

Frequency of Re-infection and Severity of Symptoms among COVID-19 PCR Confirmed Patients

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Abstract

Objective: The present study is aimed to find the frequency of re-infection and severity of symptomatology among PCR confirmed COVID-19 patients in the current wave of epidemics in Lahore and Islamabad.

Study type, settings & duration: This descriptive study was undertaken at Health Research Institute (HRI) Central Research Centre, National Institute of Health (NIH) Islamabad and HRI-NIH TB Research Centre King Edward Medical University Lahore from March 2022 to July 2022.

Methodology: A sample size of 248 patients was calculated and a pre-designed questionnaire was used to collect data. Patients receiving COVID-19-positive PCR reports from different laboratories were traced. Patients were contacted telephonically. Data was entered and analyzed using SPSS v.26.0. Symptoms among infection and re-infection subgroups were compared by using the chi-square test.

Results: Participants consisted of 119 (48%) males and 129 (52%) females with mean age of subjects as 35.96±17.94 years. Most of the 186 (75.0%) respondents were fully vaccinated, 41 (16.5%) were partially vaccinated. A total of 93 (37.5%) patients were re-infected with COVID-19 and the duration of re-infection from primary infection ranged from 2-18 months. All the symptoms showed an insignificant difference except tiredness and shortness/difficulty in breathing remained significantly more severe (p -value <0.05) in cases of primary infection as compared to re-infected cases.

Conclusion: The frequency of re-infection remained high in this study while there is not much difference in symptomatology among cases of primary COVID-19 infection and re-infection.

Key words: COVID-19, SARS-CoV-2, re-infection, symptoms.

Introduction

A novel contagion, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 became a serious concern in early 2020 and the global dashboard shows 420 million cases and 5.86 million demises related to COVID-19 till

today.¹ In general, people who catch COVID-19 infection and recover from it must be immune from re-infection but it is not the case. Immunity with COVID-19 lasts for five months or so among 83% of people, according to the study published in January 2021.² Over the last two years, repeat infections with COVID-19 have traumatized the confidence of clinicians on the ability of the immune system to sustain against the virus.³ According to the European Centre for Disease Prevention and Control, COVID-19 re-infection is considered as; having a positive report of rapid antigen or PCR test in the sample taken after ≥2 months after prior positive PCR, rapid antigen or anti-spike IgG antibodies.⁴

Important symptoms of COVID-19 include cough, fever, and shortness of breath while in more severe cases pneumonia may occur though the disease may be fatal in rare cases.⁵ It is unclear that re-infection may be milder or severe event. Chances

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Authors Contribution

SR conceptualized the project. MKM, AA & AH did the data collection. MKM & AA also did the literature search. SR & AH performed the statistical analysis. Drafting, revision & writing of manuscript were done by SR, MKM & SS.

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of more severe occurrence may present depending upon inoculum and virulence of the strain.^{6,7} Evaluation of COVID-19 patients based on symptomatology could not be established, laboratory investigation on the other hand requires huge infrastructure keeping a pandemic geography of disease. This exhausted the major resources of many developed countries leaving the developing countries aside. A scarce work on symptomatology was reported in Pakistan.⁸

The first case of re-infection with COVID-19 was presented in Hong Kong and reported in August 2020 when a 33-year-old man existed asymptotically this time and was identified to be infected with a different strain from primary infection.⁹ After this, various other countries like Italy¹⁰ and United States⁷ also unveiled the emerging re-infected cases. Many people have potential occupational exposure and are involved in a variety of jobs like labor class, market employees and healthcare workers are at higher risk of acquiring COVID-19 infection.¹¹ Various reasons for re-infection have been postulated among different classes of people including a decline in the natural immune system, occupational exposure, compromised seroconversion in prior infection, a mild episode in prior infection, carelessness in using personal protective equipment, new COVID-variants escaping the immune response and co-morbidities etc.¹²

Although natural immunity is considered as effective as vaccination the matter requires to be observed from various dimensions. Acquiring infection even after primary infection and vaccination implies great concerns for healthcare. The frequency of re-infection is not well studied further the severity of infection and symptomatology need to be explored for a better understanding of disease patterns on the other hand different physiological and environmental factors allow the virus to behave differently in various regions. Therefore, the present study is aimed to find the frequency of re-infection and severity of symptomatology among PCR confirmed COVID-19 patients in the current wave of epidemics in Lahore and Islamabad.

Methodology

This descriptive study was undertaken at the Health Research Institute (HRI) Central Research Centre, National Institute of Health (NIH) Islamabad, and HRI (NIH) TB Research Centre King Edward Medical University Lahore from March 2022 to July 2022. A minimum sample size of 222 patients was calculated by taking a confidence level of 90%, absolute precision of 5%, and expected

frequency of COVID-19 patients as 28.75%.¹³ A data of 248 patients was considered for final analysis as a non-probability purposive sampling technique was used which makes it convenient to collect data from a few more patients. Patients aged 18 years & above, both genders and having positive COVID-19 PCR in the current wave were included in this study.

A pre-designed questionnaire was used to collect demographic data and history of patients. The questionnaire was pre-tested in mock testing at Mayo Hospital Lahore. Patients or attendants receiving COVID-19-positive PCR reports from different laboratories were traced to approach the patients and considered infected. Patients were contacted telephonically. After obtaining verbal consent by explaining the purpose of the study, information was noted. Patients reported to have prior infection ≥ 2 months were labeled as re-infected. The previous report of PCR was checked for confirmation. Further questions regarding any death of blood relative due to COVID-19, habits to follow COVID-19 SOPs, job nature, and present complaints were asked. Vaccination status was also observed and patients who took at least two doses of vaccine were considered fully vaccinated, one dose as partially vaccinated, and no dose was labeled as non-vaccinated. Patients reporting wearing masks, keeping a person-to-person distance of 6 feet, and washing hands after every activity were recorded as aware of SOP's. Fever $< 100.4^{\circ}\text{F}$ was considered mild, fever $> 100.4^{\circ}\text{F}$ but did not persist was considered moderate and persistent fever of 100.4°F for continuous 3 or more days was recorded as severe.¹⁴ Similarly severity of other symptoms was also assessed on recall of having the intensity and duration of symptoms.

Data was entered and analyzed using SPSS v26.0. Qualitative variables like gender, vaccination status, histories, etc. were presented as frequency and percentages. Quantitative variables like age were presented as mean $\pm$ standard deviation. Symptoms among infection and re-infection sub groups were compared by using the chi-square test and a p -value of < 0.05 was considered as significant.

The ethical approval was obtained from the Institutional Review Board of King Edward Medical University, Lahore through reference no. 372/RC/KEMU.

Results

A total of 248 participants consisting of 119 (48%) males and 129 (52%) females were considered in the present study. The overall mean

age of subjects was 35.96 ± 17.94 years with a higher mean age of males (37.97 ± 18.26 years) as compared to (34.10 ± 17.51 years) females. A greater number of 183 (73.8%) patients belong to the territory of Islamabad while the rest of 65 (26.2%) belong to the Lahore territory. Most of the 186 (75.0%) respondents were fully vaccinated, 41 (16.5%) were partially vaccinated and 21 (8.5%) were not vaccinated. More females (10.1%) were prone to be non-vaccinated as compared to (6.7%) males. Respondents the highest numbers were students 39.9%, followed by housewives (16.1%) and health professionals (13.7%) respectively. Gender-wise distribution of the nature of job of respondents is presented in Table-1.

A total of 93 (37.5%) patients were re-infected to COVID-19 in this study where the male gender 55 (46.2%) remained to be more prone to re-infection as compared to the female gender 38 (29.5%). Other background information suggests 64.5% of respondents have had other family members infected with COVID-19, 70.2% follow the safety SOPs properly, 19.8% had COVID-related death in family or relatives and 14.1% had faced more than two episodes of COVID-19. Duration of re-infection from primary infection ranged to 2-18

months in this study. Further distribution concerning gender is presented in Table-2.

A total of twelve important symptoms of COVID-19 were assessed and the Pearson chi-square test was applied to observe the severity of symptoms among primary and re-infected cases. Most of the symptoms showed an insignificant difference (p -value > 0.05) however chest pain and shortness/ difficulty in breathing remained significantly more severe (p -value < 0.05) in cases of primary infection as compared to re-infected cases. A comparison of the severity of symptoms among primary and re-infected cases is presented in Table-3.

Discussion

From the primary emergence of SARS-CoV-2, numerous changes in its genetic material have been observed few of which confer its easy transmission, the intensity of disease, usefulness in diagnostics, and making COVID-19 vaccines and treatment. Various changes take place during virus replication to form variants and if a variant is responsible for a higher number of cases is marked as a "variant of interest". A variant of concern in addition to the above presents more severe

Table 1: Gender-wise distribution of job nature of respondents.

Nature of Job	Gender				Overall (n=248)	
	Male (n=119)		Female (n=129)		n	%
	n	%	n	%		
Desk Job	6	5.0	5	3.9	11	4.4
Field Job	10	8.4	4	3.1	14	5.6
Healthcare professional	23	19.3	11	8.5	34	13.7
Own Business	18	15.1	3	2.3	21	8.5
Labor Class	23	19.3	6	4.7	29	11.7
Student	39	32.8	60	46.5	99	39.9
Housewife	-	-	40	31.0	40	16.1

Table-2: Background information of participants.

Background Questions		Gender				Overall n=248	
		Male (n=119)		Female (n=129)		n	%
		n	%	n	%		
Did any other of your family member become PCR confirmed COVID-19 Patient?	Yes	80	67.2	80	62.0	160	64.5
	No	39	32.8	49	38.0	88	35.5
Do you practice SOPs?	Yes	81	68.1	93	72.1	174	70.2
	No	38	31.9	36	27.9	74	29.8
Did any of your blood relative die of Covid-19?	Yes	22	18.5	27	20.9	49	19.8
	No	97	81.5	102	79.1	199	80.2
Are you re-infected?	Yes	55	46.2	38	29.5	93	37.5
	No	64	53.8	91	70.5	155	62.5
Do you have more than 2 episodes of COVID-19?	Yes	14	13.9	13	14.4	27	14.1
	No	87	86.1	77	85.6	164	85.9

Table 3: Comparison of severity of symptoms among primary and re-infected cases.

Symptoms		Re-infection				Overall (n=248)		p-value
		Yes		No				
		n	%	n	%	n	%	
Fever	Mild	30	31.9	64	68.1	94	37.9	0.132
	Moderate	42	37.5	70	62.5	112	45.2	
	Severe	21	50.0	21	50.0	42	16.9	
Cough	Mild	26	30.6	59	69.4	85	34.3	0.226
	Moderate	52	40.0	78	60.0	130	52.4	
	Severe	15	45.5	18	54.5	33	13.3	
Tiredness	Mild	32	30.2	74	69.8	106	42.7	0.120
	Moderate	37	42.5	50	57.5	87	35.1	
	Severe	24	43.6	31	56.4	55	22.2	
Loss of taste/smell	Yes	44	38.9	69	61.1	113	45.6	0.383
	No	49	36.3	86	63.7	135	54.4	
	Mild	39	37.5	65	62.5	104	41.9	
Sore throat	Moderate	32	32.0	68	68.0	100	40.3	0.121
	Severe	22	50.0	22	50.0	44	17.7	
	Mild	34	38.6	54	61.4	88	35.5	
Headache	Moderate	36	35.3	66	64.7	102	41.1	0.829
	Severe	23	39.7	35	60.3	58	23.4	
	Mild	26	34.7	49	65.3	75	30.2	
Aches and pains	Moderate	40	39.6	61	60.4	101	40.7	0.799
	Severe	27	37.5	45	62.5	72	29.0	
	Yes	34	41.0	49	59.0	83	33.5	
Diarrhea	No	59	35.8	106	64.2	165	66.5	0.254
	Mild	39	38.6	62	61.4	101	40.7	
	Moderate	33	30.6	75	69.4	108	43.6	
Difficulty/Shortness in breathing	Severe	21	53.8	18	46.2	39	15.7	0.034
	Yes	21	43.8	27	56.2	48	19.4	
	No	72	36.0	128	64.0	200	80.6	
Loss of speech	Yes	22	42.3	30	57.7	52	21.0	0.203
	No	71	36.2	125	63.8	196	79.0	
	Mild	50	40.3	74	59.7	124	50.0	
Chest Pain	Moderate	27	29.0	66	71.0	93	37.5	0.052
	Severe	16	51.6	15	48.4	31	12.5	

disease, added contagion, and resistance to public health processes of diagnostics, vaccines, and therapeutics. After the first wave of COVID-19 with the original Wuhan strain, Pakistan was affected by the second wave which was predominant with the Alpha variant reported 50% more transmissible but was equally susceptible to vaccination and monoclonal antibodies being used for the original strain.¹⁵

Present data was collected during the 5th wave of COVID-19 in Pakistan and 37.5% of patients were re-infected where the male gender got 46.2% of re-infected cases remained more prone as compared to the female gender that got 29.5% cases. A Serbian study presented the results differently and calculated the incidence of re-infection with COVID-19 as 5.99/1000 person-months. Similarly, risk of re-infection was also measured to be 0.76-18.86% after 6-18 months of primary infection.¹⁶ Centers for Disease Control and Prevention (CDC) is also working to enhance the understanding of COVID-19 re-infection to plan a public health action for which a range of data sources are being assessed on how often re-

infection occurs and who is at greater risk. Further, the CDC is also publishing various datasets obtained from different sources like cohort studies for a better understanding of the physiology of re-infection.¹⁷

A recent study from New York presented only 2.5% of reinfection even in the more prone healthcare group which is also not in agreement with the present finding. This may be due to the 9-12 month duration of observation consisting of low transmission summer months further the period preceding full vaccination coverage with mRNA vaccines.¹⁸ On the other hand scenario in the present study was entirely different and re-infection was assessed from the starting period of the first infection in February 2020 in Pakistan to June 2022. This high percentage of re-infection justifies the short life span of COVID-19 antibodies as a study revealed a half-life of COVID-19 neutralizing antibodies as only 20.4 days.¹⁹

Presently 64.5% of respondents perceived to have other family members infected with COVID-19, and 70.2% follow the safety SOPs properly. It is almost double as compared to the study undertaken

in Ethiopia which revealed the perception of general people regarding adherence to SOPs, 89.8% believed it was responsibility of the individual but only 32.2% showed favorable behavior towards preventive measures against COVID-19.²⁰

A total of twelve important symptoms of COVID-19 were assessed, most of which showed an insignificant difference (p -value >0.05) though all look to be milder as compared to patients presented with primary infection, tiredness and shortness/difficulty in breathing remained significantly more severe (p -value <0.05) in cases of primary infection as compared to re-infected cases. Similarly a lower difference in cough 51.6% in primary infection is higher as compared to 43.9% re-infected cases looks insignificant while high-grade fever in 50% of primary infected cases looks significantly different from 30% in re-infected cases. Thus the study concluded possible re-infection with COVID-19 lacks definite information about causes or risk factors and advised to take special care of re-infected individuals by adherence to SOPs.²¹

In general, it is expected that a different strain of COVID-19 causes re-infection as most likely in the present study but studies undertaken gene sequencing reported few cases of re-infected with a similar strain in a short span after recovery from primary infection. Similarly, scarce literature showed the ability of re-infected patients to remain infectious to others and needs further evidence.²¹ Animal models after second inoculations with the virus presented no viral shedding from oropharyngeal, nasal, or rectal fissures, and the virus was not transferred to other faunas.^{22,23} The concept of re-infection is not very well evaluated and thus inconsistent. The difference in the definition of COVID re-infection is also present as the European Centre for Disease Prevention and Control defines re-infection as "Laboratory confirmed different episodes of infections with different strains"²⁴ while CDC believes the detection of viral RNA with time span >90 days from primary report of detection of viral RNA with or without symptoms.¹⁷

Presently, this study assumed positive real time (RT) PCR to define infection and re-infection while genotyping or gene sequencing could not be carried out which is the deficiency of this study. On the other hand, Pakistan remained under attack through five waves of COVID infections which could be used to assume the most prevalent strain in the given time of infection and re-infection. Another limitation could be recall bias in reporting symptoms as well self-reported symptom severity might be overestimated. As samples were not collected from patients genotyping or gene sequencing could not

be carried out which is also a deficiency of this study. The type of infection was not asked by the patient which is a limitation of the present study.

Conclusively, the frequency of re-infection remained high in this study while there is not much difference in symptomatology of primary COVID-19 infection and re-infection. Various factors may affect the findings like time of vaccination whether it was done before primary infection or not, the effect of co-morbidities on re-infection, and physiological factors of individuals adopting re-infection which are under consideration for the prospect of this study.

Conflict of interest: None declared.

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