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ASSOCIATION OF LABORATORY BIOMARKERS – SERUM ALBUMIN, C-REACTIVE PROTEIN, LACTATE DEHYDROGENASE AND D-DIMER WITH SEVERITY OF COVID-19 INFECTIONS

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Abstract

To assess the association of laboratory biomarkers- serum albumin, C-reactive protein, lactate dehydrogenase and D-dimer with severity of COVID-19 infections and to know the value of individual parameters in assessing severity of COVID-19 infection

A prospective observational study was conducted on COVID-19 patients of age above 18 years, admitted to a tertiary care center in coastal part of southern India. The laboratory parameters mentioned, were estimated and compared between groups i.e. severe and non-severe COVID-19. Their cut-off values were detected using the receiver-operator curve.

Totally 577 patients with a mean age of 55±16.21 years were included. Among them, 52.3% of the patients suffered from severe COVID-19 infection and 47.6% of the cases had non-severe COVID-19 infection. The median C-reactive protein, median lactate dehydrogenase and median D-dimer levels were significantly higher in patients with severe COVID-19 compared to patients with non-severe COVID-19 (64.93 mg/dL vs. 10.23 mg/dL, (393 U/L vs 249 U/L) and (0.9 µg/mL vs 0.5 µg/mL) respectively. Univariate logistic regression analysis showed that the odd's ratio of serum albumin, C-reactive protein, lactate dehydrogenase and D-dimer were 0.486 (p≤0.001, 95% CI= 0.361-0.653), 1.005 (p≤0.001, 95% CI=1.003-1.008), 1.005 (p≤0.001, 95% CI=1.004-1.006) and 3.847 (p≤ 0.001, 95% CI=2.702- 5.476). Both C-reactive protein and lactate dehydrogenase at a cutoff value of 22.5 mg/dL (0.746AUC) and 331U/L had good sensitivity and specificity in predicting severe COVID-19 infection. Multivariate logistic regression analysis showed that C-reactive protein (OR=1.004, P≤0.001), lactate dehydrogenase (OR=1.005, p≤0.001) and D-dimer (OR=1.208, p≤0.001) were statistically significant independent predictors of severity of COVID-19.

The laboratory biomarkers like C-reactive protein, lactate dehydrogenase and D-dimer can be used for predicting severe COVID-19 infections at admission. C-reactive protein, lactate dehydrogenase and D-dimer could be used in differentiating non-severe and severe COVID-19 infections with their cut off values being >22.54 mg/mL, >331 U/L and >0.5 µg/mL respectively

Keywords: *droplet spread, SARS-CoV-2, COVID-19, Inflammation, biomarkers, pandemic.*

Introduction

In December 2019, Wuhan City in China, became the epicenter of series of cases of pneumonia which was linked to the wholesale seafood market of the city [*Gorbalenya A et al., 2020*]. 2019-nCoV was the newly identified human coronavirus which was given a new name as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. What started as a cluster of pneumonia turned into a major epidemic which has been the third documented spillover of animal coronavirus to humans in a span of just two decades [*Chan J et al., 2003*]. COVID-19 uses similar mechanism as the SARS virus in entering host cells but at a slower rate and with higher accumulation concentrations within the system. This results in longer incubation periods, more shedding of the COVID-19 virus while SARS virus causes more severe disease with more symptoms. Transmission is mostly from close contact and through droplet spread.

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However, minimal viral RNA has been found on fomites including plastic and also in airborne samples [*Booth T et al., 2005*]. Infected patients may present with varied symptoms like fever, cough, fatigue, hemoptysis, diarrhea, and dyspnea and in some cases, acute respiratory distress syndrome, myocarditis and occasionally, superadded infections [*Huang C et al., 2020*]. Biomarkers measured at that time might reflect the findings of clinical examination and help in the interpretation of the disease severity and pathological development [*Pierce J et al., 2012; Kermali M et al., 2020*]. These provide objective values during the disease progression [*Gong J et al., 2020*].

Albumin is a major serum protein produced by the liver. Albumin synthesis in the liver cells is down regulated by the direct interaction of few major acute-phase cytokines in the circulation during the cytokine storm [*Ramadori G, 2020*]. In cytokine storms syndromes hypoalbuminemia is usually seen and may reflect the systemic capillary leak [*Canna S, Behrens E, 2012*]. Hypoalbuminemia is an important clinical sign. Several studies have shown that hypoalbuminemia is commonly seen in severe COVID-19 [*Zhang Y et al., 2020; Zhou F et al., 2020*]. Apart from hepatocellular injury, there may be other causes for low albumin levels such as the systemic inflammation associated with severe COVID-19 [*Qin C et al., 2020*]. As already noted, COVID-19 is a cytokine storm syndrome and systemic capillary leak shifts the albumin into the interstitial space [*Soeters P, 2019*].

C-reactive protein is a plasma protein produced by the liver. It is inducible by various inflammatory mediators like IL-6. Though it is not specific to any particular disease, it is often used as a marker for many inflammatory conditions. A rise in its level indicates worsening of the disease [*Kermali M et al., 2020*]. This concept has also been applied in prediction of COVID-19 severity; wherein increased CRP has shown to indicate increase in disease severity [*Luo X et al., 2020; Qin C et al., 2020; Zhang J et al., 2020*]. C-reactive protein and serum amyloid A (SAA) are commonly used together to monitor inflammatory diseases. However, SAA which is another acute phase reactant, is increased in both bacterial and viral infections compared to CRP. However, the use of SAA in predicting severity of COVID is yet to be validated [*Yip T et al., 2005*]. A Chinese study noted that CRP could be of great value in differentiating the mild and severe groups of COVID-19 patients even at the stage when no significant difference was found in CT scores [*Tan C et al., 2020*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Lactate dehydrogenase (LDH), an enzyme in glucose metabolism, is secreted when there is an infection or lung damage which triggers the necrosis of the cell membrane. This may also be seen in the pneumonia induced by SARS-CoV-2 [*Han Y et al., 2020*]. An Italian study gives convincing evidence in linking LDH levels to the development of COVID-19 disease [*Ferrari D et al., 2020*]. Furthermore, when LDH levels were correlated with CT scans, significantly higher levels of LDH were reflected in higher CT scores [*Xiong Y, 2020*].

D-dimer, the smallest fibrinolysis degradation product, originates from the breakdown of cross-linked fibrin. Its increasing levels indicates the activation of coagulation system and fibrinolysis [*Zhang L et al., 2018*]. Studies have shown that increased D-dimer levels were associated with increased mortality among COVID-19 patients [*Guan W et al., 2020; Zhang L et al., 2020*]. Increase in D-dimer levels in COVID-19 indicates that it is a hypercoagulable state which may be due to any one or all reasons which is cited here. Similar to many other viral infections like the Spanish flu, avian H5N1 Influenza A, COVID-19 also produces hypercytokinemia or "cytokine storm" which is a phase of aggravated pro-inflammatory response while lacking control over the anti-inflammatory response in patients [*Wong J et al., 2017*]. This might induce endothelial dysfunction, resulting in production of excess of thrombin [*Levi M, van der Poll T, 2017*]. Also, in severe Covid-19, thrombosis can be stimulated directly by hypoxia which increases blood viscosity and also by a hypoxia-inducible transcription factor-dependent signaling pathway [*Gupta N et al., 2019; Tang N et al., 2020*].

Finally, other factors of hospitalized patients come into the picture, especially of patients with severe Covid-19 disease. These patients are more

likely to be of older age groups, with underlying co morbidities, being in bed rest for a long time etc. which are all, again risk factors for thrombosis [*Harper P et al., 2007; Barbar S et al., 2010; Hess K, Grant P, 2011*].

Materials and methods

Study design: A prospective observational study which was conducted in the Department of Internal Medicine, at a tertiary care hospital, in Karnataka, India for a period of three months from 06/10/2020 to 31/01/2021.

Ethics statement and informed consent: The study was approved by the Institutional Ethics Committee (IEC number: 493/2020) A participant information sheet containing the particulars of the study was provided to the patients and the objectives of the study were explained to them. In some cases, telephonic explanation was given and consent obtained over the phone in view of patients and the relatives being isolated or put under quarantine. Informed consent was taken from all the patients. The details of the reports were kept completely confidential.

Participants with selection criteria: All adult patients who had symptoms, were diagnosed with COVID-19 (Nasopharyngeal swab RT-PCR positive) and who were admitted in our tertiary care center, in Karnataka, India were include in this prospective study. Inclusion criterion for the study was the patients more than 18 years of age and COVID-RT PCR positive who were admitted in the hospital for treatment. Exclusion criteria for the study were patients below the age of 18 years, known cases of chronic liver disease, nephrotic syndrome, known cases of autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis, autoimmune hemolytic anemia, cases of megaloblastic anemia, cases of other associated infections/ sepsis due to any cause at the time of diagnosis of COVID 19 and patients discharged against medical advice.

Sample size: Totally 636 patients were taken into the study. But 38 patients did not meet the inclusion criteria, 9 patients refused to participate and 7 withdrew their consent during the course of their treatment in the hospital. 5 patients were discharged against medical advice. The actual sample size for this study was thus 577 as shown in figure 1.

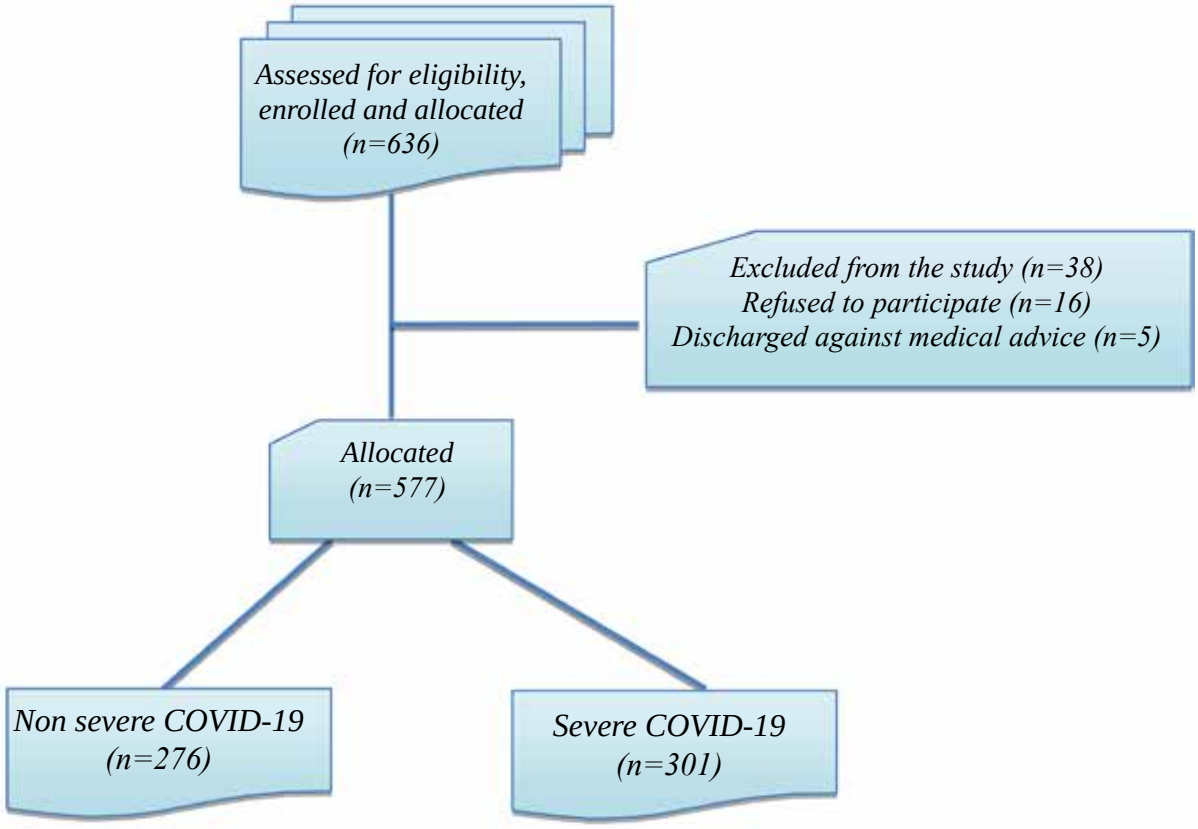

Figure 1. *Diagram of patients enrolled and participated in the study*

Data collection: Demographic details such as age and sex, clinical characteristics such as symptoms, history of comorbidities like diabetes mellitus, essential hypertension, chronic kidney disease, diagnosed malignancies and ischemic heart disease, general and systemic examination findings were taken. Laboratory investigations such as complete blood profile, arterial blood gas analysis, renal function tests, liver function tests, CRP, LDH, electrocardiogram, chest x-ray were done. Other additional investigations were done as per the admitting physician's protocol. The proforma for the study was predesigned.

Study Definitions

√ Fever was defined as an axillary temperature of 37.5°C or higher

√ Normal serum albumin levels were taken as – 3.5-5.2 *g/dL*

√ Normal serum C Reactive Protein levels were taken as those between 0-5 *mg/L*

√ Normal serum Lactate Dehydrogenase levels were taken as 125-220 *U/L*

√ Normal plasma D-dimer levels were taken as 0-0.5 *µg/mL*

COVID-19 severity: All the patients included in the study were classified according to the degree of severity of COVID-19 (severe vs. non-severe) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonias shown in table 1. However, the patient was periodically reviewed in hospital, and the highest degree of severity of the disease during the patient's course of stay in the hospital was taken into account.

Laboratory methods: Nasopharyngeal throat swab for COVID-19 RTPCR was done for all the patients enrolled in the study in the hospital Virology lab using the TRUPCR RT qPCR kit. It is a reagent system, based on real-time PCR technology, for the detection of the presence of the disease.

These RT-PCR assays performed, were in accordance with the protocol established by the Indian Council of Medical Research guidelines which was in par with the WHO guidelines.

Serum albumin was measured using bromocresol green assay, CRP and D-dimer were measured using the immunoturbidimetric assay and LDH by the lactate- pyruvate method using Roche Cobas C system.

TABLE 1.

Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia *Harper PL et al., 2007*]

Major Criteria*
1. Septic shock with need of vasopressors
2. Respiratory failure requiring Mechanical ventilation
Minor criteria*
1. Respiratory rate > 30 *breaths/min*
2. PaO2/FIO2 ratio < 250
3. Multilobar infiltrates
4. Confusion/disorientation
5. Uremia (blood urea nitrogen level > 20 *mg/dl*)
6. Leukopenia # (white blood cell count , 4,000 *cells/ml*)
7. Thrombocytopenia (platelet count , 100,000/*ml*)
8. Hypothermia (core temperature , 36.8°C)
9. Hypotension requiring aggressive fluid resuscitation

NOTES: * Validated definition includes either one major criterion or three or more minor criteria #Due to infection alone (i.e., not chemotherapy induced)

Statistical analysis

All categorical variables like gender, underlying comorbidities etc. were analyzed and reported in the form of frequency and percentages. Continuous variables with normal distribution like hemoglobin were presented as mean ± standard deviation and those with skewed distribution like albumin, CRP etc. were presented as median with interquartile distance (Q1-Q3), where required. Mann-Whitney U test was used to analyze the difference between the medians of two groups (non-severe and severe COVID-19). Chi square tests were used to correlate comorbidities of the two categories of COVID-19. These parameters were further subjected to logistic regression analysis to identify the best parameters which could be used to predict COVID-19 severity. Receiver operating characteristic curve was used to derive the cutoff value of various parameters for non-severe and severe COVID-19 group and also to know the specificity and sensitivity of the test. The p-value <0.05 was considered to be statistically significant. Data was analyzed using SPSS 23.0 (IBM SPSS statistics, USA) software.

Results

Patient demographic and baseline characteristics: Demographic and baseline characteristics patient are shown in table 2. In our study, among the 577 COVID-19 patients studied, there was a preponderance of male population. The COVID-19 patients were categorized into 2 categories as non-severe and severe category. In the severe category, about 16.5% required mechanical ventilation and 8.8% non-invasive ventilation. Others were either supplemental oxygen via venturi, non- rebreathing masks or nasal prongs. Patients presented with various comorbidities. Some patients had more than one comorbidity and this overlap could not be avoided.

Predicting factors for severity of COVID-19 disease : Median values of serum albumin, C-reactive protein, lactate dehydrogenase and D-dimer of the two categories of COVID-19 have been compared in table 3.

Further multivariate logistic regression analysis was carried out for the above-mentioned biomarkers and the comorbidities of statistical significance which is depicted in table 4. This revealed that CRP, serum LDH, D-dimer, Type 2 diabetes mellitus, essential hypertension and chronic kidney disease could be used as independent predictors for COVID-19 severity while coronary artery disease, as an independent risk factor, had borderline significance.

The laboratory biomarkers were studied with

Table 2.

Demographic and baseline characteristics of COVID-19 patients

Characteristics	Total patients (n=577)	Non severe COVID-19 (n= 276)	Severe COVID-19 (n= 301)	p value
Demographics and comorbid conditions				
Age (years) [a]	55.09±16.21	48.84 ± 16.97	60.81 ± 13.10	<0.001*
Male (n (%)] [#]	355 (61.5)	142 (51.3)	213 (70.76)	<0.001*
Female (n (%)] [#]	222 (38.5)	134 (48.7)	88 (29.23)	
Comorbidities (n (%)] [#]	366 (63.7)	127 (46.5)	239 (79.1)	<0.001*
Type 2 diabetes mellitus (n (%)] [#]	247 (42.8)	72 (26.4)	175 (57.9)	<0.001*
Essential hypertension (n (%)] [#]	226 (39.16)	77 (28.2)	149 (49.3)	<0.001*
Chronic kidney disease (n (%)] [#]	66 (1.84)	18 (6.6)	48 (15.9)	0.001*
Coronary artery disease (n (%)] [#]	118 (20.6)	40 (14.7)	78 (25.8)	0.001*
Laboratory features				
Hemoglobin (*g/dL*) [a]	12.15 ± 2.24	12.26 ± 2.17	12.08 ± 2.26	0.317
Total leucocyte counts (*cells/µL*) [b]	8000 (5700-11100)	7300 (5600-10500)	8600 (5800-12600)	0.004*
Platelet count (*cells/µL*)[b]	232000 (168000-307000)	232000 (171500-293000)	228000 (164000-313000)	0.612

Data expressed in [a] (Mean ± Standard deviation) or in [b] Median (Q1-Q3) are subjected to Mann Whitney U test. [#] Data subjected to Chi square test

Table 3

Comparison of laboratory biomarkers in non-severe and severe COVID-19

Parameters	**Non severe (*n*=276)**	**Severe (n=301)**	**p value**
Serum Albumin (*g/dL*)	4.1 (3.7-4.4)	3.8 (3.4-4.1)	<0.001*
CRP (*mg/L*)	10.23 (3.25-47.89)	64.93 (27.96 -121.86)	<0.001*
LDH (*U/L*)	249 (199-341)	393 (294.75-543.50)	<0.001*
D-dimer (µg/mL)	0.50 (0.20-1.10)	0.90 (0.40-3.02)	<0.001*

Notes: CRP- C-reactive Protein, LDH- Lactate Dehydrogenase

TABLE 4

Logistic regression analysis of parameters as risk factors for COVID-19 severity

Parameter	Univariate regression OR [95% CI (Q1-Q3)]	P value [a]	Multivariate regression OR [95% CI (Q1-Q3)]	P value [b]
Serum albumin (*g/dL*)	0.486 (0.361-0.653)	<0.001*	0.846 (0.608-1.178)	0.323
CRP (mg/L)	1.005 (1.003-1.008)	<0.001*	1.004 (1.002-1.005)	<0.001*
LDH (*U/L*)	1.005 (1.004-1.006)	<0.001*	1.005 (1.003-1.006)	<0.001*
D-dimer (µg/mL)	1.334 (1.205-1.477)	<0.001*	1.208 (1.088-1.342)	<0.001*
Type 2 diabetes mellitus	3.847 (2.702- 5.476)	<0.001*	3.123 (2.152-4.532)	<0.001*
Essential hypertension	2.479 (1.752- 3.507)	<0.001*	1.541 (1.049-2.264)	0.028*
Chronic kidney disease	2.677 (1.516- 4.729)	0.001*	1.897 (1.035-3.479)	0.038*
Coronary artery disease	2.028 (1.329- 3.096)	0.001*	1.533 (0.974-2.413)	0.065

Notes: Data expressed in a (Mean ± Standard deviation) or in b Median (Q1-Q3) are subjected to Mann Whitney U tes OR- Odd's Ratio, C.I- Confidence Interval, CRP- C Reactive Protein, LDH- Lactate Dehydrogenase *Statistically significant values
#Parameters taken for multivariate logistic regression analysis

RO[illegible] by in table 5 and figures 2 A, B, C and D.

DISCUSSION

COVID-19 disease which has evolved as an epidemic has varied presentations. In our study, we found that majority of the patients were males and also males predominated the severe COVID-19 category. The mean age of the patients was 55.09±16.21. However, the age of the patients in the severe COVID-19 category was higher than the study done by Singh AK and colleagues in India on a patient population of 242 [*Singh A et al., 2020*]. However, the mean age of the patients in their study was slightly lower than that of ours. Guan W and colleagues in China conducted a study which showed similar results except that the mean age of the population in their study was slightly lesser than ours [*Guan W et al., 2020*]. However, the meta analysis done by Zheng Z. and colleagues, in China was in par with our study as it showed severe COVID illness was seen in male patients of over 65 years of age [*Zheng Z et al., 2020*].

TABLE 5

Recommended cut-off values for laboratory biomarkers in the prediction of COVID-19 severity

Biomarker	AUC	Cut off	Sensitivity (%)	Specificity (%)
Serum albumin (*g/dL*)	0.639	<4	71.9	51.5
CRP (*mg/L*)	0.746	>22.54	80.8	62.9
LDH (*U/L*)	0.758	>331	69.5	74.2
D-dimer (*µg/mL*)	0.665	>0.5	73.5	49.5

NOTES: *Indicates statistically significant values, AUC- Area Under the Curve

Our study showed that type 2 diabetes mellitus, essential hypertension and chronic kidney disease were independent risk factors for COVID 19 severity. Singh AK showed that their patients had co-morbidities among which type 2 diabetes and essential hypertension were most common. The two Chinese meta-analysis also showed that presence of comorbidities such as type 2 diabetes, essential hypertension, cardiovascular diseases played a major role in progression of patient to severe disease [*Zheng Z et al., 2020; Zhou Y et al., 2020*]. The probable explanation could be the prolonged

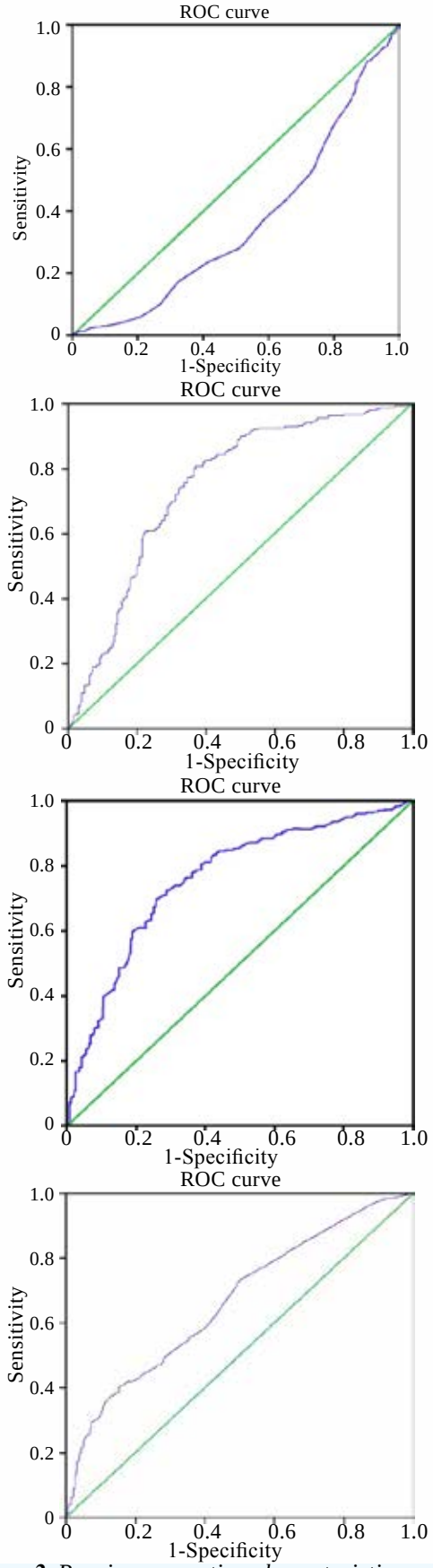

Figure 2. *Receiver operating characteristic curve analisys for Covid-19 vs (A) Serum albumin, (B) – CPR, (C) LHD and (D) – D-dimer*

states of stress leading to reduced immunity and also microvascular damage caused by type 2 diabetes, essential hypertension. The presence of chronic heart disease makes the already weakened cardiovascular musculature more vulnerable to COVID-19 [*Zheng Z et al., 2020*].

In our study, though hypoalbuminemia was seen in a large number of severe COVID patients, on logistic regression analysis, it did not prove to be an independent risk factor for severity of COVID. Zhang Y and colleagues in their study on 115 patients in China, showed that neither liver function impairment is a prominent feature of COVID nor it is associated with serious consequences [*Zhang Y et al., 2020*]. However, the Chinese study by Huang J and colleagues concluded that hypoalbuminemia was strongly associated with severity and mortality in COVID-19 patients. They also put forth the idea of the possible use of intravenous albumin in COVID-19 patients; a grey area which is yet to be explored [*Huang J et al., 2020*].

This study of ours showed that CRP was independent risk factor for COVID-19. The median values of CRP in severe cases was around six fold more than those in non-severe cases. Singh AK in India found similar results when they compared critically ill patients with non-critical patients. Qin C and colleagues in their retrospective single-centred study showed higher CRP levels in severe COVID-19 patients vs non severe patients (57.9 *mg/L* vs 33.2 *mg/L*, p <0.001) [*Qin C et al., 2020*]. The Indian study by Singh AK showed that critically ill patients of COVID-19 had a median CRP of 44.7±35.4 *mg/L* vs 30.7±25.9 *mg/L* of the non-critically ill patients [*Singh A et al., 2020*]. While our study showed a cut off of CRP of 22.54 *mg/L* between non severe and severe COVID cases, study done by Liu F and colleagues showed a cut off of 41.8mg/L between the two groups [*Liu F et al., 2020*]. The meta-analysis by Kermali M and colleagues showed a strong association of CRP with COVID severity [*Kermali M et al., 2020*].

This paper shows a good association of LDH with COVID-19 severity with a cut off of 331 U/L between non severe and severe COVID with good sensitivity and specificity. Similarly, the Chinese study by Han Y and colleagues shows a cut off of 344.5 with 96.9% specificity [*Han Y et al., 2020*]. Similarly, Ferrari D. and colleagues in Italy showed

that LDH was a potential tool in identifying false positive/ negative rRT-PCR tests in COVID. Singh A.K. and his colleagues opined that LDH could be helpful to monitor the severity of the disease and start symptomatic treatment, while the RT-PCR reports are still awaited in strong COVID suspects [*Singh A et al., 2020*].

D-dimer, according to our study, is an important tool in determining the severity of COVID. While the work done by Singh AK and colleagues in India shows a significant association with COVID-19 severity, the Chinese study by Huang et al. found that levels of D-dimer on admission could help us in determining the need of critical care in patients [*Huang C et al., 2020; Singh A et al., 2020*]. Furthermore, Zhang L and colleagues showed that D-dimer levels above >2 *μg/ mL* on admission was the optimum cut off value to predict the chances of mortality in COVID patients [*Zhang L et al., 2020*].

CONCLUSION

Many parameters have been studied extensively for prognostication of COVID-19 severity till date. Our study showed significant association of serum albumin, CRP, LDH and D-dimer with COVID-19 severity. Though multivariate analysis failed to demonstrate serum albumin as an independent predictor for severity of COVID-19, it can still be used, along with strong predictors like CRP, LDH and D-dimer, in rural hospitals of our country to efficiently triage and manage patients at the time of presentation to the health care center.

Not many studies have been done to correlate serum albumin with COVID-19 severity. Though there have been studies on association of various biomarkers with COVID-19 severity, many of them on smaller cohorts. Our study, however had larger cohorts. This is the strength of our study.

Our study however, had some limitations. Mainly, this was a single-center study with no external validation cohort. The biomarkers studied, were taken at the time of admission. We do not know if there is a change in their value as the disease progresses. Several markers like hematological parameters have not been added in this study which might have given us a better picture of underlying mechanisms. A larger study with patients from even the pediatric age group might give us better results.

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