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ORIGINAL RESEARCH

Risk factors and symptoms stratification and mortality of COVID-19 in population of Nowshera (Pakistan)

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ABSTRACT

Background & **Objectives:** COVID-19 has spread around the globe, and our country is no exception. We have been actively observing and managing these patients and have recorded the salient features including risk factors, the presenting complaints and also the trends of mortality.
We aimed to have risk factors stratification, prevalent symptoms at the time of presentation to the hospital and to determine factors contributing to mortality due to COVID-19 in population of Nowshera (Pakistan).

Methodology: In this cross sectional study, 75 cases with returned PCR results were included from 15th February 2020 to 18th April 2020. Data were entered in a format in SPSS version 25, prepared in accordance with the objectives of the study.

Results: Out of a total of 75 patients, 20 (26.67%) were females and 55 (73.33%) were males. The mean age was 36±18 y. Out of these, 29 (38.67%) patients were COVID-19 positive by PCR technique, and 46 (61.33%) were negative. The probability of virus detection was higher in male gender (OR = 1.5, Relative Risk (RR) = 1.2). A significant relation of viral infectivity was noted with history of travel to an epidemic area (p = 0.01 OR = 3.85, RR = 1.5) and history of contacts with COVID-19 infected person/s (p = 0.018, OR = 3. 5, RR = 2.3). A high mortality rate of 3/29 (10.34%) for positive COVID-19 cases was recorded. The probability of worse outcome in term of death in COVID-19 positive patients was (p = 0.5, OR = 2.1). Regarding symptoms selection; contact and travel history without any symptoms has a reliability index (RI) of 12/35 (34%) for infectivity. Cough, fever with shortness of breath (RI; 8/12(67%) for positive cases followed by fever and cough with RI of 6/10 (60%) cases etc. Sore throat (RI; 1/13(8%) and flue only (RI;0/3(0%) proved non-reliable symptoms. When plotted the survival graphs of COVID positive vs. COVID negative cases, a similar pattern was recorded that showed the mortality rate in the positive cases was not solely due to COVID-19, though being opportunistic infection, it would have contributed. We recorded refractory COVID-19 in 4/29 (13.79%) cases.

Conclusion: We conclude that male gender with history of travel to an epidemic area and contact with COVID-19 patients are strong predisposing factors. Cough, fever with shortness of breath are reliable symptoms for COVID-19 in our suspects. COVID-19 being an opportunistic infection contributes to a higher mortality in respiratory and cardiac patients.

Keyword: COVID-19; Contact history; Mortality; Symptoms stratification; Risk analysis; Survival

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INTRODUCTION

The recent emergence of a new respiratory disease called COVID-19 from a metropolitan city of the Hubei Province of China, called Wuhan, in December 2019, demonstrated its epidemic potential with a rapid spread of this virus across the globe in just two months period. This highlights the higher rate of transmissibility of this virus and further its higher morbidity and mortality, especially in aged population or people with co-morbidities and/or immune gap.[1]

COVID-19 is a highly contagious respiratory disease that is caused by novel corona virus. Its main clinical symptoms are fever, dry cough, fatigue, myalgia and dyspnea.[2] Case fatality rate of 2.3% has been reported from china, that is lower than SARS (9.5%), MERS (34.4%) and H7N9 (39%).[3]

In Pakistan, the literature so for covering the prevalence and incidence is still emerging and we found no published data. The reported data from government sources declares more than 6000 confirmed cases with 138 deaths. Punjab is the province with highest number of corona cases reaching 2000 at the time of writing this paper, and the toll is rising exponentially with each passing day.[4]

In Pakistan the virus entered on 26th February 2020, when Government of Pakistan officially declared that a student of University of Karachi with a travel history of Islamic Republic of Iran had been tested positive for COVID-19.[5]

Literature describes that this virus is an opportunistic in nature, and attacks the elderly people and patients with other co-morbidities with serious outcome, that could lead to death due to severe respiratory distress and a cytokine storm in the body.[6]

Stress has been laid on identification and stratification of patients on the basis of the risk factors, e.g., history of close contact with COVID-19 positive patients, history of travel to an epidemic area like China, Iran, Italy etc. and identification of specific symptoms, as early identification can potentiate the surveillance process.[2,3,7]

Studies from the epidemic areas have reported diverse presentation of COVID suspects/patients. A study from China reported a frequency of fever to be 82.1%, dry cough 81% and dyspnoea 50%. Lymphopenia was noted in 82.1% patients in their study.[8] Similarly, another study by Zhao D et al.[9] reported the most common symptoms to be fever and cough (78% cases). A study from China reported a higher mortality of 54/191(28.27%) from the city of Wuhan. It was attributed to older age and immunity gap in the deceased population.[10]

Present study was, therefore, designed to determine the risk factors stratification for COVID-19 in a selected portion of population, frequency of symptoms and to determine factors contributing to mortality due to COVID-19 in this population.

Research Hypotheses (Null, H_0): Hypotheses are the tentative answers for research questions. Based on literature search, following hypotheses were proposed to answers our research questions.

1. **H_{01}:** There is no relation of viral infectivity with history of travel to an epidemic area of COVID-19 in population of district Nowshera (Objective 1)
2. **H_{02}:** There is no relation of history of contact with COVID-19 patients and acquiring disease in population of district Nowshera (Objective 1)
3. **H_{03}:** There is no difference in distribution of symptoms in COVID-19 and non-COVID respiratory disorders in population of district Nowshera (Objective 2)

METHODOLOGY

This comparative study was conducted from 15th February to 18th April, 2020 at Medical Teaching Institution, Qazi Hussain Ahmed Medical Complex (QHAMC), Nowshera. A

total of 75 patients whose PCR reports were received were included in the study.

Population & Sampling:

Assuming 4% prevalence of COVID-19 in general population from the study of Zhou X et al.[11]; a reference population of 100,000 patients was estimated to reside in the catchment area of our hospital, belonging to district Nowshera (Khyber Pakhtunkhwa –Pakistan). A sample size of 75 was calculated through open epi software, an online sample size calculator, with absolute precision of 5%, confidence interval of 95%, and a drop out of 10%.

The sample was selected through consecutive, non-probability technique. All the patients from COVID clinics, or strong suspects with history of travel to an epidemic area or close contacts of COVID-19 positive patients, with PCR report received from the Khyber Medical University, Public Health Research Laboratory, irrespective of age and gender, were randomly selected.

All patients attended in emergency or outdoor patients department were excluded. Result awaiting suspects were also excluded. Similarly, patients attending the COVID-19 clinic without securing the optimum marks for selection to be enrolled of PCR testing were also excluded.

Ethical endorsement was obtained from the institutional ethical review board of Nowshera Medical College Hospital administration before the execution of the study.

Prior informed consent was obtained from all suspects and they were assured of confidentiality.

Thirty (40%) of the cases were selected from COVID-19 clinic of Qazi Hussain Ahmed Medical Complex; however, the patients whose PCR was sent by the district health authorities were also included from the available district line list, and 45 (60%) cases were received through District COVID-19 Focal Person, who is also one of the contributing authors.

All samples were sent under strict observance of protocols to the Public Health Research Laboratory of Khyber Medical University Peshawar (a designated Lab for PCR of nCoV-2019).

All of these patients, whose samples were collected, had been isolated mainly in the isolation unit of our hospital as well as designated quarantine areas; very few cases were allowed home isolation under strict observance of the health/district administration to contain the spread of the virus.

Results were received in 2- 3 days, all with positive PCR reports were isolated and kept under treatment, and their samples were repeated after 7 days of isolation/treatment. Those who were negative in repeated sample reporting were shifted to quarantine; one case that reported positive on second phase belonging to Karachi was kept under strict isolation.

Operational definitions:

Child: Article 1 of The United Nations Convention on the Rights of the Child defines a child as "for the purposes of the present Convention, a child means every human being below the age of 18 y".[12]

Adult: Young adult 19-40 y, middle-aged adult 41-60 y and older adult > 60 y.[13]

Statistical analysis:

Data were entered in SPSS 25th version and descriptive and correlation statistics were applied. The frequency and proportion of numerical and categorical variables were presented in percentages. Chi-square test was applied to show a correlation of viral infectivity to gender, history of travel, history of contacts with COVID-19 patients and symptoms stratification for COVID-19.

Relative risk of COVID-19 was determined in gender groups, history of travel and history of contacts in COVID-19 positive and negative groups using risk analysis statistics.

We applied chi-square goodness-of-fit test on our population by positive and negative groups to test the null hypothesis $\mathbf{H_{01}}$, $\mathbf{H_{02}}$ **and** $\mathbf{H_{03}}$.

RESULTS

A total of 75 cases were enrolled for viral detection of 2019nCoV on PCR technique. Out of these, 20 (26.67%) patients were females and 55 (73.33%) were males. The age range was from 2–85 y, with the mean age being 36 ± 18 y (Table 1).

Out of 75 patients, 29 (38.67%) were COVID-19 positive, and 46 (61.33%) were negative. There was no significant relation of gender with viral infectivity (p = 0.5); however, the probability of virus detection was higher in male gender (OR = 1.5) and [Relative Risk (RR) = 1.2] as compared to female gender.

Table 1: Frequency of gender and age groups and 2019-nCoV infectivity

Gender wise distribution of patients. N (%)			
PCR	Gender		Total
	Female	Male	
Negative	14 (19)	32 (43)	46 (61)
Positive	6 (8)	23 (31)	29 (39)
Total	20 (26.67)	55 (73.33)	75 (100)

PCR * AGECAT Cross tabulation					
PCR	AGECAT				Total
	< 18 y	19-35 y	35-55 y	> 55 y	
Negative	7	26	11	2	46
Positive	3	8	10	8	29
Total	10	34	21	10	75

There was a significant relation of infectivity, and relatively high probability of getting infected in cases with history of travel to an epidemic area (p = 0.01, OR = 3.85, RR = 1.5). Similarly there was a significant relation of infectivity, and relatively high probability of getting infected in cases with history of contacts with COVID-19 infected person (p = 0.018, OR = 3. 5, RR = 2.3) (Table 2).

We observed a higher mortality rate of 3/29 (10.34%). The probability of worse outcome in terms of death in COVID-19 positive patients was (p = 0.5, OR = 2.1); it was not statistically significant. This probability reduces to (OR = 1.3) on suspects selection (Table 3).

The symptomatology and clinical features have a significant relation with result positivity, like contact and travel history with RI of 12/35 (34%) for positive cases. Similarly, cough, fever with shortness of breath had RI 8/12 (67%) for positive cases followed by fever and cough with RI of 8/12 (67%) cases etc. Many cases presented with symptoms of fever and sore throat turn out to be negative with RI of 1/13 (8%); hence sore throat is less reliable symptom in COVID-19. Similarly three cases of flue alone with RI 0/3(0%) turned into a negative result, that disprove it to be a valid symptom in our population. The symptom selection has a significant relation with positivity of the result for COVID-19 *(p = 0.01).* (Table 4).

We applied survival statistics using *time to event analysis* with *Kaplan Meier Test* method, taking age in years as **time variable** and disease outcome in event. We observed that survival rate in COVID-19 has an inverse relation with an increase in age. We observed the poor survival in age > 60 y of age. But when we plotted the survival graphs of COVID positive vs COVID negative cases a similar pattern was observed that shows the mortality rate in the cases was not solely due to COVID-19, though being an opportunistic viral infection it would have contributed but the deceased had other co-morbidities as well like coronary artery diseases and respiratory diseases etc. Figure 1 shows the relationship of age and PCR with the survival of the patients.

Table 2: Viral infectivity and its relation with gender, history of travel to an epidemic area and history of contacts with an infected Covid-19 patient.

1.a .Gender-wise distribution and gender risk

Gender	PCR Report		Total	Asymptotic Significance (2-sided)-Chi Square test	Relative risk F/M	Odds Ratio F/M
	Negative	Positive				
Female	14	6	20	*p = 0.5*	*1.2*	*1.5*
Male	32	23	55			
Total	46	29	75			

1.b. Relation of viral infectivity with travel history

PCR	Travel History to an epidemic area		Total	P-value Asymptotic Significance (2-sided)-Chi Square test	Relative risk	Odds Ratio
	No	Yes				
Negative	38	8	46	*p = 0.01*	*1.5*	*3.85*
Positive	16	13	29			
Total	54	21	75			

1.c. Relation of viral infectivity with contact history

PCR	Contact History with COVID-19 positive case		Total	Asymptotic Significance (2-sided)-Chi Square test	Relative risk	Odds Ratio
	No	Yes				
Negative	22	24	46	*p = 0.018*	*2.3*	*3.5*
Positive	6	23	29			
Total	28	47	75			

Table 3: Relation of viral infectivity with gender and outcome of the disease

PCR Result	Patient Condition	Gender		Total	Asymptotic Significance (2-sided)-Chi Square test	Odds Ratio for PCR result vs Outcome
		Female	Male			
Negative	Stable	14	32	46	*0*	*0*
Positive	Died	**1**	**2**	3	*0.5*	*2.1*
	Stable	5	21	26		
	Total	6	23	29		
Total	Died	1	2	3	*0.7*	*1.3*
	Stable	19	53	72		
	Total	20	55	75		

Table 4: PCR * symptoms cross tabulation

PCR	Symptoms																		Asymptotic Significance (2-sided)
	cough with blood tinged sputum	RI	cough + SOB + Flue	RI	Fever + cough	RI	Fever + cough + flue + sneezing	RI	Fever + sore throat	RI	Flue alone	RI	No Symptoms	RI	Total				
Negative	0	100	4	67	4	60	0	100	12	8	3	0	23	34	46				*P = 0.01*
Positive	1		8		6		1		1		0		12		29				
Total	1		12		10		1		13		3		35		75				

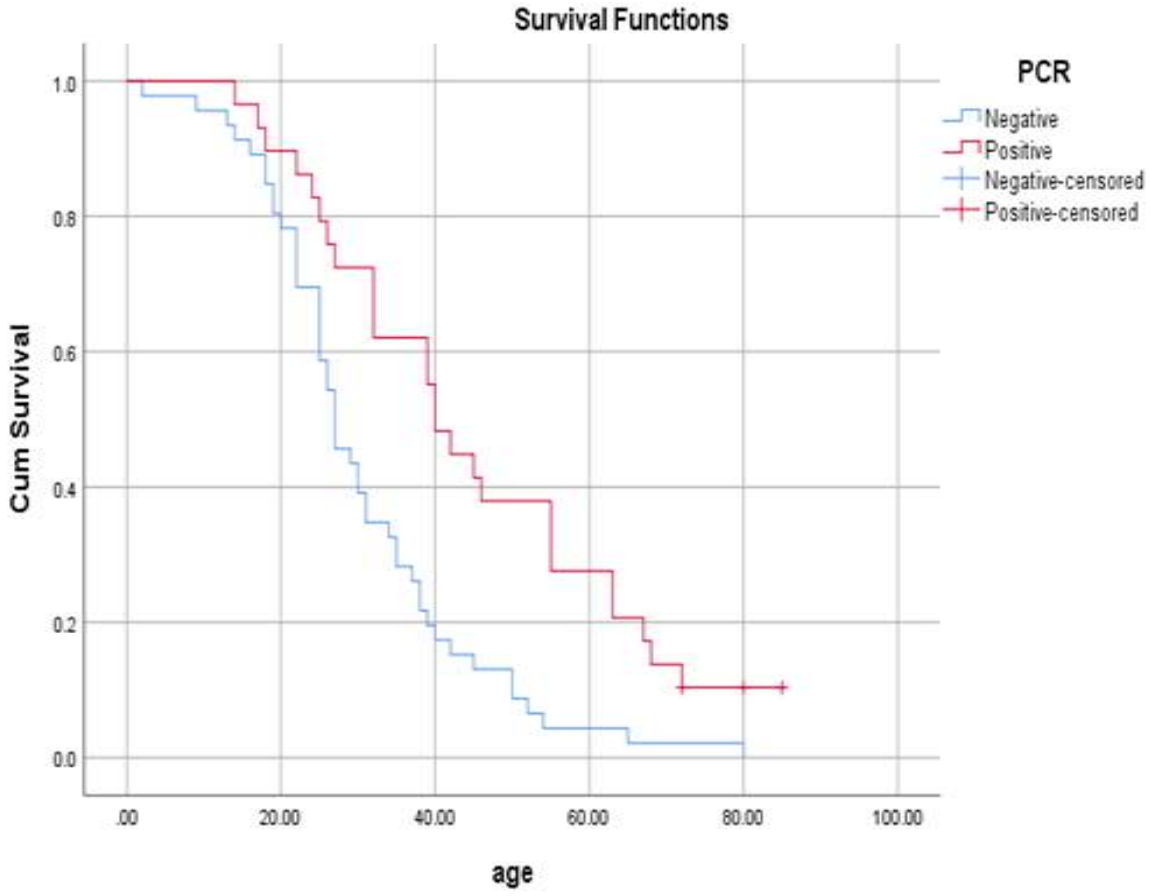

Figure 1: Relation of survival with age and PCR

DISCUSSION

Research on population is a process to answer a question, to prove or disprove an assumption or hypothesis for a specified population on a specific issue. To the best of our knowledge this is the first ever study to give information on stratification of symptoms for COVID-19 in population of Nowshera, Pakistan. This is first intervention to discuss the risk factors and to show its statistical relation with the disease. This is first intervention to discuss mortality rate and factors contributing to mortality due to COVID-19 in Pakistan.

We here tried to identify the major risk factors of COVID-19 in our population. We observed that 29 (38.67%) of the tested cases were COVID-19 positive, and 46 (61.33%) were negative. There was no significant relation of gender with viral infectivity *(p = 0.5);* however, the probability of virus detection was higher in male gender [odd's ratio (OR) = 1.5) and (RR = 1.2) as compared to female gender.

Male gender predominance is also reported from Italy and China epidemic studies. New York time has reported that corona virus is striking and felling more Italian males as compared to females in extreme of age because of their weak immunity status. They further elaborated that Italian model of mortality is a trend mirror of what they observed in China with more causality in male gender and at extreme age.[14,15.]

There was a significant relation of infectivity, and relatively high probability of getting infected in cases with history of travel to an epidemic area (p = 0.01, OR = 3.85, RR = 1.5) that rejects the **null hypothesis (H_{01}).** Studies from China have reported a significant correlation of travel history to Wuhan and getting infection as compared to those without a travel history (p = 0.01).[16,17] The findings of Zhou X et al. (17%)[17]and Tian S et al. (5%),[18] match to our study who reported a strong correlation of acquiring infection in those reporting with history of travel to high epidemic areas of China.

Similarly, there was a significant relation of infectivity, and relatively high probability of getting infected in cases with history of contacts with COVID-19 infected person (p = 0.018, OR = 3.5, RR = 2.3) which rejects the **null hypothesis (H_{02})** that there is no relation of viral infectivity with history of travel to an epidemic area. The findings of Luo L, et al.[19] and Qiu H et al.[20] match our results where they reported a higher rate of prevalence of COVID-19 in their target population with a strong history of contacts with positive COVID patients.

Regarding the clinical features/symptoms of the disease, it was observed that cough, fever and shortness of breath (SOB) has a high RI of 8/12 (67%) for case positivity, followed by fever and cough without SOB, with RI of 8/12 (67%) cases etc.

It was noted that sore throat complainants turned out to be negative with RI of 1/13 (8%); that proves sore throat as a less reliable symptom for COVID-19.

Similarly, flu alone with RI 0/3 (0%) negative result proves it as an invalid symptom in our population. The symptom selection has a significant relation with positivity of the result for COVID-19 *(p = 0.01)* that rejects the ***null hypothesis (H_{03}).*** Zhao D et al.[9] also reported fever and cough in (78%) of confirmed COVID-19 cases that strongly coincides with our findings.

We observed that survival rate in COVID-19 has an inverse relation with an increase in age. When we plotted the survival graphs of COVID positive vs COVID negative cases, a similar pattern was observed that shows the mortality rate in the cases was not solely due to COVID-19, though being an opportunistic viral infection it would have contributed.

But there were co-morbidities in the deceased; we observed in case of one female patient 85 y old was admitted in medical unit with other co-morbidities (CAD/COPD) and age factor along with COVID infectivity. Another case had coronary artery disease (CAD) and age factor. One case that was cross reported from Peshawar (Khyber Teaching Hospital) the report showed he was critically ill with CAD, and was > 75 y

old along with COVID-19 infection. That might be the reason of the Kaplan Meier test that reported insignificant difference in mortality caused by COVID-19 and vice versa.

The CDC reports 2019 shows that 53% of the COVID-19 infected patients that need ICU admission, and those 80% of the deaths were recorded in elderly people age > 65 y, while no ICU admission or deaths were recorded in age less than 19 y of age.[21]

In 4/29 (13.79%) of our patients in QHAMC the refractory COVID was recorded in repeated PCR after 10 days. All the four cases were males. It has been reported from China that cases with refractory COVID-19 were mostly males and with manifestation of fever, shortness of breath, as were our observation ($p < 0.05$)[22].

Based upon the results of our study, it is suggested that special care should be given to suspects with higher risks like in age > 60 y, and patients with immunity gaps and other co-morbidities.

It is suggested that further studies should be carried out covering maximum duration of study, maximum number of positive patients, and if possible to cover a higher number of deaths reported so far, to correlate different risk factors with morbidity and mortality of COVID-19.

CONCLUSION

Hence it is concluded that male gender, with history of travel to an epidemic area and contact with COVID-19 patients, are strong predisposing factors. Cough and fever with shortness of breath are reliable symptoms for COVID-19 in our study. Fever and oxygen dependency are strongly correlated to refractory COVID-19. COVID-19 being an opportunistic infection contributes to a higher mortality in respiratory and cardiac disease in elderly patients.

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None declared by the authors.
Authors' contribution:
HK **–** *Concept, conduction of the study work, literature search, and manuscript editing*
KH **–** *Concept, conduction of the study work, literature search,*
ST, AZ **–** *Concept, manuscript editing*

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