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RISK FACTORS ASSOCIATED WITH THE INFECTIVITY AND SEVERITY OF COVID-19 INFECTION.

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ABSTRACT

Background: The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had a profound impact on the world, causing widespread illness and death, as well as major disruptions to economies, societies, and daily life. The virus spreads easily from person to person, particularly through respiratory droplets produced when an infected person talks, coughs, or sneezes. Early symptoms of COVID-19 include fever, fatigue, dry cough, and shortness of breath, but the disease can range from mild to severe, with severe cases leading to pneumonia and acute respiratory distress syndrome.

Objective: Pakistan is facing the COVID-19 situation like the rest of the world. However, the data is restricted to address the epidemiological features and concomitant complications in symptomatic and asymptomatic COVID-19 patients. The present study aimed to focus on the symptomatology, infectivity, and severity of COVID-19 in Pakistani population with pre-existing co-morbidities.

Methodology: This cross-sectional study was designed to collect data and swab samples from suspected patients to confirm the disease prevalence and its correlation with different comorbidities. Patients were interviewed by trained health professionals about the presence and absence of symptoms and pre-morbid conditions. Detection of COVID-19 was carried out by Real time Polymerase Chain Reaction test from nasopharyngeal swabs.

Results: The overall prevalence COVID-19 was 55.4%, out of which 68% were males and 32% were females. Out of total 277 positive cases, 9.7% reported to have a close contact with a confirmed COVID-19 positive patient. Moreover, 24 out of total 26 diabetic patients (92%, $p < 0.05$) and 20 out

of 21 hypertensive patients (95%, $p < 0.05$) were presented with symptoms pointing towards presentation of severity of COVID-19. The severity of COVID-19 was also found to be increased in patients with cardiovascular disease, chronic kidney disease and chronic chest infection, though the results were not statistically significant.

Conclusion: The study concluded a greater risk of COVID-19 severity in DM and HTN patients, notably in the age range of 41 to 80 years. The data contributed can potentially help in the effective management and prevention of COVID-19 infection in the future.

KEYWORDS: Coronavirus Disease 2019; Diabetes; Hypertension; Pre-morbidities; Risk Factors

INTRODUCTION

Infectious diseases impose a worldwide health threat leading to morbidity, disability, and mortality. Infections of the lower respiratory system are one of the deadly communicable health hazards, ranked as the fourth foremost cause of mortality [1]. COVID-19, short for Coronavirus Disease 2019, is a highly infectious respiratory illness caused by the novel coronavirus SARS-CoV-2. The virus is spherical in shape and has spikes on its surface, giving it a crown-like appearance under a microscope [2]. Epidemiology of COVID-19 shows that the virus was first identified in Wuhan, China in December 2019 and quickly spread globally, resulting in a pandemic [3]. Statistics have shown that till December 2021, about 280 million confirmed cases had been reported worldwide with >5,000,000 deaths [4]. The virus is primarily transmitted through respiratory droplets produced when an infected person talks, coughs, or sneezes. Common symptoms of COVID-19 include fever, fatigue, dry cough, shortness of breath, body aches, loss of smell or taste, and sore throat. However, it's worth noting that not all infected individuals experience symptoms, and some may only have mild symptoms. In severe cases, COVID-19 can lead to pneumonia, acute respiratory distress syndrome, and even death, particularly in older adults and people with underlying health conditions [5]. The most common reported predictors that contribute towards the severity of SARS-CoV-2 infection include old age and comorbidities such as cancer, asthma, diabetes mellitus (DM), hypertension (HTN), and cardiovascular disorders (CVD) [6]. Hence, countries with a higher older age population or/and higher burden of chronic disorders are expected to have the highest mortality rates. Moreover, the intensive care unit (ICU) cases in comparison to non-ICU patients were more likely to have comorbidities such as DM and HTN [7].

Diabetes and hypertension have been found to play significant roles in progression of each other and multiple life-threatening diseases such as CVD, CKD, COPD etc. Moreover, these diseases as comorbidities reduce patient's self-recovery as well as treatment response. We reported in a previous study based on Pakistani population that, DM is one of the most common diseases in Pakistan, and its prevalence was higher in hypertensive patients and patients with renal diseases [8]. Pakistan has been one of the most effected countries with number of chronic diseases such as DM, HTN, CVD, chronic pulmonary diseases, and kidney diseases. One is responsible for the development of other and vice versa. Therefore, it very important to understand these diseases individually and their relationship with each other. Patients with diseases like DM, HTN, CKD, CVD and COPD have lower ability to fight against encountering diseases in future, one of the reasons behind this is the lower immunity. In case of viral infections specially COVID-19, rapid immune response is very important to limit the rapid viral replication and to ensure viral elimination.

In short, novel coronavirus disease 2019, caused by the SARS-CoV-2, is now sweeping across the world. Pakistan is facing the SARS-CoV-2 situation like the rest of the world. There is restricted data to address the epidemiological features and concomitant complications in symptomatic and asymptomatic COVID-19 patients. It is vital to understand the unique features of the confirmed COVID-19 cases in Pakistan because of the different population dynamics of Pakistan from the rest of the world. The present research work focuses on features of symptomatology, infectivity, severity, and mortality of COVID-19 in the case of individuals with pre-existing co-morbidities. The results of the study related to the infectivity and severity of the SARS-CoV-2 infection can be used during the screening of COVID-19 cases, hence finding high-risk patients who can be studied and managed for a better outcome in terms of morbidity as well as mortality [9].

METHODOLOGY:

Study design

A cross-sectional study was conducted among 500 suspected COVID-19 subjects. All the suspected individuals were included based on their exposure to infected patients, recent travel history, and clinical presentation. Individuals who already tested positive for COVID-19 were excluded from the study. Individuals who were already COVID-19 recovered after getting infected were also excluded from the study. Prior informed consent was taken from the study participants and ethical approval was obtained. Nasopharyngeal swabs were collected from SARS-CoV-2 suspected individuals having fever or some respiratory symptoms and/or remained in close contact with real-time polymerase chain reaction (RT-PCR) positive SARS-CoV-2 patients. The nasopharyngeal swabs were taken in the viral transport medium, properly labeled with name, date of birth, identification number, time of collection, and date of collection from the study participants, and stored in a 2-8˚C refrigerator or at room temperature if the analysis is delayed.

RNA Extraction & Amplification:

The MagPurix® viral nucleic acids extraction kit was used to extract viral RNA. The viral RNA extraction package combines MagPurix® series automated equipment with unique magnetic ZiBeads® technology. The acquired product was used for the detection of SARS-CoV2 nucleic acids. This is a description of the protocol used for qualitative detection of COVID-19 SARS-CoV-2 RNA using the Abbott m2000rt kit and reverse transcription-polymerase chain reaction (RT-PCR). The target RNA is converted to cDNA by the reverse transcriptase activity of the thermostable polymerase and amplification of three targets (SARS-CoV-2 RdRp, SARS-CoV-2 N, and IC) is carried out in the same reaction. An internal control target sequence from the pumpkin plant is included to ensure the validity of the results. The template RNA is added to the master-mix, and thermal cycling conditions are followed, including reverse transcription at 48°C for 30 minutes, 10 minutes at 95°C, and 45 cycles of 15 seconds at 95°C and 1 minute at 60°C. The detection limit is 100 copies/ml, and a cycle threshold of ≤40 is considered positive.

Data Analysis:

Data is expressed as Mean ± SEM. The analysis of the data was done by Microsoft excel (Microsoft Office 365) and Statistical Package for the Social Sciences version 26. Pearson's correlation was used to compare and analyze data and $p<0.05$ was considered as significant.

RESULTS

Geographically, Pakistan can be divided into four provinces, and we collected the samples and data from province Punjab and province Khyber Pakhtunkhwa (KPK). The overall prevalence of COVID-19 in the study population was 55.4% with 227 positive cases out of 500 suspected individuals. Age and gender-wise distribution of participants along with COVID-19 prevalence in both groups is given in table 1, where COVID-19 infectivity was higher in suspected females (58%) as compared to males (54%), while the number of male participants in total was higher (P = 0.40). We further analyzed the prevalence of COVID-19 in different age groups and found that COVID 19 was more prevalent in individuals between 21-60 years of age compared to below 20 years and above 60 years (p=0.00) **(Figure 1)**. Mean age of COVID-19 positive and negative subjects was 47 and 40 years respectively. Out of total positive COVID-19 cases, 9.7% patients reported to have a contact with confirmed COVID-19 positive patient.

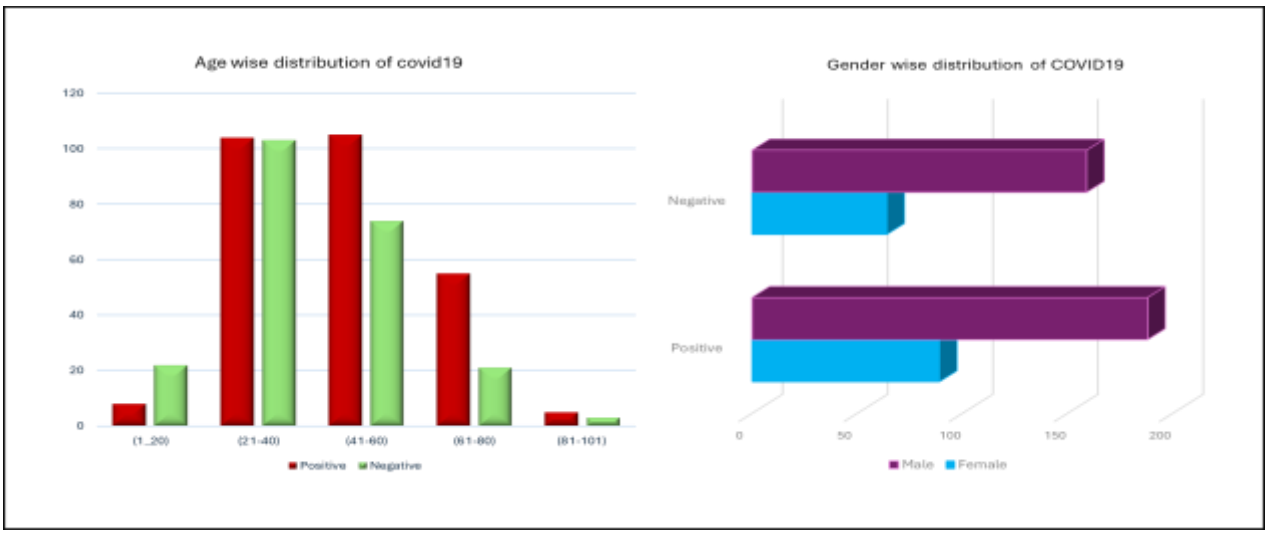

Figure 1: Age and gender wise distribution of COVID19 among study participants. (A) number of positive (red) and negative (green) COVID19 cases among different age groups ranging from 1-20 years, 21-40 years, 41-60 years, 61-80 years and 81-101 years old. (B) total number of COVID19 positive and negative cases in males (purple) and females (Blue).

The severity of disease was evaluated based on presentations of symptoms. **Figure 2** presented the clinical presentation of the 500 subjects, where out of 277 positive cases, 71.84% presented either one or more symptoms, while 28.15% were totally asymptomatic. The analysis of symptoms of symptomatic COVID-19 patients listed the fever and cough as most common presentations (P=<0.05). Diabetes and hypertension were found most prevalent diseases in the study population and had strong correlation with the prevalence of COVID-19, followed by chronic chest infection, cardiovascular disease, and kidney disease **(Table 1)**. Although the number of symptoms and severity of disease was increased in these patients as well, but the data was not statistically significant as shown in tables 3 and 4. The onset of the COVID-19 symptoms among diabetic (n = 26) and hypertensive (n = 21) patients was also investigated the results of which showed that 24 (92%, p<0.05) of the diabetic patients and 20 (95%, p<0.05) of the hypertensive patients presented with symptoms pointing towards the severity of infection. Pearson's correlation analysis of symptoms with chronic diseases and COVID-19 severity showed positive correlation between most of the symptoms such as fever, shortness of breath, diarrhea, and Diabetes mellitus (DM) (p=0.00) and Hypertension (HTN) (p=0.032), while flu and shortness of breath showed insignificant correlation with DM (p=0.053 and 0.20, respectively).

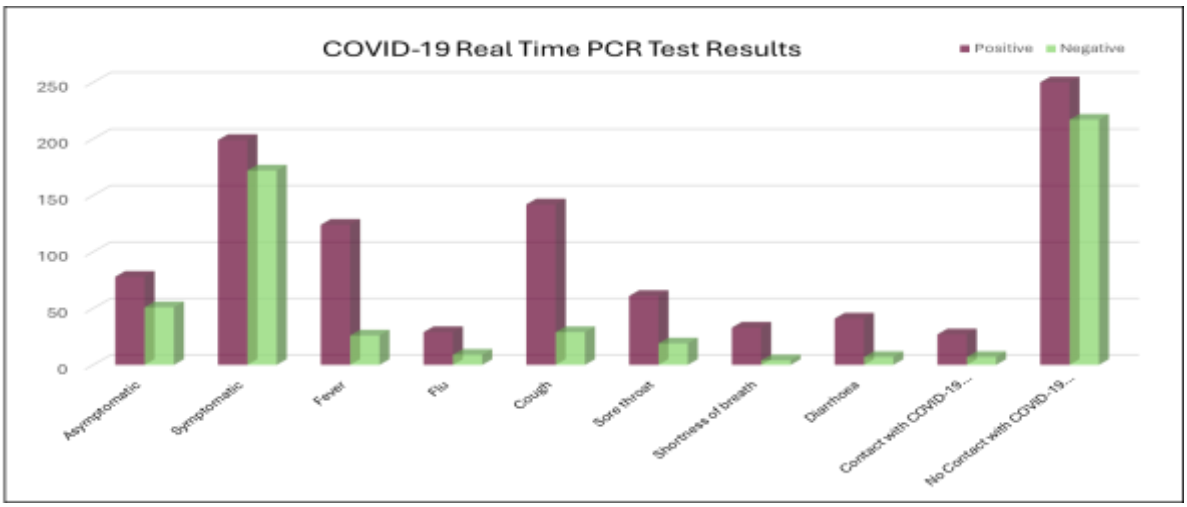

Figure 2: Clinical Profile of COVID19 suspected cases with positive (magenta) and negative (green) PCR tests.

The prevalence of DM was 6% among general population, but the prevalence of diabetes among COVID-19 positive (n=277) was higher 9.3% compared to the overall prevalence **(Table 3)**. Moreover, out of 26 diabetic COVID19 positive cases, 24 (92.3%) were symptomatic and only 2 (7.6%) were asymptomatic showing a positive correlation of DM with the severity of COVID-19 infection (p<0.05) **(Table 2)** Furthermore, out of 26 COVID-19 positive diabetic patients, 21(80.76%) did not have any history of contact with positive COVID 19 patient and 19 (90.4%) out of these were symptomatic. Remaining 5 out of 26 patients who reported history of contact with COVID-19 positive patient were all symptomatic (p<0.05). Highest prevalence of COVID 19 cases among total diabetic patients was 10% found in the age group between 41-80 years **(Table 3)**.

Table1: Correlation of COVID 19 with common comorbidities.

Medical condition		COVID-19 test results		Total	Significance
		Positive	*Negative*		
Kidney disease	*No*	*276*	*222*	498	.694
	Yes	*1*	*1*	2	
Cardiac disease	*No*	*271*	*222*	493	.105
	Yes	*6*	*1*	7	
HTN	*No*	*256*	*216*	472	.023*
	Yes	*21*	*7*	28	
Chronic chest infection	*No*	*269*	*220*	489	.196
	Yes	*8*	*3*	11	
DM	*No*	*251*	*219*	470	.000**
	Yes	*26*	*4*	30	

*HTN: Hypertension, DM: Diabetes Mellitus, * p <0.05, ** p < 0.01*

Table 2: Risk factors associated with the onset of symptoms among COVID-19 patients.

Variable		DM		Chronic chest infection		HTN		Cardiac disease		Kidney disease	
		NO	YES	NO	YES	NO	YES	NO	YES	NO	YES
Symptoms	***Asymp.***	76	2	75	3	73	5	78	0	78	0
	Symp.	175	24	194	5	183	16	193	6	198	1
Flu	***No***	227	21	241	7	232	16	242	6	247	1
	Yes	24	5	28	1	24	5	29	0	29	0
Fever	***No***	147	6	149	4	149	4	151	2	153	0
	Yes	104	20	120	4	107	17	120	4	123	1
Cough	***No***	128	7	131	4	127	8	131	4	135	0
	Yes	123	19	138	4	129	13	140	2	141	1

Sore throat	***No***	203	13	208	8	202	14	211	5	216	0
	Yes	48	13	61	0	54	7	60	1	60	1
Diarrhea	***No***	217	19	228	8	220	16	230	6	236	0
	Yes	34	7	41	0	36	5	41	0	40	1
SOB	***No***	222	22	236	8	228	16	239	5	243	1
	Yes	29	4	33	0	28	5	32	1	33	0

DM: Diabetes Mellitus, HTN: Hypertension, Asymp.: Asymptomatic, Symp. Symptomatic, SOB: Shortness of Breath

The prevalence of COVID-19 among hypertensive patients (7.58%) was also higher compared to the overall prevalence of hypertension in general population (5.6%) (p=0.032). Out of the 21 hypertensive patients, 20 (95.2%) were symptomatic and 1 (4.7%) was asymptomatic. The prevalence of HTN in different age groups and its association with the severity of disease was statistically significant (p=<0.05) with highest prevalence among 41-80 years of age **(Table 3)**.

Table 3: Age wise distribution of the clinical presentation of COVID19 positive and negative cases diabetic and hypertensive patients.

Variables				**COVID-19 test results**			
				YES Symptom		**NO Symptom**	
				Yes	***No***	***Yes***	*No*
HTN	**No**	**Age Groups**	***Under 20 Years***	5	4	4	18
			21-40 Years	72	31	25	75
			41-60 Years	64	31	17	54
			61-80 Years	37	8	4	16
			Above 80 Years	2	2	0	3
	Yes	**Age Groups**	***Under 20 Years***	0	0	0	0
			21-40 Years	1	0	3	0
			41-60 Years	9	1	1	2
			61-80 Years	10	0	0	1
			Above 80 Years	0	0	0	0
DM	**No**	**Age Groups**	***Under 20 Years***	5	4	4	18
			21-40 Years	70	28	30	75
			41-60 Years	60	15	31	55
			61-80 Years	39	4	8	17
			Above 80 Years	2	0	2	3
	Yes	**Age Groups**	***Under 20 Years***	0	0	0	0
			21-40 Years	3	0	1	0
			41-60 Years	13	3	1	1
			61-80 Years	8	0	0	0
			Above 80 Years	0	0	0	0

HTN: Hypertension, DM: Diabetes Mellitus

DISCUSSION

Researchers have discovered a connection between COVID-19 and co-morbid conditions based on the data from preliminary cases of outbreaks in China. 48 % of these cases had at least one underlying complication [10]. Recent studies based on systematic analysis have concluded that DM and HTN are the most prevalent underlying complications that not only contribute to a higher risk of SARS-CoV-2 infection but also lead to the severe presentation of the disease and higher mortality rates, especially in older people [11,12].

The objective of this study was to investigate the severity of COVID-19 among different morbidities like diabetes, hypertension, cardiovascular disease, chronic kidney disease, and chronic chest infections. The study was conducted in large cities in two provinces of Pakistan. We found that most of the participants in our study were males which may be due to social norms in Pakistan. However, females were found more prone to get infected. Moreover, older age individuals were more affected as compared to the younger age groups which were in line with previously published data [13]. We found that the correlation of severity of COVID-19 symptoms with different chronic diseases was only significant with DM and HTN and hence concluded the greater risk of COVID-19 severity in DM and HTN patients. Although this has previously been reported by different groups, this study has reported vital data from four major cities of Pakistan that focused on the role of DM and HTN and patient age in the severity of symptoms in COVID-19 patients. In summary, the study reported a prevalence of 9.3% for DM and 7.58% for HTN in COVID-19 confirmed patients and showed that the presence of these comorbidities contributed to the severity of the viral disease based on the onset of symptoms. The correlated data amongst COVID-19 and DM as a prevalent co-morbid condition is of global concern since DM is deemed to be the 21st-century pandemic because of the notable upsurge of DM in the adolescents and older age population [14]. The concurrent pandemic of COVID-19 has given rise to 'interaction' between the two pandemics of DM and COVID-19. Further research led to crucial observations between non-diabetic and diabetic COVID-19 patients; (1) elevated symptoms and severe form of COVID-19 in DM patients, (2) frequency of other co-morbid conditions in DM patients, (3) higher levels of COVID-19 biomarkers, and (4) greater need of external oxygen supply in the form of non-invasive or invasive ventilation [15]. These observations suggest that as the pandemic gets advanced, the notion that DM obstructs the innate immune system by retarding leukocytic phagocytosis and cell-mediated immune mechanism. It is also evident previously from animal model studies that altered immune mechanisms in DM as well as the decreased ability of the host to fight against chronic inflammatory cascade may lead to more prolonged and severe lung damage in MERS-CoV infection [16], a mechanism that may be correlated with the case of SARS-CoV infection.

There can be a different possible mechanism through which diabetes worsens the progression of COVID-19. It has been reported that diabetic COVID-19 patients may be influenced by the secretion of hyperglycemic hormones [17], resulting in hyperglycemia and thus disturbing the regulation of protein stability, structure, and other features (aggressive glycosylation) that leads to malfunction in receptor signaling and alters the function of immunoglobulins. Hence, diabetic individuals with glycosylation disturbance of IgG might be more susceptible to SARS-CoV-2 infection and hence are more prone to the need for ICU care and mechanical ventilation with an increased death rate [18].

HTN appears to be a risk factor for a more severe clinical expression of the SARS-CoV-2 infection in this population. HTN is an inflammation-mediated disorder with an underlying endothelial dysfunction [19]. Hence, it is essential to focus on its contribution to the Pakistani population to further study its relationship with the severity of COVID-19. Previous clinical research has made it clear that HTN is a notable risk factor for poor outcomes in individuals infected with SARS and MERS [20]. However, in the case of SARS-CoV-2, the exact mechanism by which HTN increases the rate of death remains unknown, but chronic inflammation might play a critical role in increasing mortality risk [21]. Blood pressure control in HTN patients is deemed to be a noteworthy concern to lower the burden of disease despite its effect on SARS-CoV-2 infection [22]. Besides, in hypertensive COVID-19 patients, high blood pressure was independently associated with an increased risk of heart failure, hospitalization, and mortality [23]. Like DM, the mechanistic relationship between COVID-19 and HTN may also be described using ACE2 as an entry point for SARS-CoV-2 [24]. Many studies have also implicated the connection of higher angiotensin II in COVID-19 patients with the severe form of the disease [25,26], as angiotensin II has been previously shown to induce impaired lung function, lung edemas, and lung inflammation in pneumonia [27].

CONCLUSION

SARS-CoV-2 has led to worldwide mortality. The study has put forth vital data from four major cities of Pakistan and focused on the role of DM and HTN to patient age towards the severity of symptoms

in COVID-19 patients. Both these disorders were associated with the severity of COVID-19 symptoms, thus put patients at increased risk of COVID-19 related mortality. Further studies should focus on the topic with larger number of participants and defined classification of hypertension and diabetic cases to have a clear picture of the scenario. It also opens a gateway to explore the outcome of COVID-19 and cardiovascular disease together.

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