19 symptoms such as fatigue. Moreover, other underlying factors which may accelerate the worsening postoperative complications in the short run include saturated health system and overloaded supporting services.

What the optimal perioperative management should be for the vast Chinese population, especially the optimal timing, hence still remains unclear and urgently demands evidence-based guidelines. To answer this, a multicentric cohort study is proposed in this study protocol primarily focusing on evaluation of the influence of SARS-CoV-2 infection on postoperative complications and adverse effects in surgical patients. This two-direction cohort will contain the current year of 2023 and the same time period in 2019 as historical reference.

**METHODS AND ANALYSIS**

This study protocol is reported in accordance with the Strengthening the Reporting of OBServational studies in Epidemiology (STROBE) guideline.

**Study design**

This protocol proposes a multicentric, prospective, observational cohort study targeting on patients who admit to hospital for surgeries since the general outbreak of COVID-19 pandemic in China. The prospective cohort covers the period between 16 January 2023 and 31 December 2023 with COVID-19-related information collected, including the infection history and vaccination status. The diagnoses of COVID-19 are judged based on swab tests (PCR or rapid antigen) or if any of the typical symptoms present. The main target is the prospective cohort will be internally compared between the patients with and without infection history. Historical comparison will be made against 16 January 2019 and 31 December 2019 to assess if there is a shock from the sudden outbreak and high infection rates. This choice of time covers the most recent year before the COVID-19 pandemic. Inpatients who received surgery conducted in operating room under general or regional anaesthesia are included for analysis. Outpatient surgeries, surgeries or procedures performed under local anaesthesia and intervention procedures operated in the catheter lab were excluded from analysis. This study is registered at ClinicalTrials.gov.

**Settings**

The study will be initiated at Xijing Hospital. The recruitment of participating centres is open until the end of the study date. The study sites will be involved progressively at any time point provided relevant ethical approvals. The initiation centre involves 16 departments and over 50 surgical teams. The study is currently openly recruiting and will only take participants from mainland China.

**Study investigator recruitment and training**

The investigation team consists of onsite anaesthesiologists within each centre. To ensure the quality of prospective data collection, all candidates will be required to go through standard training. Notifications on survey handouts will be passed every morning.

**Study population**

The study considers all adult inpatients undergoing surgeries (all-type procedure) admitted to study sites. Patients who refuse to respond to the COVID-19 Questionnaire will be excluded from the prospective cohort. All treatments are conducted following standard routines. The screening and selection procedure will follow the flow chart (figure 1). The study will be collecting the COVID-19-related information at the initiation study centre from 16 January 2023 until 31 December 2023. In any other participating centre, the collection will start on approval from the ethical board. The prospective cohort population is stratified by the history of SARS-CoV-2 infection of patients. The historic cohort of 2019 will be extracted on approval by the ethical committees.

**Outcome measures**

The primary outcome measure of this study is the incidence of major in-hospital postoperative complications following the definition of Clavien-Dindo classification (CDC; table 1). The event will be marked if CDC≥grade II. Secondary outcomes include the event of in-hospital pulmonary complications, admission to intensive care...
unit, in-hospital mortality rate, the total length of stay in hospital and the Comprehensive Complications Indices (CCIs; calculation detail can be found in table 1).19

The rationale of this outcome choice is based on the general consensus of increasing risks of postoperative complications associated with COVID-19 history.7 More specifically, the distinct feature of the outbreak experienced in China very much means that evidence targeting on this population or culture should be searched for. The study thus aims to provide evidence via exploring the impact of SARS-CoV-2 infection on the primary and secondary outcomes.

Data collection
The study data will be formed of two parts: (1) retrospective data of patients including the demographics, medical history, preoperative test records, surgical information and in-hospital postoperative diagnostics and test records at daily basis and (2) COVID-19 information survey for the prospective collection. An engineer will be employed to extract the first part of data from the health information system (HIS) or anaesthesia information management system (AIMS) using a predetermined data collection form (online supplemental Stable 1). The second part of the data is prospectively collected as an ad hoc procedure using an electronic online survey (online supplemental material 2). COVID-19-relevant information such as vaccination status, infection history, means of diagnoses and symptoms revealed will be collected. Trained professionals will assist the survey filling onsite to ensure survey quality. These two parts of data will be matched via a unique admission ID number in each centre. Only information of patients who provide consent for COVID-19 information will be extracted from HIS and AIMS for the prospective cohort.

The patient demographics (age, gender, body mass index) and medical history (preoperative blood tests and laboratory tests, comorbidities and chronic medications) will be obtained from HIS. The surgical information is obtained from AIMS including the grade of surgery (minor, moderate or major defined in table 2), urgency of surgery (elective or emergency), location of surgery, surgery duration (incision to end of surgery), American Society of Anesthesiology (ASA) physical status classification, anaesthesia duration (defined as the time from anaesthesia induction to extubation time for general or compound anaesthesia, time from local anaesthesia injection to out of operating room time for regional anaesthesia), type of anaesthesia (general, regional or compound), intraoperative blood loss, blood transfusion, mechanical ventilation settings and fluid management.
adjunctive medications. Postoperative information will be extracted at daily basis until discharge of patients.

**Data cleaning and imputation**
The preoperative comorbidities (table 3) will be obtained based on the combination of medical records, laboratory results, blood gas test results, electrocardiography diagnoses and medical image records. Comorbidities in respiratory, urinary, endocrine, neuropsychiatric, digestive, blood and lymphatic systems will be concluded if any of the medical records, electrocardiography diagnoses and medical image records present positive diagnostics to any disorders or conditions. If these are missing, further evaluation-based laboratory and blood gas test results will be carried out by two trained, independent professionals who are blinded from the SARS-CoV-2 infection status. To reduce the dimension of the factors involved in the analysis later, the Revised Cardiac Risk Index (RCRI, table 4) will be calculated. The postoperative complications will also judged in the same fashion as comorbidities.

The time lag between SARS-CoV-2 infection and surgeries will be calculated using the surgery date and COVID-19 diagnostic date. If no swab-test results are available, the date of development of typical symptom is used. Weight and height are imputed if either is missing via multiple imputation method with adjustment for age and gender. We anticipate low missing rate in the outcome measures as they are from medical records. Hence, any missing primary outcome measures or relevant diagnostic variables will be eliminated from the analysis. Data quality will be governed via checks of numerical range and reasonableness of data. Any ambiguous values will be assessed by a professionally trained physician; the origin will be traced back where necessary. The entries with outcome variables undetermined nor traceable will be removed. The study team tries the best to achieve the complete and correct data collection on the prospective survey. Data will be monitored and cleaned at weekly basis; other efforts on completion

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### Table 1 CDC of postoperative complications and CCI weights and single values

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Weights for CCI</th>
<th>CCI* single value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No adverse event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens include the following: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy.</td>
<td>300</td>
<td>8.7</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than those allowed for grade I complications Blood transfusions and total parenteral nutrition are also included</td>
<td>1750</td>
<td>20.9</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IIIa</td>
<td>Intervention not under general anaesthesia</td>
<td>2750</td>
<td>26.2</td>
</tr>
<tr>
<td>IIIb</td>
<td>Intervention under general anaesthesia</td>
<td>4550</td>
<td>33.7</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ ICU management</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IVa</td>
<td>Single organ dysfunction (including dialysis)</td>
<td>7200</td>
<td>42.4</td>
</tr>
<tr>
<td>IVb</td>
<td>Multiorgan dysfunction</td>
<td>8550</td>
<td>46.2</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient</td>
<td>NA</td>
<td>100</td>
</tr>
</tbody>
</table>

*CCI: calculation of CCI incorporates all complications and their severity as recorded by the CDC: CCI = √Σ (weight×ni)/2, where i denotes the CDC category and n denotes the total number observed.

CCI, Comprehensive Complication Index; CDC, Clavien-Dindo classification; CNS, central nervous system; IC, intensive care; ICU, intensive care unit.

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### Table 2 Classification of surgery grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Surgery</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Most outpatients eye surgery Minor body surface or extremity surgery</td>
<td>Fit and well</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Other types of surgery (eg, breast, primary uncomplicated orthopaedics, most plastic surgery)</td>
<td>Moderately fit and without frailty</td>
</tr>
<tr>
<td>Major</td>
<td>Most inpatients gastrointestinal, hepatobiliary, head and neck, cardiothoracic, vascular and complex orthopaedics surgery</td>
<td>Frailty, deconditioned, unwell and comorbid</td>
</tr>
</tbody>
</table>
of data include but not limit to telephone follow-up as soon as possible.

**Sample size**

No sophisticated sample size calculations were done at this exploratory stage. One of the reasons is the limited prior knowledge available with the sudden feature. The study aims to respond to the demand of perioperative management evidence, targeting primarily on the rate of major postoperative complications. Achievement of complete data set as soon as possible is thus beneficial at this phase; the online survey was constructed in a fast-to-fill and easy-to-answer manner. At daily rate of approximately 100 operations, we expect to enrol at least 10,000 in the prospective cohort. This is more than sufficient for the exploration on the primary outcome; the rule-of-thumb of 15 samples per covariate with estimated complications 7%–15% asks for at least 2000 participants.

**Table 3** Definition of comorbidities

<table>
<thead>
<tr>
<th>Terms</th>
<th>The presence in medical record</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hypertension, high blood pressure</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Coronary artery disease: myocardial infarct, heart attack, angina; history of interventional angioplasty or coronary artery bypass graft surgery; Heart failure: systolic or diastolic heart failure, CHF, cardiomyopathy; Cardiac valvular disease: aortic/mitral/tricuspid/pulmonary valvular disease</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>COPD, chronic bronchitis, emphysema</td>
</tr>
<tr>
<td>Asthma</td>
<td>Asthma, reactive airway disease</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Pulmonary fibrosis, sarcoidosis, asbestosis, silicosis, siderosis, Farmer’s lung</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Glomerulonephritis, nephritic syndrome, acute or chronic renal failure</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetes type 1 or 2</td>
</tr>
<tr>
<td>Immune system disease</td>
<td>Rheumatic diseases, rheumatoid diseases, systemic lupus erythematosus, SLE, Sjögren’s syndrome, connection tissue disease</td>
</tr>
<tr>
<td>Central nervous system disease</td>
<td>Cerebrovascular accident, stroke, transient ischaemic accident, mini-stroke</td>
</tr>
<tr>
<td>Peripheral nerve disease</td>
<td>Diagnoses affecting motor, sensory or cognitive dysfunction</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Cirrhosis, hepatomegaly, liver failure, liver disease-related ascites</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>Stomach ulcer, duodenal ulcer, history of gastrointestinal surgery</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Hypo/hyperthyroidism, thyroiditis or prescribed thyroid medications</td>
</tr>
<tr>
<td>CHF, congestive heart failure.</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical considerations**

**Exploratory data analysis, descriptions and comparisons**

Demographic characteristics will be presented using standard descriptive statistics, where continuous variables are described using mean (SD) and categorical variables are captured under median (IQR). The normality will be checked via appropriate tests such as Kolmogorov-Smirnov and density curves over histograms. Data transformation techniques such as logarithm or square-root transforms will be employed to satisfy model assumptions where necessary. Comparisons between patients with and without COVID-19 history will be carried out. Propensity scores are to be weighted by probabilities estimated via a multinomial model. Such matching is aimed to minimise the bias between two groups due to confounders such as age, gender and vaccinations. The matching will be done at rate 1:1 (COVID-19 history:no COVID-19 history). This is in case that too few non-infected patients will be observed. Longitudinal comparisons in times will also be carried out across contemporaneous periods from different phases at monthly and quarterly paces. This aims to look at the time trends and see if any issues arise due to sudden break of infections.

**Statistical modelling**

The primary outcome will be analysed using generalised linear model with Binomial family via logit link. The associated risk factors will be identified using the following variable selection algorithm. The initial covariate set will be predetermined based on previous literatures, and the clinically critical variables will be justified by experts. The
univariable analyses will be conducted with the ORs and 95% CIs reported. The search starts from the saturated model where all potential risk factors will be included (e.g., comorbidities, surgery types, ASA physical status classification, symptom severity of COVID-19 and time lags between surgery and COVID-19 infections). Multicollinearity is then checked via variation inflation factors where the variables sharing collinearity to others will be removed. The backward selection procedure will be used at last to obtain the set of variables which would explain the most of the deviation without losing too much df.

CCIs will be modelled via multiple linear regression with confounding factors controlled in the same manner. Mixed effect models will be used to see if there are differences among centres (random intercepts) and time phases (random slopes). The temporal trend of both the rate and CCIs will be explored via time series analyses where the future step forecast will be made based on the historical observations.

The time-to-event data will be modelled under different considerations. The discharge from hospital typically means that once discharged, patients will no longer be in the risk set of postoperative complications. If no censoring nor event occurs, the discharge can be dealt as an absorbing state in the process; that is, treated as the competing risk of discharge on postoperative complications. Fine and Gray competing risks approach will be used to check if assumptions are satisfied. A parametric method will be employed as the effects of each variable on the outcome are of interests. Thus, hierarchical Cox proportional hazards approaches including centre information (clinical service provider) as a random intercept. Different time phases will be considered as random slope where appropriate. HRs with 95% CIs will be reported.

The systematic model selection is informed by Akaike Information Criteria where the most optimal model fit will be advised in the algorithm. Model diagnostics including histogram checks and Q-Q plots will be applied for checking the distribution of residuals. The study is planned to be conducted under a statistical significance at 5% throughout. All tests will be two-sided. We will analyse the data using R (R Core Team V.3.6.3, Vienna, Austria).

Subgroup and sensitivity analysis
Predefined subgroups of interest include gender (male, female), history of COVID-19 (infected, none), time lag between infection and surgery (<10 days, ≥10 days), symptom severity (asymptomatic, mild or severe), vaccination status (1 dose, 2 doses, 3 doses), vaccine types (Sinovac, recombinant protein, adeno), types of anaesthesia (general, regional), ASA levels (< 3, ≥ 3), grade of surgeries (major intermediate and major), comorbidities (RCRI Score <4, ≥ 4), operation duration (<2 hours, ≥2 hours), age (<18, 18–65, ≥65) and centres. The robustness of primary outcome estimates will be assured via sensitivity analysis. Five sets of data will be imputed with estimates compared against the primary analysis where no special treatment was planned for missing values. The study data will be looked at monthly and quarterly as well to check if estimates are robust to seasonal effects. The multivariable model will also be performed after weighting by conditional probability of each patient being positive at time of surgery to ensure baseline balance.

Study investigator recruitment and training
The investigation team consists of the onsite anaesthesiologists within each centre. To ensure the quality of prospective data collection, all investigator candidates will be required to go through standard training. Notifications on survey handouts will be passed every morning.

ETHICS AND DISSEMINATION
Ethical and safety considerations
The study conforms to the provisions of the Declaration of Helsinki. The protocol was approved by the Institutional Ethic Committee of Xijing Hospital (No. KY20232002-C-1). Independent ethical approval shall be obtained for each participating centre. The collection of COVID-19 information requests informed verbal consent prior to filling questionnaires. Other information will be extracted from the medical records where signed consent is waived. The data are deidentified according to the Personal Information Protection Law of the People’s Republic of China. Any identifiable information will be eliminated in any forms of publications.

Dissemination
Findings from this study will be disseminated and shared in forms of peer-reviewed journal publications or scientific conferences.

Patient and public involvement
No patients and/or the public were involved in the study design, conduct, reporting or dissemination plans of this research.

DISCUSSION
Previous studies of perioperative prognoses for patients with COVID-19 have primarily focused on the European or US population. They are also mostly limited to the initial strains with few mentioning Omicrons. Studies over Chinese population are thus in scarce as population infections only recently started. The mutation and spread mean that the pandemic is unlikely to die out in the near future. Thus, this paper demonstrates an observational study protocol on exploration of postoperative complications evaluation since the pandemic wave in December 2022 in the mainland China. The protocol directs how evidence-based support will be investigated in aspects of data collection, extraction, design and analyses. The study has several strengths. A targeted ambidirectional observational study across China will establish one of the initiations evaluating perioperative complications under COVID-19 pandemic. The accumulated current experience will bring insights to the coming waves. Patient screening and data extraction will be performed...
systematically. The forward collection survey is done thoroughly and will be completed at the best effort. The text extractions are designed specifically to the perioperative field with verbal and imaging medical records over anaesthesia management stratified by both anaesthesiologists and engineers. All unidentified data and codes can be requested from the corresponding author, enabling our analysis to be entirely reproducible. Results from the review will be reported according to best practice, using STROBE. The limitations of this study exist. Despite the best effort made on prospective COVID-19 collection, the electronic medical records still have missing information and ambiguous entries. Thus, the rich information in the records is not used to the full potentials. Also, the observational nature means that the study will still have some deviance unexplained due to not identified confounders.

Study status
The study commenced recruitment on 16 January 2023 and aims to conclude data collection on 31 December 2023.

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Contributors
ZZ prepared, drafted and proposed statistical analyses plan. CL contributed to the conception and clinical design of the study. LW contributed in clinical design, article collections and survey design. BG and GL contributed in discussion and information collection. All authors reviewed and approved the final manuscript.

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Competing interests
None declared.

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.

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Provenance and peer review
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Supplemental material
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