Research Paper

Correlation between CT severity score and Clinical Biomarkers in predicting outcome in patients with Covid 19 Infection

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ABSTRACT
Background:
In COVID19, high levels of inflammatory markers have been related to endothelial dysfunction, cytokine storm, and coagulopathy. There is increasing data to suggest that these results impact the mortality rate in patients with severe Covid-19. The current study evaluates patients' clinical outcomes by correlating their clinical inflammatory indicators and CT Severity Score (CTSS).
Materials and Method: A retrospective, single-center, observational study was carried out on patients with COVID-19 infection who were admitted to the tertiary care KLES Dr Prabhakar Kore Hospital & MRC Belagavi.
Results: A total of 912 patients were included based on inclusion and exclusion criteria, with 80% being males and 20% being females. In the mortality group, they had a mean age of 62.5 ±12.4 and in the survival group, it was 51.1 ±16.2. The severity of COVID-19 infection was higher in patients with one or more co-morbidities, predominantly in those with T2DM. A significant positive correlation was found between serum ferritin, LDH, hsCRP, IL-6, and d-dimer and CT Severity Score (p <001) . A ROC analysis was performed, and the serum ferritin value was 331 ng/ml, with a sensitivity of 72.2% and a specificity of 56.3%; the LDH value was 375.5 U/L, with a sensitivity of 70.5% and a specificity of 63.3%. Hscrp-85.5 mg/ltr has a sensitivity of 72.2% and a specificity of 52%; IL-6 has a sensitivity of 60.2% and specificity of 60.8%; and D-dimer has a sensitivity of 70.5% and specificity of 65.2% at 643.5 ng/ml was obtained. These values can be used to screen patients and predict their prognosis.
Conclusions: In our study of 912 patients, we observed that severe COVID-19 infection was more common in elderly-aged males. The severity of the covid-19 disease was higher in patients with one or more co-morbidities, predominantly in those with T2DM. The severity of the disease, as reflected in the HRCT, positively correlated with an increase in the levels of biomarkers. Hence it is concluded that the CT Severity Score and clinical biomarker levels can be used as markers of prognosis in the patient with Covid -19 infection.
Keywords: Covid-19 infection, Mortality, Biomarkers, Prognosis.

I.   Introduction:

On January 1, 2019, the China Health Authority reported several pneumonia cases in Wuhan City, Hubei Province, central China. Instances have been tracked since December 8, 2019, and many of those afflicted worked at or lived near the nearby Hunan Seafood Wholesale Market[1]. Later then The World Health Organization (WHO) verified it as a novel coronavirus, previously known as 2019-nCoV, that was found in a patient's throat swab sample on January 7[2]. The Coronavirus Study Group has designated SARS-CoV-2 as the

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pathogen, and the World Health Organization has named the virus Coronavirus Disease-19 (COVID-19). Authorities in China reported 7736 confirmed cases and 12,167 suspected cases on January 30. Additionally, 82 confirmed cases were reported in 18 other countries[3]. The World Health Organization declared the SARS-CoV-2 pandemic a worldwide public health emergency the same day (PHEIC). In COVID-19, high levels of inflammatory markers have been related to endothelial dysfunction, cytokine storm, and coagulopathy[4]. There is rising data to suggest that these results impact the mortality rate in patients with severe Covid-19. The respiratory system involvement in covid 19 infection ranges from upper respiratory tract infections to bilateral lung involvement in the form of pneumonia and can progress to acute respiratory distress syndrome (ARDS). The most common findings of pneumonia due to covid 19 include peripheral, bilateral, ground glass opacities (GGOs) with or without consolidation or visible intralobular lines (crazy paving) or reverse halo sign (Atoll sign) or other findings of organising pneumonia[5]. The present study incorporates the demographics, levels of inflammatory markers and severity scores on HRCT scans in hospitalised patients with confirmed cases of covid 19 infection, an demonstrates their association which may aid in predicting the risk of progression and eventually management of such patients.

II. Materials and Methods:

This was a retrospective observational study done in a tertiary care hospital during the second wave of the Covid 19 infection. The data was collected by going through the case sheets of all the positive cases admitted for a period of 6 months. Only the adult patients of more than 18 years were included. Pregnant women, lactating mothers and children were excluded from the study. The data was collected from hospital medical records department with written permission. RT-PCR /CBNAAT/ RAT Positive COVID-19 patients with the fulfilment of the inclusion and exclusion criteria were included in the study. The COVID-19 blood biomarkers parameters were compared with the CT severity score. CT severity score was graded as: Mild < 8, Moderate – 8 - 15, and severe >15. The blood biomarkers that were analysed were serum Ferritin, serum HsCRP, IL-6, D-dimer levels and serum LDH levels.

STATISTICAL ANALYSIS: The data collected was entered in the MS Excel master sheet. Data was tabulated and analysed using the software OpenEpi version 3.01 and Statistical Package for Social Sciences (SPSS) version 22. Categorical data have been presented as numbers and percentages (%) and quantitative data in terms of mean and standard deviation. Categorical variables have been analysed using Pearson's chi-square test and Fisher exact tests (when the expected count of 20% of cells is less than 5). Quantitative variables have been analysed using the Student T test and ANOVA. Receiver Operator Curve (ROC) has been used for the calculation of sensitivity and specificity. A p-value of <0.05 has been considered statistically significant.

Sensitivity: Defined as ability of a test to identify correctly all those who have the disease i.e. true positive. Specificity: It is the ability of test to identify correctly those who do not have the disease i.e. true negative. Positive predictive value (PPV): The proportion of patients who test positive who actually have the disease. Negative predictive value (NPV): The proportion of patients who test negative who are actually free of the disease. Diagnostic accuracy: Is the ability of screening test to detect true positives and true negatives in the total population studied. p-value (Probability that the result is true) of < 0.05 was considered as statistically significant after assuming all the rules of statistical tests.

III. Results:

In the present study, the age of patients ranged from 20-99 years. i.e., the youngest was 20 years old and the oldest was 93 years old. Majority of the patients belonged to age group of 60 – 80 years. In the age group above 60 years, 107 patients were in the mortality group, and 245 were in the survival group. The mean age in the mortality group was 62.5 ± 12.4, and the survival group was 51.1 ±16.2. It has been observed that as age advances mortality rate increases and the survival rate decreases. In our study, patients presented with various symptoms of Covid-19, the most typical symptom were cough (65.6%), fever (64.8%), breathlessness (64.2%), and myalgia (16.9%). The most common comorbidities observed in our study were diabetes mellitus (33.8%), hypertension (30%), IHD (8.5%), chronic kidney disease (2%) and bronchial asthma (2.9%). In our study, it was observed that in the survival group, 61.5% of patients had a hospital stay of between 7 to 14 days. Similarly, in the mortality group, 76.7% of the patients died within 7 days of admission. The use of NIV in the survival group was 25.5% and in the mortality group 60.7 %, and the use of mechanical ventilators in the mortality group was 10.2% (Table 1).

HRCT scans of COVID-19 were correlated with each serum biomarker in the present study. It was observed that serum ferritin levels correlated significantly with the severity of covid 19 as assessed by the HRCT. In the mild severity the value was 187.2, moderate -484.4 and in severe group it was 998.6. The values increased with increase in CT Severity Score. The ROC curve showed area under the curve AUC-0.676 and P

value <0.001 with the cut of value of 331.0 has a sensitivity of 72.2% and a specificity of 56.3%. similarly, as the severity of covid 19 disease increased, the serum LDH levels also increased and it was observed to be significant. The ROC curve showed area under the curve AUC-0.707 and p value <0.001 with the cut of value of 375.5 has a sensitivity of 70.5% and a specificity of 63.3%. The mean values of hsCRP mild disease were 106.5, in moderate disease 129.2 and in severe disease it was 145. The ROC curve showed area under the curve AUC-0.641 and p value <0.001 with the cut of value of 85.5 has a sensitivity of 72.2% and a specificity of 52.0%. The mean levels of serum IL-6 levels were observed to be significant and the mean value in mild disease was 103.6, moderate disease was 157.7 and in severe disease it was 232.6. The ROC curve showed area under the curve AUC-0.673 and p value <0.001 with the cut of value of 76.3 has a sensitivity of 60.2% and a specificity of 60.8%. The mean values of d-dimer in mild disease was 654.4, in moderate disease 908.4 and in severe disease it was 1437.3. The values increased with increase in CT Severity Score. The ROC curve showed area under the curve AUC-0.728 and p value <0.001 with the cut of value of 643.5 has a sensitivity of 70.5% and a specificity of 65.2%.

IV. Discussion:

We analysed the records of 912 patients with COVID19 infection who were studied for biomarkers level and correlated with HRCT thorax findings to predict the prognosis. All the patients were proved to be having Covid19 infection either by RTPCR, CBNAAT or RAT method. In our study, the patient's age range was 20-99 years, with the median age of 53 years. The mean age in the mortality group is 62.5 ± 12.4 years, and in the survival group it was 51.1 ±16.2 years. Similar patterns of age distribution were observed in various other studies[6-8]. Male preponderance was observed in our current study as compared to female preponderance, with a male-to-female ratio of 4:1. A study by Saeed et al[7] also observed a higher proportion of males, (93.4%), than females, possibly due to the protective effect of estrogen in female patients. Most of the patients had dry cough (65.6%), fever (64.8%), breathlessness (64.2%), and myalgia (16.9%). Cough was closely associated with the virus' propagation by respiratory droplets. In addition to inflammatory factors, such as accumulated secretions, postnasal drip, and infections, the cough reflex facilitates the release of fluids and particles from the airways. Bhandari et al[9] observed that the most prevalent symptoms were fever, cough, and myalgia, with other symptoms such as headache and diarrhoea being seen in more than half of their patients with covid19 infection. In another study by Huang et al[10], the most prevalent symptoms observed were fever, cough, and dyspnoea. The most common comorbidities observed in our study population was Type II diabetes mellitus, hypertension, ischemic heart disease, chronic kidney disease, and bronchial asthma. In a study Bhandari et al[9], the most common comorbidities reported were Type II diabetes mellitus, hypertension, and ischemic heart disease. In a study by Wei-jie Guan et al[11] most of the patients had hypertension (16.9%), and diabetes (8.2%). Jain et al[12] observed that diabetes (42.85%) and hypertension (39.86%) to be the most common co-morbidities in these covid19 cases. Numerous studies[6,10-12] indicate that comorbidities such as hypertension, Type II diabetes, and coronary artery disease are related to have an increased risk of infection and a poor prognosis; the risk of infection also increases if there are several comorbidities. The comorbidities, particularly type II diabetes mellitus, and the severity of Covid -19 infection in these individuals may result from compromised immunity, overexpression of ACE, and glycation of ACE. The COVID-19 virus attaches to ACE II in pancreatic islet cells, causing damage that may lead to acute hypoglycemia[10]. It was also noted that type II diabetes mellitus worsens in these patients, whereas those with type I diabetes mellitus may present with diabetic ketoacidosis. As a result of hyperglycemia, alterations in coagulation abnormalities, endothelial dysfunction, and the release of inflammatory cytokines may occur, which may account for the increased severity and mortality[11].

We analysed the HRCT findings of all the patients and categorized them according to CT Severity Score - < 8 is mild, 9-15 is moderate, and >15 is severe. In our study, we observed that in mild pattern was observed in 27.0 %, moderate in 43.7 %, and severe in 29.1% of the cases. The mortality was high in patients having high severity scores. Ravindra et al[13] observed that patient's CT Severity scores were normal in 6.27%, mild in 30.9%, moderate in 38.5%, and severe in 24.2% of the cases. Of 2343 subjects, 569 had severe CT severity scores, with 205 (36.03%) dying and 364 (63.97%) surviving. The findings of this study were similar as in our study. Zhou et al[14] also observed that patients with COVID-19 who had total CT scores of 16 or more were more likely to have poor survival than those with 15 or less.

We analysed CT Severity Score with each biomarker any correlation, i.e., serum ferritin, LDH, IL-6 d-dimer, and hs-CRP levels. As the CT Severity Score increases, the mean values of serum ferritin also increase, which shows a positive correlation with the CT Severity Score. Thus, it was observed that CT Severity Score correlated with increasing serum Ferritin levels which showed a significant p value <0.001, the mean value of serum Ferritin in mild score was 187.2, with moderate score it was 484.4, and with severe score it was 998.6. We analysed the ROC curve of (AUC-0.676) and p value <0.001 with the cut-off value of 331.0, which has a sensitivity of 72.2% and a specificity of 56.3%. Similarly, we compared serum LDH with CT Severity Score; and this showed a positive correlation with a significant p value <0.001. The mean value for mild was 336.4,

moderate-391.6 and severe -536.6. As the CT Severity Score increase, the mean values of LDH also increased. AUC showed 0.70 and p value <0.001 with a cut-off value of 375.5. We compared hs-CRP with CT Severity Score, and this showed a positive co-relation with a significant p value of 0.01. The mean value for mild was -106.5, moderate -129.2, and severe -145. As the CT severity score increases, the mean values of hsCRP also increased. AUC shows 0.60 and p value <0.001 with a cut-off value of 85.5, has a sensitivity of 72.2%, and a specificity of 52.0.%. We correlated IL-6 and d-Dimer with CT Severity Score, and this showed a positive correlation with a significant p value of 0.01 and for d-Dimer <0.001. The mean value for IL6 for mild was -103.6, moderate-157.7, and severe -232.6, and in d-Dimer mild - 654.4, moderate-908.4 and severe -1437. As the CT severity score increased, the mean values also increased. AUC for IL6 shows 0.60, d-dimer 0.70, and p value <0.001for both IL6 and d-dimer, with a cut-off value of 76.3, has a sensitivity of 60.2%, and a specificity of 60.8%; and for the d-Dimer cut-off value of 643.4, has a sensitivity of 70.5%, and a specificity of 65.2%. Various other studies showed similar significant findings as in our study[12-14]. In the present study higher levels of the inflammatory markers was observed in the patients who died due to covid 19 infection but it was not statistically significant as compared to the survival group. All the inflammatory parameters had risen in mortality group patients as compared to the survival group. Almost more than 90% of the patients in the mortality group patients had CT severity score of either moderate or severe. Zhou et al[14] studied 134 COVID-19-infected patients. At various phases, the deceased group had significantly higher levels of leukocytes, neutrophils, hsCRP, prothrombin, D-dimer, serum ferritin, interleukin (IL)-2, and IL6 than the recovered group. In the deceased group, the overall CT score at the peak stage was substantially higher than in the recovered group (20 vs. 11 points). Jain et al[12] with a patient population of 735, demonstrated that only CRP, D-Dimer, and CT severity score levels may predict the outcome of death. Cut off for CRP was 45 mg/L (Sensitivity -80%, specificity – 56%), D-dimer was 1000µg/L (Sensitivity -80%, specificity – 90%). Abd El Megid et al[15] studied 305 COVID-19-infected patients and observed a significant positive correlation with CRP, ferritin, and d-dimer levels with the mortality in these patients, but none of the inflammatory marker could predict the mortality in these patients. Similarly, in our study the increasing values for inflammatory biomarkers could not predict the mortality in these patients. We believe it is important to study a large number of patients addressing confounding factors such as age, sex, symptoms, and comorbidities at the time of presentation, as there was little understanding of this new pandemic. During the first wave of the pandemic, cases were more severe and had a higher mortality rate. This could be due to awareness and knowledge of infection, CT abnormalities, treatment, and vaccination, all of which have impacted patient severity. Now, we may not have the same virulent strain; the strain may have mutated and become less virulent however, a large number of patients must be studied in order to address these challenges, thus we need to conduct research on a large sample size. Recently one study[16] has observed significant positive correlation between the neutrophil lymphocyte ratio and CT severity score, with increased ratio corresponding with higher Ct severity score. But in this study also there was no correlation of serum biomarkers with the mortality status of the covid 19 patients.

In conclusion, in our study it observed that severe COVID-19 infection was more common in elderly-aged males. The severity of the covid-19 disease was higher in patients with one or more co-morbidities predominantly in those with T2DM The severity of the disease as reflected on the HRCT score positively correlated with an increase in the levels of various biomarkers. Hence it can be concluded that the CT severity Score and biomarker levels can be used as markers of prognosis in the patient with covid -19 infection.

Limitations of the study: This was a retrospective, single-centre study, therefore the findings cannot be applied to the wider population. More cohort studies are required. Most patients in the recovered group were mild to moderate illness; the predictive value of selected risk factors may be overestimated. Therefore, well-matched groups in disease severity should be investigated to more accurately evaluate the risk factors related to the mortality of COVID-19 infection.

Table 1. Baseline characteristics

Clinical parameters	Outcome		p value
	Deaths 176 (%)	Survived 736 (%)	
Age Group 20- 40 years	7 (3.9)	188 (25.5%)	0.15
41 – 60 years	62 (35.2)	303 (41.2)	0.25
61 – 80 years	92 (52.3)	221 (30.0)	0.15
>81 years	15 (8.5)	24 (3.3)	0.56
Gender Male	116 (65.9)	615 (83.5)	0.19
Female	60 (34.1)	121 (16.5)	0.12
Symptoms Cough	146 (82.9)	656 (89.1)	0.50
Fever	145 (82.3)	679 (92.2)	0.58
Myalgia	135 (76.7)	638 (86.6)	0.45
Dyspnea	117 (66.4)	587 (79.7)	0.40

Comorbidities Diabetes Mellitus	87 (49.4)	221 (30.0)	0.10
Hypertension	56 (31.8)	218 (29.6)	0.46
IHD	24 (13.6)	54 (7.3)	0.25
CKD	6 (3.4)	12 (1.6)	0.20
Asthma	5 (2.8)	15 (2.0)	0.43
Length of Hospital stay < 7 days	135 (76.7)	256 (34.7)	0.01
7 – 14 days	37 (21)	453 (61.5)	0.08
>14 days	21 (2.3)	27 (3.6)	0.05
Use of mechanical ventilation	18 (2.1)	0	0.02
Use of NIV	96 (60.7)	188 (25.5)	0.01

Table 2. Comparison of Biomarkers with CT severity score

Biomarker		CT severity score			p value
		Mild	**Moderate**	**Severe**	
Ferritin	Min.	4.8	4.0	13.6	< 0.001
	Max.	1656	5374	10227	
	Mean	187.2	484.2	998.6	
LDH	Min.	27	4.9	5.07	<0.001
	Max.	1623	3650	2394	
	Mean	336.4	391.6	536.4	
hsCRP	Min.	0.4	1.4	0.6	<0.017
	Max.	772	2699	649	
	Mean	106.5	129.2	145.0	
IL-6	Min.	1.0	1.5	1.5	<0.011
	Max.	4754	3950	5000	
	Mean	103	157	232	
D dimer	Min.	7.9	67.0	6.6	<0.001
	Max.	5000	5937	7673	
	Mean	654.4	908.4	1437.3	

Fig. 1 ROC curve for the serum clinical biomarkers

Graph No.4: ROC curve for serum ferritin as predictor of outcome

Graph No.10: ROC curve for serum IL-6 as predictor of outcome.

Graph No.12: ROC curve for d-dimer as predictor of outcome.

Graph No.8: ROC curve for serum hsCRP as predictor of outcome

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