

## Role of prognostic factors in understanding disease severity in COVID-19 patients: Pakistan ordinance factories Hospital experience

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### ABSTRACT

**BACKGROUND & OBJECTIVE:** Coronavirus disease (COVID-19) is an emerging public health challenge. Study was conducted to determine the association of prognostic factors with disease severity in COVID-19 patients at POF Hospital, Wah Cantt. We conducted a descriptive cross-sectional study at a department of Medicine, POF Hospital, Wah Medical College (affiliated with National University of Medical Sciences) Wah Cantt.

**METHODOLOGY:** We calculated a sample size of 158 patients (WHO Calculator). The study duration was 6 months (November 2020-April 2021). The selection of COVID patients was done through non probability sampling (consecutive). Respiratory sample for all participating patients were collected (from throat or sputum). These samples were tested for SARS-CoV-2 using WHO standard. SPSS version 24 was utilized for data analysis purpose. Chi square test and independent t-test were applied. Logistic regression was applied.

**RESULTS:** Total data consist of 158 patients with COVID-19. Mean age of patients was 52.3±3.26 years. Total leukocytes count (p=0.02), absolute neutrophil count (p=0.001), C reactive protein (p=0.001), NLR (p=0.03) were comparatively greater in patients with Severe COVID-19. While absolute lymphocyte were significantly lower in severe COVID-19 patients as compared to non-severe (p=0.03). Age [OR, 1.06 ;95% CI (1.027-1.114); p=0.001], diabetes mellitus [OR, 0.281 ;95% CI (0.100-0.788) p=0.016 and Hypertension [OR, 3.045 ;(1.044-8.878)95% CI p=0.04] are significant predictors of COVID-19 severity

**CONCLUSION:** Prognostic factors of COVID-19 increased the likelihood of disease progression. C reactive protein and ALC were significant predictors of COVID-19.

**KEYWORDS:** Coronavirus Disease, SARS-CoV-2, World Health Organization.

### INTRODUCTION

Coronavirus disease (COVID-19) is an emerging public health challenge. After the declaration of COVID-19 as a pandemic, 223 countries were reported to be affected with COVID-19 (178 million confirmed cases), and globally more than 3.8 million mortalities [1]. SARS-CoV-2 infection cases are found to be highest in United States followed by Brazil and India [2]. COVID-19 is 3rd leading cause of mortality in United States after cardiovascular disease and cancer in 2020[3]. Pakistan is also drastically affected by

COVID-19 with 1,274,017 confirmed cases, 28, 466 deaths, 1,234 critical cases, and 1,222,987 recovered patients (till Oct 2021). Moreover, 41,319,385 individuals are fully vaccinated in Pakistan [4].

Evidence exist that COVID-19 different variants spread to different countries with the passage of time. WHO reported that the Alpha, Beta, Gamma, and Delta variant spread to 170, 119, 71, and 85 countries, respectively. WHO reported a new variant of SARS-CoV-2 Omicron (B.1.1.529) that origin from South Africa (24 November 2021). Omicron is associated with several mutations, high potential of

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transmissibility, and therapeutic resistance, and it could escape vaccine-induced immunity [5].

According to WHO, the case fatality rate for coronavirus disease is 2.2% (globally). This rate is affected by a number of prognostic factors, including the severity of illness, age, and underlying pre-existing conditions. The severity of COVID-19 is reported to be mild in 81% cases, severe in 14%, and critical in 5% of cases. However, fatality rate is 50% in critical cases [6]. A similar study reported gender, age, low oxygen saturation, high procalcitonin, comorbidities, low CD4 cell count, abnormal high lactate dehydrogenase level, and low albumin level as significant prognostic factors associated with COVID-19 patients [7].

These prognostic factors vary in different countries according to disease severity. These factors help in the stratification of patients based on disease and mortality risk. This process of stratification helps clinicians in optimized management including maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19) and establishing resource utilization strategies for COVID-19 patients [8].

We could not find established prognostic factors for COVID-19 by scientific community. However, available prognostic factors did not have any predictive value and are not robustly evaluated. So, they remained uncertain. Present study was planned to determine the association of prognostic factors with disease severity in COVID-19 patients at Pakistan Ordinance Factories Hospital, Wah Cantt.

### METHODOLOGY

Descriptive cross-sectional study was done at the Medicine department, POF Hospital, Wah Medical College (affiliated with National University of Medical Science) Wah Cantt. The duration of study was months (November 2020-April 2021). A sample size of 158 COVID-19 patients was calculated with 95% confidence interval, moderate severity frequency 28% [9], 7% absolute precision using WHO calculator. We selected all patients of COVID-19 during the study through non-probability sampling (consecutive). All the enrolled patients of the study signed written consent for participation in study. Ethical approval was taken from the respective ethical approval committee of POF hospital (IRB No= ERC#POFH/ERC/10/20). Both gender, age ≥18 years, and patients with COVID-19 diagnosis (using diagnostic criteria of New Coronavirus pneumonia prevention and control program) were included in study. Respiratory samples were collected from the throat or sputum. These samples are tested for SARS-CoV-2 using WHO standard (qualitative reverse transcriptase PCR). Positive results of COVID-19 were specified on the basis of a positive test from a given specimen. After admission, routine biochemical and hematological test were performed. Patients were monitored serially through chest X-rays and chest CT scan.

Severity of COVID-19 was defined on the basis of Shi et al [10] criteria as shown in table-I.

**Table-I: Severity of COVID-19 Criteria.**

Mild disease	On radiographic evaluation, findings will include mild symptoms and non-pneumonia.
Moderate disease	On radiographic evaluation, fever, respiratory symptoms plus strong evidences of pneumonia
Severe disease	Severe dyspnea, respiratory frequency (≥30/min), lung infiltrates (>50% of lung field) in the duration of 24 to 48 hours, Oxygen saturation (≤93%) and PaO2/FiO2 ratio of more than 300.
Critically ill	Respiratory failure, multiple organ dysfunction/failure, in need of mechanical ventilation, and severe septic shock require ICU monitoring and treatment.

Outcomes were measured in terms of mortality (death during data collection period), discharge or treated and patients were still admitted in hospitals (during data collection). Data were analyzed using SPSS version 24. We measured frequencies and percentages for categorical and nominal data. Mean and Standard deviation were calculated as continuous variables. Chi-square test and independent-t-test was applied. A logistic regression model was used in this study. Results with p-value ≤0.05 were considered statistically significant in our study.

### RESULTS

Total of 158 patients were included in the study. There were 101(63.9%) male and 57(36.1%) female. Mean age of patients was 52.3±3.26 years. In our study, 62(39.2%) patients were diagnosed with diabetes mellitus, while 63(39.9%) patients were hypertensive.

Respiratory symptoms were observed in 12(7.6%) patients, however only 5(3.2%) were diagnosed with malignancies. No patient was pregnant in our data.

**Table-I: Frequency distribution of severity of COVID-19 and outcome at 14 days of admission.**

Severity of COVID-19	n(%)
Asymptomatic	2(1.3)
Mild	27(17.1)
Moderate	56(35.4)
Severe	25(15.8)
Critically ill	
Critical with Ards	39(24.7)
Critical with Sepsis	4(2.5)
Critical with Septic shock	5(3.2)
<b>Outcomes at 14 days</b>	-
Treated/discharges	79(50)
Still admitted	63(39.9)
Mortality	16(10.1)

Among all the patients, 16(10.2%) were active smokers, while 142(89.8%) were non-smokers. Severity and outcomes of study are shown in (Table-I). Mean days from onset to the presentation of disease were 5.6±3.4 days. Mean total leukocytes were 8104.05±417.5 cells/μL, mean absolute neutrophil count was 6125.27±384.1 cells/μL,

mean absolute lymphocytes were 1782.01±884.1 cells/μL, mean C reactive protein 56.1±6.7 mg/L, mean neutrophil to lymphocyte ratio (NLR) was 7.5±2.4.

Total leukocytes count (p=0.02), absolute neutrophil count (p=0.001), C reactive protein (p=0.001), NLR (p=0.03) were significantly high in patients with Severe COVID-19 as shown in table-II

The majority of patients in the age group 41-70 years had severe disease (14.6% vs 1.3%) as compared to patients in age group 18-40 years (p=0.001). Diabetes mellitus also showed a significant association with the severity of COVID-19 (p=0.001), as shown in table-III. Gender (p=0.574), Smoking (p=0.581), hypertension (p=0.068),

Ischemic heart disease (p=0.216), pregnancy (p=1.00), respiratory disease (p=0.764) and malignancy (p=0.261) showed insignificant association with severity of disease.

Critically ill conditions showed significant association with prognostic factors, including gender (p=0.021), age (p=0.001), diabetes mellitus (p=0.003), and malignancy (p=0.001) as shown in table-IV. While other prognostic factors smoking (p=1.00), hypertension (p=0.759), IHD (p=0.300), respiratory (p=0.761) are non-significant.

Table-V shows Binary logistic regression analysis. Age[OR, 1.06 ;95% CI (1.027-1.114);p=0.001], diabetes mellitus[OR, 0.281 ;95% CI (0.100-0.788) p=0.016 and Hypertension [OR, 3.045 ;(1.044-8.878)95% CI p=0.04] .

**Table-II: Laboratory parameters of COVID-19 patients.**

Laboratory Parameters	Severity		p-value
	Non severe (asymptomatic, mild, moderate)	Severe (severe and critically ill)	
Total leukocytes count (Cells/μL)	7403.64±348.5	8919.58±475.2	0.02
Absolute neutrophil count (cells/μL)	5016.28±306.8	7416.5±424.9	<0.001
Absolute lymphocyte count (cells/μL)	2049.7±852.4	1470.2±820.8	<0.001
C-reactive protein (mg/L)	28.1±3.7	88.7±7.9	<0.001
NLR	3.7±0.9	12.03±3.4	0.03

**Table-III: Association between prognostic factors and Severity of COVID-19.**

Prognostic factors		Severity					p-value
		Asymptomatic	Mild	Moderate	Severe	Critically ill	
Gender	Male	2(1.3%)	14(8.9%)	36(22.8%)	16(10.1%)	33(20.9%)	0.574
	Female	0(0%)	13(8.2%)	20(12.7%)	9(5.7%)	15(9.5%)	
Age	18-40 years	2(1.3%)	16(10.1%)	13(8.2%)	2(1.3%)	0(0%)	<0.001
	41-70 years	0(0%)	11(7%)	43(27.2%)	23(14.6%)	48(30.4%)	
Diabetes Mellitus	No	1(0.6%)	22(13.9%)	41(25.9%)	11(7%)	21(13.3%)	<0.001
	Yes	1(0.6%)	5(3.2%)	15(9.5%)	14(8.9%)	27(17.1%)	
Malignancy	No	2(1.3%)	27(17.1%)	55(34.8%)	25(15.8%)	44(27.8%)	0.261
	Yes	0(0%)	0(0%)	1(0.6%)	0(0%)	4(2.5%)	

**Table-IV: Association of prognostic indicators and critically ill patients.**

Prognostic factors		Critically ill				p-value
		No critically	Critically ill with ARDs	Critically ill with sepsis	Critically ill with septic shock	
Gender	Male	68(43.0%)	29(18.4%)	0(0%)	4(2.5%)	0.021
	Female	42(26.6%)	10(6.3%)	4(2.5%)	1(0.6%)	
Age	18-40 years	33(20.9%)	0(0%)	0(0%)	0(0%)	<0.001
	41-70 years	78(48.7%)	39(24.7%)	4(2.5%)	5(3.2%)	
Diabetes Mellitus	No	75(47.5%)	20(12.7%)	0(0%)	1(0.6%)	0.003
	Yes	35(22.2%)	19(12%)	4(2.5%)	4(2.5%)	
Malignancy	No	109(69.0%)	37(23.4%)	4(2.5%)	3(1.9%)	<0.001
	Yes	1(0.6%)	2(1.3%)	0(0%)	2(1.3%)	

**Table-V: Regression model for prognostic factors (Logistic regression model).**

Prognostic factors	Regression Model				
	OR (95% CI)	p-value	Prognostic Factors	OR (95% CI)	p-value
Gender	1.43(0.491-4.197)	0.509	ANC	1.0(1.0-1.0)	0.293
Age	1.069(1.027-1.114)	0.001	ALC	0.999(0.998-1.00)	0.016
Diabetes mellitus	0.281(0.100-0.788)	0.016	CRP	1.019(1.007-1.030)	0.001
Hypertension	3.045(1.044-8.878)	0.041	NLR	1.005(0.987-1.023)	0.589
Respiratory	0.322(0.062-1.680)	0.179	LCR	1.00(0.999-1.001)	0.821
IHD	7.35(0.197- 2.736)	0.646	TLC	1.00(1.00-1.00)	0.414
Malignancy	0.268(0.20-3.611)	0.321	-	-	-
Smoking	0.399(0.082-1.933)	0.254	-	-	-
Renal	0.385(0.069-2.139)	0.276	-	-	-

## DISCUSSION

Prognostic factors guide physicians about the severity of disease and risk of mortality. COVID-19 risk factors stands alone or in combination with risk associated models play a significant role in the optimized process and resource utilization in future for patients care in COVID-19<sup>[11]</sup>.

In the present study, age, diabetes mellitus, hypertension, high CRP, and reduction in ALC are significant predictors of the Severity of COVID-19 ( $p < 0.05$ ). Kornumet al. reported that high mortality risk in type 2 diabetes mellitus is associated with pneumonia on admission in hospital, while in non-diabetic patients, its associated with community-acquired pneumonia<sup>[12]</sup>. Yang et al. reported that SARS CoV-2 patients' mortality is associated with diabetes mellitus and ambient hyperglycemia as an independent risk factor<sup>[13]</sup>. Mechanism behind poor clinical outcomes of COVID-19 diabetic patients includes, T lymphocyte response reduction, immunity disorders, neutrophil function reduction, and antioxidant system depression<sup>[14]</sup>. Another similar study reported that diabetic patients diagnosed with COVID-19 are at greater risk of disease severity associated with inflammatory factors, organ damage, and hypercoagulability<sup>[15]</sup>. Guan et al. reported that diabetes mellitus is the most influenced factor in COVID-19 patients. They are at more risk of disease development and rapid clinical deterioration<sup>[16]</sup>.

In the present study, age ( $p = 0.04$ ) is an important factor to get disease severity and poor prognosis. Li et al. reported that the high age group, high LDH level, high cytokine levels and hypertension are significant predictors of COVID-19 severity<sup>[17]</sup>. Another study reported that body temperature, peripheral oxygen saturation  $< 92\%$ , creatine kinase, male (sex) and high age group was more likely to develop severe COVID-19 (with the increasing number of prognostic factors)<sup>[18]</sup>.

In our study, Total leukocytes count ( $p = 0.02$ ), absolute neutrophil count ( $p = 0.001$ ), C reactive protein ( $p = 0.001$ ), NLR ( $p = 0.03$ ) were significantly high in patients with Severe COVID-19. A similar study reported that eosinophils and lymphocyte count was significantly lower in patients with

severe COVID-19 ( $p = 0.002$  and  $p = 0.001$ )<sup>[19]</sup>. Evidence exist that T lymphocytes and B lymphocytes were significantly lower than in critically ill patients<sup>[20]</sup>. Similar studies reported that AST, ALT, GGT, AND LDH were elevated in severe COVID-19 patients<sup>[21]</sup>. A study reported that high white blood cells count, low blood platelet count, high blood D-dimer, high blood C-reactive protein, high blood neutrophil count, and high blood bilirubin are significant predictors of COVID-19 severity<sup>[22]</sup>. Proper knowledge and dissemination of information is very important in understanding the disease at various levels<sup>[23-25]</sup>.

**Strength:** It's a new study in developing and resource limited country like Pakistan.

**Limitation:** Results of our study are not generalizable to whole population affected with COVID-19 because our study was restricted to single center. Another limitation is that we didn't consider antiviral agents and corticosteroid usage as a variable in our data. We also did not consider cytokines (pro-inflammatory) and early CD8+T (cell response) associated with COVID-19 severity. Selection bias was not controlled due to a limited number of patients.

## CONCLUSION

Prognostic factors of COVID-19 increase the likelihood of disease progression. Disease severity of COVID-19 is associated with age, diabetes mellitus, hypertension, and other laboratory parameters. We need to assess and monitor closely prognostic factors that help in the development of important and immediate interventions regarding COVID-19 severity in the health sector.

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**SyedaTurab Fatima Abidi:** Analysis and results write-up.

**Syed Asim Ali Shah:** Conception, critical revision of data.

**Lubna Ghazal:** Revision of manuscript and data interpretation.

**Tazaeen Hina Kazmi:** Final approval of the version to be published.

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