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ORIGINAL ARTICLE

Clinical outcomes and associated risk factors of Corona Virus Disease 2019 in healthcare workers of KP, Pakistan

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ABSTRACT

Introduction: Khyber Pakhtunkhwa (KP), is geographically the smallest province, characterized by high population growth and a large refugee population. It faces a set of unique obstacles in the health sector including limited human resources, low financial protection, and weak governance.

Objective: To explore clinical outcomes and factors associated with mortality among Health Care Workers (HCWs) of KPK.

Materials & Methods: It was a cross sectional study conducted over 32 district of KP. A format containing 70 variables, including demographics, comorbidity, symptoms and outcomes, was developed and shared with rapid response teams (RRT) of each district and orientation was given for its use to the teams. Data were collected onto the software IPMS (Integrated Performance Monitoring System). We obtained this information from Health Department KP.

Results: From February 2020 to 27^{th} June 2020, 1813 HCWs reported COVID-19 positive; 669 had active infection, 1133 recovered while 11 died. Median age was 34 (IQR=14) years, and 76.1% were males. Fever, cough and sore throat were present in 40.5%, 33.5% and 19.1% while comorbidity was present in ~2% of patients. 6 patients were admitted to ICU and 4 patients received invasive ventilation- none survived. After adjusting for potential confounders, age, cough, Shortness of breath (SOB), headache, diabetes and chronic lung disease were significantly associated with mortality (all p<0.05).

Conclusion: HCWs, with COVID-19, were young; predominantly males, mostly asymptomatic, and a small proportion had comorbidity. Fever, cough and sore throat were top 3 symptoms. Mortality rate was 0.6%. The outcome was poor in patients who received intensive care/invasive ventilation.

Keywords: Health Personnel; Healthcare Workers; COVID-19; SARS-CoV-2.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Corona virus 2019 (COVID-19) also called SARS-CoV-2 hit the world in December 2019 and since then 188 countries have been affected. Almost 18,854,287 people worldwide have been infected by this contagious virus causing 708,639 deaths globally.¹ According to a report submitted by World Health Organization (WHO), HCWs have accounted for 21% cases of COVID-19 globally.²

In this challenging time of COVID-19 pandemic, hospitals are getting overloaded with infected patients, both symptomatic and asymptomatic. Patient can shed the virus even in asymptomatic phase of the disease. Human to human transmission is through respiratory droplets. Health care workers are at the front line in attending and managing these patients and transmission to HCWs is known to have occurred.3 Due to close proximity and continuous repeated exposure to the contagious virus, HCWs are at an increased risk of acquiring this virus. Moreover, the sudden unpredicted heavy burden of disease and its novelty is the real challenge for healthcare system especially in a resource limited country like Pakistan.³ One of the most important routes of secondary transmission of COVID-19 is the spread through a hospital setting. Availability of insufficient accurate data on COVID-19 virulence factors, in vitro survival, incubation, and infectivity period, hindered the planning and implementing of preventive measures for HCWs initially. As a result significant number of HCWs acquired infection and became the source of transmission themselves.³

Primary exposure of an HCW to infected patients before his/her diagnosis is confirmed and work overload during duties are two important risk factors for HCWs getting COVID-19. According to Centres for Disease Control and Prevention (CDC), 9282 HCWs have been affected in the USA, out of which, 55% had exposure in their place of duty. Furthermore, Temime et al.,⁴ described that the risk of COVID-19 infection in HCWs was higher than general population due to their prolonged and close contact with the already infected patients. HCWs who handle patients' airways and/or oral cavity such as dentists, respiratory therapist, anaesthetist and intensivists are at high risk of acquiring the infection.⁴ Till date, numerous studies and systemic reviews have highlighted diversity of clinical presentation and severity of COVID-19 infection ranging from being asymptomatic to septic shock and multiorgan dysfunction.⁵ The severity and presentation of disease may vary depending on age group, gender, ethnicity and type of viral strain and viral load.⁵⁻⁷ It is assumed that the health care workers are at high risk of getting high viral load due to repeated exposure to COVID-19 infected patients and involvement in aerosol generating procures.³ Literature, however, is markedly deficient in elaborating the disease course and outcome in HCWs.

Khyber Pakhtunkhwa (KP) is one of the 4 provinces of Pakistan with a population of 35.53 million (14.69% of Pakistan population) supported by 9 teaching Hospitals. In this pandemic, HCWs are affected more in KP as compared to other provinces of Pakistan.⁸

Already published literature revealed that disease transmission is mainly dependent upon exposure and its clinical course and outcome is variable according to host demographics, ethnic background, and available healthcare facilities. Being a resource poor country with distinct ethnicity we may have unique disease pattern and transmission. To date no comprehensive research work focusing on the Indian subcontinent has been published focusing COVID-19 infection in HCWs; moreover, to date no study focusing on this issue has been carried out on such a large scale. Our study can be considered as pioneer study on this topic from Indian subcontinent and unique due to its multicentred nature at global level.

The present study was conducted to explore the clinical outcomes and factors associated with mortality amongst the HCWs of KP, Pakistan.

MATERIALS & METHODS

A cross sectional study was conducted on all HCWs infected with COVID-19 across all 32 districts of the KP province from February 2020 to 27th June 2020. Data about demographics, clinical manifestations, and outcomes of all COVID-19 affected HCWs from the Department of Health Khyber Pakhtunkhwa, Pakistan were obtained. At the beginning of the pandemic, a format containing 70 variables, including demographics, comorbidities, symptoms, and outcomes, was developed by a provincial team led by Additional Director General Health Services (ADGHS) Public Health. It was then shared with Rapid Response Teams (RRT) of each district and orientation was given for its use to the teams. Each district entered their own data onto the software IPMS (Integrated Performance Monitoring System) and shared it with Provincial Data Team daily. Provincial Data Team prepared a daily provincial report and shared it with National Command Operation Centre (NCOC) and other stakeholders. This dataset comprehensively covered updates on surveillance, morbidity, admissions, recoveries & mortalities.

Request was submitted to the Additional DG Health, Khyber Pakhtunkhwa for the permission to study the provincial COVID-19 patient data available at the department. Study protocol was submitted with the request which was examined by the authorities of the department as well as the Ethics Committee of Khyber Medical University Peshawar, KP and permission was granted. Ethical and administrative permission was obtained. All patient identifiers including names, fathers' names, and CNIC numbers were removed from the dataset.

Statistical analysis

Data were analyzed using SPSS 23 and STATA 15. Continuous variables are presented as Mean (SD) while categorical variables as frequencies and percentages. Frequencies of demographic characteristics, symptoms and comorbidities were compared between the survivors and non-survivors using the Chi Square and Fisher's exact tests. Binary logistic regression analyses were used to determine the univariate associations of demographic characteristics, symptoms, and co morbidities of the patients with patients' status. Patients' status was defined as recovered or death from the COVID-19 infection. Multivariable logistic regression was conducted with patient status as the outcome. All significant variables in univariate analysis were included in a multivariate logistic regression model with Forward selection method to identify the independent predictors and avoid overfitting of the regression model. Odds ratios (OR) along with their 95% confidence intervals, [OR (95%CI)], were used to quantify the associations between predictors and the outcomes. Sensitivity analysis was performed using the "exact logistic regression" analysis to account for the limited number of death events. The statistical significance level was set at p < 0.05 (two-sided).

RESULTS

From April 01, 2020 to June 27, 2020, 1813 healthcare workers reported as COVID-19 positive from all districts of Khyber Pakhtunkhwa (KP), Pakistan. All these patients had positive laboratory confirmation of SARS-CoV-2 infection. Lab confirmation of infection was done via RT-PCR for SARS Cov-2 on nasopharyngeal swab. None of the 1813 patients was lost to follow up. The median (IQR) age was 34 ± 14 years and almost half of patients were aged 31–50 years; 1380 (76.1%) patients were males. Of 1813 patients, 669 had active infection, 1133 recovered, while 11 died as of 27th June 2020. Among the deceased, there were 4 doctors, 4 paramedical staff, 1 nurse, 1 technician and 1 sanitary worker.

Table 1 depicts the demographic and baseline data of the study subjects. There was a male predominance (76.1%) and most cases (49.8%) were in the age group of 31-50 years. Overall 783 (43.2%) patients were symptomatic. Fever (40.5%) was the most common symptom, followed by cough (33.5%), and sore throat (19.1%). Shortness of breath was present in 5.5%, while headache and diarrhoea were each present in 3% of the patients. (Table 1).

Approximately 2% of the patients had comorbidities including cardiovascular disease / hypertension (1%), chronic lung disease (0.4%) and diabetes (0.9%). Only 1 patient was pregnant. Regarding the place of management, 1114(61.4%) patients were home quarantined. A total of 6 patients were admitted to the Intensive care Unit (ICU) and 04(0.2%) patients received invasive ventilator (Table 1).

Regarding patient status, 1133(62.5%) recovered, 669(36.9%) remained active cases, and 11(0.6%) died (Table 1).

Demographic &	Frequency	Percentage	
	>=30	689	38.0
Age (years)	31-50	902	49.8
	>=51	222	12.2
Gandar	Female	433	23.9
Gelidei	Male	1380	76.1
	Flu	80	4.4
	Fever	735	40.5
Symptoms	Sore throat	347	19.1
f=783, 43.2%	Cough	607	33.5
	Diarrhoea	54	3.0
	Shortness of breath	100	5.5
	Headache	54	3.0
	Cardiovascular / hypertension	19	1.0
Comparished it is $(n-24, 1, 00)$	Chronic lung disease	7	0.4
$CO \operatorname{Inorbidities}(II=34, 1.9\%)$	Diabetes	16	0.9
	Pregnant	1	0.06
Managamant place	Home quarantine	1114	61.4
Management place	ICU	6	0.3
Ventilation		4	0.2
	Recovered	1133	62.5
Patient Status	Died	11	0.6
	Active	669	36.9

Table 1. Demographics and baseline characteristics of health care workers with COVID-19 (n=1813).

Table 2 shows comparative analysis of characteristics for survivors and non-survivors. Non-survivors had significantly more patients above age 50 years (p<0.001). Almost all non-survivors (10 / 11) were symptomatic, with fever and cough. Shortness of breath, headache, and sore throat were higher in non-survivors (all p<0.001). Comorbidities were significantly more in

non-survivors than in survivors. Out of the 6 patients who were admitted to the ICU, 5 did not survive. None of the survivors had invasive ventilation whereas 4/11(36.4%) non-survivors received invasive ventilation. All non-survivors were admitted to hospitals, compared to 38.7% of survivors. Gender and diarrhoea showed non-significant differences.

	Patient Status				
Demographic & Clinical Values	Survivors (n=1133)		Non-survivors (n=11)		p value
	f	%	f	%	
Age (years)					
>=30	438	38.7	0	0.0	<0.001
31-50	550	48.5	3	27.3	<0.001
>=51	145	12.8	8	72.7	
Gender					
Female	248	21.9	2	18.2	0.7
Male	885	78.1	9	81.8	
Symptoms	442	43.3	10	90.9	0.002
Flu	51	4.5	1	09.1	0.40
Fever	430	38.0	10	90.9	< 0.001
Sore throat	212	18.7	6	54.5	0.003
Cough	356	31.4	10	90.9	< 0.001
Diarrhoea	33	2.9	1	09.1	0.20
Shortness of breath	66	5.8	5	45.5	< 0.001
Headache	28	2.5	3	27.3	< 0.001
Comorbidities	20	1.8	7	63.6	< 0.001
Cardiovascular / hypertension	11	1.0	4	36.4	< 0.001
Chronic lung disease	4	0.4	2	18.2	< 0.001
Diabetes	9	0.8	4	36.4	< 0.001
Pregnancy	1	0.1	0	0.0	0.9
Severity					
ICU admission	1	0.1	5	45.5	< 0.001
Ventilator requirement	0	0.0	4	36.4	< 0.001
Quarantine facility					
Hospital / Health facility	439	38.7	11	100.0	< 0.001
Home quarantine	694	61.3	0	0.0	< 0.001

Table 2. Comparison of demographics and baseline characteristics of survivors and non-survivors (n=1144).

In univariable logistic regression analysis, age, symptoms of fever, sore throat, cough, shortness of breath, and headache, and co morbidities were associated with death (Table 3). The highest OR was obtained for comorbidities (97.38), followed by diabetes (71.36), chronic lung disease (62.72), cardiovascular disease / hypertension (58.29). Lesser factors were cough (21.82), fever

(16.35), headache (14.80), shortness of breath (13.47), and presence of symptoms (13.07).

Similar results were obtained using Exact logistic regression to account for limited number of deaths (non survivors).

Table 3. Univariable	logistic reg	ression analysis	of factors associated	with death among	g health care	workers with	COVID-19.
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Variables	OR (95% CI)	p value
Age	1.04 (1.02-1.06)	< 0.001
Gender	1.26 (0.27-5.87)	0.7
Symptoms	13.07 (1.67-102.53)	0.01
Flu	2.12 (0.26-16.89)	0.5
Fever	16.35 (2.08-128.16)	0.008
Sore throat	5.21 (1.57-17.24)	0.007
Cough	21.82 (2.78-171.15)	0.003
Diarrhoea	3.33 (0.41-26.80)	0.2
Shortness of breath	13.47 (4.01-45.29)	< 0.001
Headache	14.80 (3.73-58.76)	< 0.001
Comorbidities	97.38 (26.39-359.36)	< 0.001
Cardiovascular / hypertension	58.29 (14.89-228.11)	< 0.001
Chronic lung disease	62.72 (10.16-386.99)	< 0.001
Diabetes	71.36 (17.73-287.27)	< 0.001

Multivariable logistic regression was conducted with patient status as the outcome (Table 4), as explained in Materials & Methods (Statistical analysis). Analysis was conducted separately for symptoms and comorbidities, while age and sex were included in both analyses. Amongst the symptoms, cough, shortness of breath, and headache were included in the adjusted logistic regression analysis. All three factors were significantly associated with higher risk of death (p= 0.009, p=0.04 and p=0.04 respectively). On the other hand, in adjusted logistic regression analysis for the comorbidities, only chronic lung

disease (p=0.001) and diabetes (p<0.001) were significantly associated with a higher risk of death. Age was significantly associated with an increase in the risk of death after adjustment of both symptoms and co morbidities (both p<0.001). Due to the limited number of death events, the OR (95% CI) from logistic regression were highly inflated. Therefore, sensitivity analysis was performed using the "exact logistic regression" analysis. However, similar results, with inflated ORs (95% Cis), were obtained.

Table 4. Multivariable logist	ic regression analysis of fact	tors associated with death a	among health care work	cers with COVID-19

Variables	OR (95% CI)	p value
Symptoms		
Age	1.088(1.043-1.134)	< 0.001
Cough	92.123(3.143-2700.022)	0.009
Shortness of breath	4.251(1.069-16.903)	0.04
Headache	5.317(1.088-25.976)	0.04
Comorbidities		
Age	1.046(1.020-1.071)	< 0.001
Chronic lung disease	47.905(4.783-479.833)	0.001
Diabetes	50.861(10.892-237.493)	< 0.001

DISCUSSION

Our results reveal that amongst the total 1813 health care workers, with confirmed COVID-19 from March 01 till June 27, 2020, 0.6% did not survive, 62.5% recovered while 36.9% remained active with the infection. Overall, 43.2% patients were symptomatic, with fever and cough being the most common symptoms. The majority, 73% (8/11) non-survivors were aged above 50 years. Almost all non-survivors were symptomatic and had comorbidities, including cardiovascular diseases / hypertension, diabetes and chronic lung disease and were admitted in a hospital. Most, (5/6) patients admitted to the ICU

did not survive while none of the patients on invasive ventilation survived. Amongst the symptoms, cough, shortness of breath, and headache, while amongst the comorbidities, chronic lung disease and diabetes, were significantly associated with a higher risk of death. Age was significantly associated with an increase in the risk of death after adjustment of both symptoms and comorbidities. Gender was not associated with increased risk of death.

To date, there are a limited number of publications and national situation reports that provide information on the number of HCW infections.⁹Globally, HCWs accounted for 2.5% of total COVID-

19 infections in an analysis based on cases reported till 29th March 2020.¹⁰ However, the tally varies among different countries. A publication from China CDC on 44,672 confirmed cases, as of 17th February 2020, indicated 3.8% (1688) of the infections were among HCWs.¹¹ In Italy, a situation report from 10 April 2020 reported 15,314 infections among HCW, representing 11% of all infections at that time.¹² In Spain, HCW infections accounted for 20.4% of total cases (23,728/116,386) reported to the National Centre of Epidemiology on 28th February 2020.¹⁰ According to the preliminary data released by the CDC, 19% (9,282/49,370) of total infections in the United States were attributed to HCWs.¹³ Our study shows that 7.14% (1813/25380) health care workers from KP, Pakistan, were infected with COVID-19.

Median age of our study population was 34 years. In literature, most of the studies have described comparatively higher age of HCW affected by COVID-19. Two Studies from Netherland reported mean age of affected HCW as 49 years.^{15,17} However, one study from China has described age of affected HCW as 36.5 years, similar to our results. Our study had a high proportion of male HCWs (76.1%). In contrast, studies by Kluytmans-van den Bergh MF et al.,¹⁵ Chou R et al.,¹⁸ Lai X et al.,¹⁴ Sikkema RS et al.¹⁷ mentioned a higher proportion of female HCWs affected with COVID-19 (83%, 69%, 71.8% and 83% respectively). The relatively younger age of HCWs and the predominance of males in our study may be explained by the fact that in this particular setup, frontline doctors and paramedics are usually the early or mid-career males.

In our study population, more than half of the HCWs were asymptomatic. Results from Italy also revealed that around twothird of the HCWs were asymptomatic who tested positive for COVID-19.¹⁹ The large number of asymptomatic HCW warrants regular screening of them in order to reduce the transmission of disease to patients and their families. Amongst those who were symptomatic, fever was the most common symptoms followed by cough and sore throat. These results are in line with the literature where fever has been identified as the most common symptom universally and cough and sore throat are also included in the top 5 most commonly observed symptoms amongst HCWs infected with COVID-19.¹⁴⁻¹⁶ Moreover, fever, cough and sore throat are part of clinical criteria set by CDC.

Estimated worldwide mortality is 1.3% in HCW.18 These estimates vary across different regions. According to a review published in June 2020, the highest Case Fatality Rate, 5.7%, is seen in the Eastern Mediterranean region followed by South East Asia (3.1%) while Europe showed the lowest number of deaths (0.6%)).²⁰ In China the COVID-19 related mortality amongst HCW has been reported as 0.9% and 0.6% by Lai X et al., and Zhan M et al.,^{14,21} We observed a relatively lower mortality rate of 0.6% that may be attributed to the younger age and absence of comorbidities in majority of the HCWs. In our study, only 2% HCWs had comorbidities. Literature search revealed only one study from China presenting the prevalence of comorbidities in HCWs, which included 110 HCWs and the proportion of HCWs with comorbidities was 12.7%.14 Mortality was significantly more in patients aged above 50 years, with comorbidities and symptoms. These findings are supported by a review conducted by Ing et al.²² The review reported that older age > 57yrs, male gender (90% of deaths were male physicians), and pre-existing conditions (hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease, and immunocompromised individuals) were significantly associated with COVID-19 related mortality amongst HCWs.²² In general, older age, male gender and presence of co morbidities are significant risk factors of COVID-19 associated morbidity and mortality.²¹ In contrary to the above mentioned studies, we did not find any gender specific mortality risk in our population. It can be due to racial and ethnic difference but warrants further research work to explore it.

Mortality rate amongst HCWs admitted in ICU was 83.3% while 100% patient died who received mechanical ventilation in our study. No study specifically on HCW focused on ICU related mortality, however studies from general population showed higher mortality rates when the pandemic first started (nearly 50-100%),^{23,24} but as the pandemic advanced, better understanding of the disease and proper channelling of resources led to marked decrease in mortality rate, as described by a systematic review.² ICU related mortality may depend upon healthcare resources, availability of ICU as early as needed, availability of trained and qualified staff, provision of required medication as per need. In KP, only couple of intensivists are available with limited number of ICU beds that too with insufficient facilities, all these factors may have contributed towards the high mortality in patients who received intensive care or invasive ventilation.

This is the first study focusing on HCWs who got infected with COVID-19 from the Indian subcontinent, that too focusing a complete province. Moreover, it is a comprehensive account of demographic features of HCW who suffered from disease and described risk factors of death in them; this again has not been published from this area of the globe. It gave the snapshot of the disease burden on HCW working in a limited resource under developed country. Findings unique to our study are that our COVID-19 affected HCWs were young aged with male predominance, were largely asymptomatic, and only a small proportion suffered from comorbidities. There was no gender specific high rate of death and ICU/ventilator associated mortality was almost 100%.

Our study has some limitations. Firstly, it did not include laboratory or radiological features of the disease, we thus could not categorize patients according to disease severity. Secondly, we could not assess the risk factors in terms of place of duty, working hours, department (COVID unit, aerosol generating procedure etc), and use / provision of PPE. Thirdly, our study is based upon testing the suspected HCWs and as we saw that significant numbers of HCWs were asymptomatic, this means that the disease burden in HCWs is greater than we estimated if results were based upon screening tests but that was not possible on such a large scale due to limited resources. In addition, our results, specifically the ORs obtained through logistic regression, are possibly affected by the "sparse data bias". Limited number of events (11 deaths) in the study population (1813 HCWs) has resulted in inflated ORs with wide confidence intervals. Although sensitivity analysis was performed using "exact logistic regression" analysis, still similar results with high ORs and wide confidence intervals were obtained.

CONCLUSION

The HCWs with COVID-19 infection were predominantly young males. More than half of the patients were asymptomatic, and a very small proportion had comorbidities. Fever, cough, and sore

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