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Serum Procalcitonin Levels and It's Correlation with C-reactive Protein in COVID-19 Patients

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Abstract
Aims: *This study was aimed to measure and evaluate the procalcitonin levels and correlate it with C-reactive protein in diagnosed cases of COVID-19 Patients.*
Study design: *An observational study.*
Place and Duration of Study: *Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, between 20th January 2021 and 27th February 2021.* ***Methodology:*** *We included 120 patients (70 men, 50 women; age range 18-99 years) with documented COVID-19 were reviewed. The subjects were divided into two groups: severe and non-severe COVID-19. The details were recorded on a pre-structured performa. Between groups, differences were tested using the Mann-Whitney's U-test. The receiver operating characteristic curve was plotted for procalcitonin with severity. A binary logistic regression was used to identify variables independently associated with severity. Serum PCT levels correlated with CRP level. The data was analyzed using Statistical Package for the Social Sciences (SPSS).*
Results: *Out of 120 patients, 74 patients were included in the non-severe group and 46 patients in the severe group. Patients with increased PCT levels were significantly higher ($p<0.05$) in severe cases [median 0.49 mg/L, interquartile range (IQR) 0.35-0.64] than in non-severe patients [median0.23mg/L, interquartile range (IQR) 0.12-0.32]. Binary logistic regression showed ferritin to be an independent predictor of all-cause severity supplemented with an AUC of 0.88 on ROC analysis. PCT levels were positively correlated with CRP levels.*
Conclusions*: PCT levels and CRP could serve as an early biomarker for COVID-19, early intervention could prevent progression of disease.*
Keywords*: PCT, CRP, COVID-19, Biomarker, correlation*

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I. Introduction

The novel coronavirus disease 2019 (COVID-19) that emerged in December 2019 in Wuhan (Hubei, China), has surprisingly occupied the entire globe overwhelmingly, with many countries experiencing the second wave [1]. By March 30, 2021, 127,349,248 confirmed cases of COVID-19, including 2,787,593 deaths, were reported to the World Health Organization (WHO) [2]. Even though the rapidly evolving clinical course and presentation continue to amaze the medical fraternity, cases infected with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), often present with severe pneumonia and organ targeted injuries involving the liver, heart, and kidneys [3]. With the surging devastating effects of the pandemic, the focus of scientific efforts was on developing optimal therapeutic regimens to combat the virus. Meanwhile, there was also a dire need for early risk stratification systems and biomarkers to predict disease progression, to identify high-risk patients at an early stage of the infection [4–6]. Procalcitonin (PCT) is the 116-amino acid precursor of the hormone calcitonin. Recently, several studies reported that elevated PCT levels are positively associated with the severity of COVID-19 [7–10]. In order to improve the diagnosis to distinguish between severe/critical patients and moderate patients with COVID-19 and to better predict the prognosis, the aim of this study was to investigate the role of changes in PCT values.

II. Material And Methods

2.1 Study Population

The observational study was carried out at the Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, from 20th January 2021 to 27 February 2021. A total of

120 COVID-19 patients enrolled from COVID ward of Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand in this study and divided into non-severe and severe groups. Non-sever group included 74 patients and severe group included 46 patients. All patients with COVID-19 who enrolled in the recent study were diagnosed according to the WHO interim guidance for COVID-19 (6th edition) [7]. In other words, all patients with the physician and laboratory confirmed (positive nasopharyngeal/throat swab specimens by reverse transcription-polymerase chain reaction (RTPCR)) COVID-19 infection were included, while suspected cases with similar clinical symptoms were excluded. One of the following criteria was used to determine severe COVID-19 illness: respiratory rate >30 bpm, oxygen saturation <93% on room air, arterial oxygen partial pressure (PaO2)/ oxygen concentration (FiO2) ≤300 mm Hg, and intensive care unit (ICU) admission.

2.2 Analysis of serum PCT and CRP

Serum analysis for PCT was determined on automated autoanalyzer , which works on absorbance microplate reader using sandwich ELISA method. The blood sample was collected, Serum analysis for CRP was determined on a fully automated autoanalyzer which works on absorptive spectrophotometry using Immunoturbidimetric method. The blood sample was collected, as per the standard protocol. The concentrations of PCT were expressed in ng/mL. The concentrations of CRP were expressed in mg/L.

2.3. Statistical Analysis.

Statistical data were analyzed using SPSS version 20.0. As the data that was skewed; median values were reported along with interquartile ranges (IQR) for continuous variables. Between groups, median differences were tested using the Mann–Whitney's U-test and categorical variables were compared by chi-square test. The predictive value of the PCT was evaluated by measuring the area under the receiver operating characteristic curve (AUC). The Spearman's correlation coefficient test was used for correlations between serum PCT and CRP .A "p value" below 0.05 was considered statistically significant and $p < 0.001$ considered statistically highly significant.

III. Results

A total of 120 inpatients were declared COVID-19 positive during the study duration. Out of these, 52 patients were included in the severe group, while 68 patients were included in the non-severe group. Median age of sever group was 56 (IQR: 48–67) years and median age of non-severe group was 49 (IQR: 45–64) years. The average age was higher in the severe group than in the non-severe group ($p = 0.06$) as shown in Table1. Out of 120 patients 70 patients were male and 50 patients were female. Out of 50 females 22 females were included in the severe group and 28 females in the non-sever group. Out of 68 male, 46 male were included in the severe group and 22 male were included in the non- severe group as mentioned in table 2 and figure1. The severity ratio for males was higher than for females, but this difference was not significant ($p = 0.51$). Median PCT being

0.49 (IQR: 0.35–0.64) and 0.23 (IQR: 0.12-0.32) ng/mL was found to be significantly higher in the severe group compared to the non-severe cases group respectively (p value = 0.001) as shown in table1. Median CRP being

74.2 (IQR: 63.2–90.0) and 24.1 (IQR: 10.2-36.2) mg/L were found to be significantly higher in the severe group compared to the non-severe cases group respectively (p value = 0.002) as shown in table1. Strong positive correlations were found between PCT levels and serum CRP level in mild ($r = 0.81$)

Table 1

Age and CRP levels in severe vs Non-severe group

Groups	**Age (median, IQR) (years)**	**PCT median (IQR) (ng/mL)**	**CRP median (IQR) (mg/L)**
Severe case (n=52)	56 (48-67)	0.49 (0.35-0.64)	74.2(63.2-90.0)
Non-severe case (n=68)	49 (45-64)	0.23(0.12-0.32)	24.1(10.2-36.2)
p value	0.06	0.001	0.002

$p < 0.05$ statistically significant and $p < 0.001$ highly significant IQR-Interquartile range
PCT- Procalcitonin

Table 2
Gender distribution in Groups

Groups	Male	Female
Severe	46	22
Non-severe	57	28

P value=0.51
p <0.05 statistically significant and p <0.001 highly significant

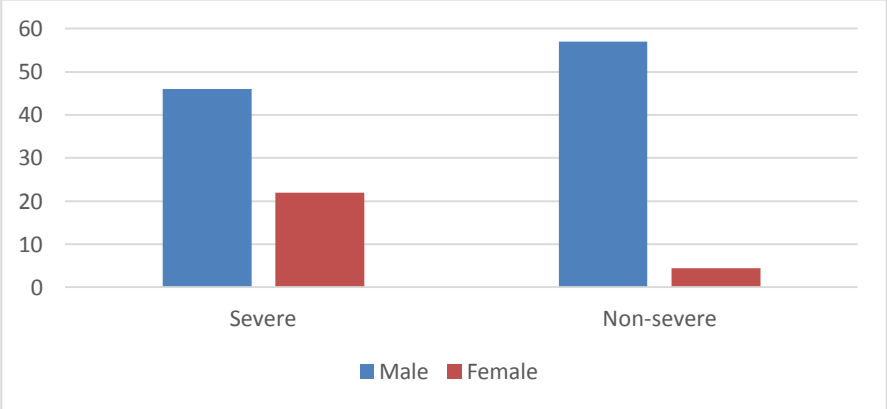
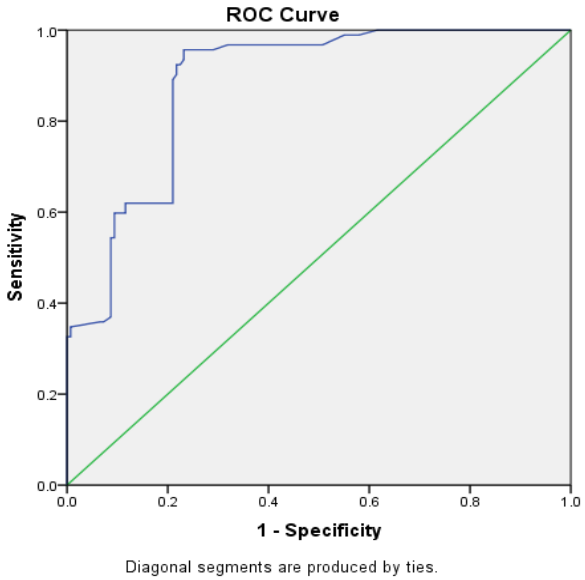


Figure 1. Gender distribution in two study group

ROC curve analysis was used to compare the performance of PCT as a predictor of severity with an AUC of 0.88 (95% CI: 0.57–0.74) as illustrated in Fig.2. The optimal cut-off for the prediction of severity was 0.55ng/ml with a sensitivity of 88% at a compromised specificity i.e. 68%.



AUC-0.88

Figure 2: *Receiver operating characteristic (ROC) curves of C-reactive protein for predicting the disease severity in COVID-19 patients*

IV. Discussion

In developing countries like India, the role of PCT is more important in risk stratification and prognostic indication as it is an inexpensive test widely available. Since it is cheaper, it is also easier to follow up in patients of COVID-19. The current study showed significantly higher PCT levels in severe cases than in non-severe patients suggesting that the PCT level may be a biomarker of disease severity and progression in patients with COVID-19. Severe COVID-19 infections are characterised by a systemic inflammatory response, and frequently present with pyrexia, raised C-reactive protein (CRP), hypoxia and lung infiltrates. Clinicians

have struggled to determine which COVID-19 patients have superadded bacterial infection requiring antibiotic treatment, leading to widespread antibiotic use.[11] Microbiological culture is a relatively insensitive technique, especially during antibiotic treatment. It can be difficult to distinguish infection and colonisation in non-sterile sites, and even in patients with sepsis only 30–50% will have a positive blood culture.[12] We cannot therefore rely on positive microbiology alone as an indicator of bacterial infection. Procalcitonin (PCT) is an inflammatory biomarker that rises in bacterial infection and falls in response to antibiotic treatment, and has greater sensitivity and specificity for bacterial infection than CRP.[13,14] PCT has been used to distinguish between influenza with and without secondary bacterial infection and is of potential value in identifying COVID-19 patients with genuine bacterial infection. Previous studies have investigated the role of PCT in COVID-19 infection. Williams et al.[15] described a retrospective analysis of PCT use in COVID-19 patients, concluding that PCT led to a reduction in antibiotic use without impacting on 28 day outcomes. Van Berkel.[16]measured PCT and CRP in intensive care unit (ICU) patients with COVID-19, diagnosed with secondary bacterial infection based on a positive culture and the opinion of two ICU physicians. They concluded that low PCT could be used to exclude secondary bacterial infection. PCT has been identified as a marker of poor prognosis in COVID19 infection[17] and it is unclear if a raised PCT is part of the inflammatory syndrome associated with COVID-19 or primarily reflects bacterial co-infection requiring antibiotic treatment. In the current study, AUC is 0.88 In other words, ROC analysis confirmed CRP as a valuable predictor of COVID-19 progression and severity

V. Conclusion

PCT levels are an indicator of disease severity and prognosis of disease. Those patients who have higher PCT level have poor prognosis, so CRP level must be monitored during course of disease

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

" 'Hemanti designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. 'Rajiv kumar Mahli' managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript."

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