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Relation of interleukin-6 levels in COVID-19 patients with major adverse cardiac events

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ABSTRACT

Elevated interleukin-6 (IL-6) levels may correlate with disease severity in COVID-19. We analyzed whether there was an association between elevated IL-6 levels and major adverse cardiac events (MACE) and/or mortality in COVID-19 patients. A retrospective chart review was performed on COVID-19 patients among four hospitals in one health system from March to May 2020, extracting information on baseline characteristics, MACE (i.e., myocardial infarction, stroke, deep venous thrombosis/pulmonary embolism, or shock requiring vasopressor support), mortality, and IL-6 levels. Of the 496 patients hospitalized with COVID-19, 191 patients had an IL-6 level drawn and 68% had elevated IL-6 levels. The elevated IL-6 population had higher odds of developing a MACE compared to the normal IL-6 population ($P < 0.0001$, odds ratio [OR] = 5.91, 95% confidence interval [CI] = 2.65–14.11). The elevated IL-6 population also had higher mortality rates (28.2% vs 5%, $P = 0.0001$, OR = 7.47, 95% CI = 2.19–39.32) and an increased incidence of a MACE and/or mortality (58.78% vs 20.00%, $P < 0.0001$, OR = 5.7, 95% CI 2.65–12.83) compared to the normal IL-6 population. Elevated IL-6 levels in COVID-19 patients may be associated with MACE and/or mortality. Monitoring IL-6 levels in COVID-19 patients may help risk-stratify patients.

As of July 2021, over 187 million people have been infected with SARS-CoV-2, and >4 million people have died from COVID-19 globally.[1] Originally thought to mainly involve the respiratory system, several COVID-19 cases indicated cardiovascular involvement leading to pericarditis, arrhythmias, and acute coronary syndrome.[2] These presentations are typically found in severe COVID-19 cases and are often associated with poor outcomes.[3] Although elevated pro-inflammatory cytokine interleukin-6 (IL-6) levels are associated with poor outcomes in patients with acute respiratory distress syndrome,[4] the correlation between changes in these biomarkers and COVID-19 patient outcomes is uncertain. The primary objective of this study was to determine if there was a correlation between elevated IL-6 levels and major adverse cardiovascular events (MACE) and/or mortality in COVID-19 patients.

METHODS

Our population comprised hospitalized patients ≥18 years within Methodist Health System from March to May 2020 who tested positive for COVID-19 by polymerase chain reaction (PCR). After obtaining a list of deidentified patients with positive COVID-19 PCR tests, a retrospective chart review was performed in the EPIC electronic medical record. Specific baseline characteristics were obtained for each patient, including age, sex, race, body mass index (BMI), smoking status, comorbidities, and medication history. Systolic heart failure was defined as an ejection fraction (EF) <45%, and diastolic heart failure was an EF >60% along with impaired left ventricular diastolic filling. Laboratory data related to the present illness were also collected. Peak admission serum IL-6 levels were noted, and IL-6 levels >5 pg/mL were defined as elevated. A MACE was defined as a composite of myocardial infarction, stroke, deep
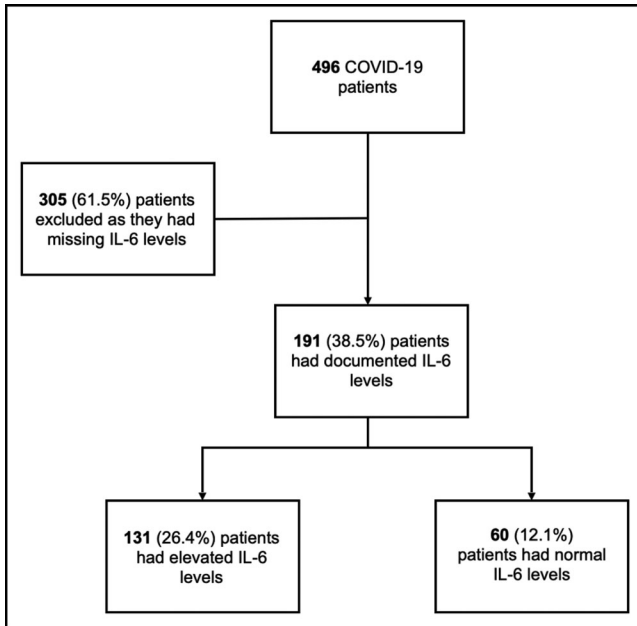
Figure 1. Retrospective cohort study flow chart.

venous thrombosis/pulmonary embolism, or shock requiring vasopressor support. The definition and criteria used to determine these outcomes are noted in the Supplemental Material. This study was approved by the WCG/Aspire Institutional Review Board on June 9, 2020.

Descriptive analysis of all the variables was performed. For normally distributed variables, the mean ± standard deviation was analyzed via the Student's t test. For nonnormal variables, the median ± interquartile range was analyzed via the nonparametric Wilcoxon-Mann-Whitney test. The chi-square test or the Fisher's exact test was used to analyze categorical outcomes. Univariate analysis was used to identify the variables that were statistically significant. Odds ratios were calculated to determine the strength of association. Multivariate logistic regression was used to control for possible confounding variables. A P value <0.05 was considered statistically significant.

RESULTS

A total of 496 patients with COVID-19 were hospitalized from March to May 2020 in our health system (Figure 1). Of these patients, 191 (39%) had an IL-6 level drawn; thus, 305 patients (62%) were excluded from this study. A total of 131 patients (26%) had elevated IL-6 levels, and 60 patients (12%) had normal IL-6 levels. Baseline characteristics of the normal and elevated IL-6 patient populations are noted in Table 1. The mean age of participants was 55 years (standard deviation [SD] 14) for those with normal IL-6 levels and 60 years (SD 13) for those with elevated IL-6 levels. More men were in the elevated IL-6 cohort (68%) than in the normal IL-6 cohort (48%). The cohorts were racially diverse; 27% and 33% were Black or African American in the normal IL-6 and elevated IL-6 groups, respectively. The mean BMI (SD) was 34.08 ± 9.60 within the normal IL-6

Table 1. Baseline characteristics and descriptive statistics of the COVID-19 patient cohort

Variable	Interleukin-6		
	Normal (N = 60)	Elevated (N = 131)	*P* value
Age (years)			
Mean ± SD	55 ± 14	60 ± 13	**0.033**
Median (IQR)	56.5 (46–65.5)	61 (50–68)	
Age group (years)			
18–29	3 (5%)	1 (1%)	0.063
30–39	7 (12%)	7 (5%)	
40–49	9 (15%)	21 (16%)	
50–59	17 (28%)	31 (24%)	
60–69	16 (27%)	44 (34%)	
70–79	8 (13%)	17 (13%)	
80+	0 (0%)	10 (8%)	
Gender			
Male	29 (48%)	89 (68%)	0.010
Female	31 (52%)	42 (32%)	
Race/ethnicity			
Black	16 (27%)	43 (33%)	0.563
White	16 (27%)	27 (21%)	
Other	26 (43%)	57 (44%)	
Comorbidities			
Coronary artery disease	5 (8%)	16 (12%)	0.466
Heart failure, systolic	5 (8%)	11 (8%)	1.000
Heart failure, diastolic	2 (3%)	6 (5%)	1.000
Stroke	4 (7%)	5 (4%)	0.470
Hypertension	38 (63%)	89 (68%)	0.397
Diabetes mellitus	23 (38%)	64 (49%)	0.148
COPD/asthma	9 (15%)	18 (14%)	0.864
Chronic kidney disease	3 (5%)	20 (15%)	0.054
Medications			
ACE-I	8 (13%)	32 (24%)	0.076
ARB	12 (20%)	13 (10%)	0.056
Beta-blockers	16 (27%)	31 (24%)	0.666
Aspirin	13 (22%)	17 (13%)	0.142
Prednisone	2 (3%)	6 (5%)	0.685
Body mass index (kg/m²)			
Median (IQR)	31.2 (28.3–38.0)	29.7 (25.5–37.5)	0.050
<18.5	0 (0%)	3 (2%)	0.047
18.5 to <25	5 (8%)	27 (21%)	
25 to <30	16 (27%)	40 (31%)	
≥30	39 (65%)	61 (47%)	

ACE-I indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 2. Incidence of elevated IL-6 levels, major adverse cardiovascular events, and/or death in the study cohort

| Cohort | Interleukin-6 | | P value |
	Normal	Elevated	
No MACE (n = 110)	50 (83%)	60 (46%)	<0.0001
MACE (n = 81)	10 (17%)	71 (54%)	<0.0001
Alive (n = 151)	57 (95%)	94 (72%)	<0.0001
Dead (n = 40)	3 (5%)	37 (28%)	<0.0001
No MACE and/or mortality (n = 102)	48 (80%)	54 (41%)	<0.0001
MACE and/or mortality (n = 89)	12 (20%)	77 (59%)	<0.0001

MACE indicates major adverse cardiovascular event.

Table 3. The risk of elevated IL-6 contributing to MACE, mortality, or MACE and/or mortality

| Outcome | Univariate model | | Multivariate model | |
	OR (95% CI)	P value	OR (95% CI)	P value
MACE	5.92 (2.65–14.11)	<0.0001	5.72 (2.65–12.33)	<0.0001
Mortality	7.48 (2.19–39.32)	0.0001	6.56 (1.91–22.54)	0.003
MACE and/or mortality	5.70 (2.65–12.83)	<0.0001	5.32 (2.56–11.08)	<0.0001

CI indicates confidence interval; MACE, major adverse cardiac event; OR, odds ratio.

level population and 31.97 ± 9.67 within the elevated IL-6 population.

In our cohort, COVID-19 patients with elevated IL-6 were older (61 [50–68] vs. 56.5 [46–65.5] years; $P = 0.03$) and had higher BMIs than the normal IL-6 population (31.21 [28.26–37.96] vs. 29.70 [25.53–37.53] kg/m^2; $P = 0.05$). Also, men had a higher odds of having elevated IL-6 compared to women (OR = 2.27; 95% CI 1.15–4.44; $P = 0.01$). The prevalence of comorbidities (i.e., coronary artery disease, congestive heart failure, stroke, hypertension, diabetes mellitus, chronic obstructive pulmonary disease/asthma, and chronic kidney disease) and number of patients on heart medications were comparable between the normal and elevated IL-6 cohorts.

The correlation between IL-6 levels and MACE and/or mortality was examined (Table 2). The incidence of MACE (54% [n = 71] vs. 17% [n = 10]), mortality (28% [n = 37] vs. 5% [n = 3]), and MACE and/or mortality (59% [n = 77] vs. 20% [n = 12]) was higher in the elevated IL-6 cohort than the normal IL-6 cohort (Table 3). Furthermore, patients with elevated IL-6 levels had higher odds of MACE, mortality, and MACE and/or mortality than the normal IL-6 population when controlled for age and BMI (Table 3).

DISCUSSION

In this study, we showed that elevated serum IL-6 levels correlated with MACE and/or mortality, independent of age and BMI, at a major Southwest US quaternary hospital. As the COVID-19 cases and death toll continue to rise, the medical community is racing to grasp a stronger understanding of the virus and to identify proper biomarkers related to COVID-19 severity. Elevated IL-6 levels are associated with increased COVID-19 severity and worsening viral disease on the cellular level.[5,6] Elevated IL-6 potentiates viral infection by inhibiting the CD8$^+$ T-cell response, synergizing with IL-17, and upregulating programmed cell death factors PD-1 and PDL-1.[6] The quick replication of SARS-CoV-2 can lead to respiratory infection and a further increase in IL-6 levels.[5] Previous studies found that patients with elevated IL-6 levels (>80 pg/mL) were 22 times more likely to experience respiratory failure than patients with lower IL-6 levels.[7] Systemic increases in IL-6 and worsened clinical outcomes have been linked to other viruses such as the Andes virus, influenza, hepatitis C, and human immunodeficiency virus.[6] Emerging data, including that of the current study, indicate that SARS-CoV-2 should be included in this list. As we discover an association between elevated IL-6 levels and poor outcomes in COVID-19 patients, there are still questions as to what extent elevated IL-6 levels correlate with cardiovascular outcomes.

With more documented cases of COVID-19, the prevalence of cardiovascular manifestations continues to rise. However, there is limited information about risk-stratifying these patients who are at risk of developing cardiac

complications and identifying those who need higher levels of care. Though COVID-19 patients often present with upper respiratory symptoms that progress to pneumonia or acute respiratory distress syndrome, cardiovascular disorders such as acute coronary syndrome, pericarditis, and myocardial injury have been described.[3] These cardiac manifestations further complicate the management of COVID-19 patients. A previous study with 416 COVID-19 patients noted that 22% of COVID-19 patients with cardiac injury required mechanical ventilation compared to 3.9% without cardiac injury. Overall in-hospital mortality was also increased.[8] The cardiac injuries in COVID-19 patients initially manifested as abnormal C-reactive protein, N-terminal pro B-type natriuretic peptide, and creatinine levels. In a study involving 191 COVID-19 patients, nonsurvivors had higher rates of acute cardiac injury and acute heart failure as well as higher levels of IL-6 and ferritin.[9] These findings of cardiovascular manifestations with aberrant biomarker levels, as well as a need to identify those patients requiring higher levels of care, was the foundation of this study.

There are limitations to our study. As this was a retrospective observational study, we were limited to identifying associations as opposed to identifying the direct cause of cardiovascular outcomes in COVID-19 patients. Another limiting factor was that 62% of COVID-19 patients at our institution did not have an IL-6 level drawn, which limited the size of our population.

In conclusion, this study showed that elevated IL-6 levels were associated with increased odds of MACE and/or mortality outcomes in a major Southwest US quaternary hospital population. This finding suggests that IL-6 levels can be used as a predictor of COVID-19 cardiovascular complications.

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