Correlation of Inflammatory Markers and CT Severity Scoring in Covid-19 Patients : An Observational Study

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ABSTRACT

Background : Inflammatory markers and CT are the important parameters that help to predict the progress of COVID-19. Correlation between these parameters and their relation to mortality would help in managing these patients.

Methods : A total of 95 patients admitted with Real Time Polymerase chain reaction confirmed COVID 19 was prospectively or retrospectively reviewed based on medical record data available in hospital during a period of 3 months from 15th Sept 2020 to 15th December 2020. Patient's basic details, Clinical findings, laboratory data and CT severity scores were recorded and analysed. Relationship between laboratory findings and CT severity scores was estimated.

Results : Age of the patient, pulse rate, respiratory rate, TLC, NL Ratio, CRP, LDH, Ferritin and D-Dimer were directly related with CT severity score and it was statistically significant (P<0.0001), which shows these values increase with increased CT severity score. Out of 42 patients who had CT severity score less than 10, only one patient died whereas 24 out of 35 patients who had CT severity score of more than 16 died (P<0.001) showing the direct relationship of CT severity score with mortality in COVID-19 patients. Inflammatory markers like CRP, LDH, Ferritin, D-DIMER, Neutrophil-Lymphocyte Ratio were Graded according to level of these markers and mortality in each grade was observed. Mortality increased with the increased level of inflammatory markers (P<0.001).

Conclusion : The inflammatory markers are directly correlated with the CT severity score in patients with COVID-19. Inflammatory markers and CT severity score are also directly related to the outcome in terms of mortality in COVID-19 patients.

Introduction :

Coronavirus Disease 2019 (COVID-19) caused by an infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused one of the largest global outbreaks in recent years, and posed a serious threat to the global public health. Considering the rapidly increasing cases of COVID-19 and disease severity, the World Health Organization (WHO) declared a global health emergency on January 30, 2020. Despite implementing worldwide combined efforts to prevent SARS-CoV-2 further transmission by quarantining the infected persons and their family members, social distancing, and schools closure, the spreading of infection could not be contained; therefore, on March 11, 2020, the WHO declared COVID-19 a pandemic. Mortality in patients who develop Acute Respiratory Distress Symptoms is high. The most common symptoms reported in COVID-19 patients are fever, cough and dyspnea. Severity of disease is classified based on clinical, laboratory and radiology characteristics. The incidence of severe COVID-19 has been reported to range from 15.7% to 26.1%[4-7]. The early identification of severe COVID-19 is of clinical importance as these patients have poor survival rates and mortality is approximately 20 times higher than that of non-severe patients.

Computed tomography (CT) is an important and effective method for the diagnosis and evaluation of the severity of COVID-19. Furthermore, ground-glass opacity (GGO) and consolidation are the main CT findings in patients with COVID-19 and are associated with the course and severity of the disease. GGO on CT is more likely to be presented in patients with severe COVID-19. In addition, some studies have reported that an increase in the extent of consolidations is more likely to be presented in the early and mid-term follow-up CT, and that consolidation lesions would serve as an alert for clinicians in the management of patients.

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Evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID- 19. Detecting these inflammatory markers early would alert the physician to take necessary actions and keeping the track of these markers will also help in knowing the progress of the disease as well as prognosis in the patient.

In this observational study, we correlated various Inflammatory markers, CT severity score with each other and also with the clinical outcome in terms of mortality in RTPCR confirmed COVID-19 cases. This would help the clinician to decide on the factors to be looked for to predict the outcome early and thus enabling to take early decisions in managing the cases accordingly.

Aim :

To establish correlation between biological markers and CT severity in RTPCR confirmed COVID 19 cases.

Materials and Methods :

Study Design : Retrospective & Prospective Observational Study

Study Setting : Tertiary Care Centre in Central India

Study Period : 3 Months

Sample Size :
Based on a previous study,
Proportion in group 1 = 0.842
Proportion in group 2 = 0.682
Estimated risk difference = 0.16
Power = 80%
Alpha error = 10%

Hence, sample size is 95 after adding 20% uncooperative / non responders based on neutrophil percentage reported in a previous study.

Methodology :

A total of 95 patients admitted with Real Time Polymerase chain reaction confirmed COVID 19 were prospectively or retrospectively reviewed based on medical record data available in hospital. Patient's basic details, Clinical findings, laboratory data and CT findings including ground glass opacities and CT severity scores were recorded and analysed. Patients were divided into mild and severe cases based on these findings. Relationship between laboratory findings and CT severity scores was estimated and a model was established based on this correlation.

Institutional Ethical Committee clearance was taken.

Statistical analysis :

Data are presented as Mean ± SD. Categorical data are expressed in frequency and percentage. Independent t-test was used to compare between survivors and Non-survivors. Chi2-test was used to compare categorical data. Multivariate analysis was performed to determine risk factors. Spearman correlation coefficient (rho) was used to correlate CT severity score with laboratory and clinical parameters. $p<0.05$ was taken as statistical significance.

Results :

A total of 95 patients were observed in this study, amongst which 66 patients survived and 29 patients died. These outcomes have been correlated with various clinical characteristics and laboratory findings and CT severity score.

Discussion :

In this study we have observed the relation between various clinical, Laboratory and CT findings in RTPCR confirmed COVID-19 cases. Our study showed that the Inflammatory markers like CRP, LDH, S Ferritin, D-dimer, neutrophil to lymphocyte

Table 1 : **Clinical characteristics of covid-19 patients in relation to outcome.**

parameter	Total N=95	Survivors N=66	Non Survivors N=29	p-value
Age in years	52.52 ± 17.92 (17-88)	47.95 ± 17.50	62.93 ± 14.09	0.0001,HS
Gender (Male/Female)	66/29	45/21	21/8	0.680,NS
Fever	67	52 (77.6)	15 (22.4)	0.008,HS
Cough	52	39 (75)	13 (25)	0.198,NS
Breathlessness	53	29 (54.7)	24 (45.3)	<0.001,HS
Altered sensorium	2	0	2 (100)	0.091,NS
Weakness	2	2 (100)	0	1.000,NS
Hypertension	33	18 (54.5)	15 (45.5)	0.021, S
Diabetes	24	16 (66.7)	8 (33.3)	0.730,NS
CVE	3	2 (66.7)	1 (33.3)	1.000,NS
IHD	7	4 (57.1)	3 (42.9)	0.462,NS
CKD	3	2 (66.7)	1 (33.3)	1.000,NS
Asthama	2	1 (50)	1 (50)	1.000,NS
Hypothyroidism	5	4 (80)	1 (20)	1.000,NS
Old PTB	3	3	0	0.551,NS

With mortality as outcome measure, various clinical characters were significantly related to the outcome. Mean age of the patients was 47.95 (17.5) years in survivors and 62.93 (14.09) years in the non survivors which was significant (p-0.0001). The other factors which were statistically significant were Fever (p-0.008) , Breathlessness (p<0.001) and hypertension (p-0.021). In terms of mortality Gender, Cough, CVE, IHD, Diabetes, CKD, Asthma, Hyperthyroidism and Old PTB were not statistically related to the outcome

Table 2 : **Clinical examination findings of COVID-19 patients in relation to outcome**

	Total N=95	Survivors N=66	Non Survivors N=29	p-value
Pulse rate	94.78 ± 14.54	89.48 ± 12.03	106.86 ± 12.53	<0.0001,HS
Respitatory rate	20.44 ± 6.78	16.93 ± 3.25	28.41 ± 5.94	<0.0001,HS
SPO2	86.33 ± 13.03	93.04 ± 6.47	71.06 ± 11.20	<0.0001,HS
SBP	120.94 ± 14.14	122.57 ± 11.13	117.24 ± 19.06	0.0907,NS
DBP	79.05 ± 7.86	80.0 ± 5.81	76.89 ± 11.05	0.0764,NS
Hb	12.38 ± 2.20	12.63 ± 2.18	11.8 ± 2.17	0.0887,NS
TLC	9831.58 ± 5628.79	8497.42 ± 3798.61	12867.93 ± 7689.21	0.0003,HS

Among the examination findings, the difference in mean pulse rate among survivors and non survivors was 17.38 which was highly significant (p<0.0001), Difference in mean Respiratory rate was 11.5 (<0.0001,HS), difference in mean SpO2 was 21.98 (<0.0001,HS) , and difference in mean TLC was 4370.51 (p-0.0003,HS). All these findings and values were directly related except SpO2 which was inversely related to the mortality.

Table 3 : **Relation of systemwise morbidities of COVID-19 patients with outcome.**

		Total N=95	Survivors N=66	Non Survivors N=29	p-value
Respiratoty syste,	Clear	32	31	1	<0.001,HS
	Crepitations	63	35	28	
CVS	Normal	95	66	29	-
	Abnormal	0	0	0	
Per abdomen	Normal	92	54	27	0.167,NS
	distented	3	12	2	
CNS	Normal	81	66	15	<0.001,HS
	Irritable	7	0	7	
	Drowsy	7	0	7	
Oxygen Requirement	No	34	34	0	<0.001,HS
	Yes	61	32	29	
NIV requirement	No	70	61	9	<0.001,HS
	Yes	25	5	20	
Need for MV	No	66	66	0	<0.001,HS
	Yes	29	0	29	
		N	%		
Outcome	Mortality	29	30.53		
	Recovery	66	69.47		

Patients who had Crepitations on auscultation had significantly higher mortality than the patients with clear lung fields (p<0.001,HS). All the patients who were irritable or drowsy died and this was statistically significant in comparison to conscious/ cooperative patients (p<0.001) suggesting the importance to look for these signs to predict outcome. Out of 61 patients who required oxygen therapy, 29 patients did not survive (p<0.001) and among 25 patients who required NIV, only 5 patients survived and 61 patients among 70 who did not required NIV survived (p<0.001). All the patients who needed mechanical ventilation died (29 patients) and 66 patients who did not need MV survived (p<0.001).

Table 4 : **Relation of Inflammatory markers and CT severity score with Outcome**

Parameter	Cut-off	Total N=95	Survivors N=66	Non Survivors N=29	p-value
CRP	<10	31	31	0	<0.001,HS
	10-50	22	17	5	
	51-100	20	12	8	
	>100	22	6	16	
LDH	<400	31	30	1	<0.001,HS
	400-800	44	30	14	
	801-1200	13	3	10	
	1201-1600	6	3	3	
	>1600	1	0	1	
Ferritin	<500	35	33	2	<0.001,HS
	500-1000	31	22	9	
	1001-1500	13	5	8	
	>1500	16	6	10	

D-DIMER	<500	43	39	4	<0.001,HS
	500-1000	16	13	3	
	1001-1500	11	8	3	
	1501-2000	8	4	4	
	>2000	17	2	15	
CT Severity Score	0	3	3	0	<0.001,HS
	1-5	24	24	0	
	6-10	15	14	1	
	11-15	18	14	4	
	16-20	24	9	15	
	21-25	11	2	9	
Neutrophil-Lymphocyte Ratio	<3.5	41	37	4	<0.001,HS
	3.5-4	26	20	6	
	4.1-4.5	13	6	7	
	4.51-5	8	2	6	
	>5	7	1	6	

Inflammatory markers like CRP, LDH, Ferritin, D-DIMER, Neutrophil-Lymphocyte Ratio were Graded according to level of these markers and mortality in each grade was observed. It is clearly seen that the mortality is directly related to the levels of inflammatory markers (p<0.001) ***(Table 4).*** Out of 42 patients who had CT severity score less than 10, only one patient died whereas 24 out of 35 patients who had CT severity score of more than 16 died (p<0.001) showing the direct relationship of CT severity score with mortality in COVID-19 patients.

Table 5 : **Multiple logistic Regression analysis to determine independent risk factors for predicting mortality in patients of covid-19.**

Parameter	Adjusted OR	95% Confidence Interval	p-value
Age in years	1.06	1.01 1.10	0.013,S
D-Dimer	4.33	1.02 19.26	0.045, S
CT severity score	4.44	1.01 20.39	0.038, S
NIV	10.37	2.18 49.12	0.003, HS

Table 6 : **Correlation of inflammatory markers and clinical findings with CT severity score in covid-19 patients.**

Markers	CT Severity Score	
	Correlation coefficient (rho)	p-value
Age in years	0.3746	0.0002, HS
Pulse Rate	0.6265	<0.0001, HS
Respiratory Rate	0.7954	<0.0001, HS
SPO2	-0.82478	<0.0001, HS
SBP	0.0918	0.3763, NS
DBP	0.0884	0.3943, NS
HB	-0.3030	0.0028, HS
TLC	0.5166	<0.0001, HS
NLR	0.7061	<0.0001, HS

CRP	0.8511	<0.0001, HS
LDH	0.7546	<0.0001, HS
Ferritin	0.7879	<0.0001, HS
D Dimer	0.7866	<0.0001, HS

Table 6 shows the correlation of inflammatory markers and other clinical findings with the CT severity score. SpO2 and Hb levels were negatively related (-0.82478 and -0.030 respectively) to the CT severity score ($p<0.0001$ and $p<0.0028$ respectively) which shows these levels fall with increased CT severity score. Age of the patient, pulse rate, Respiratory rate, TLC, NL Ratio, CRP, LDH, Ferritin and D-Dimer were directly related with CT severity score and it was statistically significant ($p<0.0001$), which shows these values increase with increased CT severity score. Systolic BP and Diastolic BP were not significantly related to the CT severity score.

ratio and TLC are directly correlated to the CT severity score, where as SpO2 and Hb levels are inversely related. CT severity score was also in direct relationship with the age of the patient, pulse rate and respiratory rate. Dong son. Et al in their study said that CT quantitative parameters were significantly correlated with laboratory inflammatory marker levels, including neutrophil percentage, lymphocyte count, lymphocyte percentage, hs-CRP level, and procalcitonin level ($p < 0.05$). These findings were consistent with our study findings. Furong zeng et al in a meta analysis said that inflammatory markers, especially CRP, PCT, IL-6 and ESR, were positively correlated with the severity of COVID-19. The association of serum ferritin with the severity of COVID-19 needs to be further clarified. Our study results are consistent with these in terms of CRP and other markers and further shows the association of Serum ferritin with the severity of the disease. In terms of mortality as outcome, it was directly associated with Age of patient, Fever, Breathlessness, Pulse rate, Respiratory Rate and negatively related with SpO2 and Hb level. High Mortality was seen in patients who needed oxygen therapy and even higher in patients who needed NIV. None of the patients who needed mechanical ventilation survived. There was no conflict of interest for this study.

Limitations of our study are that this was an observational study design, less sample size and single study site. Further studies with large sample size and different study sites are needed to confirm and generalise these findings.

Conclusion :

The inflammatory markers are directly correlated with the CT severity score in patients with COVID-19. Inflammatory markers and CT severity score are also directly related to the outcome in terms of mortality in COVID-19 patients.

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