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Correlation of Biochemical Markers with Chest CT Severity Index and Oxygen Saturation in Moderate to Severe COVID-19 Patients: A cross-sectional study

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ABSTRACT

Introduction: COVID-19, a global pandemic, has been linked to biochemical parameters such as Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Total Leucocyte Count (TLC), Neutrophil/Lymphocyte Ratio (NLR), Lactate Dehydrogenase (LDH), and liver function tests, which correlate with disease severity. Prothrombotic markers like D-Dimer and Fibrinogen levels, along with the CT Severity Index (CTSI) indicating lung involvement, are associated with clinical worsening. This study aims to observe biochemical and chest radiological profiles in moderate to severe COVID-19 patients and explore any correlations between them.

Methodology: A hospital-based cross-sectional observational study was conducted at a Medical College and Hospital in Kolkata, involving 80 symptomatic COVID-19 patients with SpO_2 ≤94%. Patients with liver, kidney, chronic inflammatory diseases, COPD, malignancy, or asthma were excluded.

Results: Out of 80 patients, 29 had moderate and 51 had severe illness. Statistically significant differences were observed in TLC, ESR, CRP, AST, ALT, A:G ratio, LDH, Fibrinogen, and D-Dimer between moderate and severe cases. The CTSI correlated significantly with TLC, NLR, CRP, AST, ALT, A:G ratio, LDH, Fibrinogen, and D-Dimer. CTSI values also differed significantly between moderate and severe COVID-19 cases.

Conclusion: Biochemical markers such as ESR, TLC, CRP, liver enzymes, LDH, D-Dimer, and Fibrinogen can help predict disease severity. These markers also correlate with radiological severity in COVID-19.

INTRODUCTION

COVID-19 is the major pandemic that the world has witnessed in the 21st century. In view of its rapid pandemic spread, it is fortunate that the disease has been asymptomatic to mild in the majority (> 80%) of the patients.[1,2,3] The clinical features varied from asymptomatic to mild symptomatic illness to life threatening pneumonia and multiorgan dysfunction. The common clinical features are fever, cough, malaise, fatigue, headache, and breathlessness. Severe disease and adverse outcome such as pneumonia, acute respiratory distress syndrome, acute kidney injury, and death are seen in elderly and individuals with comorbid conditions such as hypertension, respiratory and cardiac diseases, diabetes, cancer, etc.

Though it emerged as a systemic illness, it predominantly affected the respiratory system and shortness of

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breath remained the most common presentation of severe COVID. Many patients also suffered from hypoxia despite having no shortness of breath, famously called 'happy hypoxia'. HRCT thorax remained the mainstay of imaging modality to determine the extent of lung involvement.

COVID also grew beyond the lungs and caused Multi Organ Dysfunction Syndrome (MODS) having us to monitor various blood parameters of Complete Haemogram, Liver Function Test (LFT), Renal Function Test (RFT), Coagulation profile.

Many studies done in various countries, including China, Europe have indicated that there is correlation between various biochemical parameters from the venous blood of the patients, like Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Total Leucocyte Count (TLC), Neutrophil/Lymphocyte Ratio (NLR), Lactate Dehydrogenase (LDH), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Albumin level in blood and the clinical worsening of the patients in terms of oxygen saturation and respiratory distress.[4-8] Many studies also shown that COVID-19 is a prothrombotic state and severity is related with D-Dimer, Fibrinogen level.[9,10] Studies done in Indian context also supported this correlation.[11,12] Furthermore, the respiratory distress has also been due to involvement of lung parenchyma, which has been denoted by a relatively simplified scoring system such as CT Severity Index (CTSI). It is only rational to think that the increase in CTSI might just be the indicator of the clinically relevant respiratory worsening of the patient. This is also supported by various studies across the world.[13,14,15]

The primary objective was to document biochemical profile as well as chest radiological profile (in the form of High-Resolution Computerized Tomography of thorax) in moderate and severe COVID-19 infections. In this study, it was also intended to find out if there is any correlation between those biochemical parameters and radiological profile of these patients.

MATERIALS AND METHODS

This study is a hospital based cross-sectional observational study conducted at Covid ward, Medical College and Hospital, Kolkata, a premier COVID hospital in the city, from January 2021 to July 2022 upon clearance of the ethical committee of the institute on 27th January, 2021 (ref no- MC/KOL/IEC/NON-SPON/944/01/2021). Initially, 150 patients above the age of 18 years with COVID RT-PCR positivity were enlisted and informed consents were taken from the patient or the family member. They were classified into Mild, Moderate and Severe according to the lowest SpO_2 achieved during their hospital stay. SpO_2 of the patients were measured using pulse oximeter. Those who had SpO_2 >94% RA were classified as 'Mild', 90-94% RA were labelled 'Moderate' and those having lowest SpO_2 <90% RA were categorised as 'Severe' COVID infection.[16] Only Moderate and Severe COVID patients were included for the study. Patients with history of liver disease, kidney disease, chronic inflammatory diseases such as autoimmune diseases, Chronic Obstructive Pulmonary Disease (COPD), Asthma, chronic smoker, Lung cancer or other malignancy were also excluded. Patients younger than 18 years were also not considered. Hence, after applying exclusion criteria and also excluding mild patients, 80 patients were included for statistical analysis.

These 2 groups were studied for their blood parameters like Complete Hemogram (CBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Liver Function Test (LFT), Renal Function Test (RFT), Coagulation Profile. Biochemical parameters were done in spectrophotometric method. High Resolution Computerized Tomographic (HRCT) scan of Thorax also done in 16 Slice GE Brivo 385 CT machine to obtain their CT Severity Index (CTSI). CT Severity Index was calculated based on the percentage of involvement of each lobe of lung. Involvement of <5%=1 points, 5-25%= 2 points, 26-50%= 3 points, 51-75%= 4 points, >75%= 5 points. 5 lobes of 2 lungs are taken into consideration (3 of Right lung, 2 of left lung). Hence, the CT Severity Index can be 0-25. 0-7 is considered Mild pneumonia, 8-16 is moderate and 17-25 is severe. The data were tabulated in Microsoft excel and analyzed with SPSS V.24 software. The continuous variables were presented with mean and standard deviation. The categorical variables were presented with frequency and percentage. One way ANOVA, independent test and chi square test were used for the comparisons. The p-value ≤0.05 was considered as statistically significant.

RESULTS

Among 80 patients selected for the study, 29 patients had moderate and 51 patients had severe illness. There was strong negative correlation between the age the lowest oxygen saturation of the patients. The p-value came to be <0.001 which is statistically significant. Out of the 80 patients, males were 62.5% (50) and females were 37.5% (30). Among the 50 male patients, 36% had moderate and 64% had severe illness, while out of 30 female patients, 36.67% had moderate and 63.33% had severe illness.

There is strong negative correlation (R= -0.65) between the age of the patients and oxygen saturation (SpO_2) achieved during the hospital stay, which is statistically significant (p-value <0.01) (fig 1). Based on religion, 71.25% were Hindus, 27.5% were Muslims and 1.25% were Christians. Among the 80 samples, 63.75% were residing in urban area and 36.25% in rural area.

The table 1 compares biochemical parameters between two groups of patients, classified as moderate (N=29) and severe (N=51). Significant differences were found in several parameters. Patients in the severe group had higher erythrocyte sedimentation rate (ESR), total leuco-

cyte count (TLC), C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), fibrinogen, and D-dimer levels, all with p-values below 0.05. The albumin ratio was lower in the severe group (p=0.004). Hemoglobin, neutrophil ratio (NLR), alkaline phosphatase (ALP), urea, and creatinine levels showed no significant difference between the groups. These findings indicate worse inflammation and liver function in the severe group. They can be used to predict who can develop more severe disease.

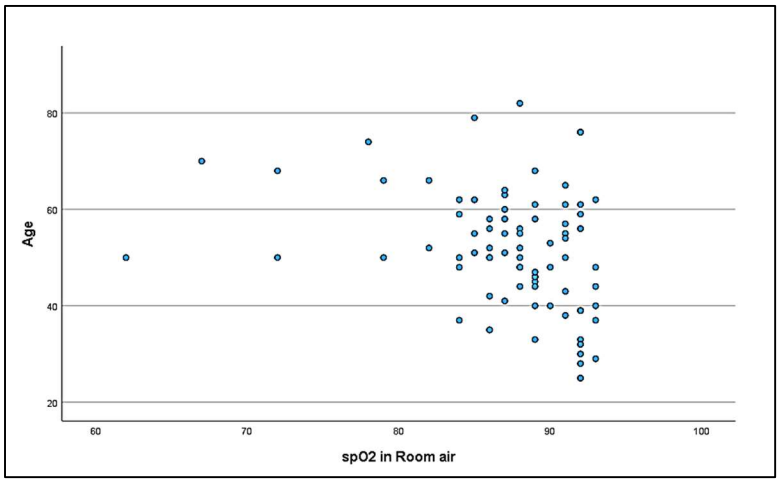

Fig 1: Scatter diagram showing correlation between age of the patients and their SpO_2

Table 1: Various biochemical parameters in Moderate and Severe COVID-19 infection

Biochemical Parameters	Moderate (N =29)	Severe (N=51)	P-Value
Erythrocyte Sedimentation Rate (mm in 1st hour) [ESR]	18 ± 9.79	39.98 ± 15.75	<0.001*
Haemoglobin (g%)	11.19 ± 1.80	11.29 ± 1.77	0.811
Total Leucocyte Count (/mm^3) [TLC]	10056.21 ± 3733.31	13312.94 ± 7404.22	0.030*
Neutrophil: Lymphocyte Ratio [NLR]	5.30 ± 3.72	13.18 ± 11.48	0.322
C-Reactive Protein (mg/L) [CRP]	20.01 ± 23.38	110.60 ± 53.19	<0.001*
Aspartate Transaminase (U/L) [AST]	53.59 ± 21.33	120.14 ± 119.50	0.004*
Alanine Transaminase (U/L) [ALT]	55.07 ± 24.28	105.71 ± 59.66	<0.001*
Alkaline Phosphatase (IU/L) [ALP]	111.79 ± 29.54	127.61 ± 61.85	0.200
Albumin: Globulin Ratio [A: G Ratio]	1.21 ± 0.41	1.02 ± 0.14	0.004*
Lactate Dehydrogenase (IU/L) [LDH]	562.28 ± 470.54	936.55 ± 515.06	0.002*
Urea (mg%)	41.34 ± 28.20	46.43 ± 22.97	0.165
Creatinine (mg%)	1.031 ± 0.39	1.220 ± 0.68	0.220
Fibrinogen (microgram/ml)	406.24 ± 161.58	576.31 ± 118.68	<0.001*
D-Dimer (microgram/ml)	1.03 ± 0.78	3.08 ± 3.01	0.001*

(*Values are statistically significant)

Table 2: Correlation of CT Severity Index with various Biochemical Parameters

Correlation of CTSI with	Pearson Correlation coefficient (r)	P value	Interpretation
Erythrocyte Sedimentation Rate (mm in 1st hour) [ESR]	0.534	<0.001*	Positive correlation
Haemoglobin (g%)	-0.008	0.942	Negative correlation
Total Leucocyte Count (/mm^3) [TLC]	0.253	0.023*	Positive correlation
Neutrophil: Lymphocyte Ratio [NLR]	0.415	<0.001*	Positive correlation
C-Reactive Protein (mg/L) [CRP]	0.852	<0.001*	Positive correlation
Aspartate Transaminase (U/L) [AST]	0.273	0.014*	Positive correlation
Alanine Transaminase (U/L) [ALT]	0.461	<0.001*	Positive correlation
Alkaline Phosphatase (IU/L) [ALP]	0.182	0.106	Positive correlation
Albumin: Globulin Ratio [A: G Ratio]	-0.394	<0.001*	Negative correlation
Lactate Dehydrogenase (IU/L) [LDH]	0.332	0.003*	Positive correlation
Urea (mg%)	0.202	0.073	Positive correlation
Creatinine (mg%)	0.218	0.052	Positive correlation
Fibrinogen (microgram/ml)	0.525	<0.001*	Positive correlation
D-Dimer (microgram/ml)	0.372	0.001*	Positive correlation

(*Values are statistically significant)

Table 3: Correlation of various Biochemical Parameters with SpO_2

Correlation of SpO_2 with	Pearson Correlation coefficient (r)	P value	Interpretation
Erythrocyte Sedimentation Rate (mm in 1st hour) [ESR]	-0.450	<0.001*	Negative correlation
Haemoglobin (g%)	-0.011	0.924	Negative correlation
Total Leucocyte Count (/mm^3) [TLC]	0.012	0.918	Positive correlation
Neutrophil: Lymphocyte Ratio [NLR]	-0.151	0.181	Negative correlation
C-Reactive Protein (mg/L) [CRP]	-0.499	<0.001*	Negative correlation
Aspartate Transaminase (U/L) [AST]	-0.069	0.543	Negative correlation
Alanine Transaminase (U/L) [ALT]	-0.099	0.381	Negative correlation
Alkaline Phosphatase (IU/L) [ALP]	0.147	0.193	Positive correlation
Albumin: Globulin Ratio [A: G Ratio]	0.348	0.002*	Positive correlation
Lactate Dehydrogenase (IU/L) [LDH]	-0.350	0.001*	Negative correlation
Urea (mg%)	-0.060	0.596	Negative correlation
Creatinine (mg%)	-0.095	0.402	Negative correlation
Fibrinogen (microgram/ml)	-0.328	0.003*	Negative correlation
D-Dimer (microgram/ml)	-0.055	0.628	Negative correlation

(*Values are statistically significant)

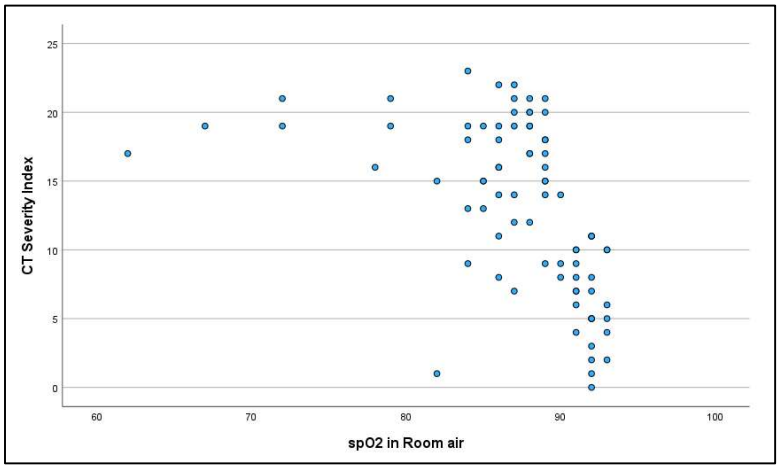

Fig 2: Scatter diagram showing correlation between CT severity index and SPO_2 of the patients

Comparison of the CT Severity Index (CTSI) between moderate (N=29) and severe (N=51) groups shows that the severe group had a significantly higher CTSI score (16.45 ± 4.38) compared to the moderate group (6.83 ± 3.43), with a p-value of <0.001, indicating a substantial difference in radiological severity.

The table 2 shows the correlation of the CT Severity Index (CTSI) with various biochemical parameters. A strong positive correlation is observed with C-reactive protein (CRP, r=0.852, p<0.001), indicating that higher inflammation levels correspond to increased CTSI scores. Erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), fibrinogen, and liver enzymes (AST, ALT) also show significant positive correlations with CTSI, suggesting these factors contribute to disease severity. In contrast, the Albumin: Globulin Ratio [A: G Ratio] shows a significant negative correlation (r=-0.394, p<0.001), indicating lower A:G ratios in more severe cases. Parameters like hemoglobin and alkaline phosphatase show weak or non-significant correlations. CTSI has significant correlation with TLC, NLR, CRP, AST, ALT, A: G Ratio, LDH, Fibrinogen, D-Dimer. (Table 3) They can be used to as parameters to predict who can develop more severe pneumonia.

The table 3 explores correlations between SpO2 levels and various biochemical parameters. A significant negative correlation is observed with C-reactive protein (CRP, r=-0.499, p<0.001) and erythrocyte sedimentation rate (ESR, r=-0.450, p<0.001), indicating that higher inflammation is associated with lower SpO2 levels. Lactate dehydrogenase (LDH) and fibrinogen also show significant negative correlations with SpO2, suggesting greater tissue damage and coagulation issues are linked to reduced oxygen saturation. In contrast, the albumin (A:G) ratio shows a positive correlation (r=0.348, p=0.002), indicating that better nutritional status may be associated with higher SpO2. Other parameters showed weak or non-significant correlations. They can be used to predict which patients are more prone to develop severe hypoxic condition.

There is moderate negative correlation between the CT severity index and lowest SpO_2 of the patient in hospital. (r= -0.502) which is statistically significant. (p-value=

<0.001). Obviously, as the degree of pneumonia increases, the desaturation also increases (fig 2).

DISCUSSION

COVID emerged as major health concern in many countries as well as in India as well. One of the metros Kolkata was no exception as well. Being a premier government hospital and COVID-hospital, Medical College and Hospital received a huge number of paient inflow suffering from spectrum of COVID disease. We studied in detail about their various blood parameters for biochemical profiling and also their HRCT thorax for assesing the severity of pneumonia and found many interesting facts.

As expected, the elder people are found to have more severe illness because of their reduced immunity power. This was also found in study done earlier in this instituition as well.[17] As this is a metro city, most the patients were of urban area.

The statistically significant difference in ESR values between Moderate and Severe COVID-19 infection (p-value <0.001) is probably because ESR is an inflammatory marker in the body. Statistically significant (p-value=<0.001) moderate positive correlation (r=0.534) between ESR values and CT Severity Index (CTSI) seconds the study done by Tezcan Kaya et al and also Rami M. Elshazli et al where they have taken ESR as a marker of predicting COVID severity.[5]

Statistically significant (p-value= <0.001) moderate positive correlation(r=0.415) between NLR values and CT Severity Index (CTSI) of the patient comes in line with study done by Rami M. Elshazli et al, AP Yang et al [5,18]. NLR encompasses two types of leukocyte subtypes, reflecting the balance of the body's neutrophil and lymphocyte count levels and the degree of systemic inflammation. More accurately, it reflects the balance between the severity of the inflammation and the body's immunity status,[19] and is thus considered an important marker of systemic inflammatory response.

Statistically significant (p-value= <0.001) difference in CRP values between Moderate and Severe COVID-19 infection is probably because CRP has been an important marker of inflammation and COVID-19 is not only a respiratory disease, but a systemic inflammatory condition. Statistically significant (p-value= <0.001) very strong positive correlation (r=0.852) between CRP values and CT Severity Index (CTSI) of the patient correlates with various studies done previously like those by Stringer D et al [6] Tian W et al [7]. Wenjie Tian et al showed in a meta-analysis done among 14 studies documenting the outcome of 4659 patients that there is increased levels of CRP, ALT, Creatinine and decreased level of Albumin in patients who have succumbed to the disease compared to those who have survived.

Statistically significant difference of AST and ALT between 2 groups and their positive correlation with CTSI has few possible explation. It has been suggested that elevated aminotransferases in COVID-19 could also originate from myositis rather than liver injury.[20] Another theory is that there is direct virus-induced cytopathic effects could play a role in LFT abnormalities in COVID-19.[21]

Statistically significant (p-value= 0.004) difference in A:G values between Moderate and Severe COVID-19 infection and statistically significant (p-value= <0.001) weak negative correlation (r= -0.394) between A: G values and CT Severity Index (CTSI) of the patient shows severity and mortality in patients with COVID-19 may be related to the properties of these proteins. A meta-analysis of 67 studies had found that low albumin levels were associated with severity and worse prognosis in patients with COVID-19.[22] Although the reasons for this association are not clear, its relationship to inflammation is believed to be one of them. A low level of albumin is related to the release of cytokines, including interleukin (IL)-6 and tumour necrosis factor (TNF)-α, and is inversely related to other markers, such as the neutrophil/lymphocyte ratio.[23] Therefore, a lower AGR value indicates more inflammation, which predicts more severity of the disease and, therefore, a greater probability of dying.

Statistically significant (p-value= 0.002) difference in LDH values between Moderate and Severe COVID-19 patients and statistically significant. (p-value= 0.003) weak positive correlation (r= 0.332) between LDH values and CT Severity Index (CTSI) of the patient is because severe infections may cause cytokine-mediated tissue damage and LDH release.[24] Since LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation, as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome, is the hallmark of the disease. A retrospective study done by Zhang Y et al in Wuhan, China found out significant increase in AST, ALT, LDH and significant decrease in Albumin level in Severe patients compared to Mild cases.[25]

The findings of this study also correlate with those findings regarding AST, ALT, LDH, A:G ratio. Fan Z et al also showed increased LFT markers to be associated with severity and increased hospital stay [26]. They also indicated raised ALP to be associated with severity with the mechanism proposed of micro steatosis. But, in our study significant correlation could not be shown between ALP and severity of the disease.

Ranucci M et al showed in a study in Italy that COVID is a procoagulant state and elevated D-Dimer and Fibrinogen is associated with increased disease severity which is also found in this study as well.[27]

This difference in CTSI values between Moderate and Severe COVID-19 infection is statistically significant (p-value= <0.001). This correlates with studies done by Yang Y et al [28], Ye Z et al [29].

LIMITATIONS

The severity of the illness was graded into moderate and severe based only upon SpO_2 and. The PaO_2/FiO_2 and PEEP could not be determined due to lack of technical support. Since it was a cross-sectional study, the cases were not followed up to assess for change in severity and alteration in biochemical markers and change in CT findings over time.

CONLCUSION

In this study we can see that the difference in mean of ESR, TLC, CRP, AST, ALT, A:G ratio, LDH, D-Dimer, Fibrinogen between the patients of moderate and severe covid infections were found to be statistically significant. Hence, they can be used to predict which patient are going to have severe COVID infection.

There is statistically significant very strong positive correlation between CRP and CT Severity Index, moderate positive correlation of ESR, NLR, ALT with CT Severity Index of the patients, weak positive correlation of TLC, AST, LDH, D-Dimer, Fibrinogen with CT Severity Index and weak negative correlation between A:G ratio and CT Severity Index of the patient was found. Therefore, these parameters can be used to predict which patients are going to develop more severe pneumonia.

There is statistically significant moderate negative correlation of ESR, CRP with SpO_2, weak negative correlation of LDH, Fibrinogen with SpO_2, weak positive correlation between A:G ratio and SpO_2 of the patients was found. Moderately negative correlation was found between SpO_2 and CT Severity Index of the patients, making them important parameters to monitor to predict about disease severity.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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