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TO ESTABLISH A RELATIONSHIP BETWEEN SERUM FERRITIN LEVELS AND TREATMENT OUTCOMES IN COVID-19 PATIENTS

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Abstract:
Background: *COVID-19, a pandemic affecting the entire world and causing significant morbidity and mortality, requires immediate evaluation and identification of reliable predictors of disease severity and outcome. COVID-19-associated fatalities are accompanied by cytokine storm syndrome. Serum ferritin is used to determine the cytokine storm.*
Aims and Objective: *The purpose of this study was to determine the role of serum ferritin in determining the severity and outcome of COVID-19.*
Materials and Methods: *From March to May 2020, a single-center, cross-sectional, observational study was conducted among SARS-CoV-2 infected patients. A real-time polymerase chain reaction was used to confirm the diagnosis (RT-PCR). The serum ferritin levels of COVID-19 positive patients were compared to their treatment outcomes.*
Results: *The study enrolled a total of 1977 COVID-19 patients. The mean age of the subjects was 43.8915.58 years, with a male predominance of 61.56 percent. The mean serum ferritin levels were 1225.6 2502.91 ng/ml in recovered patients and 285.71 391.99 ng/ml in expired patients, respectively.*
Conclusion: *Serum ferritin levels were significantly increased in COVID-19 patients who died compared to those who recovered completely, establishing it as a useful marker for assessing the severity of the infection.*
Key words: *cytokine storm, Serum ferritin, COVID-19*

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INTRODUCTION:

COVID-19 infection, which was first identified in December 2019 as a cluster of pneumonia in Wuhan, China, has rapidly spread to become a global pandemic. 1 Italy had the highest infection burden early in the pandemic, while India remained relatively unaffected, with mortality rates of 14.24 percent and 3.03 percent, respectively. 2 According to Health Ministry data published on January 14, 2021, the total number of cases in India has surpassed 10.5 million, with officially confirmed deaths totaling 1,51,727. 3 This condition is associated with a high rate of morbidity, putting a significant strain on the healthcare system and its resources. Additionally, the fatality rate is higher than that of other respiratory viral infections. As a result, it is critical to identify reliable predictors of disease severity and mortality in order to ensure prudent resource allocation and to enable earlier clinical intervention to improve clinical outcomes. Numerous biomarkers are being investigated for their potential role in predicting COVID-19 severity and prognosis. Elevated ferritin levels indicate an infection with a virus or bacteria in the body. Ferritin levels are increased when activated macrophages secrete cytokines, resulting in a cytokine storm, which can be a sign of advanced disease. 4 Due to the fact that severe COVID-19 is associated with cytokine storms, ferritin levels can be used to assess the same. We examined the relationship between serum ferritin and the severity and mortality of COVID-19 positive patients in this study. The purpose of this study was to determine ferritin serum concentrations and to correlate them with clinical outcomes.

MATERIALS AND METHODS:

This was a cross-sectional observational study conducted on patients admitted to the medicine department at Nishtar Hospital, Nishtar Medical University Multan, Pakistan between March and May 2020. The institutional ethics committee approved and cleared the study on 18/04/2020-BMCRI/PS/02/2020-21. The study enrolled patients aged 18 years of both sexes who were diagnosed with COVID-19 infection using the real-time polymerase chain reaction (RT-PCR) technique developed by ABI/Thermo Fisher - Taq Path. Patients under the age of 18 years and those unwilling to provide signed informed consent prior to the study were excluded.

Sample size estimation:

$$N = \frac{Za^2\sigma^2}{d^2}$$

$$N = \frac{1.92^2 * 400^2}{4\% \text{ of mean}} = 1676.07$$

A case record form with follow-up chart was used to record demographic information, as well as the disease's duration and clinical characteristics. We collected data on patients' clinical symptoms and the prevalence of co-morbidities such as hypertension, diabetes, and metabolic disorders such as renal, cardiac, and respiratory disorders. All participants were followed until they were discharged or died. A blood sample was taken from each patient and sent to the laboratory for analysis; only serum ferritin levels were compared to the patients' treatment outcomes. Electrochemiluminescence immunoassay (ECLIA) with a Roche COBAS analyzer system was used to determine the serum ferritin level. It was compared between patients who recovered and were discharged from the hospital and those who died during their stay. According to the state government's initial discharge policy, patients were discharged after 14 days if two consecutive throat/nasopharyngeal swabs taken 24 hours apart tested negative for SARS-CoV-2 RNA using the RT PCR technique. If the test was positive, it was repeated 72 hours later. Al mild and asymptomatic patients were discharged only after a 7-day follow-up RT-PCR technique for SARS-CoV-2 RNA was negative. If the test was positive, it was repeated 72 hours later. Patients with mild to moderate symptoms were discharged after ten days without a throat/nasopharyngeal swab test for COVID-19. For severe patients, a 14th day discharge policy was implemented based on a negative swab test, with tests repeated every third day until a negative result was obtained. Additionally, the demographics and clinical outcome were correlated. Statistical analysis was performed using R version 3.6.0, Vienna, Austria, 2019. Means and standard deviations were used to express continuous variables, while counts and percentages were used to express categorical variables. Patients were classified as survivors or non-survivors. The t-test was used to compare continuous variables and the chi-square test was used to compare categorical variables. Receiver operating curve (ROC) analysis was used to determine the optimal cut points for significant continuous variables. Multiple regression analysis was used to determine the effect of significant factors on outcome death and survival. Odds ratios with confidence intervals (CI) were estimated. Many mild and moderate cases were excluded from the analysis of the mean days of viral clearance due to the implementation of the revised third discharge policy. Statistical significance was defined as a P value of 0.05.

RESULTS:

The study enrolled 2000 patients who were admitted to Nishtar hospital in multan, pakistan and were

diagnosed with COVID-19. 33 patients were referred to various hospitals for a variety of reasons. The study included the remaining 1977 patients. All patients were classified into two groups based on their outcome: group 1 survived (1839-93.02 percent) and group 2 died (138-6.98 percent). 1419 (71.78 percent), 128 (6.48 percent), and 428 (21.65 percent) of the 1977 patients were under the ten-day asymptomatic policy, the second-day swab discharge policy, and the seventh-day swab discharge policy, respectively. The patients' demographic and clinical characteristics were analysed. The mean age of the patients was 43.8915.58 years, and the mean age of survival and death were 42.7415.15 and 59.1212.95 years, respectively, as shown in Table 1. Patients over the age of 50 were found to have a lower survival rate (only 32 percent patients survived). In 1977, the male to female ratio was 1:0.62, indicating a male predominance, as illustrated in Figure 1. Fever, dyspnea, and cough were the most common symptoms in patients who died compared to those who survived. Only 12% of those who died were asymptomatic, compared to around 50% of those who survived, Table 2.

Table 1: Age distribution among the patients

AGE	Total (n= 1977)	Survived (n=1839)	Succumbed to death (n=138)
Age (years)	43.89±15.58	42.74±15.15	59.12±12.95
Age Group			
<30 years, n (%)	419(21.19)	418(22.73)	1(0.72)
30-39 years, n (%)	452(22.86)	443(24.09)	9(6.52)
40-49 years, n (%)	369(18.66)	351(19.09)	18(13.04)
50-59 years, n (%)	356(18.01)	313(17.02)	43(31.16)
60-69 years, n (%)	238(12.04)	198(10.77)	40(28.99)
≥70 years, n (%)	123(6.22)	96(5.22)	27(19.57)

Table 2: Symptoms at the time of admission among different groups

Symptoms	Total (n= 1977)	Survived (n=1839)	Succumbed to death (n=138)
Asymptomatic, n (%)	941(47.80)	924(50.24)	17(12.32)
Fever, n %	600(30.35)	532(28.93)	68(49.28)
Dyspnea, n %	361(18.26)	275(14.95)	86(62.32)
Cough, n %	558(28.22)	489(26.59)	69(30.00)
Sore throat, n %	132(6.68)	124(6.74)	8(5.80)
Myalgia, n %	207(10.47)	192(10.44)	15(10.87)
Head ache, n %	19(0.96)	1(0.72)	18(10.98)
Others, n %	89(4.50)	80(4.35)	9(6.52)

Table 3 summarises the comorbidities of the patients included in the study. Among the 1977 patients admitted, 140 required oxygen, with 103 surviving and 137 dying. And 264 patients were admitted to the intensive care unit, with 126 surviving and 138 succumbing to disease (Table 4). The mean serum ferritin level was 341.36 747.79 ng/ml in the patients included in the study. Serum ferritin levels were found to be significantly higher in those who died versus those who survived, at 1225.6 2502.91 ng/ml and 285.71 391.99 ng/ml, respectively, and to be statistically significant with a P value of 0.001. (Table 5). ROC analysis was used to determine cutoff points for a continuous variable such as serum ferritin. Table 3 summarises the predicted cut-off points, AUC, specificity, sensitivity, and mean values for ferritin. Ferritin had an AUC of 80.08 percent with a cutoff of 352 ng/ml and a specificity and sensitivity of 76.32 and 74.6 percent, respectively (Table 6 and Figure 2).

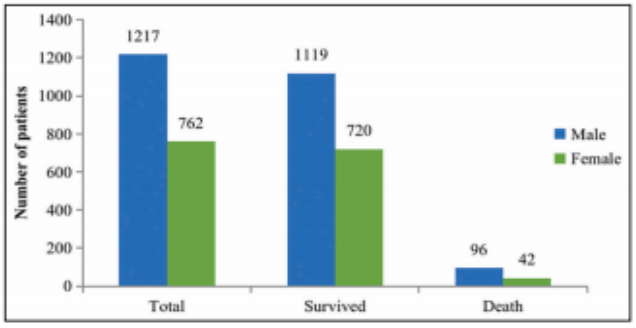

Figure 1: Sex distribution among the patients

DISCUSSION:

In agreement with these findings, Saluja et al. observed an increased male predominance at a government medical college in Kota, Rajasthan, with the majority being asymptomatic. 5 Male to female ratio was 1:0.62 in this study, indicating male predominance. The current study established that patients over the age of 50 have a lower chance of survival. There is substantial evidence in the literature to support the association between COVID-19 severity and mortality with age. Starke et al. also confirmed the positive association between increased age-related risk of COVID-19 disease severity, ICU admission, and mortality. The increased risk of disease severity per age year was noted to be 2.7 percent. 6 Similarly, a meta-analysis of 611,583 subjects found that mortality was 1.1 percent higher in subjects aged 50 years, with the greatest increase observed in patients aged 60-69 years, rather than 50-59 years. 7 The current study identified fever, dyspnea, and cough as the most common symptoms among patients who died versus those who survived. Zhang et al. also evaluated the clinical characteristics of 82 SARS-CoV-2 infection-related deaths. The researchers reported that fever (78.0 percent), cough (64.6 percent), and shortness of breath (63.4 percent) were the most frequently reported symptoms in the deceased.

Table 3: Co-Morbidities of patients among different groups

Comorbidities	Total (n= 1977)	Survived (n=1839)	Succumbed to death (n=138)
None, n (%)	1105(55.89)	1074(58.40)	30(21.74)
Diabetes only, n (%)	118(5.97)	110(5.98)	8(5.80)
Hypertension only, n (%)	94(4.75)	88(4.79)	6(4.35)
Diabetes or Hypertension with other complications, n (%)	417(21.09)	344(18.71)	73(52.90)
Chronic Kidney disease, n (%)	25(1.26)	17(0.92)	8(5.80)
Other, n (%)	219(11.08)	196(10.66)	13(9.42)

Table 4: Course of patients in the hospital

Course in the hospital	Total (n= 1977)	Survived (n=1839)	Succumbed to death (n=138)
Oxygen requirement, n (%)	140(7.08)	103(5.6)	137(99.28)
ICU requirement, n (%)	264(13.35)	126(6.85)	138(100)

Table 5: Comparison of serum ferritin among different groups

Laboratory parameters	Total (n= 1977)	Survived (n=1839)	Succumbed to death (n=138)	P-value
Ferritin (ng/ml)	341.36±747.79	285.71±391.99	1225.6±2502.91	<0.001

Table 6: Cut points, AUC, Specificity and Sensitivity noted for potential predictors

Predictor	Cut point	Survival	Death	AUC (%)	Specificity (%)	Sensitivity (%)
Ferritin (ng/ml)	352	285.71±391.99	1225.60±2502.91	80.08	76.32	74.6

Gupta et al study .'s in a tertiary care centre in India also identified fever and cough as the most prevalent symptoms (42.9 percent), followed by headache, sore throat, and breathlessness.

9 The serum ferritin level was found to be 285.71391.99 ng/ml in the group that survived, compared to 1225.6 2502.91 ng/ml in the group that died, which was statistically significant. According to Hemanth Reddy et alstudy .'s conducted in a tertiary care centre in India, serum ferritin activities were significantly increased in COVID-19 patients who died compared to those who recovered from the infection. 10 In the current mortality group, approximately 53% of subjects had diabetes/hypertension and approximately 6% had chronic kidney disease, compared to 0.92 percent in the survived group. According to a meta-analysis

focusing on developing countries, including India, the presence of comorbidities is associated with poor outcomes in COVID-19 subjects. Concurrent with these findings, data from Mexico indicate that chronic kidney disease, hypertension, COPD, obesity, and diabetes are all associated with an increased risk of death in COVID patients. 11 Zhang et al. examined the clinical characteristics of 82 COVID-19-related deaths and discovered that the majority of patients who died had co-morbidities, the most prevalent of which was hypertension (56.1 percent), and that more than half of those who died were over 60 years old. 8 The current study is significant because there is scant literature from the subcontinent correlating demographic data of

COVID-19 patients with clinical characteristics and disease outcomes.

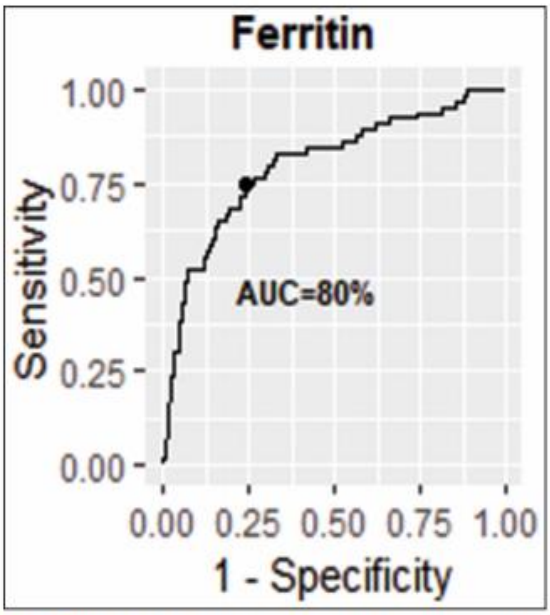

Figure 2: ROC Curve for different variables showing area under curve

Additionally, it sheds light on several significant findings that will aid clinicians in screening, treatment selection, and disease prognosis estimation. Another strength of the study is its large sample size, but the generalizability of the findings is limited due to the study's single-center design. The study did not assess the effectiveness of treatment interventions. This was not considered, as there was no specific standard protocol for managing COVID-19 patients available at the time of the pandemic.

CONCLUSION:

Serum ferritin activity was increased in the majority of COVID-19 patients. Serum ferritin levels were found to be significantly higher in COVID-19 patients who did not survive treatment compared to recovered patients. Thus, serum ferritin concentrations could be used as a simple and cost-effective prognostic marker in the management of COVID-19 patients.

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