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The preoperative evaluation of post-COVID-19 patients scheduled for elective surgery – What is important not to miss!

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Abstract. – Continuous rise in the number of COVID-19 cases, since it was first diagnosed in 2019, forced the entire medical fraternity to delay elective surgeries. The preoperative evaluation guidelines that were used in the pre-COVID-19 era underwent significant changes, adding modifications to meet the post-COVID patients' specific criteria and requirements. Currently, all patients before or at the time of hospital admission were tested using a nasopharyngeal swab, by RT-PCR for SARS-CoV-2. Apart from this, for a patient undergoing elective surgery in their post-COVID-19 period, it is mandatory to obtain a detailed history of COVID-19 disease/SARS-CoV-2 infection, to identify residual symptoms or any organ dysfunction the infection might have caused. As well as the functional optimization of the patient to achieve the best clinical and biological status before the surgery. After all the systems have been thoroughly investigated, the risk-benefit ratio needs to be calculated, keeping in mind the cytokine storm and inflammatory responses encountered postoperatively. A mere negative RT-PCR test cannot be considered as the only decisive factor to operate, as the post-COVID-19 phase can influence postoperative outcome of the patient. Hence, the pre-operative evaluation protocols of post-COVID patients should be set and followed thoroughly, in order to avoid post-surgical complications. For better surgical and post-surgical management of post-COVID-19 patients, conducting clinical tests, assessing previously administered medications, evaluating the need for deep venous thrombosis prophylaxes, and identifying subclinical inflammatory state are the measures that should be taken.

Key Words:
Post COVID-19 elective surgery, Preoperative evaluation, SARS-CoV-2 infection.

Introduction

The number of positive cases of COVID-19 infection is continuously increasing and as of 12th May 2021, a total number of 159,319,384 people have been diagnosed worldwide[1]. It has been estimated that for every one case of COVID-19 confirmed by reverse transcription-polymerase chain reaction (RT-PCR) testing, 5-10 cases have gone

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undetected, either due to the absence of symptoms or due to poor contact tracing.

The year 2020 has brought a major change in the organization of hospitals due to the overwhelming influx of COVID-19 patients over a very short duration. Healthcare institutions were compelled by the gravity of the situation to reorganize and develop new entry-exit circuits, and to increase the number of beds for the COVID-19 patients. This has led to new triage rules and restricted access to medical services for the non-COVID patients that do not require urgent medical attention. Elective surgeries have been reduced and postponed, prioritizing emergency surgeries and surgeries for neoplastic pathologies. Due to the prevailing circumstances, the waitlist of elective surgeries has become longer, substantially increasing the risk of deterioration of the clinical status of the waitlisted patients. In addition, perinatal mortality and morbidity in infected mothers have taken a toll on many countries[2].

Consequently, in 2021, surgical departments were faced with an unprecedented workload due to pending procedures. A large number of patients who were scheduled for surgery in the upcoming months were/are still suffering from post-COVID-19 syndrome ("Long COVID"/"Long Haulers"). Therefore, the preoperative evaluation guidelines that were used in the pre-COVID-19 era underwent significant changes, adding modifications to meet the post-COVID patients' specific criteria and requirements.

Currently, the common practice requires that all patients, before or at the time of hospital admission should be tested using a nasopharyngeal swab, by RT-PCR for SARS-CoV-2. Only the vaccinated patients in whom at least 10 days have elapsed since their second dose of vaccine or patients with neutralizing antibodies for SARS-CoV-2 are exempted from the RT-PCR testing. If the RT-PCR test results are positive, the surgical procedure is postponed and if this is not possible to postpone, the medical personnel involved in the treatment of the patient are required to wear complete personal protective equipment (PPE), and the patient needs to be placed in isolation after the surgery to avoid the spread of the contagion. Evaluation of risk-benefit ratio is highly important in COVID-19 positive cases requiring surgeries that cannot be further delayed. The decision-making process while evaluating the patient for elective surgeries in a post-COVID-19 phase is even more complex as the clinicians have to be cognizant of factors, such as the virus-induced organ damage, severity of the disease, and the time elapsed post-infection. Incomplete recovery from COVID-19 infection may significantly contribute to perioperative stress[3-5]. Since, both COVID-19 infection and surgical procedures have the potential to induce cytokine storm and oxidative stress, which might prove to be fatal, non-emergent surgeries should be postponed to avoid adverse outcomes[3-6].

Preoperative Evaluation of the Post-COVID-19 Patient

Few important issues that need to be addressed during the preoperative evaluation of the patients, who have suffered from COVID-19, or have had a positive test for SARS-CoV-2 in the recent past are: (a) detailed history of COVID-19 disease/SARS-CoV-2 infection, (b) identification of residual symptoms or organ dysfunctions the infection might have caused, (c) functional optimization of the patient in order to achieve the best clinical and biological status before the surgery.

As long-term effects are continuously studied, researchers have shown that apart from the lung injury, these patients might suffer from multi-organ dysfunctions, as COVID-19 presents with a multitude of pathophysiological mechanisms that might impact the long-term health status. The vast majority of patients infected with SARS-CoV-2 have a quick recovery. While, some might suffer from symptoms that may persist for weeks to months after the infection is cleared and the tests are negative. The most commonly encountered persisting symptoms can be divided into seven categories. Respiratory symptoms frequently encountered in post-COVID-19 patients are shortness of breath, cough, the need for supplemental oxygen, and pulmonary fibrosis. Cardiovascular symptoms include fatigue, chest pain, arrhythmias, worsening of heart failure, and pulmonary embolism. The CNS involvement is also witnessed, with neurological symptoms manifesting as loss of smell and taste, sleep disturbances, concentration problems, memory loss, headache, poly-radiculopathy, and encephalitis. Acute kidney injury (AKI), rashes and skin lesions are effects of the renal involvement in COVID-19, while metabolic imbalances may lead to sudden onset of type II diabetes mellitus (DM) or worsening of type II DM, worsening hypothyroidism, and persistent inflammatory syndrome. Many post-COVID-19 patients have shown long-term psychiatric symptoms such as depression, anxiety disorders and frequent mood swings. Miscella-

neous symptoms include joint pain, muscle pain and intermittent fever.

Apart from investigating the aforementioned problems, the preoperative evaluation will also include a thorough medical history taking; history of allergic reactions and chronic medication (s) taken by the patient.

Preoperative Medication

The medication taken by the patient at home before presenting for surgery must be documented and evaluated for any surgical or anesthetic risk, and decision to discontinue them preoperatively, if necessary, should be made.

1. Antiplatelet medication and anticoagulants – post COVID-19 patients might need long-term anticoagulation due to high risk of thrombotic complications of the disease.
2. Corticosteroid therapy – especially in the case of patients suffering from severe COVID-19 and secondary pulmonary fibrosis require long-term corticosteroid therapy. Corticosteroid administration cannot be interrupted suddenly, but continuing it might increase infection risk, especially in the case of septic surgical interventions.
3. Anti-diabetic drugs – will be adjusted based on glycemic levels and the anticipated fasting period. Insulin might be introduced in the treatment for short intervals.
4. Anti-psychotic drugs – usually should be continued, with an eye on possible interactions with anesthetic medication. Norepinephrine presynaptic stores are affected by monoamine-oxidase inhibitors (MAOIs), SNRIs and TCAs are increasing activity of synaptic norepinephrine. These classes of drugs have the potential of affecting peripheral adrenergic neurotransmission.
5. Statins – should be continued due to their beneficial effects on endothelial function, on stabilizing atheromatous plaques, and reduction of vascular inflammation.
6. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers – their continuation or interruption depends on the reason behind the treatment. If the treatment has been added for left ventricular dysfunction, treatment should be continued for the entire perioperative period. If these medications are used for the treatment of arterial hypertension, no recommendations exist at the time for either continuation or interruption, so in this case local protocols should be followed.
7. Beta-blockers – controversies prevail regarding the perioperative use of beta-blockers following the POISE study. The latest recommendations are that the patients on chronic treatment with beta-blockers should continue it in the perioperative period. Patients scheduled for high-risk surgery with a known history of cardiac ischemia, coronary artery disease, or multiple risk factors for coronary disease, low dose beta-blockers should be initiated, at least one week prior to the surgery. For all other types of patients, this therapy has no proven indications. Treatment with beta-blockers must never be initiated on the day of surgery.

Deep Venous Thrombosis (DVT) Prophylaxis

COVID-19 patients are at a high risk for developing thrombotic complications. Pulmonary embolism (PE) is responsible for 10% of in-hospital deaths. Without DVT prophylaxis, 40-80% of patients with high risk will develop deep vein thrombosis and up to 10% may die due to PE. The risk for DVT is high due to a number of factors: hypercoagulability caused by surgery, cancer, or hormone therapies, blood stasis in venous plexus of the lower limb perioperatively and postoperatively, decreased venous return (in the case of pregnancy, pelvic surgery, pneumo-peritoneum), dehydration, or low cardiac output. Any immobilized patient, even if this is for short period of time, is at risk of developing DVT. The risk should be stratified for all patients, starting from the time of admission and prophylaxis should be started immediately, if required. All post-COVID-19 patients must be considered as having high risk of developing DVT.

Preoperative Blood Tests

Laboratory tests should be ordered only if they bring new information about the patient, and if the results can contribute to diagnosing or adjusting treatment. All interventions should be preceded by acquisition of informed consent. The first step is evaluating the patient's physical fitness based on the ASA classification (Table I)[7], followed by laboratory tests based on the complexity of the surgery (Table II) and the age (Table III). Laboratory test based on the severity of the disease (Table IV). Pregnancy test should be performed for all women of child-bearing age. Screening for sickle cell disease should be performed in all endemic areas (Asia, Africa, Eastern Mediterranean, Middle East).

Table I. American Society of Anesthesiologists (ASA) - Physical Status (PS) Classification System.

ASA PS class	Definition	Examples (adult age)
ASA I	A normal healthy patient	Healthy, non-smoker, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only, without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Parturient' s physiologic state is significantly altered from when the woman is not pregnant, hence the assignment of ASA II for a woman with uncomplicated pregnancy. **The addition of "E" denotes: Emergency surgery.

Bui et al[9] published in January 2021 a model of preoperative assessment for patients recovered from COVID-19 who are scheduled for elective surgery. This can be a very good starting point in the evaluation of individual risk and clinical assessment of the patient before surgery.

Up to 40% of post-COVID-19 patients have altered respiratory function, and their diffusion capacity is also commonly affected[10]. Therefore, in patients with severe COVID-19, computed tomography may be preferred instead of chest X-Ray to assess the regression of pulmonary lesions or progression to pulmonary fibrosis.

Specific to post COVID-19 patients is the assessment of pulmonary function using spirometry (lung functional tests) and lung diffusion capacity tests. These procedures should be performed in every patient that suffered of moderate or severe COVID-19 and is scheduled for major surgery.

Based on these assumptions and on the protocol published by Bui et al[9] we are proposing a modified template of assessing post COVID-19, in order to have a complete view of patient status, including the assessment of the lung function, the most affected organ by SARS-COV-2 infection.

Preoperative Blood Management

In surgery where high intraoperative blood loss is anticipated, patients must be screened for the presence of anemia (hemoglobin levels). Identi-

Table II. Severity based classification of surgical procedures.

Grade	Examples
Grade 1 (minor)	Excision of skin lesions; drainage of a superficial abscess
Grade 2 (intermediate)	Inguinal hernia repair; varicose veins ablation; tonsillectomy; arthroscopy
Grade 3 (major)	Hysterectomy; transurethral resection of the prostrate; lumbar discectomy; thyroidectomy
Grade 4 (major+)	Articular prosthesis; thoracic surgeries; hemicolectomy; radical dissection at the cervical level

Table modified from the original table of "Bedreag O, Papurica M, Sandesc D. Oxford Ghid Practice de Anestezie. Hipocrate 2017; 4: 30".

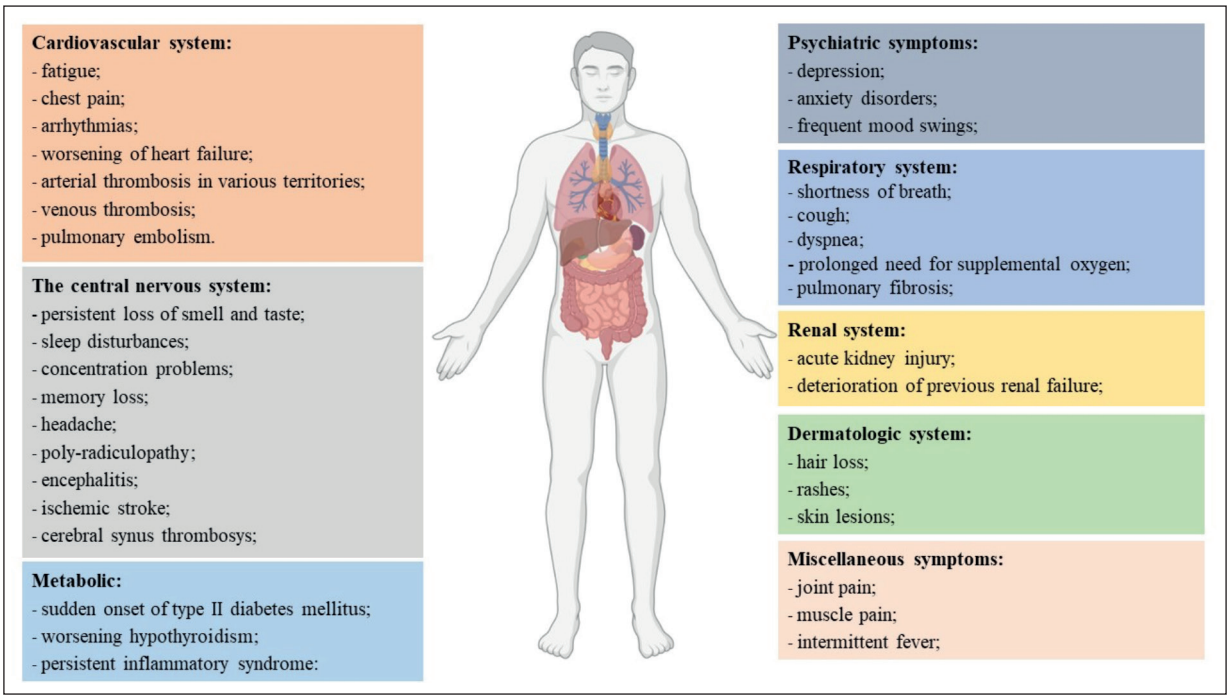

Figure 1. Post COVID-19 symptoms.

fying anemia, treating the cause and mitigating iron deficiency can improve postoperative patient outcome. In order to accomplish this goal, patients should be evaluated at least 1 week before surgery, and evaluation should include: complete blood count (CBC) (for diagnosing anemia), serum ferritin (assessment of iron storages), serum iron, and serum transferrin. These parameters will be used to calculate Transferrin Saturation TSAT (an indicator of iron available for erythropoiesis and required for iron deficiency assessment). C-reactive protein level (CRP) should also be determined (marker of inflammation, for assessing anemia due to chronic diseases). In the presence of anemia, iron deficiency should be diagnosed and corrected by iron intravenous administration before surgery[11]. TSAT below 25% in presence of ferritin level below 100 ng/mL indicates the depletion of iron reserves and leads to a diagnosis of absolute iron deficiency, and therefore, high dose of intravenous iron administration (e.g. 1 g/week) is recommended. In order to analyze all the possible clinical situations, we recommend consulting Perioperative Patient Blood Management Program[12].

Discussion

Prioritization and a proper triage are the key elements for delivering proper medical care by tertiary hospitals, especially during a pandemic, where the demand is high but the resources are limited. New guidelines were implemented based on the surging need to prioritize the surgeries, minimize the high exposure risk and tackle the issue of shortage of staff[13]. American College of Surgeons (ACS), the U.S. Surgeon General, and several medical and surgical professional societies suggest postponing elective surgical interventions during COVID-19 pandemic[14-17]. Moreover, potential modifications were made in the antenatal care and fetal procedures of COVID-19 positive patients, and where feasible, the fetal conditions were alternatively managed neonatally[18,19]. Cavalcante et al[20] stated that presence of SARS-COV-2 infection in pregnant women can lead to intrauterine growth retardation, risk of premature birth, low birthweight. Vertical transmission has not yet been proved in case of COVID-19 pregnant females. Nonetheless, intrauterine fetuses in mothers with SARS-Cov-2 infection can be exposed to pro-inflammatory milieu either directly induced by fetal or placental tissue or indirectly by maternal immune responses[20]. In COVID-19 cases, shifted Th17 immunity has been reported to induce pro-inflammatory cytokine excess, which should be kept in mind and delivery should be planned accordingly[2,21].

Table III. The area % of INOS and VEGF obtained from the different groups of the examined animals.

Grade of severity of the surgical intervention	Age (years)	Chest X-ray	ECG count (CBC)	Complete blood tests	Coagulation creatinine/ electrolytes	Urea/ Glycaemia
1	<16	-	-	-	-	-	-
1	16-60	-	-	-	-	-	-
1	61-80	+/-	-	-	-	-	-
1	>80	+	+	-	-	-	-
2	<16	-	-	-	-	-	-
2	16-60	+/-	+/-	-	-	-	-
2	61-80	+/-	+/-	+	+/-	+/-	-
2	>80	+	+	+	+	+	-
3	<16	-	-	-	-	-	-
3	16-60	+/-	+/-	+	-	+/-	-
3	61-80	+/-	+	+	+	+	-
3	>80	+	+	+	+	+	-
4	<16	-	-	+	-	-	-
4	16-60	+/-	+	+	+/-	+	-
4	61-80	+/-	+	+	+	+	-
4	>80	+	+	+	+	+	-

Based on a study conducted by Ionescu et al[11], on 2953 patients, administration of intravenous iron infusions to patients suffering from iron deficiency anemia can reduce allogenic blood transfusions (ABT) and associated risks. ABT should be preserved only for patients undergoing emergency surgeries and for patients having Hb level < 7 g/dl. Similarly, a study conducted at Wuhan Hospital China by Tao et al[22], reported that the severity of COVID-19 type of respiratory disease can be aggravated if there is underlying anemia present. Levels of C-reactive protein (CRP), procalcitonin (PCT), creatinine, erythrocyte sedimentation rate (ESR), D-dimer, myoglobin, T-pro brain natriuretic peptide (T-pro-BNP) and urea nitrogen in COVID-19 patients with anemia were significantly higher than those without anemia. The severity of dyspnea, elevated CRP, and PCT was positively associated with the severity of anemia in the study conducted by Tao et al[22]. In such cases, it is of utmost importance to investigate and to preoperatively monitor patients who have just recovered from the COVID-19 infection as the high inflammation state can lead to a pre-op and post-op cytokine storm. In addition, the oxidative stress caused by surgical interventions and cytokine storm are considered to be mutually perpetuating[3,5,23]. In atrial fibrillation patients suffering or recovering from COVID-19 infection, thromboembolic events are exacerbated. Therefore, independently from the treatment given to control the rate and the rhythm in patients suffering from atrial fibrillation, anticoagulant is considered to be an indispensable part of the treatment[24-26].

Cytokine storm has always been a major concern in post-surgical patients, especially post

Table IV. Tests prescribed based on the type of concomitant pathology.

Disease	ASA	Chest X-ray	ECG	CBC	Coagulation tests	Urea, Creatinine, Electrolytes	Astrup Parameters
Cardiovascular	2	+	+	-	--	-	-
Cardiovascular	3	+	+	+	-	+	-
Pulmonary	2	+	+	-	-	-	-
Pulmonary	3	+	+	+	-	+	-
Renal	2	-	+	-	-	+	-
Renal	3	-	+	+	-	+	-

Table modified from the original Table of "Bedreag O, Papurica M, Sandesc D. Oxford Ghid Practice de Anestezie. Hipocrate 2017; 4: 30".

Table V. Preoperative assessment of a recovered COVID-19 patient scheduled for elective surgery.

Step/test	Minor procedures and/or without general anesthesia		Major procedures		
	Asymptomatic form of COVID-19 in medical history	Moderate or severe form of COVID-19 in medical history	Asymptomatic	Moderate form of COVID-19 in medical history	Severe form of COVID-19 in medical history
Chest X-Ray	No—if pulmonary exam and O_2 sat normal	No—if pulmonary exam and O_2 sat normal	Yes	Yes	No
Chest Computed Tomography	No—if pulmonary exam and O_2 sat normal	No—if pulmonary exam and O_2 sat normal	No—if pulmonary exam and O_2 sat normal	+/- (can replace Chest X-ray)	Yes
EKG	Yes	Yes	Yes	Yes	Yes
Echo	No—if cardiac exam and vitals normal	No—if cardiac exam, NT-pro-BNP, and vitals normal	No—if cardiac exam, NT-pro-BNP, and vitals normal	Determined by H&P	Yes
CMP	Yes	Yes	Yes	Yes	Yes
CBC, with diff	Yes	Yes	Yes	Yes	Yes
PTT	No	Consider based on severity of illness	Yes	Yes	Yes
D-dimer	No	Yes	Yes	Yes	Yes
Fibrinogen	No	Consider based on severity of illness	Yes	Yes	Yes
NT-pro-BNP	No	Yes	Yes	Yes	Yes
LDH, ferritin, prealbumin	No	Consider based on severity of illness	No	Consider based on severity of illness	Yes
Spirometry (FVC, FEV1, TLC)	No	Yes	No	Yes	Yes
Lung diffusion capacity (DLCO, DLCO/VA)	No	No	No	No	Yes

Abbreviations: CXR: Chest x-ray, EKG: Electrocardiogram, ECHO: Echocardiogram, CMP: Complete metabolic panel, CBC with Diff: Complete blood count with differential, PTT: Partial thromboplastin time, LDH: Lactate dehydrogenase, nt-pro-BNP: N-terminal pro brain natriuretic peptide, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in the first second, TLC: Total lung capacity, DLCO: Diffusion capacity of the lungs for carbon monoxide. VA – alveolar volume. Table modified from the original Table of "Bui N, Coetzer M, Schenning KJ, O'Glasser AY. Preparing previously COVID-19-positive patients for elective surgery: a framework for preoperative evaluation. Perioper Med (Lond) 2021; 10".

abdominal surgeries. Its risk amplifies in the presence of septic shock, which might lead to life threatening multi-organ failure. The concentration of 12 cytokines: tumor necrosis factor (TNF)-alpha, interleukin (IL)-2, 4, 6, 8, 10, 13, IL-1beta, interferon-γ, IL-12p70, monocyte chemotactic protein (MCP)-1, MCP-1α, should be detected in the suspected cases[5,23]. Many respiratory viral infections, including COVID-19 virus, leads to the death of the infected cell, activating the innate immune response and the superfluous secretion of cytokines, which in turn gives rise to oxidative stress[3,5]. Reactive oxygen species (ROS) are extremely important for maintaining a steady state and for proper cell signaling. However, an imbalance between the ROS production and an-

tioxidant protection can lead to oxidative stress with redox reaction disturbances and organ failure. The pathophysiology of OS intertwines with inflammation, cellular level dysfunction, surgery related ischemia/reperfusion injury (IRI)[4]. The intensity of OS is entirely dependent on the amount of tissue injury due to the surgical procedure, the duration of the procedure and the anesthetic procedure instituted[4]. Taking cognizance of the OS that occurs in the severe respiratory distress syndrome in COVID-19, as well as during a surgical intervention, it is extremely important to calculate the time-gap essential to facilitate the complete recovery of the patient between the two, in order to achieve a better post-surgical outcome of elective surgeries in post-COVID infections[27]. Seven weeks gap is the proposed time, but it can vary based on the case. Moreover, prioritizing these patients for vaccination can be beneficial[6,27,28], and administration of exogenous antioxidants during this gap may further improve outcomes[29].

Conclusions

Fully recovered COVID-19 patients undergoing elective surgeries should be evaluated more rigorously compared to the non-COVID-19 population, as the subclinical inflammatory state may compromise the surgical intervention. As ongoing subclinical inflammation in the presence of oxidative stress caused by the surgical procedure can lead to fatal outcomes, a negative RT- PCR test result should be followed by pertinent lab investigations to determine the levels of pro-inflammatory cytokines such as IL-6. Recovering COVID -19 patients with higher than optimal levels of serum inflammatory markers should be rescheduled for elective surgeries to afford them the time for a full recovery and improve post-surgical outcomes.

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Conflicts of interest
The authors declare no conflicts of interest.

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