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Computed Tomography Severity Score in COVID-19: Association with Inflammatory Markers and Patient Outcome

Faisal Mehmood, Ali Hassan, Amna Ashraf, Zahid Farooq Baig, Karamat Hussain Shah Bukhari, Abdul Latif Khattak

Combined Military Hospital, Lahore/ National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To associate CT severity score with inflammatory markers and to determine outcomes of COVID-19 patients admitted to CMH Lahore.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Combined Military Hospital, Lahore Pakistan, from Mar to Jun 2021.

Methodology: Patients of COVID-19 age 18 and above, with a positive RT-PCR, were included in the study Clinical and radiological data of 200 patients was retrieved and analysed from the hospital registry.

Results: In the present study, we studied the role of inflammatory markers in predicting the severity of COVID-19. We have compared the levels of LDH, CRP, IL-6 and serum Ferritin between the two groups. LDH (p=0.015), IL-6 (p=0.001) and Ferritin (p=0.001) were significantly different between the two groups, but CRP was not (p=0.811) significant.

Conclusion: CT severity score associates well with the COVID-19 clinical severity. Our data suggest that the chest CT scoring system can predict the severity of COVID-19 disease and significantly associates with inflammatory markers.

Keywords: CT severity, Ferritin, Inflammatory markers, IL6.

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INTRODUCTION

A non-contrast High-Resolution CT (HRCT) chest imaging plays a pivotal and essential role in early disease detection, particularly in patients with false-negative RT-PCR results, as well as in managing and monitoring the course of disease.[1,2] Moreover, the imaging findings can ascertain the disease severity, significantly supporting the clinicians in their clinical judgment and ensuring effective and timely management.[3] Prognosis can also be affected by the severity of the disease in critically ill patients allowing appropriate selection of early involvement in the intensive care. Multiple studies have explored the pulmonary involvement in HRCT images using both visual and software quantitative assessments.[4]

Due to rapid disease progression, effective biomarkers would be helpful in screening and categorising patients, their clinical management, and preventing serious complications.[5,6] Biomarkers commonly evaluated to assess the severity of COVID–19 are serum ferritin, CRP (C-reactive protein), IL-6 (interleukin-6), and LDH (Lactate Dehydrogenase). LDH (isozyme 3) present in lung tissue is expected to be released in greater amounts in the circulation with severe COVID–19 infection, which can present as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome (ARDS). So raised LDH can be the hallmark of the severe disease.[7,8] Activation of immune systems by this virus releases many cytokines, including IL-6. IL6 is a multi-effective cytokine with anti-inflammatory and pro-inflammatory action contributing to host defence against infections. However, its excessive synthesis while fighting the virus leads to an acute severe systemic inflammatory response called a cytokine storm.[9] The role of its Plasma and/or bronchoalveolar levels as an early biomarker of lung injury and as a predictor of prolonged mechanical ventilation, organ dysfunctions, morbidity and mortality in lung diseases has been identified.[10] Ferritin, a degradation product of haem, is significantly elevated in COVID–19 patients with poor outcomes.

The present study aimed to analyse the initial HRCT quantitative parameters, including GGO (Ground-glass opacities), consolidation, and total lesion volume, and evaluate their relationship with clinical features of COVID-19 to assess the disease severity on admission promptly.

METHODOLOGY

The comparative cross-sectional study was conducted at dedicated COVID ICU and dedicated COVID ward of the Department of Medicine, Combined Military Hospital, Lahore Pakistan, from March to June 2021, after taking ethical approval from

Correspondence: Dr Amna Ashraf, House 392, street 11, X Block, Phase 3, DHA Lahore, Pakistan

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the Hospital Ethical Review Board (reference number 335/2021). Non-probability consecutive sampling was employed.

Inclusion Criteria: Patients of COVID-19 age 18 and above, with a positive RT-PCR, were included in the study.

Exclusion Criteria: Patients with additional findings in HRCT, like pleural effusion and structural lung damage assessing COVID-19-associated CTSS difficult, were excluded from the study. Patients with the mild disease having CTSS less than 20 were excluded from the study. Generally, those patients received outdoor treatment. Patients with positive RT-PCR but unable to get HRCT (because of a short hospital stay or critical disease) were also excluded from the study.

Informed written consent was taken from the patients. Consent of patients on mechanical ventilation or who died was taken from next of kin (family member). Data were retrospectively obtained from 200 patients admitted at CMH Lahore Pakistan from March to June 2021. Confidentiality of data was ensured by hiding the medical record number of patients from data handlers. History taking and the trainee researcher performed a physical examination. Information was collected on demography, disease severity, laboratory measurements, and radiology imaging. Data were obtained as part of standard clinical care. This study determined the association between the CTSS score and the inflammatory markers in COVID-19 patients. Patients were divided into two groups based on HRCT severity score. The CTSS was defined by summing up individual scores from 20 lung regions; scores of 0, 1, and 2 were respectively assigned for each region if parenchymal opacification involved 0%, less than 50%, or equal to or more than 50% of each region (theoretic range of CTSS from 0 to 40).[11] Group-A with a CTSS score of 20 to 30. Group-B with a CTSS score of 31-40. Disease severity was compared in both groups and compared with inflammatory markers. The researcher collected all data to maintain data quality and compliance with the study protocol.

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 26:00. For normal data, mean±SD was calculated, and for non-normal data, median and IQR were calculated. Mann Whitney U test was used to compare HRCT score with inflammatory markers, and the chi-square test was used to compare patient outcome regarding recovery versus death with CTSS. The p-value of ≤ 0.05 was considered significant.

RESULTS

Two hundred patients diagnosed with COVID-19 of either gender aged 18 years and above were enrolled in the study after taking informed written consent. Gender distribution, age distribution, and CTSS comparison are shown in Table-I.

Table-I: Association between CT Severity Score and Demographic data of COVID-19 patients (n=200)

Demographic Features		CTSS 20-30 (n=73)	CTSS 31-40 (n=127)	*p*-value
Gender	Male	46(23%)	91(45.5 %)	0.37
	Female	27(13.5%)	36(18 %)	
Age(years)	18-45	6(3%)	15(7.5%)	1.00
	46-73	36(18%)	82(41%)	
	74-99	21(10.5%)	40(20%)	

Abbreviations: Computed Tomography Severity Score (CTSS)

Mean age of partici-pants was 64.21±13.19. In the present study, we studi-ed the role of inflammatory markers in predicting the severity of COVID-19. We have compared the levels of LDH, CRP, IL-6 and serum Ferritin between the two groups. LDH, IL-6 and Ferritin significantly differed between the two groups, but CRP was not (Table-II).

Table-II: Comparison between the High-Resolution CT score AND inflammatory markers (n = 200)

Inflammatory Markers	CTSS 20-30 Median(IQR) (n=77)	CTSS 31-40 Median(IQR) (n=123)	*p*-value
LDH(U/L)	536.50 (784.75-353.25)	751.00 (973.00-374.00)	0.015
CRP(mg/L)	206.00 (267.75-143.25)	210.00 (289.00-138.00)	0.811
IL6(pg/mL)	184.00 (471.00-54.80)	248.00 (385.00-193.00)	0.001
Serum Ferritin(µg/L)	820.00 (1452.00-480.50)	572.00 (1022.00-332.00)	0.001

Abbreviations: Lactate dehydrogenase (LDH), C-reactive protein (CRP), Interleukin 6 (IL-6).

Out of 77 Low CTSS patients, 11(27.5%) patients died and 66(40.9%) patients recovered and 123 high CTSS patients, 29(72.5%) patients died and 94(59.1%) patients recovered. No statistically significant difference was found (p = 0.083), as shown in Figure.

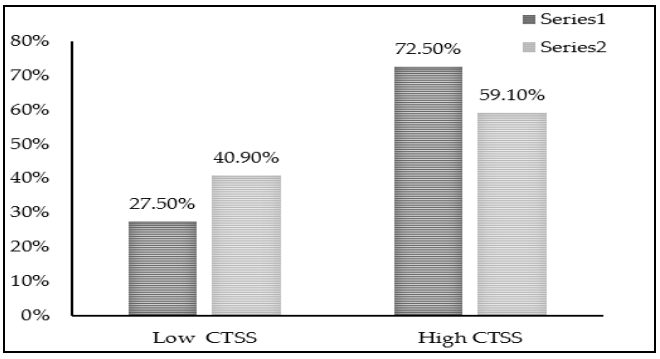

Figure: Comparison of Patient Outcome in terms of Recovery versus Death with CT Severity Score

DISCUSSION

Inflammatory markers play a significant role in predicting the severity of COVID-19 infection. Isabella D Cooper explained in a study that elevated levels of Ferritin, D-dimer, and CRP associates with the severity of COVID-19 infection.[11] The lack of early abnormalities on chest X-ray results in many false negatives. Hence, HRCT Chest is more sensitive than chest X-ray and can show abnormalities in the lung parenchyma in the early stage of the disease. The WHO advised using chest imaging as part of the diagnostic workup of COVID-19 disease whenever RT-PCR testing is unavailable, in case of delayed test results or when there is a clinical suspicion of COVID-19 with initial negative RT-PCR testing.[12,13]

Ferritin is a key mediator of immune dysregulation that contributes to cytokine storms. It has been reported that fatal outcomes by COVID–19 a cytokine storm accompanies.[14] Francone *et al*. studies the prognostic value of inflammatory markers in COVID-19. They compared the inflammatory markers in Mild disease vs. severe disease. They concluded that IL6 and CRP could be used as independent factors for predicting the severity of COVID-19.[15] There was a significant association of isolated levels of LDH, CRP and Ferritin with the severity of lung involvement. Patient outcome was significantly associated with the CTSS. The mortality ratio was very high, with a high ratio of lung involvement with elevated CTSS. Overall mortality in our study was 23.2% and 41.7%, with a severity score of HRCT, respectively. Based on the significant association with the severity of lung involvement, assessment of various biomarkers helps diagnose COVID severity without the results of PCR.

In the present study, the minimum level of Ferritin was 187, and the maximum level was 1694. Our study shows a stronger and more significant association of LDH, IL-6 and Ferritin with the severity of lung involvement based on HRCT chest of disease. IL-6, a major pro-inflammatory mediator for induction of acute phase response, has its value as a prognostic biomarker in sepsis, and various acute organ injuries have been extensively investigated.[16] There was no significant association between CRP levels and lung involvement severity in our study.

CRP is a non-specific acute-phase protein induced by IL-6 in the liver and a sensitive biomarker of inflammation, infection, and tissue damage.[17] Studies showed that it increased significantly in severe COVID–19 patients at the initial stage, signalling lung deterioration and disease progression.[18] Our study did not confirm the clinical utility of CRP levels as an indicator for severe disease and progressive inflammation because there was no significant association between CTSS and CRP (p=0.811). LDH, which acts as a non-specific indicator of cellular death, is present in lung tissue (isozyme 3) and released in large amounts in circulation in patients with severe COVID–19 infections present as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome. However, we have not studied the association between neutrophil and lymphocyte percentage and procalcitonin level. Procalcitonin level was done in selected individuals who were candidates for Tocilizumab. Our study also showed a statistically significant difference in the outcome of recovery versus death compared to different age groups.

Inflammation is closely related to the severity of COVID-19. Therefore, with increased inflammatory parameters, close attention should be paid to possible disease severity, and inflammatory markers might be promising in predicting prognosis, thus aggressive management of COVID-19 with raised inflammatory markers.

CONCLUSION

CT severity score could help to stratify patients' risk and predict the short-term outcome of patients with COVID-19. In addition, CTSS associates with the level of inflammatory markers and hence can be used to stratify patients; thus, aggressive management can be instituted early in these patients.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

FM & AH: Data acquisition, critical review, approval of the final version to be published.

AA & ZFB: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

KHSB & ALK: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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