



Worsening COVID-19 Disease Course After Surgical Trauma: A Case Series

Quinten Cuypers^{1,2}, Vincent Vandeborgh¹, Bjorn Stessel^{1,3,*}, Ina Callebaut^{1,3}, Ilse Depauw¹, Vera Saldien⁴ and Dirk Vrancken¹

¹Department of Anesthesiology and Pain Medicine, Jessa Ziekenhuis Vzw, Hasselt, Belgium

²Emergency Department, UZ Leuven, Leuven, Belgium

³Faculty of Medicine and Life Sciences, Limburg Clinical Research Center, Diepenbeek, Belgium

⁴Department of Anesthesiology and Pain Medicine, University Hospital, Antwerp, Belgium

*Corresponding author: Department of Anesthesiology and Pain Medicine, Jessa Ziekenhuis Vzw, Hasselt, Belgium. Email: bjorn.stessel@jessazh.be

Received 2022 April 30; Revised 2022 July 28; Accepted 2022 October 19.

Abstract

Introduction: Current guidelines from the American Society of Anesthesiologists recommend postponing elective surgery on COVID-19-positive patients for a minimum of four to twelve weeks. However, literature focusing on the outcomes of COVID-19-positive patients undergoing surgery is scarce. In this case series, the outcome of asymptomatic COVID-19 patients undergoing acute or semi-urgent surgery was evaluated.

Case Presentation: A case series of four patients between 32 and 82 years old with a confirmed SARS-CoV-2 infection undergoing acute or semi-urgent surgery was presented here. All four patients were asymptomatic for COVID-19, developing severe respiratory failure following endo CABG, caesarian section, a thyroidectomy, or abdominal surgery. ICU admission, together with invasive ventilation, was necessary for all patients. Two patients required venovenous extracorporeal membrane oxygenation treatment. A mortality of 50% was observed.

Conclusions: In conclusion, the present case series suggests that elective surgery in asymptomatic SARS-CoV-2 infected patients might elicit an exacerbated COVID-19 disease course. This study endorses the current international guidelines recommending postponing elective surgery for SARS-CoV-2-positive patients for seven weeks, depending on the severity of the surgery and perioperative morbidities, to minimize postoperative mortality.

Keywords: Surgical Trauma, COVID-19, SARS-CoV-2

1. Introduction

Since the start of the coronavirus disease-19 (COVID-19) pandemic, elicited by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most healthcare systems have encountered a dramatic decrease in the capacity to treat surgical patients owing to the reallocation of resources. Due to the continuing pandemic, the waiting lists for elective surgical procedures are growing (1, 2). Although research on morbidity and mortality in the non-surgical COVID population is being conducted and published extensively, not many studies have focused on the outcome of the surgical COVID-19 population. Despite the lack of a vast literature, current guidelines from the American Society of Anesthesiologists recommend postponing elective surgery for COVID-19-positive patients for a minimum of four to twelve weeks, depending on the symptomatology and comorbidities (3). Some evidence suggests that surgery performed more than seven weeks af-

ter the diagnosis of SARS-CoV-2 infection is associated with mortality similar to baseline (4, 5). Therefore, the recommended waiting period for elective surgery in asymptomatic COVID-19 patients is seven weeks unless the risk associated with the postponement of surgery outweighs the risk of postoperative complications and mortality (4, 5). In case of persistent symptoms, perioperative morbidities and mortality risk may remain high even after seven weeks, and multidisciplinary perioperative management might be required (4).

This article presents a case series of four asymptomatic patients with confirmed SARS-CoV-2 infection undergoing acute or semi-urgent surgery. Postoperatively, all four cases developed significant worsening disease course and severe respiratory complications related to the COVID-19 infection. The main objective of this study was to support the current guidelines to postpone (semi)-elective surgery in asymptomatic COVID-19 patients.

2. Case Presentation

2.1. Case 1

In March 2021, a 61-year-old male patient was hospitalized, awaiting coronary artery bypass grafting and aortic valve replacement for triple vessel coronary disease with moderate aortic stenosis. His medical history included marked obesity, insulin-dependent type 2 diabetes mellitus, chronic renal insufficiency, peripheral vascular disease, and ischemic stroke one year prior, from which he suffered no permanent disability. The decision was made to perform a hybrid approach with coronary artery bypass grafting of LAD and RCA, followed by a PCI of the circumflex artery. The day before surgery, a standard screening with a nasopharyngeal PCR swab unexpectedly returned positive for SARS-CoV-2, revealing a high viral load. At the time, the patient was on the waiting list for his SARS-CoV-2 vaccination. He expressed no respiratory or infectious symptoms. Given the severity of his coronary lesions, the decision was made to proceed with surgery the next day. Perioperatively, poor quality of the internal mammary arteries was noted, due to which revascularization of the right coronary artery could not be performed. Postoperatively, the patient was admitted to the intensive care unit (ICU). On the first postoperative day, the patient was successfully extubated, still retaining a high oxygen dependency and requiring support with a high-flow oxygen nasal cannula. A few hours after extubation, he developed active chest pain, dynamic ECG changes, and a rising high-sensitivity troponin T (peaking at 1330 ng/L, normal ≤ 14.0 ng/L), consistent with the diagnosis of perioperative myocardial infarction. Urgent coronary angiography and percutaneous coronary intervention were performed, including stenting critical ostial stenosis of the patient's right coronary artery. The postoperative chest radiography demonstrated bilateral hilar infiltrates and postoperative atelectasis. Dexamethasone 10 mg once daily was started in light of his positive COVID-19 screening and supplemental oxygen dependency. Although signs of myocardial ischemia after stenting had resolved, the patient's respiratory status slowly declined in the following days, with severe respiratory failure on postoperative day 5. A trial of non-invasive ventilation was initiated. However, despite 24 hours of NIV, his respiratory status worsened, and the team proceeded to endotracheal intubation and prone ventilation. Chest radiography showed marked bilateral pulmonary infiltrates, consistent with severe COVID-19 pneumonia. Following intubation, dexamethasone was switched to methylprednisolone 40 mg IV twice daily, and empiric antibiotic therapy (piperacillin-tazobactam) was initiated because of rising inflammatory markers. Respiratory cultures confirmed superinfection with *Serratia marcescens* and *Streptococcus pneumoniae*, for which moxifloxacin was added

based on antimicrobial susceptibility testing. Despite maximal ventilatory support and prone ventilation, oxygenation remained inadequate, and the decision was made to place the patient on venovenous extracorporeal membrane oxygenation (VV-ECMO) on postoperative day 6. After initiating VV-ECMO, adequate oxygenation and ventilation were achieved, and ventilator settings were adjusted to maximize lung-protective ventilation. In the following days, the patient's oxygen requirement gradually decreased. VV-ECMO could be stopped on postoperative day 16 without further respiratory complications. The patient was progressively weaned of ventilatory support and eventually extubated on postoperative day 24. Further revalidation was uneventful, and on postoperative day 30, he was ultimately discharged to the cardiology ward.

2.2. Case 2

An 82-year-old male patient presented to our hospital's emergency department in December 2020 because of diffuse abdominal pain and nausea. His medical history included arterial hypertension, hyperlipidemia, stable coronary artery disease, appendectomy, and a mitral valve repair following chordal rupture. Workup with abdominal computed tomography (CT) revealed small bowel obstruction, most likely caused by adhesions after previous appendectomy surgery. There were no signs of bowel ischemia. Blood work showed acute kidney injury with normal inflammatory markers. A nasopharyngeal PCR swab taken three days before admission to the hospital had been positive for Sars-CoV-2, revealing a high viral load. Upon presentation to the hospital, the patient had no supplementary oxygen requirement or respiratory complaints. He was not vaccinated for COVID-19 since vaccines were not available then. The patient was evaluated by the general surgery service and admitted for conservative management. However, due to the failure of conservative treatment, with recurrent nausea and abdominal distension, the decision for surgical treatment was taken two days later. Preoperative chest radiography showed clear lung fields. During the procedure, adhesions were cut, and since every segment of the bowel appeared viable, no resections were performed. Postoperatively, the patient was admitted to the ICU in an extubated and hemodynamically stable state. There were no signs of respiratory distress while receiving oxygen, at 4 L/minute, via nasal cannula. His C-reactive protein (CRP) had risen to 160 mg/L (normal ≤ 5 mg/L). Empiric antibiotics (Amoxicillin-clavulanic acid) were started postoperatively. The day after ICU admission, the patient demonstrated increased respiratory distress, and a high-flow nasal cannula was started. On postoperative day 3, the patient's general condition declined, with further rising inflammatory markers (CRP of 400 mg/L), abdominal

pain, and altered mental status. Chest and abdominal CT revealed persistent paralytic ileus without post-surgical complications and bilateral basal pulmonary atelectasis with minor pleural effusion. Respiratory cultures were obtained, antibiotic therapy was converted to piperacillin-tazobactam, and dexamethasone 6 mg daily was started. Cardiac ultrasound demonstrated a normal left ventricular function with no signs of fluid overload and stable mild to moderate mitral and aortic insufficiency. The patient's oxygen requirement gradually increased, and non-invasive ventilation was started on postoperative day 5. Repeat chest radiography revealed bilateral hilar accentuation with infrahilar opacification. By this time, respiratory cultures were reported positive for *Hafnia alvei*, *E. coli*, and *P. aeruginosa*, all susceptible to the patient's current antimicrobial therapy. Given the patient's continuously high oxygen requirement and progressive respiratory distress, endotracheal intubation was performed, and mechanical ventilation was started on the fifth day of his ICU stay. Two days later, the patient's respiratory status declined further, and prone ventilation started. While initially improving his overall respiratory status, refractory hypoxemia with hypercapnia started to set in. Follow-up chest radiography on day 8 revealed multiple bilateral opacities compatible with severe viral bronchopneumonia. Given the patient's age and general condition, he was not deemed a candidate for extracorporeal membrane oxygenation. Despite otherwise maximal supportive therapy, the patient's respiratory status progressively deteriorated, and the patient died after eight days of ICU care.

2.3. Case 3

A 32-year-old woman presented to our hospital in October 2021 with complaints of lower abdominal pain, headache, and sore throat. She was 36 weeks and 5 days into a spontaneous pregnancy. Her medical history included a prior caesarian section, molar pregnancy, and missed abortion. Vital signs upon admission were all normal. Bloodwork was remarkable for thrombocytopenia (platelets $88 \times 10^9/L$, range 150-400 $\times 10^9/L$), slight anemia (hemoglobin 11.3 g/dL, range 11.7-15.5 g/dL), and a slightly elevated CRP (CRP, 28 mg/L, normal ≤ 5 mg/L). White blood cell count was in the normal range, as were serum creatinine and LDH. Liver function tests were slightly elevated with an AST of 39 U/L (normal ≤ 35 U/L) and GGT of 83 U/L (normal ≤ 40 U/L). Nasopharyngeal PCR screening for SARS-CoV-2 infection upon admission was positive, with a viral load of more than 10 million copies/mL. The patient had no respiratory symptoms or fever and had refused a COVID-19 vaccine because of her pregnancy. Following her presentation, she was hospitalized for further observation. After two days, the patient developed pro-

gressive thrombocytopenia (platelets decreasing to $61 \times 10^9/L$) and increasing liver function tests (AST of 140 U/L, ALT of 90 U/L, GGT of 150 U/L), raising concern for HELLP syndrome. An emergent caesarian section was performed on the same day. Preoperatively, she experienced no respiratory symptoms with normal oxygen saturation and breathing room air. The procedure was complicated with an abdominal wall hematoma, based on an arterial abdominal wall hemorrhage visualized on CT, necessitating red blood cell transfusion and eventually a debridement three days later. Abdominal CT also revealed bilateral basal pulmonary atelectasis. Postoperatively after the debridement procedure, the patient experienced mild dyspnea and was treated with supplemental oxygen, at 2L/minute, via nasal cannula. On the 6th day of her hospital course, the patient was admitted to the ICU for hemodynamic observation. Upon admission, the patient still experienced no signs of respiratory distress, but here oxygen requirement increased to 4 L/minute oxygen. Mild bilateral basal infiltrates were confirmed on chest radiography. Amoxicillin-clavulanic acid was administered prophylactically for five days after the debridement procedure. Given her bilateral infiltrates, mild oxygen requirement, and the previous positive COVID-19 PCR test, dexamethasone 6 mg daily was initiated. Her respiratory status gradually declined on the third day of her ICU stay, and therapy with a high-flow nasal cannula was started. Follow-up chest radiography showed progression of the pulmonary infiltrates. A chest CT on day 9 of her ICU admission revealed severe bilateral consolidations, ground-glass opacities, and a large pneumomediastinum. Consecutively, she was intubated, and prone ventilation was initiated because of respiratory failure. Pulmonary pressures were minimized, given her pneumomediastinum. The next day, refractory hypoxemia was evident, and veno-venous extracorporeal membrane oxygenation (VV-ECMO) was initiated. Given the patient's clinical course and increased inflammatory markers, dexamethasone was replaced by IV methylprednisolone 40 mg twice daily, and empirical piperacillin-tazobactam was started. This was subsequently downscaled to amoxicillin-clavulanic acid for hospital-acquired pneumonia, with bacterial cultures showing *Klebsiella pneumoniae*. In the following weeks, the patient's respiratory status improved, and she was successfully decannulated on day 38 at the ICU after 28 days of VV-ECMO. The next day, a percutaneous tracheostomy was placed, after which she was successfully weaned off ventilator support. The tracheostomy was removed on day 47. The patient was neurologically alert, interactive, and co-operating in her rehabilitation, resulting in a discharge from the ICU in good health on day 52.

2.4. Case 4

In November 2021, an 82-year-old male was admitted to the hospital for a semi-urgent complete thyroidectomy because of severe refractory amiodarone-induced hyperthyroidism. The patient's medical history included arterial hypertension, mild chronic kidney disease, paroxysmal atrial fibrillation, cholecystectomy, and laparoscopic low anterior resection for stage I adenocarcinoma. The hyperthyroidism was treated with high-dose methylprednisolone, starting five weeks before the thyroidectomy. Preoperative screening 2 days before surgery with a nasopharyngeal PCR was positive for SARS-CoV-2 and showed a high viral load of more than 10 million copies/mL. The patient had been vaccinated twice with the Pfizer vaccine, respectively, seven and six months prior to this test.

Given the patient's severe symptoms of hyperthyroidism, a thyroidectomy was performed despite the patient's confirmed COVID-19 infection. In the immediate postoperative phase, the patient progressed well, with a minor cough but without any signs of respiratory distress. Methylprednisolone 8 mg daily was started as part of a tapering regimen for his preoperative high-dose methylprednisolone intake. On the second postoperative day, the patient was noted to be hypoxic with a peripheral oxygen saturation of 90% on room air without respiratory distress, for which supplemental oxygen was started. His inflammatory markers were mildly elevated, with a CRP of 58 mg/L (normal ≤ 5). Chest radiography revealed mild bilateral basal infiltrates. Methylprednisolone was replaced by dexamethasone 6 mg once daily according to local practice in COVID-19 pneumonia. In the following days, the patient's inflammatory markers and oxygen requirement gradually increased, eventually requiring transfer to the ICU on postoperative day five. Upon ICU admission, the patient's inflammatory markers were further elevated (white blood cell count of $13.62 \times 10^9/L$ (range 4.5 - 11.0) and CRP of 130 mg/L), and therapy with high-flow nasal cannula was started. The next day, his respiratory status further declined, and non-invasive ventilation (NIV) was initiated. However, this was poorly tolerated by the patient, who showed progressive respiratory distress and hypoxemia, for which he was intubated and prone. Low-dose vasopressors had been started several hours before initiation of NIV because of fluid-refractory hypotension, with progression to severe hemodynamic instability after intubation. Empiric antibiotics (piperacillin-tazobactam) were started for presumed severe septic shock. Bacterial cultures until that point had not yielded any positive results. The patient quickly developed severe hypoxic and hypercapnic respiratory failure, despite maximal respiratory support, in combination with progressive lactic acidosis due to his refractory shock state. The patient subsequently died two days

after his admission to the ICU.

3. Discussion

This case series describes four asymptomatic COVID-19 patients developing severe respiratory failure following surgery. All patients eventually required ICU admission and invasive ventilation. Two patients were put on VV-ECMO, and only two patients (50%) eventually survived.

Since the emergence of the COVID-19 pandemic, there is mounting literature pointing toward worse outcomes in COVID-19 patients undergoing surgery compared to non-COVID-19 patients. Lei et al. published a cohort study including 34 patients who all developed complicated COVID-19 pneumoniae after elective surgery (6). Admission to the ICU was required in 15 (44%) cases, and seven (21%) patients died during ICU stay. Shortly after, a more extensive and international cohort study was published by the COVIDSurg Collaborative (7). This study, including 1128 patients with perioperative SARS-CoV-2 infection, concluded that postoperative pulmonary complications occurred in 51.2% and were associated with high mortality.

Mechanisms to explain the observed high mortality rate and exacerbation rate of pulmonary complications due to SARS-CoV-2 infection in surgical patients are yet unclear.

A first hypothesis might be that these observations are due to the natural, spontaneous course of the disease itself. The activation of multiple inflammatory pathways leading to the hyperinflammation state and cytokine storm in COVID-19 has been shown to result in acute respiratory distress syndrome (ARDS) and multi-organ failure in the non-surgical population (8, 9). This hypothesis is supported by the fact that all patients described in this study developed respiratory failure meeting ARDS criteria.

One of the significant molecules described in the pathogenesis of this cytokine storm in COVID-19 is Interleukin (IL)-6 (10). Transcription of IL-6 is stimulated when SARS-CoV-2 enters the host cell by binding to the angiotensin-converting enzyme-2 (ACE2), after which IL-6 is released from the cell and binds to a membrane-bound IL-6 receptor present on immune cells. This leads to the activation of a signaling pathway that is controlled by a negative feedback mechanism. However, occupation of ACE2 by SARS-CoV-2 leads to reduced degradation of angiotensin-2 (Ang2). The increased concentration of Ang2 indirectly leads to the release of a serum IL-6 receptor, which can bind IL-6 and has the ability to trigger a widespread immune response through interaction with other signaling proteins that are expressed by immune cells, as well as by endothelial cells and fibroblasts (10).

Recent data, however, suggest that surgery itself may accelerate and exacerbate the disease progression of COVID-19 (6). Prospective studies during the early COVID-19 pandemic reported the median time from onset of symptoms to ARDS and mechanical ventilation to be 7-12 days and 10-15 days, respectively (11, 12). In contrast, disease progression was remarkably faster in three of the four described cases in this study. The time between surgery and the start of mechanical ventilation because of respiratory collapse (given that they were asymptomatic before surgery) was five days for case 2 and six days for cases 1 and 4. Only in case 3 (pregnancy) was mechanical ventilation initiated later (11 days postoperative). This suggests that concomitant surgery may accelerate a severe COVID-19 disease course, although a difference in SARS-CoV-2 variants could also influence this finding.

Second, surgical trauma itself is known to trigger an immune response (13). The local immune response in trauma plays a role in tissue repair and is mediated by the activation of different immune cells and the release of inflammatory cytokines (14). It is already recognized that excessive tissue damage elicited by severe trauma can trigger an exaggerated local and systemic immune response, which, in turn, can lead to multiple organ dysfunction (14). The effect of this immune response and possible interactions with the immune response elicited by a COVID-19 infection have not yet been investigated in a surgical population infected with SARS-CoV-2. In this population, trauma might induce a postoperative immunosuppressive state with increased susceptibility to septic complications, as described in the non-COVID surgical population (13). Another hypothesis is that surgery enhances the activation of multiple inflammatory pathways leading to a more overwhelming hyperinflammatory response and cytokine storm than already observed in the non-surgical COVID-19 population. This mechanism might be similar to the second hit phenomenon in trauma, where secondary insults (e.g., mechanical ventilation, and concomitant infection) can lead to increased immune activation and organ damage in an already susceptible trauma patient. In the same way, it could be hypothesized that surgical trauma (and everything surrounding the surgical procedure, like mechanical ventilation, transfusion, and infection) could serve as a second hit in the COVID-19-infected patient. This hypothesis seems likely given the fact that common pathways of inflammatory response after surgery, trauma, and SARS-CoV-2 infection have been described in the literature (13, 14). These pathways are all characterized by the expression of inflammatory cytokines like TNF-alpha and interleukin (IL)-6 (13, 14).

A final hypothesis to explain our observations might be a dysregulation of cortisol homeostasis. Surgery is asso-

ciated with a rise in cortisol levels postoperatively, which can remain high for several days after major surgery (15). Also, postoperative morbidity is associated with persistently high cortisol levels and disruption of cortisol circadian rhythm and regulatory mechanisms (15). Similarly, a recent meta-analysis revealed an association between severe COVID-19 disease and high cortisol levels (16). It has been postulated that COVID-19 disease might influence adrenal function and the hypothalamic-pituitary-adrenal axis (17). Multiple mechanisms to explain this interaction have been suggested, including indirect effects like microvascular thrombosis and direct effects, like a viral invasion of adrenal glands and binding of SARS-CoV-2 to ACE2 receptors in the hypothalamus and pituitary gland (17). It has also been suggested that molecular mimicry might play a role, as was demonstrated after the SARS-CoV-1 infection. Indeed, SARS-CoV-2 antibodies might also target ACTH due to similarities in amino acid structure between SARS-CoV-2 and ACTH (18). Therefore, an interaction between the effects of surgery and COVID-19 on adrenal function seems plausible and should be proven by fundamental research.

3.1. Limitations

This article has several limitations influencing its applicability to general clinical practice. Although we described several cases with a worsening COVID-19 disease course after surgery, quantitative data on this phenomenon in the COVID-19 population and comparisons to the non-COVID-19 population are still limited. Additional large prospective cohort and epidemiological studies are required to estimate the magnitude of this phenomenon. Additional studies could allow for a better understanding of the complex mechanisms behind the interactions between surgical trauma and COVID-19 disease and clarify relevant risk factors. Next, we must be aware that COVID-19 is a disease in evolution. The emergence of new variants of the SARS-CoV-2 virus, with differences in clinical presentations and severity, limits the generalizability of our findings. Current guidelines regarding the timing of elective surgery within this patient population are based on data obtained during the first wave of COVID-19, and findings might differ from current variants.

3.2. Conclusions

In conclusion, the present case series suggests that elective surgery in asymptomatic SARS-CoV-2 infected patients might elicit an exacerbated COVID-19 disease course. This study endorses the current international guidelines recommending postponing elective surgery for SARS-CoV-2-positive patients for seven weeks, depending on the severity of the surgery and perioperative morbidities, to minimize postoperative mortality.

Footnotes

Authors' Contribution: BS and ID conceived and designed the evaluation and drafted the manuscript. QC, VV, and IC collected the data. QC, VV, and DV were responsible for the first draft of the manuscript. BS, DV, VS, and ID critically revised the manuscript. QC and VV equally contributed to the manuscript and are therefore shared the first author position. All authors read and approved the final manuscript.

Conflict of Interests: The authors did not receive any funding or research support in the last five years. There were no personal financial interests, company stocks, or patents to report. None of the authors is an editorial board member of this journal.

Data Reproducibility: No new data were created or analyzed in this study. Data sharing does not apply to this article.

Ethical Approval: This study was approved under the ethical approval code of 2022/032 of the Jessa hospital (chairman Dr. Koen Magerman) on 17th March 2022.

Funding/Support: The study was funded solely by departmental funding.

Informed Consent: Due to the retrospective design of this case series and since some of these patients died during the COVID-19 pandemic, informed consent was waived.

References

- Valente R, Di Domenico S, Mascherini M, Santori G, Papadia F, Orengo G, et al. A new model to prioritize waiting lists for elective surgery under the COVID-19 pandemic pressure. *Br J Surg.* 2021;**108**(1):e12-4. [PubMed: 33640936]. [PubMed Central: PMC7799261]. <https://doi.org/10.1093/bjs/znaa028>.
- Mayol J, Fernandez Perez C. Elective surgery after the pandemic: waves beyond the horizon. *Br J Surg.* 2020;**107**(9):1091-3. [PubMed: 32383479]. [PubMed Central: PMC7267488]. <https://doi.org/10.1002/bjs.11688>.
- ASA and APSF Joint Statement on Elective Surgery/Procedures and Anesthesia for Patients after COVID-19 Infection. American Society of Anesthesiologists; 2022. Available from: <https://www.asahq.org/about-asa/newsroom/news-releases/2022/02/asa-and-apsf-joint-statement-on-elective-surgery-procedures-and-anesthesia-for-patients-after-covid-19-infection>.
- El-Boghdady K, Cook TM, Goodacre T, Kua J, Blake L, Denmark S, et al. SARS-CoV-2 infection, COVID-19 and timing of elective surgery: A multidisciplinary consensus statement on behalf of the Association of Anaesthetists, the Centre for Peri-operative Care, the Federation of Surgical Specialty Associations, the Royal College of Anaesthetists and the Royal College of Surgeons of England. *Anaesthesia.* 2021;**76**(7):940-6. [PubMed: 33735942]. [PubMed Central: PMC8250763]. <https://doi.org/10.1111/anae.15464>.
- C. OVIDSurg Collaborative, GlobalSurg C. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia.* 2021;**76**(6):748-58. [PubMed: 33690889]. [PubMed Central: PMC8206995]. <https://doi.org/10.1111/anae.15458>.
- Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *E Clin Med.* 2020;**21**:100331. [PubMed: 32292899]. [PubMed Central: PMC7128617]. <https://doi.org/10.1016/j.eclinm.2020.100331>.
- C. OVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet.* 2020;**396**(10243):27-38. [PubMed: 32479829]. [PubMed Central: PMC7259900]. [https://doi.org/10.1016/S0140-6736\(20\)31182-X](https://doi.org/10.1016/S0140-6736(20)31182-X).
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;**395**(10229):1033-4. [PubMed: 32192578]. [PubMed Central: PMC7270045]. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- Tan LY, Komarasamy TV, Rmt Balasubramaniam V. Hyperinflammatory Immune Response and COVID-19: A Double Edged Sword. *Front Immunol.* 2021;**12**:742941. [PubMed: 34659238]. [PubMed Central: PMC8515020]. <https://doi.org/10.3389/fimmu.2021.742941>.
- Iwasaki M, Saito J, Zhao H, Sakamoto A, Hirota K, Ma D. Inflammation Triggered by SARS-CoV-2 and ACE2 Augment Drives Multiple Organ Failure of Severe COVID-19: Molecular Mechanisms and Implications. *Inflammation.* 2021;**44**(1):13-34. [PubMed: 33029758]. [PubMed Central: PMC7541099]. <https://doi.org/10.1007/s10753-020-01337-3>.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;**395**(10229):1054-62. [PubMed: 32171076]. [PubMed Central: PMC7270627]. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;**395**(10223):497-506. [PubMed: 31986264]. [PubMed Central: PMC7159299]. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- Alazawi W, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and Immune Responses to Surgery and Their Clinical Impact. *Ann Surg.* 2016;**264**(1):73-80. [PubMed: 27275778]. <https://doi.org/10.1097/SLA.0000000000001691>.
- Teuben MPJ, Pfeifer R, Teuber H, De Boer LL, Halvachizadeh S, Shehu A, et al. Lessons learned from the mechanisms of posttraumatic inflammation extrapolated to the inflammatory response in COVID-19: a review. *Patient Saf Surg.* 2020;**14**:28. [PubMed: 32665786]. [PubMed Central: PMC7346848]. <https://doi.org/10.1186/s13037-020-00253-7>.
- Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. *Br J Anaesth.* 2019;**123**(5):570-83. [PubMed: 31547969]. <https://doi.org/10.1016/j.bja.2019.08.011>.
- Amiri-Dashatan N, Koushki M, Parsamanesh N, Chiti H. Serum cortisol concentration and COVID-19 severity: a systematic review and meta-analysis. *J Investig Med.* 2022;**70**(3):766-72. [PubMed: 35058334]. <https://doi.org/10.1136/jim-2021-001989>.
- Vakhshoori M, Heidarpour M, Bondariyan N, Sadeghpour N, Mousavi Z. Adrenal Insufficiency in Coronavirus Disease 2019 (COVID-19)-Infected Patients without Preexisting Adrenal Diseases: A Systematic Literature Review. *Int J Endocrinol.* 2021;**2021**:2271514. [PubMed: 34539780]. [PubMed Central: PMC8443384]. <https://doi.org/10.1155/2021/2271514>.
- Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. *Endocrine.* 2020;**68**(2):251-2. [PubMed: 32346813]. [PubMed Central: PMC7186765]. <https://doi.org/10.1007/s12020-020-02325-1>.