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CORRELATION OF SERUM FERRITIN AND LDH ON CRITICALLY ILL PATIENTS OF COVID-19 DISEASE DURING 1ST AND 2ND WAVE OF COVID 19 PANDEMIC IN TERTIARY CARE HOSPITAL, INDIA

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ABSTRACT

In both the earlier waves of COVID-19 variants, severe and fatal respiratory disease like acute respiratory distress syndrome (ARDS) became more fatal in population with comorbid conditions. Therefore, early identification of severe COVID-19 is very important for individual's precise management, including antiviral, oxygen support and intensive care unit (ICU) management. First case of COVID-19 got reported in the medical record of India on 30th January 2020 in a student who had returned from Wuhan, China. In 2020 and 2021 it was found that individuals with increased serum ferritin and LDH level landed up with severe and very severe COVID-19 if not treated timely and correctly. So correlation between S. Ferritin and LDH in 1st and 2nd wave was required to evaluate the condition of patients who remained admitted in critical care unit with or without comorbid conditions. This is hospital based cross- sectional observational study on 50-50 (total-100) critically ill patients admitted during 2020 and 2021 respectively. We found that In 2020 during the 1st wave serum LDH and serum Ferritin levels were significantly high with the mean value of 481.65 U/L and 532.56 ng/ml respectively and in 2021 during 2nd wave serum LDH and serum Ferritin levels were again significantly high with the mean value of 488.43 U/L and 667.27 ng/ml respectively. In 2020 patients with comorbid conditions showed S. LDH and Ferritin mean value of 543.47 U/L and 582.63 ng/ml respectively and in 2021 during 2nd wave it showed S.LDH and Ferritin levels mean value of 672.72 U/L and 727.38 ng/ml respectively. Both inflammatory markers were significantly more increased in the critically ill patients who presented with co-morbidities. This study will provide improved confidence to health workers working in remote areas and COVID-19 hospitals in predicting transfer of COVID-19 patients to tertiary care hospitals for critical care management at the earliest.

KEYWORDS : COVID-19, LDH (lactate dehydrogenase), Serum Ferritin, critically ill.

INTRODUCTION

Since the end of 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), which progressed into a pandemic and has become a major global health concern since then. Cross person-to-person transmission of new variants of this virus can result in severe and fatal respiratory disease like acute respiratory distress syndrome (ARDS) in humans and can be more fatal in population with comorbid conditions and severe cases may deteriorate rapidly to multiple organ damage, impaired immune function and even death. Two waves of COVID-19 with different variants and lots of other variants emerged worldwide continuously. Therefore, early identification of severe COVID-19 is very important for individual's precise management, including antiviral, oxygen support and intensive care unit (ICU) care, to improve the prognosis of the patients[1]. Lactate dehydrogenase (LDH) is an intracellular enzyme involved in anaerobic glycolysis that catalyses the oxidation of pyruvate to lactate and elevated levels are suggestive of tissue damage which associated with poor prognosis in various diseases while Ferritin is a key mediator of immune dysregulation, especially extremely increased ferritin level, via direct immune-suppressive and pro-inflammatory effects that contribute to the cytokine storm syndrome[4,5,8]. In 2020 and 2021 it was found that individuals with increased serum ferritin and LDH level landed up to severe and very severe COVID-19 if not treated timely and correctly. Both emerged as an individual markers also but there are very few studies which gives a cumulative effect of both as severity predictor. So there was a need to do comparative study of serum LDH and Ferritin between 2020 and 2021 to check the significance and corelation of both markers in critically ill patients in both the waves and there values in a patients with comorbid conditions because this kind of study can help us in early identification of severe covid and will improve the treatment pattern of mild, moderate, severe and very severe covid.

AIMS AND OBJECTIVES

To compare the corelation of serum ferritin and LDH between 2020 and 2021 in critically ill patients to get the significance of both the markers as severity indicators in 1st and 2nd waves and also its association with comorbid conditions.

MATERIAL AND METHODS

We conducted a hospital based cross-sectional observational study in dedicated COVID-19 ICU on critically ill patients of tertiary care hospital of north India, Mayo Institute of Medical Science, Barabanki, Uttar Pradesh, with sample size of 100 COVID-19 RT-PCR positive patients in which we took 50 critically ill COVID-19 patients from 2020 and 50 critically ill COVID-19 positive patients from 2021. We categorised patients into two groups first the serum LDH plus ferritin levels in 2020 and second the serum LDH plus ferritin levels in 2021 in critically ill patients and again we sub-categorised patients on the basis of comorbid conditions year wise. We took the samples for serum LDH and Ferritin at the time of admission in critically ill patients and also assessed the comorbid conditions of the patients. The medical records of patients were analysed by the research team of the Department of Respiratory Medicine. Oral consent was obtained from patients or their relatives. COVID-19 diagnosis was confirmed by the real-time reverse transcription-polymerase chain reaction (RT-PCR) assay for nasal and pharyngeal swab specimens.

Data Collection

Epidemiological, clinical, and laboratory data were obtained with data collection forms from electronic medical records and history given by patients. All data were reviewed by respiratory medicine specialists. The information recorded included demographic data, medical history and clinical examination, underlying comorbidities and laboratory findings. The severity of covid 19 was done according to the protocol of the Government of India Ministry of Health and Family Welfare[1]. We took reference range of S. Ferritin from 70 to 435 ng/ml and S. LDH range from 140 to 280 U/L. Each participant gave written, informed consent to participate in the study. The study protocol was approved by the institutional review board and the institutional ethics committee with Ref. No. MIMS/EX/2021/168.

Statistical Analysis

Data analysis was done using SPSS 20.0 Statistical software (Statistical Package for the Social Sciences). Continuous data were summarized as mean and standard deviation. Results on Categorical variables were described as frequency and percentages and its comparison was done on the chi-square test or the Fisher exact test if the cell counts were small. Univariable logistic regression was used to explore the age-adjusted model with the severity of disease, using odds ratios (ORs). A p-value of <0.05 was taken as statistically significant.

RESULTS

The comparison of mean LDH and Ferritin level using the unpaired t-test showed that mean LDH and Ferritin level was significantly more among COVID with co-morbidity patients compared to COVID without co-morbidity patients (table 1). In 2020 during the 1st wave we analysed the data of 50 critically ill COVID-19 positive patients and we found that the serum LDH and serum Ferritin levels were significantly high with the mean value of 431.00 U/L and 542.89 ng/ml in COVID patients without co-morbidity respectively that made us curious to see its correlation with data of 2021 during the second wave in covid patients without co morbidity and we found that the serum LDH and serum Ferritin levels were again significantly high with the mean value of 542.89 U/L and 592.95 ng/ml respectively. In 2020 out of 50 critically ill patients there were 23 patients who presented with one or more comorbid conditions like hypertension, diabetes mellitus, CAD, CKD, thyroid abnormalities and etc had very high levels of S. LDH and Ferritin with mean value of 551.07 U/L and 499.60 ng/ml respectively and in progression of that we evaluated the 50 critically ill COVID-19 patients of 2021 in 2nd wave and out of which 22 patents presented with comorbid conditions also had significantly raised S.LDH and Ferritin levels with mean value of 466.06 U/L and 799.04 ng/ml respectively. The mean age of the study population in 1st wave group 49.18±,14.37 1st wave group was 53.76±13.17 and over-all study population was 51.47±13.91 years (table 2). There was a total of 72 (72.0%) males and 28 (28.0%) females among study population. In the 1st wave group, there were 37 (74.0%) males and 13 (26.0%) females and 2nd wave group, there were 35 (70.0%) males and 15 (30.0%) females (table 3).

Table 1: Distribution Of Study Population According To Ldh And Ferritin Levels

			Mean	Std.Deviation	p-value
LDH	1st wave	COVID without co-morbidity	431.00	179.60	0.039*
		COVID with co- morbidity	551.07	257.54	
	2nd wave	COVID without co-morbidity	542.89	273.53	0.043*
		COVID with co- morbidity	466.06	183.99	
	Over -all	COVID without co-morbidity	487.96	236.91	0.024*
		COVID with co-morbidity	509.51	226.20	
Ferritin	1st wave	COVID without co-morbidity	576.33	483.13	0.048*
		COVID with co-morbidity	499.60	347.17	
	2nd wave	COVID without co-morbidity	592.95	342.93	0.041*
		COVID with co-morbidity	799.04	701.80	
	Over -all	COVID without co-morbidity	584.79	413.83	0.043*
		COVID with co-morbidity	646.00	564.13	

The comparison of mean LDH and Ferritin level using the unpaired t-test showed that mean LDH and Ferritin level was significantly more among COVID with co-morbidity patients compared to COVID without co-morbidity patients.

Table 2: Distribution Of Study Population According To Age

Wave	Mean	Std.Deviation	p-value
1st wave	49.18	14.37	0.510
2nd wave	53.76	13.17	
Over-all	51.47	13.91	

The mean age of the study population in 1st wave group 49.18±,14.37 1st wave group was 53.76±13.17 and over-all study population was 51.47±13.91 years.

Table 3: Distribution Of Study Population According To Gender

	Wave		Total
	1st wave	2nd wave	
Male	37	35	72
	74.0%	70.0%	72.0%
Female	13	15	28
	26.0%	30.0%	28.0%

There was a total of 72 (72.0%) males and 28 (28.0%) females among study population. In the 1st wave group, there were 37 (74.0%) males and 13 (26.0%) females and 2nd wave group, there were 35 (70.0%) males and 15 (30.0%) females.

DISCUSSION

This hospital based cross-sectional observational study was conducted in dedicated COVID- 19 ICU on critically ill patients with 50 samples of serum LDH and serum Ferritin during 1st wave of 2020 and 50 samples of both in 2nd wave of 2021. Also we checked the correlation of serum LDH and Serum Ferritin between two waves. The results displayed the elevated inflammatory markers in critically ill patients, Keeping cytokine storm in mind as pathogenesis of covid-19, it was also analysed and concluded that there was strong association of both inflammatory markers in both the waves in critically ill patients. In contrast to other studies, the severely diseased patients had higher level of inflammatory markers. LDH is accepted asan inflammatory marker generally indicating acute or chronic tissue damage. The increase in LDH levels has been reported during acute and severe lung injury and interstitial lung infections [3]. Cytokine storm syndrome in patients with COVID-19 is mediated by pro- inflammatory cytokines resulting in acute lung injury and multiorgan failure and elevation in serum ferritin level is observed in COVID-19 critically ill patients. Our study demonstrated that the levels of serum LDH and ferritin were significantly higher in the critically ill patients in both the waves. The production of LDH and ferritin is induced in viral infections or lung damage, including COVID-19 associated pneumonia and cytokine storm[3,4]. L Szarpak, et al conducted a study and also came up with similar conclusion; the current meta-analysis confirmed that serum lactate de- hydrogenase level can be used as a COVID-19 severity marker and is a predictor of survival which corelate with our study [2].. Arshad AR et al conducted a study and concluded that the serum level of

ferritin, LDH as well as CRP are the predicting factors of mortality in patients with Covid-19 infections. The ferritin level was found to be better in this regard [3]. Mei-ying Wu et al conducted a study Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID 19) pneumonia and gave the conclusion that serum LDH was validated for its potential usefulness as markers for evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia [4] with similar outcome as our study. Qeadan,F et al showed that time-spaced repeated measurements of inflammatory markers trajectory plots will provide improved confidence to the healthcare providers working in remote areas and temporary COVID-19 hospitals in predicting transfer of COVID-19 patients to tertiary care hospitals[5]. We compared our study with Li-c et al and Gandini O et al which support our conclusion in favour of positive corelation between both the markers in both waves[6,7]. Payán-Pernía S et al study further supported our finding with their conclusion of Ferritin, LDH, ALC, and CRP laboratory parameters that predict with 88% accuracy the probability of early MIV, with results indicating that LDH showed the greater area under the curve (AUC)[8].

CONCLUSION

Multiple number of covid 19 pandemic waves have been experienced by different countries globally so far. Accordingly, appropriate allocation of health resources is pivotal in avoiding overcrowding in hospitals and minimizing burden on health care systems while managing these patients. Knowledge and application of serum ferritin and LDH trajectory patterns, will help allocate valuable resources and make better predictions about disease progression. Time spaced repeated measurements of serum ferritin and LDH will identify patients with high risk of developing covid cytokine storm and that who will require intensive care resources . Serum ferritin and LDH were found to having strong correlation in such cases and emerged as severity predictors specially in critically ill patients who presented with co-morbities and also with male predominance in the severity . The findings of this study will prove to be helpful to health care workers in early and improved management of such patients, even in the remote areas and for early referral of such patients to higher centre.

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