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SERUM FERRITIN AND C-REACTIVE PROTEIN A CONFIDENT BIOMARKER IN COVID-19 PATIENTS.

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ABSTRACT

BACKGROUND: Since its initial report in Wuhan, China in December 2019, COVID-19 has spread throughout the world, with 80,651 cases and 3070 deaths. **OBJECTIVE:** This study investigates the correlation between C reactive protein (CRP) and serum ferritin in predicting disease severity in COVID-19 patients. CRP and ferritin levels were correlated with disease severity. **MATERIAL & METHODS:** With a sample size of 213, this cross-sectional analytical investigation was carried out at the Khyber Teaching Hospital in Peshawar, KP, Pakistan. The study included COVID-19 positive patients aged 18 and above, both males and females. **RESULTS:** The study found a negative relationship between disease and CRP and serum ferritin levels. As CRP and ferritin levels increase, then it indicating a severe state. Mean serum ferritin level is 1348.50 ng/ml, CRP level is 102.1518mg/ml, and mean age is 57.41 years. **CONCLUSION:** According to the results of this investigation, serum ferritin levels and CRP may be crucial markers of the severity and course of COVID-19.

KEYWORDS: COVID 19, CRP, Ferritin, Peshawar

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INTRODUCTION

Since its initial report in Wuhan, China in December 2019, COVID-19 has spread throughout the world, with 80,651 cases and 3070 deaths.[1] The WHO has raised the risk of the pandemic to a high global level. Hospitals worldwide face challenges in managing patients and reducing new cases, particularly those treated in intensive care units. Early diagnosis of serious illness is crucial for improving patient prognosis and allocating limited resources to those in need of aggressive treatment).[2, 3] The disease is a geographic public health emergency, with symptoms similar to flu, making it difficult to differentiate between them.[4] Coronavirus disease is a devastating disease that has spread rapidly and covered a large geographical area. Most cases develop into moderate and severe forms, causing respiratory distress, shortness of breath, and multi-organ malfunction, ultimately leading to death.[5] Risk stratification based on comorbidities and laboratory results is essential for early diagnosis and prognosis.[6] Laboratory markers, such as CRP, PCT, D-dimer, and ferritin, are crucial for prognosis and resource allocation.[7] Healthcare workers must identify patients' severity based on these markers to

recognize less severe cases and prevent them from developing into severe forms.[8]

Considering the incomplete understanding of the pathological and physiological processes underlying COVID-19, critically ill patients have a high death rate. However, markers and radiological studies play a significant role in proper management, as they predict lung lesion and severity.[9] The disease puts high pressure on healthcare workers, especially in intensive care units.[10] In Italy, 88% of patients required endotracheal intubation, and two-thirds of patients in the UK needed ventilation within 24 hours of admission.[11, 12] Laboratory parameters, such as hyper-ferritinemia, have strong relationships with inflammation levels. This infection is divided into four stages: mild, common, severe and critical.[13, 14] Patients are classified into pneumonia stages based on respiratory rate, oxygen saturation, and arterial blood partial pressure.[15] Most mild patients have a good prognosis, while high mortality rates are seen in critical ill patients.[16, 17]

A pentameric protein present in blood plasma, C reactive protein (CRP) has a high correlation with inflammation in the body.[18] It is produced in the liver and rises in response to T cells and macrophages releasing interleukin 6.[19] The liver produces CRP naturally, and it releases it in reaction to substances generated by adipocyte and macrophage cells.[20] It is a native protein made by the liver and contributes to early defence mechanisms and innate immunity. The normal CRP value ranges from 0.8 mg/l to 3.0 mg/l, but it is not constant in all individuals. CRP levels vary from less than 50 micrograms per litre to 500 mg per litre and can rise up to 10,000 times.[19] Chronic conditions, such as diabetes mellitus and arteriosclerosis, result in CRP levels remaining between 2mg/l and 10 mg/l.[20] Ferritin is a protein found in cells that regulates the level of iron in the body. It is globular in shape and consists of 24 subunits, forming a cage-like structure.[21] Prokaryotes and eukaryotic organisms both have ferritin, which aids in keeping iron in a soluble and safe form. It is essential for maintaining iron in a safe and soluble form and transporting it to the body where it is needed.[22] Ferritin is controlled by the amount and stable form of RNA that the cell's DNA transcribes.[23]

Ferritin is stored in two forms: ferritin and hemosiderin. Apo ferritin binds to iron and forms ferritin, while hemosiderin aggregates in reticuloendothelial cells.[24] Ferritin levels can rise quickly in the presence of infection or cancer and are linked to inflammation in the body. However, the level of ferritin may decrease in chronic situations, such as chronic disease anemia, as it shows inflammation rather than iron stores.[25, 26] The aim of this study was to find the correlation of C reactive protein and serum ferritin in Covid-19 patients.

MATERIALS AND METHODS

The study was conducted in Khyber Hospital Peshawar. The study was cross-sectional analytical investigation. This study covered all Khyber Teaching Hospital COVID-19-positive patients from March 2021 to August 2021. Male and female COVID-19 positive patients were included in this study; those who were identified as COVID-19 negative but had abnormal blood ferritin and CRP levels were eliminated. There were 213 COVID-19 patient samples collected.

Blood was taken in Gel tube (Clot Activator tube). Detections for Serum Ferritin and C-reactive protein (CRP) were done through Advance Chemical Analyzer Cobas e-411, Roche Diagnostics. CRP and ferritin test data were collected from patient files.

Convenient sampling, a non-probability methodology, was used to gather samples. The hospital in-charge oversaw the collection of secondary data. To investigate the relationship between CRP and serum ferritin levels in COVID-19 patients within the research group, a descriptive analytical investigation was conducted. Version 22 of the Statistical Package for Social Sciences (SPSS) was used for all analyses.

RESULTS

A total of 213 patients were recruited in which 33, 113, 14, and 53 patients were normal, high, mild, and moderate category respectively. Of 213 patients, 30 patients were normal ferritin levels, 109 had high ferritin levels, 26 were mild ferritin levels, and 48 were moderate ferritin levels. The serum ferritin and CRP levels were correlated with the severity of the illness using the Pearson chi square test. The Pearson chi square was 149.616, the likelihood ratio was 185.145, the linear by linear association was 93.161, and the significance

level P value was 0.0001. According to this table the significance level of p value of 0.0001 that is less than p value i.e p<0.005, it shows that COVID-19 and level of serum CRP have associated significantly. Similar to CRP, we also sought to determine whether serum ferritin levels and illness severity were correlated. Therefore, the level of significance for our statistical analysis, as indicated in the above table, is p value 0.005, which is less than p value 0.005, indicating that there is a strong link between serum ferritin and disease. Association between CRP and ferritin, the P value is 0.0001 which is less than P value 0.005 therefore we can conclude that there is association between CRP and ferritin level, we can therefore conclude that there is a positive relationship between serum ferritin and CRP since both levels rise at the same time as CRP levels in patients increase owing to severity (Table No. 1 & 2).

Table No. 1: Chi-Square test performed for serum CRP and COVID-19

Table No: 2 Categorical Ferritin Level and CRP

Test	Value	Df	Sig. (2-sided)
Linear-by-Linear Association	93.161	1	
Likelihood Ratio	185.145	6	
Pearson Chi-Square	149.616a	6	.0001

Cross Tabulation Count

Categorical		CRP				Total
		Severe	Moderate	Mild	Normal	
Ferritin Level	Severe	94	09	01	05	109
	Mild	02	09	05	10	26
	Moderate	13	14	9	12	48
	Normal	04	02	04	20	30
Total		113	34	19	47	213

The mean serum ferritin, serum CRP, and mean age level was 1348.50 ng/ml,102.1518mg/ml, and 57.41 years respectively. Whereas the median for serum ferritin level (1012), serum CRP level (60), and age (years) (60 years). The minimum serum level of ferritin, serum level of CRP, and age (groups) were 38, 13 and 20 respectively; while maximum value of serum level of ferritin, serum level of CRP, and age groups (eyars) is 42461, 545.56 and 95 respectively (Table No. 3, 4).

Table No 3: CRP, ferritin, and patients of the age.

	Age	CRP (mg/ml)	Ferritin (ng/ml)
Maximum	95	545.56	42461.00
Minimum	20	.13	38.00
Mode	60	8.53	2000.00
Median	60.00	60.1000	1012.0000
Std. Deviation	14.973	110.85498	2981.64225
Mean	57.41	102.1518	1348.5010

Table No. 4: Gender categorical CRP Cross tabulation Count

Gen	Mild	Normal	Severe	Moderate	Total
Female	7	19	36	25	87
Male	7	14	77	28	126
Total	14	33	113	53	213

Table No. 5: Gender * Categorical Ferritin Level Cross tabulation Count

Gender	Categorical Ferritin Level				Total
	Normal	Severe	Moderate	Mild	
Female	20	35	23	9	87
Male	10	74	25	17	126
Total	30	109	48	26	213

DISCUSSION

Declared a pandemic and public health emergency by the World Health Organization

(WHO), COVID-19 is an infection caused by a novel enveloped virus including RNA as genetic material; it is also referred to as SARS COV 2 or beta corona virus. This virus has a new name; it was formerly known as the 2019 novel corona virus.[27, 28] The SARS COV 2 virus and the 2019 novel corona virus share many similarities, with individuals over 60, particularly those with comorbidities, being more susceptible to the corona virus. These patients often develop SARS within 7 days of admission, highlighting the need for further research.[29, 30]

A review article shows after retrieving 52 number of papers in order to made a strong association serum ferritin and severity of illness. The findings indicated that a high serum ferritin level is associated with a poor prognosis. The meta-analysis ultimately revealed that serum ferritin has a role in indicating the severity of disease in 4992 corona disease patients from a total of 18 investigations, whereby a patient death rate of 2621 was recorded.[31] The study reveals a strong correlation between serum ferritin and CRP levels and the severity of COVID-19. This information can help healthcare practitioners manage and treat patients more effectively, potentially saving lives. The findings align with previous research by Liu et al., 2020. The association results suggest a strong correlation between C reactive protein and ferritin and the aggravation of COVID-19.[32]

In other study patients was classified into different severity categories based on radiological studies and parameters like CRP. Severe patients showed higher CRP levels than mild patients. Serum CRP can be used as an alarming predictor in patients at risk of developing into severe categories if not treated promptly. This helps manage limited resources and their proper allocation.[33]

In our finding we got the same result, by classifying the patients into three different groups of severity on the basis of capillary partial pressure of oxygen, into mild, moderate and severe category we finally concluded that those patients, showing high CRP level were having lower capillary partial pressure of oxygen, and those who were having higher or normal capillary partial pressure of oxygen showed lower level of CRP compared to severe category. This study also suggests that patients belonging to sever category, facing hypoxic condition should be facilitated by treating them in ICU or by providing oxygen therapy with the aid of ventilators.

Ianhaung et al; carried meta-analysis by pooling the result of 5350 patients from total 25 studies and finally concluded that elevated serum ferritin; CRP, PCT, and D dimer were associated with the poor outcome of the patients. In our study we also concluded that by studying serum ferritin a higher serum ferritin is seen in sever patients compared to the mild ones.[34] Katia et al., Carried their study in July 2020 by taking total number of 97 patients with mean age of 59 .9, with in hospital mortality of 45.4% and found that age, ferritin CRP and albumin were having significant correlation with the mortality. They found that the level of serum ferritin along with these other factors, if show high level are showing independent prediction of hospital mortality.[35]

Studies suggest that individuals with high levels of inflammatory markers, such as CRP and ferritin, should receive proper treatment to prevent complications and emphasize the importance of older patients. In COVID 19 patients the inflammatory response also plays a major role.[36]

CONCLUSION

The research found that serum ferritin and CRP can predict disease severity, with a negative relationship between capillary partial pressure of oxygen and CRP levels. These factors can be used to stratify patients into severity groups and manage resource allocation, especially for those in ICU and those at risk of severe disease if not treated well. The study also found that older individuals are more susceptible to infection than younger individuals.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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