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Original Research Article

Correlation of serum ferritin, LDH, CRP with chest findings-CT severity index in COVID-19 patients

Ankush Bansal[1], Aayushi Gupta[2]*, Abhishek Lachyan[3], Dhirender Choudhary[2], Roshni Sharma[4], Swati Dhania[5], Aman Bansal[6]

[1]Department of Medicine, Moolchand Hospital, New Delhi, India
[2]Department of Medicine, Lok Nayak Hospital and Maulana Azad Medical College, New Delhi, India
[3]Apex Regional STD Centre and SRL-HIV, VMMC and Safdarjung Hospital, New Delhi, India
[4]Translational Health Science and Technology Institute, Faridabad, Haryana, India
[5]Department of Anaesthesia, Medical College, Udaipur, Rajasthan, India
[6]Department of Critical Care, Shaheed Hasan Khan Government Medical College, Nuh, Haryana, India

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***Correspondence:**
Dr. Aayushi Gupta,
E-mail: aayushi138@gmail.com

ABSTRACT

Background: The COVID-19 pandemic is caused by a highly infectious virus primarily transmitted from person to person. The initial clinical manifestations of the condition are non-specific, characterized by the presence of fever and cough. These symptoms may resolve independently or escalate to acute respiratory distress syndrome (ARDS), multiple organ failure, and ultimately, mortality.
Methods: The research was conducted at Moolchand Khairatiram Hospital in the COVID-19 wards and ICU in New Delhi. The blood samples were collected and then analyzed to evaluate the following parameters: C-reactive protein (CRP), serum ferritin, and LDH are the three biomarkers of interest. The statistical significance threshold was established at a p value of less than 0.05.
Results: The study included 200 patients, 49% of whom were male and 51% of whom were female. A link was discovered between the outcome and the CT severity index. Patients who had a CT severity index of 21-25 died at the highest rate. The CT severity index and ferritin were found to have a significant relationship, with patients with elevated ferritin levels reporting the highest CT severity index scores.
Conclusions: A statistically significant association was observed between the CT severity index and the outcome, with the highest mortality rate observed in patients who had a CT severity index of 21-25. The parameters above are crucial in assessing the condition and predicting the outcome of individuals afflicted with COVID-19.

Keywords: COVID-19, CRP, CTSI, Ferritin, Inflammatory markers, LDH

INTRODUCTION

Toward the end of 2019, an unknown etiology pneumonia outbreak was reported among residents of Wuhan city located in Hubei province of China. The infectious agent causing ongoing global pandemic has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness arises as a consequence of thus pandemic is known as coronavirus disease 2019 (COVID-19). The virus in question belongs to the norovirus family, which includes the Roiniviridae, Artieviridae, and Coronaviridae families. These viruses are highly contagious and are known to induce respiratory illnesses in human beings. Individuals infected with the virus can exhibit either mild or severe symptoms. Some symptoms include fever, cough, throat pain, the common cold, and

shortness of breath. A significant proportion of people exhibit asymptomatic behavior. Symptoms can appear two to fourteen days after the infection.[1-5]

Complications include acute respiratory distress syndrome (ARDS), pneumonia, kidney failure, bacterial super-infections, abnormalities in coagulation, thrombo-embolic events, sepsis, and even mortality.

This disease rapidly spread to other regions worldwide, including the Europe, Eastern Mediterranean, Western Pacific, the Americas, and Southeast Asia. On March 12, 2020, the World Health Organization officially classified COVID-19 as a Pandemic.[1,2] Initially, it was suggested that the outbreak could be linked to the prominent seafood market, indicating a possible zoonotic transmission event. However, subsequent observations revealed a significant prevalence of human-to-human transmission. Within the initial 60-day period following the emergence of the outbreak, the pandemic disseminated rapidly and extensively across the globe, eliciting significant concern. The ongoing pandemic has led to a steady rise in the number of infected individuals and fatalities worldwide. Furthermore, it has inflicted a significant negative impact on the already vulnerable global economy.[5-7]

Various demographic features (e.g., gender and age); epidemiological features (e.g., comorbidities and smoking); laboratory parameters (e.g. albumin, cytokines, lactate dehydrogenase, C-reactive protein, D-dimer, lymphocyte, platelet, and neutrophil); clinical manifestations (e.g. chest pain, cough, expectoration, and dyspnea). Several studies have reported an association between the severity of COVID-19 and results from computer tomography (CT) imaging tests, among other factors.[8-11]

The first case of COVID-19 was reported in the Indian state of Kerala on January 30th, 2020, which coincided with the World Health Organization's declaration of COVID-19 as a public health emergency of international concern. The Ministry of Health and Family Welfare of the Government of India has taken several preventive measures to curb the transmission of the novel COVID-19 virus. These measures include promoting social distancing and raising awareness about the disease.[12]

The pathophysiology involves hematologic and immune systems, epithelial cells, and vascular systems. Several pro-inflammatory cytokines, including interleukin IL-1, IL-2, IL-6, IL-7, IL-10, tumor necrosis factor (TNF), interferon (IFN)-induced protein 10 (IP-10/CXCL10), monocyte chemoattractant protein 1 (MCP-1), granulocyte colony-stimulating factor (G-CSF) macrophage inflammatory protein 1 (MIP-1/CCL3), have been identified in the target tissue and bloodstream of individuals afflicted by COVID-19.[13-15]

The present study highlights a significant observation of lymphopenia in patients with severe disease, a distinctive feature as it is not frequently observed in patients with mild disease. Lymphopenia may be significantly attributed to the cytokine storm and subsequent inflammatory response. The observed correlation between presence of pro-inflammatory cytokines such as TNF-alpha and IL-6 and lymphopenia in bloodstream suggests a potential association between these factors. Conversely, individuals who have recovered from the condition exhibit cytokine levels comparable to those of healthy individuals.[16]

The high sensitivity of CT scans in detecting SARS-CoV-2 infection has been reported, leading to its widespread use in patient management. Our study has revealed a significant association between the severity of lung conditions and changes in laboratory test outcomes. The study has revealed that alterations in lymphocytopenia, D-dimer, LDH, CRP, and fibrinogen assays are correlated with the extent of lung involvement observed in chest CT. Amidst the ongoing public health crisis, a study was conducted to explore the association between LDH, serum ferritin, CRP levels and chest findings (CT severity index) in individuals diagnosed with COVID-19.

METHODS

This study evaluated the correlation of serum ferritin, LDH, and CRP with chest findings (CT severity index) in patients diagnosed with COVID-19.

Prospective cohort study was conducted at COVID-19 ward and COVID ICU located at Moolchand Khairatiram Hospital from December 2020 to December 2021.

A cohort of 200 patients, aged 18 years and above, who all were admitted to the hospital through the emergency room or outpatient department and tested positive for COVID-19 [the positive confirmation of the presence of the virus was obtained through a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab] were included in the study. The study excluded pregnant women and children from the sample population.

The research was conducted after obtaining approval from the IEC (institutional ethics committee) and the scientific research committee. Written informed consent was administered to each patient who was enrolled in the research. A comprehensive medical history was obtained from the participant. A comprehensive analysis of patients' blood samples was conducted, wherein various parameters were assessed. The biomarkers of interest in this study are C-reactive protein (CRP), serum ferritin, and LDH. The findings of a CT scan of the chest were documented. Furthermore, the clinical progression of all subjects was monitored throughout the observation period.

Statistical analysis

Data from 200 patients were collected and the statistical analysis of the data was conducted using IBM Inc and Statistical Package for Social Sciences (SPSS) version 21. The statistical significance level adopted for this study was $p<0.05$.

RESULTS

After applying all inclusion and exclusion criteria among 200 (100%) patients, 4.5% belonged to 19-28 years, 10% belonged to 29-38 years, 9% belonged to 39-48 years, 19.5% belonged to 49-58 years, 30% belonged to 59-68 years, 27% belonged to 69 years and above.

Table 1: Age-wise distribution of patients.

Age class interval (years)	Number	Percentage
19.0-28.0	9	4.5
29.0-38.0	20	10.0
39.0-48.0	18	9.0
49.0-58.0	39	19.5
59.0-68.0	60	30.0
69.0 years and above	54	27.0
Total	200	100.0

In the present study, among 200 (100%) patients, 49% were males and 51% were females.

Table 2: Gender-wise distribution of patients.

Sex	N	%
Female	101	51
Male	99	49
Total	200	100.0

Table 3: Distribution of patients as per their admission.

	N	%
Ward	124	62
ICU	76	38

In the present study, among 200 (100%), 124 (62%) were inward and 76 (38%) were in ICU.

Table 4: Distribution of patients as per the outcome.

Outcome	N	%
Alive	159	79.5
Expired	41	20.5
Total	200	100.0

In the present study, among 200 (100%) patients, 79.5% were alive and 20.5% expired.

Among the study population, 3% reported less than 6 CRP levels (Table 5).

Table 5: Distribution of patients as per CRP levels.

	Frequency	Percent
More than 6	194	97.0
Less than 6	6	3.0
Total	200	100.0

Among the study population, 6.5% reported more than 1500 serum ferritin levels (Table 6).

Table 6: Distribution of patients as per serum ferritin levels.

	Frequency	Percent
Less than 1500	187	93.5
More than 1500	13	6.5
Total	200	100.0

Table 7: Association of CT severity index with final outcome.

CT severity index		Final outcome		Total
		Survived	Expired	
6-10	N	21	0	21
	%	100.0	0.0	100.0
11-15	N	85	0	85
	%	100.0	0.0	100.0
16-20	N	43	10	53
	%	81.1	18.9	100.0
21-25	N	10	31	41
	%	24.4	75.6	100.0
Total	N	159	41	200
	%	79.5	20.5	100.0
P value		0.0001*, sig		

The association of CT severity index with final outcome was found to be significant, with maximum death seen in patients having CT severity index as 21-25.

Table 8: Association of CT severity index with CRP.

CT severity index		CRP levels		Total
		>6	<6	
6-10	N	20	1	21
	%	10.30	16.70	10.50
11-15	N	82	3	85
	%	42.30	50.00	42.50
16-20	N	51	2	53
	%	26.30	33.30	26.50
21-25	N	41	0	41
	%	21.10	0.00	20.50
Total	N	194	6	200
	%	100.0	100.00	100.00
P value		0.0641, Ns		

Chi-square test, level of significance set at $p<0.05$ Ns: non-significant Sig: significant.

The association of CT severity index with CRP was not found to be significant.

Table 9: Association of CT severity index with LDH.

CTSI		LDH abnormal range	LDH normal range	Total
6-10	N	18	3	21
	%	14.9	3.8	10.5
11-15	N	45	40	85
	%	37.2	50.6	42.5
16-20	N	26	27	53
	%	21.5	34.2	26.5
21-25	N	32	9	41
	%	26.4	11.4	20.5
Total	N	121	79	200
	%	100.0	100.0	100.0
P value		0.0001*, Sig		

Chi-square test, level of significance set at p<0.05 Ns: non-significant, Sig: Significant

The association of CT severity index with LDH was found to be significant, with patients having normal range of LDH reporting maximum CT severity index scores.

Table 10: Association of CT severity index with serum ferritin.

CTSI		Serum ferritin		Total
		<1500	>1500	
6-10	N	21	0	21
	%	11.2	0.0	10.5
11-15	N	85	0	85
	%	45.5	0.0	42.5
16-20	N	51	2	53
	%	27.3	15.4	26.5
21-25	N	30	11	41
	%	16.0	84.6	20.5
Total	N	187	13	200
	%	100.0	100.0	100.0
P value		0.0001*, Sig		

Chi-square test, level of significance set at p<0.05 Ns: non-significant, Sig: Significant

A significant association was observed between CT severity index and ferritin, wherein patients with elevated ferritin levels exhibited the highest CT severity index scores.

DISCUSSION

In December 2019, a cluster of unexplained pneumonia cases emerged in Wuhan City located in China, which subsequently became the focal point of investigation. In January 2020, a group of Chinese scientists discovered a novel coronavirus, which they temporarily named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In February 2020, the World Health Organization (WHO) modified its terminology to refer to the disease that had spread globally as COVID-19.

The signs and symptoms of infection may include fever, throat pain, high temperature (>37.3°C), myalgia, sputum production, cough, headache, hemoptysis, dyspnoea, and diarrhoea, in some cases, acute respiratory distress syndrome (ARDS), or secondary infection.

The existing diagnostic method for coronavirus disease involves real-time reverse transcription polymerase chain reaction (RT-PCR). However, this method has limitations, as it may result in false-negative outcomes. High-resolution CT scanning is a non-invasive and expeditious method that can be employed to screen individuals suspected of having lung disease. Additionally, this technology can provide an impartial evaluation of the severity of the illness and, consequently, the associated disease burden. The utilization of chest CT severity score (CTSS) has been employed as a semi-quantitative metric for assessing the extent of lung infection and quantifying the disease burden in COVID-19.[17-19]

The identification of clinical and laboratory factors that can serve as predictors of COVID-19 severity is an essential aspect of the ongoing efforts to combat this disease. This phenomenon is attributable to its capacity to assess the disease severity during the early phase and thus enable the expeditious evaluation of hospital resources at the right time. Therefore, it has attracted considerable interest as a potential solution for mitigating the impact of the pandemic.

In April 2020, it was observed that specific blood routine parameters, including CRP, ferritin, and CBC, exhibited significant differences between severe and non severe COVID-19 patients, thereby providing crucial insights into the severity of the disease. Nevertheless, several parameters, namely CRP, D-dimer, and albumin, exhibited significant consistency across the various studies.[20,21]

Using biological markers makes it possible to interpret subjective clinical symptoms during the examination confidently. Objective measurements are provided as the disease progresses.

In the current study, we tested whether there is a potential correlation between serum ferritin, LDH, and CRP with chest findings (CT et al) in COVID-19 patients.

The present study involved a sample of 200 (100%) patients, with 4.5% falling within the age range of 19-28 years, 10% within 29-38 years, 9% within 39-48 years, 19.5% within 49-58 years, 30% within 59-68 years, and 27% within the age group range of 69 years and above. Study population bears similarity to that of Yang et al.[8] Specifically, the latter study evaluated a cohort of 53

men and 49 women, aged between 15-79 years, comprising 84 cases with mild and 18 cases with severe COVID-19. The objective of the study was to assess the efficacy of chest computed tomography severity score (CT-SS) in distinguishing between various clinical forms of COVID-19. The study conducted by Gurung et al.[22] involved patients ranging in age from 19 to 89 years old. The age group of 50-59 years exhibited the highest proportion of cases, accounting for 25.8% of the sample.

The study population's mean age was found to be 59.06±16.05. This is comparable to the findings of Tan et al, who reported an average age of 48.89±18.47 for their patient cohort.[9] The mean age of the subjects in the study conducted by Poggiali et al was 63.1 years, with an age range of 22 to 94 years.[23] In a study conducted by Zhao et al, it was found that the median age of the 50 hospitalized patients was 55 years (IQR, 44-66).[24] Francone et al for 130 patients, reported mean age 63.2±15.8, within the range 27-90 years.[25] Carubbi et al reported median age of 65 years (range 32-93 years).[26] Beydoğan et al included 974 participants with mean age of 59.64±17.34 years.[27]

In the present study, among 200 (100%) patients, 49% were males and 51% were females. Tan et al stated that among 27 SARS-COV-2, 41% were males.[9] Yang et al among 102 patients stated that there (53 men and 49 women, 15-79 years old, 84 cases with mild and 18 cases with severe disease).[8] Zhao et al reported 40% were women among 50 patients.[24] Poggiali et al among 123 patients reported 91 males and 32 females.[23] Francone et al reported 84 males, 46 females among 130 patients.[25] Carubbi et al among sixty-one patients reported 22 females and 39 males.[26]

Beydoğan et al among 974 COVID-19 patients reported: 572 males (58.7%) and 402 females (41.3%).[27]

In the present study, 200 (100%) reported cough, 83 (41.5%) reported shortness of breath, and 196 (98%) reported fever. This is in accordance with the findings of Tan et al where the most common symptoms were fever (88%), followed by cough (44%), and then fatigue (33%).[9] Zhao et al reported most common symptoms of COVID-19 patients in this study were cough (82%), fever (64%), and respiratory distress (42%).[24]

Within the study cohort, only 3% reported CRP levels within the normal range (<6), while the majority of 97% reported CRP levels exceeding the normal threshold (>6). Consistent with the findings of Beydoğan et al, patients who experienced complications during COVID-19 treatment exhibited higher CRP levels (79.9 mg/dl versus 41.85 mg/dl, $p<0.001$) compared to those with mild disease.[27]

In the present study, 6.5% reported abnormal (more than 1500) serum ferritin levels in patients with severe disease. This is in accordance with the findings of Terpos et al, where serum ferritin emerged as a poor prognostic factor in which higher ferritin levels were associated with more severe ARDS.[28]

The current study involved the implementation of chest CT severity scoring, which was conducted by assessing the extent of involvement in each lobe of the lung (3 on the right and 2 on the left). The study employed a semi-quantitative scoring system as outlined by Chang et al.[29] The study revealed that the highest score observed among the cases was 15, which was recorded in 26 patients. The majority of the patients (85 out of 200) had a score ranging from 11 to 15. Consistent with the findings of Gurung et al, the highest CT score observed in the present study was 12, with 24 patients exhibiting this score.[26] Previous studies have indicated that individuals who have a cumulative CT score of 16 or higher exhibit a 6.9 times higher likelihood of experiencing a poor prognosis in comparison to those with less than 16 points.

The present study revealed a significant association between the CT severity index (CTSI) and the final outcome. Notably, patients exhibiting a CTSI ranging from 21-25 displayed the highest mortality rates. The present study's findings align with those of Francone et al, who reported that a CT score of ≥ 18 was linked to a higher risk of mortality and was a significant predictor of death in both univariate and multivariate analysis.[25]

In our study, most number of patients with high CRP levels (>6) was found among patients with CTSI between 11-15 (42.3%). 21.1% of patients with high CRP levels (>6) had a CTSI between 21-25. The association of CTSI with CRP was not found to be statistically significant. It suggests that patients having higher CTSI (severe disease) had higher CRP levels but patients with low CSTI can also have high CRP levels. This may be due to the diverse nature of illness and varied course of progression. This is in accordance with the study by Beydoğan et al which showed patients with higher CRP levels had thorax CT density scores 7.35 times higher which was indicated to be severe.[27]

In the current study, the association of CTSI with LDH was found to be significant, with patients having a normal range of LDH who reported maximum CT severity index scores. Also, patients who expired did not have elevated LDH levels. This showed that according to our study, LDH was not a poor prognostic marker of COVID-19 disease. This was found contrary to the study by Terpos et al where LDH was found to be a poor prognostic marker and could be used in predicting cases with severe disease.[28]

The association of CTSI with ferritin was found to be significant, with patients having raised ferritin levels reporting maximum CT severity index. This was found to be the same as seen in a study of Terpos et al, where serum ferritin emerged as a poor prognostic factor where

higher ferritin levels were associated with more severe ARDS and more mortality.[28]

CONCLUSION

The study was conducted in the COVID-19 wards and ICU at Moolchand Khairatiram Hospital in New Delhi. The study included 200 patients, and the results indicated a significant association between the CT severity index and the outcome. Patients with a CT severity index of 21-25 had the highest mortality rate. A significant association was observed between the CT severity index and ferritin levels; patients with elevated ferritin levels reported higher CT severity index scores. A weak to moderate correlation was observed between LDH and CT-SS. An association was observed between the severity score of the chest CT scan and the increased biomarker serum ferritin. The parameters above indicate the condition and potential outcome of individuals afflicted with COVID-19. This data can provide valuable insights for patient management and aid in selecting optimal treatment strategies.

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