Original Article

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Biochemistry Section

Early Predictors of Severity in Newly Diagnosed COVID-19 Patients: A Cross-sectional study

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ABSTRACT

Introduction: Corona virus disease 2019 (COVID-19) is a pandemic that has claimed many lives and consumed financial resources globally in the recent past. In this context, it is necessary to evaluate the role of different 'low-cost' and routine serum biochemistry markers in predicting the severity of illness in patients with COVID-19. There are many studies are available in this regard to assist clinicians to predict the severity of COVID-19, but were from high end laboratories which include costlier markers.

Aim: To study the routinely done serum biochemistry markers which are of lower cost to determine their role individually and in combination in the early prediction of on-going severity of diagnosed COVID-19 patients.

Materials and Methods: This was a descriptive and cross-sectional study,conducted in Department of Biochemistry and Microbiology at Mehdi Nawaz Jung Institute of Oncology and Regional Cancer Center (MNJIO & RCC), a tertiary cancer care institute at Hyderabad, India for a period of three months during the pandemic second wave, from August to October 2021. A total of 100 subjects of 35 to 75 age group who were Reverse-Transcriptase-Polymerase Chain Reaction (RT-PCR) positive for SARS-COV2 were included in this study. At the same time of swab, venous blood collected for Lactate Dehydrogenase (LDH), Alanine Aminotransferase (ALT), Albumin, C-Reactive Protein (CRP) and Ferritin and electrolytes sodium, potassium were estimated. These subjects were followed for ten days to categorise the severity, whether home quarantined or hospitalised. The numerical data was recorded as master chart in MS Excel spread sheet, and was imported to the free trial software, IBM SPSS Statistics (version 28.0) and analysed.

Results: Age and sex did not show any significance (p=0.12&0.62) but smoking, alcoholism and co-morbidities had a significant association with the level of illness (p<0.001). Serum LDH, CRP and Ferritin were qualified as significant (p<0.001) markers to predict the ongoing severity. The relationship between the LDH, Ferritin and CRP and the severity is expressed as Odds Ratios (OR) with 95% confidence intervals. The combined use as markers for these three parameters had 0.99 area under curve with a best predictive efficacy at 100% sensitivity and 80.3% specificity with positive likelihood ratio of 5.07.

Conclusion: Routine chemistry parameters are cost-effective as they are readily available, of lower cost and can be used in combination and also time saving investigations helpful in predicting the need for hospitalisation so as to assure the safety of COVID-19 patients.

Keywords: Biomarkers, Coronavirus disease 2019, C reactive protein, Ferritin, Lactate dehydrogenase

INTRODUCTION

The COVID-19 is the most concerning pandemic of the early quarter of the 21st century with higher mortality rates, which is a respiratory and systemic inflammatory syndrome [1]. There are three waves so far and fourth pandemic wave is impending with alarms from China. Inspite of the satisfactory recovery rate, the rapidity of its spread by aerosol transmission is hugely alarming to shut down the social life on a global scene throwing the tantrums in all aspects of human life. The contributory role of laboratory medicine is far beyond aetiological detection [2]. Many laboratory parameters are shown to be deranged in patients with COVID-19, and some of these may also be considered significant predictors of adverse clinical outcomes. The most frequent abnormalities were lymphopenia, increased values of CRP, LDH, Erythrocyte Sedimentation Rate (ESR) and D-dimer, as well as decreased concentrations of serum albumin and haemoglobin [3]. The methods that can be used to predict the development of severity of illness are of great value for treatment and prognosis of COVID-19 infection. The establishment of these methods depends on an understanding of the pathogenesis of the disease [4].

However, the available studies are from high end labs worldwide with inclusion of costlier parameters like Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-60), D-Dimer etc., but cheaper and routinely done parameters like LDH, ALT, Albumin, CRP and Ferritin and electrolytes individually or as a multimarker approach, for the early prediction of severity in COVID-19, are limited (data was not available during the time of this study), warranting more research [4]. This is important in India, especially at primary and secondary level healthcare set-ups.

In this present study, we aim to study the utility of some selected cost-effective parameters of routine clinical chemistry in predicting the severity in newly diagnosed COVID-19 patients.

MATERIAL AND METHODS

This was a descriptive and cross-sectional study, conducted in Department of Biochemistry and Microbiology at Mehdi Nawaz Jung Institute of Oncology and Regional Cancer Center (MNJIO & RCC), a tertiary cancer care institute at Hyderabad, India for a period of three months during the pandemic second wave, from August to October 2021. Suspected COVID-19 patients referred from Outpatient Department (OPD) were tested for RT-PCR. This study was approved by the ethical committee of MNJIO&RCC, no. 082021/2021. Written Informed consent was obtained from all patients.

Inclusion criteria: COVID-19 patients were identified based on a "positive" or "detected" RT-PCR of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) assay of a specimen obtained from a nasopharyngeal/oral swab. The patients who were referred for RT-PCR test were ruled out for cancer diagnosis from their outpatient tickets or case records, to remove cancer bias.

The subjects were of 30-75 age group of both genders; and were suffering from influenza like symptoms. These subjects were those with cured cancer and visiting for their regular follow-up. However, smoking, alcoholism and/or the common morbidities like Asthma, thyroid, diabetes and hypertensives were not excluded.

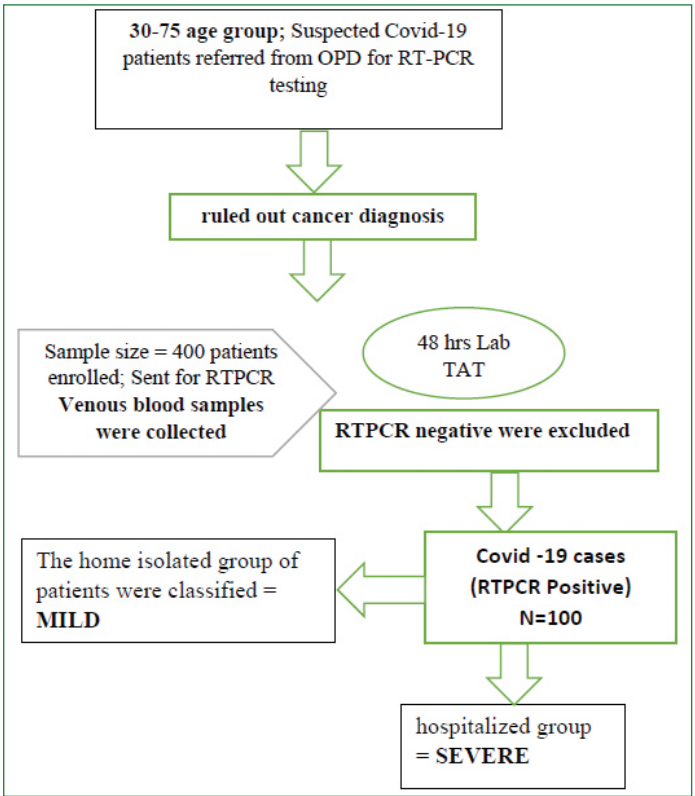
Exclusion criteria: All the cancer patients undergoing active chemo or radiotherapy and also those who already undergone any radical surgical procedures, and those who recovered from COVID-19 illness and re-visiting or for re-testing after treatment were excluded from the study to avoid confounders. The data of enrolled subjects who tested RT-PCR negative were also excluded later in the data processing.

The sample size calculation: The sample size was calculated for confidence level 95%, margin of error 5% and population proportion taken as 50% (N≥385) [5]. We have enrolled 400 subjects, but after total exclusion process, one hundred subjects (100) were qualified (positive RT-PCR) for final data processing, n=100.

Procedure

Data collection: The sample collection data entry operators have recorded the demographic profile of patients, their proximity to containment zones, visit to hotspot, direct contact history and previous travel history and occupation, influenza like clinical symptoms and presence of risk factors like diabetes and hypertension with drug history. The subjects were also healthcare workers and the attenders of patients.

2.7 Methodology: The laboratory Turnaround Time (TAT) for RT-PCR was 24-48 hours. Venous blood samples were collected immediately after swab sample done. Serum was separated from 3cc of collected blood after 30 minutes of clot formation and then centrifuging at 5000 rpm for 10-15 minutes, at room temperature and stored at-20ºC until assayed. All the seven parameters were analysed by latest methods and instrumentation, as follows: LDH, ALT, Albumin and CRP {UV kinetic, IFCC kinetic, Bromocresol Green (BCG) and latex Immunoturbidimetric methods respectively; on XL-640, Transasia} and Ferritin {Chemiluminescence (CLIA) method} and sodium, potassium (ISE method, Easylyte, Transasia) were estimated. The sample selection and processing are represented in an algorithm flow chart in [Table/Fig-1].



[Table/Fig-1]: The sample selection and processing: Flowchart.

The home isolated group and hospitalised group of patients were classified as mild and severe categories, respectively.

STATISTICAL ANALYSIS

The participants' baseline data categorical variables were reported as counts. Data was organised and the demographics, symptoms were tested for association to the severity of illness with the chi-square test. Age was represented as mean±SD, median and interquartile range. The p-value<0.05 was considered significant (two-sided and were performed at a significance level of α=0.05). The numerical data was recorded as master chart in MS Excel spread sheet, and was imported to the free trial software, IBM SPSS Statistics (version 28.0) and analysed. The Receiver Operating Characteristic curve (ROC) was plotted to further appraise the relationship of chemistry markers with status of severity and the Area Under the Curve (AUC) calculated. The cut-off values were determined as the maximum value giving the best balance between sensitivity and specificity.

RESULTS

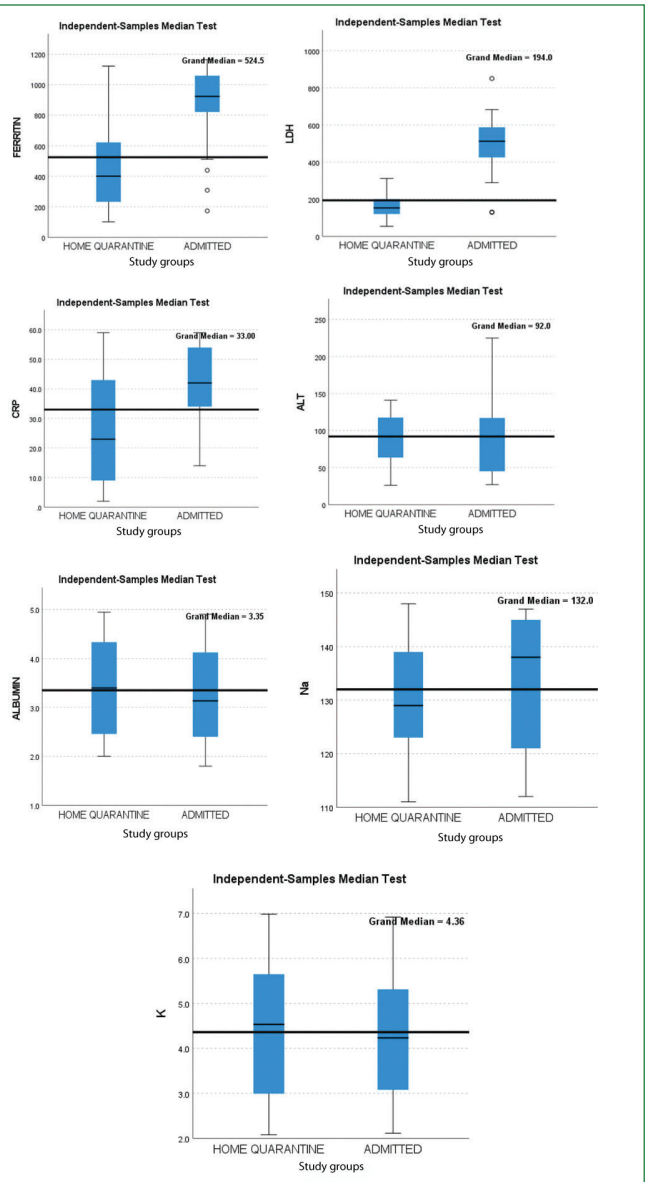
All subjects with any one or more symptoms who were tested RT-PCR positive for SARS COV-2 were analysed. Their demographic and clinical characteristic data is presented in [Table/Fig-2]. Home quarantined subjects are clinically considered as mild (n=71) and admitted subjects are "severe" (n=29) in level of COVID-19 illness. The patient's average age is 51.74 years with a Standard Deviation (SD) 11.89 ranged from 35 to 75 years and is a non Gaussian distribution with a median 52.5 years. There are in total 59 males and 41 females (N=100).

Baseline data: The subjects are classified to two age groups, 35 to 60 (n=76) and 61 to 75 (n=24). Chi-square test did not show any association between the younger and older age groups to the severity of illness (χ^2=2.461, p=0.117). The association of gender with the severity of infection is also not found (χ^2=0.247, p=0.619). Risk factors namely smoking and alcoholism are significantly associated (p=0.017&0.001, respectively) with the severity of COVID-19. The comorbidity factors like asthma, diabetes and cardiovascular problems like hypertension are also found to be significantly associated with the status of illness (p=0.004*, <0.001 and <0.001 respectively), whereas suspected or previous cancer history is not (p=0.203). There are three other categories found in significance are occupational, i.e., healthcare workers (p=.005); and close contacts of COVID-19 (p=0.006) patients and also residents of red containment zones (p=0.009). In the clinical symptoms, both dyspnea and fever are significantly associated with the severity of COVID-19 infection (<0.001). Sore throat is the least complained (40%) and fever (65%) is most prominent among admitted (12% & 27%) as well as in total subjects [Table/Fig-2].

S. no	Variables	Home quarantined	Hospitalised	Total N=100	Statistical χ^2 test value	p-value
1	**Age (year)**					
	35-60	57	19	76	2.461	0.117
	61-75	14	10	24		
2	**Gender**					
	Male	43	16	59	0.247	0.619
	Female	28	13	41		
3	smoking	5	7	12	5.699	0.017*
4	Alcoholism	7	11	18	10.993	<0.001*
5	Asthma	8	11	13	8.208	0.004*
6	Previous (or) suspected Malignancy	15	3	18	1.622	0.203
7	DM	10	14	24	13.197	<0.001*
8	HTN/CABG*	13	24	37	29.978	<0.001*
9	Healthcare Worker (HCW)	24	2	22	7.747	0.005*
10	Resident of hotspot	3	6	9	6.815	0.009*

11	Contact with confirmed case	37	25	62	7.471	0.006*
12	Sore throat	28	12	40	0.032	0.857
13	Cough	34	17	51	0.949	0.330
14	cold	37	20	57	2.386	0.122
15	Dyspnea	25	21	46	15.063	<0.001*
16	Fever	38	27	65	16.772	<0.001*

[Table/Fig-2]: The demographic and clinical characteristics of patients.
*CABG: Coronary artery bypass graft



[Table/Fig-3]: The Box plots of two levels of COVID severity groups and comparing by independent sample median test with respect to each of measured routine serum markers values of FERRITIN, LDH, CRP, D) ALT, Albumin, Sodium (Na) and Potassium (K).

As the data of the serum parameters were skewed, the median and interquartile range values are computed. Kruskal Wallis and Independent Median test non parametric comparisons are done for these parameters in non severe and severe groups. The markers, Ferritin, LDH and CRP are significantly elevated (p=<0.001) in admitted (923 vs 400; 512 vs 153; 42 vs 23) in admission subjects than the subjects who were under home quarantine [Table/Fig-3,4]. The markers, ALT, Albumin and electrolytes sodium, potassium did not show any significant difference in both the groups. Hence, these four markers are removed from further analysis.

Measurement of association: In the next phase of analysis, we did *binary logistic regression*, for predictive analysis, to explain the relationship between the independent variables (the 3 markers, LDH, Ferritin and CRP) and the dependent variable, severity/admission is on the logit scale, is expressed as OR. Under the assumption of no multicollinearity among the independent variables, all the three continuous categorical variables are a model fit with p-value <0.001. As the data distribution of LDH is more skewed than CRP and Ferritin (1.248 Vs-0.035 & 0.283, respectively), we did base 2 logarithmic transformation of LDH data (skewed reduced to 0.351 from 1.248) for a more Normality approximation to the other two variables. This predicts the probability of developing severe COVID illness (admission) occurring based on a one-unit change in an independent variable when all other independent variables are kept constant. The LDH and Ferritin has shown having significant odds (83.83 and 9.8, respectively).

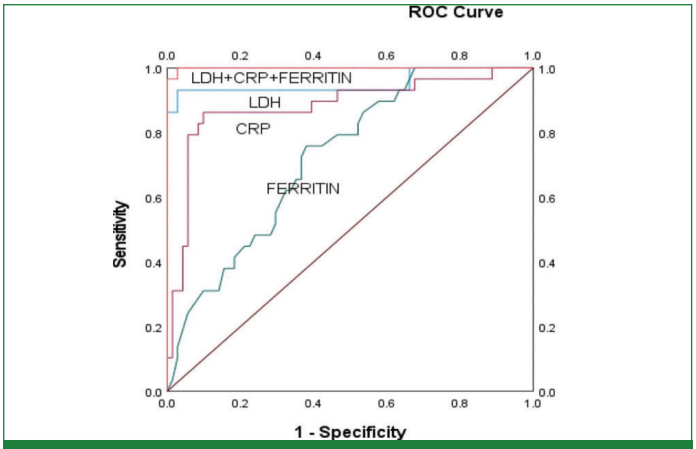
Measurement of discrimination: ROC curve analysis was done to compare the performances of LDH, ferritin and CRP as the predictor of severity of COVID-19 illness as illustrated in [Table/Fig-5,6]. LDH has a slightly better predictor of severity, with an AUC of 0.952 and at the best cut-off value chosen, 505 U/L, it has 100% sensitivity and 90% specificity. The biomarker Ferritin had AUC of 0.882 with the cut-off value 405 ng/mL, showed 96.6% sensitivity, 67.6% specificity. The CRP showed an AUC of 0.727 and at a cut-off of 89 mg/L, it has 95.8% and 23.8% sensitivity, specificity, respectively. The combination of all three markers has high AUC, 0.999 with 100% sensitivity and 80.3% specificity. The positive and negative likelihood ratios are shown along with each individual parameter [Table/Fig-5-6].

DISCUSSION

The inflammation process in the lung is, variably progressive and is highly unpredictable in SARS-COV-2 infection, hence, early biomarkers are in COVID-19 are of high clinical value to guide the management. This study showed that biological factors like age or sex have no impact on the severity of COVID-19 illness (p=0.117 and 0.619). The risk factors like smoking and alcoholism showed a significant (p<0.05) association and comorbidities like hypertension, asthma and hyperglycaemia significantly influenced the hospitalisation with rapid progress of COVID-19 illness. The past or postmalignancy status did not affect but their close contact exposure had a strong prelidiction to the progression of the disease.

Parameter (normal range)	Grand Median (IQR)	Median (IQR)*		Kruskal-Wallis Test p-value	Independent Median test p-value
		Home Quarantined (Non Severe)	Admitted (Severe		
Ferritin (13-150 ng/mL)	524.50 (311-847)	400 (231-631)	923 (816.5-1074.5)	<0.001	<0.001
LDH (135-214 U/L)	194.00 (129-351.75)	153 (120-200)	512 (405-595.50)	<0.001	<0.001
CRP (<5.0 mg/L)	33.000 (14-49.75)	23 (9-43)	42 30.5-54.5)	<0.001	<0.001
Albumin (3.5-5.2 g/dL)	3.351 (2.40-4.33)	3.4 (2.4-4.3)	3.1 (2.3-4.2)	0.526	0.826
ALT (<45 IU/L)	92 (55-117.75)	92 (63-118)	92 (44.5-118.5)	0.536	0.880
Na (136-145 mmol/L)	132.00 (122-140.75)	129 (123-139)	138 (120-145)	0.294	0.430
K (3.5-5.1 mmol/L)	4.362 (2.99-5.65)	4.5 (2.9-5.6)	4.2 (3-5.5)	0.846	0.509

[Table/Fig-4]: Routine serum Biochemistry parameters in the two levels of COVID-19 illness showing median and Interquartile range (Q1 or 25% & Q3 or 75%) with comparison by the two non parametric tests.
*IQR: Inter Quartile range



[Table/Fig-5]: ROC curves of the parameters and with combination.

Parameter	AUC	Asymptotic 95% CI*	Optimum cut-off value	Sensitivity %	Specificity %	LR+	LR-
LDH	0.952	0.891-1.000	505 U/L	100	90	10	0
Ferritin	0.882	0.797-0.967	405 ng/mL	96.6	67.6	2.98	0.05
CRP	0.727	0.626-0.828	89 mg/L	95.8	23.8	4.2	0
Combined	0.999	0.996-1.000	As above	100	80.3	5.07	0

[Table/Fig-6]: ROC analysis of proven significant routine serum parameters.
ROC: Receiver operating characteristic; AUC: Area under curve; CI: Confidence Interval; *Lower bound-upper bound; LR+=Likelihood ratio of a positive test=SN/(1-Sp); LR-=Likelihood ratio of a negative test=(1-SN)/Sp.

Healthcare workers predominantly had a mild infection (91.6%) and only two (8.3%) had to get admitted showing a significance for non severe infection. This finding can be biased, as they may have had treatment or oxygen facilities established at home. The three of the chosen parameters were highly correlating with the risk of worsening (CRP, LDH, Ferritin) of COVID-19. Among those studied, ALT, Albumin and electrolytes Sodium and Potassium were not qualified as predictors and they were not studied further to test if any combined association.

The clinician perspective is to investigate CRP in any acute conditions as it is a cheaper and popular investigation for the fevers and it rises rapidly within 6 to 8 hours and gives the highest peak in 48 hours from the disease onset [6]. CRP levels are correlated with the level of inflammation, and its concentration level is not affected by factors such as age, sex, and physical condition [7]. The CRP levels detected in severely ill patients have been higher than those of mild or moderate patients and quick recognition of potentially critical patients has an important role in the management of this disease [8,9]. The present study showed a significant raise (median 23 vs 42 mg/L, $p<0.001$) in severe illness and with a cut-off value of 89 mg/L, has 95.8% sensitivity and 23.8% specificity. But the odds ratio did not show a significant association between the unit raise and severity (1.377, 95%CI, 0.4-4.5; p=0.6). These findings are consistent with Gao Y et al., study, (18.8 vs 39.4 mg/L). Several researchers found a significant increase of CRP with levels on average 20 to 50 mg/L in patients with COVID-19 [10,11].

Increased levels of LDH, ALT, AST, and total bilirubin and decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients [12]. Knowing that the primary site of the SARS-CoV-2 attack is the lower respiratory tract together with the fact that LDH is an important marker of lung damage may explain, at least partly, why this enzyme's level is elevated in most COVID-19 patients [12-16]. Yuan J et al., suggested a direct correlation between the decline of LDH with viral mRNA elimination, suggesting that a constitutive decrease in LDH probably predicts a favorable response to the course of COVID-19 patients [17]. Pourbagheri Sigaroodi A et al., suggest 280 U/L as a cut-off level for LDH to predict poor prognosis whereas, 505 U/L was our best cut-off value [12]. The present study showed an association that is significant ($p<.001$) with OR 83.8 (95% CI, 6.4-1095). The non severe subjects were having a median value of 153 and the hospitalised subjects had 512 U/L, at the beginning of COVID-19. In a pooled analysis of nine published studies, elevated LDH levels were associated with a~6-fold increase in odds of developing severe disease in patients with COVID-19 [18]. Another twenty-eight studies reported LDH levels in severe vs. non sever groups. The level of LDH in the individual groups varied (MD=154.49; 95% CI: 121.24, 191.73; P<0.001) [19].

The cell destruction may also release ferritin, although ferritin is an acute phase reactant and it is reasonable to assume that higher serum ferritin levels in severely affected COVID-19 patients might indicate a greater extent of organ damage [12]. The IL-6 and serum ferritin levels were elevated in non survivors compared to survivors throughout the clinical course and increased with illness deterioration [20]. Gómez-Pastora J et al., and Ahmed S et al., demonstrated ferritin levels on admission around 1400 ng/mL, and 1096.4 ng/mL, respectively, to indicate a rapid progression to fatality [20,21]. Rajanna AH et al., showed ferritin levels of a cut-off value of 352 and in the survived group, 285.71±391.99 ng/mL [22]. Present study shows ferritin levels raised more than 405 ng/mL is predictive of severe or hospitalised COVID-19 illness whereas the present hospitalised group had a median value, 923 ng/mL (IQR 816.5-1074.5).

The LDH and Ferritin had significant odds in binary logistic regression analysis (83.8, 95% CI 6.4-1095, $p<0.001$; 9.8, 95% CI,1.49-64.7, $p=0.017$) than the CRP to predict the likelihoodness of developing a serious progress of COVID-19. Among these, LDH has a slightly better predictor of severity, with an AUC of 0.952 and at the best cut-off value chosen, 505 U/L, it has 100% sensitivity and 90% specificity. The combination of all three markers has high AUC, 0.999 with 100% sensitivity and 80.3% specificity. The normal reference ranges for the seven parameters of this study are shown in [Table/Fig-4], to compare with the cut-off values chosen in ROC curve analysis.

The results in one of a review, revealed that while severe COVID-19 cases displayed higher values of ALT, AST, and total bilirubin compared to non severe patients (mean differences of 7.48, 12.07, 3.07), value of albumin was significantly lower in severe cases (mean differences of-6.15); highlighting that abnormal values of liver-related examinations may contribute to reflect the progression of the disease toward an unfavorable outcome [12]. We failed to confirm that albumin along with increased LDH, ALT was significantly lower in a progression group than an improvement/stabilisation group as it was recommended by Liu and Huang et al that, albumin and ALT as appropriate biomarkers with the ability to discriminate between severe and non severe groups [14,23]. There are studies which showed there was a significant electrolyte disturbance in the severity of COVID-19 [24,25]. The present study did not show any significance with regard to either sodium or potassium levels in either of mild or severe COVID-19, at the beginning phase of illness when we collected those blood samples.

Limitation(s)

The base line values of subjects were not available to compare with any abnormalities due to COVID-19 infection. The effect of on-going malignancy and the immunocompromised status is not established on the COVID induced abnormalities in the parameters. The present study involved a small sample in a single hospital. There could be a possibility of overfitting in the analyses.

CONCLUSION(S)

Laboratory medicine can provide the essential assistance to discriminate between severe and non severe COVID-19. Present study proved that these routine biochemistry tests, namely, LDH, ferritin and CRP which are cheaper in cost profile and available

in every laboratory and can also be used in combination and are also rapid investigations, which help in predicting the need for hospitalisation so as to assure the safety of COVID-19 patients.

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