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Original study

Effect of general anaesthesia with mechanical ventilation on biomarkers of lung inflammation/injury in COVID-19 survivors – A cohort study

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Abstract

Background: **A rise in biomarkers of lung injury with intraoperative mechanical ventilation in patients with healthy lungs may herald postoperative pulmonary complications (POPC). However, perioperative cytokine responses to mechanical ventilation in patients with previous SARS-CoV-2 associated pulmonary involvement are unknown.**
Objectives: **To monitor proinflammatory cytokine responses to intraoperative mechanical ventilation in Corona virus disease-19 (COVID-19) survivors with COVID-associated pulmonary involvement and determine utility of these biomarkers in predicting POPC.**
Design: **A prospective cohort study.**
Setting: **Operating room, postoperative recovery area.**
Methods: **Twenty-four patients with previous COVID-related lung involvement (group 1) and 20 patients with no/presumably no COVID-19 infection (group 2) undergoing various surgeries under general anaesthesia were recruited. General anaesthesia and ventilation were managed similarly in two groups. Bronchoalveolar lavage fluid (BALF) samples were collected at onset of ventilation and at end of surgery. Serum samples were collected at same timepoints and 1-hour postoperatively.**
Main outcome measures: **Concentrations of interleukin-8 (IL-8) and tumour necrosis factor α (TNFα) were measured using Enzyme-linked immunosorbent assay, interleukin-6 (IL-6) by Chemiluminescence immunoassay and C-Reactive protein (CRP) by immunoturbidimetry on automated analyzers.**
Results: **Patient demographics were comparable in both groups except age and American society of Anaesthesiologists classification. Rise of BALF IL-6 and IL-8 was more significant in group 1 ($P < 0.001$), compared to group 2 ($P < 0.05$ for IL-6 and $P < 0.01$ for IL-8). A significant increase in serum IL-6 correlated well with serum CRP at several timepoints in group 1. In both groups, BALF and serum TNF α was below detection limit. Only one patient in group 1 developed POPC.**
Conclusions: **Despite a significant perioperative elevation of IL-6 and IL-8 in BALF, when mechanically ventilated, incidence of POPC did not increase in COVID survivors with prior COVID-associated pulmonary involvement. However, this needs to be validated on a larger sample size.**

Keywords: **Remote COVID-19 pulmonary involvement, mechanical ventilation, cytokines, postoperative pulmonary complications.**

This observational study was approved by Institute Ethics Committee (Name: Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi, India; Protocol number: EC/08/17/1250, Chairperson of the ethics committee: Dr. Atul Sharma; Date of approval: 06-05-2022). A written informed consent was taken from all the patients recruited. The study was conducted in accordance with the Declaration of Helsinki and the STROBE guidelines were adhered to.

Introduction

Intraoperative mechanical ventilation is one of the risk factors for postoperative pulmonary complications (POPC). Several studies demonstrate mechanical ventilation induced postoperative rise of biomarkers[1-5]. An early detection of this postoperative rise of inflammatory mediators can predict the occurrence of POPC6,7. However, all this published literature is on non-injured lungs.

In critical care settings, mechanical ventilation of Acute-respiratory distress syndrome (ARDS) afflicted lungs showed an elevated cytokine response[8]. However, cytokine responses of the 'pre-injured' lungs to the relative short duration of intraoperative mechanical ventilation are not well studied. Given the scale of the pandemic, the probability that a patient scheduled for surgery under general anaesthesia (GA) being previously infected with SARS-CoV-2 and with a Corona virus disease (COVID) associated pulmonary involvement is high. However, the utility of biomarkers to predict POPC and perioperative morbidity in this patient cohort has never been explored. Also, not much is known regarding the pulmonary consequences of intraoperative mechanical ventilation in these COVID-19 survivors.

Hence, the current study was undertaken to determine the effect of intraoperative mechanical ventilation on lung inflammatory markers in 'COVID-19 survivors with COVID-associated pulmonary involvement'. We aimed to evaluate the association of biomarkers with occurrence of POPC. We intended to correlate the severity of COVID-19 associated lung infection as determined by CT severity score during SARS-CoV-2 infection with the perioperative biomarkers. We also aimed to evaluate difference in hospital stay in patients with and without COVID-associated pulmonary involvement.

Methods

Study population

After approval from Institute Ethics Committee (Name: Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi, India; Protocol number: EC/08/17/1250, Chairperson of the ethics committee: Dr. Atul Sharma; Date of approval: 06-05-2022), a total of 44 adult patients, American Society of Anaesthesiologists (ASA) physical status I – III scheduled for extra thoracic surgery under GA were enrolled for this prospective cohort study at a tertiary care hospital (Total study duration: December 2021 to March 2023). Patients with lung pathology (Chronic obstructive pulmonary disease, interstitial lung disease, previous pulmonary tuberculosis etc.), ongoing immunosuppression, an elevated leukocyte count, clinical signs of a systemic infection, intra-thoracic surgery and ASA class IV were excluded from the study. A written informed consent was taken from all the patients recruited. The study was conducted in accordance with the Declaration of Helsinki and the STROBE guidelines were adhered to.

Patients were categorized as follows depending on the prior COVID-19 status.

Group 1: Patients with 'moderate to severe' COVID-19 infection defined as patients confirmed positive for SARS-CoV-2 prior to surgery and with >1 of following: a) pulmonary symptoms during COVID infection b) chest X-ray/ Contrast enhanced computed tomography (CECT) chest findings suggestive of COVID-19 infection c) oxygen supplementation during COVID-19 infection. The X-ray findings suggestive of SARS-CoV-2 infection included consolidation, interstitial thickening, ground glass opacities, pulmonary nodules, pleural effusion, pneumothorax. The CECT findings implying SARS-CoV-2 pneumonia included ground glass opacity, crazy-paving, consolidation, fibrosis, subpleural lines, pleural effusion and lymphadenopathy. Patients with > 6-week interval between COVID-19 infection and the scheduled surgery were included for the study.

Group 2: Patients with 'no or presumably no' COVID-19 infection defined as patients who were either truly never infected with SARS-CoV-2 or despite being infected, remained undiagnosed or asymptomatic for COVID.

As none of the reported studies have explored the markers of lung inflammation in COVID -19 survivors when mechanically ventilated, we recruited 24 consecutive patients with moderate to COVID-19 infection over 1 year duration. Twenty patients were recruited in group 2.

Procedure and data collection

Demographic data such as age, gender, body mass index (BMI), ASA grade with comorbidities were noted. An attempt was made to match the baseline characteristics among the study groups. Details of COVID-19 infection like symptoms, chest X-ray and CECT chest findings, hospitalisation, medications, oxygen delivery device, ventilator requirement and duration of hospital stay were recorded for group 1. In cases where CECT chest was available, CT severity score was noted (0 to 25).

Anaesthesia management

Anaesthesia was induced with inj. propofol 2 to 2.5 mg kg-1 and fentanyl 2 mcg kg-1. Trachea was

intubated following intravenous administration of atracurium 0.5 mg kg-1.

Ventilation strategies

Patients were mechanically ventilated on volume control mode: Vt of 6 ml kg-1 predicted bodyweight, an inspiratory/expiratory ratio of 1:2, FiO2 of 0.5, PEEP 5 cmH2O and a respiratory rate adjusted to maintain EtCO2 35 to 45 mm Hg and airway plateau pressure < 30 cm H2O. Anaesthesia was maintained with isoflurane in 50% oxygen: air mixture. Oxygenation and ventilation parameters like SpO2, EtCO2, peak airway pressure, compliance and minute ventilation were monitored. Type and duration of surgery were recorded.

Bronchoalveolar lavage fluid (BALF) and blood sample collection

Bronchoscopy was performed through endotracheal tube using Ambu R a Scope TM4 Broncho Regular 5.0/2.2, Denmark. With the distal end of the scope wedged in the right middle lobe, sterile saline solution (10 ml) was instilled, gently aspirated and placed immediately on ice. BALF collection was performed twice, just after the intubation (baseline) and at the end of surgery. Venous blood (5 ml) was also collected in serum separating vial at three time points – just after intubation (baseline), at the end of surgery and one-hour post-surgery. BALF and blood samples were centrifuged at 3000 rpm for 10 minutes. The BALF supernatant and serum samples were stored at -80°C until analysed.

Cytokine measurements

Concentration of C-reactive protein (CRP), Tumour necrosis factor α (TNF α), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) was measured in each sample of BALF supernatant and serum. TNF α and IL-8 was measured by sandwich Enzyme-linked immunosorbent assay (ELISA) kits (Diaclone SAS, France) on-spectrophotometer (Xmark microplate spectrophotometer, BIO RAD USA) as per manufacturer's instructions. IL-6 levels were analysed by Chemiluminescent immunoassay (CLIA) on DXI 800 immunoassay analyser (Beckman coulter). CRP levels were measured by immunoturbidimetric assay on Cobas C702 systems (Roche). All samples were run in duplicate and analysed.

POPCs like occurrence of unexpected hypoxemia necessitating supplementary oxygen, bronchospasm, pulmonary infection, aspiration pneumonitis, ARDS / acute lung injury, atelectasis, pleural effusion, pulmonary edema, pneumothorax were noted till 30 days postoperatively. The length of hospital stay was also recorded.

Statistical analysis

Data was recorded in a predesigned proforma and managed on an excel spreadsheet. Categorical variables were summarized as frequency (percentage) and analyzed using $\chi 2$ or Fisher's exact test. Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range and analyzed using either parametric (independent t-test) or nonparametric tests (Mann Whitney U-test), as appropriate. Pearson or Spearman correlation analysis was performed as required. Statistical analysis was performed using SPSS software version 24. P value < 0.05 was considered statistically significant.

Results

Study population

The patient flow is depicted in Figure 1. Over the study duration of 1 year, we screened a total of 146 patients who were at some time point infected with SARS-CoV-2, as confirmed by a positive report. Of these, 24 patients who fulfilled our inclusion criteria of prior COVID-19 associated lung involvement were recruited in the group 1. Twenty patients were enrolled in group 2. Thus, a total of 44 patients were recruited for the study.

Baseline data are presented in Table I. With respect to the demographics, no significant intergroup differences were found in gender and BMI. However, patients in group 1 were significantly older, with a higher ASA grade than group 2.

The median duration of surgery in either group was similar (120 min in group 1 versus 135 min in group 2).

COVID-19 associated history in Group 1

In the patients recruited, the interval between being tested as SARS-CoV-2 positive and the scheduled surgery was between 6 months to 2 years. Fever (96%), dry cough (62%), breathlessness (46%), loss of smell (38%) loss of taste (33%), headache (25%), body-ache (17%), sore-throat (12%) and diarrhoea (12%) were the common symptoms. Consolidation, pleural effusion, pleural thickening, ground glass opacities, interstitial thickening were the common Chest X-Ray and CT findings reported. The CXR (n=9) and CT scan (n=3) were not available in few patients. Most of the patients received oxygen support via face mask (71%), rest being nasal prongs (17%), HFNC (12%) and CPAP (4%). One of the recruited patients had a prior history of invasive mechanical ventilation, but due to haemolysed blood sample and an inadequate BALF sample, the patient had to be excluded

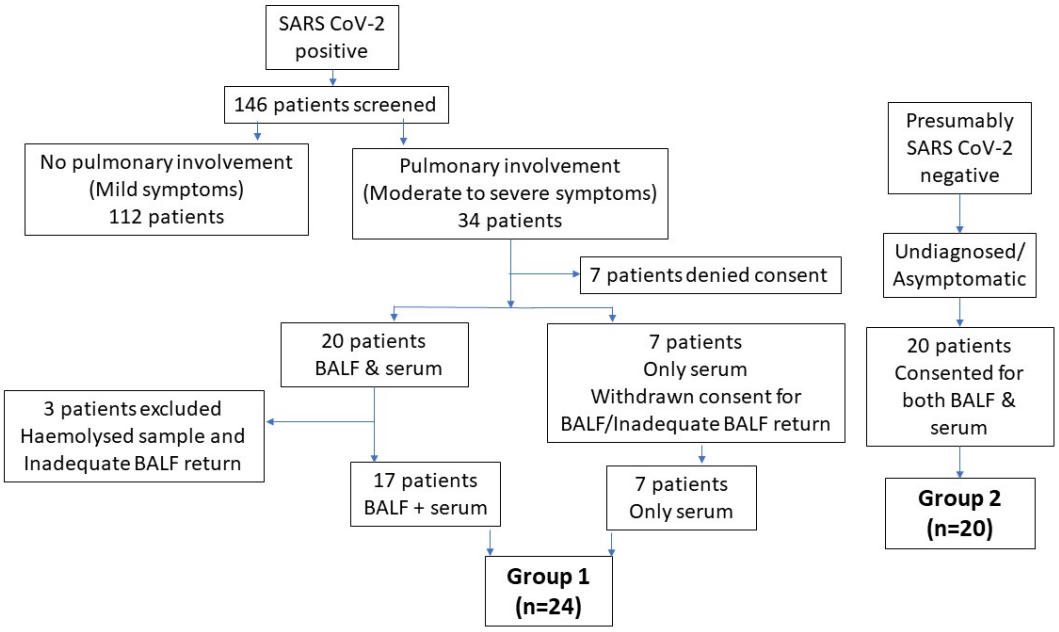

Fig. 1 — Patient flow diagram (BALF- Bronchoalveolar lavage fluid).

Table I. — Demographics and Surgery profile.

Parameters	Group 1 (n = 24)	Group 2 (n=20)	P value
Female: Male	11:13	6:14	0.35
Age	56.6±11.7	35.3±12.1	< 0.00001*
BMI (kg/m2)	26.0 ± 5.20	24.9 ± 4.38	0.48
ASA grade I	9	17	0.02*
ASA grade II	13	3	
ASA grade III	2	0	
Surgical characteristics			
Urology	8 (33%)	7 (35%)	
Gastrointestinal surgery	8 (33%)	6 (30%)	
Plastic surgery	16.5%	25%	
ENT surgery	16.5%	10%	
P < 0.05 significant. (BMI- Body mass index, ASA- American society of Anaesthesiologists, ENT- Ear, nose and throat).			

from our study. Patients were either treated with steroids (83%), remdesivir (12%) or were treated symptomatically (8%). Out of the 24 patients, 4 patients were managed at home with oxygen support and steroids/symptomatic treatment due to the non-availability of hospital beds. The median duration of hospital stay during COVID-19 infection was 7 days.

Cytokine profiles in BALF

Median IL-6 and IL-8 levels in BALF for both the groups at 2 time points are presented in Table II. The intergroup comparison at each timepoint for each of this biomarker showed no significant difference However, the levels of IL-6 and IL-8 increased significantly from baseline towards the end of surgery in both the groups. This increase in IL-6 and IL-8 was greater in group 1 (P <0.001) compared to group 2 (Table II). Levels of TNF α (< 8 pg ml-1) and CRP (< 0.5 mg dl-1) were below the detectable limits in both the groups despite the serial dilutions.

Cytokine profiles in serum

Serum levels of each biomarker (IL-6, IL-8 and CRP) in both the groups at 3 timepoints are presented in Table II. Serum levels of IL-6 were significantly elevated at baseline in Group 1 compared to Group 2 (P< 0.004). However, 1-hour past surgery, the levels significantly increased from baseline in each of the groups (p < 0.01) (Table II, Figure 2). For IL-8 and CRP, there was no intergroup difference at any timepoint. Also, intraoperative rise of these biomarkers was not significant in either of the groups. TNF α (< 8 pg ml-1) was below the detection limits in both the groups despite the serial dilutions.

Table II. — Median values of biomarkers in BALF and serum at various time points in study groups.

Biomarker		Baseline	End of surgery	1hr post-surgery
BALF IL-6	Group 1	4.15 (0.51 – 11.75)	16.1 (9.18 – 70.3) α***	
	Group 2	7.50 (1.77 – 20.7)	20.6 (13.4 – 92.1) α**	
BALF IL-8	Group 1	42.5 (31.7 – 125.9)	439.7 (158.6 – 954.9) α***	
	Group 2	151.4 (37.8 – 405.8)	498.6 (82.6 – 949.6) α*	
Serum IL-6	Group 1	5.91 (2.75 – 15.5)	14.9 (7.67 – 32.6)	24.5 (15.4 – 64.2) β***
	Group 2	2.60 (1.41 – 6.70)	7.81 (4.65 – 28.0) α*	21.6 (6.94 – 45.3) β***
Serum CRP	Group 1	4.65 (1.25 – 11.2)	5.40 (1.40 – 10.6)	5.20 (2.60 – 16.9)
	Group 2	2.85 (0.83 – 13.2)	3.15 (0.85 – 6.13)	3.45 (0.93 – 6.20)
Serum IL-8	Group 1	30.4 (27.6 (35.0)	33.23 (25.2 (55.1)	35.73 (27.4 – 121.8)
	Group 2	30.2 (28.2 – 35.9)	32.7 (30.2 – 48.7)	33.6 (30.5 – 49.3)

α - Significant difference between values at baseline and end of surgery; β - Significant difference between values at baseline and 1hr post-surgery; *P < 0.05, ** P < 0. 01 and *** P < 0.001; (IL – Interleukin, CRP – C Reactive Protein, BALF- Bronchoalveolar lavage fluid).

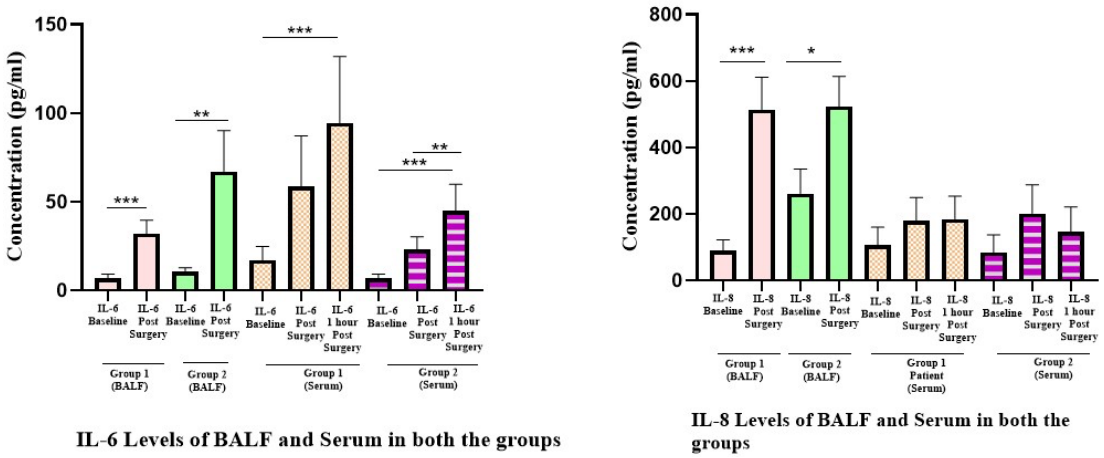

Fig. 2 — Comparison of serum levels of IL-6 and IL-8 in BALF and serum in both the groups (*P < 0.05, ** P < 0. 01 and *** P < 0.001).

Correlation among biomarkers

For each of the biomarkers (IL-6, IL-8 and CRP) detected in serum , there was a significant correlation between its levels at various timepoints in both the groups (Figure 3 and 4). In group 1, serum IL-6 demonstrated a significant correlation with serum CRP at various timepoints (Figure 3). However, no correlation was noticed between the same biomarkers in group 2 (Figure 4). Unlike serum, levels of IL-6 and IL-8 in BALF did not correlate significantly at various timepoints in either group. Also, there was no correlation between biomarkers in BALF and serum at any timepoint in both the groups.

Association between biomarker levels and occurrence of POPC

In group 1, despite a significant rise of IL-6 and IL-8 in the BALF, POPC (hypoxemia) was detected in a single patient. No patient in group 2 developed POPC.

Correlation between COVID-19 related CT score and perioperative biomarker levels

Available CT did not correlate with the perioperative change in the levels of biomarkers.

Median duration of hospital stay in group 1 was 2 days and 3 days in group 2, but again depended on the surgery performed.

Discussion

In the present study, the intraoperative rise of IL-6 and IL-8 in BALF was significantly greater in patients with prior COVID-19 associated pulmonary involvement than in patients with presumably no past COVID infection. However, patients who had COVID-19 associated lung involvement did not show an increase in incidence of POPC following intraoperative mechanical ventilation when compared to the relatively healthy cohort.

The BALF demonstrated a significant rise in inflammatory mediators (IL-6 and IL-8) from

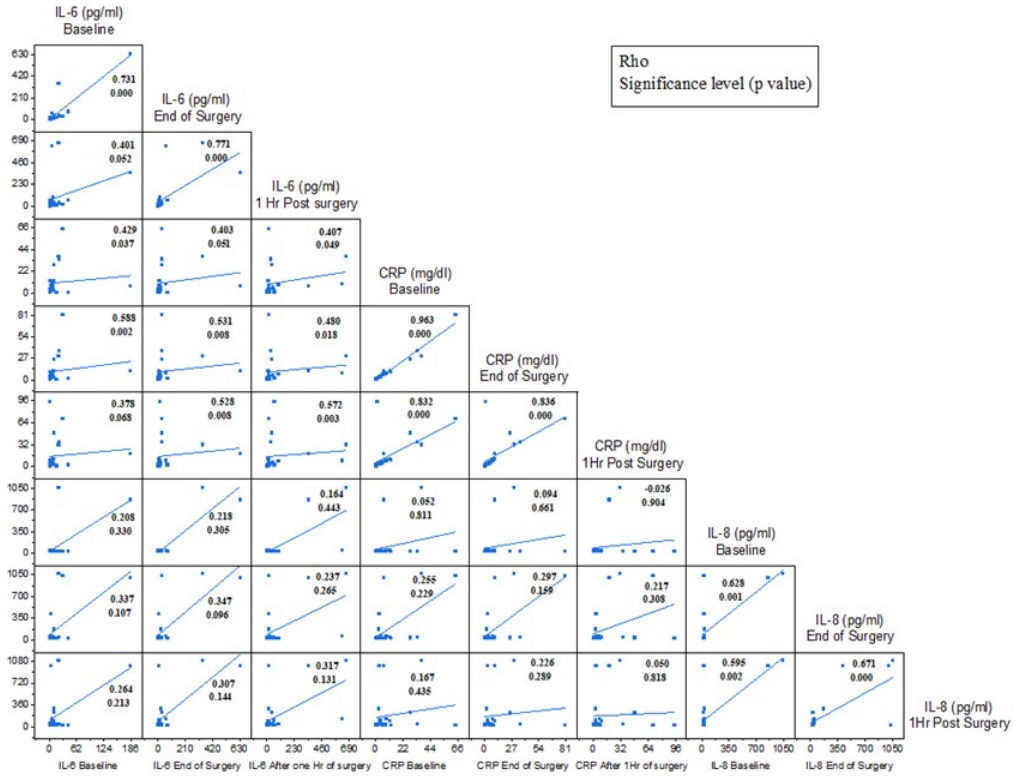

Fig. 3 — Correlation between serum levels of IL-6, IL-8 and CRP in group 1.
(Rho value indicates positive or negative correlation while p value indicates the level of significance of the correlation. P value < 0.05 is considered significant).

baseline towards the end of the surgery in both the groups (Table II). However, this increase was more pronounced in lungs previously afflicted with COVID-19 infection compared to the non-infected lungs (group 1, P < 0.001 vs group 2, P < 0.01). A greater prominence of these cytokines in BALF suggests the pulmonary origin of these inflammatory mediators as quoted in the study by Bhargava M. et al[9]. Our study outcomes were consistent with the findings of Meier T et al.[4], where intraoperative mechanical ventilation resulted in a predominant rise in BALF levels of IL-6 while TNF α remained below detectable limit (<10 pg ml-1). Several studies have reported a perioperative rise in BALF as well as plasma levels of IL-6, IL-8 and TNF α[1-5,10-13]. This emphasizes the role of IL-6 and IL-8 as key inflammatory mediators associated with surgery and ventilator-induced lung injury.

It was 1-hour past surgery that serum levels of IL6 showed a significant increase (P < 0.001) in both the study groups (Table II). This could probably be explained by the fact that, as an immediate marker of mechanical ventilation induced lung injury, the initial predominant cytokine rise was limited to BALF. Later, with a slow release of these mediators into the systemic circulation, the levels of IL-6 increased significantly in the serum as well, 1-hour after the surgery. Probably, had the markers been traced longer post-surgery, an increase in the serum levels of other biomarkers too could be expected. In group 1, the significantly elevated serum levels of IL-6 correlated with serum CRP levels at various time points (Figure 3). This could be due to the fact that IL-6 stimulates the acute expression of CRP by the hepatocytes14,15.

A significant elevation of IL-6 and IL-8 in BALF of patients in group 1, did not reflect clinically as increased POPC. The authors here thereby stress that despite the perioperative rise in the biomarkers of lung injury in COVID-19 survivors with a moderate to severe COVID associated pulmonary involvement, there was no evidence of an increase in incidence of POPC, which is a more important and a meaningful outcome. Of the 24 patients in group 1, one patient with a considerable perioperative rise of serum IL-6 (0.89 pg ml-1 at baseline to 64.24 pg ml-1 at 1-hour post-surgery) and CRP (1.4 pg ml-1 at baseline to 94.4 pg ml-1 at 1-hour post-surgery) developed postoperative hypoxaemia. This can probably be attributed to the prolonged free flap surgery (t=14 hrs). The incidence of POPC within 30 days was 4% in our study vis a vis 2.8% reported in a previous multicentric study[16]. This could be because we recruited patients with not less than moderate to severe pulmonary involvement, where residual impairment can be expected. Two patients in group 1 exhibited persistent breathlessness post-COVID (a 73-year-old male for sigmoidectomy; t=

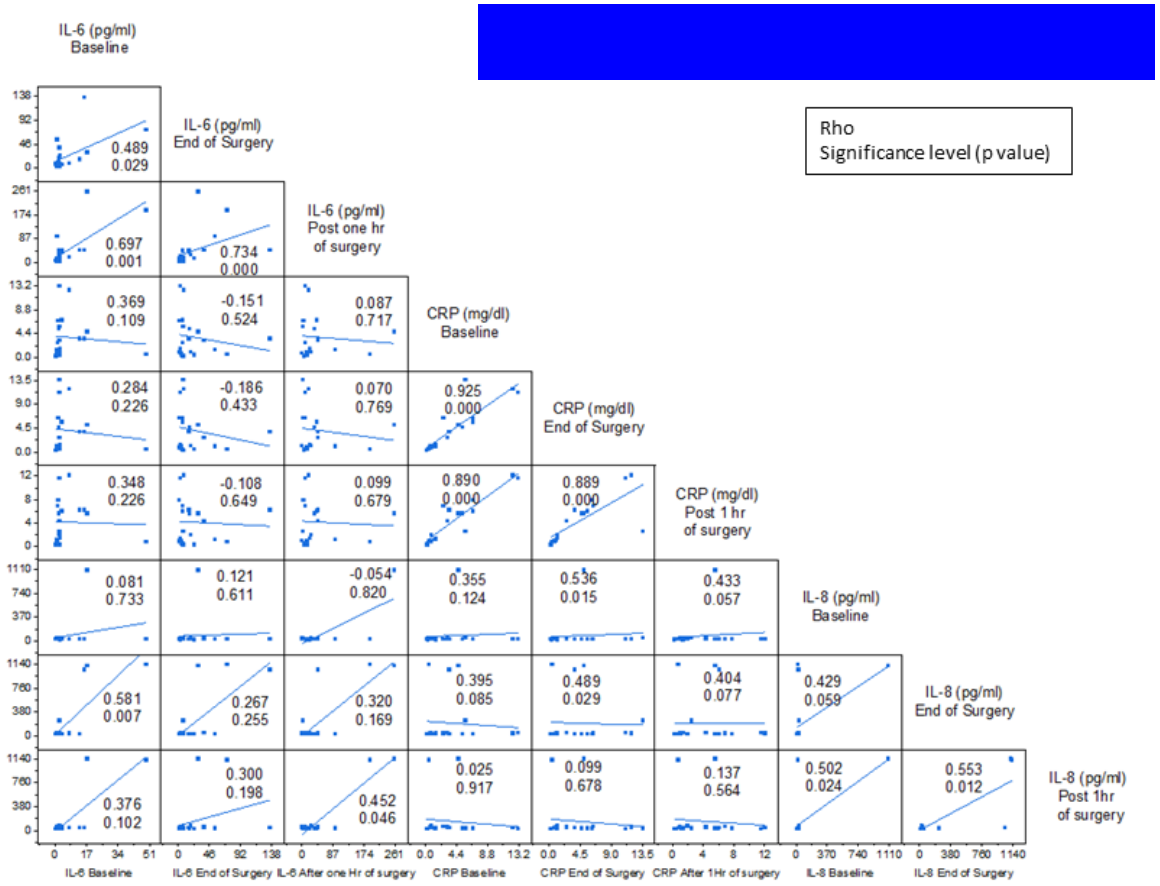

Fig. 4 — Correlation between serum levels of IL-6, IL-8 and CRP in group 2.
(Rho value indicates positive or negative correlation while p value indicates the level of significance of the correlation. P value < 0.05 is considered significant).

240 min and a 65-year-old male for laparoscopic cholecystectomy with hernia repair; t =120 min). However, no POPC were reported in either. Hence, BALF and serum biomarkers did not identify patients at risk of POPC in our cohort. These findings were in accordance with the study by Serpa Neto A.1 who concluded that none of the biomarkers had sufficient prognostic accuracy in predicting POPCs. However, growing evidence suggests that patients who develop POPCs show a larger perioperative change in plasma biomarkers[6,7].

In the patients that we recruited, surgery > 6 weeks after COVID-19 infection did not seem to increase POPCs. Our data was in line with the results from COVID Surg Collaborative and Global Surg Collaborative16 and Deng JZ. et al. 17 who concluded that surgery > 7 weeks after COVID-19 diagnosis is not associated with increased POPC. The retrospective study design and lack of information on whether patients with a confirmed SARS-CoV-2 infection were symptomatic or asymptomatic constitute a limitation of this study by Deng JZ. However, longer the duration between SARS-CoV-2 infection and surgery, POPC probably decrease progressively.

We used CT severity score to evaluate the extent of lung lesions during COVID-19 infection[18-20]. These scores did not determine the predictability of perioperative rise in biomarkers. The data available was also insufficient to draw a conclusion regarding the difference in length of hospital stay in both groups.

For the first time biomarkers were explored for their utility in predicting POPC in COVID-19 survivors. We measured inflammatory mediators in BALF, to evaluate lung parenchyma as a source of mechanical ventilation induced cytokine release. However, the concentrations of cytokines in the BALF may not accurately represent local lung inflammation due to dilution during the sample collection process. We hope that our single-centre experience will add to the growing body of literature on 'perioperative biomarkers after a remote COVID-19 infection'.

This study has a few limitations. A relatively small number of patients constitutes the major limitation. The study results need to be validated on a larger sample size and the generalisability of the results is yet to be determined. We acknowledge that although we attempted to control potential variables, certain confounding factors did exist which may have affected our findings. Group 2 showed a greater predilection towards a younger and lower ASA risk population. This selection

bias was probably due to refrain in performing relatively invasive bronchoalveolar lavage in older and higher ASA grade controls. Although the four studied biomarkers are accredited important for lung inflammation / injury, other lung specific biomarkers could have performed better. Future research can highlight the utility of these lung specific biomarkers to predict POPC in COVID-19 survivors. Studies directed towards determining the incidence of POPC after a specific major surgery in a vulnerable population can be planned.

In conclusion, our study demonstrated a significant intraoperative rise of IL-6 and IL-8 in BALF of patients with prior COVID-19 associated pulmonary involvement compared to a healthy cohort when ventilated mechanically. However, of the 24 patients with moderate to severe COVID infection, only 1 patient developed POPC suggesting that the rise in inflammatory mediators does not translate clinically to an increase in the incidence of POPC.

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Conflicts of interest: None.

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Data sharing: The data and/or analyses during/after the conduct of the study is not publicly available but may be obtained from the corresponding author upon reasonable request.

References

1. Serpa Neto A, Campos PP, Hemmes SN et al. Kinetics of plasma biomarkers of inflammation and lung injury in surgical patients with or without postoperative pulmonary complications. Eur J Anaesthesiol. 2017;34(4):229-238.
2. Weingarten TN, Whalen FX, Warner DO et al. Comparison of two ventilatory strategies in elderly patients undergoing major abdominal surgery. Br J Anaesth. 2010;104(1):16-22.
3. Michelet P, D'Journo XB, Roch A et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology 2006; 105:911–919.
4. Meier T, Lange A, Papenberg H et al. Pulmonary cytokine responses during mechanical ventilation of noninjured lungs with and without end-expiratory pressure. Anesth Analg. 2008;107(4):1265-1275.
5. Wrigge H, Uhlig U, Zinserling J et al. The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg. 2004;98(3):775-781.
6. D'Journo XB, Michelet P, Marin V et al. An early inflammatory response to oesophagectomy predicts the occurrence of pulmonary complications. Eur J Cardiothorac Surg. 2010;37(5):1144-1451.
7. Kaufmann KB, Heinrich S, Staehle HF, Bogatyreva L, Buerkle H, Goebel U. Perioperative cytokine profile during lung surgery predicts patients at risk for postoperative complications-A prospective, clinical study. PLoS One. 2018;13(7):e0199807.
8. Ranieri VM, Suter PM, Tortorella C et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1999;282(1):54-61.
9. Bhargava M, Wendt CH. Biomarkers in acute lung injury. Transl Res. 2012;159(4):205-217.
10. Shen Y, Zhong M, Wu W et al. The impact of tidal volume on pulmonary complications following minimally invasive esophagectomy: a randomized and controlled study. J Thorac Cardiovasc Surg. 2013; 146:1267–1273; discussion 1273–1274.
11. Cree RT, Warnell I, Staunton M, et al. Alveolar and plasma concentrations of interleukin-8 and vascular endothelial growth factor following oesophagectomy. Anaesthesia 2004; 59:867–871.
12. Kooguchi K, Kobayashi A, Kitamura Y, et al. Elevated expression of inducible nitric oxide synthase and inflammatory cytokines in the alveolar macrophages after esophagectomy. Crit Care Med 2002;30:71—76.
13. Van der Woude MC, Bormans L, van der Horst RP, et al. Pulmonary levels of biomarkers for inflammation and lung injury in protective versus conventional one-lung ventilation for oesophagectomy: A randomised clinical trial. Eur J Anaesthesiol. 2020;37(11):1040-1049.
14. Hidayat F, Labeda I, Sampetoding S, et al. Correlation of interleukin-6 and C-reactive protein levels in plasma with the stage and differentiation of colorectal cancer: A cross-sectional study in East Indonesia. Ann Med Surg (Lond). 2021;62:334-340.
15. Jones SA, Novick D, Horiuchi S, Yamamoto N, Szalai AJ, Fuller GM. C-reactive protein: a physiological activator of interleukin 6 receptor shedding. J Exp Med. 1999;189(3):599-604.
16. COVIDSurg Collaborative, GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021; 76: 748–758.
17. Deng JZ, Chan JS, Potter AL, et al. The Risk of Postoperative Complications After Major Elective Surgery in Active or Resolved COVID-19 in the United States. Ann Surg. 2022;275(2):242-246.
18. Wasilewski PG, Mruk B, Mazur S, Półtorak-Szymczak G, Sklinda K, Walecki J. COVID-19 severity scoring systems in radiological imaging - a review. Pol J Radiol. 2020 Jul 17;85:e361-e368. doi: 10.5114/pjr.2020.98009.
19. Gurumurthy B, Das SK, Shetty S, Veerabhadrappa RC, Kosinepalli SS, Dharamaraju SH. CT severity score: an imaging biomarker to estimate the severity of COVID-19 pneumonia in vaccinated and non-vaccinated population. Egypt J Radiol Nucl Med. 2022;53(1):88.
20. Sharma S, Aggarwal A, Sharma RK, Patras E, Singhal A. Correlation of chest CT severity score with clinical parameters in COVID-19 pulmonary disease in a tertiary care hospital in Delhi during the pandemic period. Egypt J Radiol Nucl Med. 2022;53(1):166.

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