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Editorial

Surgery after a previous SARS-CoV-2 infection: data, answers and questions

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Since its emergence in December 2019, the global impact of the SARS-CoV-2 corona virus has been profound. By March 2021, more than 121 million people worldwide had been infected, of whom 2.7 million had died [1]. In a typical year, more than 300 million surgical procedures are performed worldwide [2]. It is, therefore, unsurprising that the COVID-19 pandemic has significantly impacted on the safe and timely delivery of surgical care. For example, more than 28 million surgical procedures were delayed or cancelled during the first wave of the pandemic alone [3]. Further, a significant proportion of the millions who survived SARS-CoV-2 infection now require surgery for such important indications as cancer, cardiovascular disease or debilitating arthritis. Healthcare providers increasingly face a critical new question. When is the safest time to operate on a patient with prior SARS-CoV-2 infection?

Assessment

Pre-operative assessment is a crucial component of optimal surgical care. The assessment represents an opportunity to identify prognostically important comorbidities, mitigate risks for acute complications and, importantly, facilitate an informed discussion about peri-operative risk. Knowledge about risk informs decisions on optimal timing of surgery. For example, a patient with a drug-eluting coronary stent experiences elevated risk when surgery is performed sooner than 6 months after stent insertion [4], while a patient with a prior venous thromboembolism experiences the greatest risk from temporary withholding of anticoagulation when surgery is performed within the first month of a thromboembolic episode [5]. It is recognised that surgery during active SARS-CoV-2 infection is associated with increased risks of death and pulmonary complications [6, 7]; hence, it should be deferred whenever possible. Yet once the active infection has resolved and the patient is no longer infectious, when might elective (or 'scheduled') surgery safely proceed? Relevant data are limited. The COVIDSurg collaboration reported the outcomes of 122 patients who had elective cancer surgery following previous SARS-CoV-2 infection (defined by positive nasopharyngeal swab test) and had no evidence of active infection at the time of surgery [6]. In this relatively small cohort, the unadjusted risks of death and pulmonary complications were elevated when surgery proceeded during the period from 7 to 28 days following a positive SARS-CoV-2 swab. These findings mirror those of a French multicentre cohort study [7], where 147 patients who had surgery within 5 to 30 days of a positive SARS-CoV-2 nasopharyngeal swab test experienced higher unadjusted risks of 30-day mortality than patients without a prior infection. Based on these early data, some national bodies recommended delaying scheduled surgery in patients with prior SARS-CoV-2

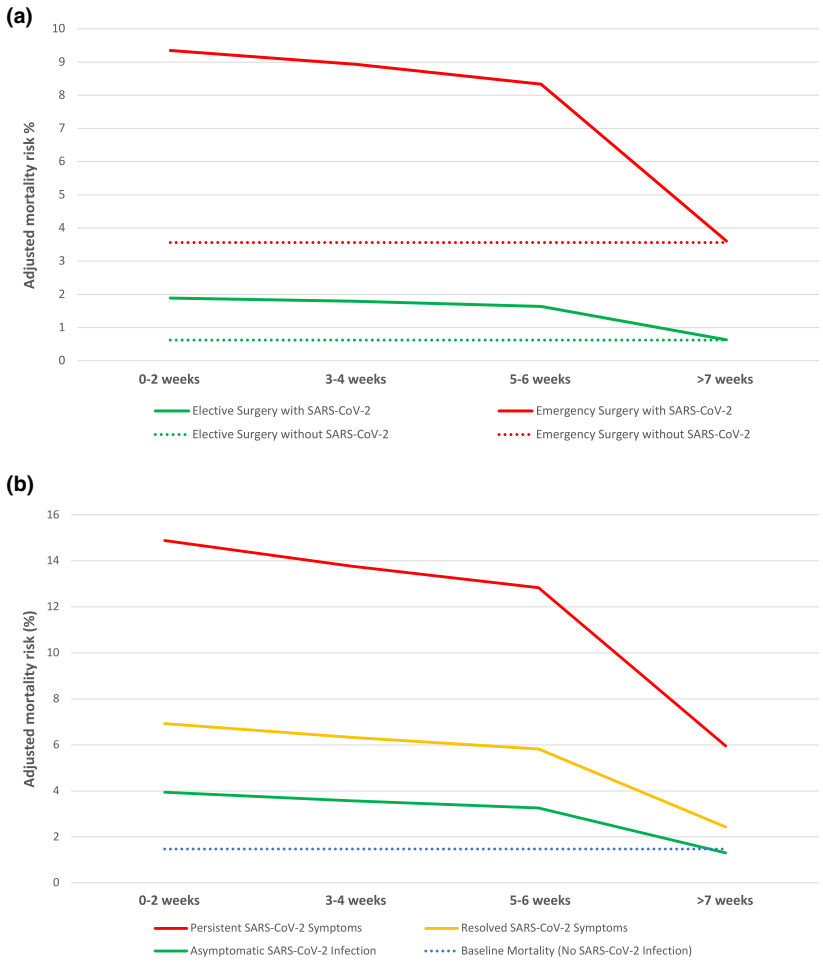

Figure 1 Changes in adjusted postoperative mortality risk with increasing time intervals from SARS-CoV-2 diagnosis to surgery. Solid lines denote changes in adjusted postoperative mortality risk (y-axis) in patients with SARS-CoV-2 infection with increasing time intervals from infection to surgery (x-axis). (a) – sub-groups defined based on whether patients had emergency surgery or elective surgery. (b) – sub-groups defined based on whether patients had an asymptomatic infection (green line), symptomatic infection with symptoms resolved by the time of surgery (orange line) or symptomatic infection with symptoms persistent up to surgery (red line). Dotted lines denote the adjusted postoperative mortality risk in patients without any known prior SARS-CoV-2 infection.

infection. For example, in December 2020, the American Society of Anesthesiologists and Anesthesia Patient Safety Foundation stated that scheduled surgery should be delayed for at least 4 weeks after SARS-CoV-2 infection whenever feasible [8], with longer delays for patients who developed a symptomatic infection, required hospitalisation or were admitted to a critical care unit. In this issue of *Anaesthesia*, the COVIDSurg Collaboration provides compelling new data to inform the safe scheduling of elective surgery after SARS-CoV-2 infection [9].

The GlobalSurg-COVIDSurg Week multicentre cohort study included an impressive 140,727 patients from 1674 hospitals in 116 countries. At each site, investigators captured information on almost all patients who had surgery during a one-week period between 5 October 2020 and 1 November 2020 (data could be collected over up to four blocks of 7 consecutive days). Epidemiological studies that capture information on many patients across many hospitals in a short period of time are increasingly common in peri-operative research. Notable examples include the European Surgical Outcomes Study (EuSOS) [10], International Surgical Outcomes Study (ISOS) [11] and African Surgical Outcomes Study (ASOS) [12]. The GlobalSurg-COVIDSurg Week cohort included 3137 patients with known prior SARS-CoV-2 infection. About 80% of them were diagnosed based on a positive reverse transcription-polymerase chain reaction (RT-PCR) swab, 5% were based on symptoms alone, and 45% were

asymptomatic infections. What were the key findings? Patients with prior SARS-CoV-2 infection experienced higher risks of 30-day mortality and pulmonary complications than uninfected patients until 7 or more weeks had elapsed from the initial diagnosis of infection. Elevated risk persisted in sub-groups defined by procedure complexity (major vs. minor surgery) and urgency (elective vs. emergency surgery) (Fig. 1a). Importantly, the presence of symptoms during a previous SARS-CoV-2 infection influenced subsequent peri-operative risk. For someone whose infection was asymptomatic, peri-operative risk had returned to that of someone with no prior infection once 7 weeks had passed from the initial diagnosis. However, if a patient had symptoms during the infection, especially if symptoms remained persistent up to surgery, peri-operative risk remained above baseline levels even when 7 or more weeks had elapsed (Fig. 1b).

Evidence

While the GlobalSurg-COVIDSurg Week study provides the strongest data to date addressing the timing of surgery after SARS-CoV-2 infection, it has limitations. First, the pragmatic challenges imposed by a very large global cohort study meant that the level of clinical detail that could be feasibly captured was limited. The dataset did not capture some prognostically important characteristics, the accuracy of data elements may be variable, and the diagnostic criteria for pre-operative SARS-CoV-2 infection were not standardised to RT-PCR testing alone. These limitations have implications for statistical analyses, especially related to residual unmeasured confounding. For example, information on patients' ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) scores [13] would have improved risk adjustment when evaluating the association between prior SARS-CoV-2 infection and pulmonary complications. Additionally, patients who had surgery sooner after a SARS-CoV-2 infection likely had indications for surgery (e.g. cancer, trauma) that also led to increased risk. Given the limitations in detailed data collection, the capacity for adequate statistical risk adjustment for such confounders is also similarly limited. Second, the diagnosis of previous SARS-CoV-2 infection was dependent on appropriate laboratory tests having been done or the presence of symptoms. Thus, patients who had asymptomatic infections and did not undergo testing would have been misclassified as not having had a prior SARS-CoV-2 infection. Missed SARS-CoV-2 infections are a relevant concern given the high proportion of infected patients who remain asymptomatic [14] and variable access to SARS-CoV-2 laboratory testing in many countries. Nonetheless, misclassification of prior SARS-CoV-2 infection status was, if anything, a conservative bias that reduced the magnitude of differences between the exposure arms. Third, the study did not include sub-group analyses related to some clinically important characteristics (e.g. general anaesthesia) that may have plausibly modified the impact of prior SARS-CoV-2 infection on outcomes. Fourth, the mechanisms linking prior SARS-CoV-2 infection to poor outcomes remain unclear. The SARS-CoV-2 coronavirus directly affects the lungs; hence, the resultant increase in pulmonary complications is unsurprising. Nonetheless, the virus affects many other organ systems to cause myriad adverse effects, including myocarditis, arrhythmias, thromboembolic events, acute stroke and kidney injury [15]. All these sequelae are relevant to the peri-operative setting. Indeed, surgical patients with SARS-CoV-2 infection have elevated risks of complications other than pulmonary events, including cardiac arrest, acute kidney injury [16] and thrombotic events [17].

Practice

How should clinicians modify practice based on these new data? At the minimum, the results support a general strategy of delaying elective surgery, whenever feasible, for 7 or more weeks after SARS-CoV-2 infection, at which point there is a marked decrease in mortality and risk returns to baseline. Such decisions should be individualised. The acute risks of proceeding with surgery soon after recent SARS-CoV-2 infection must be weighed against the risks of delaying surgery for time-sensitive conditions such as cancer, ischaemic heart disease or critical neurological disease. Even if the optimal choice for an individual patient is to proceed with surgery within 6 or fewer weeks after SARS-CoV-2 infection, information about elevated peri-operative risk should be conveyed as part of the informed consent process. Importantly, there are now reasonably equivalent non-operative treatment options for conditions that would typically necessitate urgent surgery, an example being initial antibiotic therapy for uncomplicated appendicitis [18]. Further, the severity of SARS-CoV-2 infection, as manifested by development and persistence of associated symptoms, has an important impact on subsequent peri-operative risk. For patients who had symptomatic infection, and especially for those with persistent symptoms, the risk still remains elevated above baseline once 7 or more weeks have passed since the initial diagnosis. A recent consensus-based statement from anaesthesia and surgical societies in the UK [19] (published shortly after the GlobalSurg-COVIDSurg Week study [9]) recommends delaying surgery, whenever feasible, for a

minimum of 7 weeks after known SARS-CoV-2 infection. Work is still required to effectively translate these new research findings and consensus-based recommendations into clinical practice. Many patients have been waiting months for their scheduled surgery because of delays by the initial waves of the COVID-19 pandemic. Effective communication is needed for these patients to understand why surgery might be delayed further in the presence of resolved but recent SARS-CoV-2 infection. Additionally, surgeons' clinics, outpatient pre-operative evaluation clinics and hospitals will need to develop new processes-of-care to facilitate early identification of patients with recent SARS-CoV-2 infection. Such processes will help mitigate risks of accidental last-minute cancellations of scheduled surgery.

Future research

The study also identifies critical new questions that merit further research. For example, research is needed to identify mechanisms for poor peri-operative outcomes related to prior SARS-CoV-2 infection, develop risk stratification tools (e.g. biomarkers, exercise tests, lung function tests) to identify high-risk individuals among the subset with prior infection, define the role – if any – for tests (e.g. antibody tests) to ascertain prior unrecognised SARS-CoV-2 infection in surgical patients, and develop interventions to reduce peri-operative risk in patients with prior infection. Research on better prediction and prevention of complications in patients with prior SARS-CoV-2 infection is especially critical to better individualising decisions on proceeding with surgery for time-sensitive conditions.

The GlobalSurg-COVIDSurg Week study provides broader lessons for advancing research in the peri-operative setting. The success of this global study is a testament to the well-organised leadership team at the National Institute for Health Research Global Health Research Unit on Global Surgery, collaborative clinician-researchers across 116 countries, efficient electronic central data capture systems, pragmatic data capture forms and a research culture that promoted global collaboration. For example, the named author for the primary manuscript is the research group (i.e. COVIDSurg Collaborative and GlobalSurg Collaborative), with the collaborator listing including thousands of investigators drawn from the participating hospitals. Such large collaborative endeavours certainly have many strengths. They can recruit very large numbers of patients in a relatively short period of time. The gains in sample generalisability, statistical power and efficient study completion are readily apparent. Nonetheless, there are key limitations that cannot be ignored. Many volunteer study site investigators may be either full-time clinicians or trainees [20], as opposed to trained research personnel. Such site investigators may have limited capacity to collect some clinically important baseline characteristics (e.g. frailty) or postoperative outcomes (e.g. acute delirium) that rely on high-quality training to ensure reliable ascertainment. Further, prospective data collection with informed consent is often not feasible in large epidemiological studies that seek to include thousands of patients in a very short period of time. Without informed consent procedures, longitudinal follow-up of study participants after hospital discharge (e.g. standardised 30-day follow-up) is typically challenging. Thus, while collaborative studies have a clear, and expanding, role in peri-operative research, they do not replace smaller single-centre or multicentre studies with more detailed prospective data collection procedures.

Indeed, the growth of large multicentre collaborative studies points to the need for quality standards specifically tailored for such research. For example, these standards could specify optimal endpoints that are both valid but also feasible for large studies staffed largely by trainees or volunteer clinicians. Such quality standards will only enhance the future role of multicentre collaborative studies such as the GlobalSurg-COVIDSurg Week study. Provided that the research question, study design and team are strong, efficient and high-quality collaborative global research in the peri-operative setting is possible, this is to be commended and must be continued.

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