Original Research Article

Application of simple assessment and grading system (CT-RAGS) to predicting clinical outcome of COVID-19

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Abstract

Background: During the ongoing pandemic of corona virus disease 2019 (COVID-19), prompt diagnosis is crucial to achieve swift and optimal clinical decision making and judge the precaution level necessary on a mission to help prevent nosocomial infections in the hospital. Various evidences have documented that early diagnosis and intervention are associated with a better prognosis. The reference standard diagnostic method for COVID-19 is reverse-transcription polymerase chain reaction (RT-PCR) that directly quantifies viral load from a nasopharyngeal swab, sputum, or endotracheal lavage. However, the sensitivity of this method is unclear because false-negative results have been reported in patients with insufficient specimens or those in the initial stage of infection. The turnaround time is also long, ranging from a few hours to days. Hence the need for a Diagnostic Test with Quick turnaround, which has good Sensitivity and has acceptable Specificity, and is also able to quantify the Disease load, and therefore help in clinical decision making and prognostication. Initial studies had revealed that HRCT Chest ticks all the above boxes, and hence this Study was taken up at our Institution to assess the Utility of the initial CT scans, and to grade the pulmonary involvement using a marking system devised by us, and compare it with the Clinical and Biochemical parameters for reliability.

Aim of the study: The use of Computed Tomography of Chest, to identify, assess and quantify lung damage by COVID 19 infection, through an easy and uniform reporting system, early in the course of the hospital stay, helps in clinical decision making and prognostication.

Materials and methods: A large consecutive cohort of 704 patients who were RT-PCR positive at the initial visit was prospectively studied during 75 days of the current COVID19 pandemic. A non-contrast HRCT of the chest was performed within 48 hours of admission in all the patients along with a baseline blood test for biomarkers. A simplified report Suggestive/ Not Suggestive of COVID-19 was used by the entire Faculty uniformly, and in CT positive patients, a simple grading of one to four (by CT-RAGS) was applied to indicate the extent of lung damage. The cases were followed up to assess the effectiveness of the gradation system, particularly concerning the need for specialized care and oxygen administration.

Results: Among the 704 patients scanned, 281(39.9%) patients showed typical CT signs of COVID-19. 351 (49.8%) patients showed normal lung parenchyma and 72 (10.2%) patients showed findings of Non-COVID infections. GGOs were the only findings in 154 (54.8%) patients and GGO with consolidation was seen in 110 (39.1%) patients and predominant consolidation was noted in 8 (2.8%) patients. Applying CT-RAGS, Grade:1 disease was noted in 154 (54.8%) patients, Grade:2 in 92 (32.7%) patients, Grade:3 in 23 (8.1%) patients, Grade : 4 in 12 (4.2%) patients. Among the patients with Early disease of Grade I and II, only GGOs was the most common pattern, while patients with advanced (3 and 4) disease, the predominant CT pattern was GGO with consolidation. In all the Grade 4 patients Consolidation +/- GGO was the finding. 51 (18.1%) patients required High Flow Oxygen Therapy, while only 8 (2.8%) patients in early disease (Grade 1 and 2) required Oxygen administration at some stage. There were 16 deaths (5.6%) in the advanced disease while only one patient (0.3%) of early grade died, due to Non - COVID reasons (Myocardial Infarction).

Conclusion: HRCT of the chest for COVID-19 infection proves to be a useful clinical tool. Pandemic reporting requires the use of a simple Standardized Format and a simple and practical grading system (CT-RAGS), by all Radiologists in the Institution. Our proposed grading system (CT-RAGS) provides a quick, overall estimate of Lung damage which correlates well with other blood biomarkers for prognostication.

Key words

COVID-19 Pneumonia, Diagnosis, Computed Tomography, Grading system, Clinical prognosis.

Introduction

The Novel COVID- 19 pandemic is posing unprecedented challenges to medical professionals worldwide. The high contagiousness of the present Novel COVID infection which has spread from Wuhan, China, since December 2019 with a short incubation time and Contact/ Respiratory Droplets has resulted in epidemiological problems of epic proportions and has demanded isolation of individuals and communities a like [1]. The overwhelmed logistic capability of the health care system and the emergence of asymptomatic carriers of infection of late has contributed to delay in diagnosis of infection initially, and under detection, due to technical issues [2]. The detection of nucleic acid fragments by RT-PCR is the diagnostic gold standard worldwide; However resource limitations, sampling errors and low viral dose in early disease have hampered its exclusive reliability [3]. Plain Radiographs have limited use at presentation, mainly to rule out co-morbid causes of Respiratory illness and ARDS and for follow-up in ICUs. CT scan has emerged as a very practical tool for providing a quick assessment of lung damage in Swab positive patients, while RT-PCR negative but clinically suspected patients have also benefitted from an initial CT study, although routine use of chest CT for disease

screening was discouraged by current guidelines. But in the context of the pandemic with a daily increase in caseloads, the RT-PCR test results take longer while a CT study result is available in 5 minutes [4]. Hence, the role of an initial CT in symptomatic patients for clinical decision making on the need for quarantine/ admission and disease prognostication needs to be reassessed [5]. In this background, at our Institution in Chennai, State of Tamil Nadu, India, which has seen a large number of patients, the diagnostic challenges have evolved from detection and isolation of patients with positive travel history, and their primary contacts, to a screening of all secondary contacts. The clinical diagnosis at the triage level was followed by laboratory investigations for COVID-19 and the Nasopharyngeal swab for RT-PCR. In all swab positive patients, the clinical decision making to quarantine or admits a patient to a COVID Care Center or a Tertiary care hospital with or without oxygen therapy and additional medication, depending on detection and quantification of pulmonary involvement by Chest CT and prognostication using the CT grade and biomarker levels, at the initial visit [6]. At the Department of Radiology, the initial Imaging in all Symptomatic patients was done by a Digital Chest Radiograph in a dedicated OPD Room and Internal transmission to a Remote Reporting Station [7]. A quick reading of the Radiograph, mainly to rule out NON-COVID infections and ARDS due to known causes and associated co-morbidities, was communicated through a standardized Report. All clinically indicated patients then underwent a Nasopharyngeal Swab test subjected to RT-PCR, and the patients were isolated till result: in all RT-PCR patients, baseline blood tests were performed upon admission for estimation of biomarkers. Within 48 hours of admission or if urgently indicated, we performed a non-contrast HRCT of the chest at the earliest possible time [8]. The CT study was reported at a Remote Workstation, and a Standardized Report was issued. As recent studies have demonstrated unequivocally that Early Institution of proper Medication and O2Therapy helps reduce the Hospital Stay and also reduces the risk of Mortality, based on an overall estimate of pulmonary damage, we evolved a Radiological Assessment and Grading System (CT-RAGS), based on the 'CT 0- 4' grading system proposed which permitted an easy, reliable and fast estimation of lung damage, and the Grade was conveyed to a panel of experts for correlation with biomarker levels to assess the disease severity and for further decision making [9, 10].

Materials and methods

The approval of the Institutional Ethical Committee was obtained. The requirement to obtain the consent of the patient was waived due to the pandemic situation. This prospective study was performed during the period of March (04.03.20) - May (15.05.20) and a consecutive cohort of 704 COVID- 19 suspect cases (clinical triage followed by lab investigations and Nasopharyngeal swab) patients were subjected to High Resolution Computed Tomography of the chest with either 128 section scanner (GE USA) or 16 slice scanner (TOSHIBA JAPAN), dedicated for COVID - 19 studies at our Institution. All the studies were done without any contrast media, using 128 VK, 180 mAS standard Lung protocol, and post-study Reconstruction using Bone filter and edge enhancement was performed. The radiation dose was a mean of 13.1 mGy units. All National and Institutional guidelines for staff protection were followed. The images were transmitted by PACS to a remote workstation where either the first or second author with experience of 25 and 10 years in chest radiology respectively, studied all the cases and reported on them using a standardized format. The predominant signs of the COVID infection alone were found mentioned in the report, to avoid clutter and to ensure uniformity of reporting in the Department of Radiology. The Terms (GGO, Consolidation, Halo sign, Reverse Halo sign, Crazy pavement sign, and vascular sign) were all defined as per the glossary of Fleischner Society for Thoracic Imaging and the common lexicon proposed by the European Society of Radiology. We felt encouraged to

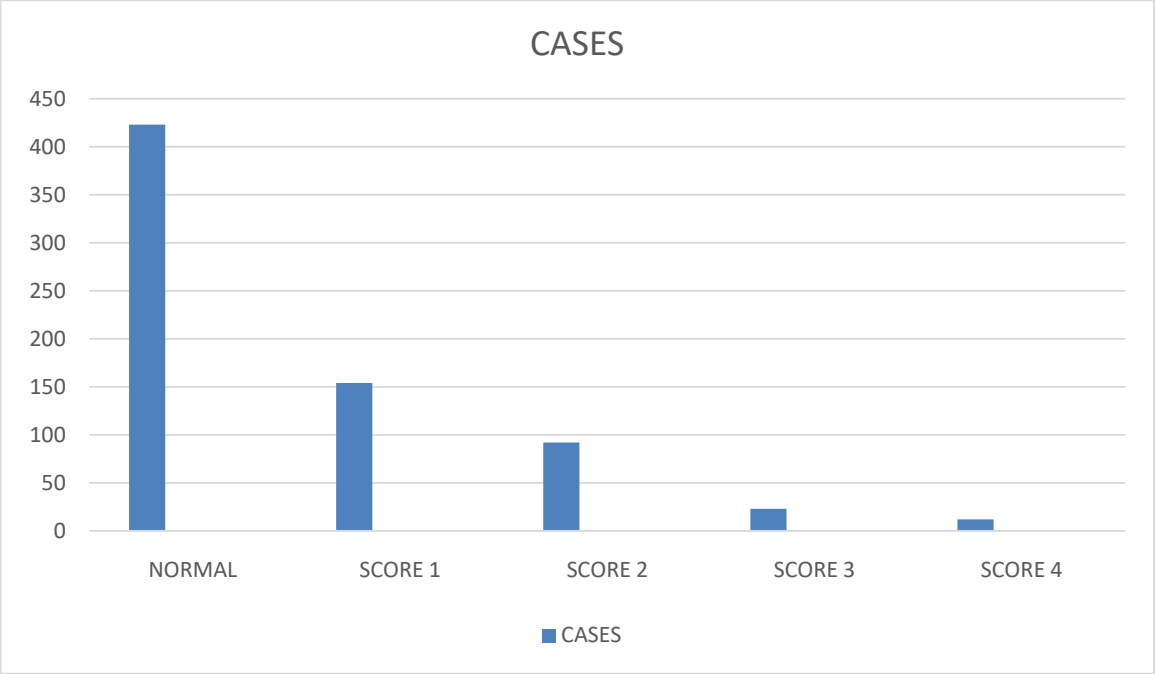
evolve a simplified reporting format after perusing the RAD report by RSNA. The final result of the study was reported as either Suggestive or Not- Suggestive of COVID infection for clinical purposes. Statistical analysis was done using the JMP statistical software program (JMP Pro, version 15.0.0; SAS) and R software (R version 3.6.2, The R Foundation for Statistical Computing). Quantitative variables were expressed as mean ± standard deviation (range) or median and inter quartile range based on the normality of data. Categorical variables were presented as the percentage of the total. The comparisons of quantitative variables were evaluated using a non-paired *t*-test or Mann-Whitney U test and categorical data using the Pearson χ^2 test. The comparisons of AUC and κ values were conducted using one-way repeated measures analysis of variance, according to the normal distribution assessed by the Shapiro-Wilk test, and post hoc family-wise error correction for multiple comparisons with paired *t*-test. All *P* values correspond to two-sided tests and the statistical significance level was set at Holm-Bonferroni-corrected $P < .05$.

Results

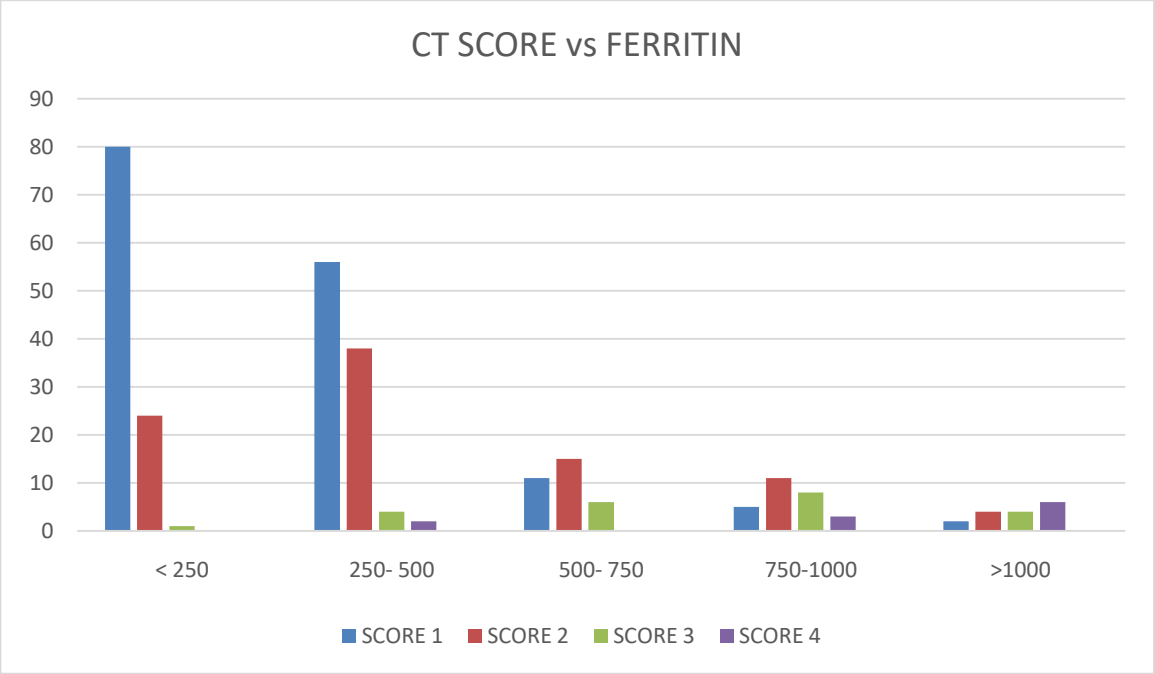
A total of704 patients were scanned (Mean Age: 43.75) were investigated and included 426 males (mean age: 42), 278 Females (mean age: 45.5). 684 patients who were RT-PCR positive at the initial visit and 15 patients who were awaiting results with subsequent positivity were subjected to CT and 281 (39.9%) patients showed one or other signs typical of COVID -19 pneumonia on CT. A total of 423 (60.1%) patients did not show any positive signs. Hence CT showed sensitivity 39.91% (36.28% - 43.64%) and specificity 96.74% (94.60% - 98.21%) with 95% CI.

The predominant sign of COVID-19 pneumonia was Ground Glass Opacity seen in 146 (51.9%) patients. There was GGO with consolidation (areas of obscured bronchovascular structures along with predominant GGOs) was seen in 118 (41.9%) patients. A Predominant Consolidation was noted with or without air bronchograms in 8 (2.8%) patients, with focal involvement of subpleural parenchyma. This could explain the transient pleural effusion reported in a few case studies by others. The CT signs were also correlated in relation to the day of presentation, defined as: 1-7 days - Rapid progression 216 patients (76.9%) ; 8-14 days– Advanced stage 63 patients (22.4%) ; > 14 days – Resolving stage 2 patients (0.7%). The Reverse Halo sign (Central GGO surrounded by consolidation) was seen in 28 (9.9%) patients during the Rapid Progression phase. The halo sign (central high-density consolidation with surrounding GGO) was seen in 4 (1.4%) patients during the advanced stage and the Crazy Pavement sign (GGOs with accentuated interlobular septa) was observed in 9 (3.2%) patients during the Advanced and Resolving stages. Also, the vascular sign (Thickened or prominent intralesional vessel) was seen in advanced stages 31 (11%) patients. No pulmonary cavity or pneumatoceles were seen in any of the cases. No significant pleural effusion was noted in any of our cases. The predominant distribution was commonly noted in the posterior segment of the upper lobes and superior/ posterior and lateral basal segments of the lower lobes. Most of the cases were bilateral (248 cases - 88%) and unilateral involvement was noted in 33(12%) cases, usually in the rapid progressive stage and involving the lower zone of the Right lung. A single area of GGO was noted in 21 (7.4%) cases and commonly involved the lower zone of the Right lung. 423 of RT-PCR cases had no CT signs and were discharged after regular 3 drugs medical therapy as per institutional guidelines and after two consecutive negative RT-PCR tests. 35 (12.4%) patients who were reported as per our CT-RAGS as GRADE 3 or 4 had their oxygen saturation monitored continuously and High Flow Oxygen administered in all 35 (12.4%). Patients with Grade 2 and above 127 (45%) cases also received additional anti-inflammatory medications. The Mean Admission duration was 14 days and patients were discharged after two negative swab results. There were 23 (3.3%) deaths (**Graph – 1 to 8**).

Graph - 1: CT scores among cases and controls.



Graph – 2: CT score vs serum ferritin level.

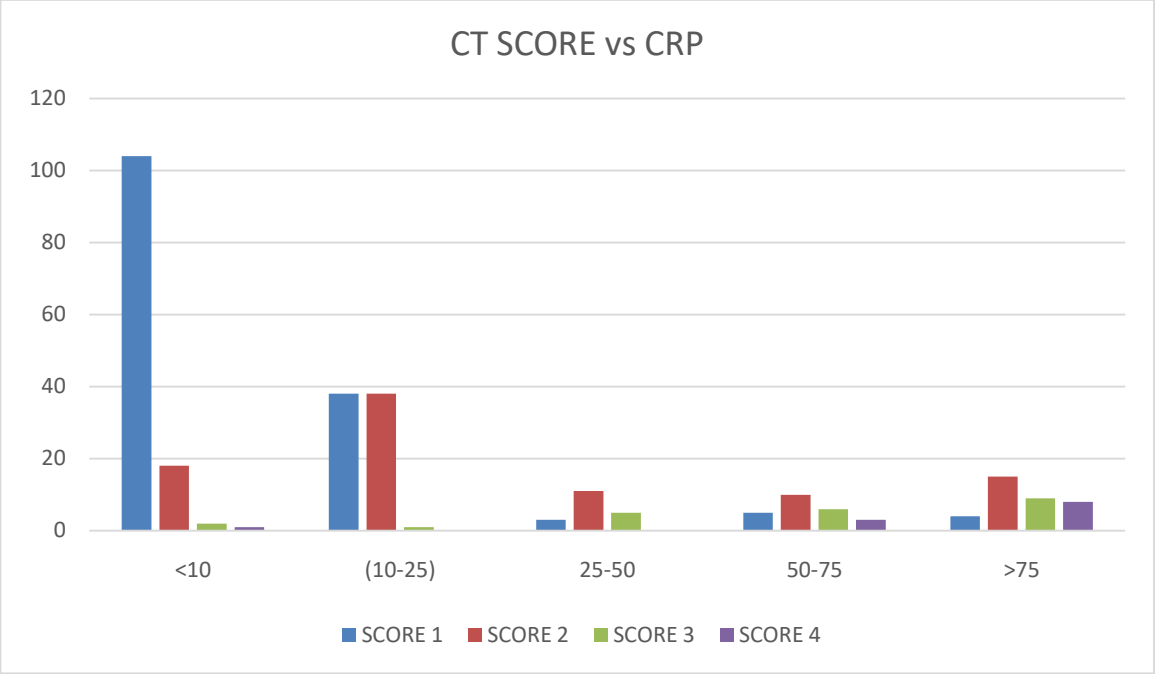


Discussion

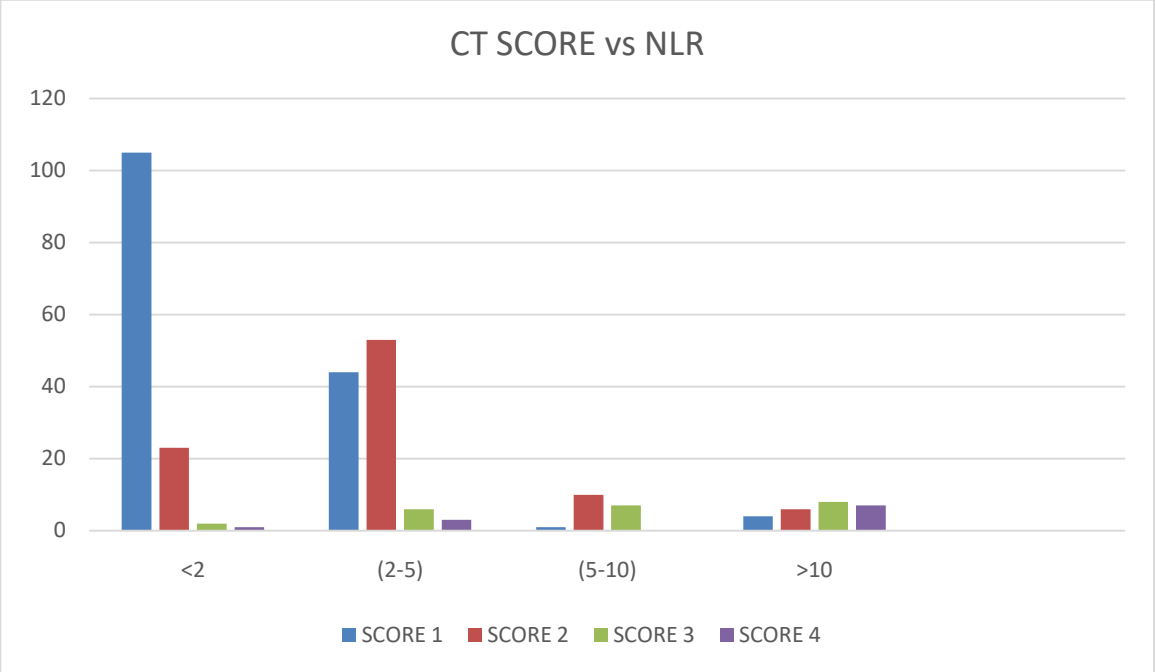
Early detection of COVID-19 Infection in clinically suspected patients with isolation and appropriate medical treatment improves early recovery and reduces the risk of morbidity and mortality [11]. As patients can be a source of transmission early in the prodromal phase itself, early diagnosis is crucial but as the definitive diagnosis of COVID-19 Pneumonia requires detection of the RNA in the swab or secretions, chest CT was used only in RT-PCR positive patients or in patients under isolation awaiting RT-PCR results [12]. The early chest CT changes are variable and mild, but it has been observed that when the disease involves one or two segments or lobes the symptoms of dyspnea

are absent or mild. But as the disease progresses the Ground Glass opacities change to Consolidation with an increase in the area of involvement of the segment/ lobe (melted sugar appearance) [13]. The lung alveolar epithelium is destroyed progressively and vascular permeability is increased during the Acute phase (0-7 days). In this set of patients, the role of CT is to evaluate the lung damage and quantify it to predict whether these patients can be identified early from the extent of lung damage [14].

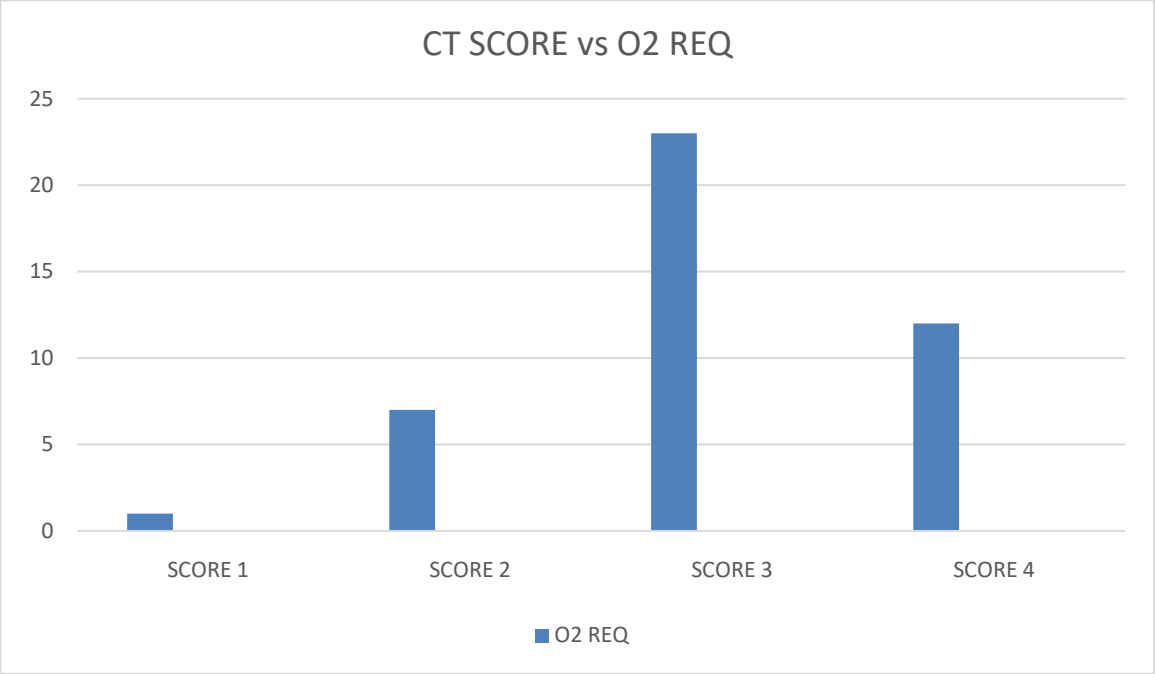
Graph – 3: CT score vs CRP level.



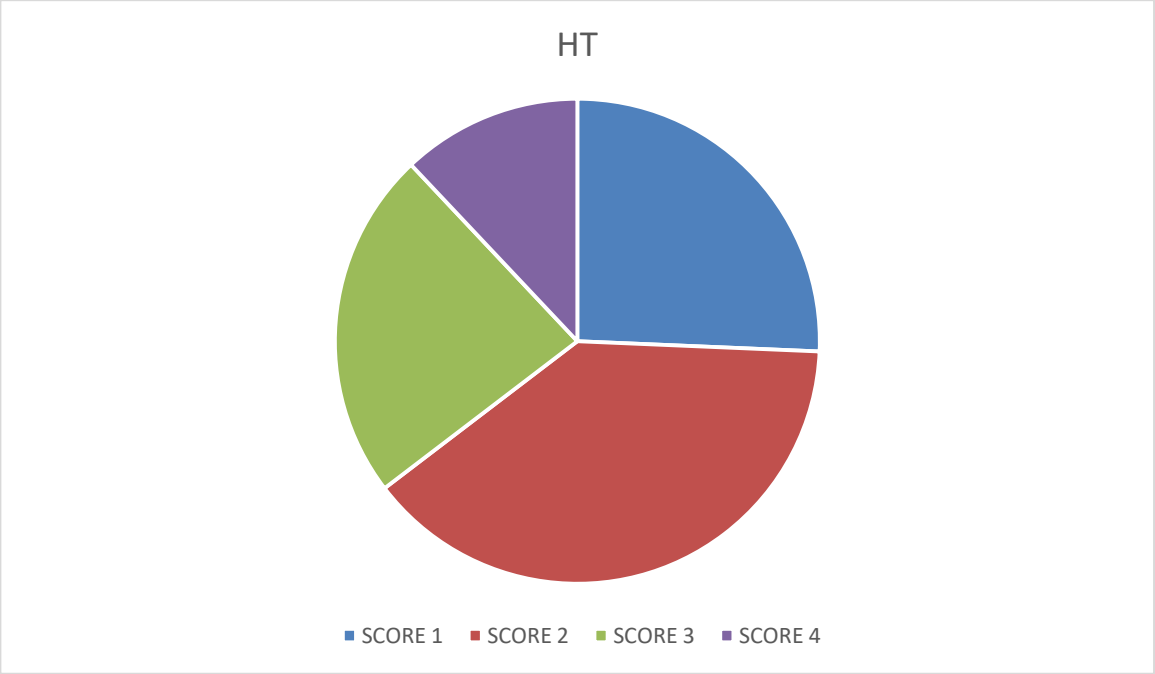
Graph – 4: CT score vs NLR.



Graph – 5: CT score 02 REQ.



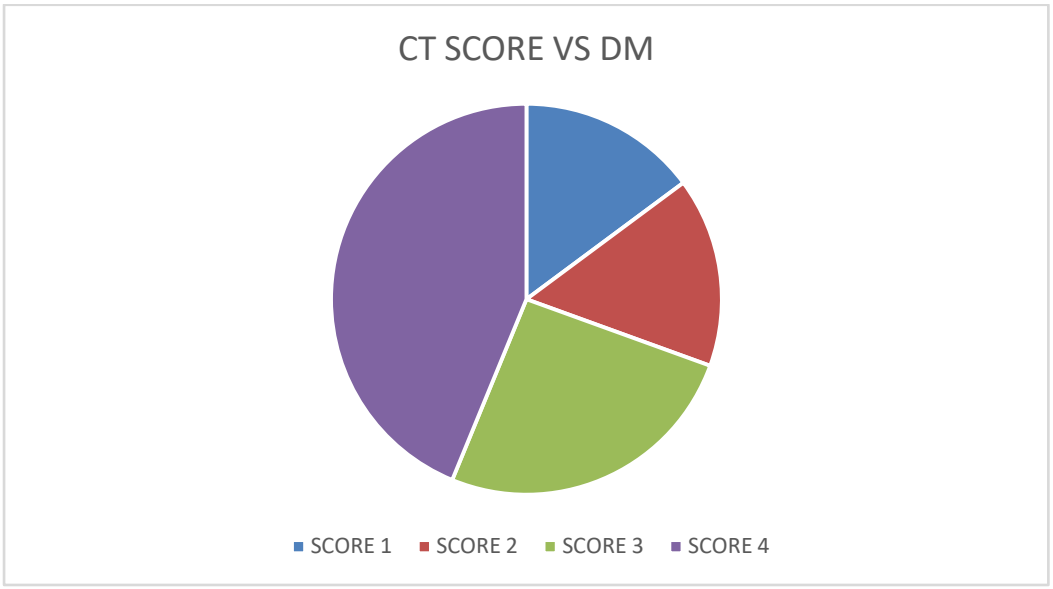
Graph – 6: CT score vs HT.



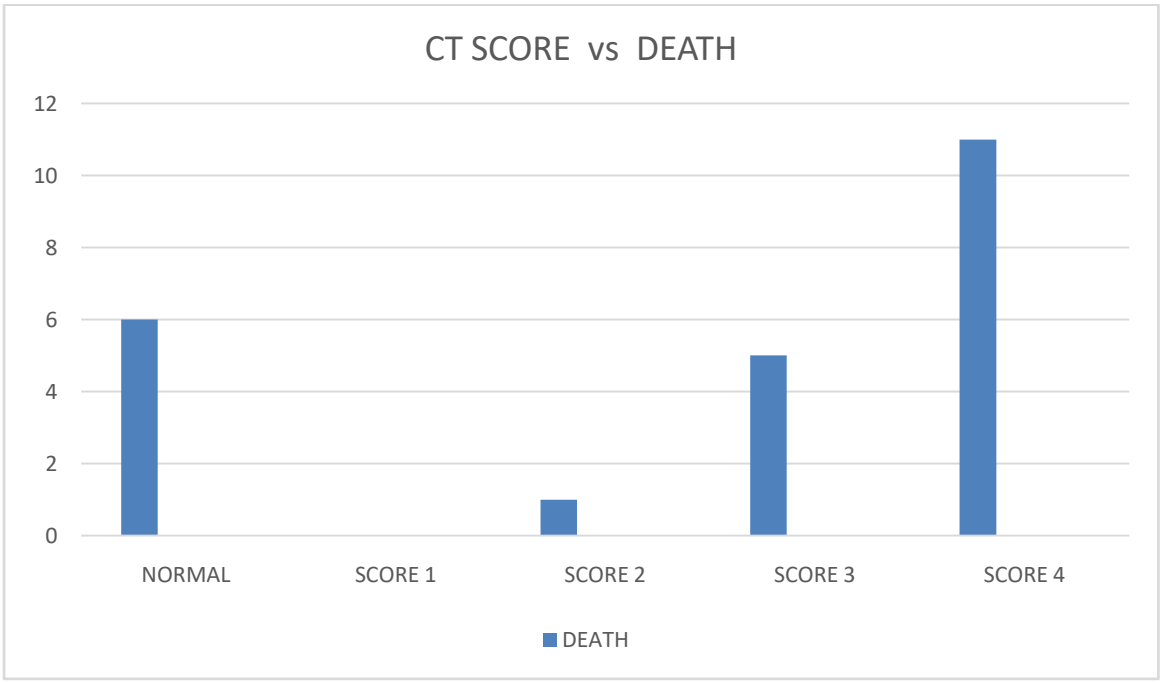
Thus the initial CT serves not only to detect CT signs typical of COVID infection to help in the diagnosis of COVID-19 Pneumonia especially where RT-PCR is inconclusive or awaited but also to reliably identify the subset of patients who may need institutional isolation and ICU care, to preclude a cytokine storm thus reducing mortality and morbidity. The innate immunity is activated and Pro-inflammatory and unregulated immune responses result in the so-called cytokine storm with a further cascading of lung damage causing ARDS. At this point, the ventilation is seriously impaired and may require emergency and high volume continuous oxygen inhalation and even ECMO [15]. So a follow-up CT study done at such a peak of infection in the

Rapid Progression Phase (8-14 days) may show the full extent of lung damage, is justified except in the few patients in whom the lung damage is severe at the presentation itself possibly due to huge viral load as evidenced by bilateral and extensive multilobar GGO's detected by the initial CT study after which the inflammation is overcome in most of the cases with treatment and lung damage resolves slowly with or without fibrosis. Hence, our choice was an initial CT in all RT-PCR positive patients and a follow-up CT if necessary [16]. Also, the detection rate for initial CT was 39.91% (36.28%-43.64%) with 95% CI. The average time from initial symptom onset to RT- PCR test was 3.01 days +/- 3 SD. The average time from initial symptom onset to CT was 3.17 days +/- 3 SD. The average time between CT scan and the biomarker test was 2 +/- 1 day [17].

Graph – 7: CT score vs DM.



Graph – 8: CT score vs death.



There were isolated instances where chest CT was done before confirming RT-PCR positivity. These patients were admitted only to an acute respiratory unit and shifted to COVID wards only after swab positivity. More importantly in all patients, an initial chest x-ray taken as protocol revealed non- COVID causes of acute symptoms in some patients and helped to reduce demand for urgent chest CT [18]. All chest X-ray positive cases, reported with a simple qualitative scoring of mild /moderate /severe grade were subjected to CT study only if RT-PCR was positive or awaiting results but included only if subsequently positive. But we found the COVID-RADS gradation proposed by them for a mere diagnosis of COVID -19 infection alone to be complicated to train. Moreover, we wanted to develop a simple common template of gradation for both plain X-ray and CT study, which could in the future, be amenable to Artificial Intelligence enabled automated software assessment of the lung disease. We decided to develop and apply our grading system incorporating only the predominant CT signs associated with COVID-19 infection [19]. The feedback from the panel of physicians was to avoid words like 'Indeterminate and Normal' in the template as CT is used as an adjunct to the gold standard RT- PCR and 'Probably COVID' was avoided due to poor specificity of CT features. The request for an overall estimate of lung damage was met with a whole lung assessment using thick slab coronal images, which found favor with physicians due to the similarity with chest x-ray and could be useful for comparison with follow-up x-ray. The main thrust of an initial CT study was to identify the patients who require institutional critical care and avoid crowding by moving milder cases for admission elsewhere. The Moscow study done during the same period has revealed that such an approach was rewarding and follow up CT study proved only 3.5% of mild diseases progressed to Grade 3 or above and the Negative Predictive Value of 'CT 0- 4' system was 96.7% (95% CI: 95.6-99.6). Our experience too was similar and we were able to identify all Grade 4 cases (12-1.7%) who died subsequently and among those who needed oxygen supplementation only 13.2% were Grade 2 and the rest were Grade 3 and above, thus indicating tertiary care only for advanced grades. We also found that this correlated well with the blood biomarkers [20].

Conclusion

Our proposed Radiological Assessment and Grading System (CT-RAGS) which was applied to the results of the CT studies were found practical and easy by the Residents and Faculty of the Department of Radiology. The treating physicians on rotation from various medical specialties too found the quantification of lung damage by COVID infection using our grading system a quite useful clinical tool and correlated well with the other established biomarkers for disease severity. Implementation of routine reporting of radiographic severity scores for diseases such as COVID-19 pneumonia may meet skepticism in radiology. Adding tasks to growing workloads is seldom popular. However, Au-Yong and colleagues show that severity scoring may be practical, potentially adding only seconds to a subset of chest radiograph reports. In addition, some groups have explored the use of artificial intelligence to provide automated severity scoring or to assist radiologists in scoring, with a good correlation to human scoring and equivalent prognostic power.

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