Risk factors associated with mortality in COVID-19 patients: a retrospective case control study

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Abstract

Background: COVID-19, a novel disease, appeared in December 2019 in China and rapidly spread across the world. This study aimed to investigate and find out the factors responsible for death of COVID patients by comparing with recovered patients.

Methodology: A retrospective, case control study was conducted from August 2020 to October 2020 in three hospitals of Poonch division, AJK. Total 192 patients who have been admitted in a hospital with symptoms of COVID-19 and positive PCR test, including 152 recovered from the infection and 40 died, were enrolled in the study. Data of age, gender, occupation, body weight, temperature, diabetic status, hypertension, cardiovascular disease, lungs disorder, kidney disorder, tuberculosis, cancer and smoking was collected for all patients and entered in a datasheet. Different factors were then compared statistically between recovered and dead patients.

Results: Died patients had significantly higher age ($P=0.000$) and body temperature ($P=0.000$) as compared to recovered patients. Heart disorder, lungs disorder, older age, diabetes and hypertension were found to be significant risk factors of the death in COVID-19 patients. Mortality rate was found to be significantly higher in patients with heart disorder ($P=0.000$; $OR=5.07$), lungs disorder ($P=0.000$; $OR=4.0$), older age ($P=0.000$; $OR=3.44$), diabetes ($P=0.001$; $OR=2.49$) and hypertension ($P=0.024$; $OR=1.84$) as compared to the COVID-19 patients without these factors. Mortality rate was also higher for the patients with smoking and some kidney disorder but not significant ($P=0.170$ and 0.191 respectively). Among the died patients, 39 (97.5%) had 1 (2.5%) or more than one of the risk factors were present while 1 patient had no obvious risk factor.

Conclusion: The study concludes that heart disorder, lungs disorder, older age, diabetes and hypertension are significant risk factors of the death in COVID-19 patients. More the risk factors accumulate in a person, higher will be the risk of death.

Background

Corona viral disease commonly known as COVID-19 is now declared “once-in-a-century” pandemic reaching across the world [1]. Fundamentally, two factors made this disease such a threat, first; the exponential rate of transmission and the second; it can kill apparently healthy adults in addition to its known risk for old ages [2]. Unfortunately, there has been a significant suspicion in understanding of scientific community regarding disease transmission before /without onset of symptoms. As of now, human-human viral contraction during incubation period of symptomatic patients is widely reported [3]. According to “John Hopkins ABX guide”, elder people and those with co-morbidities such as cancer, chronic kidney disorders, chronic obstructive pulmonary disorder (COPD), compromised immune system, serious cardiovascular disease, sickle cell anemia and type II diabetes are highly at risk of serious illness [4].

Center for disease control and prevention (CDC) has recently updated the list of underlying medical conditions potentially exacerbating COVID-19 infection. The list is meant to facilitate clinical care of patients however, it is strongly recommended to stay in touch with science for updates as situation is constantly evolving regarding knowledge about co-morbidities [5]. Our current knowledge about co-morbidities such as asthma, hypertension, cardiovascular disease, and chronic lung disorders are based on mixed or limited evidence that simply means more investigation are needed [5]. Reason behind inconsistencies in data may include heterogeneity of meta-data; as most of the surveys are being conducted on data available online. There are also reports about spatial variation in COVID-19 severity, affected by local determinants such as racial composition, population density and socio economic conditions [6]. In developing countries such as Pakistan, COVID-19 has already posed a state of emergency as number of fatalities has sharply increased. In many cases, patient’s clinical history is not available and any underlying condition is likely to worsen the illness that may lead to death. Therefore, it is highly merited to conduct local case control studies for hand on knowledge important for clinical, research and public health policy matters. The present retrospective case control study was aimed to gain better insight of morbidity and mortality dynamics of COVID-19 and to clarify and highlight the role and contribution of different co-morbidities and patients' factors in death of COVID-19 patients, especially in the region of Azad Jammu and Kashmir.

Methods

Study Design, Place and Duration

This was a retrospective, case control study conducted during August 2020 to September 2020 in Sheikh Khalifa Bin Zayd Al-Nahyan district headquarter (DHQ) hospital Rawalakot, district headquarter (DHQ) hospital Palandari, and district headquarter (DHQ) hospital Bagh, AJK.

Inclusion criteria

In current study, patients who have been admitted in one of the three hospitals with clear symptoms of COVID-19 and positive PCR test were included while the patients with or without symptoms and positive test who were not been admitted in hospital for COVID-19 were not included.

Patients and Data

A total of 192 patients fulfilling the inclusion the criteria were enrolled retrospectively. These included 152 patients who recovered from the infection and 40 patients who died of the COVID-19 in hospital. Clinical data and home addresses of all enrolled patients was retrieved from hospital and the missing data was collected by meeting the patients in hospital during follow-up in case of recovered patients or by meeting the relatives and retrieving the medical history of died patients. The data was divided in two categories i.e. i- patients history and symptoms, and ii- co-morbidities. The patients history and symptoms included name, area of residence, profession, age, gender, body weight and average body temperature during the hospital stay. Co-morbidities included patient's diabetic status, hypertension history, heart disorder, any lungs disorder, any kidney disorder, tuberculosis, cancer, smoking, any liver disorder, autoimmune disorders and any other illness. Strict compliance of standard operating procedure SOPs (for COVID-19) was ensured while obtaining the data and meeting the patients.

Statistical analysis

All the obtained data was entered in a datasheet of statistical package for social sciences (SPSS), version 16.0. Data about age, body weight and body temperature was quantitative while the data of all other factors was qualitative. Qualitative data was analyzed using Chi square test and quantitative data was analyzed using independent sample Student's T-test. A value of P less than 0.05 was considered as significant statistically. Odd ratio along with 95% confidence interval of recovered and dead patients was calculated for qualitative factors while mean, median, standard deviation, minimum and maximum values were calculated for quantitative factors of both died patients and recovered patients. The data about patients' area of residence, profession, tuberculosis, cancer, liver disorder, autoimmune disorders and any other illness was not included in the final analysis to ensure unbiased results because the data about these factors was insufficient not available for all patients.

Results

Distribution of risk factors in died patients

Seven of the qualitative risk factors were analyzed for their distribution and concentration in dead patients ($n=40$). These were: older age, heart disorder, lungs disorder, diabetes, hypertension, kidney disorder and smoking. The last two, though have non-significant effect on risk of death in current study, might have some contribution to the death in combination with others. Among 40 died patients, 3 had combinations of 5 factors present at same time (7.5%), 4 patients had combinations of 4 risk factors (10%), 14 patients had 3 risk factors combined at same time (35%), 9 patients had 2 risk factors (22.5%), 9 had only one risk factor (22.5%), while 1 (2.5%) patients had no risk factor at all (Table 1). The most frequent risk factor was older age, which was present in 29 out of 40 died patients, followed by diabetes (17) and lungs disorders (17), then hypertension (15), heart disorder (12), smoking (6) and then kidney disorder which was present in only 4 of the died patients

(Table 1; Table 2). In the current study, 97.5% of the patients who died of COVID-19, had one or more than one risk factors present along with corona virus infection. However, 1 patient (2.5%) had no other obvious risk factor except corona virus infection as the patient was a non smoker, non diabetic female of 45 years with no hypertension, cardiac, lungs or kidney disorder.

Patients' factors and co-morbidities

A total of 10 health conditions reported as co-morbidity with reference to COVID-19 were documented as commonly occurring and hence were analyzed. These included diabetes, lungs disorder, renal impairment, cardiovascular diseases, tuberculosis, cancer, and hypertension. The data about gender, age, fever, body weight and smoking was also recorded.

Data showed that, co-morbidities such as diabetes, lungs disorder, cardiovascular diseases, and hypertension were statistically significant factors influencing risk of mortality. Among the factors with quantitative data, age and fever were significantly different between dead and recovered patients while body weight difference was statistically non-significant. Among qualitative factors, gender, smoking and kidney disorder were found as non-significant factors. Patients' area of residence, profession, tuberculosis, cancer, liver disorder, autoimmune disorders and any other illness were not included in the final analysis because of insufficient data for both.

Qualitative Factors

Heart disorder: Heart disorders were found to be most significant risk factor of death for COVID-19 patients in the current study as the risk of death in patients with heart disorder was found to be 5.07 times higher as compared to those without any cardiovascular disease (*OR: 5.07; 95% CI: 2.30-11.17*). The rate of death in patients with heart disorder was 57.1% while the same for patients without heart disorder was 16.4%, significantly higher in patients with heart disorder (*P=0.000*). The heart disorder is a powerful predictor of death in COVID-19 patients (Table 2).

Lungs disorders: A total of 33 patients in the study had lungs disorders, out of which, 51.5% died. The risk of death was calculated to be 4 times higher for the COVID patients with lungs disorders (*OR: 4.0; 95% CI: 2.24-7.26*) as compared to those with healthy lungs. Out of the total 149 patients without any lungs disorder, 23 (14.5%) died and the rate of death was significantly lower as compared to those with any lungs disorder (*P=0.000*). So, the lungs disorder is a very significant risk factor of death in COVID-19 patients (Table 2).

Diabetes: Diabetes was appeared as a significant risk factor in the study. A total of 43 patients were reported to be diabetic out of them, 17 (39.5%) were died conversely, 23 out of 149 (15.4%) non-diabetic patients died. The percentage of death was significantly higher in diabetic patients as compared to non-diabetic patients (*P=0.001*). Odds ratio of death for diabetic patients was 2.49 (95% CI: 1.5-4.1) as compared to non-diabetic patients. So, the diabetic patients have about 2.5 times more risk of death if infected with COVID-19 as compared to non-diabetic ones (Table 2).

Hypertension: Hypertension was appeared to be another significant risk factor associated with death in COVID-19 patients (Table 2) as 32.6% of the hypertensive patients died in the study as compared to 17.1% of the non-hypertensive patients and the rate of death was significantly higher in hypertensive patients (*P=0.024*). The hypertensive patients had almost double the risk of death (*OR: 1.84; 95% CI: 1.11-3.06*) as compared to non-hypertensive patients (Table 2).

Kidney disorder: A total of 11 patients in the study had some kidney disease in the present study out of which, 4 (36.4%) died as compared to 36 out of 181 (21%) patients without kidney disorder and the difference of death rate was not significant statistically (*P=0.191*). The odds of a patient to die was 2.17 as compared to the patients without kidney disorder but it was not significant (95% CI: 0.67-7.05). So, the kidney disorder was not found as a significant risk factor of death in present study (Table 2).

Smoking: Only 18 of the patients were reported as smokers in the study and the difference in death rate of smokers and non-smokers was not significant (i.e. 33.3% in smokers as compared to 19.5% in non-smokers (*P=0.170*). The odds ratio for

death in smokers was 1.9 as compared to death in non-smokers but it was non-significant with a 95% CI of 0.76 to 4.75 (Table 2).

Gender: A total of 120 patients were male and 72 were female. No difference in death rate of male and female was found in the study as the death percentage was 20.8% ($P=1.00$) for both genders with an odds ratio of 1.0 for both (Table 2).

Quantitative Factors

Age : Age was found to be a significant different both in quantitative and qualitative analysis (Table 2; Table 3). In quantitative analysis, the age of died patients was found to be significantly higher ($P=0.000$) as compared to the age of recovered patients. The mean age of died patients was 66.28 ± 15.07 year with median age of 67.5 years ranging from 30 to 95 years, while the mean age of recovered patients was calculated to be 43.07 ± 16.65 years with median age of 40 years ranging from 8 to 90 years (Table 3; Figure 1).

To analyze qualitatively, the patients were divided in two groups' viz. I. <60 and II. ≥ 60 . The percentage of mortality was significantly higher in group II ($P=0.000$) as 29 out of 61 (47.5%) in the died as compared to 11 out of 131 (8.4%) group I. Odds ratio of death for group II was calculated as 3.44 as compared to the group I with 95% confidence interval from 2.40 to 4.95. So, the COVID-19 patients with 60 years or above age have a 3.44 times more risk of death as compared to those with age below 60 years (Table 2).

Body temperature: All the patients included in the study were symptomatic with higher than normal body temperature. By temperature we mean the average body temperature of patients recorded during their stay at hospital. The body temperature was reported to be significantly higher in patients who couldn't survive at the end as compared to recovered patients ($P=0.000$). The median body temperature of died patients was calculated to be 102 with mean of 101.9 ± 1.03 ranging from 99 to 104 Fahrenheit whereas the median temperature was 101 for recovered patients with mean of 100.84 ± 1.51 , ranging from 98 to 104 Fahrenheit (Table 3; Figure 1).

Body weight: Mean body weight of the dead patients was slightly higher as compared to the mean body weight of recovered patients as it was 72.55 ± 11.1 kg with median value of 74 and ranging from 52 to 99kg while the mean body weight of recovered patients was 68.7 ± 13.22 kg ranging from 30 to 100 with median of 70kg (Table 3). The difference however, was non-significant statistically ($P=0.092$).

Discussion

The current study was a retrospective case control study comparing different factors and co-morbidities between deceased and recovered COVID-19 patients to clarify the risk of death in patients with different factors and to identify the risk factors responsible for death. We analyzed data of 192 patients belonging to same geographical area, having same ethnic origin and remained in similar conditions during illness and treatment duration. Moreover, maximum possible factors were included in analysis, so that the effect of extraneous variables can be minimized. In analysis, 6 of the 10 factors were found to be significantly associated with mortality among COVID-19 patients which are: older age, high fever, lungs disorder, heart disorder, diabetes, and hypertension whereas, gender, body weight, smoking and kidney disorder were found to be non-significant. Except for 1, all deceased patients had one or more risk factors along with corona virus infection and the mortality rate was found to be 2.5% for patients without any of the risk factors.

Older age (60 years or above) was identified as a significant risk factor in the study increasing the risk of death by about 3.44 times as compared to the patients having age less than 60 years. Median age of deceased patients was 67.5 years while it was 40 years for the recovered patients. Old age has consistently been reported for disease severity and mortality of the patients infected with COVID-19 [7-14] and even the patients infected with MERS and SARS previously [15-16]. Weaker immunity and probability of age related complications are normally attributed to old age that of course, make elderly people prone to severe infections and death. Patients with older age may not have a stronger immunity as s of younger people and

they also have a possibility to develop the lung disorder and injury more rapidly than the younger patients as some evidences have previously been provided [7-8,17-18]. Current study supports the previous reports and it has cleared that the older age is also a significant risk factor for mortality in COVID-19 patients of this region as it is in other areas of the world. This is critical to note in countries like Pakistan with low average age and life expectancy that individuals of ≥ 60 years are highly vulnerable and becomes so pertinent where such individuals with multiple co-morbidities belong to working class and are directly exposed.

Cardiovascular diseases are always a big risk factor of mortality and in case of COVID-19 patients, it has been reported as a serious threat enhancing the risk of death to many folds [13, 19-22]. This study also pointed out that cardiovascular disease is a a serious threat raising risk of death up to 5 folds as only less than one half of the reported COVID patients with heart disorder in current study could survived and the percentages of death were 57.1% and 16.4% respectively in patients with and without CVDs with odds ratio of 5.07. So, the fact that cardiovascular disorders are associated with increased mortality among COVID-19 patients has more strongly established in the study.

COVID-19 infection targets the respiratory system and so, the previous respiratory disorders can worsen the situation of the patients which may lead to death. It has been reported that respiratory disorders are very strong predictors of death and a previous lungs disorder increases the odds of death in COVID-19 patients [7,10,11,13,21]. The present study is consistent with previous results in this regard and concludes that the presence of a respiratory disorder contributes significantly in increasing the risk of death in COVID-19 patients.

Diabetes mellitus and hypertension are two rapidly increasing disorders all over the world. In current study, 43 patients were diabetic (22.4%) and 46 (23.9%) were hypertensive. The high percentage of diabetes and hypertension in the studied patients may be attributed to the higher mean age of all patients (47.7 ± 18.6 years) as these disorders are always associated with older age. Among these 43 patients with diabetes 17 (39.5%) died of the COVID-19 while out 46 patients with hypertension, 15 (32.6%) died. Both of the disorders were found significantly associated with mortality with odds ratio of 2.49 and 1.84 respectively. These results are consistent with previous reports on the topic as both the diabetes and hypertension have been reported as significant risk factors for mortality among COVID-19 patients [10-13,20,22-24]. Higher risk of mortality caused of these co-morbidities may be due to an impaired immunity, high coagulation activity in diabetic patients, high inflammation [14, 23-24] and the older age of patients. It can be concluded that persons with diabetes and hypertension will be at higher risk of fatality if infected with COVID-19.

It has been demonstrated that smoking increases the risk of death in COVID-19 patients as smoking directly have damaging effects on respiratory tract and the corona viruses also target the same [10, 12]. An odds ratio of 1.90 was found for death of smokers as compared to non smokers in the study but it was not significant as only 18 out of total 192 (6.25%) patients were smokers. Death percentage in smokers was 33.4% compared to 19.5% in non smokers but it was not significant probably because of less total number of smokers. The smoking is considered as a bad habit in the area and mostly smokers hesitate to show that they are smokers. Moreover, the female gender is almost totally non smoker in the area. Because of these reasons, the number of smokers is low in the study and the results are non significant but this finding cannot be conclusive and studies involving more number of smokers are needed to confirm the fact. Smoking was not found as significant factor for mortality in a previous study as well [13] because of low number of smokers in the study. However, it seems that smoking will have an association with severe disease and higher mortality risk as also reported previously [10,12].

In the current study, kidney disorder was not identified as a significant risk factor for mortality in COVID-19 patients as it was previously reported to be a significant predictor of death [10]. Our finding is not consistent to previous reports but the results cannot be conclusive as we find only 11 patients out of 192 (5.7%) with some kidney disorders and the analysis on such a small fraction of patients cannot lead to a decision. So, the role of kidney disorders in death of COVID-19 patients is not clear in the current study and needs more investigations with larger number of patients.

In the current study, 120 patients were male and 72 were female. The analysis showed no difference of death rate between both genders as 20.8% of both male and female were died with an odds ratio of 1.0 for both. This result is not consistent with previous reports demonstrating that males have more risk of mortality than females [7,10,14,25-26]. Previously, higher mortality rate in male sex was attributed to higher rate of co-morbidities and smoking but in the current study does not find higher rate of other disorders in male than female. Smoking is linked to the male gender in the current study as all the smoker patients belonged to male gender but still the mortality rate was not different. However, infection prevalence seems to higher in male gender as compared to female gender as 62.5% of the patients were male. This may be attributed to the local fact that male gender has more exposure to infections because of more outdoor activities compared to female who mostly remain at home in the area. Still, nothing can be decided about prevalence as the study was not designed to find prevalence.

The current study evaluated the risk factors for mortality in COVID-19 patients in a controlled way. Age, cardiovascular disorders, respiratory disorders, diabetes, and hypertension were found to be significant risk factors while kidney disorders, smoking and gender were non-significant factors in the study. The significant factors should be given more consideration in COVID-19 patients and the role of non-significant factors in current study needs specific investigations with larger samples size.

Conclusion

The study concludes that heart disorder, lungs disorder, older age, diabetes and hypertension are significant risk factors of the death in COVID-19 patients and the risk of death increases with accumulation of factors. More the risk factors accumulate in a person, higher will be the risk of death. Smoking and kidney disorder are also associated with risk of death in the patients of COVID-19 but there association was not significant. Proportion of died patients without any of the studied risk factors was only 2.5%.

Declarations

Authors' contributions

MM designed the study, analyzed the data and wrote the initial draft of manuscript. SK, SN, NI, and MNH collected and organized the data. MFK wrote the manuscript parts and critically reviewed the manuscript. KSA and AM critically reviewed and improved the manuscript. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

All data will be made available by the corresponding author upon request.

Ethics approval and consent to participate

The Ethics committee of University of Poonch Rawalakot approved the study (UPR/HAEC/M1/S7/2020).

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests.

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Tables

Table 1: Frequency and distribution of different risk factors present in deceased patients

No. of risk factors	Old age	Heart disorder	Lungs disorder	Diabetes	Hypertension	Kidney disorder	Smoking	No. of patients
5	✓	✓	✓	✓	✓	x	x	1
5	✓	✓	✓	✓	x	✓	x	1
5	✓	x	✓	✓	✓	✓	x	1
4	✓	x	✓	✓	x	x	✓	1
4	x	x	✓	✓	✓	✓	x	1
4	✓	x	x	✓	✓	x	✓	1
4	✓	✓	✓	x	✓	x	x	1
3	✓	x	✓	x	✓	x	x	1
3	x	✓	x	✓	x	x	✓	1
3	x	x	✓	✓	✓	x	x	1
3	✓	✓	x	x	✓	x	x	3
3	✓	x	✓	✓	x	x	x	2
3	✓	x	x	✓	✓	x	x	1
3	✓	x	✓	x	x	✓	x	1
3	✓	x	x	✓	x	x	✓	2
3	✓	✓	x	✓	x	x	x	1
3	x	✓	x	x	✓	x	✓	1
2	✓	✓	x	x	x	x	x	2
2	✓	x	✓	x	x	x	x	3
2	✓	x	x	x	✓	x	x	1
2	x	✓	x	x	✓	x	x	1
2	✓	x	x	✓	x	x	x	2
1	✓	x	x	x	x	x	x	4
1	x	x	✓	x	x	x	x	3
1	x	x	x	✓	x	x	x	1
1	x	x	x	x	✓	x	x	1
0	x	x	x	x	x	x	x	1

Table 2. Comparison of qualitative risk factors between deceased and recovered patients

Factor	Level	Died (n=40)	Recovered (n=152)	OR (Risk)	95% CI For OR	P Value
Gender	Male	25 (20.8%)	95 (79.2%)	1.0	0.76-1.31	1.000
	Female	15 (20.8%)	57 (79.2%)	1.0	0.64-1.57	
Age	60 or Above	29 (47.5%)	32 (52.5%)	3.44	2.40-4.95	0.000
	Below 60	11 (8.4%)	120 (90.9%)	0.38	0.24-0.61	
Diabetes	Diabetic	17 (39.5%)	26 (60.5%)	2.49	1.50-4.11	0.001
	Normal	23 (15.4%)	126 (84.6%)	0.69	0.53-0.91	
Any Lung Disorder	Yes	17 (51.5%)	16 (48.5%)	4.0	2.24-7.26	0.000
	No	23 (14.5%)	136 (85.5%)	0.64	0.49-0.84	
Kidney Disorder	Yes	4 (36.4%)	7 (63.6%)	2.17	0.67-7.05	0.191
	No	36 (21.0%)	145 (79.0%)	0.94	0.85-1.05	
Heart Disorder	Yes	12 (57.1%)	9 (42.9%)	5.07	2.30-11.17	0.000
	No	28 (16.4%)	143 (83.6%)	0.74	0.06-0.38	
Smoking	Yes	6 (33.3%)	12 (66.6%)	1.90	0.76-4.75	0.170
	No	34 (19.5%)	140 (80.5%)	0.92	0.80-1.06	
Hypertension	Yes	15 (32.6%)	31 (67.4%)	1.84	1.11-3.06	0.024
	No	25 (17.1%)	121 (82.9%)	0.78	0.61-1.01	

Table 3. Comparison of age (years), body weight (kg) and average temperature (Fahrenheit) between deceased and recovered patients

	Died Patients (n=40)				Recovered Patients (n=152)				P Value
	Mean	Median	SD	Min-Max	Mean	Median	SD	Min-Max	
Age	66.28	67.5	15.07	30-95	43.07	40	16.65	8-90	0.000
Body Weight	72.55	74	11.1	52-99	68.70	70	13.22	30-99	0.092
Temperature	101.90	102	1.03	99-104	100.84	101	1.51	98-104	0.000

Figures

Figure 1

Distribution of age and average body temperature in dead and recovered patients