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Original Research Article

To Study the Correlation of Quantitative CRP (C Reactive Protein) and CTSS (CT Severity Score) on Admission as a Predictor of Severity of COVID-19

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Abstract:

Objective: To determine the correlation of C-reactive protein (CRP) levels and Computed Tomography Severity Score derived from High Resolution Computed Tomography at the time of admission with the clinical outcome among COVID-19 patients.

Methods: Single centre, prospective, observational study enrolled all the participants who fulfilled the selection criteria and visited the hospital/emergency. The data were collected in a paper-based questionnaire. For this study, the level of C- Reactive Protein was measured and interpreted. The mean and the median CT severity score was measured. The value of coefficient of correlation between the CRP and CT severity score was seen and results derived.

Results: The mean CRP levels among the participants who were alive and died was 143 and 233 mg/dl, respectively. The P-value of the T-test suggest that the difference in the levels of CRP was highly significant ($p < 0.0001$). The mean and the median CT severity score among the participants that did survive the COVID-19 infection was 14.5 and 16, respectively. The mean and the median CT severity score among the participants who did not survive the COVID-19 infection 19.8and 22, respectively. The difference in the mean CT severity score among the participants who did and did not survive the COVID-19 infection in the present study was statistically highly significant ($p<0.0001$). The value of coefficient of correlation between the CRP and CT severity score also indicated a liner and strong relationship between CRP levels and CT severity score ($r = (+) 0.70$)

Conclusion: C - reactive protein levels and HRCT score/parameters at the time of admission both successfully predicted the adverse outcome among COVID-19 patients admitted to the ICU. There was high degree of correlation between the CRP and HRCT, thus, eitherof the two can be utilized for the risk stratification and triage of patients for admissionto ICU or Hospital.

Keywords: CRP (C REACTIVE PROTEIN) and CTSS (CT SEVERITY SCORE).

Introduction

At the beginning of the COVID-19 pandemic, the physicians and clinical scientists were clueless about various dimensions of the novel-SARS-2 Corona virus's infectivity, pathogenicity, and clinical features. However, it was quickly realised that only a small proportion of all COVID-19 positive patients suffer from a severe disease requiring mechanical ventilation. Most patients recover without any complications or long-term disability. [1-3] However, given the sudden surge in the number of COVID-19 cases, especially at the peak of a COVID-19 wave and the limited number of hospital beds especially the ICU beds, physicians were faced with an ethical dilemma in prioritizing patients for admission to hospitals and ICU beds. [4-7]

Sometime after the pandemic began, several large scale hospital-based studies reported the clinical characteristics, laboratory markers, and outcomes among hospitalized patients suffering from Covid-19. These studies suggested that COVID-19 is associated with significant inflammation of various organ systems of the body resulting in neurologic, cardiovascular, coagulation, and other end-organ

manifestations. [8] The end-organ damage in a person suffering from severe COVID-19 is preceded by pathologic changes similar to several other infections. Thus, several biomarkers which are elevated during infection are also increased in COVID-19. Hence, identifying markers of disease severity may assist healthcare personnel to triage COVID-19 positive patients who would benefit the most from admission to thehospital or ICU. Physicians, Pathologists, and Radiologists started looking for clinical clues which can assist in predicting the outcome among hospitalized COVID-19 patients. The lab-based models were built around the pathological markers of inflammation including Interleukins (IL), C-Reactive Protein (CRP), Tumour Necrosis Factor-Alpha (TNF-α), Procalcitonin, D-Dimer, and other markers(21–24). The radiological models were built around the changes in lungs seen either on X-ray and/or CT-Scan. [9-13]

Empirical evidence suggests that the levels of CRP among COVID-19 positive patients correlate with severity of infection (and underlying inflammation) and progression to respiratory failure (or need for mechanical ventilation). Therefore, CRP may be used as a potential indicator of prognosis among COVID-19 patients. [14] A systematic review involving 22 studies reported that 10 studies reporting the prognosis of COVID-19 included CRP as a part of their prognostic score. [15-21] The authors of the systematic review suggest that measuring the level of CRP upon admission and monitoring its level during the treatment among COVID-19 patients can assist the physician in risk stratification and tailoring the treatment. [22-28] Thus, CRP could assist the physician in deciding which COVID-19 patient will benefit immensely from hospitalization or treatment. The use of CRP as a biomarker in COVID-19 may present a quick and accessible tool in clinical management, provide information around likely disease progression and assist with early therapeutic, ventilation and palliative care discussions. [29-31]

As mentioned earlier one of the hallmarks of COVID-19 is extensive involvementof the pulmonary system culminating in ARDS leading to respiratory failure and unfortunately death among a significant proportion of all hospitalized patients. The extent of lung involvement may assist the physician in triaging and risk stratification of patients to decide who will benefit from treatment. Thus, radiologic investigations including chest X-rays and CT -scans can assist in assessing the degree of pulmonary involvement. [32]

Materials and Methods

Study Design: This was a single centre, prospective, observational study.

Study Settings: The present study was conducted at the Department of Anaesthesiology and Department of Medicine, L N Medical College & Research Centre and affiliated J K Hospital, Bhopal. It is a tertiary care institute.

Study Duration: The total duration of the study was 18 months

Study Outcomes:

Primary Outcome Parameters:

1. The correlation between the C-reactive Protein and following clinical outcomes: (a)Admission to ICU, (b)Mechanical ventilation, (c) Mortality, and (d) Duration of stay in hospital.
2. The correlation between the CT severity score and following clinical outcomes: (a) admission to ICU (b) mechanical ventilation, (c) mortality, and (d) duration of stay in the hospital.
3. The correlation between the CT severity score and C Reactive Protein level at the time of admission.

Secondary Outcomes:

1. Duration of ICU stay.
2. Number of days oxygen therapy required.
3. Number of days ventilator support required.

Sample Size Calculation: We enrolled all the participants who fulfilled the selection criteria and visited the hospital/emergency department during the period of participant's recruitment. Following this we enrolled a total 645 participants in the present study.

Participant's recruitment: The recruitment of the participants and primary datacollection was started once the protocol was approved by the Institute's ethical committee. The participants were recruited into the study after verifying that they fulfilled the following selection criteria.

Inclusion Criteria:

1. Patient tested positive for novel SARS Corona-2 virus (COVID-19) on RT-PCR.
2. Patients aged 18 years or above.
3. Patients of all genders.
4. Patients who underwent HRCT and C-Reactive Protein testing within 24 hoursof admission.
5. Patients/legal guardians who gave written informed consent to take part in thestudy.

Exclusion Criteria:

1. Patient's advised home isolation for COVID-19.
2. Patient aged <18 years,
3. Pregnant females.
4. Patients who had already received terminal diagnosis.
5. Patient/legal guardian's refusal to take part in the study.

Participants Definition: A person diagnosed with COVID-19, admitted to the hospital, and fulfilling the above-mentioned selection criteria.

Sampling Methodology: We employed non-probability purposive sampling methodology strategy for recruiting participants for the present study. All COVID-19 patients coming to the emergency department and fulfilling the selection criteria during the period of participants recruitment.

Data Collection: The data were collected in a paper-based questionnaire. The questionnaire was approved by the ethical committee before starting data collection.

Plan and Procedure: On arrival at the emergency department/hospital, all patients with symptoms suggestive of COVID-19 were assessed by a physician and their samples were sent for RT-PCR.

Measurement of C-Reactive Protein Levels: For this study, the level of C- Reactive Protein was measured using Latex Test Kit.

Interpretation of CRP levels

- Less than 3 mcg/ml: Normal (level seen in most healthy adults).
- 3 to 10 mcg/ml: Minor elevation.
- 10 to 100 mcg/ml: Moderate elevation.
- 100 -500 mcg/ml: Marked elevation.
- >500 mcg/ml: Severe elevation.

Chest CT Scan: Chest CT imaging was performed using a 16-detector CT scanner (GE Optima). All patients were examined in the supine position and CT images were then acquired during a single inspiratory breath-hold. The direction of lung scanning was from the apex of the lung to the costophrenic angle. All CT images were independently reviewed by two consultant radiologists with more than 10 years of experience, blinded to the clinical data and laboratory indicators, in a standard clinical picture archiving and diagnostic system workstation. We assessed the chest CT scan on a total of 14parameters as follow: ground glass opacity, consolidation, reticular pattern, lesions distribution (peri broncho vascular or peripheral), side of lung involvement, crazy paving, pleural effusion, number of lung zones involved, Interlobular septal thickening, air bronchogram, emphysema, tree-in-bud pattern, and CT severity score.

Calculation of CT severity score:

- There are 5 lobes (3 lobes in right lung and 2 lobes in left lung. Further, there are 18 segments in both lungs: 10 segments in right lung and 8segments in left lung.
- For calculating the CT severity score, the 18 segments of both lungs were divided into 20 regions. The posterior apical segment of the left upper lobe was subdivided into apical and posterior segmental regions, whereas the anteromedial basal segment of the left lower lobe was subdivided into anterior and basal segmental regions.
- The lung opacities in all the 20 lung regions were objectively evaluated on chest CT images using a system attributing score of 0, 1, and 2 if parenchymal opacification involved 0%, less than 50%, or equal to or more than 50% of each region, respectively. The CT-SS was defined as the sum ofthe individual scores in the 20 lung segment regions, which may range from 0 to 40 points.

End Point of Study: The study was terminated if:

- A participant decided to withdraw from the study,
- A participant suffered a terminal event (due to any reason).
- The participant was discharged from the hospital.

Observation Chart

Table 1: Distribution of study participants by age (n=468)

Age (Years)	**Outcome**		**Total**
	Good (n, %)	**Poor** (n, %)	(n, %)
<=50	102	7	109
	32.90	**4.43**	**23.29**
51-60	67	39	106
	21.61	**24.68**	**22.65**
61-70	70	54	124
	22.58	**34.18**	**26.50**
71-80	70	53	123
	22.58	**33.54**	**26.28**
>80	1	5	6
	0.32	**3.16**	**1.28**
Total	310	158	468
Pearson chi2(4) =	P-value = 0.032		
Mean (SD)	**58.9 (11.88)**	**66.3 (8.54)**	
Median	59	67	P <0.0001
Range	**41 81**	**50 84**	

Table 2: Distribution of study participants by the duration of symptoms(n=468)

Duration (Days)	Outcome		P-value
	Good (n, %)	**Poor** (n, %)	
Duration of Symptoms			
Mean (SD)	7.6 (3.46)	10.8 (3.42)	0.001
Range	3 11	5 16	
Hospital Stay			
Mean (SD)	8.6 (3.08)	11.8 (2.98)	
Range	4 -14	7 17	0.003
ICU Stay			
Mean	4.6 (1.41)	5.8 (1.78)	0.021
Mechanical Ventilation			
Mean	2.1(1.45)	3.8 (1.37)	

Table 3: Distribution of Inflammatory marker levels among participants (n=468)

CRP	**Good**	**Poor**	**P-value**
Mean (SD)	143.7 (101.6)	233.8(152.1)	< 0.0001
Median	120	190	
Range	6 - 554	43 - 785	
CRP Level Category (n, %)			
Minimal	3	0	P <0.0001
	0.97%	**0.00**	
Moderate	113	26	
	36.45%	**16.46%**	
Marked	190	121	
	61.29%	**76.58%**	
Severe	4	11	
	1.29%	**6.96%**	
Total	310	158	

Table 4: CT Score among participants (n=603)

CT Score	Outcome			Chi-Squared
	Good n, (%)	**Poor** n, (%)	Total n, (%)	**P-Value**
<=10	100	33	133	P <0.0001
	32.26	**20.89**	**28.42**	
11-20	102	43	145	
	32.90	**27.22**	**30.98**	
21-30	108	75	183	
	34.84	**47.47**	**39.10**	
31-40	0	7	7	
	0.00	**4.43**	**1.50**	
Total	310	158	468	P <0.0001
Mean	14.5	19.8	-	
Median	16	22	-	
Range	**4-48**	**6-33**	**-**	

Table 5: Distribution of CRP levels and CT severity score among participant(n=468)

CT Severity Score	**CRP Levels**				
	Minimal	**Moderate**	**Marked**	**Severe**	**Total**
<=10	3	75	55	0	133
	100.00	**53.96**	**17.68**	**0.00**	**28.42**
11-20	0	56	89	0	145
	0.00	**40.29**	**28.62**	**0.00**	**30.98**
21-30	0	8	167	8	183
	0.00	**5.76**	**53.70**	**53.33**	**39.10**
31-40	**0**	**0**	**0**	**7**	**7**
	0.00	0.00	0.00	46.67	1.50
Total	**3**	**139**	**311**	**15**	**468**
Pearson Chi2 = 334.03 P-value <0.001					
Coefficient of Correlation [r] **(+) 0.70**					

Results

Overall, in each age group category, the participants with the adverse outcome in the present study were older in comparison to participants with favorable outcome. The mean age of the participants who had good and adverse outcomes was 59.9 and 66.3 years, respectively. The T-test for the difference in the mean age of the participants who had favourable and adverse outcomes was statistically significant ($p < 0.001$).

The mean duration for admission to the hospital among participants who had good and poor outcomes was 7.6 and 10.8 days, respectively ($P < 0.0001$). The mean duration of hospital stay among participants who had good and poor outcomes was 8.6 and 11.8 days, respectively ($P = 0.0031$). During their stay at the hospital, several COVID-19 positive patients developed complications during the treatment. Overall, in the present study, ARDS was the most common complication, followed by septicemia.

Above table illustrate the mean, median and range of CRP values among the patients discharge alive (in stable health conditions) and who died during the treatment. The mean CRP levels among the participants who were alive and died was 143 and 233 mg/dl, respectively. The P-value of the T-test suggest that the difference in the levels of CRP was highly significant ($p < 0.0001$). Moreover, the upper side range of CRP values was more than 40% higher among those with poorer outcomes. Among the participants with favorable outcomes, the marked and severe levels of CRP were observed in only 61% and 1.2% participants. In comparison, among the participants with poorer outcome, the marked and severe levels of CRP were observed in only 76% and 6.9% participants, respectively.

The mean and the median CT severity score among the participants that did survive the COVID-19 infection was 14.5 and 16, respectively. The mean and the median CT severity score among the participants who did not survive the COVID-19 infection 19.8 and 22, respectively. The difference in the mean CT severity score among the participants who did and did not survive the COVID-19 infection in the present study was statistically highly significant ($p<0.0001$).

Above table shows the distribution and association between CRP levels and the CT severity score among the participants. There was a linear trend in the CT severity score and CRP Levels. As we move from minimal elevation of CRP levels to severe levels of CRP levels, the CT severity score increased. The value of coefficient of correlation between the CRP and CT severity score also indicated a liner and strong relationship between CRP levels and CT severity score ($r = (+) 0.70$)

Statistical Analysis:

All the data were collected in a paper-based data collection form. Thereafter, the data were coded and entered in Microsoft Excel. The coded data were imported into Stata 17.1 version for analysis. For the continuous data, the author calculated the mean, median, mode, and standard deviation. Quantitative data confirming the properties of the normal distribution are presented as means ± standard deviation. The data showing the properties of the non-normal distribution are presented as median and the interquartile range. For discrete data, the author calculated and reported frequency, proportion, and percentage. We used logistic and linear regression for determining the association between the dependent variable (primary outcomes) and independent variables. Comparison of continuous variables with baseline values was analysed using a student's t-test in each group. Categorical variables were analysed using chi- square (χ^2) tests. A P-value < 0.05 was considered statistically significant.

Conclusion

1. COVID-19 patients who were admitted to hospital sooner had better chance of survival than those who were admitted more than one week after the onset of symptoms.
2. The patients who died and who required mechanical ventilation had significantly higher levels of CRP on admission in comparison to those who did not suffered any adverse outcome.
3. The patients who died and who required mechanical ventilation had significantly worse HRCT parameters including CT severity score, number of lung lobes & segments involvement in comparison to those who did not suffered any adverse outcome.
4. There was high degree of correlation between the HRCT finding and CRP levels at the time of admission.

Declarations:

Funding: None.
Conflicts of interest/Competing interests: None.
Availability of data and material: Department of Anaesthesiology and Department of Medicine, L N Medical College & Research Centre and affiliated J K Hospital, Bhopal. It is a tertiary care institute.
Code availability: Not applicable.
Consent to participate: Consent taken.
Ethical Consideration: There are no ethical conflicts related to this study.
Consent for publication: Consent taken.

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