ORIGINAL ARTICLE:

ASSOCIATION OF PHYSICAL AND NEUROPSYCHIATRIC MORBIDITIES WITH THE SEVERITY AND MORTALITY OF COVID-19 PATIENTS IN PAKISTAN

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Abstract

Objective:

To find out the association of co-morbidities; risk factors and physiological and neuropsychiatric side effects with the severity and mortality of COVID-19 patients in our set of population.

Method

Covid-19-positive patients (151) ages 18-80, were recruited, (June 2022 to May 2023) from Ziauddin Hospital, after informed consent and approval from Ethics Committee. The questionnaire recorded patients' demographic variables, laboratory investigations, past medical history, and family history. Follow-up co-morbidities, recovery, death, or LAMA (Leave Against Medical Advice) data was taken from hospital records. Analyses were done using (SPSS) software. P-values of <0.05 were considered significant.

Results

Out of 151 patients; females were 56 (37%) and males 95 (63%). Among these 82(54.3%) recovered, 52(34.4%) passed away and 17(11.2%) LAMA. Deaths in males 40(26.4%), were higher, compared to females 12(7.9%). Overall 84 (56%), suffered severe infection, 24 (16%) moderate and 43 (28%) mild. The most common risk factors were complications of the heart (hypertension) 35(42.7%) followed by diabetes 27 (32.9%) ($p<0.001$). Neuropsychiatric manifestations such as depression 36(23.8%), was highest among post covid-19 complications, 14 (17.07%) patients had stroke out of which 9(17.3%) could not survive. The most common cause leading to covid 19 severity was Pneumonia 76(80%) then diabetes 63(80%) and hypertension

69(78%) (p<0.001). Majority of patients, 88(58.3%) were above 50 years of age, 35(23.2%) between 25-50 and 28(185%) <25 years.

Conclusion

The most common risk factor of Covid-19 were complications of the heart and diabetes. Highest post Covid-19 complication among survivors was depression. The highest complication leading to death was Pneumonia.

Keywords

Covid-19; Mortality: Heart: Physical and Neuropsychiatric, Comorbidities

Introduction

In any pandemic, co-morbidities can play havoc in society and predispose individuals with acute or chronic clinical conditions from morbidity to mortality. In the Covid-19 pandemic lungs were anticipated to be the most vulnerable organ and any individual with lung problems would be at the highest risk of infection. Earlier studies from China reported poorer clinical outcomes of patients with any comorbidity, than those without diseases. Their data of 1590 hospitalized patients from 575 hospitals in China revealed Chronic obstructive pulmonary disease (COPD) as the most susceptible comorbidity followed by diabetes and hypertension.(1). A study on 2813 patients from Europe found chronic respiratory impairment of 631 (22.4%) as the most common comorbidity followed by congestive heart failure 290 (10.3%), chronic renal failure286 (10.2%), chronic liver failure112 (4%), immune incompetence 584 (20.8%), and diabetes 613 (21.8%) (2). Researchers have categorized Covid-19 into 3 phases; viral illness, immune-mediated inflammatory lung injury, post-acute sequelae and patients from different geographical areas showed diversified responses due to different underlying biological mechanisms (3).

In Pakistan a few studies from Punjab have reported the impact of comorbidities, the majority focused on clinicopathological factors or epidemiology (4-5). Covid-19 was described as a biphasic illness, leading to complications that can be life-threatening, and cause death either by rapid viral replication or by complications of different organs. Understanding the link between human genetics and epidemiology, it is important to understand the underlying mechanisms of covid 19 affecting our population in relation to comorbidities.

This study was designed to find out the association of comorbidities with the severity and mortality of covid-19 patients in our set of population.

Method

In this study, n=151 Covid positive patients were recruited from Ziauddin Hospital and University. The samples were collected between June 2022 to May 2023 after receiving approval from the Ziauddin Ethics Review Committee (Ref Code: 5360522BKBC). The informed consent was taken from participants comprising females and males between the ages of 18-80. Patient with post chemotherapy and radiotherapy and with any malignant condition was excluded. All participants' data was collected by questionnaire. The parameters assessed were age, weight, BMI, socioeconomic status, laboratory investigations, past medical history, family history, and demographic variables. The patient's clinical condition in terms of other co-morbidities and health status either alive, dead, or LAMA (Leave Against Medical Advice) was also recorded from the hospital record. All analyses were carried out using the IBM statistical package for the social sciences (SPSS) software. Qualitative data such as (gender, symptoms of Covid-19, and status of diabetes) were presented as frequency and percentage and quantitative data such as age and blood pressure were presented as mean and standard deviation. Categorical variables with the groups of mild, moderate, and severe patients of Covid-19 were assessed by applying the Chi-Square test. P-values of <0.05 were taken into consideration as significant.

Results

Out of a total of 151 Covid-19 patients; 28(18.5%) patients were of age less than 25 years, 35 (23.2%) patients were of age between 25 to 50 years, and the majority 88 (58.3%) of the patients were of above 50 years of age. Most of the patients 95 (62.9%) were male and 56 (37.1%) were female. Ethnicity distribution showed that 119 (78.8%) patients were Urdu-speaking followed by Sindhi and Punjabi. With respect to occupation, 49(32.45%) of the population were employed, 15 (9.93%) women were housewives, 25(16.55%) patients were students and 25(16.55%) patients were unemployed and 37(24.5%) patients were retired (Table-1).

Table 1: Demographic Characteristics of Study Subjects

Study Variables	Frequency (n)	Percentage (%)

Age groups		
<25 years	28	18.5
25-50 years	35	23.2
>50 years	88	58.3
Gender		
Female	56	37.1
Male	95	62.9
Ethnicity		
Urdu Speaking	119	78.8
Pathan	4	2.6
Punjabi	11	7.3
Sindhi	14	9.3
Others	3	2.0
Occupation		
Employed	49	32.45
House Wife	15	9.93
Student	25	16.55
Unemployed	25	16.55
Retired	37	24.50

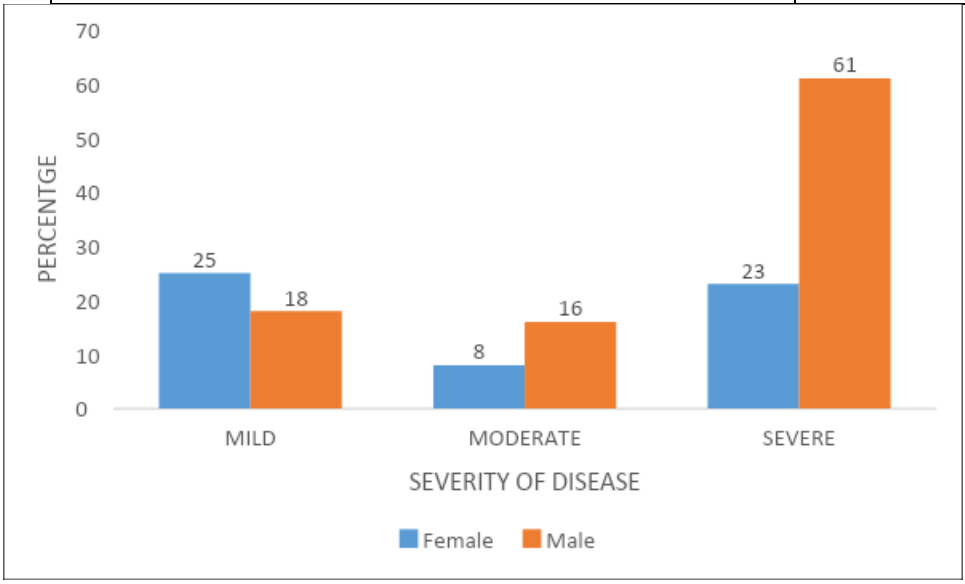


Figure 1: Distribution of severity of Covid-19 among males and females

The association between Covid-19 severity and gender was non-significant with a P-value=0.105. Furthermore, it can be observed that the proportion of male patients is less in the mild group as compared to moderate and severe groups. In the study of patients with severe disease, the majority were male **(Figure 1).**

Table 2: Association of co-morbidities with the severity of covid-19

Co-morbidities	Severity of Covid-19 n(%)			p-value
	Mild 43 (28%)	Moderate 24 (16%)	Severe 84 (56%)	
Hypertension	6(7%)	13(15%)	69(78%)	<0.001*
Diabetes	5(6%)	11(14%)	63(80%)	<0.001*
Heart Disease	0(0%)	6(12%)	42(88%)	<0.001*
Epilepsy	0(0%)	1(100%)	0(0%)	<0.124
COPD	0(0%)	2(8%)	22(92%)	<0.006*
Asthma	7(32%)	5(23%)	10(45%)	<0.304
Bronchitis	2(18%)	5(45%)	4(36%)	<0.029*
Pneumonia	2(0%)	18(19%)	76(80%)	<0.001*
Depression	18(50%)	7(19%)	11(31%)	<0.0001*
Stroke	0(0%)	1(7%)	13(93%)	<0.031*
Hepatitis C	0(0%)	0(0%)	2(100%)	<0.097
Dengue	4(57%)	2(29%)	1(14%)	<0.589

Chi-square test applied; Significance level set at *<0.05. COPD: Chronic obstructive pulmonary disease.

Overall 84 (56%), suffered severe infection, 24 (16%) moderate and 43 (28%) mild. The most common cause leading to severity was Pneumonia 76(80%) then diabetes 63(80%) and hypertension 69(78%). The severity of Covid-19 was compared with the co-morbidities showed the significant association of severity with heart disease 42(88%) (P<0.001), hypertension 69(78%) (P<0.001), diabetes 63(80%) (P<0.001), COPD 22(92%) (P <0.006), pneumonia 76(80%) (P<0.001) and stroke 13(93%) (P<0.031). Most of the patients with severe Covid-19 were

hypertensive or had heart disease, diabetes, COPD, and stroke. The 50% prevalence of depression was reported high in all mild patients. Most of the patients with severe Covid-19 have a high prevalence of hypertension compared to moderate Covid-19 (Table 2).

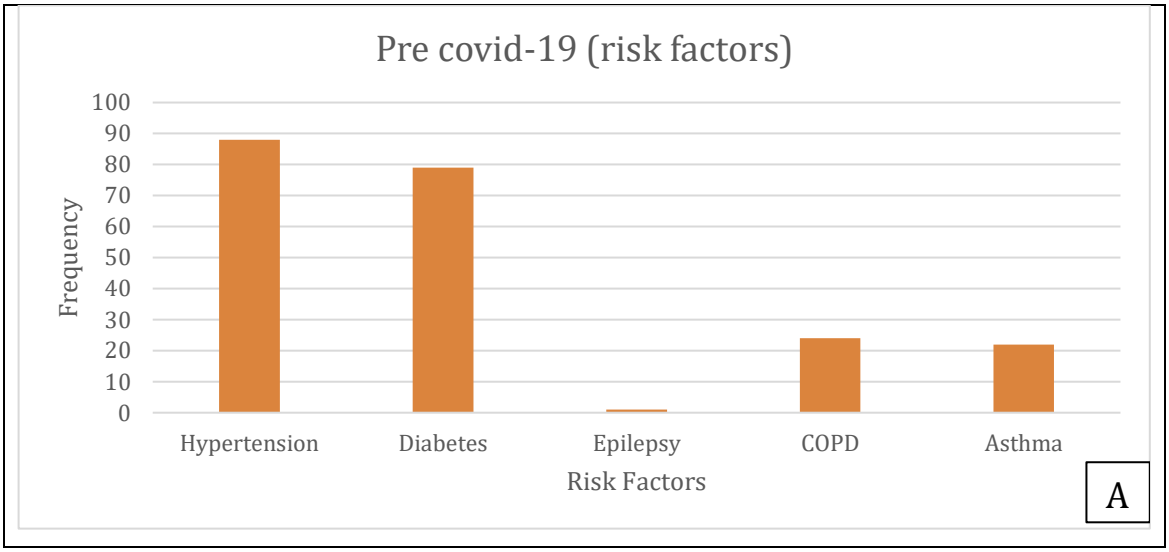
TABLE 3: Association of Demographics, Co-Morbidities and After Covid Morbidities With The Mortality

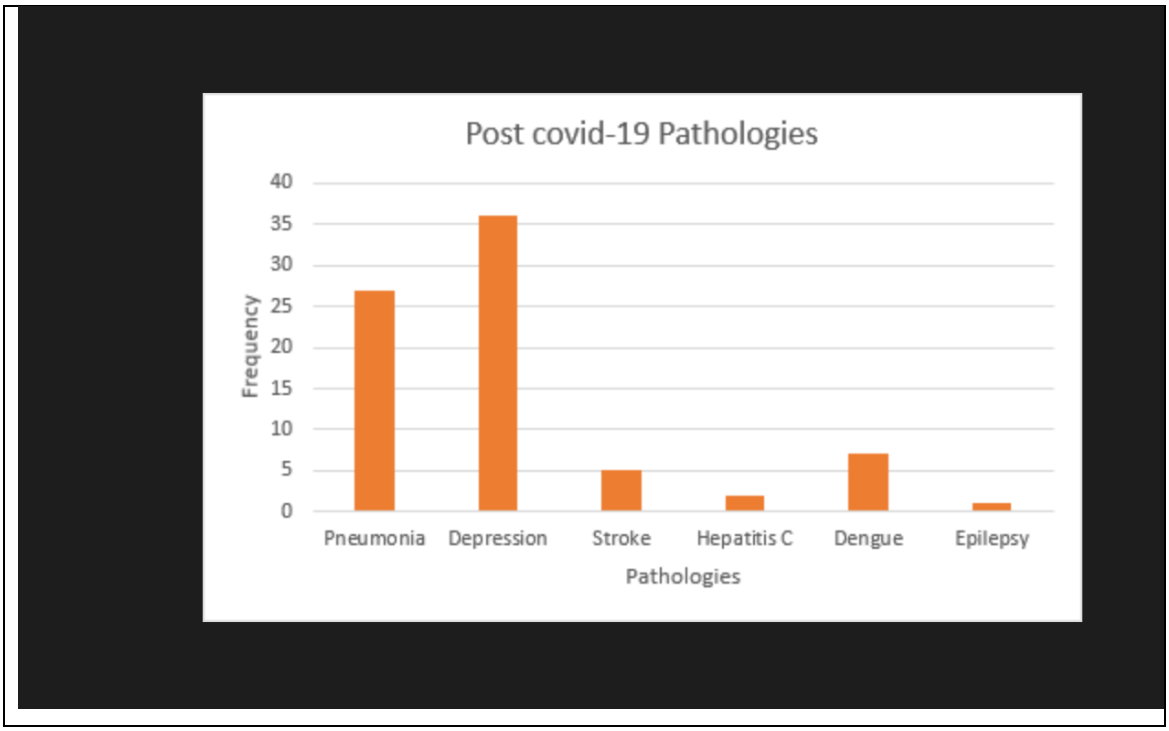
Variable n(%)	Alive n=82(54.4)	Death n=52(34.4)	LAMA n=17(11.2)	P value
AGE GROUPS				
≤ 25	27(32.9)	0(0)	1(5.88)	<0.001*
25-50	24(29.2)	8(15.3)	3(17.6)	<0.001*
≥ 50	31(37.8)	44(84.6)	13(76.47)	<0.001*
GENDER				
MALE n=95	43(52.4)	40(76.9)	12(70.5)	0.015*
FEMALE n=56	39(47.5)	12(23.07)	05(29.4)	0.013*
BODY LOCATIONS AND DISEASES (*Some patients had Multiple Morbidities) *P* values were calculated by comparing with and without symptoms				
HEART				
HYPERTENSION n=84	35(42.7)	43(82.69)	6(35.3)	<0.001*
ISCHEMIC HEART n=49	13(15.9)	32(61.53)	4(23.5)	<0.001*
LUNGS				
PNEUMONIA n=96	27 (32.9)	52(100)	17(100)	<0.001*
ASTHMA n=22	20(24.4)	2(3.8)	0	0.006
COPD n=24	8(9.8)	15(28.8)	1(5.9)	<0.001*
BRONCHITIS n=11	11(13.4)	0	0	<0.001*
GASTROINTESTINAL				
DIABETES n=80	27 (32.9)	41(78.84)	12(70.6)	<0.001*
DIARRHEA n-31	31 (37.8)	0	0	<0.001*

NEUROLOGICAL				
DEPRESSION n=36	36(43.9)	0	0	<0.001*
EPILEPSY n=1	1(1.2)	0	0	<0.001*
STROKE n=14	5(6.1)	9(17.3)	0	<0.001*
VIRAL INFECTION				
DENGUE n=7	7(8.5)	0	0	<0.001*
HEPATITIS C n=2	2(2.4)	0	0	<0.001*

LAMA= Leave Against Medical Advice, COPD: Chronic obstructive pulmonary disease

Out of 151 patients; females were 56 (37%) and males 95 (63%). Among these 82(54.3%) recovered, 52(34.4%) passed away and 17(11.2%) LAMA. Deaths in males 40(26.4%), were higher, compared to females 12(7.9%). The most common risk factors were complications of the heart (hypertension) 35(42.7) followed by lungs (pneumonia) 27(32.9) and diabetes 27 (32.9) (p<0.001). Majority of patients, 88(58.3%) were above 50 years of age, 35(23.2%) between 25-50 and 28(185%) <25 years (Table 3).





COPD: Chronic obstructive pulmonary disease

Figure 2 (A-B): Pre covid-19 Risk Factor (2A) and Post covid-19 pathologies among covid-19 patients (2B).

Co-morbidities that have been declared as risk factors worldwide were evaluated showed that; 88(58.3%) patients had hypertension, 79(52.3%) diabetes mellitus, 48(31.8%) heart disease, 1(0.7%) epilepsy, 24(15.9%) COPD and asthma was reported in 22(14.6%) patients (Figure 2A). However, patients during Covid-19 infection developed other pathologies which included , depression in 36(23.8%), pneumonia in 27 (32.9%), stroke in 14(9.3%), bronchitis in 11(7.3%), Hepatitis C in 2(1.3%), and dengue in 7(4.6%) **(Figure 2B).** The most commonly prevalent risk factors among the COVID-19 patients in our population were pneumonia, hypertension, diabetes and heart disease, whereas, post covid-19 was depression.

DISCUSSION

In our population, the highest post Covid-19 morbidity among survivors, compared to pneumonia [27 (32.9%)] and other pathologies, was depression [36(43.9%)]. The corona viruses are called neuro-invasive causing neuropsychiatric manifestations such as depression, agitation, seizure, and stroke etc. In our study 14 (17.07%) of covid-19 patients had a stroke out of which 9(17.3) could

not survive Covid-19 can access the CNS by attaching to the ACE2 receptors after crossing the blood-brain barrier and cause cellular senescence, neurodegeneration and demyelination, increasing aging of the brain (6,7). Researchers also observed that psychiatric or neurological may persist after recovery.

Heart-related diseases were the most significant risk factors of morbidity and mortality due to Covid-19 with 42(88%) developed severe infections leading to death. Earlier studies on Covid-19 reported that it mainly causes respiratory tract infections and patients with respiratory problems were more susceptible to morbidity and mortality (8, 9). Another single-center study from Wuhan, China reported Covid-19 as the sole cause of pneumonia, they named it NCIP (novel coronavirus (2019-nCoV)–infected pneumonia) which led to 4.3% mortality (10). Later reports from other parts of the world found ischemic heart disease as the main cause of mortality suggesting indirect effects of Covid-19 on cardiovascular outcomes, which is in accordance with our study (11, 12). Even out-of-hospital incidences of cardiac arrests were found to increase in the United States and Italy, during COVID-19 (13, 14). Other cardiac complications due to Covid-19 reported from studies around the world with higher risk of mortality (15) included ventricular arrhythmias, shock (16), myocarditis (17), myocardial injury (18), as well as less or no access to health care (19). These findings suggest that the pandemic may be affecting the heart through an unknown mechanism that is not fully understood.

The major rise in ischemic heart disease-related deaths in the population increases the possibility that the pandemic had significant collateral consequences on cardiovascular outcomes (11). Whether they are infected or not, patients with cardiovascular disorders during the pandemic have an increased risk of developing a serious illness (20). Concerns have also generated questions about how this has impacted the availability and demand for acute cardiovascular care during the Covid-19 pandemic (21). Increased mortality has been reported particularly in CVDs due to both "direct" infections and "indirect" alterations in healthcare. In this regard, COVID-19 has major effects on people and health systems: (i) Direct consequences from infection, and (ii) Indirect effects of extreme system stress and resulting behavioral modifications (21).

Through both acute and chronic processes, including plaque rupture, destabilization, and maintenance of a chronic inflammatory state that results in long-term COVID syndrome and

ultimately increased rates of myocardial infarction, which proved that COVID-19 has been linked to the development and progression of CHD (22). The pandemic has indirectly increased the burden of CHD through unhealthy habits including cigarette use, decreased physical activity, economic collapse and its consequences, and frequent pauses and delays in cardiac care. People having baseline CHD at the time of contracting COVID-19 infection are more likely to experience acute cardiac episodes, which increases the risk of mortality (22). Hospitalizations for acute myocardial infarction, and cardiac catheterization laboratory activations for ST-segment elevation myocardial infarction have significantly decreased during the pandemic as patients with acute coronary syndromes who need urgent treatment are avoiding medical care and dying at home. This could be due to worries about contracting the virus in a hospital setting and deaths at home have risen dramatically in areas of the United States hardest hit by COVID-19 due to cardiovascular events (11).

COVID-19 has infected the majority of the world's population and it has been observed that COVID-19 mortality was higher among the elderly and in people with preexisting noncommunicable diseases (NCDs), such as obesity, diabetes, and coronary heart disease (CHD) (20).

The Covid-19 infected majority of the world's males, especially the older population, who got critically ill and were admitted to the ICU (10). In this study, 95 (63%) males were infected, out of which 40 passed away. Recovery in females even with severe infection was better. Researchers agreed that males were at higher risk of infectivity and compared to females required ICU admission which may be due to diversity in immune responses or the protective effect of sex hormones or Genetic predispositions, however, sex-related determinants of morbidity and mortality by COVID-19 remain unclear (23).

Diabetes was the second most at-risk comorbidity for Covid-19 in our study with 80% of developing severe infection. Many studies reported diabetes as the second highest comorbidity, amongst which (24) through univariable analysis, found a higher death rate of diabetic patients when they calculated the odds of in-hospital death.

The advanced age combined with Diabetes is the second most at-risk comorbidity for Covid-19. Poorly controlled blood sugar levels in diabetic patients suffering from COVID-19 may aggravate

the inflammatory response and contribute to adverse outcomes. Therefore, further studies are required with a larger sample size to confirm the severity of Covid-19 with diseases.

CONCLUSION

A significant association between co-morbidities especially Hypertension, pneumonia and depression with the severity and post Covid-19 complications was found in patients. Patients with pre-existing such diseases experienced more severe Covid-19 symptoms which include pneumonia, cytokine storm and respiratory distress. These findings highlight the need for public health initiatives and tailored interventions to safeguard vulnerable groups, particularly those who have heart and lung diseases along with neurological disorder.

PATIENTS' CONSENT.

Written informed consent was obtained from all study participants after explaining to them the objectives, rationale, and benefits of the study.

COMPETING INTEREST:

The authors declared no competing interest.

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AUTHOR(S) CONTRIBUTION/UNDERTAKING FORM

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2.	Dr. Sadia Farrukh	Agha Khan University	Statistical analysis and Editing	
3.	Dr. Ashok Kumar	Ziauddin University	Blood Sample collection and clinical guidance	
4.	Dr. Saeeda Baig	Ziauddin University	Study Conception, Supervision and Original Draft and Manuscript Writing