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Original Article

Long-term Consequences, Chances of Re-infection, and Outcomes among Cases Recovered with Severe COVID-19 at a Tertiary Care Centre in Central India

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ABSTRACT

COVID-19 has a wide disease spectrum. Different presentations may be seen in different people, with uncertain long-term fate. The amount and longevity of immunity provided among the infected also vary from person to person which might in turn affect the chances of re-infection. Current study tries to uncover the incidence, disease severity and outcomes amongst those who have been previously hospitalized for COVID-19. A prospective cohort study where all patients admitted to intensive care facility at the tertiary care center were followed up for any occurrences of re-infection for more than one year. All cases were followed up telephonically and at scheduled visits to the hospital by trained personnel. A total of 410 cases with a mean age of 59.8 years, including 310 (75.6%) males and 100 (24.4%) females. Among these 410 patients 287 remained alive till the end of study period. Re-infection rates among recovered ICU admitted seriously ill patients were 1.4% whereas the rate of ICU re-admission due to COVID-19 re-infection was only 0.7%. Re-infection among female was 1.1% whereas in male was 1.5%. ICU readmission rate among female was 1.1% while in male was 0.5% only. The chances of re-infection in female were seen less than that in males, but the severity of re-infection in females was found to be higher. COVID-19 re-infection in previously severely infected COVID-19 patient is not so common. The chances of a severe disease among such cases are even rarer.

Keywords: *COVID-19; ICU patients; re-infection; SARS-CoV-2*

ABSTRAK

COVID-19 memiliki spektrum penyakit yang luas. Presentasi yang berbeda dapat dilihat pada orang yang berbeda, dengan keadaan jangka panjang yang tidak pasti. Jumlah dan masa kekebalan yang diberikan di antara orang yang terinfeksi juga bervariasi dari orang ke orang yang pada gilirannya dapat mempengaruhi kemungkinan infeksi ulang. Studi saat ini mencoba mengungkap kejadian, tingkat keparahan penyakit, dan hasil di antara mereka yang sebelumnya dirawat di rumah sakit karena COVID-19. Sebuah studi kohort prospektif di mana semua pasien yang dirawat di fasilitas perawatan intensif di pusat perawatan tersier ditindaklanjuti untuk setiap kejadian infeksi ulang selama lebih dari satu tahun. Semua kasus ditindaklanjuti melalui telepon dan pada kunjungan terjadwal ke rumah sakit oleh personel terlatih. Sebanyak 410 kasus dengan usia rata-rata 59,8 tahun, termasuk 310 (75,6%) laki-laki dan 100 (24,4%) perempuan. Di antara 410 pasien 287 tetap hidup sampai akhir masa studi. Tingkat infeksi ulang di antara pasien yang dirawat di ICU yang pulih dan sakit parah adalah 1,4% sedangkan tingkat masuk kembali ke ICU karena infeksi ulang COVID-19 hanya 0,7%. Infeksi ulang pada wanita adalah 1,1% sedangkan pada pria adalah 1,5%. Tingkat penerimaan kembali ICU pada wanita adalah 1,1% sedangkan pada pria hanya 0,5%. Kemungkinan infeksi

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ulang pada wanita terlihat lebih kecil dibandingkan pria, tetapi tingkat keparahan infeksi ulang pada wanita ditemukan lebih tinggi. Infeksi ulang COVID-19 pada pasien COVID-19 yang sebelumnya terinfeksi parah tidak begitu umum. Kemungkinan penyakit parah di antara kasus-kasus seperti itu bahkan lebih jarang.

Kata kunci: *COVID-19; infeksi ulang; pasien ICU; SARS-CoV-2*

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INTRODUCTION

COVID-19 often presents with an extensive clinical spectrum varying from asymptomatic infection to severe life-threatening viral pneumonia often requiring admission to intensive care, and sometimes even leading to death.[1] Persisting symptoms, and unforeseen organ dysfunction has been observed subsequently to SARS-CoV-2 infection in an escalating quantum of those who have recovered, as was observed in the past during SARS outbreak.[2] However, since COVID-19 is not a classical disease, we need to keep vigil about gaining new insights in it and an uncertainty prevails concerning its long-term health sequelae amongst those who have recovered from it. This is of immediate relevance and warrants attention since patients presenting with grave disease including those requiring mechanical ventilation during their initial medical admission, for whom long-term complications, persisting symptoms and sometimes who might lack a complete recovery on discharge.[3] This is an initial general concept that the patients who have recovered from COVID-19 natural infection generate a robust immune response which help in clearing the virus.

However, currently it is not very clear whether such primary exposure or disease confers a shielding immunity to successive infections with this virus. Recent studies suggest that antibodies generated after a recent COVID-19 infection might help in providing some protection against re-infection in most patients but despite this, re-infection or break-through infection is possible.[4] From previous research, it is clear that despite the presence of antibodies re-infection is common with other human corona viruses.[5] According to a recent report the working epidemiological case definition for re-infection after initial infection of COVID-19 was suggested as two positive tests at an interval of at least 102 days with one interim negative PCR test report.[6] Few case series show that recurring COVID-19 infections might be worse in approximately 20% of patients and even severe complications may occur among the higher those with advanced age and immune-compromised patients.[7] Re-infection with COVID-19 is not limited to any particular stain, there are multiple variants with a differing genetic sequence, thus causing re-infection.[8]

Subsequently, to the emergence of the newer mutants and variants of concern of COVID-19 from the UK, India and South Africa; It becomes indispensable to see whether these newer mutants cause any infection to patients who were affected with this disease during the 'first wave' prior to the appearance of these variants.[7] It is thought that as there is priming of adaptive immune response by the previous infection, re-infection is usually associated with milder symptoms, protection from severe disease but the robust response has also been reported.[9,10]

There might be numerous SARS-CoV-2 re-infection cases than have been currently reported.[11,12] It is very difficult to estimate the true prevalence of these re-infections as the genome sequencing data are not available in most COVID-19 cases and many of the asymptomatic and mildly symptomatic patients were not seeking medical advice. For

identification of true prevalence of COVID-19 re-infection population-based studies are more useful.

It might often be challenging to differentiate between COVID-19 relapse, re-infection and RT-PCR re-positivity in a few cases. Recently, Yahav et al had suggested that re-infection is considered in those case who become negative after infection and again became PCR positive after more than 90 days.[13] Two of the meta-analyses performed during early phase of the pandemic reported that re-infection or re-positivity were rare but such case reports and studies were performed without considering genome sequencing data.[14]

Few studies have shown that subsequent infection is possible in those persons already having a previous exposure to COVID-19. Therefore, practicing social distancing and wearing mask at all public places, irrespective of history of prior infection or vaccination is very essential to prevent the spread of further waves of the current pandemic. Without which, it's likely that the SARS-CoV-2 virus may continue to transmit and circulate in various populations despite the achievement of herd immunity by vaccination or natural infection.[15]

This study is concerned with the detection of re-infection if any, the associated disease severity and the outcome of such re-infection during the subsequent waves of COVID-19 infections among ICU hospitalized patients during the earliest wave of this disease.

MATERIALS AND METHODS

Research Design

This study consisted of cohorts enrolled prospectively at a Tertiary Care Center, in Central India, Madhya Pradesh. Study was started after due approval from institutional human ethical committee reference number, IECBMC/2021/32.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. We included and followed up all critically ill ICU patients with laboratory-confirmed SARS-CoV-2 PCR positivity via recommended throat swabs or nasopharyngeal swabs,
2. Those who were discharged from the institute between August 2020 to November 2020 during the first wave of COVID-19.

Exclusion Criteria:

1. Those who refused to participate,
2. Those who died before the follow-up visit,
3. Those who could not be contacted.

All discharged patients met uniform discharge criteria according to the Government of India IMCR Guidelines for COVID-19.[16]

Patient Follow-ups

Phone calls were used to schedule follow-up visits and done by trained medical staff. Post-discharge such patients were contacted in the order of their symptom onset date as per initial admission record. If the follow-up appointment was missed, 2 more chances on further dates were provided. Follow-up consultations were done with face-to-face interviews and examinations performed by trained medical personnel.

Data Analysis

Data were abstracted and fed into computer on excel sheets, percentages and proportions were calculated using the same software.

RESULTS AND DISCUSSION

During the study 410 cases in total between the ages of 1-month old to 95 years, and population having mean age 59.8 years. More than half i.e. 209 (51%) patients were between 51 to 70 years of age. The sex distribution of study cases was observed to have 310 (75.6%) males versus 100 (24.4%) females. Among 410 patients, 287 remained alive after first wave was over (shown in Table 1). Between first wave and second wave during the study, 5 persons died with the reasons behind their death remaining unclear and not directly related to COVID-19.

A single dose of vaccine was received by 196 (partially vaccinated) while 78 were vaccinated by both the doses of vaccination before second wave of COVID-19. Among these 287 individual only 4 were infected in the second wave of and only 2 were admitted in ICU. The two patients those who were re-admitted in ICU were partially vaccinated. Former being a 48 years old female and later one a 50-year-old male. The other two who were admitted in general ward were 32 years old male, he was fully vaccinated and other one was youngest patient 10 months old non-vaccinated male child, all four were discharged successfully. The mean age of those re-infected was 33±19 years and this study population comprising of 25% females and 75% males as shown in Figure 1. Only female patient was having hypertension as a co-morbidity.

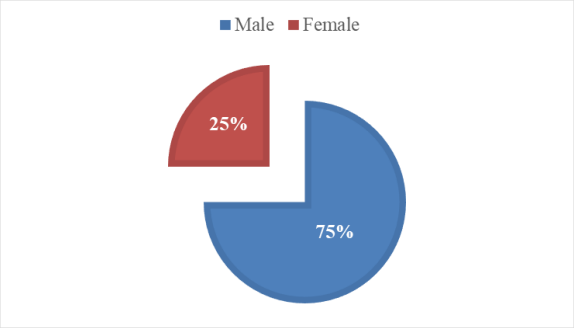

Figure 1. Sex Wise Distribution of Re-infected Patient

Re-infection rate among recovered ICU admitted seriously ill patients was 1.4% whereas the rate of ICU re-admission due to COVID re-infection was only 0.7%. Re-infection among female was 1.1% whereas in male was 1.5%. ICU readmission rate among female was 1.1% while in male was 0.5% only. The chances of re-infection in female were seen less than that in males, but the severity of re-infection in females is more was found to be higher.

Table 1. Age-Wise Distribution of Study Cohorts

No	Age group (year)	Patients			Deaths		
		Male	Female	Total	Male	Female	Total
1	≤ 30	18	7	25	2	1	3
2	31–40	34	8	42	6	2	8
3	41–50	58	16	74	8	3	11
4	51–60	70	33	103	23	6	29
5	61–70	86	20	106	32	9	41
6	> 70	44	16	60	22	9	31

In a meta-analysis study by Ghorbani et al, the overall estimation of reinfection, was 3% (95% CI: 0.8–5), recurrence was 133 (95% CI: 105–160), with readmissions being 75 (95% CI: 54–96) per 1000 patients[17], but in our study rate of re-infection leading to hospitalization was only 0.7%. This is close to the study done by Arafkas et al. where the prevalence of re-infection was reported as zero.[18] Other study done by of Ren et al. reported a re-positivity of 12%, while Piri et al. concluded in their systematic review a recurrence rate between 2.3% to 21.4%.[19,20] In addition their review indicates that the recurrence was 47.7% in male and 53.3% in female which is in contrast to our study in

which recurrence was most common in male than female. In our study males were three times more affected than females.[20]

In some of the studies, re-infected, recurrent, and readmitted cases were either asymptomatic or had mild to moderate symptoms[17], but in our study all patients were symptomatic, some of them even had rare symptoms and complications like hepatitis which were rarely seen earlier.[21] This may be attributed to the reason that asymptomatic or patients with mild symptoms were not reported to near medical facilities and therefore they did not get tested for COVID 19. Few patients even had severe symptoms in the second phase of infections of the disease, implying that the severity of its subsequent infection may vary according to the demographics, health status of the patients, and immune system status.[22,23]

In the study incidence density per 100,000 person days was 1.0 (95%, CI 0.5–1.5) among persons having previous history of infection and 15.1 (95% CI, 14.5–15.7) for persons lacking such infection in the past.[24] Our findings are in agreement to the to those of Harvey and colleagues, who found that persons with a positive diagnostic RT-PCR test for SARS-CoV-2 and for antibodies to it were much less likely to develop SARS-CoV-2 infection within initial 3 months than those with absence of antibodies.[25]

CONCLUSIONS

COVID-19 re-infection in previously severely infected COVID-19 patient is not so common. The chance of having a severe disease in these patients upon re-infection is even rarer. However, large scale population based elaborate case control study may be required in this field in order to provide further insights.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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