Original article

Correlation of inflammatory biomarkers with disease severity in hospitalised patients of COVID-19 at presentation

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ABSTRACT

Background: The course of COVID-19 ranges from asymptomatic infection to life threatening critical illness. Inflammatory biomarkers have vital role in predicting outcome, disease severity and disease prognosis in COVID-19 cases. This study aims to observe the correlation of these biomarkers with disease severity in COVID-19.

Patients and methods: This cross-sectional study was conducted in Chughtai Institute of Pathology from February 2021 to May 2021. Blood was collected from 1300 hospitalized adult PCR confirmed COVID-19 patients categorized in mild to critical disease classes. Asymptomatic cases, patients having coagulopathies and those who received plasma infusion were excluded from the study. Blood was analyzed for serum Interleukin-6 (IL-6), Ferritin, C-reactive protein (CRP), procalcitonin and D Dimers. Data was analyzed using SPSS 23.0.

Results: From the study patients, 65.3% (n=849) were male and 34.7% (n=451) were female. Majority of the cases (43.5%, N=565) belonged to moderate group whereas only 0.6% (N=8) were in critical group. Study population had a mean age of 56 (±13.98) years. Serum IL-6 was taken as marker of disease severity, showed significant positive correlation with CRP (r =0.52), ferritin (r =0.33), D-dimers (r =0.32) but no correlation with procalcitonin (r =0.17) using spearmen correlation coefficient. All patients with critical disease had IL-6 levels above 1000pg/ml.

Conclusion: The inclusion of inflammatory biomarkers in routine panel of COVID-19 patients can allow risk stratification of COVID-19 patients in different disease severity groups as cases with critical disease had higher levels.

Keywords:

COVID-19, Inflammation, IL-6, Complications, D-dimers, Ferritin, CRP, PCT

INTRODUCTION

Majority of the individuals infected with COVID-19 show mild symptoms like generalized body weakness and do not have severe disease.[1,2] On the contrary, around one fifth of the individuals of COVID-19 develop severe life-threatening infection and require emergency medical interventions like oxygen therapy or mechanical ventilation. [2] Commonly encountered symptoms in confirmed cases of COVID-19 are fever, shortness of breath, difficulty in breathing and generalized weakness.[3,4] Less commonly reported symptoms include abdominal pain, nausea, vomiting, loose stools, headache and myalgia.[4] In some of the cases, sudden loss of olfactory sensations and dysgeusia also been documented.[5] Evidence of the virus has been found in oropharyngeal/nasal secretions, sputum, saliva, tears and other body secretions.[6] Chinese studies suggest that children were less susceptible to COVID-19 as compared to adult population, whereas population greater than 65 years of age were more vulnerable.[7]

Laboratory analysis of various biomarkers have a vital role in predicting outcome in COVID-19 patients during their disease course.

Previous clinical studies have demonstrated that neutrophilia, lymphopenia, thrombocytopenia, elevated liver enzymes and lactate dehydrogenase were the most important predictors of poor disease outcome in COVID-19 patients.[8,9] Temporal progression of markers like CRP and creatinine kinase (CK) paly major role in predicting outcomes and disease complications in COVID-19 patients, but more studies are required to confirm the present findings.[9] Many treatment protocols have been suggested with great emphasis on the use of high dose steroids but the effectiveness of this treatment is still unclear.[10]

Laboratory biomarkers can provide valuable information which can significantly impact patient care. Assessment of biomarkers in COVID-19 can be useful in classification of disease severity, designing hospital admission criteria, identification of high risk population, and assessing response to the therapies as

Conflict of interest: The authors declared no conflict of interest exists.

Citation: Batool H, Khan MD, Chughtai OR, Chughtai AS, Ashraf S, Amir S. Correlation of inflammatory biomarkers with disease severity in hospitalised patients of COVID-19 at presentation. J Fatima Jinnah Med Univ. 2021; 15(4):171-176.

DOI: https://doi.org/10.37018/SELQ5005

levels of these inflammatory biomarkers reduce with successful treatment.[11] Leukopenia, lymphopenia and high AST can help in diagnosis of COVID-19.[11,12] Increased IL-6, raised levels of CRP, Ferritin, D Dimers, LDH, cardiac troponins along with lymphopenia and increased neutrophil lymphocyte ratio are helpful in assessing disease severity.[11,13] Severe cases of COVID-19 are associated with increased leucocyte count, neutrophils and raised level of inflammatory biomarkers such as CRP, procalcitonin (PCT), ferritin, IL-6 and tumor necrosing factor.[14] Patients with less severe disease tend to have lower levels of CRP, PCT, ESR, Ferritin and IL-6 compared with those having severe disease.[15] Studies have also observed significant increase in CRP, D-Dimers, AST and LDH levels in high disease severity groups.[16] Decreased levels of CRP, IL-6, TNF-alpha and IL-10 are associated with successful response to therapy.[11] Inflammatory biomarkers like IL-6 , Ferritin, PCT, CRP, LDH, cardiac troponins along with hematological markers such as lymphocyte count and neutrophil to lymphocyte ratio can aid in predicting prognosis of infection.[17, 18]

Complications like kidney failure, muscle injury, acute myocardial infarction, secondary infections, internal hemorrhage and stroke are most commonly encountered in SARS-CoV-2 infection [9]. Biomarkers representing alterations in these proteins may prove to be useful for health care providers in understanding the disease pathogenesis, initial diagnosis, risk stratification and deciding treatment plans for COVID-19 patients.[11]

Current evidence linking changes in biomarkers to the severity of disease process in COVID-19 is not sufficient with a few studies suggesting an association but other studies showing no association.[19-21] Modulation in critically ill patients of COVID-19 are associated with macrophage function, degranulation of proteins and complement activation. [22] This study aims to analyze the commonly tested biomarkers in blood of COVID-19 patients and observe the levels in different categories of the infection. Inflammatory biomarkers evaluated in this study include IL-6, CRP, procalcitonin, ferritin and D-dimers and their correlation with disease severity was observed.

PATIENTS AND METHODS

This was a cross-sectional study conducted at Chughati Institute of Pathology from February 2021 to May 2021. The study was ethically approved from the Institutional Review Board. Blood samples were collected from 1300 adult male and female patients having mild to severe symptoms admitted in Isolation Wards, Corona Care Units and High Dependency Corona Units of different private and government hospitals. All these patients were already categorized in different disease severity groups by the hospital authorities for admission in respective wards. Patients categorized as having mild disease were admitted in isolation wards. Moderate disease category group was admitted in corona care units and patients with severe and critical disease were admitted in high dependency units and intensive care units. The patients who booked for the laboratory investigations admitted in these hospitals were contacted and history was taken in detail by the authors. They were explained about the nature of the study and consent was taken from the patients/guardians. Clinical findings were reviewed from the medical record already present with the patients to confirm the disease categorization and positive history findings. Our laboratory representatives visited the patients for sample collection wearing adequate personal protective equipment according to biosafety protocols. All the tests were done free of cost and reports were shared with the patients. Clinical examination was not done and clinical findings were noted only base on history given by patients. Sample size was calculated with 95% Confidence interval. All patients were diagnosed cases of COVID-19 confirmed by RT-qPCR and their specimen were taken during the first week of admission in the hospital. Asymptomatic cases, patients having coagulopathies and those who received plasma infusion were excluded. Patient's age, gender, place of admission, symptoms, disease severity group (based on hospital categorization) and status of mechanical ventilation was recorded on a pre designed proforma. This study took into account four groups i.e., mild, moderate, severe and critical disease. The disease categorization in COVID-19 is done on the basis of Chinese guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection (trial version 5).[23] Clinical examination findings along with hospital investigations, like chest imaging, oxygen saturation which were used for disease categorization were also reviewed however the data was not correlated with any of the biomarker results. The laboratory tests for this study included serum IL-6 (cutoff level 7 pg/mL), Ferritin (Reference interval Adult Male: 20 - 250 ng/mL, Adult Female: 10 - 120 ng/mL), CRP (Cutoff level $\leq 0.50 mg/dL$) Procalcitonin (Reference Interval Adult Male: <0.08 ng/ml Adult Female: <0.05 ng/ml) and D Dimers (Cutoff level 250ng/mL) . Whole blood was collected in sodium citrate vacutainer from each patient for D Dimers. For all other analytes, 5 ml blood

Table 1. Gender wise distribution of patients in different disease groups

Disease Category	Male	Female
Mild (Symptoms like fever, headache, cough, lethargy sore throat, diarrhea, without shortness of breath or abnormal findings on chest imaging)	25 % (n=323)	16% (n=207)
Moderate (Evidence of respiratory disease on clinical examination or chest imaging with SpO_2 >94% on room air)	30% (n=396)	13.3% (n=169)
Severe (Evidence of >50% lung involvement on chest imaging with SpO_2 <94% on room air and a respiratory rate of >30 breaths per minute)	10% (n=125)	5.2% (n=72)
Critical (Evidence of respiratory failure requiring mechanical ventilation with septic shock and/or multi-organ failure)	0.3% (n=5)	0.2% (n=3)

Table 2: Mean value of biomarkers analyzed in the study in different disease severity groups .

Biomarker	All groups	Mild	Moderate	Severe	Critical	p-value *
Serum IL-6 (pg/mL)	203.25±518.77	15.96±25.24	123.58±193.62	773.22±743.37	4202.50±900.04	<0.001
CRP (mg/dL)	6.34±6.99	2.99±4.24	7.24±6.69	12.14±8.22	21.97±8.19	<0.001
Ferritin (ng/mL)	1071.3±1167.3	769.30±899.1	1240.55±1255.20	1361.16±1317.95	1989.01±1913.00	<0.001
D-dimers (ng/mL)	935.00±975.1	673.18±797.44	1054.81±1007.71	1266.87±1110.87	1646.62±1410.54	<0.001
Serum procalcitonin (ng/mL)	3.83±15.2	1.78±9.15	4.59±16.79	6.81±21.10	13.19±30.32	<0.001

*p value of <0.05 reflects that there was a significant difference between means in all disease severity groups.

was collected in serum separator tube and centrifuged at 3000 RPM prior to analysis. IL-6 was conducted at Roche Cobas 6000 using electrochemiluminescence as assay principle, D Dimers was conducted at Abbott Architect ci8200 and all other analytes were conducted at Abbott Alinity using chemiluminescence as assay principle. Data was analyzed using SPSS 23.0. For numeric data we calculated mean and standard deviation while qualitative variables like gender and disease categories were represented using frequencies and percentages. Spearman's correlation coefficient was used to study the relation of other inflammatory biomarkers with Interleukin 6 which was used as the marker for disease severity. ANOVA and Post Hoc Tukey's test was used to find out significant mean difference among groups. A p-value of <0.05 was considered significant.

RESULTS

Among total of 1300 patients, 65.3 percent (N=849) were male and 34.7 percent (N=451) were female. Mean age was 56±13.98 years. When categorized on the basis of disease severity, 40.8% (N=530) were categorized as mild disease group, 43.5% (N=565) were classified as moderate group, 15.2% (N=197) had severe disease whereas only 0.6% (N=8) were categorized as Critical group (Table 1). Patients' symptoms were not correlated individually with biomarkers but were only used for disease categorization. Levels of inflammatory biomarkers were increased as the disease severity was increased (Table 2).

Post Hoc analysis was used to do pairwise comparison of groups to find out significant mean difference in each pair and a p value of <0.05 was considered significant Table 3.

All patients with mild disease (N=530) had IL-6 value of less than 100pg/ml. All patients with critical disease had IL-6 above 1000pg/ml. There was a significant difference in the mean IL-6 and CRP levels among different disease severity groups (p-value < 0.001). Also, significant difference (p-value <0.05) was found in the levels of Ferritin and D Dimers between Mild disease and other disease groups. There was no difference in mean Procalcitonin levels in all disease severity groups. The differences in the mean value of ferritin and D Dimers were not significant between the critical and severe disease group.

Correlation of IL-6 levels with other inflammatory biomarkers was studied using Spearman's correlation coefficient. Serum IL-6 levels showed significant positive correlation with CRP (r =0.52), Ferritin (r =0.33), D-Dimers (r =0.32) but no correlation with Procalcitonin (r =0.17) (Table 4).

DISCUSSION

Rapidly spreading COVID-19 is a threat all over the world with new variants posing more danger. Although most cases are asymptomatic or mild having a good prognosis, some of the cases can turn out to be severe or critical resulting in death.[24] Lack of effective therapeutic guidelines make it important to highlight the role of inflammatory biomarkers monitoring disease progression. Studying these biomarkers can help to classify the patients in disease severity categories which can help to design treatment protocols in COVID-19 patients.[25] Proinflammatory cytokines are reported to be increased in COVID-19 patients with worsening symptoms.[26,27]

In this study IL-6 level was higher than normal in different disease severity groups and significant

Table 3: Post Hoc analysis for comparison of means

Biomarker	Comparison Groups along with means		p-value
Serum IL-6 (pg/mL)	Severe (773.2)	Mild (15.9)	<0.001
		Moderate (123.5)	<0.001
		Critical (4202.5)	<0.001
	Mild (15.9)	Moderate (123.5)	<0.001
		Critical (4202.5)	<0.001
CRP (mg/dL)	Severe (12.1)	Mild (2.99)	<0.001
		Moderate (7.24)	<0.001
		Critical (21.97)	<0.001
	Mild (2.99)	Moderate (7.24)	<0.001
		Critical (21.97)	<0.001
Ferritin (ng/mL)	Severe (1361.1)	Mild (769.3)	<0.001
		Moderate (1240.5)	0.57
		Critical (1989.0)	0.42
	Mild (769.3)	Moderate (1240.5)	<0.001
		Critical (1989.0)	0.01
D-Dimers (ng/mL)	Severe (1266.8)	Mild (673.1)	<0.001
		Moderate (1054.8)	0.03
		Critical (1646.6)	0.68
	Mild (673.1)	Moderate (1054.8)	<0.001
		Critical (1646.6)	0.02
Serum Procalcitonin (ng/mL)	Severe (6.8)	Mild (1.78)	<0.001
		Moderate (4.5)	0.29
		Critical (13.1)	0.64
	Mild (1.78)	Moderate (4.5)	0.12
		Critical (13.1)	0.14

Table 4. Correlation of other inflammatory biomarkers with IL-6 using spearman's correlation coefficient

Inflammatory Biomarker	Spearman Correlation Coefficient	p-value
CRP	0.52	<0.001
Ferritin	0.33	<0.001
D Dimers	0.32	<0.001
Procalcitonin	0.17	<0.001

difference was observed in disease categories. Patients with severe disease had IL-6 value between 500 to 1000 pg/ml whereas patients with critical disease requiring mechanical ventilation had IL-6 value above 1000 pg/ml. This is in accordance with the study done by Satis and coauthors who found a direct correlation between Interleukin-18 with IL-6 and other inflammatory biomarkers. The authors stated that Interleukins have a direct correlation with disease severity and increased level of biomarkers associated with poor disease outcome. A level of IL-18 above 500pg/ml was associated with increased risk of admission in ICU.[28]

CRP and D Dimers levels were also analyzed in present study and found to have a significant difference in all disease severity categories. CRP is a non-specific acute phase reactant but has proved to be a valuable inflammatory marker to assess disease severity in COVID-19. These findings are consistent with other studies suggested that elevated CRP levels can be related with the development of lung lesions during early COVID-19 stages.[29,30] With a mean level of 935ng/ml, significantly high levels of D-dimers in this study depict increased risk of coagulopathy during infection. Pneumonia and hypoxia in COVID-19 leads to activation of coagulation pathway and ultimately fibrinolysis and DIC resulting in multiorgan failure.[31,32] High D Dimers on admission can predict mortality rate during hospital stay with patients having higher levels having higher probability of developing pulmonary embolism.[33] Treatment of COVID-19 patients with anticoagulants has shown to improve disease progression.[34]

In the current study Procalcitonin (PCT) level was studied in all patients. Procalcitonin is a marker of bacterial infection and points towards more severe form of COVID-19 disease. The results showed a higher level of PCT in patients on mechanical ventilation. Elevated PCT levels have a strong association with poor prognosis in COVID-19 and point towards bacterial co infection and development of complications.[35,36]

A recent study explored the predictive value of inflammatory biomarkers in COVID-19 and found that biomarkers like Ferritin, D-dimers, IL-6, PCT, WBC count and CEA and found these biomarkers to be independent disease prognostic factors in COVID-19.[37] The authors used biomarkers values to construct overall survival nomogram in COVID-19 patients and used it for diagnosis and disease management. Ferritin was associated with worse symptoms in current study, however, some of the severe and moderate disease severity patients also showed low ferritin level which can be attributed to iron deficiency. A recent meta-analysis revealed that inflammatory parameters including IL-6 along with other interleukins point towards poor disease outcome in COVID-19 and must be screened serially during the disease course.[38] Another recently published study stated that WBC ratios, CRP and IL-6 was positively associated with disease severity in COVID-19 infection with high specificity and sensitivity.[39]

The main limitation of this study was lack of changing values during the disease course but despite of this, the study documented significant difference in inflammatory biomarkers in different disease severity groups of COVID-19. This suggests that these biomarkers can predict future severity of the disease.

CONCLUSION

Quantitative measurements of biomarkers reflect the disease pathophysiology in COVID-19, helping the health care workers to recognize disease severity. Inflammatory biomarkers, in particular IL-6 can be an

aid in risk stratification as patients with severe and critical disease had higher levels of the biomarkers studied .

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