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Original Article

Pathology Section

Correlation of CO-RADS Score with Inflammatory Markers in COVID-19 Patients: A Retrospective Analysis at a Designated COVID Centre of Kolhapur, India

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) Reporting and Data System (CO-RADS) score in Computed Tomography (CT) scan of the chest is a priority investigation in early identification of the disease. Although, a CT scan gives a clear parenchymal picture of the condition, it has its disadvantages of the cost and specificity in the prognosis of COVID-19. In addition, clinical studies have revealed its decreased utility in assessing the severity of the disease.

Aim: To understand the correlation of the CO-RADS score with various inflammatory markers and explore the changes in CO-RADS score with the severity of COVID-19 infection.

Materials and Methods: The present study is a retrospective observational study in a designated COVID-19 centre in Kolhapur, India. The radiological and pathological records of 64 cases for two months (September to October 2020) were reviewed and charted. The present study included all the cases over 18 years. The authors excluded pregnant women, patients with tuberculosis, interstitial lung disease, and pulmonary malignancy with a view of interference with the radiological presentation of COVID-19. Along with demographics, biomarkers like Total Leucocyte Count (TLC), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-Dimer, Interleukin-6 (IL-6), Procalcitonin (PCT), and serum ferritin were retrospectively reviewed and documented. The CO-RADS score, as reported by an expert radiologist, was noted down. Pearson's correlation coefficient was used to correlate the CO-RADS score with various inflammatory markers.

Results: The authors found significant high positive correlation of CT score with LDH (r=0.754; p-value <0.001), moderate positive correlation with IL-6 (r=0.503; p-value <0.001), low positive correlation with CRP (r=0.477; p-value <0.001) and PCT (r=0.461; p-value <0.001). The correlation between the CT score with serum ferritin (r=0.284; p-value=0.023), total leukocyte count (r=0.260; p-value=0.038) and D-dimer (r=0.242; p-value 0.050) was negligible.

Conclusion: The CO-RADS CT score is associated with the severity of COVID-19 disease and with mortality. The CO-RADS score showed a high positive correlation with LDH values of the present study. The LDH seems to be a promising marker and has to be further evaluated in assessing early COVID-19 infection with a multi-centric and more extensive sample size approach.

Keywords: Computed tomography, Coronavirus disease 2019, Lactate dehydrogenase, Pneumonia

INTRODUCTION

Within a short period of timeline, the pandemic of COVID-19 disease emerged to become public health emergency of international concern [1]. The COVID-19 initially appeared in China and has affected more than one million patients worldwide. This condition has devastated the healthcare systems and resources across the world [1]. With the advent of these, many interventions like quarantine, self-isolation, and an increase in the number of dedicated hospitals have been enforced by various governments across the world [1]. Also, with the gradual recognition of this disease, newer modalities of diagnosing and predicting prognosis started establishing. Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), the CO-RADS sscore of CT and various inflammatory markers like LDH, D-dimer, PCT, IL-6, TLC and serum ferritin have been extensively studied [2-5]. The COVID-19 infection has specific symptoms and signs like fever, dry cough, myalgia/fatigue, sputum, headache, and shortness of breath. The above said markers and chest imaging aid the diagnosis of the infection. Chest CT scan has been used as a priority investigation in early identification of the disease since the changes in lung CT manifest earlier than RT-PCR testing [6-8]. The sensitivity and specificity of chest CT have been reported between 80-90% and 82.9-96%, respectively [7]. Typical findings on CT are consolidation, linear opacities, crazy paving, bronchial wall thickening, and of course, elevated CT scores. These findings have been linked with the severity of the disease, and the requirement of critical support reported in various studies [7,8]. Positive correlation of inflammatory markers and severity of the COVID-19 infection have been reported [9-13].

The CO-RADS assessment allows categorisation of the non enhanced scans into groups related to the probability of the patient having confirmed COVID-19 with lung involvement. Further, it is a non invasive and relatively simple test that can rapidly diagnose COVID-19. It is easy to use and has substantial agreement among radiologists with different experiences [12,13]. Its capability to differentiate the radiological findings related to a low and high probability of COVID-19 is good. Although, CT scan gives a clear parenchymal picture of the disease, it has its disadvantages of the cost and its specificity in the prognosis of COVID-19 [13]. Clinically, studies have revealed its decreased utility in assessing the critically of the disease [14-19]. With this background, goal of the present study was to correlate the CO-RADS score with various inflammatory markers and explore the changes in CO-RADS score with the severity of COVID-19 infection.

MATERIALS AND METHODS

A retrospective observational study in a designated COVID-19 centre in Kolhapur was conducted on the cases of clinically diagnosed COVID-19 infection. Necessary permission from the Institutional Review Board was taken (DYPMCK/442/2021/IEC). First, the authors reviewed the radiological and pathological records of cases

for two months (September to October 2020). Then, the authors did the data charting for three months (May to July 2021).

Inclusion criteria: Clinical records of patients with clinical symptoms of COVID-19 infection (based on severity) that underwent a high-resolution CT scan of the chest were included in the study.

Exclusion criteria: The cases with ages less than 18 years were excluded from the study. In addition, the authors excluded pregnant women, patients with tuberculosis, interstitial lung disease, and pulmonary malignancy with a view of interference with a radiological presentation of COVID-19.

Sample size calculation: Based on a pilot study on 20 cases, the authors found that correlation coefficient with CO-RADS scores with one of the markers to be at least 0.45. With a 95% confidence interval and 95% power, the authors found the minimum sample size to be 58. Hence, the authors included 76 cases fitting the eligibility criteria in the initial screening during the period. But, due to the non availability of data in 12 patients, the authors had only 64 cases in the present study.

Study Procedure

Definitions for the categorisation of COVID-19 were adapted using World Health Organisation (WHO) guidelines [20]. Critical COVID-19 was defined by the presence of Acute Respiratory Distress Syndrome, (ARDS) sepsis, septic shock, or other conditions that would typically require the provision of life sustaining therapies such as mechanical ventilation (invasive or non invasive) or vasopressor treatment. Severe COVID-19 infection was defined by the presence of oxygen saturation <90% on room air, respiratory rate >30 breaths/min in adults, signs of severe respiratory distress (accessory muscle use, inability to complete whole sentences, etc.,). Non severe COVID-19 infected patients were those patients who were not categorised into severe and critical COVID-19 infection.

Research methods: Age, sex, co-morbidities, clinical symptoms, vital signs and laboratory indices, results of routine blood tests and biomarkers like TLC, CRP, LDH, D-Dimer, IL-6, PCT, and serum ferritin were retrospectively reviewed and documented. Based on the above three categories, the CO-RADS score was cross tabulated. In addition, the authors noted and compared the outcome of the patients, i.e., alive or dead, and differences of these biomarkers among the two groups.

Radiological scoring system: A scoring system developed by Yang R et al., has been utilised [21]. It depended on the opacification degree in the lung. Regarding the lung anatomical structures, all 18 lung segments were subdivided into 20 regions, which were then evaluated subjectively using scoring grades from 0 to 2; hence, 0 referred to no involvement, while 1 and 2 represent less than and more than 50% involvement, respectively. The summation of individual's scores of 20 regions pointed to total CT-SS score, which ranged from 0 to 40 points. The radiological terms that were established in use according to the Fleischner Society include Ground-Glass Opacity (GGO), crazy paving pattern, and pulmonary consolidation [22]. The expert radiologist reported CO-RADS scoring, and the authors noted down scores in the records.

STATISTICAL ANALYSIS

The data was collected, compiled, and analysed using Epi Info (version 7.2). The authors used sample size based on correlation coefficient formula using the online calculator by clinical and translational science institute for sample size calculation. The qualitative variables were expressed in terms of percentages. The normality of the data was tested using the Kolmogorov-Smirnov test. The authors defined the quantitative variables in terms of mean and standard deviations for normal data and terms of the median and Interquartile Range (IQR) in non normal data. The difference between medians of more than two groups was tested using the Wilcoxon rank-sum test. The difference between the two proportions was analysed using chi-square or Fisher exact test. To test the difference medians of the two groups, Mann-Whitney U test was used. Pearson's correlation coefficient was used to find the correlation between the quantitative variables. All the analysis was two-tailed, and the significance value was set at 0.05.

RESULTS

The authors have included 64 cases in the present study. The mean age of the cases was 55.77±14.65 years, with 79.69% of males in the present study. The authors noted 68.75% of the patients were swab positive [Table/Fig-1]. Of 64 cases, 35.93% had a non severe type, 43.75% had a severe type, and 20.32% were a critical type of COVID-19 infection.

The distribution of various blood parameters has been tabulated in [Table/Fig-2].

Demographic details	Frequency	Percentage (%)
Age (Mean±SD)	55.77	14.65
Gender		
Female	13	20.31
Male	51	79.69
Swab (RT-PCR)		
Positive	44	68.75
Negative	20	31.25
Co-morbid conditions		
Diabetes mellitus	22	34.37
Hypertension	24	37.50
Ischaemic heart disease	6	9.37
Bronchial asthma	8	12.50
COPD	10	15.62
On immunosuppressive drugs	5	7.81
Cancer	4	6.25
WHO severity of disease		
Non severe	23	35.93
Severe	28	43.75
Critical	13	20.32

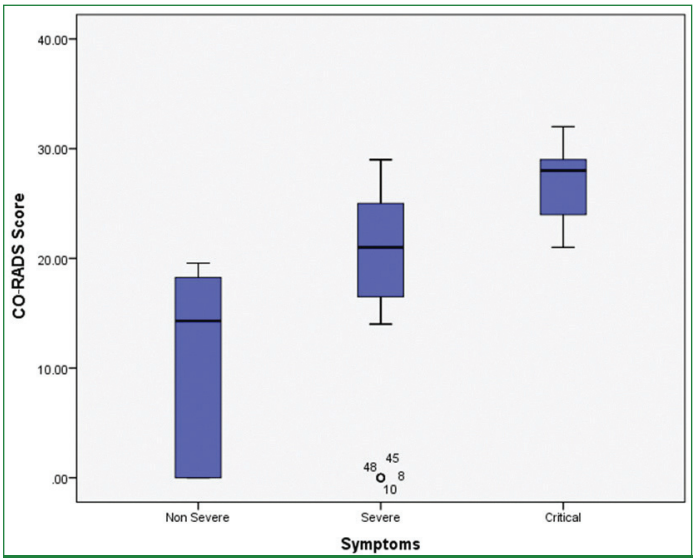
[Table/Fig-1]: Demographic details of the present sample.
SD: Standard deviation

Laboratory parameters	Median	Inter quartile range
C-Reactive protein (mg/L)	33.65	15 to 76.40
D-Dimer (ng/mL)	483.10	229.85 to 1208.50
Haemoglobin (g/dL)	12.35	11.20 to 13.20
Interleukin-6 (pg/mL)	6.50	2.30 to 15.55
Lactate dehydrogenase (U/L)	610.50	348.15 to 761.50
Procalcitonin (ng/mL)	1.27	0.03 to 4.50
Serum ferritin (ng/mL)	398	225.00 to 663.00
Total leukocyte count (WBC's/µL)	8900	6600 to 12460.50

[Table/Fig-2]: Distribution based on the laboratory parameters.

Among non severe cases, the median CO-RADS CT score was 14.30 (IQR=0 to 18.50); among severe cases, the median score was 21.48 (IQR=16.37 to 24.94), and among critical cases, the median score was 27.80 (IQR=24.44 to 29.32) [Table/Fig-3]. There was a significant difference between the median scores based on the severity of the disease (p<0.001). The mean CO-RADS score among alive critical cases was 24.18±9.15, and dead critical cases were 29.14±1.26. This difference was statistically significant. However, due to fewer deaths among non severe and severe cases, the average values of CO-RADS score were not possible [Table/Fig-4]. The authors found significant high positive correlation of CT score with LDH (r=0.754; p-value <0.001), moderate positive correlation with IL-6 (r=0.503; p-value <0.001), low positive correlation with CRP (r=0.477; p-value <0.001) and PCT (r=0.461; p-value <0.001).

The correlation between the CT score with serum ferritin (r=0.284; p-value=0.023), total leukocyte count (r=0.260; p-value=0.038) and D-dimer (r=0.242; p-value 0.050) was negligible [Table/Fig-5].



[Table/Fig-3]: Distribution of CO-RADS CT score based on the severity of the disease.

Severity of the disease	CO-RADS score				p-value
	Alive		Death		
	Mean	SD	Mean	SD	
Non severe	10.30	8.61	-	-	-
Severe	18.71	8.80	21.60	-	-
Critical	24.18	9.15	29.14	1.26	<0.001

[Table/Fig-4]: Distribution of the cases based on severity of disease and mortality.

Markers	Correlation with CO-RADS CT score	
	r	p-value
Lactate dehydrogenase (U/L)	0.754	<0.001
C-Reactive protein (mg/L)	0.477	<0.001
D-Dimer (ng/mL)	0.242	0.05
Interleukin-6 (pg/mL)	0.503	<0.001
Procalcitonin (ng/mL)	0.461	<0.001
Serum ferritin (ng/mL)	0.284	0.023
Total leukocyte count (WBC's/µL)	0.260	0.038

[Table/Fig-5]: Correlation of various inflammatory markers with CO-RADS CT score.
r: Pearson's correlation coefficient

DISCUSSION

The RT-PCR is a specific test, but its high turnaround time delays the specific management in severe and critical patients of COVID-19 infection. In addition, chest CT scans are not cost effective in low-resource settings to diagnose COVID-19 disease [3,4]. So, the authors aimed to correlate the CO-RADS score with various inflammatory markers, which will assist the clinician in deciding over the early specific management. The authors found that LDH had a significantly high positive correlation with CT score, and D-dimer had little correlation.

In the present study, the authors found an increasing trend of CO-RADS score with the severity of the disease (p<0.001). Francone M et al., reported the CT scores were significantly higher in the critical category (20.3±3) than compared with the mild category (8.7±4) [23]. Further, the CT scores of the severe category (17.4±3.1) were significantly higher than the mild category. But there was no significant difference among the critical and severe types in their study. But, when the authors compared the mild cases with severe and critical cases (combined), there was a significant difference in the CORAD scores. A study conducted by Sun D et al., reported the area under the curve for total lesion CT score for predicting the severity of COVID-19 infection was 93.8 (95% CI=86.8 to 100; p-value <0.001) [24]. The best cut-off they determined had sensitivity and specificity of 91.3 and 91.8%, respectively. Other quantitative CT parameters like GGO score, consolidation score, GGO/ total lesion score, and consolidation/ total lesion score has the area under the curve of 90.7 (82.6-98.9), 87.0 (76.9-97.2), 68.7 (56.5 81.0) and 71.5 (59.4-83.6), respectively to predict the prognosis of the disease. All these scores were less superior to the total CT score in prediction. Feng Z et al., reported the median CT scores among the stable COVID-19 patients was 6 (4-9), and among progressive cases, it was 10 (7-15), and this difference was significant (p<0.001) [25]. Upon logistic regression analysis of various factors, they reported CT severity score as one of the crucial factors predicting the severity and mortality among their sample. After adjusting for the confounding factors, the CT severity score reported an odds ratio of 1.32 (1.14-1.54) on univariate analysis and 1.19 (1.01-1.41). With this, the authors can opine that the CT scores are good predictors for assessing the severity of the disease.

The [Table/Fig-6] compares the present study with other different studies [25-29]. The CO-RADS score of critical patients who died was significantly higher when compared to those who were alive on follow-up. Francone M et al., analysed their data of COVID-19 patients using Kaplan Meier survival analysis and found that CT score was an independent predictor of death (HR=3.74; 95% CI=1.10 to 12.77; p-value=0.0348) [23]. Further, their study also reported that a CT score more than or equal to 18 was highly predictive of patient mortality in short-term follow-up. Eighteen similar findings were also reported by Feng Z et al., in their study [25]. Salaffi F et al., applied receiver operating characteristic analysis to CT score of their cases using death as the outcome and reported that the area under the curve was 0.843 (95% CI=0.778-0.895; p-value <0.001), indicating CT score to be an excellent test to predict mortality [30]. The mean CT score of the survivor group was 7.5 and among the deceased group were 14.5 in a study conducted by Abbasi B et al., [31]. Similar results were reported by and Sun D et al., Hu Y et al., [24,32].

Study	Main inference
Present study	LDH and IL-6 are major markers with positive correlation with CO-RADS score
Garachh MN et al., [26] (Compared markers in mild and severe group of COVID-19 infection)	The average levels of various inflammatory markers like LDH, D-dimer, CRP, PCT, TLC, Serum ferritin and IL-6 were significantly higher among severe group when compared to mild group
Zhang J et al., [27]	LDH, CRP and serum ferritin correlation was the best with CO-RADS score
Feng Z et al., [25]	CT score correlated significantly with LDH, D-dimer and CRP levels
Tan C et al., [28]	CRP levels were having better correlation with CT score
Chen LD et al., [29]	IL-6 was only independent explanatory variable for CT severity score

[Table/Fig-6]: Comparison of present study findings with various similar studies [25-29].

With the catastrophic increase in the newly diagnosed and severe cases, the management of the extreme cases gets affected. It is vital to triage these patients and accordingly treat them in priority. Timely identification of high-risk cases ending up in multi-organ failure and risk stratification with more individualised plans will be helpful. But, in low resource settings and cost-related issues, we will need a marker almost as specific as CO-RADS. The LDH seems to be a promising marker in this regard since it correlates well with the CO-RADS score. The LDH is one of the crucial enzymes in anaerobic metabolism. It is a marker of various tissue injuries, known for its ubiquitous course.

Tissue damage triggers the release of LDH in the bloodstream. Depending on the type of injury, it is elevated up to seven days in the blood. Some of the most common causes where the authors find raised LDH are acute myocardial infarction, pulmonary embolism, hepatitis, acute renal failure, and anaemia [32]. Evidence also suggests increased serum LDH levels among patients with severe

COVID-19 infection [26]. Raised LDH on admission in patients with COVID-19 infection has been consistent with the development of ARDS and thus associated with the criticality of the disease [26]. Cell damage and inflammation are central in the pathological basis of pulmonary tissue damage. The SARS-CoV-2, the aetiological agent for COVID-19, is an Ribonucleic Acid (RNA) virus affecting the immune system. Higher LDH levels have been associated with the COVID-19 mRNA clearance ratio. This positive sense RNA is postulated to activate inflammasomes. These triggers induce cellular pyroptosis and aggressive symptoms. This could be one of the explanations for the association of raised LDH in COVID-19 patients with ARDS [26].

Limitation(s)

The present study had some limitations. It was a retrospective study with small sample size. Serial changes in CT score with changes in the inflammatory markers followed-up prospectively would have been interesting evidence. However, the present study was unique in correlating all the inflammatory markers with CT scores and finding the best out of it in providing additional guidance for planning the management of the patients. The study's strength was the adequate power (95%) to generalise it to the study population.

CONCLUSION(S)

The CO-RADS CT score showed an increasing trend with the severity of COVID-19 disease in the present study. The CO-RADS CT score was significantly higher among the critical deceased patients when compared to the survivors. The CO-RADS score showed a high positive correlation with LDH values of the present study. LDH seems to be a promising marker and has to be further evaluated in assessing early COVID infection with a multi-centric and more extensive sample size approach.

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