Risk stratification in SARS-CoV-2 positive patients undergoing surgery

Corona virus disease, first identified in the population of Wuhan, China in December 2019 has rapidly spread across the globe causing widespread devastation. It has been declared as a pandemic on the 11th of March 2020. [1] It has spread rapidly and easily since human beings had no immunity to the novel virus. No vaccine has been developed nor there an established pharmacological prophylaxis to the virus to date. With nation-wide lockdown which started from March 25th 2020, all elective surgical procedures have been suspended at health care facilities all over India. The lock-down restrictions were lifted in a phased manner from 1st June, 2020. People started resuming their duties and the hospitals became fully operational.

With the increasing trend of COVID-19 cases in India but with resumption of elective surgeries at health care facilities, it becomes necessary to operate on patients infected with SARS-CoV-2 more often. However, little is known of the effect of COVID-19 on the perioperative outcomes. Patients with COVID-19 are a vulnerable group as surgical intervention could stimulate the stress responses, thereby amplifying the pro-inflammatory and immunosuppressive responses.[2,3] It is necessary to do a risk stratification of the surgical cases to balance the complications of surgery due to COVID-19 and the risks of delaying surgery.

Complications of surgery due to COVID-19:

According to the coronavirus guidelines, COVID-19 is generally categorised into mild, moderate, severe and critical.[4] Mild and moderate cases account for more than 4/5th of COVID-19 patients.[5] Early identification of the severe and critical cases is essential as they are associated with poor outcomes, particularly if not intervened timely.[6] From the surgical point of view, it is necessary to identify the patients with COVID-19 who are likely to have poor outcomes with surgery.

Kayani et al. in their study on patients who underwent hip fracture surgery found that patients with COVID-19 had increased postoperative complications and higher mortality rate (3 times greater) compared to those without COVID-19.[7] They found that COVID-19-positive patients had increased risk of postoperative complications (89.0% versus 35.0% respectively), more critical care unit admissions and increased length of hospital stay compared to COVID-19-negative patients. Lower respiratory tract infections, thromboembolic disease and acute kidney injury were found to be the most common complications.

The COVID-Surg collaborative group performed an international cross-speciality cohort study on 1128 patients across 24 countries and observed that the overall mortality was 23·8% (268 of 1128 patients).[8] Pulmonary complications occurred in 577 (51·2%) patients and accounted for 82·6% (219 of 265) of all deaths.

Doglietto et al. in their study on a surgical cohort of patients (41 patients with COVID-19, 81 controls) observed a significant mortality in the COVID-19 group (8 patients [19.51%] vs 2 patients in control group [2.44%]. [9]They reported that patients with COVID-19 were approximately 13 times more likely to have complications than controls. Pulmonary and thrombotic complications were significantly associated with COVID-19.

Thakrar et al. in a prospective observational study on 43 patients presenting to their center with hip fractures found that 4 patients tested positive for SARS CoV-2 among the seven mortalities encountered.[10] They reported that a positive COVID-19 test result in patients with hip fractures was associated with a 2.4-fold increase in risk of 30-day mortality.

Deng et al. in their clinical study on a non-surgical cohort of 109 patients who died and 116 patients who recovered from COVID-19 found that complications such as ARDS, acute cardiac injury, acute kidney injury, shock, and DIC were more common in the death group.[11]

Risk factors for poor prognosis in patients with COVID-19:

Though spine surgeons are not on the frontline in treating patients with COVID-19, knowledge of the risk factors associated with poor prognosis in a patient with COVID-19, particularly in the surgical cohort is absolutely essential. A wise decision on the management options should be based on a thorough understanding of these factors. Though the evidence on this topic is still emerging, it is necessary for surgeons to be up to date on the existing

evidence. **Table 1** summarizes the various risk factors that have been studied to effect prognosis in COVID-19.

Demographic variables:

Many studies including those by **Zhou et al,[12] Chen et al,[13] Zhang et al,[14]** and **Liu et al.[15]** found that older age was associated with a poor prognosis in COVID-19. **Doglietto et al.** found that age was found to be a significant factor for complications; for each additional year, there was a 1.04 higher OR for complications.[9]

The COVID Surg Colloborative found that male sex and age 70 years or older were independent risk factors for mortality in patients infected with SARS-CoV2.[8] This was similar to the findings of **Albitar et al.[16]**

Parohan et al. performed a meta-analysis of risk factors for mortality in COVID-19 and concluded that older age (≥65 years old) and male sex were associated with greater risk of death from COVID-19 infection.[17] Older age was associated with a 459% (over fourfold) increased risk of COVID-19 mortality.

Co morbidities:

Smoking: Kayani et al. found that smoking was associated with a 15 fold increase in postoperative mortality. [7] Findings of **Guan et al.[18]** and **Liu et al.[15]** also suggested smoking to be associated with increased risk of complications.

Smoking particles can distort airway architecture and inhibit ciliary airway clearance. The secretion of IL-22 responsible for the lung protection may be inhibited by nicotine.[19] Smoking can exert its immunosuppressive effects on immune surveillance through functional impairment of the dendritic cell system. Nicotine can also impair the immune response by local secretion of catecholamines and corticosteroids.[20] The expression of the membrane-bound respiratory ACE-2 host receptors can be upregulated, thereby increasing virus-cell binding and translocation of the virus into lung tissues.[21]

Hypertension: Many studies including those by **Wang et al.[22]** and **Yang et al.[23]** have reported hypertension as a risk factor for poor prognosis. **Fang et al.** reported that the use of Renin- Angiotensin System (RAS) Inhibitors may alter the ACE2 expression and influence

the virulence of COVID-19.[24] However, more recent studies by **Mehra et al.[25], Mancia et al.[26],** and **Reynolds et al.[27]** have challenged this and called for more definitive studies. A review by **Luciano et al.[28]** summarized that there is no scientific support to claim that hypertension or its treatment with RAS inhibitors contribute to unfavourable outcomes in COVID-19. They commented that age or other key factors that contribute to health were not considered as potential confounders in risk prediction in the studies to date.

Kayani et al. observed that multiple (greater than three) comorbidities(cardiac, respiratory, abdominal, neurological, musculoskeletal) were associated with 13-fold increase in postoperative mortality.[7] **Wang et al.** reported that underlying respiratory disease was a major risk factor for mortality.[22]

Parohan et al. in his meta-analysis (aforementioned) concluded that hypertension and diabetes were associated with over two-fold, and cardiovascular diseases, COPD (chronic obstructive pulomonary disease) and malignancies were associated with over three-fold higher risk of COVID-19 mortality, respectively.[17] Hypertension and diabetes were idenitifed as independent risk factors for mortality in the study by **Albitar et al.** as well.[16]

Nandy et al. performed a meta-analysis of 16 published studies with 3994 patients on the impact of various comorbidities on serious events in COVID-19.[29] They found that presence of COPD, chronic kidney diseases, and cardiovascular diseases had a 6.6, 5.3, and 4.5 times, respectively, greater chances of progressing to severe events. Diabetic patients had 3.07 fold higher chances of severe events according to their analysis.

Clinical parameters:

Patients with clinical signs of pneumonia and respiratory rate >30 breaths/min, severe respiratory distress or SpO2< 90% on room air are considered to have severe COVID-19 and carry worse prognosis compared to mild/moderate cases.[30]

Lab and radiological parameters:

Liao et al. in their retrospective cohort study published in The Lancet reported that the incidence of coagulopathy was higher in patients who had mortality, with abnormal coagulation tests or typical signs, including bleeding, thrombotic complications, and unexplained organ failure.[31] Dynamically monitoring platelet count, D-Dimer, prothrombin

time and neutrophil to leucocyte ratio may provide reliable and convenient method to assess severity of COVID-19.

Zhou et al. in their study published in The Lancet on 191 patients who were hospitalized with COVID-19 found that elevated D-Dimer levels and high SOFA (sequential organ failure assessment) score could help early identification the patients with poor prognosis.[12]

For patients with diabetes and COVID-19, **Chen et al.** reported that increasing odds of in-hospital death were associated with elevated CRP, whereas risk factors for poor prognosis were lower albumin and higher CRP.[12]

Yang et al concluded that elevated neutrophil to leucocyte ratio is an independent prognostic factor in COVID-19 patients.[32]

Lee Dickens et al. proposed a simple 48h 'Rule-of-6': using ferritin > 600 µg/L, LDH > 600U/L and CRP > 60 mg/L to aid early identification of COVID patients at risk of disease progression.[33]

In patients with mild/moderate symptoms due to COVID-19, **Zhang et al.** observed that CT chest features such as ground-glass opacity, reticular/linear, air bronchogram, or consolidation shadow were associated with poor prognosis.[14]

Tabatabaei et al. reported that chest CT features of consolidation, air-bronchograms, crazy paving, central lung involvement, and pleural effusion are more commonly observed in the critically ill patients.[34]

Table 2 summarizes the clinical, radiological and laboratory criteria to distinguish mild, moderate and severe COVID-19.

Surgical parameters:

The COVID-Surg Colloborative group identified American Society of Anesthesiologists (ASA) grades 3–5, surgery for malignant disease, emergency surgery, and major surgery as independent risk factors for mortality in patients infected with SARS-CoV2.[8]

Recommendations

We recommend that thresholds for surgery during the SARS-CoV-2 pandemic should be raised compared to normal practice. Men aged 70 years, Pt qualifying in "Rule of 6",CT chest

grades 3-4,ASA grade 3-5 undergoing emergency surgery are at particularly high risk of mortality, so these patients may benefit from their procedures being postponed.

Conclusions:

Identification of various risk factors for mortality/complications in COVID-19 is necessary to improve the prognostic stratification of cases and provide appropriate multidisciplinary care. Knowledge of these factors can allow for more informed discussion with the COVID-19 patients and attendants regarding the surgical decision. The decision of surgical management has to be individualized based on the condition of the patient, the risk factors and the "essentiality" of surgery. Patient safety-driven algorithms which have clinical relevance have to be designed to provide appropriate surgical care to the patient. The facilities available at the hospital to deal with sick COVID-19 patients also have to be kept in mind before taking a decision. Since how long the COVID-19 outbreak shall prevail is unknown, a wise decision on whether to perform surgery/ delay for a specific time-frame/ defer surgery has to be taken to provide optimal outcomes.

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Table legends:

Table 1: Risk factors which have been studied to have poor prognosis in COVID-19

Table 1	
Demographic variables	Older age Male gender
Co-morbidities	Smoking Hypertension(controversial) Cardiovascular diseases Chronic obstructive pulmonary disease Chronic kidney disease Malignancy
Laboratory parameters	Elevated D-Dimer levels High SOFA (sequential organ failure assessment) score Low albumin Increased WBC count Lymphopenia Low platelet count Elevated prothrombin time High neutrophil to leucocyte ratio 'Rule-of-6'[ferritin > 600 μg/L, LDH > 600U/L and CRP > 60 mg/L]
Radiological parameters	Chest CT features : ground-glass opacity, reticular/linear, air bronchogram, or consolidation shadow
Surgical parameters	ASA grades 3–5 Surgery for malignant disease Emergency surgery Major surgery

Table 2: Clinical, radiological and laboratory guidelines to identify clinically severe COVID-19. Provided by the MOHFW (Ministry of Health and Family Welfare), India[30]

Table 2			
	Mild	Moderate	Severe
Clinical Criteria			
SPO_2	> 94 % in Room Air	90 - 94 % in Room Air	< 90 % in Room Air
RR	< 24 / min	24 – 30	> 30
	No Pneumonia	Pneumonia +	Pneumonia ++
CT Chest Criteria			
	Normal or < 25 %	25 % - 75 %	75 % to 100 %
	Grade I	Grade II / III	Grade IV
Laboratory Findings (Expected)			
NLR	< 3.2	> 3.2	> 5.5
CRP	< 40	40 – 125	> 125
Ferritin	< 500	> 500	> 800
D-Dimer	< 0.5	> 0.5	> 1.0
LDH	< 300	300 – 400	> 400
IL6	< 4.8	5 – 50	> 80
LFT	Normal	Slight Derangement	Moderate Derangement