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RESEARCH ARTICLE

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Effectiveness of different vaccine platforms in reducing mortality and length of ICU stay in severe and critical cases of COVID-19 in the Omicron variant era: A national cohort study in Iran

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Abstract

Various severe acute respiratory syndrome coronavirus 2 vaccines with different platforms have been administered worldwide; however, their effectiveness in critical

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease-2019; HR, hazard ratio; ICU, intensive care unit; MCMC, Medical Care Monitoring Center; MD, mean difference; MST, median survival time; PH, proportional hazard; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SHR, subgroup hazard ratio; WHO, World Health Organization.

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cases of COVID-19 has remained a concern. In this national cohort study, 24 016 intensive care unit (ICU) coronavirus disease-2019 (COVID-19) admissions were included from January to April 2022. The mortality and length of ICU stay were compared between the vaccinated and unvaccinated patients. A total of 9428 (39.25%) patients were unvaccinated, and 14 588 (60.75%) patients had received at least one dose of the vaccine. Compared with the unvaccinated, the first, second, and third doses of vaccine resulted in 8%, 20%, and 33% lower risk of ICU mortality in the adjusted model, with risk ratio (RR): 0.92, 95% confidence interval (CI): 0.84–1.001, RR: 0.80, 95% CI: 0.77–0.83, and RR: 0.67, 95% CI: 0.64–0.71, respectively. The mean survival time was significantly shorter in the unvaccinated versus the fully vaccinated patients (hazard ratio [HR]: 0.84, 95% CI: 0.80–0.88); $p < 0.001$). All vaccine platforms successfully decreased the hazard of ICU death compared with the unvaccinated group. The duration of ICU stay was significantly shorter in the fully vaccinated than in unvaccinated group (MD, −0.62, 95% CI: −0.82 to −0.42; $p < 0.001$). Since COVID-19 vaccination in all doses and platforms has been able to reduce the risk of mortality and length of ICU-stay, universal vaccination is recommended based on vaccine availability.

KEYWORDS
comorbidity, COVID-19, ICU stay, mortality, SARS-CoV-2, vaccine

1 | INTRODUCTION

The coronavirus 2019 (COVID-19) pandemic before August 2022 resulted in above 6 million deaths across 230 countries and territories worldwide.[1] In Iran with 86 022 837 population, the first case of COVID-19 was reported on February 19, 2020, and 7 541 586 patients and 144 258 deaths have been reported so far.[2] Accordingly, several attempts were made to produce vaccines to control the dissemination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and decrease the morbidity and mortality rates.[3–6] The World Health Organization (WHO) has introduced above 280 vaccines with different mechanisms of action against COVID-19.[7,8]

Although herd immunity can be achieved when adaptive immunity occurs in a high percentage of the population worldwide. To prevent a high number of morbidities, mortalities, and economic crises during the epidemic, a wide proportion of the population should gain immunity via vaccination,[9] as having been proved in many other infections such as influenza and meningitis, in which mass vaccination played an effective role in obtaining the herd immunity.[10]

The rapid progress of multiple vaccines with different platforms resulted in the development of a negative public attitude toward COVID-19 vaccination; however, COVID-19 vaccines have been highly effective in curtailing symptomatic and severe forms of COVID-19 and its associated mortality.[8] Moreover, a modest reduction in vaccine effectiveness was observed against mild disease with some variants; however, its effectiveness against severe forms of disease remained high at least 6 months after immunization with two doses.[11] The efficacy rates against symptomatic COVID-19 range from 70.4% to 95% for different vaccine types.[2–4] However, the efficacy of COVID-19 vaccines has been challenged by the emergence of several variants with significantly increased transmissibility.[12,13]

On November 26, 2021, the WHO declared the SARS-CoV-2 variant-of-concern, B.1.1.529 (Omicron), with many mutations, which increased transmissibility and immune evasion after natural infection and vaccination by reducing the neutralizing antibody response to the Omicron variant compared with the original strain of SARS-CoV-2 or the Delta (B.1.617.2) variant in vaccinated individuals.[11]

As in February 2021, the national SARS-CoV-2 vaccination campaign was commenced in Iran, the target of which were the high-risk groups, including the elderly, patients with chronic diseases, and healthcare workers as the first priority.[14,15]

However, there are limited data on the vaccine effectiveness in critically-ill patients compared with noncritical COVID-19 patients.[16] To evaluate the effectiveness of vaccination for severe and critical COVID-19 cases during the sixth wave caused by the Omicron variant, considering the number of administered doses and used vaccine platforms, this large national retrospective cohort study was conducted to compare intensive care unit (ICU) mortality and the length of ICU stay between the unvaccinated and vaccinated patients as prespecified objectives.

2 | METHODS

2.1 | Study design and setting

This national retrospective cohort study was conducted in 696 hospitals in 31 provinces of Iran (61 medical universities) from January 21, 2022 to April 11, 2022. The STROBE guideline on reporting was followed.

2.2 | Study source and population

The data were retrieved from the national system of the Medical Care Monitoring Center (MCMC) of Iran's Ministry of Health and Medical Education and collected from 191 433 hospitalized COVID-19 patients, including 24 016 ICU admissions.

The inclusion criteria were adult patients aged ≥18 years, confirmed diagnosis of COVID-19 by clinical and/or paraclinical parameters, and ICU admission criteria for critical COVID-19 (namely acute respiratory distress syndrome, sepsis, septic shock, or other conditions normally requiring life-sustaining therapies such as mechanical ventilation [invasive or non-invasive] or vasopressor therapy), and the criteria for severe COVID-19 (namely oxygen saturation <90% on room air, respiratory rate >30 breaths/min, and signs of severe respiratory distress [accessory muscle use and inability to complete full sentences]), according to the WHO's protocol and the regularly updated COVID-19 disease guidelines against COVID-19 disease prepared by Iran's national headquarters.[17,18] Incomplete data registry for COVID-19 vaccination was defined as exclusion criterion.

2.3 | Vaccination

COVID-19 vaccination status was defined as follows[19,20]:

1. Unvaccinated: no history of vaccination.
2. Partially vaccinated: a single dose of vaccination (after 2 weeks).
3. Fully vaccinated: two or three doses of vaccination (after 2 weeks).

To evaluate the effect of the third dose (booster), separate analysis was performed.

The COVID-19 vaccines used in Iran and their platforms are as follows: *viral vector-based vaccines* (Ad26.COV2.S [Johnson and Johnson], ChAdOx1 nCoV-19 or AZD1222 [AstraZeneca], Gam-COVID-Vac [Sputnik v]), *nucleic acid vaccines* (BNT162b2 [Pfizer], mRNA-1273 [Moderna]), *inactivated virus vaccines* (BBV152 [Bahar-at], Fakhravac, Iranbarkat [Vero Cell] [Sinovac], BBIBP-CorV, COVILO [Sinopharm]), and *vaccines with a protein subunit* (Razi Cov Pars [CovPars], FINLAY-FR-2, PastuCovac [Soberana], and CinnaGen Vaccine [SpiKoGen]).

2.4 | Data collection

The hospitalized patients' information, including their demographics (name, age, sex, and city of residence), clinical signs and symptoms, comorbidities, COVID-19 disease severity, ventilatory support (noninvasive and invasive), vaccination status, length of ICU stay, and ICU mortality, was recorded in the system. The information on suspected-probable-definite COVID-19 hospitalized patients was recorded daily in the "hospitalized pneumonia cases" and "deaths from pneumonia" forms of the MCMC database. These data were collected at the hospital level. The hospital's nursing office was in charge of registration, and the Crisis Management Headquarters was in charge of supervising registration.

2.5 | Statistical analysis

Data were reported as mean ± standard deviation, median and interquartile range, and frequency (percentage), where applicable. The relationships between different characteristics and vaccination (unvaccinated vs. any received dose) were analyzed using the χ^2 test. The crude and multivariable log-binomial regression models were applied to estimate the risk ratio (RR) of being fully vaccinated, adjusted for other covariates, with a 95% confidence interval (CI). The RR < 1.00 would indicate that vaccination was correlated with a lower mortality risk. The differences in survival rates among different subgroups were analyzed by plotting the Kaplan–Meier curve and represented as the median survival time (MST). The Cox proportional hazard (PH) model was fitted to the data to estimate the hazard ratio (HR) with 95% CI. The PH assumption was also evaluated. The subgroup hazard ratio (SHR) was calculated if needed. Furthermore, the cumulative incidence function curves were drawn to compare the lengths of ICU stay among the subgroups considering the ICU discharge. Moreover, the crude and multivariable linear regression models were fitted to evaluate the adjusted effect of vaccination on the mean difference (MD) of length of ICU stay.

The three adjusted RRs were tabulated: The adjusted[1] RR shows the estimate of the characteristics controlling for the vaccine effect; the adjusted[2] RR shows the effect of full vaccination versus no vaccination status in each corresponding characteristic subgroup, including the interaction effect (vaccination status by characteristics) in the model; and the adjusted[3] RR shows the estimate of the corresponding factor adjusted for vaccination status as well as all other factors. Regressions with random effects were fitted to consider the observed and unobserved covariates to reach unbiased estimations. Moreover, the results were not significantly different before and after including the random effect. Statistical analyses were conducted using Rstudio (4.0.3) at $p = 0.05$.

3 | RESULTS

3.1 | Baseline characteristics

In this study, 191 433 hospitalized COVID-19 cases were evaluated from January 2022 to April 2022. Of these patients, 24 016 (12.75%) ICU admissions were included in the study, of whom 13 121 (54.6%) were males and 10 895 (45.4%) were females with a mean age of 66.9 ± 18.0 and 67.8 ± 17.3 years, respectively (Table 1). Among all ICU patients, 958 (3%) needed to be readmitted to the ICU. These patients had no significant difference in terms of gender, age, number of comorbidities, number of vaccine doses, or platforms with those who had one ICU admission. Moreover, 11 864 (49.4%) patients had no comorbidity, and 1718 (7.15%) had three or more comorbidities, including hypertension (n = 6617, 27.55%), heart diseases (n = 5384, 22.42%), diabetes mellitus (n = 4653, 19.37%), and lung diseases (n = 1374, 5.61%). Furthermore, 225 (2.0%) female patients were pregnant at the time of ICU admission (Table 1).

In total, 14 588 (60.75%) patients had received the vaccine in which one, two, and three doses were 1073 (7.36%), 8156 (55.91%), and 5359 (36.73%), respectively (Supporting Information: Table 1). Of those patients receiving the first and second doses, 7751 (62%) persons did not get a booster dose, and 4653 (37.31%) persons had received inactivated virus vaccines as the booster dose, as the most

TABLE 1 Demographics and clinical characteristics of ICU admitted COVID-19 patients.

Characteristics	Total *N* (%)	Unvaccinated *N* (%)	Vaccinated (any dose) *N* (%)	One dose *N* (%)	Two doses *N* (%)	Three doses *N* (%)
Total	24 016 (100)	9428 (39.26)	14 588 (60.74)	1073 (4.47)	8156 (33.96)	5359 (22.31)
Sex[a]						
Male	13 121 (54.63)	4967 (52.68)	8154 (55.90)	550 (51.26)	4373 (53.62)	3231 (60.29)
Female	10 895 (45.37)	4461 (47.32)	6434 (44.10)	523 (48.74)	3783 (46.38)	2128 (39.71)
Age[a] (years)						
18–25	479 (1.99)	257 (2.73)	222 (1.52)	52 (4.85)	140 (1.72)	30 (0.56)
25–35	1060 (4.41)	508 (5.39)	552 (3.78)	71 (6.62)	396 (4.86)	85 (1.59)
35–45	1531 (6.37)	653 (6.93)	878 (6.02)	92 (8.57)	581 (7.12)	205 (3.83)
45–55	2084 (8.68)	853 (9.05)	1231 (8.44)	135 (12.58)	763 (9.36)	333 (6.21)
55–65	3757 (15.64)	1380 (14.64)	2377 (16.29)	163 (15.19)	1267 (15.53)	947 (17.67)
≥65	15 105 (62.90)	5777 (61.27)	9328 (63.94)	560 (52.19)	5009 (61.41)	3759 (70.14)
Age[a] (years)						
<65	8911 (37.10)	3651 (38.73)	5260 (36.06)	513 (47.81)	3147 (38.59)	1600 (29.86)
≥65	15 105 (62.90)	5777 (61.27)	9328 (63.94)	560 (52.19)	5009 (61.41)	3759 (70.14)
Hypertension[a]	6617 (27.55)	1985 (21.05)	4632 (31.75)	305 (28.42)	2436 (29.87)	1891 (35.29)
Heart diseases[a]	5384 (22.42)	1514 (16.06)	3870 (26.53)	238 (22.18)	1987 (24.36)	1645 (30.70)
Diabetes[a]	4653 (19.37)	1399 (14.84)	3254 (22.31)	213 (19.85)	1725 (21.15)	1316 (24.56)
Kidney diseases[a]	946 (3.94)	273 (2.90)	673 (4.61)	49 (4.570)	359 (4.40)	265 (4.94)
Liver diseases	140 (0.58)	53 (0.56)	87 (0.60)	9 (0.84)	56 (0.69)	22 (0.41)
Immunocompromised	134 (0.56)	50 (0.53)	84 (0.58)	7 (0.65)	47 (0.58)	30 (0.56)
Lung diseases[a]	1374 (5.61)	447 (4.74)	900 (6.17)	67 (6.24)	465 (5.70)	368 (6.87)
Comorbidities[a]						
0	11 864 (49.40)	5639 (59.81)	6225 (42.67)	508 (47.34)	3718 (45.59)	1999 (37.30)
1	6221 (25.90)	2080 (22.06)	4141 (28.39)	302 (28.15)	2240 (27.46)	1599 (29.84)
2	4213 (17.54)	1258 (13.34)	2955 (20.26)	185 (17.24)	1552 (19.03)	1218 (22.73)
≥3	1718 (7.15)	451 (4.78)	1267 (8.69)	78 (7.27)	646 (7.92)	543 (10.13)
Pregnancy[a]	225 (0.94)	111 (1.18)	114 (0.78)	25 (2.33)	80 (0.98)	9 (0.17)

Abbreviation: ICU, intensive care unit.

[a] $p < 0.001$ using the χ^2 test.

frequent platform used across the country (Supporting Information: Figure 1).

The most frequently reported symptoms on ICU admission were respiratory distress, cough, and generalized body pain in 13 170 (53.9%), 9611 (39.4%), and 6121 (25.1%) patients, respectively (Supporting Information: Figure 2).

Of patients requiring invasive mechanical ventilation, some (32.2%) were unvaccinated, and the others (23.1%) were fully vaccinated (Supporting Information: Figure 3A). Regarding different vaccine types, intubation was required in 28.6% and 14.3% of the patients receiving protein-based and messenger RNA (mRNA) vaccines, respectively (Supporting Information: Figure 3B).

3.2 | Mortality characteristics of the ICU-admitted COVID-19 patients

Among 24 016 ICU admissions, 7962 (33.15%) died in the ICU, of whom 4629 (58.14%) were males. The ICU mortality occurred in 3594 of 9428 (38.12%), 384 of 1073 (32.43%), and 4020 of 13 515 (29.74%) patients in the unvaccinated, partially vaccinated, and fully vaccinated groups, respectively.

The risk of ICU mortality was 14% higher in male patients compared with females (adjusted[1] RR, 1.14, 95% CI: 1.08–1.20; $p < 0.001$).

The mortality risk increased with age, being almost four times higher in patients aged above 65 years compared with the 18–25-year-old patients (adjusted[3] RR, 3.82, 95% CI: 2.87–5.09, $p < 0.001$).

Regarding comorbidity, patients with hypertension, chronic lung diseases, and diabetes mellitus had 19%, 21%, and 24% increased risk of death, respectively ($p < 0.001$). Moreover, the mortality risk significantly increased as comorbidities increased by 5% in one comorbidity, 7% in two comorbidities, and 12% in three or more comorbidities ($p < 0.001$).

Interestingly, a significant increase in the ICU survival rate was noticed in the pregnant ICU patients, with 85% less risk of progression to death in this group (adjusted[3] RR, 0.15, 95% CI: 0.02–0.21; $p < 0.001$) (Table 2).

3.3 | Effects of vaccination on the mortality: Kaplan–Meier survival analysis

The overall mortality risk was 25% lower in the fully vaccinated patients compared with the unvaccinated patients in the multivariable analysis (adjusted RR, 0.75, 95% CI: 0.72–0.79; $p < 0.001$). Compared with the unvaccinated, the first, second, and third doses of vaccine led to 8%, 20%, and 33% lower risk of ICU deaths in the adjusted model with (RR: 0.92, 95% CI: 0.84–1.001), (RR: 0.80, 95% CI: 0.77–0.83), and (RR: 0.67, 95% CI: 0.64–0.71), respectively (Table 3). The MST was significantly shorter (13 days) in the unvaccinated versus fully vaccinated patients (15 days) (HR: 0.84, 95% CI: 0.80–0.88; $p < 0.001$) (Figure 1A). Figure 1B shows the

TABLE 2 Mortality distribution of COVID-19 ICU-admitted patients based on vaccination status and risk ratio (95% CI) of mortality adjusted for vaccination status and the studied variables (sex, age, comorbidities, etc.).

Factor	Total mortality N (%)	Unvaccinated mortality N (%)	Partially vaccinated mortality N (%)	Fully vaccinated mortality N (%)	Adjusted[a] RR (95% CI)	Adjusted[b] RR (95% CI)	Adjusted[c] RR (95% CI)
Total mortality	7962/24 016 (33.15)	3594/9428 (38.12)	348/1073 (32.43)	4020/13 515 (29.74)	-	-	-
Sex							
Female	3333 (41.86)	1581 (43.99)	162 (46.55)	1590 (39.55)	Reference	0.76 (0.72–0.80)**	Reference
Male	4629 (58.14)	2013 (56.01)	186 (53.45)	2430 (60.45)	1.14 (1.08–1.20)**	0.79 (0.75–0.83)**	1.16 (1.12–1.20)**
Age (years)							
18–25	46 (0.58)	31 (0.86)	4 (1.15)	11 (0.27)	Reference	0.54 (0.28–1.04)	Reference
25–35	127 (1.60)	66 (1.84)	10 (2.87)	51 (1.27)	1.08 (0.72–1.61)	0.82 (0.58–1.15)	1.25 (0.89–1.74)
35–45	271 (3.40)	156 (4.34)	11 (3.16)	104 (2.59)	1.98 (1.38–2.83)**	0.56 (0.44–0.69)**	1.81 (1.33–2.45)**
45–55	482 (6.05)	271 (7.54)	34 (9.77)	177 (4.40)	2.63 (1.87–3.72)**	0.51 (0.43, 0.60)**	2.21 (1.64–2.97)**
55–65	979 (12.3)	447 (12.44)	31 (8.91)	501 (12.46)	2.68 (1.91–3.77)**	0.70 (0.63, 0.78)**	2.54 (1.90–3.40)**
≥65	6057 (76.07)	2623 (72.98)	258 (74.14)	3176 (79.00)	3.76 (2.70–5.24)**	0.80 (0.77–0.83)**	3.82 (2.87–5.09)**

(Continues)

TABLE 2 (Continued)

Factor	Total mortality *N* (%)	Unvaccinated mortality *N* (%)	Partially vaccinated mortality *N* (%)	Fully vaccinated mortality *N* (%)	Adjusted[a] RR (95% CI)	Adjusted[b] RR (95% CI)	Adjusted[c] RR (95% CI)
Hypertension							
No	5546 (69.66)	2762 (75.85)	228 (65.52)	2592 (64.48)	Reference	0.77 (0.74–0.80)**	–
Yes	2416 (30.34)	868 (24.15)	120 (34.48)	1428 (35.52)	1.19 (1.13–1.26)**	0.75 (0.71–0.81)**	–
Heart disease							
No	6351 (79.77)	3032 (84.36)	283 (81.32)	3036 (75.52)	Reference	0.80 (0.77–0.83)**	–
Yes	1611 (20.23)	562 (15.64)	65 (18.68)	984 (24.48)	0.97 (0.90–1.04)	0.73 (0.67–0.79)**	–
Diabetes mellitus							
No	6264 (78.67)	2955 (82.22)	267 (76.72)	3042 (75.67)	Reference	0.79 (0.76–0.85)**	–
Yes	1698 (21.33)	639 (17.78)	81 (23.28)	978 (24.33)	1.24 (1.16–1.32)**	0.70 (0.65–0.76)**	–
Immunocompromised							
No	7921 (99.49)	3574 (99.44)	345 (99.14)	4002 (99.55)	Reference	0.78 (0.75–0.81)**	–
Yes	41 (0.51)	20 (0.56)	3 (0.86)	18 (0.45)	1.05 (0.75–1.47)	0.58 (0.34–0.99)*	–
Lung diseases							
No	7416 (93.14)	3390 (94.32)	327 (93.97)	3699 (92.01)	Reference	0.77 (0.74–0.80)**	–
Yes	546 (6.86)	204 (5.68)	21 (6.03)	321 (7.99)	1.21 (1.09–1.34)**	0.84 (0.74–0.96)*	–
Number of comorbidities							
0	3690 (46.35)	1995 (55.51)	144 (41.38)	1551 (38.58)	Reference	0.77 (0.73–0.81)**	Reference
1	2124 (26.68)	835 (23.23)	110 (31.61)	1179 (29.33)	1.14 (1.06–1.21)**	0.77 (0.71–0.82)**	1.05 (1.01–1.10)*
2	1508 (18.94)	564 (15.69)	65 (18.68)	879 (21.87)	1.21 (1.18–1.36)**	0.71 (0.65–0.77)**	1.07 (1.02–1.12)*
≥3	640 (8.04)	200 (5.56)	29 (8.33)	411 (10.22)	1.27 (1.12–1.40)**	0.78 (0.68–0.89)**	1.12 (1.05–1.20)**
Pregnancy							
No	7957 (99.94)	3591 (99.92)	347 (99.71)	4019 (99.98)	Reference	0.78 (0.75–0.80)**	Reference
Yes	5 (0.06)	3 (0.08)	1 (0.29)	1 (0.02)	0.07 (0.02–0.21)**	0.41 (0.04–3.93)***	0.15 (0.06–0.39)**

Abbreviations: CI, confidence interval; ICU, intensive care unit; RR, risk ratio.

[a]The adjusted[1] RR shows the estimate of the characteristics controlling for the vaccine effect (unvaccinated vs. fully-vaccinated).

[b]The adjusted[2] RR shows the effect of full vaccination versus no vaccination status in each corresponding characteristic subgroup including the interaction effect (vaccination status by characteristics) in the model.

[c]The adjusted[3] RR shows the estimate of the corresponding factor adjusted for vaccination status as well as all other factors.

*$p < 0.05$; **$p \leq 0.001$; ***$p = 0.44$.

TABLE 3 Crude and adjusted analyses for risk ratio of mortality and mean difference of ICU stay for vaccination status of COVID-19 ICU admitted patients.

	RR (95%CI)				MD (95%CI)			
	Crude analysis	*p*	Adjusted Analysis[a]	*p*	Crude analysis	*p*	Adjusted Analysis[a]	*p*
Fully vaccinated versus not vaccinated	0.78 (0.75–0.81)	<0.001	0.75 (0.72–0.79)	<0.001	−0.57 (−0.77 to −0.38)	<0.001	−0.62 (−0.82 to −0.42)	<0.001
Not vaccinated	–		–		–		–	
Dose 1	0.85 (0.78–0.93)	<0.001	0.92 (0.84–1.001)	0.05	−0.63 (−1.10 to −0.17)	0.06	−0.46 (−0.93 to −0.004)	0.048
Dose 2	0.81 (0.77–0.84)	<0.001	0.80 (0.77–0.83)	<0.001	−0.59 (−0.81 to −0.37)	<0.001	−0.58 (−0.80 to −0.36)	<0.001
Dose 3	0.74 (0.70–0.78)	<0.001	0.67 (0.64–0.71)	<0.001	−0.55 (−0.79 to −0.30)	<0.001	−0.69 (−0.94 to −0.44)	<0.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; MD, mean difference; RR, risk ratio.

[a]Adjusted analysis of risk ratio of mortality (95% CI) for age, sex, and comorbidities.

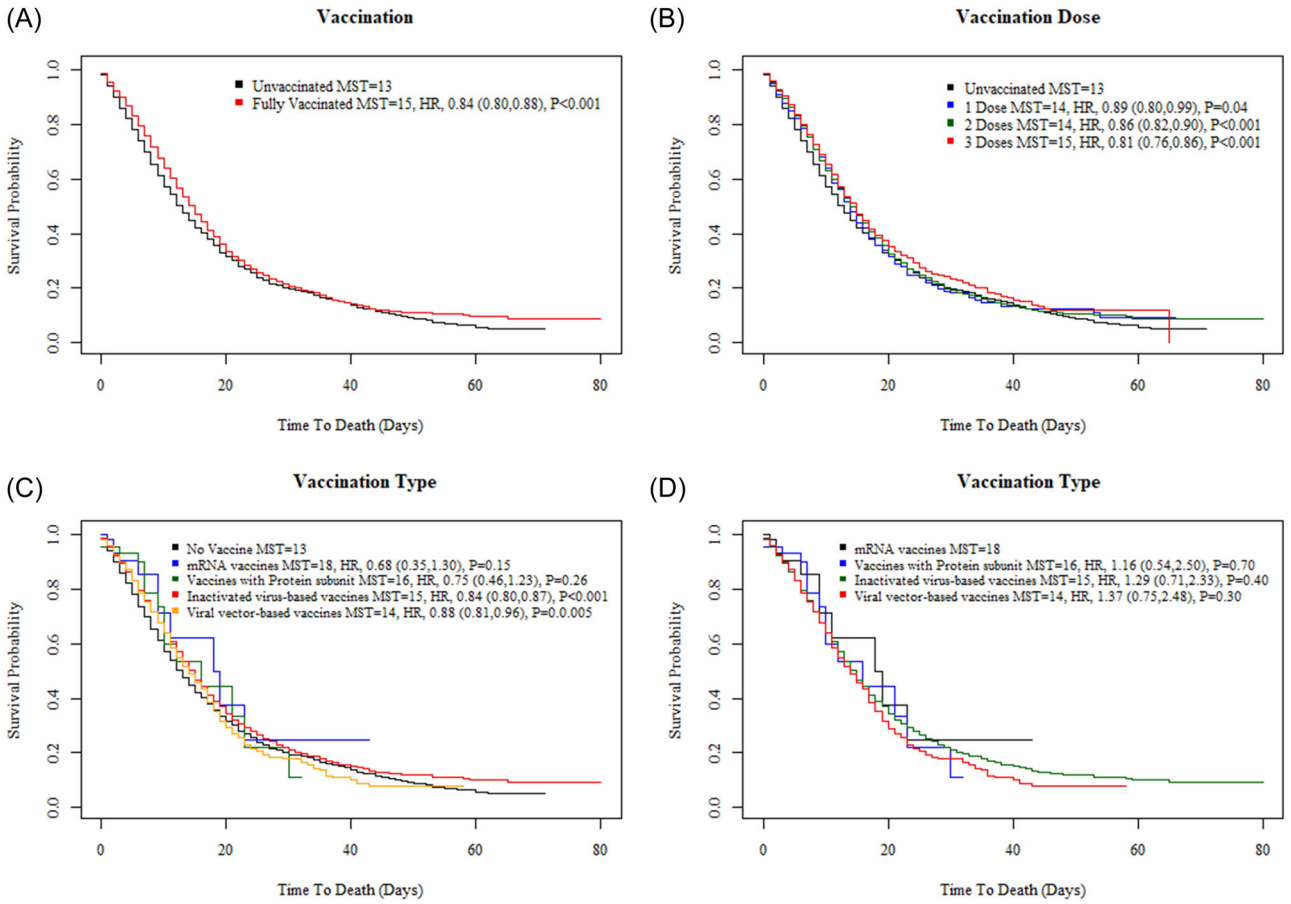

FIGURE 1 Kaplan–Meier survival analysis of COVID-19 ICU admitted patients and hazard ratio (95% CI) of mortality for (A) unvaccinated versus vaccinated patients (patients who received at least two vaccine doses), (B) different doses of vaccination, (C) different types of vaccines versus unvaccinated, and (D) different types of vaccines versus mRNA vaccines. CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MST, median survival time; mRNA, messenger RNA.

Kaplan–Meier estimator for the hazard of ICU death with different vaccine doses. Our data indicated that vaccination successfully decreased the hazard of ICU death compared with the unvaccinated group. However, this effect was different in various vaccine platforms: 32% with mRNA ($p = 0.15$), 25% with protein-based subunit ($p = 0.26$), 16% with an inactivated virus ($p < 0.001$), and 12% with viral vector-based vaccines ($p = 0.005$) (Figure 1C). The highest MST in the vaccine platforms was 18 days for mRNA vaccines; however, no statistically significant difference was observed between the mRNA vaccines and other vaccine platforms

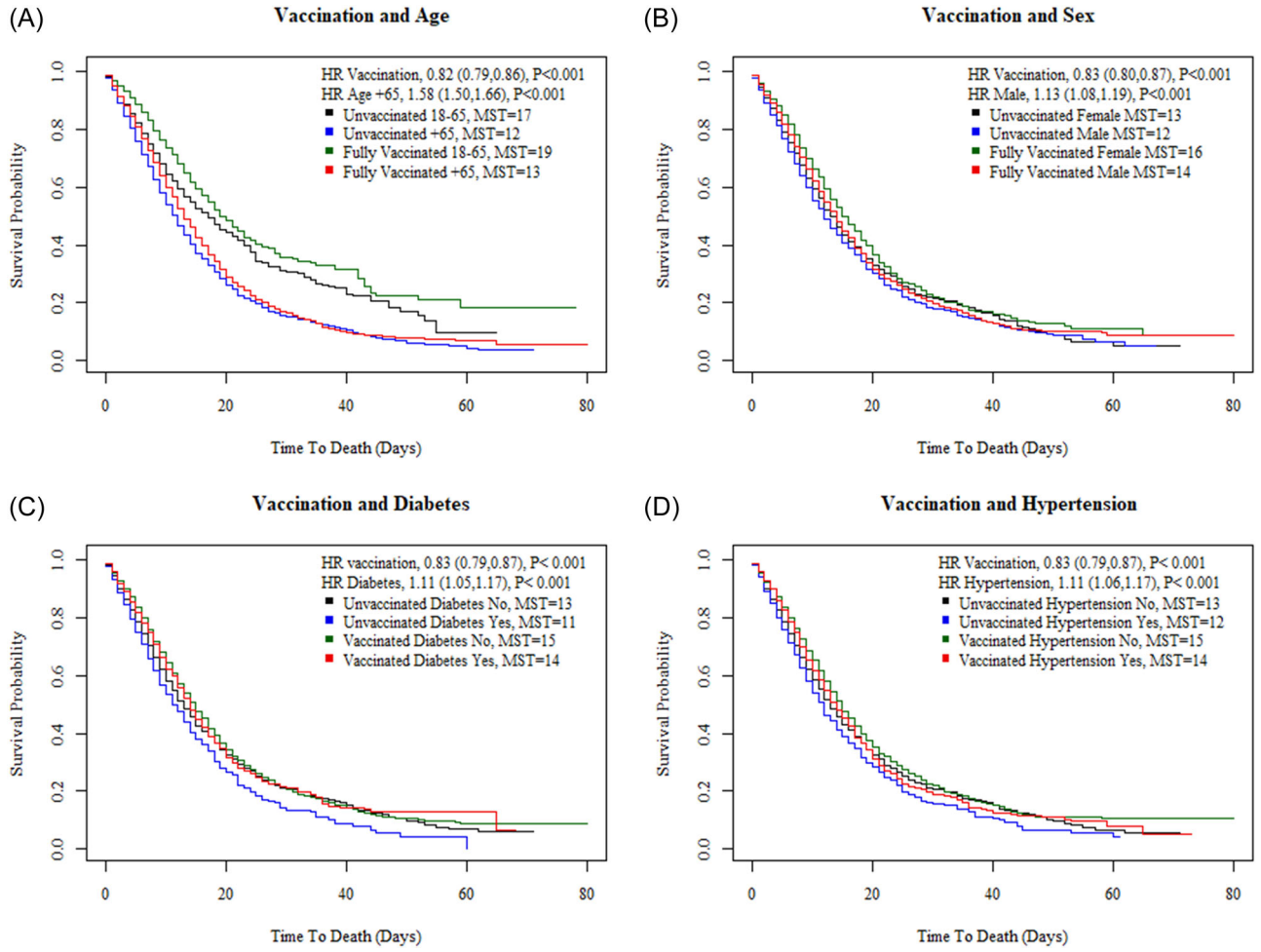

FIGURE 2 Kaplan–Meier survival analysis of COVID-19 ICU admitted patients and hazard ratio (95% CI) of mortality with regard to vaccination status and (A) age groups >65 or <65 years, (B) sex groups, (C) diabetic patients, and (D) hypertensive patients. CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MST, median survival time.

in terms of MST and hazard of mortality (Figure 1D). Full vaccination status was associated with significantly higher MST in patients aged below 65 years (Figure 2A). The fully vaccinated males had 2 days, while the females had 3 days longer MST than the unvaccinated of the same gender group (Figure 2B).

Vaccination significantly protected against mortality in diabetic and nondiabetic patients (HR: 0.83, 95% CI: 0.79–0.87). The fully vaccinated diabetic patients survived 3 days longer compared with the unvaccinated diabetic patients (14 vs. 11 days, Figure 2C). Similarly, the fully vaccinated hypertensive patients had 2 days longer survival than the unvaccinated hypertensive patients (14 vs. 12 days, Figure 2D).

The mortality risk was almost similar in the fully vaccinated male and female groups ([adjusted^2 RR, 0.79, 95% CI: 0.75–0.83] and [0.76, 95% CI: 0.72–0.80], respectively). In terms of ICU mortality in different age groups, in the fully vaccinated group, the risk of mortality was significantly lower in the 35–45 and 45–55-year-old groups by 44% and 49% compared with the older age group, respectively. Moreover, the mortality risk decreased by 20% in the fully vaccinated patients aged above 65 years compared with the unvaccinated ones (adjusted^2 RR, 0.80, 95% CI: 0.77–0.83; $p < 0.001$) (Table 2). Kaplan–Meier survival analysis of COVID-19 ICU admitted patients and HR (95% CI) of mortality regardless of vaccination status is presented in Supporting Information: Figure 4. The MST significantly decreased every 10 years after age 25 compared with the 18–25-year-old age group, to approach 12 days with 3.37 folds (2.52, 4.51, $p < 0.001$) hazard of mortality in patients 65 years or older (Supporting Information: Figure 4A). Male patients had a 12% less chance of ICU survival, and their MST was 1 day shorter than their female cohort (SHR of 1.12 [1.08, 1.18], $p < 0.001$, Supporting Information: Figure 4B). Both diabetic and hypertensive ICU-admitted patients had less MST than patients without such comorbidities (Supporting Information: Figure 4C,D).

Cumulative incidence function curves of COVID-19 ICU admission (days) with regard to vaccination status is shown in Supporting Information: Figure 5. The cumulative incidence function indicated that the fully vaccinated patients younger than 65 years had 20% higher ICU discharge probability compared with the unvaccinated patients in the same age group, while this probability was 24% in patients older than 65 years (Supporting Information: Figure 5A,B).

In ICU patients with comorbidities, the fully vaccinated group, compared with the unvaccinated, had higher probability of discharge from the ICU by 34% (SHR of 1.34 [1.23, 1.46], $p < 0.00$), 26% (SHR of 1.26 [1.17, 1.34], $p < 0.00$), in diabetic and hypertensive patients, respectively (Supporting Information: Figures 5C–F).

3.4 | Length of ICU-stay

Adjusted for all study variables, the patients who were fully vaccinated had significantly lower ICU length of stay (adjusted[3] MD, −0.62, 95% CI: −0.82 to −0.42; $p < 0.001$) (adjusted[3] SMD, −0.05, 95% CI: −0.07 to −0.03; $p < 0.001$) (Supporting Information: Table 2). The patients aged above 65 years stayed significantly longer in the ICU by an average of 1.3 days (MD: 1.30, 95% CI: 0.56–2.04; $p < 0.001$) (Table 3).

4 | DISCUSSION

The overall mortality rate in the ICU patients was 32.6% for 696 Iranian medical centers with 24 016 ICU admissions with documented severe and critical COVID-19 cases during the Omicron wave. The fully vaccinated patients significantly had less probability of progression to death compared with the unvaccinated patients, regardless of the vaccine type and administered doses. Vaccination decreased the mortality risk by 25% in patients after adjusting for the independent risk of covariates. The length of ICU stay was also remarkably shorter in the fully vaccinated compared with the unvaccinated patients.

In terms of vaccination status, 1, 2, and 3 doses of vaccination resulted in an 8%, 20%, and 33% decrease in the mortality risk compared with the unvaccinated group. Lopez Bernal et al.[21] observed a 51% decrease in COVID-19-related risk of death by a single dose of vaccination or 95% protection after two doses of vaccination with BNTn2b.[22] In another study on non-ICU admitted patients, 79%, 13%, and 8% of deaths were reported in the unvaccinated, partially-, and fully-vaccinated patients, respectively.[23]

Several studies have discussed the efficacy of different vaccine platforms.[24–26] However, one of the strengths of this study was that four different vaccine platforms were compared in a real-life setting for a large population. In another study, four vaccines from two mRNA and adenovirus-based platforms were discussed. The efficacy rates of Pfizer, Moderna, AstraZeneca, and Janssen vaccines were 95%, 94.1%, 70.4%, and 66.9%, respectively. This review study showed that these vaccines were effective in reducing the incidence and severity of SARS-CoV-2 infection.[25] In a study, the safety and efficacy of three vaccine platforms of mRNA-inactivated virus and viral vector-based were compared, and the researchers found that all platforms decreased the risk of severe infection. The risk of infection was 83% lower after two doses of vaccination. Moreover, the risk of infection was 3% lower in mRNA vaccines compared with non-replicating viral vector and inactivated vaccines. A subgroup analysis of efficacy after a single dose of mRNA and nonreplicating viral vector vaccines showed a 25% higher risk of infection compared with the two doses of the vaccine. The administration of heterologous booster doses of COVID-19 vaccination was associated with durable humoral and cellular immune responses in individuals receiving homologous vaccines in their primary series. The results of a study published in Cell Reports Medicine provide information about mixed vaccine types in both primary vaccination and vaccine booster schedules, which is particularly important for middle- and lower-income countries to reinforce vaccine programs.[27,28]

According to the national COVID-19 vaccination protocol in Iran, the injection of the first and second vaccine doses were of homologous platforms; however, for the booster dose, it was recommended to administer a heterologous vaccine to achieve higher efficacy.[29]

In different relevant investigations, vaccination resulted in lower intubation rates, particularly in fully vaccinated patients. In a study, Tenforde et al. reported 24.7% intubation in the unvaccinated group versus 12% in the vaccinated patients.[6]

There was also a significant difference in the length of ICU stay between the vaccinated and unvaccinated groups. The ICU stay for patients who did not receive any vaccine was half a day longer than the vaccinated group. If the duration of half a day is calculated for all unvaccinated patients, it is clear that the number of hospitalization days and the use of resources have increased significantly which is a heavy and avoidable burden for the healthcare system.[30] Accordingly, the importance of vaccination is more highlighted in light of lowering the length of hospital and ICU stay and decreasing the burden on economic and human resources. Desai et al.[31] stated that the length of hospital and ICU stay in vaccinated patients was significantly shorter than that in the unvaccinated patients. This finding was in contrast with those declared by Sevinc et al.,[8] who reported no difference. This could be attributed to the participants' age, different vaccine types (CoronaVac of inactivated vaccines), or a different variant of COVID-19.

In our study, the highest risk of ICU mortality was observed in patients aged ≥65 years, who had approximately four times higher risk of progression to death than young adults aged 18–25 years. The patients aged ≥65 years formed 63% of our study population, with 76.1% of the total ICU deaths. COVID-19 vaccines can effectively decrease mortality in this vulnerable group.[32] Le Borgne et al. demonstrated the critical impact of age on hospital mortality and the necessity of protecting vulnerable elderly population as much as possible.[33] The present data revealed that the fully vaccinated patients aged above 65 years had a 24% higher probability of ICU discharge compared with the unvaccinated patients of the same age group.

Since the risk factors for ICU mortality were older age, male gender, diabetes mellitus, and chronic obstructive pulmonary diseases,[34] our study indicated that the presence of three or more comorbidities increased the risk of mortality by 27%. Accordingly, patients with hypertension and diabetes mellitus had 19% and 24% higher mortality risk. Sentongo et al. showed that the mortality risk

was significantly higher in the patients with hypertension and diabetes mellitus by 82% and 48%, respectively, compared with those without comorbidities.[35] In the stratified risk analysis of the fully vaccinated patients in the present study, the survival probability was higher by 34% in the diabetic patients and 26% in the hypertensive patients compared to the unvaccinated patients with the same comorbidities.

The hazard of death was significantly higher in males compared to females, similar to Indian and Pakistani ethnicities[36] and across all age groups,[37] which stressed the role of sex hormones in immune response.[38,39]

Several studies have indicated that COVID-19 disease has significant adverse effects on pregnancy with high maternal and perinatal morbidity and mortality.[40,41] However, our present data reported five (2.22%) ICU deaths among the 225 pregnant patients. Pregnancy in our study population was notably associated with improved ICU survival, and fully vaccinated pregnant women experienced less probability of ICU death by 59% than the unvaccinated pregnant patients. In another study, pregnancy was associated with a 2.23-time higher risk of ICU admission than nonpregnancy among the COVID-19 patients. However, it was not associated with a statistically significant increase in mortality.[42] Such a finding does not support better survival, as other studies have indicated poor pregnancy outcomes with the COVID-19 disease.

The lower ICU mortality rate in pregnant women could be due to hormonal factors and the fact that they are mainly younger and noncomorbid populations. Larger studies in this population are required to further examine and verify the present findings. One of the limitations of the present study was the relatively short research period to detect the adverse reactions of the COVID-19 vaccine as a safety concern. We also had limitations in the availability of different vaccine platforms across the country.

Determining SARS-Co-V2 variants has been undertaken regularly by laboratories licensed by the Ministry of Health and Medical Education using next-generation sequencing across the country. The viral sequencing of all ICU patients in our study was not feasible due to cost considerations. The data on viral sequencing during the Omicron wave, conducted by Iran's Ministry of Health and Medical Education (unpublished data), showed that 83.2% of SARS-Co-V2 PCR positive cases during our study period were of omicron variants, including, BA.1, BA.1.1, BA.2. In addition to the limitations of retrospective studies, there were other limitations in our study, such as insufficient information about ICU care data, and a lack of data of the greater number of comorbid conditions.

5 | CONCLUSION

COVID-19 primary vaccination and its booster doses play a critical role in reducing morbidity and mortality in ICU patients. Globally, the number of COVID-19 cases is trending down; however, the vulnerable and older population are still suffering from severe and critical COVID-19 diseases, often requiring ICU care. With the increasing number of severe COVID-19 patients, the health systems have witnessed a shortage of intensive care resources, including healthcare workers in critical care medicine, ICU beds, and mechanical ventilators, which increases the pressure on critical care capacity.

Since the covid-19 vaccination in all doses and platforms has been able to reduce the risk of mortality and length of ICU stay, universal vaccination is recommended based on the availability of each type of vaccine.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the study: Hamidreza Jamaati, Maryam Hajimoradi, Fariba Ghorbani, Shadi Shafaghi, Fatemeh Sadat Hosseini-Baharanchi, Rayka Malek, Saeed Karimi, Sima Noorali, Majid Mokhtari, Makan Sadr, Abdolreza Mohamadnia, Batoul Khoundabi, Seyed Mohsen Zahraei, Seyed Mohammad Reza Hashemian. *Data acquisition and analysis*: Rayka Malek, Fatemeh Sadat Hosseini-Baharanchi, Maryam Hajimoradi, Hamidreza Jamaati, Fariba Ghorbani, Shadi Shafaghi, Yunes Panahi. *Study data interpretation*:Hamidreza Jamaati, Majid Mokhtari, Fariba Ghorbani, Shadi Shafaghi, Rayka Malek, Fatemeh Sadat Hosseini-Baharanchi, Maryam Hajimoradi, Farzaneh Dastan, Esmaeil Mortaz, Katayoun Tayeri, Fatemeh Behtaj, Hassan Vaezi, Mohammad Mehdi Forouzanfar. *Drafting the study manuscript*: Maryam Hajimoradi, Fariba Ghorbani, Shadi Shafaghi, Hamidreza Jamaati, Fatemeh Sadat Hosseini-Baharanchi, Rayka Malek, Majid Mokhtari, Saeed Karimi, Yunes Panahi, Sima Noorali, Batoul Khoundabi, Makan Sadr. *Critical revision for important intellectual content*: Hamidreza Jamaati, Majid Mokhtari, Maryam Hajimoradi, Fariba Ghorbani, Shadi Shafaghi, Abdolreza Mohamadnia, Makan Sadr, Seyed Mohsen Zahraei, Seyed MohammadReza Hashemian, Farzaneh Dastan, Esmaeil Mortaz, Katayoun Tayeri, Fatemeh Behtaj, Hassan Vaezi, Mohammad Mehdi Forouzanfar. *Final approval of the version to be published*: All authors. *Agreement to be accountable for all aspects of the work*: All authors. Shadi Shafaghi had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material. The data that supports the findings of this study are available in the supplementary material of this article

ETHICS STATEMENT

National Committee for Ethics in Biomedical Research of Iran had declared a prior mandate that all COVID-19 patients admitted to any

medical facility must be made fully aware of their potential participation to research projects. All patients were requested to sign an informed consent form which contained the permission to transfer their electronic data, confidentially, to the HIS (hospital information system) which are connected to the national registry of the Medical Care Monitoring Center (MCMC) of the Iranian Ministry of Health for data collection, future investigations, and research. This study was approved by the Iran National Committee for Ethics in Biomedical Research (Ethic code: IR.NIMAD.REC.1401.011) and followed the ethical guidelines of the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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