Original Article

Utility of various inflammatory markers in predicting outcomes of hospitalized patients with COVID-19 pneumonia: A single-center experience

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ABSTRACT

Aim: The aim of the study is to study the utility of various inflammatory markers in predicting outcomes of hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia. **Primary Objective:** The primary objective of the study is to analyze the correlation between various inflammatory markers and in-hospital mortality. **Secondary Objectives:** The secondary objective of the study is to assess the correlation between the inflammatory markers and clinical category of patients, and other outcomes such as length of hospital stay and need for invasive ventilation. **Methods:** A retrospective cross-sectional observational study was done in 221 hospitalized patients who were diagnosed with COVID-19 pneumonia in a tertiary care hospital in South India from May 2020 to July 2020. Clinical and laboratory data of patients diagnosed with COVID-19 pneumonia were collected. This included epidemiological data, clinical data, laboratory parameter (neutrophil: lymphocyte [N: L] ratio, C-reactive protein [CRP], ferritin, interleukin-6 [IL-6], lactate dehydrogenase, D-dimer, and procalcitonin), treatment details, and outcomes. **Results:** IL-6 levels >60.5 pg/mL and D-dimer levels >0.5 mcg/mL predicted in-hospital mortality with sensitivities of 80% and 76.7%, respectively. N: L ratio and CRP levels had good correlation with the need for oxygen supplementation and/or invasive ventilation. **Conclusions:** Judicious use of COVID-19 biomarkers could help in disease prognostication and thereby provide guidance to devise appropriate management strategies.

KEY WORDS: Coronavirus disease 2019 biomarkers, Coronavirus Disease 2019 pneumonia, C-reactive protein, D-dimer, ferritin, interleukin-6, lactate dehydrogenase, neutrophil: lymphocyte ratio, procalcitonin

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INTRODUCTION

The novel coronavirus disease 2019, a viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), emerged in Wuhan city of

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China toward the end of the year 2019.[1] At present, it has spread all across the globe and seems to have turned our lives topsy-turvy. A lot still remains to be unveiled and understood about this growing pandemic.

The early identification of patients who are likely to deteriorate will help in effective utilization of the limited medical resources we have at present. Elevation of inflammatory markers such as C-reactive protein (CRP) and ferritin and changes such as lymphocytopenia have been previously reported in coronavirus disease 2019 (COVID-19) patients, but little is known about their correlation with disease severity.[2] Computed tomography (CT) imaging of chest plays an important role in assessing the severity of the disease.[3] However, it has certain limitations such as cost factor, logistic aspects in terms of isolation precautions, and patient safety due to high oxygen requirement or ventilatory support.

Exploring and identifying routine laboratory parameters to assess the severity of the disease will enable the optimal allocation of limited human and technical resources in the ongoing pandemic. Clinical monitoring and early initiation of appropriate treatment strategies can then be devised to manage patients appropriately, reduce the mortality, and improve other outcomes. Therefore, it becomes necessary to determine the utility of various inflammatory markers in predicting outcomes of hospitalized patients with COVID-19 pneumonia.

MATERIALS AND METHOD

Study design
A retrospective cross-sectional observational study was done in 221 hospitalized patients who were diagnosed with COVID-19 pneumonia in a tertiary care hospital in South India from May 2020 to July 2020. Our institutional review board approved this study. Informed consent was waived as per the review board's recommendations, since there was no active intervention involved for the purpose of this study. The privacy and confidentiality of patients were maintained as per norms.

Data collection
We retrospectively collected the clinical and laboratory data of patients diagnosed with COVID-19 pneumonia. This included epidemiological data, clinical manifestation, comorbidities of patients, laboratory parameters such as CRP, neutrophil: lymphocyte (N: L) ratio, ferritin, interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-dimer, procalcitonin (PCT), various drugs used in the treatment along with the mode of oxygen supplementation, and final outcome. After collection of all required data and careful medical chart review, the clinical data of laboratory-confirmed patients were compiled and tabulated.

Diagnosis of COVID-19 pneumonia was confirmed by nasopharyngeal swab for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT PCR). According to our institution protocol, patients were divided into Category A, B1, B2, and C mainly based on their oxygen saturations on presentation and comorbidities were present. Category A and B1 included mild cases. Category A includes patients who are maintaining SpO2 of above or equal to 94% in room air and have no associated comorbidity. Category B1 includes patients maintaining SpO2 of above or equal to 94% in room air and with associated comorbidity such as diabetes mellitus, hypertension, coronary artery disease, and chronic kidney disease (CKD). Category B2 includes moderate cases wherein patients maintain SpO2 in the range of 90%–93% in room air, with or without any comorbid condition. Category C includes severe cases with patients having SpO2 of <90% in room air, with or without any comorbid condition.[4]

Inclusion criteria
All hospitalized patients aged 18 years and above with laboratory-confirmed diagnosis of COVID-19 pneumonia in our institution were included in the study.

Statistical analysis plan
All continuous variables were expressed as mean ± standard deviation, if they were normally distributed. Nonnormally distributed continuous variables were expressed as median (interquartile range). Comparison of normally distributed continuous variables if any was done using independent sample *t*-test. Comparison of pre- and postcontinuous variables was done by paired *t*-test, if the distribution is normal. All nonnormally distributed continuous variables were compared by Mann–Whitney U-test. Comparison of normally distributed continuous variables between more than two groups was done by ANOVA. Categorical variables were compared using either Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve was drawn to identify the optimal cutoff points of biomarkers to know its prognostic value. ROC curves were compared using DeLong method. Data entry was done in Microsoft Excel 2007 spreadsheet. Data analysis was carried out by IBM SPSS statistics for windows version 25.0, Armonk, NY, USA, IBM Corp. All $P < 0.05$ were considered statistically significant.

RESULTS

221 COVID-19 RT-PCR-positive patients were included in this study. The mean age of the patients was 60 years with male predominance Male = 70.1% and Female = 29.9%. Fever (175 patients, 79.2%) was the most common symptom followed by shortness of breath (151 patients, 68.3%) and cough (114 patients, 51.6%) while a few patients (69 patients, 31.3%) had other symptoms such as myalgia (63 patients, 28.5%), loose stools (5 patients, 2.3%), and sore throat (1 patient, 0.5%). Most of the patients in our sample population had one or other underlying comorbid condition. The most commonly present comorbidity was diabetes mellitus (111 patients, 50.2%),

followed by hypertension (101 patients, 45.7%), coronary artery disease (36 patients, 16.3%), hypothyroidism (27 patients, 12.2%), preexisting pulmonary diseases such as asthma, interstitial lung disease, chronic obstructive pulmonary disease, and tuberculosis (20 patients, 9%), and CKD (11 patients, 5%).

18 patients (8.1%) belonged to Category A (mild disease), 61 patients (27.6%) belonged to Category B1 (mild disease), 55 patients (24.9%) belonged to Category B2 (moderate disease), and 87 patients (39.4%) belonged to Category C (severe disease). On arrival, 83 patients (37.6%) were able to maintain saturations (SpO2) in room air. 43 patients (19.5%) required O2 supplementation through nasal prongs, 11 patients (5%) required face masks, 33 patients (14.9%) required nonrebreathing face mask, 45 patients (20.4%) required noninvasive ventilation/high-flow nasal cannula, and 6 patients (2.7%) were intubated.

Steroids were used in 170 patients (76.9%) with dexamethasone (150 patients, 67.9%) being more commonly used than methylprednisolone. Majority of patients (203 patients, 91.9%) were started on anticoagulation unless there was any contraindication. Remdesivir was the most commonly used antiviral drug, i.e., in 94 patients (42.5%). Tocilizumab, ritonavir-lopinavir, favipiravir, and plasma exchange were used in a small minority of patients.

In-hospital mortality rate was 15.8% (35 patients). Among the patients who got discharged, 157 patients (71%) were discharged without domiciliary oxygen support and 29 patients (13.1%) required home oxygen therapy.

Among the nonsurvivors, 30 patients (85.7%) had breathlessness as presenting complaint with a significant *P* value of 0.016. Similarly, among the nonsurvivors, 31 patients (88.6%) belonged to Category C on presentation, which had a significant *P* = 0.0001.

Table 1 depicts the median values of N: L ratio, ferritin, IL-6, LDH, CRP, D-dimer, PCT in survivors, and nonsurvivors, respectively. On admission, values of N: L ratio, ferritin, IL-6, LDH, CRP, and D-dimer had significant *P* value in predicting in-hospital mortality.

As per area under receiver operating characteristics (AUROC) [Figure 1], IL-6 and D-dimer predict mortality better than other markers [Table 2].

Even though AUROC is higher in IL-6 and D-dimer, comparison of ROC curves between biomarkers did not reveal statistical significance by DeLong's method.

ROC was used to derive a cutoff value for the biomarkers (N: L ratio, ferritin, CRP, D-dimer, and IL-6) in predicting in-hospital mortality. We derived an optimal cutoff point using Youden's index which has got discriminating power.

Here, the term cutoff value refers to the value above which in-hospital mortality is predicted [Table 3]. Among the biomarkers, IL-6 with a cutoff value of 60.5 pg/mL was found to have maximum sensitivity (80%) and a specificity of 65%, followed by D-dimer with a cutoff value of 0.5 mcg/mL had a sensitivity of 76.7%, and specificity of 60%. Ferritin with a cutoff value of 674 ng/mL had a sensitivity of 60% and specificity of 76%. CRP with a cutoff value of 96 mg/L had a sensitivity of 56.7% and specificity of 75%. N/L ratio with a cutoff value of 10.688 had a sensitivity of 56% and specificity of 76%.

ANOVA was used to compare biomarker levels between various categories. Table 4 reveals the mean values and

Table 1: Biomarkers in survivors versus nonsurvivors

Parameters on admission	Median value (IQR)		*p* value
	Survivors (*n*=186)	Nonsurvivors (*n*=35)	
N: L ratio	5 (3.2-9.8)	11 (5.4-20.6)	0.014
Ferritin (ng/mL)	389 (166-654)	780 (402-1503)	0.001
IL-6 (pg/mL)	43 (17-91)	120 (68.5-217)	0.006
Serum LDH (U/L)	383 (287-462.5)	578 (376-805.5)	0.0001
CRP (mg/L)	55 (18-94)	112 (70-188)	0.0001
D-dimer (mcg/mL)	0.4 (0.2-0.7)	0.85 (0.48-6.25)	0.005
Serum PCT (ng/mL)	0.09 (0.05-0.22)	0.59 (0.18-1.05)	0.35

N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PCT: Procalcitonin, IQR: Interquartile range

Table 2: Biomarkers and area under the curve

Parameters	Area	95% CI	
		Upper band	Lower band
N: L ratio	0.669	0.556	0.783
Ferritin	0.729	0.636	0.822
CRP	0.668	0.551	0.785
D-dimer	0.739	0.641	0.836
IL-6	0.740	0.659	0.821

N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, CRP: C-reactive protein, CI: Confidence interval
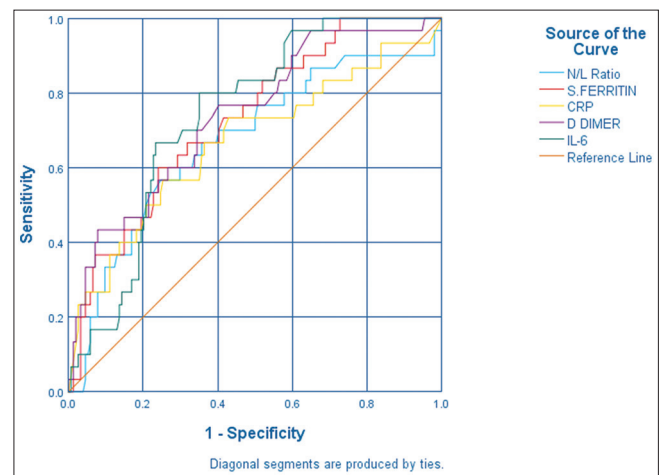

Figure 1: Area under receiver operating characteristics showing interleukin-6 and D-dimer as better predictors of mortality than other markers

standard deviation of N: L ratio, ferritin, IL-6, LDH, CRP, D-dimer, and PCT in Category A, B1, B2, and C. Between categories, N: L ratio, IL-6, LDH, and CRP values had significant *P* value.

Post hoc test done between categories revealed N: L ratio, LDH, CRP, and IL-6 between Category A and Category C, Category B1 and Category C, and Category B2 and Category C showed variation with significant *P* value. Similarly, serum ferritin between Category A and Category C showed variation with significant *P* value. D-dimer and PCT values did not show much variation between categories.

Correlation between biomarkers and duration of hospital stay was also studied [Table 5]. Duration of hospitalization of 193 patients was ≤14 days, and for 28 patients, it was >14 days. N: L ratio and CRP levels on admission were better predictors of the duration of hospital stay with a significant *P* value.

N: L ratio, LDH, and CRP levels had good correlation with the need for oxygen supplementation and/or invasive ventilation with significant *P* values as given in Table 6.

DISCUSSION

The rapidly spreading pandemic, COVID-19 caused by the SARS-CoV-2, has put an enormous burden on health-care systems, globally. Clinically, COVID-19 encompasses broad spectrum of symptoms ranging from mild ILI (influenza-like illness) to severe acute respiratory distress syndrome with multisystem involvement.[5] It is the need of the hour to frame effective testing strategies which will enable physicians to triage patients accordingly and initiate treatment with appropriate monitoring, as needed with the limited resources, we have at present. Biomarkers are quantitative indicators which reflect the underlying pathological processes that take place in the body.[6]

In COVID-19 infection, biomarkers seem to be valuable, cost-effective tools to guide treatment as compared to imaging procedures such as CT chest. There are many biomarkers related to COVID-19 infection such as N: L ratio, ferritin, CRP, D-dimer, LDH, and PCT, to name a few. However, there are only few studies that have come up so far regarding the usefulness of these biomarkers in COVID-19 infection.[7,8] Hence, this retrospective study was conducted to understand the use of these COVID-19 biomarkers in disease prognostication and correlation between these markers and clinical severity of the disease and outcomes.

SARS-CoV-2 binds to the cell surface receptor of ACE-2 by the spike glycoprotein and enters the cell cytoplasm, where it releases RNA genome and replicates, resulting in the formation of new viral particles.[9] Then, the cell disintegrates and the virus spreads to other cells.[9] The immune dysregulation initiated by pyroptosis (pro-inflammatory form of apoptosis) with rapid viral replication leads to massive release of inflammatory mediators.[10] The disease which starts as a simple viral infection goes out of control after a while and progresses toward a deadly result with development of the cytokine storm and serious organ damage.

Many patients infected with COVID-19 develop a fulminant immune response due to cytokines leading to alveolar infiltration by monocytes and macrophages.[11] IL-6 is one of the main inflammatory mediators.[12] IL-6 levels are found to be elevated in more than one-half of patients with COVID-19.[12] Levels of IL-6 were found to be associated with respiratory failure, inflammatory response, need for mechanical ventilation and/or intubation, and mortality in COVID-19 patients.[13,14] In a meta-analysis conducted by Aziz *et al*., it has been reported that mean IL-6 levels were more than three times higher in patients with complicated COVID-19 compared with those with noncomplicated disease, and IL-6 levels were associated with mortality risk.[14]

Table 3: Biomarkers sensitivity in predicting mortality and specificity in predicting mortality

Parameters	Cutoff value	Sn (%)	Sp (%)
N: L ratio	10.688	56	76
Ferritin (ng/mL)	674	60	76
CRP (mg/L)	96	56.7	75
D-dimer (mcg/mL)	0.5	76.7	60
IL-6 (pg/mL)	60.5	80	65

Cutoff value: Value above which mortality is predicted. Sn: Sensitivity in predicting mortality, Sp: Specificity in predicting mortality, N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, CRP: C-reactive protein

Table 4: Biomarkers among the three categories

Parameters	Mean±SD				*p* Value
	Category A (*n*=18)	Category B1 (*n*=61)	Category B2 (*n*=55)	Category C (*n*=87)	
N: L ratio	6.38±6.49	5.49±5.19	7.80±8.89	14.95±15.49	0.0001
Ferritin (ng/mL)	323.41±231.85	582.81±948.97	595.52±552.24	753.84±678.54	0.179
IL-6 (pg/mL)	61.17±128.39	89.72±131.04	73.75±86.16	161.91±229.31	0.008
LDH (U/L)	374.33±143.55	283.86±160.50	379.02±133.08	528.63±263.95	0.0001
CRP (ng/mL)	46.40±32.55	47.94±54.53	71.24±53.68	97.38±61.94	0.0001
D-dimer (mcg/mL)	0.38±0.39	0.79±2.75	1.77±4.53	14.79±76.21	0.254
Serum PCT (ng/mL)	0.17±0.26	0.75±3.85	0.18±0.22	0.64±1.16	0.445

N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PCT: Procalcitonin, SD: Standard deviation

Our study also showed that IL-6 had maximum sensitivity in predicting in-hospital mortality among patients with COVID-19 infection.

Elevated levels of D-dimer indicate increased risk of abnormal blood clotting, and D-dimer assays are commonly used in clinical practice to exclude a diagnosis of venous thromboembolism. Elevated levels of D-dimer were also found to be related with higher mortality rate of community-acquired pneumonia.[15] Patients with severe community-acquired pneumonia had significantly higher D-dimer levels, and D-dimer within normal range indicated low risk for complications.[16] In a mouse model of SARS-CoV disease, it was shown that augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin and finally lead to diffuse alveolar damage and acute lung injury.[17] A virus infection may develop into sepsis and induce coagulation dysfunction. Hence, in addition to venous thromboembolism, D-dimer might be a manifestation of severe virus infection. Moreover, the increase of D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system and then increase the level of D-dimer.[18,19] Our study also reflected similar finding showing D-dimer to be a sensitive predictor of mortality next to IL-6.

Direct cytopathic effect of SARS-CoV-2 on lymphocytes may be attributed to the affinity of the virus for lymphocytic ACE receptors.[20] High N: L ratio with increase in neutrophils may be indicative of the patient's response to inflammatory insult in response to stress, which, when overwhelming, induces lymphocyte apoptosis.[21] There are hypotheses that neutrophil extracellular traps released by neutrophils contribute to organ damage and death in COVID-19 patients.[7] Fox *et al.* and Yao *et al.* documented that neutrophil infiltration in the pulmonary capillaries of the three autopsy samples of COVID-19 patients further support the theory that neutrophils may be responsible for mortality in severe COVID-19 infection.[22,23] In our study, N: L ratio was found to be reliable marker in predicting in-hospital mortality, duration of hospital stay, and need for invasive ventilation.

The function of ferritin including iron binding and storage is associated with the immune and inflammatory response.[24] Elevation of serum ferritin levels predicts a poor outcome in hospitalized patients with influenza infection.[24] In the present study, ferritin was less sensitive than D-dimer and IL-6 in predicting in-hospital mortality.

When inflammation or tissue damage happens, CRP can be significantly increased in serum, which is usually used as an important biomarker in the current clinical practice.[25] On the other hand, PCT, the precursor of calcitonin, is a kind of glycoprotein without hormone activity, is found to be significantly higher in bacterial infection, and remains normal or only slightly increased in viral infection.[26] Similarly, in our study too, PCT did not show any correlation with disease mortality or other disease outcomes.

Limitation
The main limitation of our study is its retrospective design. Due to this, the impact of various drug and other interventions on the primary and secondary outcomes from the illness could not be analyzed. However, we could ensure complete data capture for all the patients in the study since a uniform protocol was followed in our center in terms of initial monitoring and assessment.

CONCLUSIONS

Among the various inflammatory markers that are used, IL-6 and D-dimer were found to be sensitive predictors of in-hospital mortality due to SARS-CoV-2 pneumonia. N: L ratio and CRP on admission seemed to correlate with duration of hospitalization and need for oxygen

Table 5: Biomarkers and duration of hospital stay
Parameters on admission	Mean value		p Value
	≤14 days (*n*=193)	>14 days (*n*=28)	
N: L ratio	9	16	0.002
Ferritin (ng/mL)	619	778	0.284
IL-6 (pg/mL)	109	137	0.440
Serum LDH (U/L)	405	499	0.051
CRP (ng/mL)	69	104	0.004
D-dimer (mcg/mL)	6.1	9.5	0.733
Serum PCT (ng/mL)	0.46	0.80	0.431

N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PCT: Procalcitonin

Table 6: Biomarkers and oxygen requirement
Parameter	Mean value						p Value
	Room air (*n*=83)	Nasal prongs (*n*=43)	Face mask (*n*=11)	NRBM (*n*=33)	NIV/HFNC (*n*=45)	Mechanical ventilation (*n*=6)	
N: L ratio	5.85	7.72	15.97	11.44	17.20	6.02	0.0001
Ferritin (ng/mL)	543	587	583	595	874	858	0.241
IL-6 (pg/mL)	83	97	49	167	138	226	0.074
LDH (U/L)	303	374	288	479	577	734	0.0001
CRP (ng/mL)	50	73	59	88	97	141	0.0001
D-dimer (mcg/mL)	0.80	1.64	0.57	25.35	10.24	0.80	0.230
PCT (ng/mL)	0.56	0.39	0.37	0.31	0.65	0.74	0.978

N: L ratio: Neutrophil: lymphocyte ratio, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PCT: Procalcitonin, NRBM: Nonrebreathing mask, NIV: Noninvasive ventilation, HFNC: High-flow nasal cannula

supplementation/invasive ventilation in hospitalized COVID-19 patients. Among the markers, N: L ratio, CRP, IL-6, and LDH showed a significant difference in predicting clinical severity. LDH levels correlated with need for oxygen supplementation. Serum PCT values had poor correlation with either mortality or need for invasive ventilation.

Judicious use of these various markers is helpful in correctly identifying the severity of COVID-19 pneumonia and predicting the outcomes. This would thereby help in guiding appropriate treatment strategies. Larger prospective studies could throw more light on the impact of treatment protocols guided by these biomarkers on the eventual outcomes due to this severe viral infection.

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Conflicts of interest
There are no conflicts of interest.

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