

Evaluating laboratory parameters for diagnostic accuracy in COVID-19 patients in a tertiary care Government Hospital in Greater Noida, UP, India

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Received: 11-08-2021 / Revised: 07-11-2021 / Accepted: 12-12-2021

Abstract

Introduction: The occurrence, development, mechanism of prognosis and immune status of patients with COVID-19 are still unclear. Timely identification of virus carriers is vital not only to prevent their spread but also to more efficiently control disease progression. **Objective:** In this study, we have assessed the hematological characteristics of the patients. This study aimed to evaluate the accuracy of laboratory parameters in predicting cases with positive RT-PCR for COVID-19. **Material and Methods:** This was a cross sectional study that included 32 RTPCR +ve and 64 RTPCR -ve cases over a period of 5 weeks. The blood samples were collected from symptomatic patients presented to the cough OPD of the hospital and undergoing RT-PCR testing for Covid-19 between 9am to 4 pm on consecutive working days till the sample size requirement for RT-PCR negative patients was met. On the day of swab sampling, blood sampling was done for each participant included in our study as mentioned in the sampling method above. All tests were performed in an appropriate autoanalyser after complying internal quality control. **Results:** Units The mean age of patients included in this study was 33 years. The frequency of male versus female patients included in this study was 60:40 while percentage ratio of them got infected were 28% and 21% respectively. The mean CT value of RT-PCR test was found to be 22.7, while mean PCT value was merely 0.3. The mean ferritin value came out to be 133.5 and mean D-dimer values calculated to be just 1.3. The mean LDH and CRP levels were 340.4 and 12.6 respectively. The sensitivity and specificity for procalcitonin analysis among these patients were 97% with CI (93.8-100) followed by serum ferritin with 82%, CI (70-94) and CRP levels were having just 77.3%, CI (61.2-93.4). **Conclusion:** In the current study, the AUC of procalcitonin and serum ferritin were above 0.80; thus, they are effective markers and have very good predictive value for predicting COVID-19. It seems that these blood laboratory parameters could be used in screening cases with positive RT-PCR for COVID-19. However, serum LDH, D Dimer, and vitamin D levels or liver function tests, renal function tests remain insignificantly linked with covid-19 positivity rate in this study.

Keywords: COVID-19, serum LDH, Procalcitonin, RT-PCR.

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Introduction

In the early stages of covid-19 disease, symptoms of severe acute respiratory infection occur, with some patients rapidly developing acute respiratory distress syndrome (ARDS) and other serious complications, which are eventually followed by multiple organ failure[1].

Therefore, early diagnosis and timely treatment of critical cases is very crucial. At present, the occurrence, development, mechanism of prognosis and immune status of patients with COVID-19 are still unclear. Timely identification of virus carriers is vital not only to prevent their spread but also to more efficiently control disease progression. To the best of our knowledge, while most published articles have discussed the clinical features and imaging findings of COVID-19, few studies have addressed the diagnostic and prognostic value of abnormal laboratory findings [2]. Irrespective of its inherent definition[3], the contributory role of laboratory medicine is far beyond etiological detection and it is now almost undeniable that this branch of medical science is effectively involved in epidemiologic surveillance, determination of prognosis, patient follow-up, and, last

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but not least, therapeutic monitoring of a wide range of human diseases, including COVID-19[4,5].

In this study, we have assessed the hematological characteristics of the patients. The role of clinical laboratory data in the differential diagnosis of severe forms of COVID-19 has not been definitely established. This study aimed to evaluate the accuracy of laboratory parameters in predicting cases with positive RT-PCR for COVID-19.

Material and Methods

This was a cross sectional study that included 32 RTPCR +ve and 64 RTPCR -ve cases over a period of 5 weeks. The blood samples were collected from symptomatic patients presented to the cough OPD of GIMS, Greater Noida and undergoing RT-PCR testing for Covid-19 between 9 am to 4 pm on consecutive working days till the sample size requirement for RT-PCR negative patients was met. Any positive patient was included in the RTPCR +ve group during screening. Sampling of RT-PCR positive patients was done on the day of new admissions to the isolation ward of GIMS, Greater Noida to meet the required number of RTPCR +ve patients (32 patients). On the day of swab sampling, blood sampling was done for each participant included in our study as mentioned in the sampling method above. About 2 ml of venous Blood was collected in EDTA vial for CBC estimation and 2 ml of blood was collected in citrate vial for doing D-dimer. For Biochemical analysis, 3 ml of blood was collected in plain vial. All tests were performed in an appropriate autoanalyser after complying with internal quality control. Test results were received from the lab for research purpose and all enrolled patients were provided with the reports.

The data were collected and collated in Microsoft Excel sheet. Data were presented as frequencies and percentages for qualitative and

categorical variables. Mean with standard deviation or median with interquartile range was reported for continuous variables depending upon their distribution type. Appropriate statistical tests were applied for identifying significant statistical difference in the distribution of variables included in our study. Categorical and qualitative variable were tested using chi-square or Fisher's exact test. Testing of continuous variables were carried out using independent Student t-test/ Mann-Whitney U- test or One way analysis of variance/ Kruskal-Walli's test whichever was appropriate based on the distribution of data and the number of groups comparison made.

Differences in the blood laboratory parameters levels between the RT-PCR positive and negative patients were assessed using Student's t-test. Receiver operating characteristic (ROC) curve and AUC were used to analyze the optimal cut-off for prediction of positive RT-PCR cases. In this study, AUC 0.9 to 1 is defined as excellent accuracy, 0.8 to 0.9 as very good, 0.7 to 0.8 as good, 0.6 to 0.7 as sufficient, 0.5 to 0.6 as bad, and < 0.5 as poor (useless test). All statistical analyses were carried out at 5% level of significance and p-value 0.05 was considered significant.

Results

Units

The mean age of patients included in this study was 33 years. The frequency of male versus female patient included in this study were 60:40 while percentage of male and female patients who got infected were 28% and 21% respectively. Age of patients in this study have AUC 75% with CI (65-85). However, LDH, D Dimer, and vitamin D levels or Liver function tests, Renal function tests remain insignificantly linked with covid positivity rate among this cohort. (table 1,2 and fig.1,2)

Table 1. showing area under curve of different inflammatory lab parameters.

Area Under the Curve

| Test Result Variable(s) | Area | Std. Error ^a | Asymptotic Sig. ^b | Asymptotic 95% Confidence Interval | |
|-------------------------|------|-------------------------|------------------------------|------------------------------------|-------------|
| | | | | Lower Bound | Upper Bound |
| Ferritin | .820 | .061 | .000 | .700 | .940 |
| LDH | .624 | .113 | .174 | .402 | .846 |
| PCT | .971 | .017 | .000 | .938 | 1.000 |
| CRP | .773 | .082 | .003 | .612 | .934 |
| Vit D3 | .521 | .105 | .816 | .315 | .728 |

The test result variable(s): Ferritin, LDH, PCT analysis, CRP, Vit D3 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption, b. Null hypothesis: true area = 0.5

Table 2: table showing area under curves of different liver function parameters.

Area Under the Curve

| Test Result Variable(s) | Area | Std. Error ^a | Asymptotic Sig. ^b | Asymptotic 95% Confidence Interval | |
|-------------------------|------|-------------------------|------------------------------|------------------------------------|-------------|
| | | | | Lower Bound | Upper Bound |
| TBIL | .514 | .050 | .785 | .415 | .612 |
| DBIL | .359 | .047 | .005 | .266 | .452 |
| IBil | .714 | .045 | .000 | .625 | .802 |
| ALT | .502 | .050 | .972 | .403 | .600 |
| AST | .544 | .050 | .376 | .446 | .642 |
| ALP | .505 | .051 | .925 | .404 | .605 |
| Total PROT | .265 | .043 | .000 | .180 | .350 |
| ALBUMIN | .312 | .047 | .000 | .221 | .403 |

The test result variable(s): TBIL, DBIL, IBil, ALT, AST, ALP, TPROT, ALBUMIN has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption, b. Null hypothesis: true area = 0.5

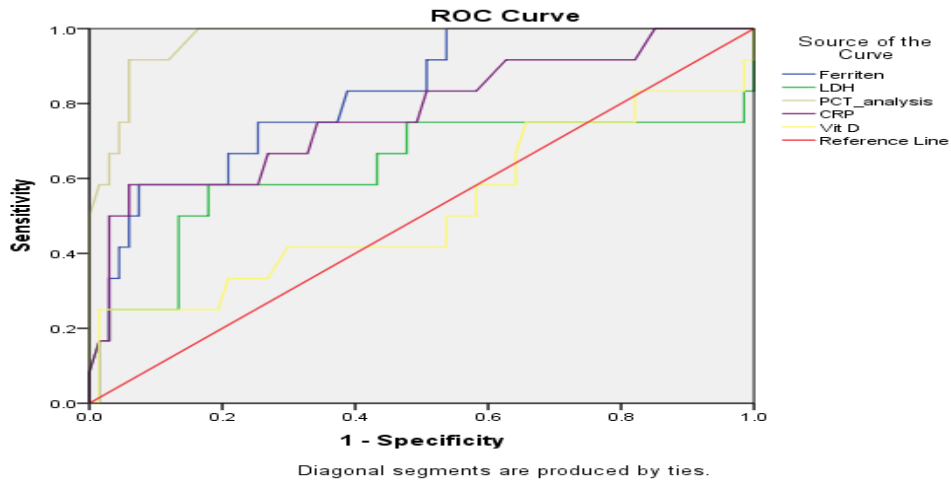


Fig 1. ROC curves showing sensitivity and specificity of different inflammatory laboratory parameters.

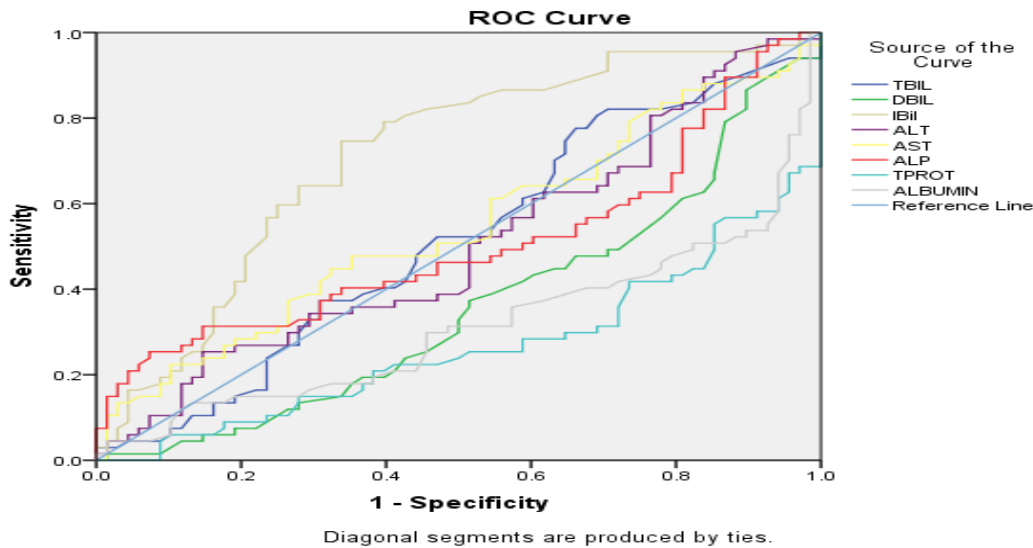


Fig.2: ROC curves showing sensitivity and specificity of liver function parameters.

The mean CT value of RT-PCR test was found to be 22.7. while mean PCT value was merely 0.3. The mean ferritin value came out to be 133.5 and mean D-dimer values calculated to be just 1.3. The mean LDH and CRP levels were 340.4 and 12.6 respectively. The sensitivity and specificity for procalcitonin analysis among these patients were 97% with CI (93.8-100) followed by serum ferritin with 82%, CI (70-94) and CRP levels were having just 77.3%, CI (61.2-93.4). (table and fig. 1) On correlation regression analysis, we observed that CT values of RT-PCR test were found to be negatively correlated with D Dimer values. PCT analysis were correlated with ferritin, CRP and LDH. Ferritin values were correlated with PCT, LDH, and CRP. D dimer were correlated only with CT values in negative manner. LDH levels were correlated with PCT, CRP and ferritin values. CRP levels were correlated with PCT, ferritin and LDH levels. Vitamin D levels were not found to be correlated with any inflammatory markers in this study. (table 3)

Table 3: correlation analysis of different inflammatory lab parameters.

Correlations analysis

| | | CT Value | PCT analysis | Ferritin | D-Dimer | LDH | CRP | Vit_D_cat3 | Vit_D_cat2 |
|----------|---------------------|---------------|--------------|--------------|---------------|---------------|---------------|------------|------------|
| CT Value | Pearson Correlation | 1 | .185 | .145 | -.439* | .108 | .179 | -.076 | -.025 |
| | Sig. (2-tailed) | | .610 | .359 | .019 | .476 | .235 | .616 | .869 |
| | N | 50 | 10 | 42 | 28 | 46 | 46 | 46 | 46 |
| PCT | Pearson Correlation | .185 | 1 | .243* | .023 | .776** | .621** | -.101 | -.107 |
| | Sig. (2-tailed) | .610 | | .031 | .853 | .000 | .000 | .363 | .335 |
| | N | 10 | 84 | 79 | 65 | 83 | 83 | 83 | 83 |
| Ferritin | Pearson Correlation | .145 | .243* | 1 | .104 | .296** | .253** | -.128 | -.144 |
| | Sig. (2-tailed) | .359 | .031 | | .317 | .001 | .005 | .159 | .115 |
| | N | 42 | 79 | 122 | 95 | 122 | 122 | 122 | 122 |
| D-Dimer | Pearson Correlation | -.439* | .023 | .104 | 1 | .156 | .118 | .028 | .027 |

| | | | | | | | | | |
|------------|---------------------|-------|---------------|---------------|------|---------------|---------------|---------------|---------------|
| | Sig. (2-tailed) | .019 | .853 | .317 | | .130 | .254 | .791 | .794 |
| | N | 28 | 65 | 95 | 95 | 95 | 95 | 95 | 95 |
| LDH | Pearson Correlation | .108 | .776** | .296** | .156 | 1 | .663** | .017 | .050 |
| | Sig. (2-tailed) | .476 | .000 | .001 | .130 | | .000 | .849 | .574 |
| | N | 46 | 83 | 122 | 95 | 131 | 130 | 130 | 130 |
| CRP | Pearson Correlation | .179 | .621** | .253** | .118 | .663** | 1 | .050 | .059 |
| | Sig. (2-tailed) | .235 | .000 | .005 | .254 | .000 | | .571 | .508 |
| | N | 46 | 83 | 122 | 95 | 130 | 130 | 129 | 129 |
| VitD3_cat3 | Pearson Correlation | -.076 | -.101 | -.128 | .028 | .017 | .050 | 1 | .915** |
| | Sig. (2-tailed) | .616 | .363 | .159 | .791 | .849 | .571 | | .000 |
| | N | 46 | 83 | 122 | 95 | 130 | 129 | 130 | 130 |
| VitD3_cat2 | Pearson Correlation | -.025 | -.107 | -.144 | .027 | .050 | .059 | .915** | 1 |
| | Sig. (2-tailed) | .869 | .335 | .115 | .794 | .574 | .508 | .000 | |
| | N | 46 | 83 | 122 | 95 | 130 | 129 | 130 | 130 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

Discussion

Fan et al.[6] analyzed the hematological indices of COVID-19 infected patients between the intensive care unit (ICU) and non-ICU patients. They showed lymphopenia and raised lactate dehydrogenase (LDH) were associated with higher rate of ICU admissions. Many patients with MERS-CoV had liver function abnormalities with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and LDH [7]. Also laboratory data on SARS have shown that most patients had elevated CRP levels, lymphopenia, leukopenia, and elevated levels of aminotransferase, LDH and creatine kinase[8]. A series of recently published articles have reported the epidemiological and clinical characteristics of patients with COVID-19 disease, but data regarding the laboratory characteristics of infected individuals are limited[9-11]. Chen et al., found that LDH had significantly increased in most patients, while albumin had decreased, but ALT and AST showed no significant changes[1]. The mentioned values were also reported for patients with MERS-CoV, where elevated ALT, AST and LDH was observed. Another study indicated that 2–11% of patients with COVID-19 had liver comorbidities and 14–53% of cases had abnormal ALT and AST levels during progression of COVID-19 disease[12]. Furthermore, Shi et al. studied patients whose COVID-19 diagnosis was confirmed by computed tomography (CT) scan while in the subclinical phase and found that incidence of AST abnormality among these patients was significantly lower than those diagnosed after the onset of symptoms[13]. Therefore, liver injury is more prevalent in severe cases compared to mild cases of COVID-19. In another report, Yang et al. found no difference in the incidence of abnormal liver function between survivors (30%) and non-survivors (28%)[9]. Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment[12]. In the present study, ROC curve was used to analyze the specificity and sensitivity of different variables in suspected COVID-19 patients. The AUC of laboratory parameters such as ALT, CRP, AST, LDH, and D dimer indicated that they could not be used to predict the presence of COVID-19 disease, while those of ferritin and procalcitonin were above the reference line of ROC curve, indicating that they were good predictors of the disease. The data in contrast with results reported by Wang et al.[14] and Gao et al. In the current study, the AUC of CRP, ALT, LDH, were below 0.80; thus, they are not effective and have poor predictive value for predicting COVID-19. It seems that, some blood laboratory parameters could be used in screening cases with positive RT-PCR for COVID-19. It has also been reported that some COVID-19 patients have increased prothrombin time (PT) together with prolonged activated partial thromboplastin time (aPTT). Adding to these abnormalities, elevated D-dimers further support the occurrence of coagulopathy which is an important indicator of disease progression. It was previously established that inflammation-related parameters are highly elevated in acute phases. COVID-19 makes no exception to this rule, whereby the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin are increased in the sera of these patients, albeit with different values. It is worth mentioning that while the diagnostic value of ferritin and

procalcitonin is superior to CRP, the latter may potentially be of greater value than the former for predicting disease progression. Li et al. detected ferritin levels above the upper limit of the reference range in 49 out of 54 (90.7%) COVID-19 patients and showed that the ferritin levels decreased as hs-CRP decreased, but they were significantly higher than the upper reference range for at least 5 days after hs-CRP returned to normal[15]. Previous studies have shown that soluble CD-163 (sCD-163), which represents the activation of macrophages, increases parallel to ferritin during the acute inflammation stage [16], suggesting that ferritin measurement may provide diagnostic value and can be used for diagnostic purposes in COVID-19[17,18]. As presented, increased levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (Bil) and decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients. Changes were not limited to the indicated parameters since elevated creatine kinase (CK) and increased creatinine (Cr) were also demonstrated in earlier studies. 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 [19] may explain, at least partly, why this enzyme's level is elevated in most COVID-19 patients[20-22]. The emergence of severe disease due to the injury of non-pulmonary organs may also instigate abnormal values of kidney- and liver-related biochemical parameters. Guan et al. reported that ALT and AST levels in COVID-19 patients were elevated in 21.3% and 22.2% of cases, respectively[23], which may mirror virus-mediated liver impairment. The results of a recent study also revealed that 2–11% of COVID-19 patients had liver comorbidities and 14–53% had abnormal levels of ALT and AST[24]. Analysis of creatinine in 149 cases demonstrated that 28.8% of COVID-19 patients had an increased levels, representing SARS-CoV-2's ability to induce kidney injury[25]. The prognostic significance of laboratory tests is not limited to the valuable data represented by simple CBC examinations, as increased PT and D-dimer values may be indicative of a worse prognosis[20]. Tang et al. reported a significant difference in the occurrence rate of coagulopathy in terms of disseminated intravascular coagulation (DIC) between COVID-19 patients who died of the disease compared to those who survived (71.4% vs 0.6%). In a study reporting the results of 13 severe of 140 COVID-19 patients, increased procalcitonin values were 25% vs 0% in ICU patients compared to non-ICU patients, respectively[20]. A study by Zhang et al. on 140 COVID-19 patients, including 58 severe cases, further supported the previous data. They reported that increased levels of D-dimer along with elevated procalcitonin and CRP levels could help clinicians effectively discriminate between severe and non-severe COVID-19 cases. Taken together, t PT and D-dimer values coupled with follow-up of altered patterns of procalcitonin and CRP levels may provide a simple and rapid method of predicting disease prognosis. Notably, it has been reported that hyperferritinemia can activate macrophages, which increases the secretion of pro-inflammatory cytokines, and the subsequent inflammation is mainly responsible for organ damage. Although ferritin is a positive acute

phase reactant and serum level of this intracellular protein increases during inflammation, dying cells may also release ferritin. Thus, it is reasonable to assume that higher serum ferritin levels in severely affected COVID-19 patients might indicate a greater extent of organ damage. Liu et al. also reported that albumin was significantly lower in a progression group than an improvement/stabilization group (36.62 vs 41.27 g/l, $P = 0.006$). In agreement, Huang et al. introduced decreased albumin along with increased LDH, ALT, and total bilirubin levels as appropriate biomarkers with the ability to discriminate between severe and non-severe groups[20]. In a large cohort of 1099 patients from 552 hospitals, Guan et al. reported a higher degree of abnormal liver aminotransferase levels in patients with severe disease than non-severe subjects[23]. Although lab diagnostics efficiently contribute to the early identification of SARS-CoV-2 infection, there is evidence that laboratory medicine may also provide essential assistance to discriminate between severe and non-severe COVID-19. The large variations in the clinical features of the disease, spanning from asymptomatic to fatal, necessitates the identification and application of novel laboratory biomarkers to rapidly and economically predict COVID-19 prognosis

Conclusion

In the current study, the AUC of procalcitonin and serum ferritin were above 0.80; thus, they are effective and have very good predictive value for predicting COVID-19. It seems that, these blood laboratory parameters could be used in screening cases with positive RT-PCR for COVID-19. However, serum LDH, D-Dimer, and vitamin D levels or liver function tests, renal function tests remain insignificantly linked with covid positivity rate in this study.

Considering the significant findings in laboratory parameters evaluated in this study, one can hope to model or predict the results of coronavirus testing based on routine laboratory tests. Based on the findings of this study serum procalcitonin and serum ferritin have very good accuracy in predicting cases with positive RT-PCR for COVID-19. However, serum LDH, D Dimer, and vitamin D levels, liver function tests, renal function tests remain insignificantly linked with covid positivity rate among this cohort.

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Conflict of Interest: Nil Source of support: Nil