

# ROLE OF SERUM BIOMARKERS TO ASSESS DISEASE SEVERITY AND OUTCOME OF COVID-19 CRITICAL PATIENTS IN INTENSIVE CARE UNIT

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## ABSTRACT

**Objective:** To determine the role of serum biomarkers to assess disease severity and outcome of COVID-19 critical patients in intensive care unit (ICU).

**Material and Methods:** In this cross-sectional study, all the admitted patients who had positive SARS-CoV2 PCR tests during period of 1<sup>st</sup> April 2020 to 31<sup>st</sup> July 2020 were included. Their biochemical and inflammatory markers were analyzed and assessed for severity and outcome of disease.

**Results:** Out of the total 523 COVID PCR Positive cases, total 303 patients admitted during these four months, who presented with moderate (193), severe (59) and critical (51) disease. 110 patients were kept in ICU depending upon their supplemental oxygen requirements or mechanical ventilation support to keep their oxygen saturation as per desired clinical standards. Among them, 225 patients were male and 78 were females with median age 39.37 ± 15.45. Mostly patients belonged to age group ≥ 50 yrs. Critical patients in ICU showed dramatically changes in serum ferritin, C-Reactive Protein (CRP) and Lactate Dehydrogenase (LDH) levels. 75 (24.75%) Patients were on maximum oxygen support while 35(11.5%) on mechanical ventilation with 221(72.9%). Out of these 303 patients, 29(9.57%) died, 175 (57.75%) recovered and discharged while 99(32.67%) were still under treatment but stable.

**Conclusion:** To conclude our findings following parameters should be monitored for the prognosis of acutely ill Covid 19 patients like age > 50 years, CRP > 50mg/L, Serum ferritin >1000 ng/ml, LDH > 400 U/L, CK ≥ 500 ul/L especially in resource poor settings. This can help in assessing disease severity and may also possibly prevent further morbidity with early intervention and effective management among admitted patients.

**Key Words:** Ferritin, CRP, LDH, COVID-19, Prognosis.

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## INTRODUCTION

SARS-CoV-2 causing COVID-19 since Dec 2019, have rapidly spread from China (Wuhan) to other countries around the globe causing an overwhelming number of infections and deaths [1]. SARS-CoV-2 virus has about 80% similarity to SARS-CoV but the later one showed higher affinity for Angiotensin-converting enzyme 2 (ACE2) receptors. Although, COVID-19 is initially identified as a Pneumonia like disease but current studies suggest that it is disease affecting any system of body [1] Increased risk of deaths is seen in older people and those with comorbid, however younger people without any comorbid conditions may also be affected and can present with multiple complications [2]. Early identification and timely management of seriously ill patients can significantly reduce the mortality [3]. COVID-19 is more contagious than other coronaviruses and lethal than seasonal flu, despite of its low mortality rate than SARS and

MERS CoV [4].

The WHO declared corona virus outbreak as the sixth public health emergency of international concern (PHEIC), and global pandemic on January 30, 2020 [5]. First case of COVID 19 infection was reported in Pakistan on February 26, 2020, that effected total population of Pakistan around 204.[6] 5 million by 27 march,2020.6 Its rapid spread and progression with lack of specific therapeutic approach resulted in an epidemic situation [7]. Due to its high ability of transmission leads to pandemic crisis worldwide with increased hospitalization of effected patients. Therefore along clinical and radiological parameters, laboratory biomarkers have an important role to play in disease diagnosis, prognosis, monitoring treatment response and outcome of the disease [3].

In COVID -19, the excessive immune response, called a cytokine storm, arises from overproduction of pro-inflammatory cytokines that can progress to Adult Respiratory Distress Syndrome (ARDS), multi-organ failure and ultimately may result in death [8]. Testing facilities for these cytokines and chemokines are not frequently available in most of

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the laboratories. Several other biochemical/inflammatory markers can also help in the assessment of disease severity and outcomes. These include serum Ferritin, CRP, LDH, Creatinine kinase (CK), LFTs and RFTs that can play a vital role in monitoring disease progression. Serum ferritin concentration is directly proportional to the total iron stores in the body and as positive acute phase reactant. It is upregulated by pro-inflammatory cytokines interleukin-1-b (IL-1) and tumor necrotizing factor-a (TNF-a). Several studies indicate that serum ferritin levels are higher in maximum of hospitalized patients infected with SARS-CoV2 virus especially in those who are critically ill [10]. Among the various inflammatory markers assessed, ferritin, CRP, LDH and CK were closely related with severity of disease specially in ICU patients. The serum levels of these markers may be used as prognostic markers mainly in resource poor settings [11]. Similarly this study compiles the laboratory data of above mentioned parameters that might be helpful in showing the prognosis from moderate to severe disease and outcome of the COVID-19 patients admitted in our tertiary care hospital for future guidance of clinicians.

## MATERIAL AND METHODS

This cross-sectional study conducted by the department of pathology Combined Military Hospital Malir, during the months of Apr 2020 to July 2020 after taking permission from Hospital Ethical Committee. It includes SARS-CoV-2-PCR test positive patients with moderate to severe disease admitted in ICU. Informed consent was taken from all the patients. Patients samples were collected in Gel tube with aseptic technique. LFTs includes total bilirubin (Bil), Alanine transaminase(ALT) ,and albumin (Alb) whereas RFTs includes urea and creatinine, LDH, albumin and CRP, CK were measured by Photometric method on state-of-Art Roche chemistry auto-analyzer Cobas C-501, while serum Ferritin was measured by Electro Chemiluminescence (ECLIA) method on State-of-Art Roche Endocrine auto analyzer Cobas e-411. Serum Sodium (Na) and Potassium(K) were measured by direct Potentiometry on EasyLyte analyzer. The patients were monitored for their disease course and the outcome was followed subsequently. Patients who had mild dyspnea were categorized as having moderate disease while patients who had severe dyspnea requiring supplemental oxygen therapy / or mechanical ventilator support were categorized as having severe and critical disease respectively. Operational definitions followed while entering and

analyzing data were mentioned tabular form:

Biochemical markers with normal range	Moderate disease (normal to slightly raised)	Severe disease (high levels)	Critical disease (very high levels)
S. Ferritin ( 24-336 nml/l)	≥ 336- 500 nml/l	≥ 500 - 1000 nml/l	≥ 1000 nml/l
S.CRP ( 6mg/l)	≥ 10- 50 mg/l	≥ 50 – 100 mg/l	≥ 100 mg/l
S.LDH ( 230-460 u/l)	250 - 446 u/l	≥ 446- 600 u/l	≥ 600 u/l
S. CK ( 25- 190 u/l)	≥ 190-500 u/l	≥ 500-1000 u/l	≥ 1000 u/l
S.ALT (42u/l)	≥ 42-60 u/l	≥ 60- 90 u/l	≥ 90 u/l
S. Bilirubin ( 3-18umol/l)	≥ 17-25 umol/l	≥ 25- 35 umol/l	≥ 35 umol/l
S. albumin ( 30-50g/l)	30 g/l	20 g/l	≤ 20 g/l
S. potassium ( 3.5- 5.0 mmol/l)	3.5 mmol/l	3.2 mmol/l	≤ 2.2 mmol/l
S. urea ( 3.3- 6.7 mmol/l)	≥ 7-9 mmol/l	≥ 9- 20 mmol/l	≥ 20 mmol/l
S. creatinine ( 62-120 umol/l)	≥ 120- 130 umol/l	≥ 130- 150 umol/l	≥ 150 umol/l

The statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) version 25. Both mean and standard deviation were calculated for continuous variables. The Chi-square test were applied for comparison of various categorical variables. p-value of <0.05 was considered statistically significant. A receiver operating characteristic (ROC curve) was obtained to analyze the predictive parameters (S. ferritin, S.LDH and CRP) for disease severity.

## RESULTS

Out of 523 COVID-19 positive patients, 303 (57.9%) patients admitted during the four months in our hospital, we observed the pattern of inflammatory biomarkers who presented with moderate 193(63.69%), severe 59 (19.47%) and critical 51(16.83%) disease with 110 (36.3%) required ICU care. Out of 303, 225 (74.25%) patients were male and 78 (25.74%) were female with median age 39.37 ± 15.45. Majority of these patients 188 (62%) belonged to age group ≥ 50 years (table-1). High levels of serum ferritin, CRP and LDH were observed in 171 (56.4%), 55 (18.15%) and 105 (34.65%) patients respectively. Whereas very high values of serum ferritin, CRP and LDH were noted in 97 (32%), 205 (67.6%) and 88 (29%) patients admitted in ICU (figure-1). Amongst the 110 ICU patients with severe and critical disease, significant differences in the serum ferritin (P = 0.001), CRP (P = 0.001) and LDH levels (P =0.045) were found depending upon

severity of disease (shown in table-2) which was statistically significant too. 75 (24.75%) Patients were on maximum oxygen support while 35(11.5%) on mechanical ventilation with 221 (72.9%). These findings were primarily observed in patients with known comorbidities like Hypertension, Diabetes, chronic pulmonary diseases (table-1). Out of these 303 patients, 29 (9.57%) died, 175 (57.75%) recovered and discharged while 99 (32.67%) were still under treatment but stable.

**Table-1: Showing demographic data of 303 hospitalized patients during four months period.**

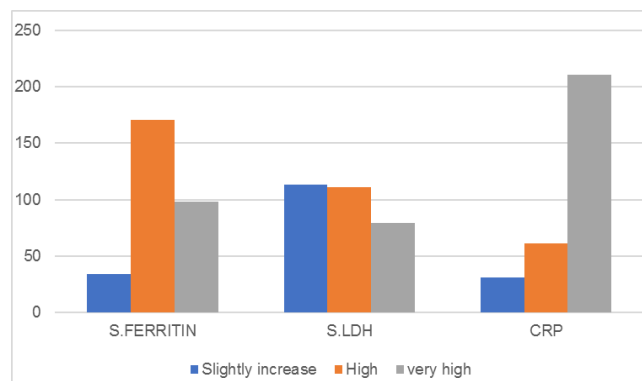
Gender	
Males	225 (73.5%)
Females	78 (25.74%)
Age Group	
30- 49 yrs	115 (38%)
50- 80yrs	188 (62%)
<b>Mean</b>	<b>39.37 ± 15.45</b>
Total Comorbid	
Hypertension	64(28.9%)
Diabetes	73 (33%)
Ischemic heart disease	55 (24.8%)
Chronic kidney disease	41 (18.5%)
Chronic liver disease	19 (8.59%)
Chronic pulmonary disease	51 (23.07%)
No Comorbid Patient Outcome	
Discharged	175 (57.75%)
Still under treatment	99(32.67%)
Death	29(9.57%)

**Table-2: Showing correlation of severity of disease with biochemical markers and outcome of ICU patients using chi-square test (n=110).**

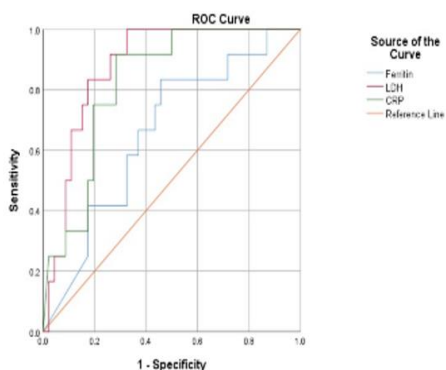
Biomarkers(n=110)	Severe disease (n=59)	Critical disease (n=51)	p- value
S. Ferritin (n=94, 85.45%)	59	35	P= 0.001
S. CRP (n=110, 100%)	59	51	P=0.001
S. LDH (n=81, 73.6%)	52	29	P= 0.025
S. CK (n=46,41.8%)	13	33	P= 0.002
S. Albumin (n=31,28.18%)	9	22	P=0.002
S. ALT (n=64,58.18%)	44	20	P =0.035
S. Bilirubin (n=82, 74.5%)	37	45	P = 0.002
S. Urea (n=65, 59%)	28	37	P= 0.022
S. Creatinine (n=33,30%)	11	22	P= 0.002
S. Potassium (n=27,24.54%)	5	21	P= 0.05
Recovered/ Discharged (n=32,29%)	23	09	P= 0.005
Still admitted (n=49,44.54%)	34	15	P= 0.002
Death (n=29, 26.36%)	2	27	P= 0.001

**DISCUSSION**

Worldwide confirmed cases of COVID-19 have reached to almost 21756357, resulting 771635 deaths till 17 August 2020 [12]. In this study, most of the affected patients of COVID-19 with less severe symptoms, have shown a good prognosis [13]. Most critically ill patients were old age group having comorbidities. This was consistent with a study by Wang DW [14]. Moreover, our study showed most common age suffered with severe COVID 19 infection was 52 ± 5 years which was lower than mentioned in various studies [13-15]. In accordance with Terpos [2], Wu *et al* [15], this study also found that the disease severity directly related with levels of serum ferritin, CRP, LDH and CK in COVID-19 patients, but the pattern of this relation become less significant with patients recovery (p=0.10) as reported by Wang DW [14]. Zhou *et al*[16] in his study supported an association between high ferritin value and death, but no multivariate statics was available. In our study, CRP was elevated in 67.6% of patients. Detailed analysis shows that median CRP level was around 40 mg/L in survivors, while >100 mg/L in non-survivors, suggesting good association with severity of disease and outcome as in the study by Guan *et al* [1]. Increased LDH in 40% has also been linked with higher risk of ARDS and death as observed by Wu C *et al* which was comparable to our findings[18]. Fall in serum CK and LDH has been significantly correlated with SARS CoV-2 RNA clearance that could help in assessing a favorable outcome in COVID-19 infected patients [9]. In recently published studies, 44-70% of



**Figure-1: Showing details of infectivity markers of total 303 hospitalized patients during four months period.**



**Figure-2: Showing ROC curve of infectivity markers like serum ferritin, LDH and CRP in ICU patients.**

hospitalized patients with COVID-19 the key clinical feature was myalgia or fatigue [18] and increased CK was found in up to 33% of COVID patients as in our study, high serum CK in COVID cases suggesting that this virus may also cause viral myositis[19]. In Dong C's [20] study, the authors have highlighted that low serum Potassium was common in COVID-19 patients, and the association of hypokalemia was confusing due to frequent loss of Potassium resulting from the degradation of ACE2 receptors. Our study also revealed similar findings that the serum value of albumin and serum potassium were inversely associated with the COVID-19 severity. Therefore they can be used as prognostic indicator in critically ill patients. Clinicians should consider high ferritin, CRP, LDH and CK, which might be considered as risk assessment and to analyze disease severity in COVID-19 hospitalized patients. In our study we also found other biomarkers that had significant association between the different stages of disease from moderate to critical such as deranged LFTs, RFTs. These abnormalities are an indication that COVID-19 is a multi-organ disease as mentioned by other studies [15,16]. Our findings consistent with various studies like age >50 years, Ferritin >1000 ng/ml, CRP >50 mg/L, LDH >400 U/L, serum K and albumin <2 and <20 g/L respectively need close monitoring to assess disease progress and clinical management preventing fatal complications in these subjects [18,19]. There are certain limitations in this study like some of inflammatory markers like interleukin [6], procalcitonin, serum lactate, Pro BNP, D-Dimers can't be assessed due to the limitations of resources and this is a single centered cross-sectional study done in short duration and lack of follow up of recovered patients. A multicenter studies and meta-analyses are required further to support decision-making by the clinicians in the tertiary care setups. Despite the fact that we found significant associations in this study, but still more studies are needed to analyze the significance of these biomarkers including clinical correlation and follow up of the treated patients to observe any post COVID changes in lab parameters.

## CONCLUSION

In a resource poor setting, our findings support the regular monitoring of easily available biomarkers like high levels serum Ferritin, CRP, LDH, CK with low levels of serum potassium and albumin can be as prognostic indicators. This can help in timely intervention so as to improve patient's outcome, reduce mortality and aid in targeted

management of COVID-19 affected individuals mainly in ICU settings.

## AUTHOR CONTRIBUTION

**Hamid Jamal Siddiqui:** Literature search

**Shagufta Yousaf:** Material and methods and discussion

**Fatima Sana:** Introduction and statistical analysis

**Abeera Ahmad:** Data interpretation, data analysis

**Ghulam Murtaza:** Drafting, literature review

**Hannah Ahmad:** Data collection, data interpretation

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