Predictors of Disease Severity in Adult Covid-19 Patients Admitted in Mayo Hospital, Lahore, Pakistan

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ABSTRACT

Objective: To assess disease severity, based on clinical presentation and laboratory investigations.

Study Design: Observational study.

Place and Duration of Study: COVID-19 Isolation Unit of Mayo Hospital, Lahore from 15th March to 31st May, 2020.

Methodology: Four hundred and forty-five COVID-19 RT-PCR positive patients of either gender in age group of 18-80 years, admitted in isolation wards, high dependency units (HDUs) and intensive care units (ICUs) of the Hospital, were selected for the study via simple random sampling. Clinical presentations and laboratory investigations were recorded for all patients. Kruskal-Wallis test, Pearson Chi-square test, boxplots and ROC curve were used to analyse the data. A p-value ≤0.05 was considered statistically significant.

Results: Out of the 445 cases, a male predominance 286 (64.3%) was observed with majority of patients 324 (72.8%) having mild disease, 73 (16.4%) moderate, 25 (5.6%) severe and 23 (5.2%) having critical disease. D-dimer was considered to be the best discriminatory marker to assess disease severity with an overall accuracy of 92.1%.

Conclusion: Fever, sore throat, shortness of breath, body aches, abdominal pain, anosmia and aguesia were the predominant symptoms in majority of patients belonging to different categories based on disease severity. Inflammatory markers like D-dimers and ferritin levels determined the overall disease severity with a high accuracy.

Key Words: Disease severity, Clinical presentation, Laboratory investigations, RT-PCR.

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INTRODUCTION

COVID-19 has taken the world by a storm. It has wrecked havoc with the lives of millions of people worldwide. As of 12th April, 2021, 136 million people have been affected with 2.94 million deaths attributed to this deadly virus.[1]

The disease has been relapsing and recurring in waves, owing to its varied presentation from the involvement of respiratory tract to affecting cardiovascular, neurological, gastrointestinal, hepatic, musculoskeletal and almost every organ system of the body.[2] COVID-19 affects people of all age groups. In China, the median age of patients was 30-79 years with a male preponderance.[3-7] The virus mainly affected individuals having comorbidities like diabetes, hypertension, cardiovascular and cerebrovascular disorders.[8-11] Following a heavy influx of COVID-19 patients with multiple and varied presentations, it was decided to carry out a study that would highlight the various abnormalities observed in the clinical, laboratory and radiological findings that predict the course of the disease in the admitted patients.

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The idea was to generate data from the Pakistani population. At the time when this study was started, only limited international data was available. The study also intended to help the healthcare providers identify risk factors enabling them to devise a strategy that will minimise disease progression and formulate treatment guidelines.

The objective of this study was to assess disease severity, based on clinical presentation and laboratory investigations.

METHODOLOGY

This observational study included 445 cases of COVID-19, admitted in Mayo Hospital, Lahore, from 15th March to 31st May, 2020. Diagnosis was made based on PCR positive result and only those patients were enrolled in the study, and the date of PCR positivity was taken as first day of illness. The patients were categorised as mild, moderate, severe and critical, based on their initial presentation. The patient's disease was classified as mild, moderate, severe and critical, according to the guidelines issued by the Ministry of National Health Services, Regulations and Coordination, Government of Pakistan.[12]

Mild cases were those who had symptoms of COVID-19, like cough, shortness of breath or difficulty in breathing, fever, chills, repeated shaking with chills, muscle pain, headache, sore throat, loss of taste or smell, but without any hemodynamic compromise, need for oxygen or chest X-ray findings, oxygen

saturation≥ 94%. Moderate disease patients were those who had hypoxia (Oxygen saturation <94% but >90%) or chest X-ray with infiltrates involving <50% of the lung fields. Severe disease patients were those who had clinical signs of pneumonia (fever/cough) plus either respiratory rate >30, severe respiratory distress, SpO_2 ≤ 90% on room air, chest X-ray involving >50% of lung fields. Critical category had either ARDS, multiorgan dysfunction or septic shock.

Informed written consent to be enrolled for the study purpose and data collection was taken from all the patients having mild and moderate disease and from the attendants in cases of severe and critical disease. All vitals, laboratory and radiological data throughout the course of illness, were noted from the medical records and the most deranged (highest or lowest) values of all the variables were taken to predict the outcome.

The data was analysed using IBM SPSS Statistics 20.0. The quantitative data was expressed as mean ± S.D and median (IQR: Q1-Q3) and comparison was made among groups by using Kruskal-Wallis test as the data was skewed. Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to test the normality of data. Boxplots were used to present duration of stay in the hospital as per status, and inflammatory markers as per severity of disease. ROC curve was used to determine cut-offs of d-dimers for discrimination of severity. Pearson Chi-square test was applied to see association of severity of disease with gender, history, symptoms and presence of chronic diseases, where expected counts were more than 5 in all cells. And likelihood ratio test was applied where assumption of expected frequencies was violated. P-values ≤0.05 was considered significant.

RESULTS

Out of a total of 445 COVID-19 cases, average age was calculated to be 54.6 ± 10.4 years and 286 (64.3%) of them were males. They were categorised into four groups as per disease category. A large majority, i.e. 324 (72.8%) were labelled to have mild disease, 73 (16.4%) moderate, 25 (5.6%) severe, and 23 (5.2%) of them were critical. The average age for male and female patients was not different overall being 55.4 ± 10.3 years for males and 53.3 ± 10.4 years for females. All groups predominantly had more males except moderate category that had 53.4% females. Also travel and contact history had significant association, with mild category having maximum cases with positive travel and contact histories. ($p<0.001$ and 0.003, respectively).

The signs and symptoms also had significant association with severity except for cough, flu-like illness, diarrhea and vomiting with p-values 0.644, 0.511, 0.876 and 0.550, respectively. Sore throat, body aches, anosmia and aguesia had higher percent of positive cases in the mild category group (all values $p<0.001$). Fever, shortness of breath and abdominal pain were more common in patients falling in the severe and critical groups (all values $p<0.001$). All chronic diseases showed a significant association with severity of disease except malignancy with p-value 0.064. Respiratory illness was more common among severe and critical cases, while diabetes was more common among moderate and severe cases. Hypertension was most prevalent among severe cases followed by moderate and critical. Ischemic heart disease was most prevalent among critical, while cerebro vascular disease (CVD), chronic kidney disease (CKD) and chronic liver disease (CLD) were most prevalent among severe cases. The history of smoking was least prevalent among mild and most among severe cases (Table I).

It was noticed that all the markers measured had a significant difference among four groups by severity of disease. Among vitals, the systolic and diastolic blood pressures were significantly low in critical cases, while relatively higher in severe cases. Respiratory rate and pulse were significantly higher in severe and critical cases. Hemoglobin, white blood cell counts, platelet counts were all significantly higher in critical cases. Basophils and eosinophils were significantly lower in mild and lymphocytes were lower in the severe category. In the liver profile, ALT and AST levels were significantly higher for critical, while alkaline phosphatase, albumin and bilirubin were high in mild cases but were all in the normal range so had no significant association with disease severity. Urea, BUN and creatinine were all significantly higher in severe disease group. All inflammatory markers increased significantly with severity of disease. Magnesium, potassium, calcium and phosphate were highest for severe, sodium was highest for mild. Prothrombin time, APTT and INR values differed among the various categories of disease but remained within the usual range (Table II).

It was noted that the duration of hospital stay was prolonged for cases with mild or moderate disease with a median stay of 20 and 24 days, respectively; while those with severe disease had a median stay of 7 days and critical only 3 days. The reason for prolonged stay in mild and moderate cases was the time taken for complete recovery and two consecutive COVID PCR negative reports. In severe and critical cases, the patients died during the 3-7 days period following admission.

Correlation of the inflammatory markers with severity of disease showed that LDH had a slow increase with increase in severity, whereas CPK was different but not very discriminatory. CKMB was equally raised among moderate and severe cases and low in mild but high in critical cases. CRP was also raised with severity of disease. D-dimers could be considered the best discriminatory marker (among 6 tested) for differentiating the severity of disease with serum ferritin level as the second best (Table II).

When the cut-offs were derived by using ROC curve for d-dimer levels, it was noticed that 98.8% of mild cases had levels ≤450, 75.3% of moderate cases had d-dimer levels in the range of 451 – 990, and 87.0% of critical cases had d-dimer levels above 2900. The overall accuracy of the marker to determine severity was 92.1% (Table III). Figure 1 shows comparison of ROC curves for serum ferritin and d-dimers.

Table I: Distribution of cases for chronic diseases in relation to severity of disease.

		Group								p-value
		Mild		Moderate		Severe		Critical		
		n	%	n	%	N	%	n	%	
Any respiratory illness	Yes	11	3.4	9	12.3	5	20.0	**8**	**34.8**	<0.001
	No	313	96.6	64	87.7	20	80.0	15	65.2	
Diabetes	Yes	32	9.9	23	31.5	**8**	**32.0**	3	13.0	<0.001
	No	292	90.1	50	68.5	17	68.0	20	87.0	
HTN	Yes	37	11.4	31	42.5	**14**	**56.0**	9	39.1	<0.001
	No	287	88.6	42	57.5	11	44.0	14	60.9	
IHD	Yes	7	2.2	7	9.6	2	8.0	**5**	**21.7**	0.001
	No	317	97.8	66	90.4	23	92.0	18	78.3	
CVD	Yes	2	0.6	1	1.4	**3**	**12.0**	2	8.7	0.004
	No	322	99.4	72	98.6	22	88.0	21	91.3	
CKD	Yes	8	2.5	12	16.4	**11**	**44.0**	4	17.4	<0.001
	No	316	97.5	61	83.6	14	56.0	19	82.6	
CLD	Yes	11	3.4	1	1.4	**5**	**20.0**	3	13.0	0.003
	No	313	96.6	72	98.6	20	80.0	20	87.0	
Malignancy	Yes	**0**	**0.0**	**2**	**2.7**	**0**	**0.0**	**0**	**0.0**	**0.064**
	No	324	100.0	71	97.3	25	100.0	23	100.0	
Smoking	Yes	59	18.2	32	43.8	**12**	**48.0**	9	39.1	<0.001
	No	265	81.8	41	56.2	13	52.0	14	60.9	

Values in bold indicate significant value for each category.

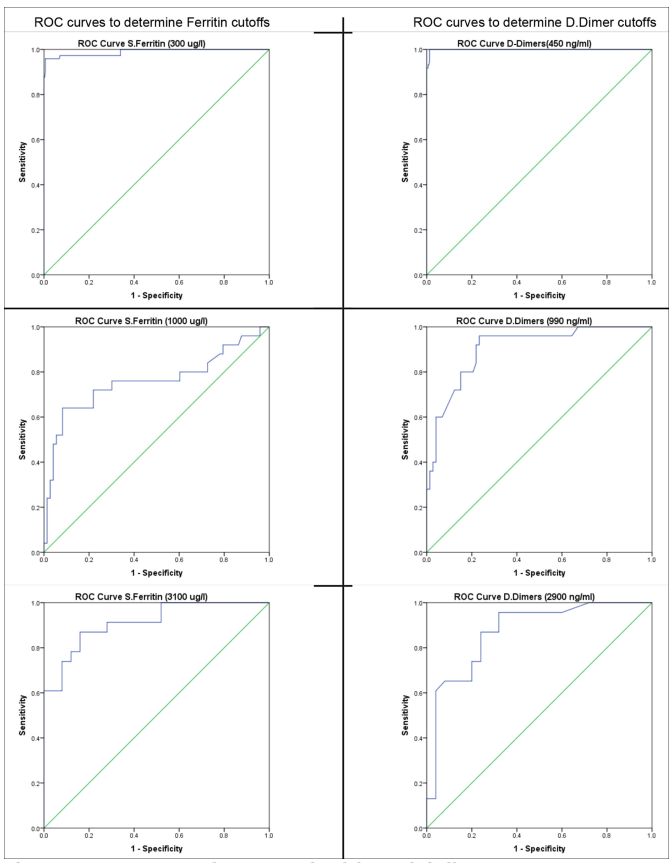

Figure 1: ROC curves for serum ferritin and d-dimers.

DISCUSSION

COVID-19 has had diverse presentations ever since the first case was admitted in the Hospital. Fever was the most common initial symptom presenting in the majority of patients,[13-15] alongwith flu-like illness, cough and shortness of breath. With the passage of time, patients presented with headache, body aches, abdominal pain, diarrhea, anosmia and ageusia. These symptoms had a significant association with the severity of disease with sore throat, body aches, anosmia and ageusia being more common in the mild category, while patients with fever, shortness of breath and abdominal pain had a more severe disease. Smokers and patients with an underlying comorbid condition like diabetes, hypertension, ischemic heart disease, respiratory disease, CVD, CKD or CLD developed a more severe disease and; hence, the highest mortality.[16] Apart from smoking, comorbidities were present in the majority of patients, the most common being hypertension followed by diabetes.[17,18]

Patients in the critical category also showed a high WBC count with a predominance of PMNs ($p<0.001$) suggesting sepsis. Apart from neutrophilia, these patients also had leukopenia ($p<0.001$) that contributed to a high mortality in this group. These results somewhat correlated with a study conducted by Yang Zhao et al. that suggested neutrophilia, leukopenia in addition to low C3 and $CD4^+$ T cells to be the immunity-related risk factors that could predict a high mortality in COVID-19 patients.[19] Further studies are needed to explain the role of these features and markers for a better understanding of the disease.

The biochemical profile of the patients, including the LFTs, and RFTs also had a role in assessing disease severity as these markers were found to be slightly higher in the critical and severe category compared to mild and moderate category of patients. This finding may partly be attributed to the underlying comorbid diseases like CLD, hypertension, diabetes and CKD or could possibly be due to the direct effect of the virus on these organ systems.

Table II: Characteristics of cases as per severity of disease.

		Group												p-value
		Mild			Moderate			Severe			Critical			
		Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	
	Age	55.0	48.0	62.0	54.0	49.0	63.0	**60.0**	**57.0**	**65.0**	58.0	47.0	65.0	0.006
	Days after diagnosis	20.0	19.0	21.0	23.0	17.0	25.0	**7.0**	**5.0**	**10.0**	**3.0**	**2.0**	**4.0**	<0.001
Vitals	Systolic	120.0	115.0	130.0	120.0	110.0	135.0	120.0	110.0	145.0	**90.0**	**85.0**	**90.0**	<0.001
	Diastolic	80.0	70.0	80.0	80.0	70.0	90.0	80.0	70.0	90.0	**55.0**	**50.0**	**60.0**	<0.001
	RR	16.0	14.0	18.0	16.0	12.0	18.0	30.0	22.0	30.0	**32.0**	**30.0**	**34.0**	<0.001
	Pulse	92.0	84.0	96.0	98.0	94.0	100.0	100.0	98.0	102.0	**106.0**	**102.0**	**110.0**	<0.001
	Temperature	99.0	98.6	100.0	100.8	100.3	101.3	101.0	100.3	101.4	**101.0**	**100.0**	**102.0**	<0.001
CBC	HB	11.8	10.6	12.6	11.2	10.5	12.0	**10.9**	**10.4**	**11.8**	11.9	10.6	13.8	0.002
	WBC	6.4	.0	9.5	7.8	5.8	10.4	**11.0**	**9.9**	**13.2**	**14.7**	**13.9**	**16.7**	<0.001
	PLT	297.0	212.5	368.0	302.0	273.0	378.0	309.0	289.0	401.0	**378.0**	**276.0**	**490.0**	0.001
	PMNS	63.6	54.4	78.2	**46.9**	**43.9**	**56.9**	56.3	45.7	65.2	**70.9**	**65.0**	**75.0**	<0.001
	LYMPHO	29.5	23.4	34.6	18.5	16.3	21.0	19.4	15.8	21.0	**16.1**	**12.3**	**16.5**	<0.001
	BASOPHILS	**2.0**	**0.0**	**2.0**	3.0	3.0	4.0	3.0	3.0	5.0	3.0	3.0	6.0	<0.001
	EOSINOPHILS	**1.0**	**0.0**	2.0	3.0	2.0	4.0	3.0	2.0	4.0	**3.0**	**2.0**	**4.0**	<0.001
Bio-Chemistry	Bilirubin	**0.6**	**0.4**	**0.8**	0.4	0.4	0.5	0.4	0.3	0.5	0.4	0.3	0.6	<0.001
	ALT	22.0	16.0	26.0	31.0	23.0	37.0	**32.0**	**24.0**	**36.0**	29.0	24.0	54.0	<0.001
	AST	27.5	20.0	34.0	33.0	24.0	43.0	32.0	24.0	43.0	**36.0**	**27.0**	**56.0**	<0.001
	ALK PHOSPHATE	**92.0**	**73.5**	**118.0**	87.0	68.0	99.0	89.0	67.0	99.0	87.0	66.0	100.0	0.025
	Albumin	**4.4**	**3.9**	**4.7**	3.7	3.2	4.0	3.7	3.6	3.9	3.6	3.2	3.9	<0.001
	Urea	33.0	25.0	39.0	**56.0**	**45.0**	**75.0**	**54.0**	**43.0**	**89.0**	48.0	34.0	78.0	<0.001
	BUN	**15.0**	**12.0**	**17.0**	21.0	17.0	30.0	21.0	19.0	48.0	20.0	17.0	35.0	<0.001
	Creatinine	1.2	0.9	1.3	0.7	0.5	0.9	**0.6**	**0.5**	**1.3**	**0.8**	**0.4**	**1.1**	<0.001
	Urine PH	**6.0**	**5.8**	**6.1**	5.7	5.5	6.0	5.6	5.5	6.0	5.7	5.5	6.0	<0.001
	Blood sugar level	**109.0**	**99.5**	**154.0**	102.0	98.0	109.0	109.0	100.0	129.0	104.0	99.0	114.0	0.020
	D-Dimer	**296.5**	**264.0**	**349.0**	**678.0**	**550.0**	**879.0**	**1876.0**	**1056.0**	**2817.0**	**4590.0**	**3425.0**	**6234.0**	<0.001
	LDH	**213.0**	**178.0**	**256.0**	**238.0**	**209.0**	**301.0**	**278.0**	**209.0**	**301.0**	**390.0**	**309.0**	**473.0**	<0.001
	CPK	**128.0**	**103.0**	**180.0**	**134.0**	**109.0**	**156.0**	**145.0**	**124.0**	**176.0**	**189.0**	**132.0**	**231.0**	<0.001
	CKMB	**16.0**	**12.0**	**20.0**	23.0	20.0	28.0	24.0	20.0	28.0	**34.0**	**27.0**	**59.0**	<0.001
	CRP	**0.3**	**0.2**	**0.4**	**0.8**	**0.5**	**1.5**	**7.2**	**2.5**	**13.2**	**19.6**	**17.2**	**21.3**	<0.001
	Serum Ferritin	**173.5**	**97.5**	**226.5**	**789.0**	**567.0**	**1029.0**	**2301.0**	**987.0**	**3009.0**	**3982.0**	**3425.0**	**4029.0**	<0.001
Serum Electrolytes	Na+	**143.0**	**139.0**	**145.5**	134.0	130.0	138.0	135.0	134.0	138.0	134.0	132.0	139.0	<0.001
	K+	4.2	3.8	4.4	4.4	3.9	4.7	4.5	3.9	4.9	4.2	3.8	4.9	0.001
	CL-	102.0	96.0	105.0	102.0	100.0	106.0	**104.0**	**100.0**	**107.0**	102.0	99.0	103.0	0.001
	MG+	1.9	1.7	2.3	2.2	1.8	2.3	2.1	2.0	2.5	2.3	1.9	2.5	<0.001
	Ca+	9.3	8.8	9.5	9.2	8.6	9.7	**8.8**	**8.3**	**9.2**	9.3	8.6	10.0	0.016
	PO4+	3.6	3.0	4.1	3.8	3.2	4.2	**4.2**	**3.2**	**4.8**	3.9	2.9	4.9	0.006
Bleeding Order	PT	12.0	11.0	13.0	**13.0**	**12.0**	**14.0**	**13.0**	**12.0**	**14.0**	12.0	12.0	14.0	<0.001
	APTT	**35.0**	**33.0**	**36.0**	32.0	30.0	33.0	32.0	30.0	33.0	**31.0**	**30.0**	**34.0**	<0.001
	INR	1.1	1.0	1.1	1.1	1.1	1.2	1.1	1.0	1.2	**1.1**	**1.0**	**1.2**	<0.001

The one with bold values are either significantly higher or lower than other groups.

Table III: D-dimer and serum ferritin levels as discriminatory marker for severity of disease.

	Lab values	Group									
		Mild (n=324)		Moderate (n=73)		Severe (n=25)		Critical (n=23)		Total (n=445)	
		n	%	n	%	n	%	N	%	n	%
D. Dimer (ng/mL)	≤450	320	98.8	2	2.7	0	0.0	0	0.0	322	72.4
	451 - 990	4	1.2	55	**75.3**	4	16.0	0	0.0	63	14.2
	991 - 2900	0	0.0	16	21.9	15	**60.0**	3	13.0	34	7.6
	>2900	0	0.0	0	0.0	6	24.0	20	**87.0**	26	5.8
S. Ferritin (µg/mL)	≤300	301	92.9	2	2.7	0	0.0	0	0.0	303	68.1
	301 - 1000	23	7.1	49	**67.1**	7	28.0	0	0.0	79	17.8
	1001 - 3100	0	0.0	21	28.8	14	**56.0**	3	13.0	38	8.5
	>3100	0	0.0	1	1.4	4	16.0	20	**87.0**	25	5.6

As suggested by Zhang et al, drug toxicity, hypoxia or cytokine storm may contribute to transient liver injuries in COVID-19 patients.[20] The over-expression of the ACE-2 receptors in the tubular cells of the kidney alongwith a raised BUN and creatinine also point to the vulnerability of CKD patients to the SARS-CoV-2 virus.[21]

Among the inflammatory markers, D-dimers, serum ferritin and CRP were significantly raised in the moderate, severe and critical cases with higher levels suggesting a more serious disease.[22] In a local study, CRP, ferritin and LDH were raised in about 90% of the severe cases and in about 70% of the mild category patients, as well.[15] This was in slight opposition to the present study as these markers were found to

be normal in the mild category patients. Cardiac biomarkers like LDH, CPK and CK-MB were also linked with the severity of the disease; the more serious the disease, the raised the marker levels. This enzyme assay helped in recognizing myocardial injury in COVID-19 patients and we inferred that if it is done at an earlier stage of the disease, it could prevent cardiac failure in these patients.[23]

Duration of hospital stay had a very different pattern. Patients falling in the mild to moderate category had a longer duration of stay in the hospital compared to the patients having severe and critical disease. Patients with more serious disease succumbed to their illness earlier, mainly because of underlying comorbidities, ventilator associated lung injury, multi-organ failure and an exaggerated immune response.

This study had certain limitations. The data collected from the patients was during the first wave of COVID-19, so clinical and laboratory data that was found significant then may have become redundant by the time of its publication. Secondly, certain markers like IL-6, pro-calcitonin were not readily available at that time so their relationship to the severity of disease could not be assessed. Thirdly, it was conducted on a small number of patients belonging to a specified area, so the findings cannot be generalised to the whole Pakistani population.

CONCLUSION

This single centered study conducted during the first wave of the pandemic showed a significant interplay of clinical, laboratory and radiological factors responsible for disease severity. Advancing age, smoking and presence of comorbid conditions, mainly hypertension and diabetes, were found to have a significant association with the severity of COVID-19 infection. D-dimers, serum ferritin and cardiac enzymes were helpful markers in assessing the severity of disease.

ETHICAL APPROVAL:

Ethical approval was taken from the Institutional Review Board (IRB) of King Edward Medical University, Lahore prior to initiation of the study.

PATIENTS' CONSENT:

Informed written consents to be enrolled for the study purpose and data collection were taken from all the patients having mild and moderate disease and from the attendants in cases of severe and critical disease

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

TN: Conceived designed the study, paper write-up.
BA: Data collection and statistical analysis.
BS: Proof-reading and discussion.
FS, KN, MN: Result compilation.

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