

# IJMA



## INTERNATIONAL JOURNAL OF MEDICAL ARTS

*1/2022 (volume 4, Issue 1)*



<http://ijma.journals.ekb.eg/>

Print ISSN: 2636-4174

Online ISSN: 2682-3780

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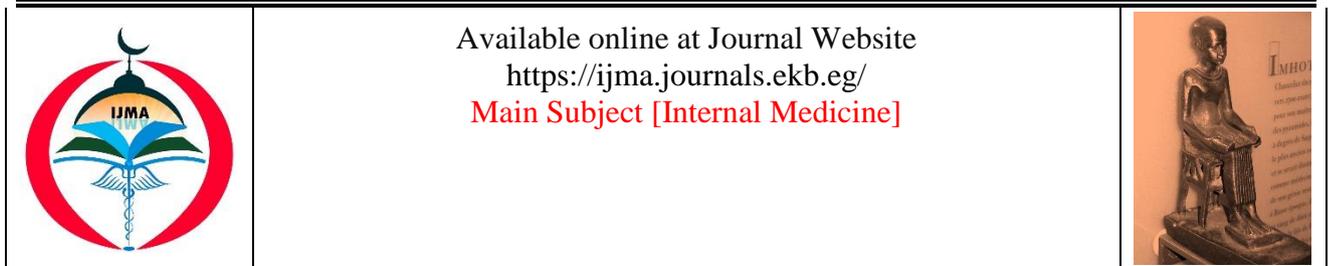
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 Main Subject [Internal Medicine]

## Original Article

# Cross-Sectional Study on Association between Inflammatory Markers and Chest Computed Tomography Severity Score in COVID-19 at Admission

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## ABSTRACT

### Article information

Submitted: 02-11-2021

Accepted: 24-12-2021

DOI: 10.21608/IJMA.2021.103044.1384

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**Citation:** Rojaramani K, Reddy SVP, Thulasiram K. Cross-Sectional Study on Association between Inflammatory Markers and Chest Computed Tomography Severity Score in COVID-19 at Admission. IJMA 2022 Jan; 4 [1]: 2009-2016 [DOI: 10.21608/IJMA.2021.103044.1384].

**Background:** The great uncertainty is associated with the disease progression, as the risk of severe COVID-19 is not uniform among all patients.

**The aim of the work:** The aim of this work is to study the association between biomarkers and CT severity score at the time of admission in patients with COVID pneumonia.

**Patients and Methods:** A cross-sectional study was conducted over a period of three months [April 2021 to June 2021] based on data obtained from the records of patients; admitted with laboratory-confirmed SARS-COV-2 infection. The current study included a total of 299 patients; admitted to ICU/COVID ward with COVID-19. Study tools included; serum CRP, serum ferritin, D-dimer, and CT severity score obtained from HRCT chest.

**Results:** The Receiver operation curve [ROC] drawn for D-dimer, Ferritin, and CRP vs. severe lung involvement in HRCT thorax; Area under the curve [AUC] for ferritin - 0.648, AUC for D-dimer - 0.561, AUC for CRP- 0.497. The results suggest that raised serum ferritin is better in the prediction of severity of lung involvement in HRCT than D-dimer and CRP. Serum ferritin [0.171], D-dimer [0.72], and CRP [0.024] are biomarkers with HRCT lung involvement and their corresponding correlation coefficient values.

**Conclusion:** The present study demonstrated a significant correlation between serum ferritin and the severity score of HRCT when compared to other inflammatory markers.

**Keywords:** CRP; D-Dimer; Serum ferritin; Computed Tomography; COVID-19.



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## INTRODUCTION

The index case of COVID-19; was found in Wuhan, China. Coronavirus disease of 2019 [COVID-19] was caused by Severe acute respiratory syndrome coronavirus 2 [SARS-COV-2], which was labeled a global pandemic by the World Health Organization on March 11, 2020<sup>[1, 2]</sup>. COVID-19 mainly involves the respiratory system leading to severe respiratory distress leading to mortality. It's important that we still have various presentations. Thrombo-

embolism is considered an important event for increased mortality and can be mainly identified by inflammatory markers. By assessing the inflammatory markers we can predict the severity of the disease. Early intervention helps in halting the progression of the disease<sup>[3]</sup>. D-Dimer, serum ferritin, and C-reactive protein [CRP] are the commonly used biomarkers in assessing the severity of the disease. Hypercoagulability is one of the causes of mortality, assessed by D-dimer, a fibrin degradation product<sup>[4]</sup>. CRP and serum ferritin are widely

used markers of acute inflammation that are elevated markedly at the initial stage, even before the development of High-Resolution Computed Tomography [HRCT] outcomes [5]. Ferritin levels are considerably higher in COVID-19 affected individuals who had had worse outcomes [6].

Previous research on SARS-CoV has shown the importance of dynamic changes in numerous biomarkers, as well as their predictive value in determining disease severity and outcome. Proteomic and metabolomic screening of COVID-19 sera identified 93 proteins that showed distinct modulation in severely ill patients when compared to non-severe and non-COVID-19 sera. The complement system, macrophage activity, and platelet degranulation are all involved in the majority of these proteins [7]. Changes in some of these proteins could be potential biomarkers for making the initial diagnosis, forecasting the outcome of SARS-CoV-2 reverse transcription polymerase chain reaction [RT-PCR] testing, staging and risk stratification of presenting patients, treatment planning, and recognizing the pathogenesis of COVID-19 [7].

Initial laboratory investigations with a high neutrophil count, lymphopenia, raised CRP, and elevated lactate dehydrogenase were the most significant predictor of mortality in SARS-CoV patients, according to previous studies [8-10].

In individuals with COVID-19, inflammatory biomarkers such as CRP, ferritin, procalcitonin, Serum Amyloid A [SAA], and IL-6, as well as the less widely used PSP, were considerably elevated. The presence of these biomarkers was linked to the severity of the disease. Initial and serial measurements of these indicators, as well as other parameters, could aid in risk classification and follow-up evaluation of illness progression and improvement [11-13].

As the disease worsened, laboratory parameters such as ferritin, Interleukin [IL] – 6, IL-10, neutrophil to lymphocyte ratio [NLR], CRP, serum viral load, and certain coagulation parameters all elevated [14]. During the progression from mild to severe/critical disease, particularly in non-survivors, an increased trend in procalcitonin, CRP, ferritin, and the most

important cytokine, IL-6, was frequently detected. These markers can be measured over time to predict disease progression, severity, and mortality [13, 15, 16]. In severe disease and non-survivors, changes in coagulation markers, such as prolonged PT, high D-dimer, and elevated fibrinogen or FDP, were prevalent [17, 18]. The current study was focused on inflammatory biomarkers such as CRP, D-Dimer, and serum ferritin.

## THE AIM OF THE WORK

In the present setting, we had a varying presentation with clinical correlation and CT score severity; hence, with the background in mind, the study aims to investigate the association between inflammatory biomarkers at the time of admission with [HRCT] chest findings.

## PATIENTS AND METHODS

A Cross-sectional study was conducted in Sri Venkateshwara Ram Narayan Ruia Hospital [SVRRGGH], Tirupati; from July 2021 to September 2021 [three months duration]. All cases that tested positive for SARS – CoV-2 by reverse transcriptase-quantitative polymerase chain reaction [RT-PCR] above the age of 18 years presenting to SVRRGGH hospital in this period for admission were included in the study. All subjects from both genders, willing to participate in the study, were included. Patients with chronic diseases, connective diseases, malignancy, and others vulnerable to raised inflammatory markers, pregnancy, and cases that are not willing to participate in the study were excluded. Indications such as hypoxia i.e. patients presented with an oxygen saturation level less than 94%, indeterminate chest X-ray, concern for disease progression, and worsening of respiratory symptoms were considered as indications for CT chest in this study.

The study was conducted in patients admitted in COVID wards and ICU. After obtaining written consent from all the participants, all patients were subjected to routine laboratory investigations like; complete blood count, renal function tests, liver function tests, along with biomarkers like; CRP, serum Ferritin, and D-dimer. Radiological evaluation was performed

by HRCT chest. The disease severity was classified into mild to severe based on CT severity scoring. The CT severity score was calculated based on the extent of lobar involvement with a total score of 25. Each of the five lung lobes was visually scored, on a scale of 0-5, with 0 indicating no involvement, 1- indicating less than 5% involvement, 2- indicating 5-25% involvement, 3- indicating 26-49% involvement, 4- indicating 50-75% involvement, and 5- indicating more than 75% involvement. The severity of the disease is classified as mild [score less than or equal to 8], moderate [score ranging from 9 to 15], severe [score range from 16 to 25].

This study was approved; by the Institutional Ethics Committee dated 31 July 2021, reference number: 148/2021. Informed written consent; was obtained from all patients before their enrollment in this study.

### Statistical analysis

Using descriptive statistics, the data were summarized. Statistical significance was defined as a p-value of <0.05. When comparing those who had elevated levels of biomarkers to those who did not, relative risks of various markers were estimated for the development of severe HRCT involvement. Elevated D-dimer, CRP, and ferritin levels were compared to normal levels to determine the relative risk. For elevations, the markers were evaluated, and the results were calculated accordingly. Wherever appropriate, ROC analysis was used. To determine the strength of the association, Pearson correlation coefficients were calculated for escalating biomarker levels and lung involvement in HRCT chest.

## RESULTS

The total number of participants in the study is 299 with male to female ratio of 1.84:1 [194 male patients, 105 female patients]. The most common age group affected is 51 to 60 years [31.7%] followed by 41 to 50 years [24%]. The least common age group affected is 91 to 100 years [1%]. The mean age of patients was 51.8 years.

There was no significant association between gender and lung involvement severity [RR of 1.18,  $p=0.57$ ]. In patients with significant lung involvement, the average age was  $51.7\pm 12.7$  years, while that of patients with non-severe lung involvement was  $51.3\pm 14.3$ . There was no significant relationship between age and the severity of lung involvement [ $p=0.85$ ].

### Risk factors

In the present study, 56% [170 patients] of the patients had risk factors. The common risk factors observed were diabetes mellitus [78 patients], hypertension [56 patients], chronic kidney disease [19 patients], coronary artery disease [11 patients] and respiratory disease [6 patients].

In 78 patients with diabetes, 26 had mild, 32 had moderate and 20 had severe lung involvement. In 56 patients with hypertension, 21 had mild, 19 had moderate and 16 had severe lung involvement. In 19 patients with chronic kidney disease [CKD], two had mild, two had moderate and 15 had severe lung involvement. In 11 patients with Coronary Artery Disease [CAD], two had mild and nine had severe lung involvement. In six patients with respiratory disease, one had moderate and five had severe lung involvement. Among 170 patients with risk factors, 51 have mild, 54 have moderate and 65 had severe lung involvement.

Study showed that patients with coronary artery disease, chronic kidney disease, and respiratory disease had severe lung involvement compared to normal individuals.

The correlation coefficient values with HRCT lung involvement were 0.351 for diabetes and 0.114 for hypertension. It indicates severity of lung involvement is more in patients with Diabetes compared to Hypertension

### Oxygen saturation

At the time of presentation 38.8 % [116 patients] had low saturation [ $<94\%$ ], 57.8% [173 patients] had normal saturation at presentation [ $>94\%$ ].

### HRCT chest

HRCT chest was normal in 80 patients [26.8%] whereas, abnormality in HRCT chest was detected in 219 patients [73.2%]. Among 116 patients with low saturation, on HRCT, 74 patients had severe lung involvement, 8 patients had mild lung involvement and 34 had moderate lung involvement.

Among 173 patients with normal saturation, on HRCT, eight patients had severe lung involvement, 71 patients had mild, 14 patients had moderate and 80 patients had no lung involvement.

Mean CRP value among males was 5.298 and among females were 5.427. Out of 199 males, 108 had normal and 86 had abnormal CRP values and among 105 females, 48 had normal and 57 had abnormal CRP values.

Mean D-dimer value among males was 1.418 and among female was 1.279. Out of 199 males 98 had normal and 96 had abnormal D-dimer values. Out of 105 females 48 have normal and 57 have abnormal D-dimer values. Mean Ferritin value among males is 492.64 and among females is 432.87, out of 199 males 68 have normal ferritin and 126 have abnormal ferritin values.

The mean values of D-dimer and serum ferritin is more in males and CRP is more in females.

### D-dimer

Among individuals with normal D-dimer levels, CT was normal in 84 individuals, mild involvement were seen in 33, moderate involvement in 21, and severe involvement in 18 individuals. In individuals with abnormal D-dimer levels, CT was normal in 43 individuals, mild involvement in 37, moderate involvement in 28, and severe involvement in 35 individuals.

### Ferritin

Among individuals with normal ferritin levels, CT was found to be normal in 76

individuals, 24 had mild involvement, 30 had moderate involvement, and 19 individuals had severe lung involvement. Among individuals with abnormal ferritin levels, CT was normal in 36 individuals, 41 had mild involvement, 31 had moderate involvement, and 42 individuals had severe lung involvement.

### CRP

Among individuals with normal CRP levels, CT was found to be normal in 62 individuals, 33 had mild involvement, 8 had moderate involvement and 6 individuals had severe lung involvement. Among individuals with abnormal CRP levels, CT was normal in 48 individuals, 54 had mild lung involvement, 41 had moderate lung involvement, and 47 individuals had severe lung involvement.

There was a strong association found between elevated values of serum ferritin and HRCT severity score [p-value -0.02]. We also found that CRP and D-Dimer did not have a significant association with HRCT severity score [p-value for D-dimer- 0.2, p-value for CRP- 0.226] [Fig. 1, 2, 3]. The receiver operation curve [ROC] drawn for ferritin [Fig. 4], D-dimer [Fig. 5], and CRP [Fig. 6] vs. severe lung involvement in HRCT thorax; Area under the curve [AUC] for ferritin – 0.648; AUC for D-dimer - 0.561; AUC for CRP- 0.497. These findings suggests that raised serum ferritin is better in the prediction of severity of lung involvement in HRCT than D-dimer and CRP.

Serum ferritin [0.171], D-dimer [0.72], and CRP [0.024] are biomarkers with HRCT lung involvement and their corresponding correlation coefficient values. Relative Risk [RR] was also calculated which gives information on the probability of the risk of developing severe lung involvement on HRCT among the patients in whom biomarkers were elevated compared to patients in whom biomarkers were not elevated. RR serum ferritin was 2.71, D-dimer was 1.65, and CRP was 1.09.

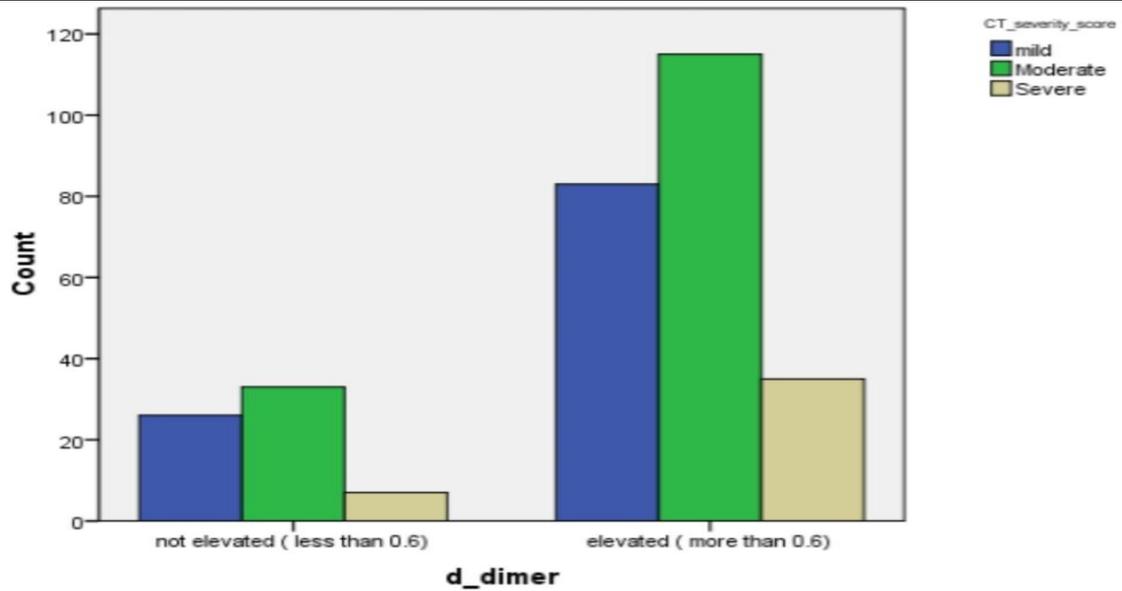


Figure [1]: D-dimer and CT severity score

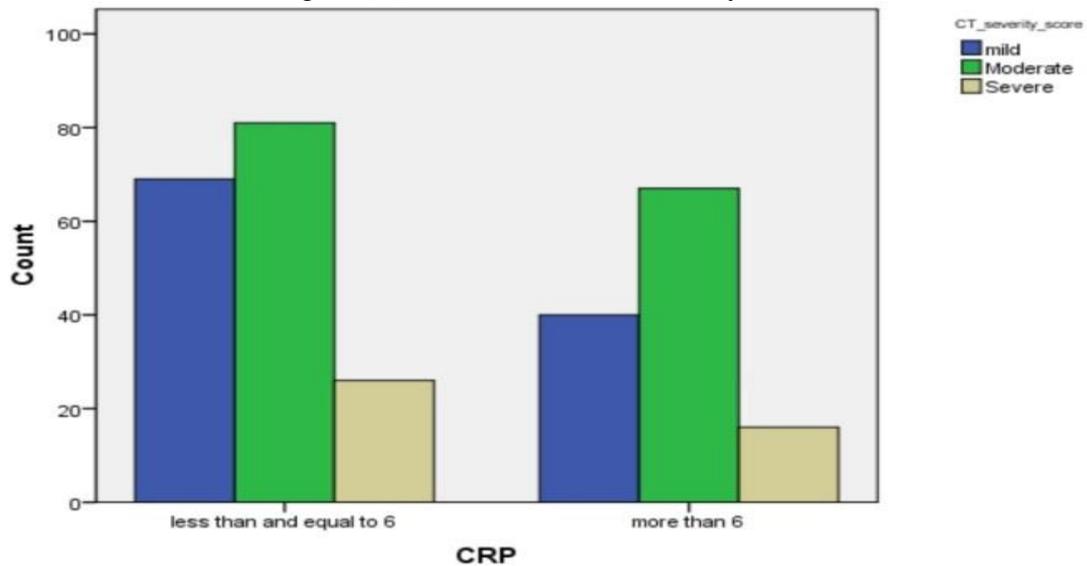


Figure [2]: CRP and CT severity score

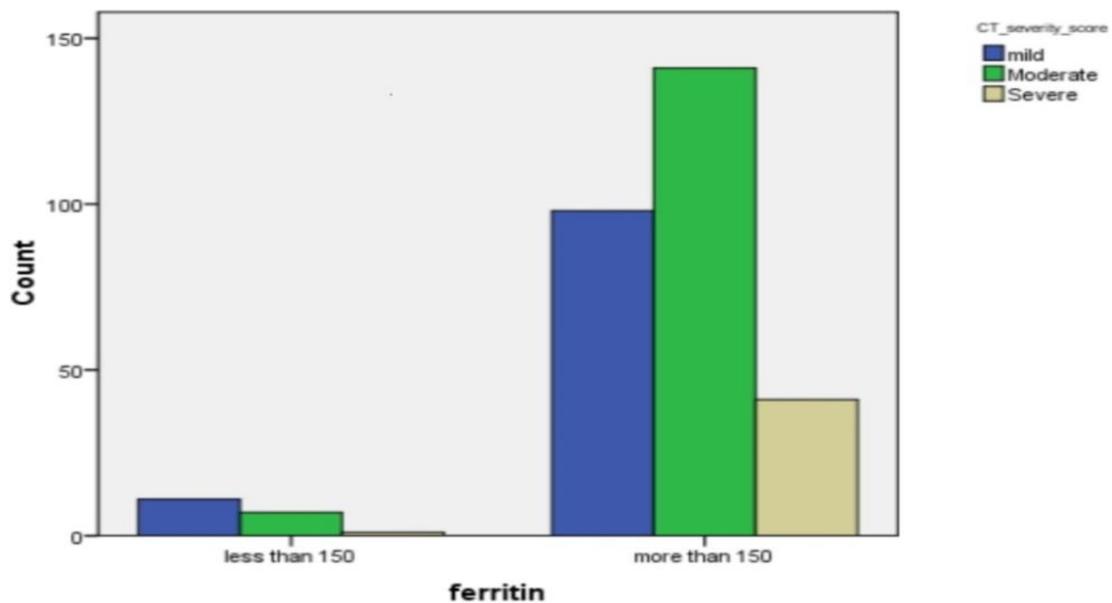


Figure [3]: Ferritin and CT severity score

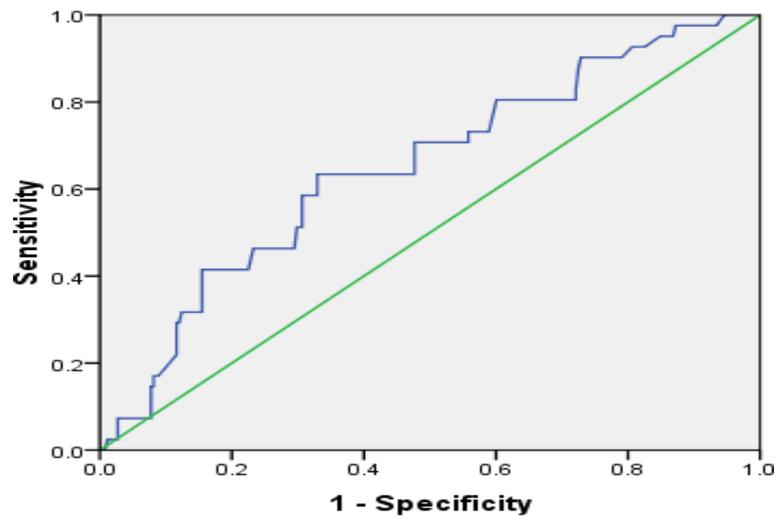


Figure [4]: ROC for serum ferritin vs. HRCT thorax severe lung involvement [CT scores >15]; AUC: – 0.648

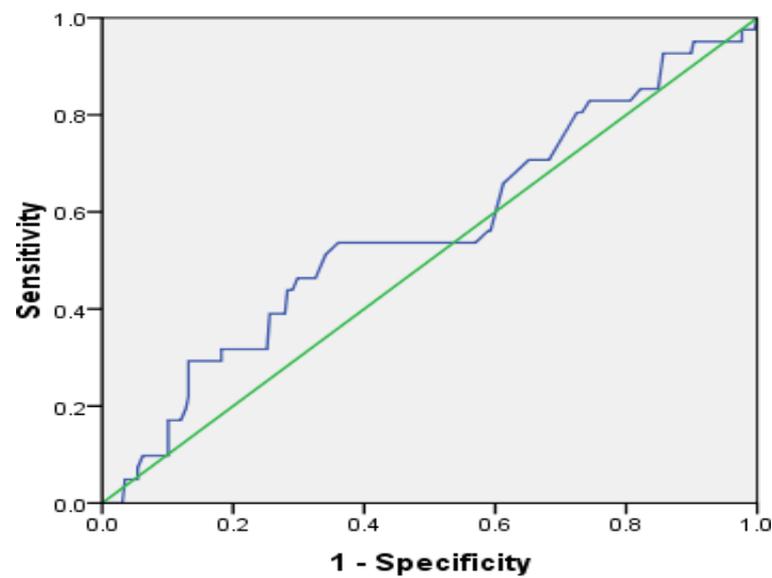


Figure [5]: ROC for D-Dimer vs. HRCT thorax severe lung involvements [CT score >15]; AUC: – 0.561

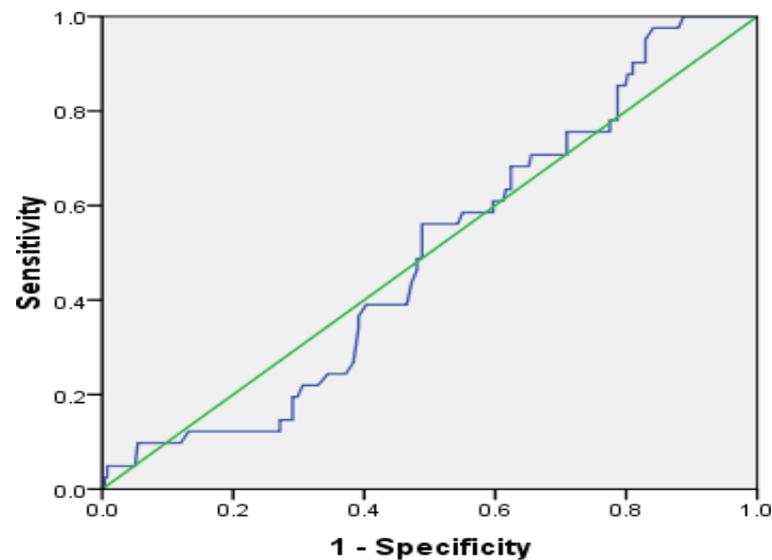


Figure [6]: ROC for CRP vs. HRCT thorax severe lung involvement [CT score >15]; AUC: – 0.497

## DISCUSSION

The goal of the present study is to determine the severity of COVID-19 based on the level of biomarkers and the severity of HRCT. D- Dimer levels were found to be significantly higher in all COVID-19 deaths, indicating that coagulation mechanisms had been activated. Patients in this situation may develop sepsis, which is one of the most common causes of disseminated intravascular coagulation [DIC] <sup>[3]</sup>. Ferritin is a key mediator of immunological deregulation that leads to cytokine storms, which have been proven to be the cause of the majority of catastrophic outcomes. As a result, people with high ferritin levels may face major problems <sup>[19]</sup>. CRP is a sensitive biomarker of inflammation, infection, and tissue damage that is found in the acute phase of life <sup>[20]</sup>. CRP levels were found to be much higher in severe COVID-19 patients in the onset of the disease, which is an indication of disease progression, according to studies. When compared to D-dimer and CRP, elevated Ferritin has a stronger and more significant correlation with the severity of lung involvement [based on HRCT chest].

In India, a few similar studies have been carried out to investigate the association between inflammatory markers and CT severity score as it is a pandemic with less evidence. Kurri *et al.* <sup>[21]</sup> observed in their study that the disease severity was significantly correlated with CTSS and D- dimer. Severe COVID-19 was also associated with a high NLR and moderately elevated inflammatory markers [CRP, Ferritin, IL-6]. CTSS >15 and D-dimer >2.4 correlate strongly with mortality. CTSS has the greatest diagnostic accuracy for stratifying the disease severity and predicting the mortality among the compared markers/ characteristics. No other inflammatory markers have demonstrated a significant positive correlation either with CTSS or patient mortality outcomes.

### Limitations of the study

The study was conducted based on data at the time of admission. Therefore, no data were available for follow up of serial levels of biomarkers and HRCT. Also, there were no

details on follow-up of clinical conditions of patients.

### Conclusion

The study found that the patients with risk factors like coronary artery disease, chronic kidney disease, respiratory disease, hypertension and diabetes mellitus had severe lung involvement compared to normal individuals. Furthermore, the patients with elevated biomarkers had more severe lung involvement compared to individuals with normal levels of biomarkers. In conclusion, the present study demonstrated a significant correlation between serum ferritin and the severity-score of HRCT when compared to other inflammatory markers. Overall, the present work proves that we have a strong correlation between inflammatory markers and severity of HRCT and outcome of COVID-19.

### Financial and Non-financial Relationships and Activities of Interest

None

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1/2022

# International Journal

<https://ijma.journals.ekb.eg/>

Print ISSN: 2636-4174

Online ISSN: 2682-3780

# of Medical Arts