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Brief communication

A Hospital-Based Study of Interleukin-6 In Covid-19 Positive Patients Investigating Its Correlation with Other Biochemical Markers of Thromboembolic Manifestation and Tissue Damage in North-East India.

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ABSTRACT

Background: Interleukin-6 (IL-6) is proposed to be associated with the severity of Coronavirus disease. However, the association of IL-6 with other established biomarkers of COVID-19 is not congruently found everywhere.
Aims & objectives: The present study was undertaken to evaluate the association of IL-6 with other established biomarkers of COVID-19 i.e CRP, D-Dimer, Ferritin, LDH, high sensitive troponin I (hs-cTnI) and Total leucocytic count (TLC).
Methodology: In a retrospective cross-sectional study in North Eastern India, levels of IL-6, CRP, D-dimer, Ferritin, LDH, and Total Leucocytic count in 100 COVID-19 positive adult patients were measured using fully automated analyzers. Data were collected from the hospital database. Trend analysis of IL-6 and its correlation with mentioned biomarkers was performed using Pearson's bivariate correlation analysis.
Results: Correlation analysis made by Pearson correlation revealed that the correlation of IL-6 was highly significant with CRP ($r=0.719$, $P<0.001$), D-Dimer ($r=0.540$, $P<0.001$), Ferritin ($r=0.232$, $P<0.030$), LDH ($r=0.485$, $P<0.001$) and Pro-calcitonin (PCT) ($r=0.677$, $P<0.001$). There was no significant correlation of IL-6 with hs Trop I ($r=0.116$, $P=0.341$) and total leucocytic count (TLC) ($r=0.77$, $P=0.465$).
Conclusion: The present study established a significant relationship of IL-6 with the other biomarkers that signified pulmonary thromboembolism in COVID-19 like D-Dimer and other inflammatory markers like serum ferritin, PCT, and CRP. However, no relationship of IL-6 was found with the cardiac injury marker hsTropI.

INTRODUCTION

Interleukin-6 (IL-6) is a pleiotropic cytokine released by a variety of cell types such as immune cells[1, 2]. IL-6 was proposed to be associated with the severity of Coronavirus disease[3]. Coronavirus may activate these regulated host immune responses[4-6]. The purpose of this study was to determine the levels of IL-6 and evaluate its association with clinical presentations and other established biomarkers for covid 19[7] like CRP, D-dimer, Ferritin, LDH, Total Leucocytic count both baseline and trend in COVID-19 patients. Although IL-6 is an inflammatory biomarker, biomarkers like D-dimer signify pulmonary thromboembolism[8], while serum ferritin and CRP are other markers of inflammation. Serum ferritin which acts as an acute phase reactant protein finds a special importance among the COVID-19 prognostic markers. Serum ferritin indicates both acute and chronic inflammation and marks the activation of the macrophage monophage system[9]. Hence, the relationship of IL-6 with all these parameters needs to be explored to have a comprehensive idea about the inflammatory system in COVID-19 and its consequences. However, there are several discrepancies found in this relationship that are dependent on specific geographical areas. With this lacuna, we undertook the present study with the research question of whether an increase in IL-6 in COVID-19 patients in our region is associated with the biomarkers of pulmonary thromboembolism and other markers of inflammatory procedures.

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METHODOLOGY

The present study was undertaken as a retrospective cross-sectional study that involved the collection of data of IL-6, CRP, D-dimer, Ferritin, LDH, and Total Leucocytic count levels in 100 COVID-19 positive adult patients admitted in the Apollo Hospitals Guwahati, befitted with inclusion and exclusion criteria. Data have been collected from the hospital database. Trend analysis of IL-6, its correlation with mentioned biomarkers, clinical presentations, and mortality was established.

All tests were performed by dedicated kits in Fully automated analyzers and were monitored using routine quality control procedures. The CV for all tests was within 10% of the variation.

The data obtained were analyzed using SPSS 22.0 software for Windows. Statistical significance was considered at P value <0.05 for a 95% confidence interval.

Inclusion Criteria

-Confirmed Covid-19 (RAT or RT-PCR Positive) hospitalized patients

- Age>18 years
- Documented IL-6 level analyzed at baseline and subsequently

Exclusion Criteria

-Chronic inflammatory disease

- Malignancy
- Connective tissue disease
- Age< 18 years

RESULTS

Trend analysis of IL-6 values showed an increased trend for death cases. Correlation analysis made by Pearson correlation (Table 1) revealed that the correlation of IL-6 was highly significant with CRP (r=0.719, P<0.001), D-Dimer (r=0.540, P<0.001), Ferritin (r=0.232, P<0.030), LDH (r=0.485, P<0.001) and Pro-calcitonin (PCT) (r=0.677, P<0.001). There was no significant correlation of IL-6 with hs Trop I (r=0.116, P=0.341) and total leucocytic count (TLC) (r=0.77, P=0.465).

DISCUSSION:

Results of our study (Table 1) showed that the inflammatory mediator IL-6 is directly associated with the pulmonary thromboembolic marker D dimer and acute phase reactant serum ferritin level. However, our findings are novel in the fact that they did not match with some earlier studies in other parts of the world which did not find any correlation between IL-6 with serum ferritin and D dimer[10]. The findings of our study signify that in our region changes in the IL-6 are closely related to the changes in thromboembolic risks and other consequences of either acute or chronic inflammation. Serum ferritin itself is a marker of both acute and chronic inflammation and is a robust indicator of activation of the macrophage monocyte system of the body that in turn signifies the activation of the cytokine storm, a hallmark of COVID-19-mediated tissue damage. The heavy chain of ferritin is directly related to the changes in the cytokine system that finally regulates the inflammatory response of the body[11]. Ferritin has been also reported to be directly linked to lymphocyte function and hence to the total leukocyte count (TLC) [12]. In our present study, although we did not carry out the analysis between serum ferritin and TLC level, we observed no significant relationship of IL-6 with TLC also (r = 0.077, P = .465). However, we observed a direct relationship between IL-6 and the tissue hypoxia indicator LDH (r = 0.48, P <.001). Neither we found any significant relationship between the IL-6 and cardiac tissue injury marker hs TropI (r = 0.116, P = .34: Table 1).

CONCLUSION: From these observations, we can suggest that in our study population, changes in IL-6 can effectively predict changes in the risk of thromboembolic manifestations, tissue hypoxia, and acute phase inflammatory reactions. However, our study excludes IL-6 as a cardiac risk factor as no significant relationship was found between it and hs TropI.

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CONFLICT OF INTEREST: Nil

Table 1: Correlation analysis of IL-6 with other biomarkers in COVID-19

Analytes	**Pearson's correlation coefficient (r)**	**P value***
CRP	0.719	<.001.
D-DIMER	0.540	<.001
Ferritin	0.232	.030
LDH	0.485	<.001.
PCT	0.677	<.001.
hsTropI	0.116	.34
TLC	0.077	.465

* Statistical significance was considered at P value <0.05 for a 95% confidence interval.