Assessing the Impact of Inflammatory Markers and CT Severity Score on Disease Severity of COVID-19 Patients Admitted to ICU at a Tertiary Hospital

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Abstract

Background: In December 2019, SARS-COV-2 infection emerged in Wuhan, China causing COVID-19 and subsequently spread throughout the globe. A great uncertainty is associated with the disease progression, as the risk of severe COVID-19 is not uniform among all the patients. Systemic inflammation has been reported as a predictor for COVID-19 outcomes. Elevated levels of inflammatory markers are shown to be associated with endothelial dysfunction, cytokine storm and coagulopathy in COVID-19. There is a growing body of evidence, that these findings exert influence in the causation of mortality in patients with severe Covid-19. The present study is carried out with an aim to evaluate the clinical outcomes of patients by interrelating their clinical severity with inflammatory markers and CT (Computed tomography) severity score (CTSS).

Objectives: The aim of the study is to correlate COVID-19 severity with inflammatory markers and CT severity score. We also aim to determine the optimal cut-off values for inflammatory markers and CT severity scores in order to establish their interrelationship to the disease severity.

Materials and Methods: It is a hospital-based retrospective observational study. The study was conducted over a period of four months (July 2020 to October 2020) based on data obtained from the records of patients, admitted with a laboratory confirmed SARS-COV-2 infection. The current study included a total of 84 patients, admitted to ICU with the severe COVID-19. Study tools included serum CRP, serum ferritin, D-dimer, neutrophil-to-lymphocyte ratio (NLR), interleukin-6 (IL-6) and 25-point CT severity score obtained from HRCT (high resolution computerized tomography) chest.

Results: Out of 84 patients recruited, 54 patients were survivors and 30 patients were non-survivors (deceased). 78% of the study population was male and 22% was female. For survivors, average CTSS was 12.43 ± 5.7 and whereas average CTSS for non-survivors was 18.87 ± 4.68(p<0001). Average D-dimer was 2.5 ± 1.43 in the survivor group and 3.39 ± 0.95 for non-survivors (p=0.004). Correlation coefficient of CTSS with FiO2 is 0.685 (p<0.0001). The optimal cut-off value for predicting mortality for D-dimer is >2.4 (p<0.0012) and for CTSS is >15 (p<0.0001).

Conclusion: The disease severity was significantly correlated with CTSS and D-dimer. Severe COVID-19 was also associated with a high NLR (neutrophil to lymphocyte ratio) and moderately elevated inflammatory markers (CRP, Ferritin, IL-6). CTSS >15 and D-dimer >2.4 correlate strongly with mortality. CTSS has the greatest diagnostic accuracy for stratifying the disease severity and predicting the mortality among the markers/ characteristics compared.

The present study is based on data and subsequently spread throughout the globe. A great uncertainty is associated with the disease progression as the risk of severe COVID-19 is not uniform among all the patients. COVID-19 disease affects different people in dissimilar ways. Some people might not even notice any significant clinical symptoms prior to their clinical deterioration but caught by HRCT in early stage. Therefore, HRCT is found to be a valuable tool in identifying patients with COVID-19 infections, when clinical symptoms are nonspecific or sparse. Early diagnosis is crucial to optimise the treatment and to escalate their care to ICU. Current studies advocate that patients with severe COVID-19 are found to have high levels of inflammatory markers when compared to mild or moderate patients. Elevated levels of inflammatory markers are shown to be associated with endothelial dysfunction, cytokine storm syndrome (CSS) and coagulopathy in COVID-19 disease. A cytokine storm is an overreaction of the body’s immune system. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome progressing to acute lung injury, (ALI), and acute respiratory distress syndrome, (ARDS). The present study is carried out to evaluate the clinical outcomes of patients by interrelating their clinical severity with the raised inflammatory markers and CT severity score.

Material and Methods

The present study is based on data

Introduction

In December 2019, SARS-COV-2 infection emerged in Wuhan, China causing COVID-19 disease...
The study was conducted over period of four months (July 2020 to October 2020). In the present study, a total of 84 severe COVID-19 patients were recruited, 54 patients were ICU survivors and 30 patients were non-survivors (deceased). The study tools included were, clinical characteristics like SpO2 (oxygen saturation at the time of admission), inflammatory markers such as serum CRP, Ferritin, D-dimer, NLR, IL-6, and radiological findings (CT severity score) retrieved from the medical records.

### Inclusion Criteria

All patients aged >18 years. Patients with a confirmed positive SARS-COV2 RT- PCR report.

### Exclusion criteria

Pregnancy or breastfeeding.

Mild/moderate patients, who did not need supplemental oxygen.

### Study conduct and design

It was a retrospective observational study. Patients were categorised as ICU survivors and non-survivors based on their final mortality outcomes. Of the total 84 patients recruited, 54 patients were ICU survivors and 30 patients were non-survivors (deceased). The study was approved by the institutional ethics committee, School of medical science and research, (SMSR) Greater Noida, Uttar Pradesh.

### Statistical Methods

All the data obtained was analysed statistically using Microsoft excel, Statistical Package for Social Sciences (SPSS) software ver. 21.0. Categorical variables were expressed in number and percentages (%). Continuous variables were presented as mean ± SD and median. Quantitative variables were compared using Mann Whitney test;516.5Median (25th-75th percentile) test;322Median (25th-75th percentile) test;681Median (25th-75th percentile) test;0.004* Mann Whitney test;767.5Median (25th-75th percentile) test;0.228 Mann Whitney test;681Median (25th-75th percentile) test;0.061. The total severity score (TSS) is classified by Fleischer Society Glossary, ground glass-opacity (GGO), crazy-paving pattern and consolidation at thin section. CT was evaluated bya semi-quantitative scoring system used to estimate the pulmonary area involved with COVID-19 related abnormalities. Bilateral lungs are divided into five lung zones according to the anatomical structure of lung: left upper lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe. Each lung zone is assigned a score which was based on the following criteria: score 0, 0% involvement; score 1, less than 5% involvement; score 2, 5% to less than 25 % involvement; score 3, 25 % to less than 50 % involvement; score 4, 50 % to less than 75 % involvement; and score 5, 75 % or greater involvement.

### Results

Table 2 shows that CTSS and D-dimers are found to be positively associated with the disease severity.

Table 3 shows that FiO2 at the time of admission related significantly only with CTSS (p <0.001). The total duration of oxygen supplementation is related significantly to D-dimer levels (p= 0.061).

Figure 2.1 to 2.5 depicts the strength
of correlation between inflammatory markers and CTSS with FiO2.

Figure 2.6 to 2.10 depicts the strength of correlation between inflammatory markers and CTSS with the days of supplemental oxygen requirement.

In our ROC analysis to find the cut-off values, sensitivity and specificity of inflammatory markers and CTSS for predicting mortality we found that CTSS value of >15 had the strongest correlation with mortality with an AUC of 0.801 (95% CI, 0.700 - 0.880, p < 0.0001). CTSS has 83.33% sensitivity (95% CI) and 68.52% specificity (95% CI) for predicting mortality. The overall diagnostic accuracy of CTSS was 73.81%.

Among the inflammatory markers, D-dimer with a cut-off of >2.4 had the best diagnostic accuracy of 59.52% for predicting mortality. The AUC for D-dimer was 0.681 (95% CI, 0.570 to 0.779, p = 0.0012) and sensitivity of 86.67% and specificity of 44.44%.
In the present study, 84 patients with severe Covid-19 were recruited. Patients were categorised as ICU survivors and non-survivors based on their mortality outcomes. Clinically, disease severity was categorised based on their oxygen requirements. All the patients on admission to ICU required oxygen therapy. All patients were treated with dexamethasone 6 mg IV once daily, Remdesivir (a broad-spectrum antiviral nucleotide prodrug), and appropriate antibiotics to cover the secondary bacterial infections. Additionally, heparin thromboprophylaxis was considered for most of the patients after excluding the relevant contraindications.

Of the 84 patients recruited, 54 (64%) patients were survivors and 30 (36%) patients were non-survivors. There were 42 male patients and 12 female patients in the survivor group and 24 male and 6 female in the non-survivor group. There was a strong gender bias in favour of male when compared for mortality (male: female, 4:1). The mean age for survivors was 57.6 years and 58.3 years for non survivors. Our study indicated that most of the non-survivors were middle aged men with underlying co-morbidities. Hypertension was most common co-morbidity (56%), HTN (48.83%). Their study results were found to be similar to our study. However, in studies conducted by Lian et al.2 and Xiong et al.8 there was a female preponderance noted in the mortality outcomes. This difference in association may be due to different national or study demographic.

Majority of the patients on admission were noted to have fever, dry cough and shortness of breath with chest discomfort. ICU non-survivors were found to be more hypoxic on admission (average SpO2<75.07) when compared to survivors (average SpO2>81.96).

However, total duration of oxygen requirement was found to be more in the survivor group, this is most likely indicative of subsequent clinical recovery. Yang, et al.7 stated that, severe Covid-19 patients were significantly more likely to have concomitant hypertension and cardiovascular co-morbidities. In our study out of 84 patients 78% of them had one or more underlying co-morbidities. Hypertension was most common co-morbidity (55%) followed by diabetes mellitus (52%). 32% of the patients were found to have other co-morbidities like chronic obstructive pulmonary disease, thyroid dysfunction, bronchial asthma, cardiovascular disease, etc. Bhandari et al.3 had noticed, most of their patients were men in the fifth and sixth decade of age group with underlying co-morbidities, diabetes (56%), HTN (48.83%). Their study results were found to be similar to our study. However, in studies conducted by Lian et al.2 and Xiong et al.8 there was a female preponderance noted in the mortality outcomes. This difference in association may be due to different national or study demographic.

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al. and Huang et al. have demonstrated similar findings in their study.

In the present study, non-survivors were noted to have a PaO2/FiO2 (P/F) ratio of 73 which is indicative of severe ARDS whereas survivors were found to have a PaO2/FiO2 (P/F) ratio of 112 which comes under moderate category of ARDS. Huang et al. also observed that most patients were extremely hypoxic on admission to ICU.

Our study demonstrated a high NLR value for both the survivors and non-survivors. NLR in survivors was 7.9 while in non-survivors it was 11.8. This indicates that a high NLR (neutrophil lymphocyte ratio) is significantly associated with the disease severity and thus may be used for prognostication. In our patients there was elevation in D-dimer (2.5 in survivors and 3.4 in non-survivors). D-dimer was also positively associated with the disease severity (p < 0.004). Patients with severe COVID-19, have been found to have raised D-dimer levels due to activation of coagulation cascade secondary to endothelial injury. Elevated D-dimer levels represent the underlying coagulopathy and the patients have an increased tendency to develop vascular complications. Tang, et al10 and Yang et al., also concluded that abnormal coagulation results, especially markedly elevated D-dimer are common in deaths with NCP (novel corona virus pneumonia).

The present study signified a positive association between disease severity/ mortality and CTSS. Studies conducted by Yang et al., Chen et al., Bhandari, et al. and Ding et al. have also noted similar findings regarding the accuracy of CT severity score in evaluating the disease severity and mortality.

Correlation co-efficient analysis of FiO2 (at admission) and CTSS we found a strong positive association between the two (p=0.0001). D-dimer also has a positive correlation with the increased total duration of O2 requirement with a p value (p=0.037). However, we did not find any correlation between other inflammatory markers (CRP, Ferritin and IL-6) and disease severity. This may be attributed to the early usage of steroids in ICU admitted patients. Additionally, disproportionate rise could be partly contributed by the underlying co-morbidities and subsequent immunocompromised states. At the same time, insignificant p values need to be interpreted with caution, as non-significance does not necessarily rule out the disease severity.

Receiver operating characteristic curve (ROC) analysis for CTSS, depicted, AUC 0.801 (95% CI 0.700 to 0.880), for predicting the mortality with a significant p value (p<0.0001). We also found that CTSS, cut-off was >15, and a sensitivity of 83.33% and 68.52% specificity for predicting the mortality. CTSS had a positive predictive value of 59.5%, and negative predictive value of 88.1% with a diagnostic accuracy of 73.81%. In a study conducted by Raoufi et al.12 to evaluate the correlation between chest computed tomography (CT) scan findings and outcomes of COVID-19 cases. They found a significant correlation between CT scan Severity Score (CTSS) (p <0.0001), and pulmonary artery CT diameter (p = 0.01) with mortality. They also found that the best cut off point of chest CTSS was 12 with 75.82% (95% CI: 56.07%-88.98%) sensitivity and 75.78% (95% CI: 70.88%-80.10%) specificity. These results are similar to that of our study. The lower cut-off can be attributed to the study design. This study included all symptomatic patients whereas we only included the ones with severe COVID-19.

No other inflammatory markers have demonstrated significant positive correlation either with CTSS or patient mortality outcomes. However, D-dimer has an AUC of 0.681 and cut-off value for mortality of D-dimer >2.4 (p=0.0012). Sensitivity was 86.67% and specificity 44.44%. D-dimer also had a PPV of 46.4%, NPV 85.7% and a diagnostic accuracy of 59.52%. Zhang et al.13 have also reported similar results. However, their cut-off value was >2.0 pg/ml.

In our study we conclude that, inflammatory markers (CRP, Ferritin, D-dimer and IL-6) were elevated in all patients (survivors and non-survivor) admitted to ICU with severe Covid-19. However, their elevation was not found to have a strong correlation to the disease severity. D-dimer showed modest correlation with mortality. CTSS showed a strong and significant correlation with the disease severity and mortality.

Limitations

1. It is a retrospective observational study.

2. Results obtained were restricted to patients admitted to a tertiary hospital, hence, small sample size is a limiting factor for generalizing the results. Multi centre trials with a large population may be needed to conclude the external validity.

Conclusion

In the present retrospective observational study, we found that the severe COVID-19 disease was more likely to occur in middle aged men with the underlying co-morbidities. Inflammatory markers cannot be used independently to predict disease severity and need to be interpreted in concordance with the underlying medical condition of the patients. D-dimer showed modest correlation with mortality. Whereas CTSS showed a strong and significant correlation with the disease severity and mortality.

References