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ORIGINAL RESEARCH ARTICLE

ASSOCIATION OF CRP AND D-DIMER WITH CT SEVERITY SCORING IN COVID-19 PATIENTS

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ABSTRACT

Background: Corona virus disease 2019 (COVID-19) has become a global public health issue with significant impacts upon the healthcare delivery systems. Previous studies have consistently found elevated levels of C-Reactive Protein and D-dimer with disease severity. In this study, we aimed to investigate the relationship between C-Reactive Protein, D-dimer level and Computed Tomography severity score in patients with SARS-COV-2 pneumonia.

Methods: Our study included 76 patients with COVID-19, admitted in COVID Unit of Chitwan Medical College and Teaching Hospital from June 2020 to December 2020. We included COVID-19 cases confirmed by a RT-PCR test and those undergoing High resolution Computed Tomography of chest and having C-Reactive Protein and D-dimer levels done on admission. A semi-quantitative CT score was calculated based on the extent of lobar involvement (0:0%; 1, < 5%; 2:5–25%; 3:26–50%; 4:51–75%; 5, > 75%; range 0–5; global score 0–25.

Results: Overall the median CTSS was 15. Mild, moderate and severe CT severity scoring was reported in 5.3%, 60.5% and 34.2% respectively and D-dimer progressively increased across the CTSS severity groups. The difference was significant for CRP, P = 0.007 but not for D-dimer, P = 0.42. Moreover, higher CTSS scores were significantly associated with higher ICU stay, lower recovery rate and higher O2 requirement at discharge.

Conclusions: Radiological severity of COVID-19 pneumonia has significant association with elevated C-Reactive Protein level but not with D-dimer level and other routine laboratory parameters.

INTRODUCTION

COVID-19 infection has become pandemic with significant impacts upon the healthcare delivery systems and socioeconomic milieu. The clinical manifestations of COVID-19 vary from asymptomatic carriers, fever, dry cough, shortness of breath, fatigue to patients requiring Incentive Care Unit(ICU) admissions and assisted ventilator support with increased mortality.[1]

In the management of patients with COVID-19,a High Resolution Computed Tomography(HRCT) Scan of chest plays a crucial role in the early disease identification.[2]Since the outbreak of COVID-19 worldwide, studies from different countries have consistently found elevated levels of C-Reactive Protein(CRP) and D-dimer correlating with the severity of the disease process.[3,4]Therefore, we proposed the hypothesis that the D-dimer and CRP level may predict severity of changes in CT scan of chest. In this study, we aimed investigate the relationship between CRP, D-dimer level and Computed Tomography severity score (CTSS) in patients with Severe and Critical COVID 19 pneumonia.

METHODS

We performed a prospective observational study including all patients with COVID-19, admitted in COVID Unit of Chitwan Medical College and Teaching Hospital located in Bharatpur, Chitwan District, Nepal during a 6 months period from June 2020 to December 2020. COVID-19 was diagnosed through areal time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test from a nasopharyngeal and oropharyngeal swab according to the World Health Organization(WHO) guidelines. We included COVID-19 cases confirmed by a RT-PCR test and undergoing HRCT chest and having CRP and D-dimer levels done on admission. Patients with normal chest CT findings and those with any other chronic chest CT findings as of pulmonary edema and interstitial lung disease were excluded from the study. This study was approved by the institutional review board of CMCTH.

Complete blood count, electrolytes, renal and liver function test, coagulation profile, CRP, D-dimer, myocardial enzymes were collected on admission. Turbidimetric immunoassay method was used for the quantitative measurement of CRP and

nephelometry for D- dimer estimation. High resolution scan of chest were performed in the radiology department using a Siemens 128 slice, Somatom definition AS+ (CTAWP92544; Siemens Healthineers, Erlangen, Germany). All volumetric chest CT scan was assessed at lung window of 1500 WW and - 500 WL and mediastinal window of 400 WW and 60 WL using 3D Multiplanar reformation for better assessment of the extent of the disease. Two consultant radiologists with more than 5 years of experience in thoracic imaging performed the CT image analysis.

CT Severity was assessed using the following scoring system which depends on the visual assessment of each lobe involved.[5,6] Particularly, 5 scores were allotted according to the involvement of each of the five lung lobes: 0 point, noinvolvement; 1 point, less than 5% involvement; 2 points, 5%-25% involvement; 3 points, 26%-49% involvement; 4 points, 50%- 75% involvement; 5 points, more than 75% involvement. The total CT score was the sum of the scores of the individual lobes ranging from 0 to 25.The sum of the lobar scores indicates the overall severity: Mild, 7 or less; Moderate, 8-17; Severe, 18 or more. Clinical severity of the COVID-19 patients was classified into mild, moderate, severe and critically ill.[10]

Data was analyzed using Statistical Package for Social Sciences (SPSS) for windows version 16. Standard descriptive statistics was used to describe the data. Chi-square test was used to test associations between categorical variables. Box plot was constructed to find out differences in CRP and D-dimer levels and different CT severity categories based on CT severity score. P-value <0.05 was considered statistically significant.

RESULTS

The median age of the patients (n=76) was 55 years with Inter Quartile Range (IQR) of 44 to 64 years. Fifty-two (68.4%) patients were males. The median duration of the symptoms before admission was 6 days (IQR: 4 – 7 days). The most frequent presenting symptomwas cough (86.8%), followed by fever (85.5%) and shortness of breath (68.4%). Hemoptysis was present in five patients (6.6%). Forty-eight (63.2%) patients had at least one co-morbidity; hypertension, was the commonest (40.8%) followed by type 2 diabetes mellitus (38.1%) (Table 1).

Table 1: Clinical characteristics of the patients with COVID-19 (n = 76)

Characteristics	Frequency (%)
Age (years), median (IQR)	55 (44 – 64)
Gender, n (%)	
Male	52 (68.4)
Female	24 (31.6)
Duration of symptoms (days), median (IQR)	6 (4 – 7 days)
Presenting symptoms, n (%)	
Cough	66 (86.8)
Fever	65 (85.5)
SOB	52 (68.4)
Fatigue	23 (30.3)
Muscle soreness	19 (25.0)
Loss of taste/smell	7 (9.2)
Headache	10 (13.2)
Diarrhoea	11 (14.5)
Hemoptysis	5 (6.6)
Comorbidity present, n (%)	48 (63.2)
Comorbidity, n (%)	
HTN	31 (40.8)
T2DM	29 (38.1)
COPD	3 (3.9)
PTB	4 (5.3)

IQR= Inter Quartile Range, SOB=Shortness of breath, HTN=Hypertension, T2DM= Type 2 diabetes mellitus, PTB= Pulmonary tuberculosis, COPD= Chronic Obstructive Pulmonary Disease

Table 2: Demographic and clinical characteristics of the patients (n = 76) categorized according to CT severity score (CTSS)

Variables	Mild CTSS (n = 4)	Moderate CTSS (n = 46)	Severe CTSS (n = 26)	p-value
Age (years), median(IQR)	48.5 (38 – 62)	54.5 (44.2 – 65.0)	56 (44.2 – 64)	0.380
Male gender, n (%)	2 (50.0)	34 (73.9)	16 (61.5)	0.398
Duration of symptoms (days), median(IQR)	7 (3 – 7)	7 (4 – 7)	5 (4 – 7)	0.321
Symptoms, n (%)				
Cough	4 (100.0)	38 (82.6)	24 (92.3)	
SOB	3 (75.0)	28 (60.9)	21 (80.8)	0.367
Hemoptysis	-	2 (4.3)	3 (11.5)	
Comorbidity present, n (%)	1 (25.0)	32 (69.6)	15 (57.7)	0.161
Comorbidity, n (%)				
HTN	-	21 (45.6)	10 (38.5)	0.161
T2DM	-	20 (43.5)	9 (34.6)	
Clinical severity				
Mild	3 (75.0)	9 (19.6)	-	
Moderate	1 (25.0)	21 (45.7)	2 (7.7)	<0.001
Severe	-	15 (32.6)	21 (80.8)	
Critical	-	1 (2.2)	3 (11.5)	

Clinical variables				
RR	22 (20 – 25)	24 (20 – 30)	28 (24 – 35)	0.028
SpO2	95 (93 – 96)	91 (87 – 93)	86 (79 – 87)	<0.001
Hb	11.8 (11.2 – 12.7)	12.2 (11.4 – 13.8)	12.6 (11.2 – 14.2)	0.748
Hct	33.5 (31.8 – 35.1)	37.2 (33.8 – 39.5)	36.7 (32.9 – 40.3)	0.302
Treatment received, n (%)				
Antibiotics	4 (100.0)	46 (100.0)	26 (100.0)	-
Remdesivir	2 (50.0)	29 (63.0)	22 (84.6)	0.066
Steroids	4 (100.0)	46 (100.0)	26 (100.0)	-
Heparin	4 (100.0)	44 (95.7)	26 (100.0)	0.580
Ionotropes	-	3 (11.5)	3 (11.5)	0.004
HFNC	-	11 (23.9)	15 (57.7)	0.001
Mechanical ventilation	-	1 (2.2)	4 (15.4)	0.125

RR= Respiratory Rate, Hb=hemoglobin, SpO2= oxygen saturation, Hct= Hematocrit, HFNC=High Flow Nasal Canula

Out of the total participants the median CT Severity Score (CTSS) was 15 (11 – 18). Based on the CTSS, the patients were categorized as patients with mild CTSS (4, 5.3%), moderate CTSS (46, 60.5%) and severe CTSS (26, 34.2%).

Table 2 shows the demographic and clinical characteristics of the patients, categorized according to CT severity score (CTSS). There were no significant differences in age, sex, duration of symptoms, presenting symptoms and co-morbidity status between the three CT severity groups. There was a significant association between clinical severity and CT severity scores. A larger proportion of patients with severe CTSS required O2 via High Flow Nasal Canula (HFNC) and vasopressor support (Table 2).

Table 3 illustrates the laboratory parameters as well as outcome characteristics of the patients (n = 76) categorized according to CT severity score (CTSS). Elevated WBC count was significantly associated with severe CTSS group. Among the different biochemical parameters, CRP and D-dimer progressively increased across the CTSS severity groups. However, the difference was significant for CRP, but not for D-dimer (Figure 1 and 2). Moreover, higher CTSS scores were significantly associated with ICU stay, lower recovery rate and higher O2 requirement at discharge (Table 3).

Table 3: Laboratory characteristics and outcome of the patients (n = 76) categorized according to CT severity score (CTSS)

Variables	Mild CTSS (n = 4)	Moderate CTSS (n = 46)	Severe CTSS (n = 26)	p-value
WBC count, n (%)				
Decreased (<4000/ mm^3)	1 (25.0)	2 (4.3)	3 (11.5)	
Normal (4000 – 11000/mm^3)	3 (75.0)	40 (87.0)	14 (53.8)	0.015
Elevated (>11000/ mm^3)	-	4 (8.7)	9 (34.6)	
Lower lymphocyte count(<1100/mm^3), n (%)	2 (50.0)	21 (45.7)	12 (46.2)	0.986
Biochemical parameters, median (IQR)				
Urea	19 (14.3 – 24.7)	25 (17.9 – 41.4)	28 (16 – 36)	0.317
Creatinine	0.6 (0.5 – 0.8)	0.8 (0.6 – 1.0)	0.8 (0.7 – 1.0)	0.311
FBG	116 (111.2 – 126)	133 (110 – 208)	117 (108 – 223)	0.776
SGOT	37 (23 – 58)	47 (34 – 74)	48 (38 – 78)	0.468
SGPT	58 (36 – 77)	55 (33 – 94)	51 (33 – 81)	0.927
CRP	21.4 (6.6 – 35.4)	68.3 (23.7 – 138.0)	99.3 (80.9 – 174.1)	0.007
D-dimer	503.5 (308.7 – 7317.5)	615 (382.5 – 2182)	942 (480 – 2710)	0.412
Elevated CRP (>10 mg/L), n (%)	3 (75.0)	45 (97.8)	26 (100.0)	0.014
Elevated D-dimer (>500 ng/ml), n (%)	2 (50.0)	30 (66.7)	19 (73.1)	0.625
Outcome parameters, n (%)				
ICU stay required	-	22 (47.8)	19 (73.1)	0.010
Mortality	-	1 (2.2)	4 (15.4)	0.082
Improved	4 (100.0)	37 (80.4)	12 (46.2)	0.004
O2 requirement at discharge	-	2 (4.3)	7 (26.9)	0.016

WBC= White Blood Cells, FBG= Fasting blood glucose, SGOT= Serum Glutamic Oxaloacetic Transaminase, SGPT=Serum Glutamic Pyruvic Transaminase, CRP= C-reactive Protein, ICU= Incentive Care Unit

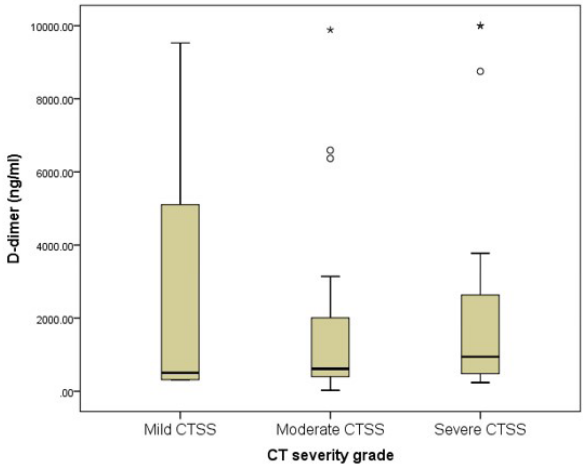

Figure 1: Boxplot diagram showing differences in serum D-dimer in different severity groups based on CT severity scoring (CTSS) index

The patients were categorized based on CRP and D-dimer level into moderately- and highly-elevated groups. Highly elevated CRP was significantly associated with, higher CTSS and prolonged hospital stay. However, there was no significant difference in other patient outcomes between the two groups (Table 4). For D-dimer, there was a significant association between improvement rates and D-dimer elevations (Table 4). No other significant associations were observed between D-dimer categories and other variables including patient outcomes.

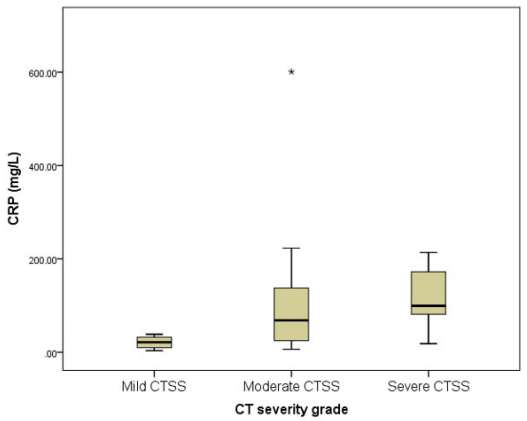

Figure 2: Boxplot diagram showing differences in serum CRP in different severity groups based on CT severity scoring (CTSS) index

Table 4: Association of CRP and D-dimer levels with symptoms, CT severity scores and patient outcomes

Variables	CRP		p-value	D-dimer		p-value
	Moderately elevated (n = 25)	Highly elevated (n = 49)		Moderately elevated (n = 29)	Highly elevated (n = 21)	
Symptoms, n (%)						
Fever	23 (92.0)	40 (83.3)	0.30	26 (89.7)	17 (81.0)	0.38
Cough	23 (92.0)	41 (83.7)	0.32	25 (86.2)	17 (81.0)	0.62
SOB	12 (48.0)	39 (79.6)	0.005	25 (86.2)	12 (57.1)	0.03
Fatigue	7 (28.0)	16 (32.7)	0.68	7 (24.1)	7 (33.3)	0.47
CTSS, median (IQR)	12 (8.5 – 14.5)	17 (12.5 – 19)	<0.001	15 (12 – 18)	15 (12 – 19)	0.47
Outcome parameters, n (%)						
ICU stay required	11 (44.0)	30 (61.2)	0.22	17 (58.6)	13 (61.9)	0.81
MV required	0 (0.0)	5 (10.2)	0.16	2 (6.9)	2 (9.5)	1.0
Mortality	2 (8.0)	3 (6.1)	1.00	2 (6.9)	1 (4.8)	1.0
Improved	19 (76.0)	32 (65.3)	0.43	24 (82.8)	11 (52.4)	0.03
Hospital stay (days), median (IQR)	6 (4.5 – 8.5)	8 (6 – 11)	0.009	7 (6 – 12)	8 (6 – 9.5)	0.15

MV= Mechanical Ventilation

DISCUSSION

The findings of this study imply that quantitative CRP analysis can be useful in determining the severity of COVID-19 and may provide additional assistance for clinical treatment strategy planning. The severe COVID-19 group had a higher average age than the non-severe group, which was consistent with previous research findings.[7]In contrast to prior findings, there was no significant difference between the groups in terms of co-morbidities or primary initial symptoms on admission.[8] Our sample had a young age (Mean=55 years) and a male inclination. This can be explained by the unique traits of the Nepalese population.[9]

A number of existing literatures suggests that the presence of risk factors, such as hypertension, diabetes, chronic lung, and coronary artery disease, is associated with a poor prognosis, and that the outcome is considerably worse when numerous

risk factors are present. Although there was no statistically significant link between the presence of risk factors and CT severity scores in our analysis, there was a significant link (p 0.010) between ICU admission and severe CT Severity Score.[10] Although COVID-19 therapy is still based on purely empirical decisions rather than the evidence of large clinical trials, we hypothesized that CT prediction of disease progression and its correlation with clinical-laboratory findings might be useful in assisting medical staff in triaging patients and timely establishing symptomatic treatment.[11]

Lung and immune system damage are the main pathological changes of COVID-19 infection.[12] As a fast and easy method of screening for pulmonary infection, CT scan analysis can not only assess the existence of pulmonary infection, but it can also serve as a guide for determining the type of pathogen, providing specific diagnostic benefits. According to ZhongNanshan's latest study, COVID-19 diagnosis with CT scan alone had a sensitivity of 76.4%, and CT scan application utilization in COVID-19 was deemed useful.[13] The prognosis of patients can sometime be predicted by the CT severity score.[14] The usefulness of the CT scan in the diagnosis and assessment of COVID-19 was suggested by Chen Lin et al. studies.[15]

The ability to track lung lesions using CT dynamic imaging was poor. It is essential to develop a simple index that has a strong correlation with pulmonary pathological changes. CRP is a well-known marker of severe infection and systemic inflammation. CRP levels are correlated to the severity of inflammation, and their concentration is unaffected by age, gender, or physical condition.[16] CRP levels can be used to diagnose pneumonia early,[4] and CRP levels in patients with severe pneumonia were high. In evaluating and diagnosing severe pulmonary infectious diseases, CRP level is an important marker.[17] CRP levels were found to be linked to lung lesions and the severity of the disease. This suggests that CRP levels may indicate lung lesions and disease severity in the early stages of COVID-19.

Furthermore, our results showed significant correlation between the serum CRP levels and CT severity score. Studies have also indicated that using CRP as a predictor for the risk of disease progression may be utilized to identify patients at an early stage.[18] Our results were compatible with recent research that found the CRP level at admission to be a sensitive and early predictor of COVID-19 severity.[19,20] Moreover, there was a positive correlation with CT severity scoring and CRP levels.[21] It is difficult to conduct a broad panel of biological analyses on admission in general practice for urgent stratification, but the routine test of CRP could predict disease severity and direct management of COVID-19 patients.

Similarly, D-dimer may be used as a prognostic predictor, with higher levels indicating more serious conditions.[22,23]Also in our study D-dimer progressively increased across the CTSS severity groups. However, the difference was not significant for D-dimer. It's unclear if the increase is due to the virus's direct effects or the inflammatory reaction in the body as a whole.[22,24] Our findings showed increased length of ICU stay and increased oxygen requirement with increasing CT severity scores. The increase in oxygen requirement may be attributed to the virus's direct damage to the lungs, which causes inflammatory changes in the alveolar wall, limiting oxygen exchange and ultimately contributing to acute respiratory failure, pulmonary fibrosis, and death.

Our study has some limitations. First, it was a single-center study. Second, only 76 patients were included, so our findings will need to be confirmed in a larger cohort sample. Third, we have not analyzed chest X-ray findings in our data. Fourth, other inflammatory biomarkers such as interleukin 6 (IL-6), ferritin and pro-calcitonin were not included as they were done only in a few severe cases.

CONCLUSION

CRP level was significantly associated with COVID-19 severity score of Chest CT scan but not the D-dimer level. Therefore, for early detection of severity of COVID-19, CRP on admission can be useful to facilitate the guidance of treatment decisions.

CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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