

## ORIGINAL ARTICLE

# SEVERITY OF INFLAMMATION IN COVID-19 PATIENTS WITH DIABETIC CO-MORBIDITIES - A HOSPITAL BASED STUDY

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## ABSTRACT

**Background:** Diabetic co-morbidities in recent past pandemic were becoming a challenge to the clinicians. COVID-19 is a respiratory infectious disease caused by SARS-COV-2 virus. World health organization declared COVID-19 pandemic in Feb 2020. The objective of this study was to determine the severity of inflammation in COVID-19 patients with diabetic co-morbidities in a hospital based study.

**Material and methods:** This descriptive study covering 176 patients was conducted in Hayatabad Medical Complex Peshawar from 25 April 2021 to 21<sup>st</sup> October 2021. Receiver operating characteristics (ROC) curve was used as statistical tool to determine the relationship of clinical sensitivity of different inflammatory markers in diabetic COVID-19 patients to predict the outcome. Post-stratification Chi square test was used at 5% level of significance.

**Results:** Out of 176 patients, 149 (84.7%) patients were discharged satisfactorily while 27 patients expired during hospitalization. Mean with SD for age was  $53.28 \pm 13.73$  years, for D dimer was  $13.14 \pm 2.61$  ug/ml and for CRP was  $16.73 \pm 11.78$  mg/l. Median of serum Ferritin was 1120 ng/ml. There was a significantly higher inflammatory markers values of D-dimer ( $p=0.001$ ) and ferritin ( $p=0.001$ ) in diabetic versus non diabetic COVID Patients. D-Dimer was main decisive prognostic indicator in diabetics with COVID-19 to predict mortality/worst outcome with an Area under Curve (AUC) of (0.929 95%CI 0.88-0.96) followed by Serum ferritin (0.868 95%CI 0.78-0.95). There was a significant association of Diabetes with Mortality ( $p<0.001$ ) in COVID-19 patients.

**Conclusion:** The clinical sensitivity of d-dimer and ferritin toward mortality in COVID-19 patients with diabetic co-morbidities is significantly high in our population. Diabetes alone has a significant positive association with worst outcome in covid-19.

**KEY WORDS:** COVID-19; Ferritin; Mortality; Diabetes mellitus.

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## INTRODUCTION

Diabetic co-morbidities in recent past pandemic were becoming a challenge to the clinicians involved in the direct management of COVID-19 hospitalized patients. Covid-19 is a respiratory disease and was first reported to the World Health Organization (WHO) in Dec 2019 from Wuhan, a Metropolitan city of China. WHO declared the global emergency in response to rapid rise in cases of COVID-19 in China and

neighboring countries by the end of February 2020.<sup>1</sup> According to the World Health Organization, the worldwide total number of confirmed Covid-19 cases have crossed 586,681,197 with 6,410,961 deaths. It has been reported that by 9<sup>th</sup> Aug 2022, 4.88 billion people are vaccinated which is 62.6% of the world population.<sup>2</sup> Regarding the national burden, By 9<sup>th</sup> Aug 2022 the number of laboratory confirmed cases have reached to 1565,000 in Pakistan with 30,508 deaths and 62000 active cases.<sup>3</sup> Khyber Pukhtunkhwa province has reported a total number of COVID-19 cases of 222000 and 6332 confirmed deaths.<sup>3</sup>

In general high prevalence of Diabetes mellitus makes it clinically an important risk factor in COVID-19 patients. This is becoming more important when the world is asking for more restrictions on mobility. Literature has reported higher risk of complications and more mortality in diabetic patient as compared to non-diabetics.<sup>4,5</sup> Working group of China CDC (Centre

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of Disease control) reported 21000 Covid-19 cases with 5% prevalence of diabetes and a higher mortality in the study groups. Similarly Diabetes tripled the risk of hospitalization in COVID-19.<sup>6</sup> Regarding the previous experience with MERS (Middle East Respiratory Syndrome) the mortality reported in diabetes with MERS was 35%.<sup>7</sup> A study reported in New England Journal of Medicine revealed that 585 of the covid-19 patients hospitalized were diabetic and 345 of those patient met the worst outcome (expired).<sup>8</sup> Data has demonstrated that the poor glycemic control in Diabetic patients predisposes to a higher risk of infection in COVID-19 and higher frequency of hospitalization and worst outcome in term of mortality.<sup>9</sup>

The inflammatory markers show higher degree of variation in Diabetics with COVID-19. A study reported median values of D-dimer 1509ng/ml in diabetics and 515ng/ml in non diabetic covid-19 patients.<sup>10</sup> Furthermore serum levels of other inflammatory markers like C-Reactive Protein, Ferritin, ESR and LDH were significantly higher in Covid patients with diabetic co-morbidities ( $p < 0.01$ ) as compared to non-diabetic Covid patients.<sup>11</sup> Thus this warrants that patients with diabetes are more prone to develop inflammatory storm leading to sever disease and death eventually.

In Pakistan the literature regarding the pandemic association with diabetes and inflammatory sequel is scanty and therefore present study was conducted to determine the severity of inflammation in COVID-19 patients with diabetic co-morbidities in a hospital admitted patients. This study will generate valid reliable information based on verifiable and replicable data that supports the significance of relationship of co-morbidities like diabetes with worst outcome in COVID-19. This will help clinicians to categorize patients based on the risk factors stratification to achieve better results of the treatment.

## MATERIALS AND METHODS

This descriptive study was conducted in department of Hematology, Hayatabad Medical Complex Peshawar from 25 Apr, 2021 to 21<sup>st</sup> Oct, 2021

Sample size was calculated using Non-probability consecutive sampling, Using Open-Epi software. A sample size of 176 shall represent the true population based on the anticipated proportion of 34% mortal-

ity in COVID-19 cases with deranged inflammatory markers, keeping 95% confidence level and 6% absolute precision due to feasibility issues.<sup>12</sup>

Inclusion criteria were all hospitalized COVID-19 patients. Only covid-19 patients where CBC, Ferritin and d-dimers tests are advised and outcome was known irrespective of age and gender were included. Exclusion Criteria were all COVID-19 patients where the outcome was not known or LAMA (Leave without medical advice) patients.

Data was collected after obtaining ethical approval from the Hospital Ethical & Review Board via ERC No (316/HEC/B & PSC/2020 Dated 15th May 2020) and notification No (346/HEC/B & PSC/2020 Dated 10th Dec 2020). Patients as per sample selection criteria were included and data from individuals was collected after obtaining written informed consent.

We collected 3 ml of venous blood by vein-puncture under aseptic techniques. Then test was performed on COBAS-511 (Roche Diagnostics). A value of  $< 0.5$   $\mu\text{g/ml}$  for d-dimer was considered as normal<sup>10</sup>. For serum ferritin, 2 ml blood in Gel bottles was centrifuged. Serum ferritin was measured on COBAS-511 (Roche Diagnostics). A value of  $< 500$   $\mu\text{g/l}$  was taken as normal.<sup>12</sup> All the required information shall be collected on the predesigned pro forma prepared in accordance with the objectives of the study.

Data was analyzed using SPSS version 25.0. Quantitative variables like age and laboratory values were described in terms of Mean with standard deviation. Categorical variables like gender, outcome and presence of co-morbidities were described as frequencies and percentages. Outcomes were stratified on inflammatory markers, hematological markers, age, gender, and co-morbidities. Post-stratification Chi square test was used at 5% level of significance. Receiver operating characteristics (ROC) curve was used as statistical tool to determine the relationship of clinical sensitivity of different inflammatory markers in diabetic COVID-19 positive patients to predict the worst outcome.

## RESULTS

Out of 176 patients, 149 (84.7%) patients were discharged satisfactorily while 27 patients expired during hospitalization. Mean and SDs for age was  $53.28 \pm 13.73$  years. Mean and SDs for D dimer was

**Table 1. Descriptive statistics of inflammatory markers of patients**

		Age (Years)	D dimer ( $\mu\text{g/ml}$ )	S Ferritin (ng/ml)	CRP Level (mg/L)
N	Number of patients	176	144	144	141
	Missing	0	32	32	35
Mean		53.28	13.14	1378.81	16.73
Median		55	2	1120	13.7
Std. Deviation		13.73	2.61	1067.37	11.78
Range		87	86.88	5331	66.7
Minimum		3	0.12	101	0.3
Maximum		90	87	5432	67

13.14+2.61 ug/ml. Median for serum Ferritin was 1120 ng/ml. Mean and SDs for CRP was 16.73+11.78 mg/l. (Table 1)

Regarding the association of an increased inflammatory markers in patients with pre-existing Diabetes, it was observed that there was a significant higher deranged d-dimer values in diabetics vs non-diabetic COVID patients (p<0.001). A similar statistically significant findings were noted for deranged values of

ferritin in diabetic Covid-19 patients as compared to non-diabetic COVID patients (p=0.03). No significant association of CRP values was noted between the two groups (p=0.257). (Table 2)

The values of the inflammatory markers vary in diabetic vs non-diabetic COVID-19 patients. There was a significantly higher inflammatory markers values i.e. D-dimer (p<0.001) and ferritin (p<0.001) in groups of diabetic vs non diabetic COVID Patients. (Table 3)

**Table 2: Association of Diabetes with raise in inflammatory markers**

		D-Dimer Category (ug/ml)		Total	p-values
		<5	>5		
Diabetes	Yes	0	19	19	0.001
	No	97	28	125	
Total		97	47	144	
		Ferritin Category (ng/ml)		Total	p-values
		<500	>500		
Diabetes	Yes	0	19	19	0.03
	No	25	100	125	
Total		25	119	144	
		CRP Category (mg/L)		Total	p-values
		<10	>10		
Diabetes	Yes	4	14	18	0.257
	No	44	79	123	
Total		48	93	141	

**Table 3. Inflammatory markers values in diabetic vs non diabetic COVID Patients**

Inflammatory marker	Diabetes	Number of patients	Mean SD/ Median		Significance	Test
D dimer (ug/ml)	Yes	19	45.97	15.59	0.001	Independent t-test
	No	125	8.16	17.70		
S Ferritin (ng/ml)	Yes	19	2792.63		0.001	Mann Whitney U Test
	No	125	1163.91			
CRP Level (mg/L)	Yes	18	19.47	10.76	0.293	Independent t-test
	No	123	16.33	11.92		

**Table 4. Association of Outcome of COVID-19 patients with Diabetes Mellitus (n=176)**

		Diabetes Mellitus		Total	P Value
		Yes	No		
Outcome	Discharged satisfactorily	0	149	149	< 0.001
		0.00%	94.90%	84.70%	
	Expired	19	8	27	
		100.00%	5.10%	15.30%	
Total		19	157	176	
		100.00%	100.00%	100.00%	

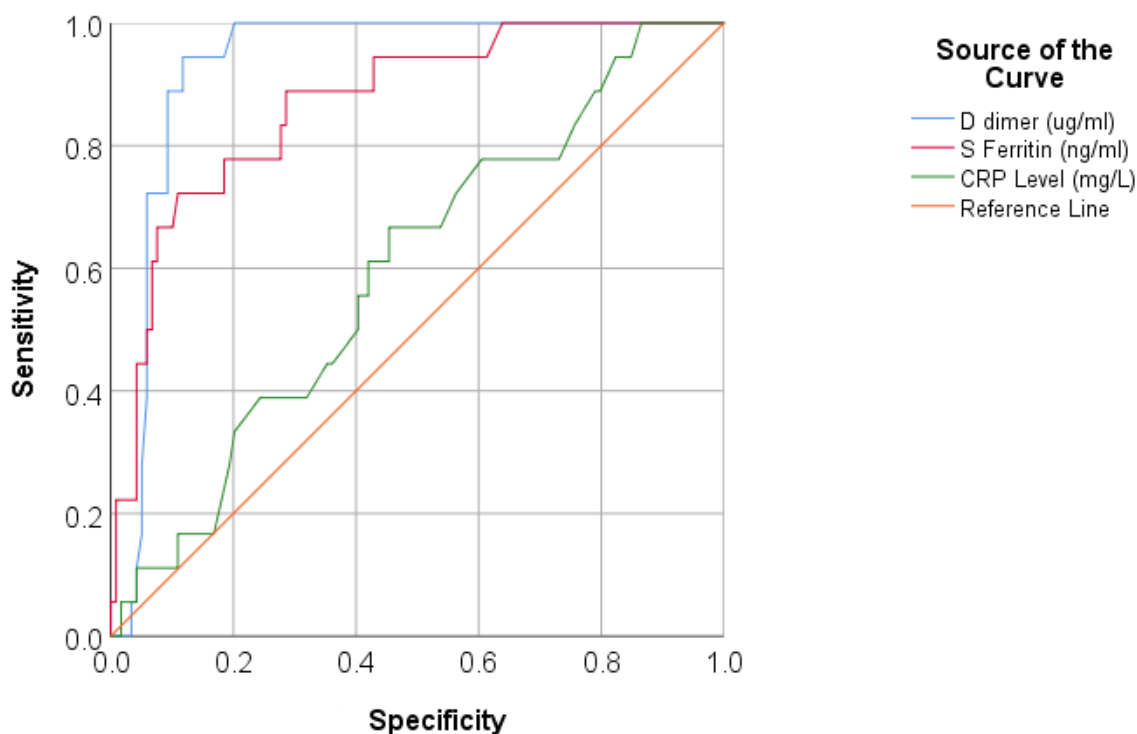
**Table 5. Area Under the Curve for different inflammatory markers of diabetic patients predicting mortality in COVID-19**

Test Result Variable(s)	Area	Std. Error <sup>a</sup>	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
D dimer (ug/ml)	0.929	0.022	0.000	0.886	0.973
S Ferritin (ng/ml)	0.868	0.043	0.000	0.784	0.953
CRP Level (mg/L)	0.596	0.068	0.188	0.463	0.729

The test result variable(s): D dimer (ug/ml), S Ferritin (ng/ml), CRP Level (mg/L) has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5



**Fig 1. ROC Curve showing clinical sensitivity of inflammatory markers in diabetic patients predicting worst outcome in term of mortality**

Using chi-square test it was observed that there was a significant association of Diabetes with Mortality ( $p < 0.001$ ) in COVID-19 patients. (Table 4)

D-Dimer was main decisive prognostic indicator in diabetics with COVID-19 to predict mortality/worst outcome with an Area Under Curve (AUC) of (0.929 95%CI 0.88-0.96) followed by Serum ferritin (0.868 95% CI 0.78-0.95). (Table 5, Fig 1)

**DISCUSSION**

Diabetic patients due to low pulmonary functions were more susceptible to admission in high dependency units, intensive care units and mechanical

ventilation. There is an increase in inflammatory storm in such patients with ultimately deranged values for inflammatory markers like d-dimers, ferritin and CRP etc. In present study we observed higher values for Mean and SD of d- dimer was  $13.14 \pm 2.61$  ug/ml in diabetic patients. Median for serum Ferritin was 1120 ng/ml. Our findings were in concordance with the findings of Mishra Y et al.<sup>10</sup> They reported median values of D-dimer 15.09ug/ml in diabetics and 5.15ug/ml in non diabetic covid-19 patients. We also observed that Mean and SDs for CRP was  $19.47 \pm 10.76$  mg/l in diabetic patients, but the difference in values for the non diabetic Covid patients

was not statistically significant ( $p=0.293$ ).

A study from Italy reported two-third of the patients with diabetes had a fatal disease in COVID 19 infection and expired<sup>13</sup>. There was a significant association of Diabetes with Mortality ( $p<0.001$ ). D-dimer is a marker of hypercoagulability state. COVID-19 has been demonstrated as disorder of the abnormal coagulations state and studies have demonstrated that d-dimer of  $>2000\text{ng/ml}$  has been associated with higher mortality in diabetics as compared to non diabetics Covid-19 patients.<sup>14,15</sup> There was a significantly higher inflammatory markers values; D-dimer ( $p=0.001$ ) and ferritin ( $p=0.001$ ) in groups of diabetic vs non diabetic COVID Patients. This shows the association of diabetes with an increased in an inflammatory response in term of an increased in the values of d-dimer and ferritin. Our accumulative analysis showed that diabetic Covid-19 patients are more prone to develop coagulative dysfunction and inflammation than non diabetic Covid-19 patients.

A study reported by Onder et. al. in JAMA recommend that for therapeutic and clinical purposes the Covid-19 patients may be categorized on the basis of cut-off values of d-dimers in age, gender and patients with co-morbidities like diabetes, hypertension and cardiovascular diseases. And this must be added to national surveillance system to determine the high risky population more vulnerable to meet fatal outcome.<sup>16</sup> Similarly a meta-analysis reported a 3.9 times higher mortality in patients with deranged d-dimer to meet worst outcome in term of death.<sup>17</sup>

We further observed that D-Dimer was main prognostic indicator in diabetics with COVID-19 to predict mortality/worst outcome with an Area Under Curve (AUC) of (0.929 95%CI 0.88-0.96) followed by Serum ferritin (0.868 95%CI 0.78-0.95). In one of our previous intervention regarding the hematological and inflammatory biomarkers in COVID-19, we observed that the d -dimer values in both the waves (1<sup>st</sup> and 4<sup>th</sup> wave) proved to be reliable for predicting the severity and mortality of COVID-19.<sup>18</sup> Diabetes further aggravates the severity of infection, hyper-coagulability and increases the mortality in COVID-19. A retrospective cohort from china reported in LANCET that diabetes to have an OR of 2.85 (95% CI, 1.35 to 6.05;  $p < 0.001$ ) for in-hospital mortality.<sup>19</sup>

## CONCLUSION

Diabetes has a positive association with worst outcome in Covid-19. The clinical sensitivity toward mortality of d-dimer and ferritin in COVID-19 patients with diabetic co-morbidities is significantly high. D-dimer is a main prognostic factor that predicts mortality in COVID-19 followed by CRP and serum ferritin levels.

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**CONFLICT OF INTEREST**

Authors declare no conflict of interest.  
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**AUTHORS' CONTRIBUTION**

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	HK, SK
Acquisition, Analysis or Interpretation of Data:	HK, SK, FK
Manuscript Writing & Approval:	HK, SK, FK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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