ORIGINAL ARTICLE

Correlation of various co-morbidities of COVID-19 patients with persistent COVID-19 PCR positivity: A prospective study at Nishtar Hospital Multan.

Shahzad Alam Khan[1], Faisal Ramzan[2], Talha Rasheeq[3], Muhammad Khalid[4], Arooj Fatima[5]

ABSTRACT… Objective: To investigate the correlation between various co-morbidities of COVID-19 patients with persistent PCR positivity in hospitalized patients. **Study Design:** Prospective Observational. **Setting:** Nishtar Medical University, Multan COVID Isolation Wards, and ICU. **Period:** 15 September 2020 to 14 September 2021. **Material & Methods:** The study sample included 162 hospitalized patients who underwent COVID-19 PCR testing at admission, 4 weeks, and 8 weeks, and their comorbidities data were collected. Multiple regression analysis was performed to determine the relationship between co-morbidities and COVID-19 PCR positivity. **Results:** Among 162 patients, seventy-nine (48.8%) were male and the mean age of the patients was 53.46±15.81 years. Out of 162 patients, 70 (43.2%) tested positive for COVID-19, while 92 (56.8%) tested negative. Among 70 patients who had positive PCR, 45(64.28%) patients had prolonged positive PCR (at 4 weeks) and out of 45, 29 (64.45%) again remained positive at 8 weeks. While carrying out the multiple linear regression, the results indicated that the presence of hypertension, diabetes, and lung disease was positively associated with persistent COVID-19 PCR positivity (at 4 and 8 weeks). However, no significant association was found between persistent COVID-19 PCR positivity and liver disease, malignancy, and ischemic heart disease. **Conclusion:** The study highlights the importance of considering co-morbidities like diabetes, hypertension, and lung disease, in predicting persistent COVID-19 PCR positivity in hospitalized patients. Further research is needed to confirm these findings and investigate the underlying mechanisms of these associations.

Key words: Co-morbidities, COVID-19, Coronavirus, Diabetes, Persistent, PCR.

INTRODUCTION

Atypical pneumonia (COVID-19) broke out in Wuhan, China, in December 2019, and it soon spread to other regions of the world.[1] There were 679,726,820 confirmed cases worldwide as of February 27th, 2023, and 6,798,632 people passed away as a result of the disease.[2] Pakistan's first instance was reported on February 26, 2020, and by February 27, 2023, there had been 1,576,939 cases reported with 30,643 fatalities, according to the COVID portal Pakistan.[3,4]

Pakistan has a high prevalence of chronic diseases such as diabetes, hypertension, ischemic heart disease, chronic liver disease, chronic lung disease, and cancer. The International Diabetes Federation estimates 7.1 million Pakistanis have diabetes.[5] Hypertension affects one-third of Pakistani adults, making it a major public health issue.[6] Ischemic heart disease is also prevalent due to DM and hypertension. Chronic pulmonary illnesses have grown due to 13.4% of adult smoking.[7] Chronic viral hepatitis has increased chronic liver disease rates.[8] The COVID-19 epidemic in Pakistan was worst for people with co-morbidities. This study seeks to link chronic diseases to COVID-19 using several factors.

Data relating to COVID-19 PCR positivity duration and co-morbidities is lacking and little work is done on it.[9,10,11] Moreover, results in these studies are not consistent and COVID-19 PCR positivity duration ranged from 8 to 20 days after symptoms onset. However, Zhou F[12] has reported that time

1. MBBS, FCPS, Assistant Professor Medicine, Nishtar Medical University, Multan.
2. MBBS, PG Trainee / Medical Officer, CPEIC, Multan.
3. MBBS, FCPS, Associate Professor, Bakhtawar Amin Medical College / Hospital, Multan.
4. MBBS, MD Trainee, Nishtar Medical University, Multan.
5. MBBS, FCPS, Senior Registrar, Nishtar Hospital, Multan.

Correspondence Address:
Dr. Shahzad Alam Khan
Department of Medicine,
Jinnah Hospital, Nishtar Road, Multan.
shahzadalam17735@gmail.com

to negative PCR may range from 15-37 days after symptom onset. The impact of age, intensive care unit (ICU) admission, comorbidities, and ethnicity remain unclear.

As this study investigated COVID-19 patients' co-morbidities and persistent PCR-positive in hospitalized patients, so the present study is valuable in various ways. First, it shows the frequency of comorbidities in hospital patients and emphasizes the need for lifestyle changes and preventative actions to minimize chronic illness in Pakistan. Secondly, it can also help policymakers address the country's high comorbidity rate. Finally, the study might lead to future research on comorbidities in Pakistan, including risk factors, treatment, and results. Persistent PCR positivity in high risk groups with poor prognosis overemphasizes the need of new drug development for these high risk groups to decrease ongoing viral shedding.

MATERIALS & METHODS
IERB gave ethical approval (16806) before data collection. The study followed the Helsinki Declaration ethics. This study used purposive sampling and informed consent was taken from patient or patient's family. The patients admitted to The Nishtar Medical University, Multan COVID isolation wards, and ICU from 15 September 2020 to 14 September 2021, were enrolled.

The collected data contained Demographics, Co-morbid conditions, and COVID-19 PCR positivity. Co-morbid conditions were labeled based on history and medical records. At admission, after baseline investigation, a nasopharyngeal sample for COVID-19 PCR was obtained. PCR was repeated at the 4th and 8th weeks. PCR positivity was considered to be persistent if it remained positive after 4 weeks.

Statistical software, such as SPSS v.26 was used for data analysis. The collected data was analyzed using descriptive statistics, such as mean, standard deviation, and frequency distribution for qualitative parameters like age, gender, and co-morbidities like DM, hypertension, IHD, liver disease, lung disease, and malignancy. The

frequency of PCR-positive patients at admission, 4 weeks, and 8 weeks was noted and also their various co-morbid conditions' frequency in PCR-positive patients at different time intervals was also noted. Multiple linear regression was used to examine the relationships between co-morbidities (DM, hypertension, IHD, lung disease, liver diseases, and malignancy) and persistent PCR positivity.

RESULTS
Among 162 patients, seventy-nine (48.8%) were male. 159(98.1%) were married and only 03(1.8%) patients were unmarried. The mean age of the patients was 53.46 ± 15.81 years. Out of 162 patients, 135 (83.3%) reported having a fever while 27 (16.7%) did not have a fever. Out of 162 patients, 59 (36.4%) had diabetes, hypertension was present in 101(62.3%) patients, and ischemic heart disease in 26 (16.0%). Similarly, 32 (19.1%) patients had pre-existing lung disease (Table-I).

Out of 162 patients, 70 (43.2%) tested positive for COVID-19, while 92 (56.8%) tested negative. (Figure-1) Out of those 70 who tested positive for PCR, 28 (42%) patients had diabetes, and 49(70%) had hypertension. 13 (18.6%) had IHD, 13 (18.6%) with lung, and 4 (5.7%) had malignancy. Among 70 patients who had positive PCR, 45(64.28%) patients had prolonged positive PCR (at 4 weeks) in which 37% (17) were diabetics and 20% (9) had IHD, diabetes, and lung disease. And out of 45, 29 (64.45%) again remained positive at 8 weeks, in which diabetic and hypertensive constituted 31% (9) as shown in Figure-1.
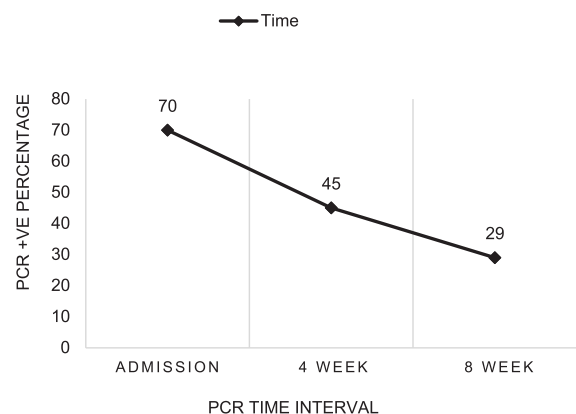

Figure-1. PCR +ve with time

While carrying out the multiple linear regression between hypertension, diabetes, malignancy, ischemic heart disease, lung disease, and liver disease with the PCR results, done at admission, at 4 weeks, and at 8 weeks. Looking at the coefficients table, among the six co-morbidity variables, no variable was statistically significant at admission but at 4-week hypertension (p=0.001), diabetes (p = .026), lung disease (p = .046) were statistically significant predictors of COVID-19 PCR positivity. At 8 weeks, hypertension (p=0.036), diabetes (p=0.05), and lung disease (p=0.044) had a statistically significant relationship with the COVID-19 PCR positivity which shows hypertension, diabetes, and lung diseases are the strongest predictors of persistent PCR positivity as shown in Table-II.

DISCUSSION
Based on the results of this study, it can be inferred that some comorbidities have a significant association with COVID-19 PCR results. Specifically, diabetes, hypertension, and lung disease were found to have a statistically significant positive relationship with COVID-19 PCR results, indicating a higher likelihood of a positive test result in individuals with these comorbidities. On the other hand, liver disease, malignancy, and ischemic heart disease did not show any significant association with COVID-19 PCR results.

Among 162 patients, seventy-nine (48.8%) were male and the mean age of the patients was 53.46±15.81 years. The median age of the study population was 48.0 years (IQR 35.0–62.0, range, from 18.0–90.0 years), and 128 patients (44.9%) were men, which was nearly consistent with the study.[13] Regarding the prevalence of co-morbidities, our study population had 62% hypertensive, 36% diabetics, and 19 % were with lung disease.

Hypertension		Diabetes		Ischemic Heart Disease		Malignancy		Lung Disease	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
101 (62%)	61 (38%)	59 (36.4%)	103 (63.3%)	26 (16%)	136 (84%)	05 (3.1%)	157 (96.9%)	32 (19.8%)	131 (80.2%)
Total 162(100%)		Total 162(100%)		Total 162(100%)		Total 162(100%)		Total 162(100%)	

Table-I. Frequency of Co-Morbid conditions

Co-Morbidities	1st PCR [a] (At admission)		2nd PCR [a] (At 4 Weeks)		3rd PCR [a] (At 8 Weeks)	
	β *	95% CI for β (sig)	β *	95% CI for β (sig)	β *	95% CI for β (sig)
Hypertension	.217	-.060, .504 (.122)	-.472	-.681, -.192 **(.01)**	-.295	-.452, -.016 **(.036)**
Diabetes	.057	-.179, .297 (.627)	-.252	-.441, -.028 **(.026)**	-.232	-.369, -.000 **(.050)**
Malignancy	-.091	-.752, .231 (.296)	.100	-.186, .684 (.233)	.026	-.323, .437 (.767)
IHD [c]	-.008	-.242, .220 (.925)	-.037	-.245, .154 (.660)	-.038	-.219, .139 (.658)
Lung disease	.108	-.107, .374 (.273)	-.189	-.421, -.004 **(.046)**	-.199	-.377, -.006 **(.044)**
Liver disease	.076	-.149, .400 (.368)	-.105	-.395, .081 (.195)	-.035	-.258, .167 (0.672)

[a]= dependable variable   *= standardized coefficient   [c]=ischemic heart disease,
The bold letter shows a significant result

Table-II. Multiple linear regression between Co-morbidities and PCR positivity

A study done by Batool et al.[14] had 42% of diabetics, which is slightly higher, that can be due to the rural area of our study which has more physically active adults and their study area was the urban population. Chaudhry A et al.[15] in 2020 also reported the prevalence of hypertension at 67% and diabetes at 45%, as due to stress and steroid use, diabetes might be unmasked.

While carrying out the regression analysis, hypertension was the most consistent co-morbidity which was associated with the persistent PCR positivity which is consistent with the research done by Aldhaeefi et al[16] where the presence of hypertension (OR: 1.4, 95% CI 1.0-2.1, p-value=0.03) showed a strong correlation with PCR positivity at 4 and 8 weeks. Xu, Kaijin, et al[17] reported that age >70 years and hypertension delayed the viral shedding with an average duration of >15 days.

Another co-morbid condition which delayed the viral shedding was diabetes, probably due to prolonged steroid use and diabetes itself which made the immunological response less potent and led to delayed viral shedding. In our study, diabetes was strongly associated with persistent PCR positivity at 4 and 8 weeks. Chen, Xiaoping, et al[18] reported similar results where diabetes and hypertension both delayed the viral shedding for more than 2 weeks after multivariate regression analysis. But many studies also reported the shorter duration of positive PCR[19] and early shedding of viral RNA in diabetes.[20] Pre-existing lung disease was also related to persistent viral shedding in our study which is also consistent with a previous study done in which COPD (OR 1.78, 95% CI: 1.53–2.08, $p < 0.001$) and diabetes (OR 1.21, 95% CI: 1.15–1.26, $p < 0.001$) were associated with prolonged viral shedding.[21]

Our study had some contrasting results with other studies pertaining to IHD and malignancy which showed negative association with persistent viral shedding. In a case report, PCR remained positive even after 59 days despite antiviral treatment in a lymphoma patient describing the immunocompromised state[22], so was proved in another study done in Wuhan on cancer patients.[23]

LIMITATIONS
One limitation of this study is that it was conducted on a relatively small sample size. Additionally, the study did not control for potential confounding variables, such as age and gender, which may have influenced the results. Future research on a larger and more diverse sample, controlling for potential confounders, would be beneficial in confirming these findings.

CONCLUSION
In conclusion, this study provides evidence of a significant association between diabetes, hypertension disease, lung disease, and persistent COVID-19 PCR positivity, highlighting the importance of comorbidities in predicting COVID-19 outcomes. However, laboratory data alone may not be sufficient in predicting COVID-19 outcomes, and other factors such as comorbidities may need to be considered in the assessment of COVID-19 risk. Persistent PCR positivity in high risk groups with poor prognosis also overemphasizes the need of new drug development for these high risk groups to decrease ongoing viral shedding.
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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Shahzad Alam Khan	Concept of idea, Manuscript writing.	
2	Faisal Ramzan	Literature search, Data collection.	
3	Talha Rasheeq	Data analysis, Grammer Check.	
4	Muhammad Khalid	Data collection, Proof Reading.	
5	Arooj Fatima	Data collection, Proof Reading.	