Electrocardiographic abnormalities in patients with COVID-19 pneumonia and raised interleukin-6

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ABSTRACT

Background: Cardiac injury is associated with high mortality in patients with COVID-19 infection. Electrocardiographic changes can give clues to the underlying cardiovascular abnormalities. Raised inflammatory markers like raised interleukin-6 (IL-6) are associated with arrhythmia, heart failure, and coronary artery disease. However, past studies have not highlighted the electrocardiographic abnormalities in patients with COVID-19 infection with raised IL-6 levels. This study compared the electrocardiogram (ECG) changes in COVID-19 patients with high and normal IL-6 levels. **Methods:** A retrospective analysis of ECG of 306 patients with COVID-19 infection was done, out of which 250 patients had normal IL-6 levels, whereas 56 patients had raised IL-6 levels. IL-6 levels were measured in all the patients. Detailed clinicodemographic profile of all the serial COVID-19 patients admitted with moderate to severe COVID-19 pneumonia was noted from the hospital record section. Electrocardiographic findings and biochemical parameters of all the patients were noted. **Results:** Out of 56 patients with raised IL-6 levels, 41 (73.2%) patients had ECG abnormalities compared to 177 (70.8%) patients with normal IL-6 levels. This difference was not statistically significant. However, ECG abnormality such as sinus tachycardia was significantly more common in patients with raised IL-6 levels than those with normal levels. Among patients with raised IL-6 levels who were discharged, 5 (16.6%) had sinus tachycardia, 2 (6.6%) had ST/T wave changes as compared to 15 (57.6%), and 10 (38.4%) who had tachycardia and ST/T wave change respectably succumbed to death. This difference was statistically significant. **Conclusions:** Sinus tachycardia followed by atrial fibrillation and right bundle branch block are common ECG changes in patients with COVID-19 infection with raised IL-6. The possible association of cardiac injury in patients with COVID-19 infection with coexisting raised IL-6 levels should be explored further.

Keywords: COVID-19, electrocardiogram, IL-6, SARS-CoV-2

Introduction

Cytokine storm, inflammation, raised interleukin-6 (IL-6), and other cytokines have been associated with AF, heart failure, coronary artery disease, torsades de pointes (TDP). IL-6 has been evaluated as an effective tool in predicting severity in patients with COVID-19 infection. IL-6 plays a critical role in inciting cytokine storms, leading to acute lung injury and acute respiratory distress syndrome in these patients. Elevated level of IL-6 mediates immune dysregulation leading to stimulation of the coagulation cascade and increased risk of prothrombotic events.[1]

This is evident because IL-6 inhibition has been associated with an improved prognosis of COVID-19 infection.[1,2] COVID-19 is associated with reports of myocarditis, decompensated heart failure, and acute coronary syndrome.[3,4]

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Kevin *et al.* reported that about 22% of intensive care unit patients had cardiovascular involvement.[5] The coordinated action of ion channels controls the electrical activity of the human heart. IL-6 modulates INa+ (inward sodium channel), ICa + L (voltage-gated L-type Ca), and IK+ (delayed rectifier K current potassium channel) currents, which results in cardiac instabilities predisposing to cardiomyopathy, arrhythmias like AF and TDP. Cardiac delayed rectifier K current (IK) contributes prominently to normal repolarization; altered IL-6 mechanisms that decrease ICa+L density, reduce intracellular Ca transients, and impair cardiac contractility are also likely to promote supraventricular arrhythmia.[6-12]

The electrocardiogram (ECG) is the simplest and readily available method to screen for the possible presence of cardiac abnormalities.

Nonetheless, ECG features of COVID-19 pneumonia patients with raised IL-6 are still undefined. It is important for physicians in intensive and primary care managing COVID-19 patients with cytokine storms to anticipate and be prepared for dealing with arrhythmic cardiac emergencies. This study explored ECG abnormalities in COVID-19 pneumonia patients with raised IL6. This study aimed to evaluate the different rates of ECG abnormalities and markers of sudden cardiac arrest in COVID-19 pneumonia patients with raised IL-6.

Methods

This study was conducted in the Emergency Medicine department of a tertiary care center in Uttarakhand. Patients admitted with moderate to severe COVID-19 pneumonia, confirmed using reverse-transcription polymerase chain reaction test, were included in the study. From the hospital record section, detailed demographic, clinical, and biomedical data were obtained retrospectively of all the patients admitted from November 1, 2020 to March 31, 2021. The institutional ethics committee approved the study via letter-number—AIIMS/IEC/20/255, dated 09/05/2020, and Clinical Trial Registry of India via letter-number CTRI/2020/05/025216 [Registered on: 16/05/2020]. A total of 306 patients with COVID-19 pneumonia who were admitted to the intensive care unit were included in the study, out of whom 250 patients had ECG changes and 56 patients had raised IL-6 levels.

Inclusion and exclusion criteria

Patients with an old history of coronary artery disease or old myocardial infarction and those already on antiarrhythmic drugs or with abnormal serum potassium (K+) were excluded from the analysis. Chest X-ray and computerized thoracic tomography (CT) scan were performed as indicated. The demographic characteristics, clinical, and laboratory data on admission were recorded. ECG was done at baseline and during hospitalization as indicated. Cardiac biomarkers and markers of inflammation were done as clinically indicated. Clinical improvement was defined as the resolution of fever for ≥48 h

and no supplemental oxygen requirement. Treatment as per ICMR and hospital protocol was given to all patients. Routine hematological testing, including hemoglobin (Hb) concentration, white blood cell, platelets (PLT), neutrophil and lymphocytes counts, serum glucose, urea, creatinine, electrolytes, liver and renal function tests, albumin, ferritin, and cardiac biomarkers were done as per institutional protocol.

Electrocardiography

ECG was recorded with 25 mm/s and 1 mV/cm calibration and a 0.05–150 Hz filter setting. A cardiac electrophysiologist performed ECG analysis. The ECGs were analyzed for the following parameters: rhythm, conduction defects, ST-segment, T wave abnormalities, and arrhythmias. Patients with left bundle branch block (LBBB) were excluded from ST-segment and T wave analyses, and in patients with RBBB, leads V1–V4 were excluded from ST-segment and T wave analysis. ST-segment depression was diagnosed when a horizontal or downsloping displacement of the ST segment below the isoelectric line ≥0.5 mm, persisting at 0.08 s from the J point, was detectable in at least two contiguous leads. ST-segment elevation was diagnosed when the J point was elevated by ≥1 mm, and morphology was judged to be compatible with an ischemic or pericarditis origin. An abnormal T wave was diagnosed in the case of T wave inversion ≥1 mm in at least two contiguous leads (except V1 and aVR). PR interval was measured from the beginning of the *P* wave and the end of the R wave, and QRS interval was measured from the beginning of the Q wave to the end of the S wave. ECG indices like T peak to end interval (Tp-e) and Tp-e/QTc, and index of cardiac electrophysiological balance (iCEB), measured by QTc/QRS, were measured.[13-17] The Tp-e interval was defined from the peak of the T wave to the end of the T wave. Measurements of the Tp-e interval were performed from precordial leads, and the longest Tp-e interval was recorded. The QT interval was defined as the interval from the onset of the QRS complex to the end of the T wave. QT intervals were measured from all leads, and the longest QT interval was recorded. The R–R interval was measured and used to compute the heart rate. Correct QT interval (QTc) was calculated using Bazett's formula: $QTc = QT\sqrt{(\text{R-R interval})}$. Tp-e/QT ratios were calculated from these measured values.[13-17]

Clinical outcome

We divided the patients into two groups who had raised IL-6 levels compared to patients with normal IL-6 levels. ECG changes were compared in both groups. We also compared ECG changes among 250 patients who expired and were discharged from the hospital.

Statistical analysis

Data are reported as mean and standard deviation (SD) for continuous variables and number and proportions for discrete variables. We present data as mean ± SD for continuous variables and proportions for categorical variables. Data were analyzed using SPSS Statistics for Windows, Version 23.0 (IBM

SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp). Mean values of variables were compared by paired or independent sample *t*-test, and *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of patients in COVID-19 pneumonia with and without raised IL-6 are shown in Table 1. The mean age of the patients with raised IL-6 Levels was 57.56 ± 15.5 years. The common comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and renal dysfunction were present in both groups. However, acute respiratory distress syndrome (9;16%) and type 2 respiratory failure were significantly more common in patients with raised IL-6 levels. Also, oxygen requirement was more in this group of patients. The mean IL-6 values in patients with raised IL6 were 88.23 ± 221.27 pg/mL. ECG abnormalities were present in around 70% of patients in both groups. Tocilizumab was used in 6 (10.7%) patients with raised IL-6. Both groups had sick patients with mortality of near 50%. The Charlson comorbidity index was used to compare the baseline health status of the groups. Charlson comorbidity index for the total COVID-19 pneumonia group without and with raised IL-6 was 1.88 ± 1.56 (10-year survival of 83.58 ± 19.87) vs. 1.96 ± 1.61 (10-year survival of 82.34 ± 20.86). Table 2 compares ECG findings in patients with normal IL-6 levels who expired and those discharged. ECG findings were noted in 177 (70.8%) patients with normal IL-6 levels. Sinus tachycardia (28;31.4%), LBBB (5;5.6%), and RBBB (15;16.8%) were more common in patients who succumbed as compared to those discharged.

Total COVID cases ECG features: out of 250 patients, 124 recovered from being discharged from the hospital, whereas 124 had in-hospital mortality. Sinus tachycardia and AF were the most common arrhythmia. Both were associated with high mortality. Intraventricular conduction defects, RBBB more commonly than LBBB were associated with high mortality [Table 2]. Ventricular premature complexes were associated in a small percentage of patients but with mortality. Other parameters like ST–T changes and QT prolongation were not significant. Table 3 compares ECG changes of patients with normal and raised IL-6 levels. Sinus tachycardia (20; 35.17%) was significantly more common in patients with raised IL-6 levels.

ECG changes in raised IL 6 subgroup

Out of total 56 patients, 26 died during the hospital course and 30 recovered successfully and were discharged. Sinus tachycardia, ST–T changes were the most common abnormalities and were significantly related to mortality [Table 4]. Also, AF and RBBB were associated with mortality, but the numbers were low. QT prolongation was seen in around 10% of patients without any electrolyte abnormality or hydroxychloroquine use in these patients. Most QTc prolongation was mild except for one patient with QTc >500 ms.

Table 1: Baseline characteristics of patients with normal and raised IL-6 levels

Parameter	Patients with normal IL-6 Level (*N*=250; 81%)	Raised IL 6 group (*N*=56; 19%)	*P*
Age (years) (mean±SD)	55.94±15.84	57.56±15.5	0.9
Male	214 (85.6%)	46 (82.1)	0.17
Hypertension	36 (14.4%)	7 (12.5%)	0.3
Diabetes mellitus	51 (20.4%)	7 (12.5%)	0.05
Renal dysfunction	11 (4.4%)	4 (7.4%)	0.7
Chronic obstructive pulmonary disease	7 (2.8%)	15 (2.6%)	0.69
Acute respiratory distress syndrome	17 (6.8%)	9 (16%)	0.006
Type 2 respiratory failure	3 (1.2%)	5 (8.9%)	0.003
Type 1 respiratory failure	16 (6.4%)	4 (7.1%)	0.187
Supplemental oxygen requirement	201 (80%)	49 (87.5%)	0.003
Systolic Blood pressure (mmHg)	126.47±20.2	116.20±15.4	0.87
Diastolic Blood pressure (mm Hg)	74.91±12.99	70.71±14.3	0.97
Respiratory rate (breaths/minute)	24.3±2.9	27.3±4.9	0.19
Heart rate (bpm)	90.65±13.25	96.65±13.25	0.64
SpO$_2$ (%)	95.5±4.7	94.35±4.66	0.7
Temperature (degree Fahrenheit)	98.5±0.5	98.82±0.61	0.5
Hemoglobin (gm/dL)	11.50±2.3	11.2±3.4	0.56
Total leukocyte count	10.45±4.65	9.76±4.87	0.6
Neutrophils (%)	83.79±9.58%	85.05±9.71%	0.43
Lymphocyte (%)	10.11±7.5%	9.608±7.947%	0.51
Creatinine (mg/dL)	1.0±1.18	1.63±1.18	0.487
Remdesvir (%)	111 (44.4%)	34 (60.7%)	0.03
Tocilizumab (%)	Nil	6 (10.7%)	<0.00001
ECG abnormalities (%)	177 (70.8%)	40 (71.4%)	0.44
Charlson Comorbidity Index (mean±SD)	1.88±1.56	1.96±1.61	0.3

Abbreviations: ECG: electrocardiogram, IL6: interleukin 6, SGOT: serum glutamic-oxaloacetic transaminase, SD: standard deviation

The ECG parameters like heart rate, *P* wave duration, PR interval, QRS duration, QTc interval, T peak—T end, and T peak—T end/QTc, QTc/QRS were not significant between patients who were discharged vs. who died during hospital course [Table 5].

Discussion

The most common presentation of COVID-19 infection is fever, cough, and shortness of breath. COVID-19 infection can affect almost all body systems, including the cardiovascular, neurological, renal, hematological, gastrointestinal, and respiratory systems. Cardiovascular manifestations of COVID-19, such as acute coronary syndrome, acute heart failure, myocarditis, pericarditis, pulmonary embolism, and AF have been reported in previous studies.[1-6] These cardiovascular manifestations can be diagnosed with the help of ECG and cardiac biomarkers in the Emergency Department. In this study, out of 306 patients with moderate to

Table 2: Comparison of electrocardiographic findings of patients with normal IL-6 levels who were expired or discharged (*n*=177; 70.8%)

Parameter	Discharged 88 (48.0%)	Death N=89 (50.2%)	P
Sinus tachycardia	7 (7.9)	28 (31.4)	<0.00001
Sinus bradycardia	2 (2.2)	1 (1.1)	0.35
Atrial fibrillation	0	9 (10.11)	0.00028
First degree AV block	4 (4.5)	1 (1.1)	0.09
II Degree AV block	0	0	
III Degree AV block	0	0	
LBBB	1 (1.1)	5 (5.6)	<0.0058
RBBB	1 (1.1)	15 (16.8)	<0.00001
Fragmented QRS complex	3 (3.4)	2 (2.2)	0.366
Q wave	4 (4.5)	1 (1.1)	0.68
ST depression	9 (10.2)	15 (16.8)	0.76
ST-elevation	5 (5.6)	5 (5.6)	NS
T inversions pathological	14 (15.9)	14 (15.7)	NS
QT prolongation	12 (13.6)	11 (12.3)	0.544
Atrial premature complexes	1 (1.1)	3 (3.3)	0.15
Ventricular premature complex	0	4 (4.4)	0.014
Ventricular tachycardia	0	1 (1.1)	0.22
Low-voltage QRS	8 (9.0)	9 (10.1)	0.392

Abbreviations: AV: atrioventricular, ECG: electrocardiogram, IL-6: interleukin 6, LBBB: left bundle branch block, RBBB: right bundle branch block

Table 3: Comparison of electrocardiographic changes in patients with normal and raised IL-6 levels

Parameter	Normal IL-6 (250)	Raised IL-6 group (56)	P
Sinus tachycardia	14.8% (37)	35.17% (20)	<0.002
Sinus bradycardia	1.2% (3)	0	0.43
Atrial fibrillation	3.6% (9)	7.69% (2)	0.89
First degree AV block	2.8% (7)	1.78% (1)	0.74
II Degree AV block	0	0	
III Degree AV block	0	0	
LBBB	2.4% (6)	0	0.269
RBBB	6.4% (16)	7.69% (2)	0.51
Fragmented QRS complex	2% (5)	0	0.318
Q wave	2% (5)	0	0.318
ST depression	9.6% (24)	5.35% (3)	0.418
ST-elevation	4% (10)	3.5% (2)	0.99
T inversions pathological	11.2% (28)	12.5% (7)	0.57
QT prolongation	9.2% (23	10.71% (6)	0.515
Atrial premature complexes	1.6% (4)	1.78% (1)	0.84
Ventricular premature complex	1.6% (4)	1.78% (1)	0.84
Ventricular tachycardia	0.4% (1)	0	0.65
Low-voltage QRS	6.8% (17)	7.14% (4)	1

Abbreviations: AV: atrioventricular, ECG: Electrocardiogram, IL-6: interleukin 6, LBBB: left bundle branch block, RBBB: right bundle branch block

severe SARS-COVID-19 pneumonia, 250 patients had normal IL-6 levels and 56 had raised IL-6 levels.

Around 70% of patients with COVID-19 pneumonia reported ECG abnormalities such as sinus tachycardia, ST–T wave changes, conduction abnormalities, and ventricular tachycardia. Previous studies have also highlighted these ECG abnormalities such as tachycardia, ST–T wave changes, and arrhythmias.

It is well known that severe COVID-19 infection induces a hyperinflammatory response leading to the release of multiple cytokines such as IL-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-alpha). Previous studies have observed a statistically significant negative correlation between IL-6 and respiratory failure. Thus, IL-6 has been implicated as a prognostic marker of the need for a mechanical ventilator and mortality. It has been observed that IL-6 levels increase with disease severity and correlate with mortality. This study compared electrocardiographic abnormalities in patients with normal and raised IL-6 levels.[9,10]

In this study, acute respiratory distress syndrome and type 2 respiratory failure were significantly more common in patients with raised IL-6 groups. It was found that more patients in the raised IL-6 group required supplemental oxygen than the other group. Studies in the past have highlighted the significance of IL-6 as a severity and mortality marker in patients with moderate to severe COVID-19 pneumonia. IL-6 has been found to affect the treatment protocol of patients with SARS-CoV-2 infection. Tocilizumab has been used in patients with raised IL-6 levels.[1,8]

Sinus tachycardia followed by AF was the most common arrhythmia. Most AF patients were on supplemental oxygen support, and AF was associated with mortality in all patients. AF occurred with normal serum potassium (K+) levels. Causation of arrhythmias appears multifactorial in a COVID-19 patient. Metabolic derangements, hypoxia, acidosis, neurohormonal and autonomic imbalance, and catecholaminergic stress may be responsible for arrhythmias. AF has been reported in 10% of intensive care patients and predicts an adverse prognosis.[18-21]

AF may affect hemodynamics and should be restored urgently to sinus rhythm. In severe COVID-19, CD4+ T cells have a peripheral expression profile of an exhausted state, and numbers are suppressed in the peripheral blood. It is postulated that a significant influx of CD4+ T cells into cardiac tissues causes inflammatory cytokine profiles involved in AF causation. Pericytes may have a multimodal role in immune responses, edema, increased interstitial hydrostatic pressure, tissue inflammation, and fibrosis that may lead to AF.[21-25] Also, altered IL-6 functional expression leading to persistent atrial inflammation is found commonly in supraventricular arrhythmias, including AF leading to higher risks of death and cardiovascular events in these patients.[26]

Most common ECG abnormality noted was sinus tachycardia, which also correlated with mortality. Severe infection induces sympathetic activity, which may lead to sinus tachycardia, a predictor of mortality.[26] Increased sympathetic drive induces calcium entry into cardiac myocytes and a spontaneous release

Table 4: Comparison of ECG characteristics in patients with raised IL-6 group who expired and discharged

Parameter	Total cases(*n*=56)	Death (*n*=26)	Discharge (*n*=30)	*P*
Sinus tachycardia	35.17%	57.69% (15)	16.67% (5)	0.0013
Sinus bradycardia	Nil	Nil	Nil	
Atrial fibrillation	3.5% (2)	7.69% (2)	Nil	0.2978
First degree AV block	1.78% (1)	0	3.33% (1)	0.63
II Degree AV block	Nil	Nil	Nil	
III Degree AV block	Nil	Nil	Nil	
LBBB	Nil	Nil	Nil	
RBBB	3.5% (2)	7.69% (2)	Nil	0.2978
Fragmented QRS complex	Nil	Nil	Nil	
Q wave	Nil	Nil	Nil	
ST depression	5.35% (3)	7.69% (2)	3.33% (1)	0.50
ST elevation	3.5% (2)	7.69% (2)	0	0.8
T inversions pathological	12.5% (7)	23% (6)	3.33% (1)	0.058
ST T changes	21.42% (12)	38.46% (10)	6.66% (2)	0.0063
QT prolongation	10.71% (6)	19.23% (5)	3.33% (1)	0.1265
Atrial premature complexes	1.78% (1)	3.84% (1)	Nil	0.63
Ventricular premature complex	1.78% (1)	3.84% (1)	Nil	0.63
Low-voltage QRS	7.14% (4)	7.69% (2)	6.66% (2)	0618
Early repolarization	1.78% (1)	3.84% (1)	Nil	0.63

Abbreviations: AV: atrioventricular, ECG: Electrocardiogram, IL-6: interleukin 6, LBBB: left bundle branch block, RBBB: right bundle branch block

Table 5: Electrocardiographic parameters comparison between discharged and death group in cohort with raised IL 6

Parameter	Discharged (mean±SD) (*n*=30)	Death (mean±SD) (*n*=26)	*P*
Heart rate (bpm)	95.73±19.15	97.48±14.79	0.35
P wave duration (ms)	96.38±13.54	98.07±14.15	0.33
PR interval (ms)	146.19±19.07	144.92±21.54	0.41
QRS duration (ms)	89.30±18.71	89.55±11.48	0.47
QTc (ms)	433.77±35.66	440.96±23.57	0.19
T peak - Tend	63.57±12.16	67.77±25.28	0.34
T peak - Tend/QT	0.1454±0.027	0.25±0.24	0.14
QT/QRS	4.976±0.641	5.699±1.194	0.30

Abbreviations: Bpm: beats per minute, IL 6: interleukin 6, ms: milliseconds

of calcium from the sarcoplasmic reticulum, which contributes to arrhythmogenesis.[27]

Intraventricular conduction defects: the most common intraventricular conduction defect was RBBB, and both patients had in-hospital mortality. RBBB may signify right ventricular involvement or pressure overload due to lung involvement and pulmonary embolism. There might be conduction system involvement due to missed cardiac involvement at a later stage.

ST–T changes were significantly more in patients who died in the hospital course. COVID-19 is associated with hypercoagulopathy and endothelial dysfunction, which may predispose to myocardial ischemia. Since not all patients underwent coronary angiography, a more dedicated study is required to reach a definite conclusion.

We compared COVID-19 groups with and without raised IL6. We did not find any significant difference between markers of sudden cardiac death compared to other studies that compared COVID-19 patients and normal controls.[28,29] Also, echocardiography was not done in all cases for electrocardiographic abnormalities to be correlated to structural abnormalities.

COVID-19 may have a hyperinflammatory or hypoinflammatory response.[30] Hyperinflammatory responses have elevated cytokines that may injure the host, and elevated IL-6 is known to have cardiotoxic effects.[1-4] Recently Wegeberg *et al.* have shown that elevated levels of interleukin-12 may serve as a potential indicator of dysfunctional heart rate variability in diabetic patients.[31] Our study shows significant arrhythmia and ECG changes in this population and is essential for primary care and emergency physicians dealing with COVID-19 to be prepared to arrhythmic cardiac emergencies in this subset of patients. Further studies with IL-6 levels and cardiac imaging need to be done to look for structural effects and also studies to look at whether anticytokine therapies can reverse these adverse effects.

Limitations

Cardiac biomarkers and echocardiography were not performed in all patients. COVID -19-related direct infection of the myocardium, hyper-inflammation-induced cardiomyopathy, and coronary artery thrombosis due to hypercoagulability is also a possibility for arrhythmia.

Conclusions

Most patients with raised IL-6 levels are associated with ECG abnormalities. Sinus tachycardia, RBBB, AF, ST–T changes are expected and predict adverse outcomes. The possible association of cardiac injury in patients with COVID-19 infection with coexisting raised IL-6 levels should be explored further.

Key Points

1. COVID-19 patients with raised IL-6 have significant electrocardiographic abnormalities and cardiovascular risk for arrhythmias.
2. Sinus tachycardia, RBBB, AF, and ST–T changes are common in COVID-19 patients with raised 1L-6 and predict adverse outcomes.

Author contribution

Dr. Nidhi Kaley and Prakash Mahala contributed equally to the paper and are joint first authors.

Take Home Message

1. COVID-19 is associated with raised cytokines, IL-6, and inflammatory state. This may result in cardiac injury and electrocardiographic changes.
2. Sinus tachycardia, right bundle branch block (RBBB), atrial fibrillation (AF), and ST–T changes are associated with raised

IL-6 in COVID-19 pneumonia patients and predicts adverse outcome.

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Conflicts of interest

There are no conflicts of interest.

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