

FACTORS RESPONSIBLE FOR SEVERITY OF INFECTION IN COVID 19 PATIENTS: A MULTICENTER STUDY

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Abstract

Background & Objective: After the Spanish Flu world has seen epidemics of SARS and MERS; however, these epidemics have no comparison to the magnitude of devastation caused by COVID-19. This virus originated from Wuhan, China and spread to every nook and corner of the world within weeks. In three months World Health Organization had labeled it as a pandemic. This novel deadly virus shows no discrimination of race or age. Everyone is equally at risk of developing the infection; however, clinical severity is thought to be influenced by age and the presence of comorbidities. Furthermore, an increased rate of intensive care admissions, length of stay, need for mechanical ventilation, and mortality have been reported in patients with COVID-19 infections having comorbidities. The objective of this study was to evaluate the Factors responsible for clinical severity of COVID 19 infection in patients presenting to tertiary care hospitals in Lahore.

Methods: This Descriptive observational study was conducted simultaneously at three tertiary care hospitals in Lahore. A total of 200 confirmed patients with COVID-19 infection by RT PCR were included in the study. The case records of all the inpatients in the General Corona ward, Isolation wards, HDUs and ICUs were analyzed. Data analysis was performed in SPSS 20. Age, gender, and comorbid including Diabetes, hypertension, ischemic heart disease were recorded and their relationship with the severity of COVID 19 infection was studied by applying the Spearman's rank correlation and Fisher's exact test.

Results: Out of the total 200 patients 54.5% were male and 45.5% were female, with a mean age of 58.29 ± 15.20 years. Critical and severe disease was seen in 33% and 63% of patients respectively. Most frequent comorbidities reported were Hypertension (HTN), Diabetes (DM), ischemic heart disease (IHD), and lung diseases. A statistically significant positive association was observed between the severity of COVID 19 infection and increased age, diabetes. Hypertension was most frequently reported comorbid but association was not statistically significant. However, patients who had HTN along with ischemic heart disease had a statistically significant positive association with the severity of the disease.

Conclusion: Advanced age, diabetes Mellitus and hypertension when present in patients with ischemic heart disease have a statistically significant association with clinical severity of patients suffering from COVID 19 infection.

Keywords: COVID 19, Clinical Severity, Age, Comorbidities, Diabetes (DM), Hypertension (HTN), Ischemic heart disease (IHD).

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Clusters of mysterious pneumonia appeared in Wuhan China by the end of December 2019 which were later confirmed to be caused by a novel Corona virus known as COVID-19 / SARS-CoV-2 virus.¹ COVID-19 infection was initially spread by animals to humans, but later human to human transmission by respiratory droplets became the main transmission mode.² Both symptomatic and asymptomatic individuals with the infection are reported to spread the infection, which has led to its spread in masses like wildfire.³ Ultimately, this epidemic was labeled as a pandemic by World Health Organization (WHO) in early 2020. This pandemic has created havoc in many highly developed and developing countries which included the likes of America, Brazil, Mexico and India to name a few.⁴

The first case of COVID 19 was reported in Pakistan on the 26th of February 2020. Initially, this spread was confined to people with a history of foreign travel but within weeks local transmission became the major cause of spread. Within a year from the detection of the first case in Pakistan, the number of COVID-19 cases had escalated from a few thousand to more than 3 million in 2021. COVID-19 infection is a continuing menace and carries a huge burden of morbidity and mortality, Spectrum of disease ranges from mild symptoms in 80% comprising mainly of fever, cough to more serious symptoms in 15%, which include dyspnea and require hospitalization, 5% of patients develop life-threatening complications like pneumonia, sepsis/ DIC, ARDS, thromboembolic phenomenon etc. and require ICU admissions.¹ Monárrez-Espino et al have reported factors like older age, gender, Diabetes Mellitus and obesity to be responsible for a severe COVID-19 infection along with more need for intensive care admissions and need of intubation.⁵⁶ A Chinese study had reported increased age, raised D dimer level and a higher qSOFA score to be associated with the severe disease having a poor prognosis.^{7,9} As Compared to the previous epidemics of SARS and H1N1, COVID-19 infection is reported to be responsible for severe infection leading to ARDS in older patients having comorbidities.¹⁰ According to the data of

the International Diabetes Federation Pakistan is in 7th place in harboring the largest population of diabetes. Similarly, Hypertension, ischemic heart disease and Obesity are also on the rise here. Many international studies have studied the effect of comorbidities on the clinical severity of COVID-19 Infection however there is a scarcity of data in this regard in our local Pakistani population. Thus, we intend to study the effect of comorbidities on the clinical severity of COVID-19 infection in our local population so that these patients could be triaged early and appropriately managed in hospitals.

METHODS

This descriptive observational study was conducted at three tertiary care hospitals in Lahore, including Lahore General Hospital, Jinnah Hospital Lahore and Chaudhary Muhammad Akram Teaching Hospitals, Lahore. A total of 200 patients were included after calculating the sample size of 194, keeping the expected proportion of Covid-19 cases of 30% as mild cases, 56.9% as moderate cases, 10.1% as severe cases, the margin of error as 5% and confidence interval as 95%¹¹. After taking approval from the Hospital ethical committee, 200 COVID-19 RT-PCR positive patients more than 18 years of age were enrolled in the study. A Confirmed case was defined as a patient with positive RT-PCR of SARS-CoV-2 in either nasal or pharyngeal swab specimens. Patients who had a negative RT-PCR of SARS-CoV-2 or who were less than 18 years of age were excluded from the study. Patients with a BMI of more than 35 were labeled as Obese. WHO criteria were used for labeling the patients as having diabetes. Already diagnosed patients with hypertension, ischemic heart disease, lung disease, and chronic kidney disease who were already on treatment before admission with COVID -19 infection were labeled as having the comorbidities.

Case records of all the inpatients of the General Corona ward, Isolation wards, HDUs and ICUs were analyzed and recorded on a pre formed questionnaire in the first phase. In the second phase, the data were entered into the statistical package for social sciences (SPSS) version 20 for statistical analysis. Data contained both

qualitative and quantitative variables.

COVID-19 infection was classified as mild, moderate, severe and critical according to Pakistan Ministry of Health clinical management guidelines of COVID-19.¹² Factors including age, gender and comorbidities like diabetes, hypertension, BMI, ischemic heart disease, lung disease, chronic kidney disease and smoking were recorded. Qualitative variables i.e., gender, mode of oxygen supplementation and comorbidities, were presented as frequency and percentages. The quantitative variables, i.e age were presented as mean and standard deviation. The relationship with the severity of COVID 19 infection was studied by applying the Spearman's rank correlation and Fisher's exact test.

RESULTS

Out of the 200 patients enrolled in our study, 54.5% were male and 45.5 % were female. The mean age was 58.29 ± 15.20 years (ranges from 20 to 94 years). A major chunk of our patients 55% were between 51 to 70 years of age. Severe disease was seen in 63% of our patients and 33% had critical disease, whereas only two of our patients had a mild COVID-19 infection.

Five patients maintained their oxygen saturation

Table 1: Mode of Oxygen supplementation

Oxygen Modality	Frequency (N 200)	Percent %
Room air	5	2.5
Nasal Cannula	52	26
Face mask	51	25.5
Non rebreathing face mask	34	17.0
CPAP BIPAP	43	21.5
HFNO	2	1.0
Mechanical ventilation	13	6.5
Total	200	100.0

on room air, rest of them needed supplemental oxygen in some form. Commonest oxygen modality used was nasal cannula (table 1).

A significant positive association ($p < 0.000$, r_s

Table 2: Co-morbid percentage and Disease Severity ($p < 0.05$ significant)

Comorbid	No of patients (N 200)	Percentage %	Relation r_s	p value
Hypertension	121	65	0.129	0.070
Diabetes	111	55.5	0.226	0.001
Ischemic heart disease	33	16.5	0.080	0.258
HTN+ DM	84	42	0.131	0.065
HTN+IHD	36	18	0.157	0.027

0.284) was reported between severity of COVID-19 infection and age of patients. Similarly a positive association was reported between age and outcome of patients ($p < 0.001$, $r_s .226$). The p-value between the severity of COVID-19 infection and gender was insignificant ($p < 0.577$, $r_s -.040$).

Comorbidities were reported in 77% of our patients out of which commonest reported comorbidities were hypertension 60.5%, diabetes 55.5%, ischemic heart disease 16.5% lung diseases 15% respectively. Many patients in our study sample had multiple comorbidities out of which 42% had both hypertension and diabetes whereas 18% had both hypertension and ischemic heart disease. A statistically significant p-value < 0.05 and a positive r_s association was found on applying Spearman's rank correlation between the severity of COVID 19 infection and age of patients, diabetes and HTN+IHD (table 2).

However Statistically insignificant p-value > 0.05 was found between the severity of COVID 19 infection with hypertension, ischemic heart disease. However, in patients who suffered from both hypertension and

Table 3: Comorbid and Disease Severity Cross tabulation ($p < 0.05$ significant)

		Severity				Total	Fisher Exact's Test (p value)
		Mild	Moderate	Severe	Critical		
Comorbid	Yes	0 (0%)	3 (1.5%)	91 (45.5%)	60 (30 %)	154 (77%)	0.000
	No	2 (1%)	3 (1.5%)	35 (17.5%)	6 (3%)	46 (23%)	
Total		2 (1%)	6 (3 %)	126 (63%)	66 (33%)	200 (100%)	

ischemic heart disease had a statistically significant association with severity of COVID-19 infection. Association between co-morbidities and severity of COVID-19 infection was statistically significant with a $p < 0.000$ on applying the Fisher's exact test (table 3).

DISCUSSION

COVID-19 is a public health emergency of international concern (PHEIC) which has affected millions of people in the world and is a leading cause of mortality. The fatality rate in Pakistan is 2.1% which is much lower than the rest of the world as the fatality rate in the rest of the world is around 2.3%. In our study the Spectrum of COVID 19 infection was narrow comprising mostly of severe and critically ill patients, this is contrary to the findings of a Chinese study in which 14% of their patients had severe disease and 5% had the critical disease.¹ Major factor responsible for this Spectrum of disease severity in our patients could be that the mild cases were mostly managed at home and later as the number of cases increased exponentially in Pakistan most of the patients even with the moderate disease required 1-5L of oxygen were preferably managed at homes because of saturation and lack of beds in hospitals.

Our study uncovered multiple risk factors which were responsible for the increased severity of COVID-19 infection. The factors which had a high impact on the severity of infection included older age, cardiovascular diseases, diabetes. Older age was the first and far most important factor responsible for the severity of COVID 19 infection which was also confirmed by our study in which 96% of patients had severe/ critical disease requiring HDU/ICU admissions out of which 49% of patients were more than 60 years of age. Moreover, in the previous epidemics of SARS and MERS older age was an important predictor of mortality.¹³ Similar results have been reported by Wu Z who in their study reported 22.8% of patients with serious infections as being more than 70 years of age.¹ Opal SM, in their study on sepsis, proposed age-related weak humoral and cell-mediated immunity to be the main factor responsible for failure in controlling the

inflammatory response and viral replication resulting in grave outcomes.¹⁴

Male gender was another important risk factor for acquisition of COVID 19 infection as 54.5% of our study population was male. The findings of Chen N et al are very similar to our findings they reported 67% of their patients as being male.¹⁵ Higher occupational exposures of males could be a possible explanation for higher rates of infection in them. Hiroki U in their meta-analysis reported majority of their patients as being male and also reported a severe COVID 19 infection in them as compared to the female population of the study.¹⁶ However the findings of our study were contrary to their findings as we found no significant association between male gender and severity of COVID 19 infection. The findings of Guan et al support our findings as they also did not find any significant gender difference in requirements of ICU care in patients with COVID 19 infection.¹⁷

The presence of cardiovascular disease was a common finding in our patients as, 65% had HTN, 16.5% had ischemic heart disease and 18% had both HTN and IHD. The presence of both essential Hypertension and undiagnosed hypertension in our population can be a possible explanation for this finding. Paul SS have similarly reported HTN as the commonest comorbid in patients with COVID 19.¹⁸ Initially it was thought that activation of angiotensin-converting enzyme 2 receptors by SARS- CoV-2 virus which are present in both the vessels and lung make them vulnerable to COVID 19 infection as these patients are already on ACE inhibitors for the control of hypertension but later this concept was largely disapproved.¹⁹ Contrary to our findings, Sanyaolu A have reported poor outcomes in patients with hypertension either because of HTN itself or as a result of other cardiovascular comorbid.²⁰ However we found a severe COVID-19 infection in patients who suffered from hypertension and ischemic heart disease both in contrast to patients who only suffered from HTN.

Diabetes was the second commonest comorbid reported in our patients. Around 425 million people are suffering from diabetes worldwide, this value is

expected to cross 700 million by the year 2045.²¹ Diabetics are a vulnerable segment of the population who already have a weakened immune system. Multiple local and international studies have reported increased severity, progression of disease, need of ICU care and mortality in COVID 19 patients suffering from diabetes.^{22,23} Similarly Bode B documented hyperglycemia either because of diabetes or as a side effect of steroid therapy to be an independent risk factor for increased severity and increased mortality moreover they reported higher mortality in patients with uncontrolled glycemia.²⁴ As most patients with diabetes are older in age and have multiple coexistent diseases like HTN, IHD and CRF, therefore presence of multiple comorbidities along with diabetes is one of the factors responsible for severe disease and fatal outcomes in patients suffering COVID 19 infections.²⁵

Our study has unraveled many important risk factors responsible for the severity of COVID-19 infection but it has certain limitations. One of the limitations of our study was that the majority of our study population had a severe infection. This limited our ability to study the infection in the general population as they were lesser in number. Additionally, we were only able to study patients admitted to the hospital, which may not represent all patients with covid-19 infection. Future studies should focus on patients with milder infections to better understand the natural history of the infection.

However, our study does have several strengths. First, our study population was well-characterized and included detailed information on demographics, clinical features, and outcomes. Second, we had many patients with covid-19 infection, which allowed us to identify rarer characteristics and outcomes of the infection. Finally, our study was conducted at multiple centers, which increases the generalization of our findings.

CONCLUSION

In conclusion, our study provides important insights into the characteristics and outcomes of COVID-19 infection in a large, well-characterized cohort of patients. Early diagnosis and having a history of expo-

sure to COVID-19 seem to reduce the risk of developing a severe case of the virus. However, older individuals, those with a fever, fatigue, cough, hypertension, diabetes, and ischemic heart disease are all more at risk for developing a severe case of COVID-19. It is essential to pay attention to cases with these risk factors to prevent poor prognosis.

Conflict of Interest

None

Funding Source

None

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