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Original article

Association of disease severity and death outcome with vaccination status of admitted COVID-19 patients in delta period of SARS-COV-2 in mixed variety of vaccine background

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ABSTRACT

To understand the effectual role of COVID-19 vaccination, we must analyze its effectiveness in dampening the disease severity and death outcome in patients who acquire infection and require hospitalization. The goal of this study was to see if there was an association between disease progression in admitted COVID-19 patients and their prior vaccination exposure. A prospective cohort study based on 1640 admitted COVID-19 patients were carried between June 2021 and October 2021. Depending on vaccination exposure they were divided into vaccinated (exposed) and unvaccinated (unexposed) groups, excluding partially vaccinated patients. Disease severity was assessed at admission on severity index scale. Disease progression to mortality or need of mechanical ventilation and survival were taken as outcome. Absolute difference with 95%CI and Risk Ratio were calculated using cross tabulation, Chi square test and multivariable logistic regression analysis. Among 1514 total analyzed cohort (median age, 53 years [IQR, 17,106]; 43.7% from 46 to 65 years of age group, 56.2% males,33.4% with no comorbid factor for disease progression) 369(24.4%) were vaccinated breakthrough cases and 1145(75.6%) were unvaccinated controls. 556(36.7%) progressed to death or mechanical ventilation, 958(63.3%) patients survived and were discharged home. Disease progression to death or mechanical ventilation was significantly associated with decreased likelihood of vaccination (24.9% among vaccinated breakthrough vs 40.5% unvaccinated controls, [Absolute difference −15.6% 95%CI (−10.2% to −20.6%); RR 0.615 95%CI (0.509, 0.744); p <.001]). This association was stronger for old age population and for increase time span between second dose of vaccine and onset of symptoms. There was no statistically significant difference among different types of vaccination and occurrence of outcome when compared to unvaccinated controls (RR 0.607(0.482, 0.763); 0.673(0.339, 1.33) and 0.623(0.441, 0.881) for Inactivated virus vaccine, mRNA and Adenovirus vector-based vaccine respectively. The patients who were fully vaccinated against SARS-COV-2 die or shift to mechanical ventilation less frequently than unvaccinated COVID-19 admitted patients.

1. Introduction

After having an irremediable damage with deadly SARS-COV-2, world is looking forward the vaccine immunity. It had barely overcome the previous strains with arrival of vaccine that the variants of concern (VOC) got entry from different regions of the world and the most lethal among them delta variant B.1.167 spread from India since late 2020 (Planas et al., 2021; Flemming, 2021; McCallum et al., 2021). Now the voices of B.1.1.529, a variant of

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concern, named Omicron from South Africa and some countries from Europe are raised to frighten the people around the globe. Delta variant also known as B.1.167.2 is considered to spread faster than any other variant (Planas et al., 2021). Delta variant of SARS COV-2 is considered to be responsible for the 4th wave of COVID 19 in Pakistan. As of July 2021, it was responsible for nearly all new SARS-CoV-2 infections in Pakistan and other regions of the world like United states of America (Hasan et al., 2021; Dyer, 2021). Human body responds to SARS COV-2 involving innate immune response and antigen specific response related to B and T cells type (Naaber et al., 2021). In convalescent and vaccinated patients, the receptor binding protein (RBD) is the major target of serum neutralizing activity, and it has several antigenic sites identified by neutralizing Abs. Due to a combination of immune selection pressure in infected hosts and natural abrupt and slow antigenic drift, various mutations in N- terminal domain (NTD) and receptor binding protein (RBD) of spike proteins, SARS-CoV-2 variants are evolving, with possibility of immune evasion and vaccination failure, raising questions about the long-term durability of COVID-19 immunizations both after natural infection and vaccination. (McCallum et al., 2021; Planas et al., 2021; Niesen et al., 2021; Mlcochova et al., 2021) In phase 3 clinical trial, various types of vaccine against SARS-CoV-2 showed efficacy ranging from 51 percent to 94 percent against the original strain D614G (Evans and Jewell, 2021; Haas et al., 2021; Creech et al., 2021; Puranik et al.,2021). Following the emergence of the delta variant, vaccine efficacy against symptomatic infection has been dropped with all types of vaccines. (Planas et al., 2021; Sanderson, 2021).

As the vaccine efficacy against the infection is not 100%, there are chances of breakthrough cases as the ratio between vaccinated and unvaccinated will keep on growing among general population. Up till now the vaccine efficacy has been discussed in term of prevention of symptomatic infection and hospitalization for COVID-19. Protection against SARS-CoV-2 infection, as well as progression of disease severity and respiratory failure leading to death following a breakthrough infection, must be taken into account when understanding the protective features of COVID-19 vaccinations because prior vaccination exposure is expected to mitigate the disease severity by activating humoral and cellular immunity (Naaber et al., 2021). So, we have designed a study to see the effect of previous vaccination exposure on disease progression and outcome in patients of COVID-19 in the background of mixed types of vaccination available in the country.

2. Material and methods

A prospective cohort study was conducted among admitted patients of COVID 19 at Sir Sadiq Abbasi Hospital Bahawalpur, which is a COVID designated hospital since the start of pandemic. Study was carried out from June 2021 to October 2021, during 4th wave of COVID 19 in Pakistan which is thought to be blown by Delta variant of SARS-COV-2. The study screened all participants aged 18 and above for prospective eligibility on a daily basis by reviewing hospital admission logs and computerized medical information of isolation wards, High Dependency Units(HDU) and Intensive Care Units (ICU). The study comprised participants who required admission with a clinical and radiological diagnosis of acute COVID-19 with or without positive molecular report. Their vaccination status its type and duration since second dose of vaccine were noted at the time of admission by interviewing the patient and counter checking the status through website of COVID-19 vaccination dash board provided by National Command and Control Authority (NCOC) by putting National Identity card number of each patient through central record of hospital. As there were mixed variety of vaccine available in Pakistan from March 2021. So, Sino Pharm BBIBP vaccine and Sinovac, CoronaVac vaccine were both categorized as inactivated virus vaccine type, mRNA 1273 Moderna, Pfizer BioNTech as mRNA vaccine, ChAdOx1 [recombinant] AstraZeneca and Gam-COVID-Vac Sputnik V as Adenovirus vector based vaccine. Participants were assessed for disease severity at admission on severity scale Index provided by WHO. Depending on vaccination status participants were divided into two groups; vaccinated (Exposed) Unvaccinated (Unexposed) groups. Patients from both groups were assessed for hypoxemia and requirement of oxygen at admission to hospital. Patients were monitored for disease progression and development of respiratory failure requiring non-invasive or ventilator support leading to Intensive Care Unit Admission. Patients from both vaccinated and unvaccinated groups were observed for composite end outcome of death or shifting to invasive ventilator support and survival leading to discharge.

To find out association between prior vaccination status with reference to its type and severity of disease and progression to death among hospitalized patients of COVID-19, we compared group of fully vaccinated with unvaccinated excluding partially vaccinated patients. Absolute differences in occurrence of events and outcomes among both groups were calculated. Cross tabulation, Chi Square model and logistic regression model were used with co variables of age, sex, severity of disease, presence or absence of comorbid factors, age groups (Tenforde et al., 2021; Yuan et al., 2021; Mir et al., 2021; Grijalva et al., 20212021; Takemoto et al., 2020; Anon., 2021; Collier et al., 2021; Goldshtein et al., 2021), $\geq$66 yrs.), vaccination type hypoxemia at admission and hospital stay in days. Relative Risk RR was calculated, <1.0 showed that that there are less chances of disease severity and death outcome in vaccinated COVID-19 hospitalized patients. Vaccine efficacy against disease severity and worst outcome was calculated as (1-RR) 100. SPSS version 20 was used for data analysis, statistical significance was determined by 95%CIs not including the null or a two-sided P <.05.

3. Results

From June 1st,2021 to October 31st,2021, total 1640 patients were admitted out of those 126 patients were partially vaccinated or they have received at least one dose of vaccine or other than categorized type of vaccine, so, were excluded from the analytic population. Total analyzed cohort was 1514 patients with median age of 53 years Inter Quartile Range IQR (17,106), 851(56.2%) were male patients, maximum patients were from age group 46–65 years and $\geq$66 years, 662(43.7%) and 340(22.5%) respectively. There were 1009(66.6%) patients who had some comorbid condition for getting severe disease with COVID-19.

Among total analyzed population 369(24.37%) were fully vaccinated (Inactivated virus vaccine 67.2%, Adenovirus vector based vaccine 26.8 % and mRNA 6%) and 1145(75.63%) were unvaccinated.

722(47.7%) patients developed critical illness or required Intensive care within first 24hrs of admission and 556(36.7%) patients were died or shifted to mechanical ventilation. Two hundred and seventy (17.8%) patients required no oxygen within 24 hrs. of admission or had mild to moderate disease and total 958(63.3%) were discharged after improving on room air or minimum oxygen support. In 1020(67.4%) outcome was attained in 0–5 days, median hospital stay 4 days IQR (1, 77). In death and discharge group it was 5.0, IQR (1, 77) and 3.0, IQR (1, 52) respectively. Majority patients from both vaccinated and unvaccinated groups were from age group 17–45 and 46–65 with median age 50 and 53 from vaccinated and unvaccinated groups respectively. Median age in death group was 60 IQR (18,106) and 49 IQR (17,101) for discharge

group. Risk factors to develop severe COVID were less commonly present in vaccinated cases as compared to unvaccinated controls (62.1% Vs. 68.1%). Old age > 75 years and pregnant patients were more unvaccinated 78.2% and 88.2% respectively. Vaccine breakthrough cases developed hypoxemia at admission and needed intensive care less likely as compared to unvaccinated controls [67.2% Vs. 87% %; absolute difference, −19.8%; 95%CI (−14.8% to −25.1%), RR 0.773, 95%CI (0.717, 0.833) P <.001] and [33.1% Vs. 52.4% %; absolute difference, −19.3%; 95%CI (−25.2% to − 13.5%): RR 0.631, 95%CI (0.54, 0.73); P <.001] respectively. Characteristics of vaccinated (exposed) and unvaccinated (unexposed) groups are discussed in Table 1.

Table 1
Characteristics of admitted patients with COVID-19 according to their vaccination status.

Characteristics	Vaccinated (Breakthrough cases) (n = 369) %	Unvaccinated (Controls) (n = 1145) %
Age, median(IQR),Y	50(18,94)	53(17,106)
Age, yrs		
17–45	140(38)	372(32.5)
46–65	144(39)	518(45.2)
≥66	85(23)	255(22.3)
Gender		
Male	213(57.7)	638(55.7)
Female	156(42.3)	507(44.3)
Risk factors		
Cardiovascular disease (CVD)	99(26.8)	302(26.4)
Diabetes Mellitus (DM)	72(19.5)	219(19.1)
Old Age (>75 yrs.)	29(7.9)	104(9.1)
Pulmonary disease	8(2.1)	20(1.7)
Immunosuppressive drugs	3(0.8)	8(0.7)
Obesity	11(3)	61(5.3)
Pregnancy	4(1.1)	30(2.6)
Chronic Kidney Disease (CKD)	3(0.8)	22(1.9)
Chronic Liver Disease (CLD)	0(0)	3(0.3)
No Risk Factor	(140)37.9	365(31.9)
Inactivated virus based vaccine	248(76.2)	0
mRNA vaccine	22(6)	0
Adenovirus vector based vaccine	99(26.8)	0
Disease Severity		
Mild disease	11/369(2.9)	4/1145(0.35)
Moderate disease	108/369(29.3)	142/1145(12.4)
Severe disease	128/369(34.7)	399/1145(34.8)
Critical illness	122/369(33.1)	600/1145(52.4)
Hypoxemia at Admission	248/369(67.2)	996/1145(87)
Intensive Care Required	122/369(33.1)	600/1145(52.4)

Maximum period between second dose of vaccination and breakthrough cases was 4 months,majority patients 314(85.1%) had time lapse of 2 weeks to 3 months and only 55(14.9%) had >3 months' time span between second dose of vaccine and break through infection with COVID-19. Those who had more than three months' time lapse, 43(78.2%) were died or shifted to mechanical ventilation and out of them 30(70%) were from age group ≥66 years and other had DM or cardiovascular diseases as comorbid conditions along with age group as a risk factor with p <.001. vaccination exposure was found uncommonly among high risk groups like old age, DM, CVD, CKD and pregnancy most importantly as shown in the Table 1. Among pregnant patients only 4 (11.8%) were vaccinated before getting their pregnancy and all (100%) were discharged after improving while 30(88.2%) were unvaccinated and among them 21(70%) were died or shifted to invasive ventilation. Pearson correlation shows a negative correlation between death outcome and vaccination status in pregnancy, R^2 −0.464; p <.01.

For survival and discharge outcome, 277(75.1%) from vaccinated group and 681(59.5%) from unvaccinated group achieved the outcome [Absolute difference 15.6%, 95%CI (10.1% to 20.6%); RR 1.26, 95%CI (1.17, 1.36); P <.001] meaning that vaccinated patients admitted with COVID-19 are 1.26 times more likely to get better outcome. Patients from age group 46–65 and older are more likely to get benefit of vaccination exposure in term of survival, 73.6% Vs. 54.4% [Absolute difference 19.2; 95%CI (9.6% to 27.9%); RR 19.2, 95%CI (9.6 to 27.9); p <.001]. As shown in Table 2, vaccinated patients who were hypoxemic at admission were 1.17 times more likely to improve than unvaccinated patients p <.01. vaccinated patients as compared to unvaccinated group have more chances of short hospital stay of 0–5 days for survival outcome, RR 1.22,95%CI (1.12,1.32); p <.001.

For outcome of death or shifted to mechanical ventilation, 92 (24.9%) from vaccinated and 464(40.5%) from unvaccinated group attained the outcome [Absolute difference −15.6% 95%CI (−10.2% to −20.6%); RR 0.615 95%CI (0.509, 0.744); p <.001] so, vaccinated patients are 0.615 times less likely, and 38% decreased chances to die after they get admission for COVID-19. Among total deaths in breakthrough vaccinated cases, 43(46.7%) got their second dose of vaccine minimum of >3 months before getting infection. Fig. 1 explains the association of death outcome in relation to vaccination exposure and other contributing factors. Interestingly there was no difference between type of vaccination given to patient in term of death outcome i.e., RR 0.607 95%CI (0.482, 0.763) for Inactivated virus vaccine, RR 0.673 95%CI (0.339, 1.33) and 0.623 95%CI (0.441, 0.881) for mRNA and Adenoviral vector vaccine respectively. So, there were 39.3% decreased probability of getting poor outcome from inactivated virus vaccine, 32.7% and 37.7% from mRNA and Adenoviral vector based vaccine respectively(Fig. 2).

Table 2
Association between Discharge Outcome and Vaccination Exposure.

Subgroups	Vaccinated n (%)	Unvaccinated n (%)	Absolute difference 95%CI	Relative Risk 95%CI	P value
Overall	277/369(75.1)	681(/1145(59.5)	15.6(10.1 to 20.6)	1.26(1.17,1.36)	<0.001
Age groups yrs.					
18–45	124/140(88.6)	294/372(79)	9.6(2.2 to 15.7)	1.12(1.03,1.21)	<0.01
46–65	106/144(73.6)	282/518(54.4)	19.2(9.6 to 27.9)	1.36(1.19,1.53)	<0.001
≥66	47/85(55.3)	105/255(41.1)	14.2(2.0 to 25.9)	1.34(1.05,1.71)	<0.05
Hypoxemia at admission	156/248(62.9)	553/996(55.5)	7.4(0.52 to 13.9)	1.17(1.05,1.31)	<0.01
Hospital Stay					
0–5 days	215/272(79)	484/748(64.7)	14.3(8.1 to 19.9)	1.22(1.12,1.32)	<0.001
6–10 days	41/68(60.3)	132/234(56.4)	3.9(−9.5 to 16.4)	1.07(0.86,1.34)	>0.05
11–15 days	14/20(70)	49/103(47.5)	22.5(−1.4 to 40.6)	1.47(1.03,2.09)	0.05

Subgroups	Vaccinated n(%)	Unvaccinated n(%)	Absolute Difference 95% CI	RR 95% CI
Overall	92/369(24.9)	464/1145(40.5)	-15.6(-10.2 to -20.6%)	.615(.509,.744)
Age groups				
17-45 yrs.	16/140(11.4)	78/372(21)	-9.6(-2.2 to -15.8%)	.545(.330,.900)
46-65 yrs.	38/144(26.4)	236/518(45.5)	-19.1(-10.4 to -26.9%)	.579(.434, .773)
>66 yrs	38/85(44.7)	150/255(58.8)	-14.1(-1.89 to-25.8%)	.760(.587, .983)
Gender				
Male	49/213(23)	252/638(39.5)	-16.5(-9.4 to -22.9%)	.582(.447, .758)
Female	43/156(27.6)	212/507(41.8)	-14.2(-5.6 to -21.9%)	.659(.501, .867)
Comorbid conditions				
Old Age	13/29(44.8)	65/104(62.5)	-17.7(2.36 to -36.3%)	.717(.466. 1.11)
DM	19/72(26.4)	98/219(44.7)	-18.3(-5.4 to -29.3%)	.590(.390. .991)
CVD	35/98(35.7)	157/302(52)	-16.3(-4.9 to -26.7%)	.687(.516, .915)
Pulmonary Disease	1/8(12.5)	7/20(35)	-22.5(-15.9 to -46.5%)	.357(.052, 2.45)
Obesity	4/11(36.4)	25/61(41)	-4.6(-25.9 to -29.2%)	.887(.384, 2.05)
No risk factor	19/140(13.6)	72/365(19.7)	-6.1(1.54 to -12.53%)	.688(.432, 1.09)
Need of ICU care	92/122(75.4)	461/600(76.8)	-1.4(6.2 to -10.3%)	.925(.587. 1.45)
Admission hypoxemia	92/248(37.1)	463/996(46.5)	-9.4(-2.5 to -15.9%)	.679(.510, .904)
Vaccination type				
Inactivated Virus	61/248(24.6)	464/1145	-15.9(-9.5 to -21.6%)	.607(.482, .763)
mRNA vaccine	6/22(27.3)	464/1145	-13.2(7.86 to -27.6%)	.673(.339, 1.33)
Adenoviral Vector	25/99(25.3)	464/1145(40.5)	-15.2(-5.41 to -23.25%)	.623(.441, .881)

Fig. 1. Diabetes Mellitus (DM), Cardio Vascular Disease (CVD) Intensive Care Unit (ICU). Forest plot containing effect sizes shows significant risk reduction of death among vaccinated group in all age groups and more significantly in middle and older groups, irrespective of gender. Breakthrough vaccinated cases who required ICU care had no significant risk reduction with vaccination exposure. Risk reduction was observed among all vaccine types.

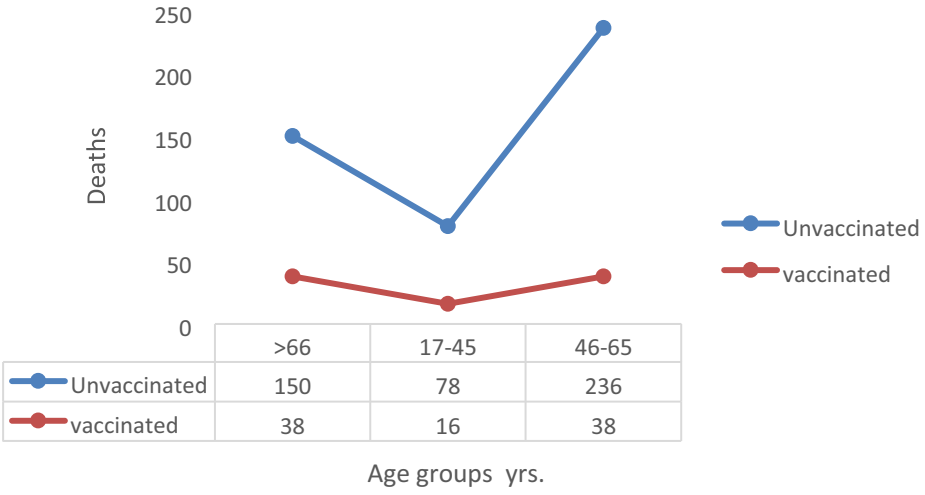

Fig. 2. Explains that death outcome was more common in older age group as was in unvaccinated patients and vaccinated also. Vaccination gives equal protection to age group 46–65 and ≥66 years without including the comorbidities.

4. Discussion

In this analysis of admitted adult patients with diagnosis of COVID-19 in a COVID dedicated hospital of South Punjab, Pakistan between June 2021 and October 2021, vaccination exposure was found significantly less commonly among these patients. In this analytic cohort, patients who had vaccination exposure regardless of its type had more mild illness, lesser chances of severe illness and getting admission to Intensive Care Unit as compared to unvaccinated patients. Vaccinated COVID 19 patients who need admission for their illness had lesser chances of hypoxemia at admission as compared to unvaccinated patients. Among total admission with COVID-19 during delta period, death occurred in 36.7% patients and among them 16.5% were vaccinated. Moreover,

vaccinated patients after getting illness and admission to hospital for their illness had 24.5% deaths or shifted to mechanical ventilation as compared to unvaccinated patients 40.5%. So, the death outcome was associated with decreased likelihood of vaccination. There was no difference in risk reduction of death outcome among different vaccination types. As 24.6% from inactivated vaccine type recipients, 27.3% from mRNA and 25.3% from Adenoviral vector based vaccine received death outcome or shifted to mechanical ventilator support after getting sick enough to require hospital admission for COVID-19. These findings strongly suggest that patients with vaccine breakthrough infections have a lower chance of getting severe COVID-19 infection and worst outcome of death than those who have not been vaccinated regardless of vaccine type.

The data suggest that vaccination can attenuate the disease progression and prevent the worst outcome in vaccine breakthrough cases in addition to its role of prevention of hospitalization as shown by the post marketing trials of various vaccines. So, the benefits of vaccine are underestimated in term of its role of prevention of hospitalization alone (Vasileiou et al., 2021; Abu-Raddad et al., 2021).

Study period includes the delta period in Pakistan, and maximum patients admitted were from this period i.e. July to September 2021. Whereas vaccination was opened up for all age groups from 15th of May 2021, maximum period between breakthrough infections and second dose of vaccination was three to four months. Almost 46.7 percent of total deaths in breakthrough vaccinated cases received their second dose of vaccination at least 3 months before to become infected. As a result, vaccinated cases were considered to have at least three months of durable immunity against severe infection. Even so, there were some breakthrough cases that required admission due to disease severity, however their mortality rate was lower than that of unvaccinated patients. Concerns about waning immunity arise with some power in order to instigate the health authorities around the world to seriously look after the matter (Naaber et al., 2021; Sanderson, 2021; Cai et al., 2021).

Patients with significant comorbidities, who are heavily skewed in hospital setting, are more likely to be concerned about vaccine failure against severe disease than patients with no comorbidities. Vaccination exposure was found less commonly among these groups like old age, DM, Cardiovascular Diseases, Chronic Kidney Disease and most importantly pregnancy. Chances of disease severity and death outcome were increased in vaccinated breakthrough cases with increase in time period between second dose of vaccination and infection with COVID-19 (Tenforde et al., 2021; Yuan et al., 2021). It was even denser in old age and patients with comorbidities like DM and cardiovascular diseases, rising the concerns about waning of immunity in vaccinated patients with passage of time (Naaber et al., 2021). Findings may also help the authorities to give the booster dose to old age population and patients with comorbidities.

There is an unresolved question to be answered with requirement of more research that whether it would be wise to give booster of previous available first generation vaccines which were made against former strains or there should be some strategy to change the vaccine formulation according to change in strain type, as followed in seasonal flu (Mir et al., 2021; Grijalva et al., 20212021). In developed countries like UK and USA who had vaccinated their majority populations far before the arrival of delta variant, still had substantial mortality in delta period in vaccinated breakthrough cases although it was more common in immunocompromised and old age patients (Tenforde et al., 2021). Whether it is waning immunity with passage of time or the new strains are escaping immunity against vaccinations, confounders are still to be found out (Flemming, 2021; Yuan et al., 2021; Planas et al., 2021).

Pregnant patients were excluded from the vaccination trial for safety concerns, so, a large high risk group was left unattended before the arrival of Variants of concern (VOC) leading to increased mortality in unvaccinated pregnant patients as shown in the results (Takemoto et al., 2020; Anon., 2021). Majority post marketing studies show that vaccine is safe and immunogenic during pregnancy both for mother and fetus and should be given on priority basis (Collier et al., 2021; Goldshtein et al., 2021).

Majority research done is for COVID-19 vaccine role of prevention of hospitalization, while its role in halting the disease progression and attaining the worst outcome of death had been undermined so far. This study shows that vaccination exposure clearly decreases the chances of disease progression, need for ICU care and death outcome, regardless of type vaccination (Puranik et al., 2021; Evans and Jewell, 2021). Results are even hopeful for the countries like Pakistan which do not have free access to mRNA vaccine for the whole population. So, it is wise to vaccinate whole population as soon as possible in order to dampen the disease transmission and severity in infected patients.

5. Conclusions

Prior vaccination exposure regardless of its type was significantly associated with decreased severity of disease, its progression to death or shifting mechanical ventilation in patients of COVID-19 who require admission for illness. Findings were consistent with risk reduction of worst outcome in vaccinated breakthrough cases as compared to unvaccinated patients. This study has some limitations. Since, it was an observational study some confounders could not be controlled. Firstly, the study included only hospitalized breakthrough cases, so, the results cannot be applied on outpatient treated breakthrough cases, though the criterion of hypoxemia being most common reason for admission to hospital can give some assessment application. Secondly, sample size of vaccinated breakthrough cases was limited preventing assessment of disease progression stratified by vaccine type and time since vaccination. So, we need some longitudinal population based studies in patients who are vaccinated and follow up for a long time to develop COVID-19 breakthrough infections and severity of disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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