

## Research Article



## Retrospective Analysis of C - Reactive Protein, Haematological Biomarkers and Coagulation Profile in Patients of SARS-Cov-2 in a Tertiary Care Hospital of Eastern India

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### ABSTRACT

**Introduction:** Blood tests play an important role in the early detection of disease given that they provide doctors with information about inflammatory processes. A complete blood count (CBC) is easy and inexpensive to perform. These parameters can be used alone as markers of inflammation. Their mutual ratio is also an indicator of early inflammation.<sup>4</sup> In light of previous studies, the use of circulating biomarkers instead of inflammation and immune system has been considered a prognostic indicator for COVID-19 positive patients.

**Aims/ objective:** To examine the role of biomarkers from peripheral blood samples in the diagnosis of hospitalized COVID-19 patients with a history of fever.

**Materials and Method:** Haematological biomarkers and coagulation profile was compared between RT-PCR positive and negative patients. Systemic inflammatory index (SII) was calculated by multiplying thrombocyte count with neutrophil count and dividing the value by lymphocyte count. Neutrophil lymphocyte ratio (NLR) was calculated by dividing absolute neutrophil count by absolute lymphocyte count. Platelet lymphocyte ratio (PLR) was calculated by dividing absolute platelet by absolute lymphocyte count. Fisher exact test and unpaired t-test were used to compare categorical and continuous data respectively.

**Results:** Analysis was done on 57 retrospective cases of RT-PCR positive patients and 61 RT-PCR negative patients with history of fever. COVID-19 positive patients showed leukopenia, neutropenia, thrombocytopenia, and lymphocytosis. SII and NLR decreased and PLR increased. PT and APTT were generally within normal limits in most of the patients. There was significant difference between two groups with respect to lymphocyte counts and PLR.

**Conclusion:** The most standardized non-invasive and inexpensive tests such as CBC, coagulation and biochemical tests are available to assess disease severity for wise allocation of medical resources in developing countries such as India where resources and care are limited.

**Keywords:** COVID-19, Haematological Indices, NLR, Coagulation, Biochemical Marker.

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### INTRODUCTION

First case of COVID-19 that was caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) was reported in Wuhan, China in December 2019 and this disease has evolved from a small epidemic outbreak into a global pandemic within 6 months affecting more than 150 million individuals across the globe.<sup>1,2</sup> In India, first case of COVID-19 was reported on 30<sup>th</sup> Jan 2020 from the state of Kerala. There was a positive history of travel from Wuhan in the patient. And from that time, more than 20 million patients have been affected from COVID-19 across the globe.

India has witnessed one of the world's most COVID-19 crises with daily infection rate reaching as high as 4 lakhs and daily death reaching as high as 4000.<sup>1</sup> We have also witnessed crippling of healthcare infrastructure with an acute shortage of ICU beds, oxygen supply, ventilators etc. In the fight against COVID-19 disease, there was an urgent requirement to recognise clinical, biochemical and laboratory markers of disease progression to severe and critical forms. These laboratory predictors could help in better evidence based clinical management by highlighting the patients who need urgent attention to stop the disease progression and planning optimum distribution of resources in the ongoing pandemic specifically in developing countries like India with limited human and technical resources.

Although COVID-19 is expected to present primarily as a respiratory infection, current data suggest that it may cause systemic infections involving multiple systems including cardiovascular, respiratory, gastrointestinal, nervous, hematopoietic and immune.<sup>3</sup> Patients' clinical symptoms include fever, non-productive cough, dyspnea,



myalgia, fatigue, and radiographic evidence of pneumonia. Severe cases can lead to organ dysfunction (eg, shock, acute respiratory distress syndrome [ARDS], acute heart injury, and acute kidney injury) and death.<sup>4</sup> Given the short-term onset of acute respiratory distress syndrome in post-hospitalized patients and the mortality associated with COVID-19, early diagnosis is critical.

The pathogenesis of COVID-19 is complex, involving multiple systems including the hematopoietic, haemostasis, and immune systems. There is striking evidence for hyperinflammatory features in critically ill patients, consisting of elevated serum C-reactive protein (CRP), procalcitonin, D-dimers, and hyperferritinemia.<sup>5</sup> Moreover, lymphopenia has strong association with disease severity.<sup>6</sup> Both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are asymptomatic systemic factors in many diseases such as cardiovascular disease, cancer, autoimmune disease, and COVID-19. It has emerged as an excellent predictor of inflammation.<sup>7</sup> The “cytokine storm” (CS) of COVID-19 leads to the worst stages of the disease. Increased serum expression of interleukin (IL)-2R and IL-6 appears to predict severity and prognosis in COVID-19 patients.<sup>8</sup>

Blood tests play an important role in the early detection of disease given that they provide doctors with information about inflammatory processes. A complete blood count (CBC) is easy and inexpensive to perform. CBC includes values such as white blood cell count, neutrophil count, lymphocyte count, and platelet count (PLT). These parameters can be used alone as markers of inflammation. Their mutual ratio is also an indicator of early inflammation.<sup>4</sup> In light of previous studies, the use of circulating biomarkers instead of inflammation and immune system has been considered a prognostic indicator for COVID-19 positive patients.

This study examines the role of biomarkers from peripheral blood samples in the diagnosis of hospitalized COVID-19 patients with a history of fever.

## MATERIALS AND METHODS

A retrospective study was carried out in a private sector hospital of eastern India where the patients having history of fever were admitted during 1st May 2021 to 15th August 2021. A retrospective study was conducted in a private hospital in the East India in patients with a history of fever between 1 May 2021 and 30 August 2021. A total of 150 patients with suspected COVID-19 were included. RTPCR was performed on all patients and classified into COVID-positive and COVID-negative patients.

### Inclusion criteria

All patients aged 18 years and older who were positive by real-time reverse transcriptase polymerase chain reaction (RT-PCR) were included and categorised in COVID-19 positive cases.

Patients were also classified as survivors and non-survivors.

### Exclusion criteria

Patients with a history of thromboembolic/cardiovascular disease, inflammatory bowel disease, hematologic disease, surgery or trauma within the past 6 months, or bedridden patients, pregnant women, having liver or renal disease, cancers, or taking drugs that affect haemostasis were excluded from our study.

All the laboratory reports of the patients were collected. Haematological biomarkers and coagulation profile was compared between RT-PCR positive and negative patients. Systemic inflammatory index (SII) was calculated by multiplying thrombocyte count with neutrophil count and dividing the value by lymphocyte count. Neutrophil lymphocyte ratio (NLR) was calculated by dividing absolute neutrophil count by absolute lymphocyte count. Platelet lymphocyte ratio (PLR) was calculated by dividing absolute platelet by absolute lymphocyte count.

### Statistical Analysis

Data were analyzed with the statistical package SPSS 25 program. Fisher's exact test was used to analyze critical patient variables expressed as numbers and percentages. Unpaired t-tests were used for analysis of parametric continuous variables and presented as both mean and standard deviation.  $P < 0.05$  was considered statistically significant.

## RESULTS

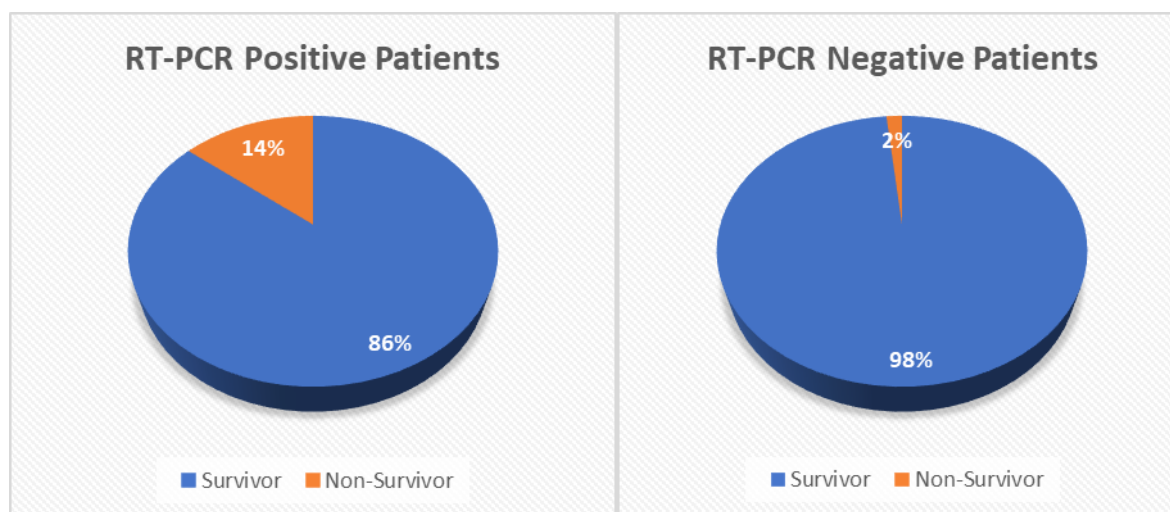
Analysis was done on 57 retrospective cases of RT-PCR positive patients and 61 RT-PCR negative patients with history of fever which met our inclusion and exclusion criteria.

**Table 1:** Comparison of baseline demographic and clinical characteristics between two groups

Parameters	Positive (n = 57)	Negative (n=61)	P-Value
Age in years (mean $\pm$ SD)	54.43 $\pm$ 13.77	52.35 $\pm$ 14.17	0.42 (Unpaired t-test)
Gender			0.71 (Fisher exact test)
Male	31	36	
Female	26	25	
Survivor Status			0.014 (Fisher exact test)
Survivor	49	60	
Non-Survivor	8	1	
BMI in kg/m <sup>2</sup> (mean $\pm$ SD)	24.81 $\pm$ 4.03	24.93 $\pm$ 3.94	0.8704 (Unpaired t-test)
SpO <sub>2</sub> in % (mean $\pm$ SD)	88.23 $\pm$ 8.81	92.26 $\pm$ 6.44	0.005 (Unpaired t-test)

SD = Standard Deviation



**Figure 1:** Comparison of two group based on survivor status**Table 2:** Comparison of haematological parameters (mean  $\pm$  SD) between two groups

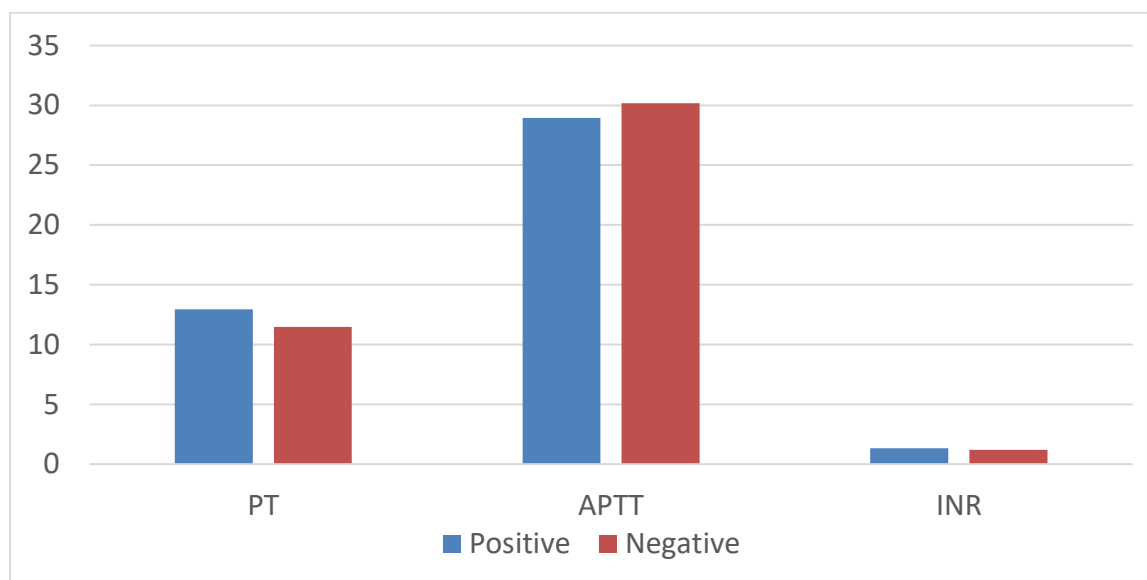
Parameters	Positive (n = 57)	Negative (n=61)	P-Value
Haemoglobin	12.95 $\pm$ 1.27	11.46 $\pm$ 2.32	<0.0001
Total Leucocyte Count/mm <sup>3</sup>	9.42 $\pm$ 4.68	12.16 $\pm$ 4.72	0.002
Absolute Neutrophil Count/mm <sup>3</sup>	5.98 $\pm$ 1.04	6.33 $\pm$ 1.16	0.09
Absolute Lymphocyte count/mm <sup>3</sup>	2.85 $\pm$ 0.98	2.37 $\pm$ 0.92	0.007
Platelet count/mm <sup>3</sup>	219.21 $\pm$ 89.49	257.63 $\pm$ 92.83	0.02
Erythrocyte Sedimentation Rate in mm/hr	21.24 $\pm$ 6.68	15.39 $\pm$ 4.75	<0.0001
NLR	3.59 $\pm$ 1.93	4.71 $\pm$ 2.26	0.005
PLR	126.75 $\pm$ 78.31	114.78 $\pm$ 54.83	0.34
SII	836.39 $\pm$ 98.65	968.51 $\pm$ 89.66	<0.0001

**Table 3:** Comparison of haematological parameters (mean  $\pm$  SD) between Survivor and Non-Survivor of RT-PCR positive patients

Parameters	Survivor (n = 49)	Non-Survivor (n=8)	P-Value
Haemoglobin	13.14 $\pm$ 1.25	11.88 $\pm$ 0.93	0.009
Total Leucocyte Count/mm <sup>3</sup>	8.73 $\pm$ 4.35	13.33 $\pm$ 2.39	0.005
Absolute Neutrophil Count/mm <sup>3</sup>	5.31 $\pm$ 1.01	8.81 $\pm$ 0.78	<0.0001
Absolute Lymphocyte count/mm <sup>3</sup>	3.03 $\pm$ 0.88	2.19 $\pm$ 0.46	0.01
Platelet count/mm <sup>3</sup>	212.27 $\pm$ 78.38	261.09 $\pm$ 68.29	0.10
Erythrocyte Sedimentation Rate in mm/hr	21.24 $\pm$ 6.68	25.37 $\pm$ 4.57	0.10
NLR	3.29 $\pm$ 1.84	6.13 $\pm$ 1.53	0.0001
PLR	118.63 $\pm$ 67.46	172.17 $\pm$ 49.73	0.04
SII	726.27 $\pm$ 85.55	1551.43 $\pm$ 67.85	<0.0001

**Table 4:** Comparison of coagulation profile (mean  $\pm$  SD) between two groups

Parameters in mean $\pm$ SD	Positive (n = 57)	Negative (n=61)	P-Value
Prothrombin Time (PT)	12.95 $\pm$ 1.27	11.46 $\pm$ 2.32	<0.0001
Activated Partial Thromboplastin Time (APTT)	28.94 $\pm$ 3.68	30.17 $\pm$ 4.29	0.10
International Normalized Ratio (INR)	1.34 $\pm$ 0.20	1.19 $\pm$ 0.27	0.0009



**Figure 2:** Comparison of coagulation profile between two groups

**Table 5:** Comparison of coagulation profile (mean  $\pm$  SD) between Survivor and Non-Survivor of RT-PCR positive patients

Parameters in mean $\pm$ SD	Survivor (n = 49)	Non-Survivor (n=8)	P-Value
Prothrombin Time (PT)	12.13 $\pm$ 1.18	17.63 $\pm$ 0.97	<0.0001
Activated Partial Thromboplastin Time (APTT)	27.87 $\pm$ 3.55	35.43 $\pm$ 3.29	<0.0001
International Normalized Ratio (INR)	1.29 $\pm$ 0.17	1.53 $\pm$ 0.09	<0.0001

## DISCUSSION

Given that COVID 19 is highly contagious and has a high mortality rate, early diagnosis of the disease is required. A definitive diagnosis of this disease is made by the presence of virus in real-time PCR analysis. If factors such as a large number of samples, limited number of staff trained to perform the above tests, or inadequate laboratory capacity is there then it can extend the time to receive results. Therefore, this study demonstrates the potential for early diagnosis of COVID-19 through simple, inexpensive, and accessible tests such as a CBC.

In our study, COVID-19 positive patients showed leukopenia, neutropenia, thrombocytopenia, and lymphocytosis. SII and NLR decreased and PLR increased. PT and APTT were generally within normal limits in most of the patients. There was significant difference between two groups with respect to lymphocyte counts and PLR.

Although there are clear relationships between bacterial infections and neutrophilia, and between viral infections and lymphocytosis, they have not been definitively established. Therefore, peripheral blood NLR has been used to distinguish between these types of infections. In some studies, NLR is higher in patients with fever due to bacterial infection than in those with fever due to viral aetiology, but in our study, NLR was decreased in COVID-19-positive cases.<sup>4</sup> SII has been proposed as a prognostic indicator in the follow-up of patients with sepsis.<sup>9</sup> In this study, SII was found to be significantly lower in COVID-19 positive patients.

Inflammatory cytokines can significantly affect the actions of hematopoietic cells, primarily neutrophils, lymphocytes and monocytes. In the present study, similar survival status as in previous studies, the differences in WBC and absolute neutrophil counts between the two groups were statistically significant.<sup>2,10-13</sup> Superimposed bacterial pneumonia observed by Li et al. in some non-survivor patient of COVID-19 could be one of the reasons.<sup>14</sup> Lippi et al. and Liu et al. reported that thrombocytopenia was associated with the likelihood of severe COVID-19 illness and death.<sup>15,16</sup>

Derived ratios such as NLR, PLR and MLR are relatively stable and thus better reflect the inflammatory process compared to the absolute cell counts documented by several authors.<sup>10, 13, 17-20</sup> Wang et al. looked at various combined parameters and concluded that NLR and RDW-SD were the best haematological indices to help predict the severity of COVID-19 patients, followed by NLR and RDW-CV.<sup>10</sup> NLR and RDW-CV were the combined parameters that emerged as the most diagnostically efficient markers in predicting severe disease in studies on COVID-19.<sup>21</sup>

Microorganisms and their components trigger the expression of tissue factor, stimulating the immune system to release pro-inflammatory cytokines that activate the coagulation cascade, leading to disseminated intravascular coagulation (DIC).<sup>22</sup> Among 184 COVID-19 patients, Klok et al. observed thrombosis incidence to be 31%.<sup>23</sup>

Fibrinolysis results in the release of D-dimers and other fibrin degradation products (FDPs) into the circulation,



levels of which are diagnostic of thrombosis.<sup>24</sup> A number of authors have documented the role of elevated D-dimer and FDP levels in COVID-19 on disease severity and survival status.<sup>7,25,26</sup> Zhang et al. and Zhou et al. showed that admission D-dimer levels  $>2.0 \mu\text{g/mL}$  and  $>1 \mu\text{g/mL}$  were associated with mortality in COVID-19 patients.<sup>7,25</sup>

Our study had certain limitation as analysis on D-Dimer and fibrinogen level was not done in our study. In an index study, ROC analysis showed that D-dimer with a cut-off value of 890 ng/ml was able to predict severe disease with high sensitivity and specificity. Therefore, D-dimer may serve as an early indicator of severity for improved management of COVID-19 patients.

Fibrinogen is a serum glycoprotein produced by the liver. Upon activation of the coagulation system in tissue and vascular injury, thrombin triggers the conversion of fibrinogen to fibrin, resulting in thrombus formation. Tang et al. found that elevated PT and D-dimer and decreased fibrinogen were associated with DIC in patients with severe COVID-19.<sup>27</sup> On the contrary, Thachil et al. showed a prothrombotic predisposition in critically ill patients with very high levels of fibrinogen, similar to Zou et al. study and the current study.<sup>28,29</sup> However, in advanced stages, thrombolysis reduces fibrinogen levels and increases fibrin degradation products.

Thrombin time (TT) showed an increasing trend with disease intensity and mortality which was statistically significant. Our findings are similar to Long et al., though, Hans et al. could not establish any such trend.<sup>30,31</sup>

Thrombin time (TT) showed a trend of increasing with disease intensity and mortality, which was statistically significant. Our results are similar to those of Long et al. however, in the study of Hans et al. no such trend was observed.

## CONCLUSION

In our study, low levels of leukocytes, neutrophils, platelets and high levels of haemoglobin, lymphocytes were found to be of value in terms of early diagnosis of COVID 19. In addition, low NLR and SII values and high PLR and CRP values are also indicative of COVID-19. The most standardized non-invasive and inexpensive tests such as CBC, coagulation and biochemical tests are available to assess disease severity for wise allocation of medical resources in developing countries such as India where resources and care are limited. It is very important if it can serve as a guide in planning and allocating resources to huge population in the middle of such a pandemic.

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