



Factors Associated With Post-Vaccination COVID-19 Infection Leading to Hospitalization in Chaharmahal and Bakhtiari Province: A Case-Control Study

Kosar Farhadi Babadi¹ , Seyed Saeed Hashemi Nazari^{2*} , Amir Kavousi² , Ali Ahmadi³ , Mohadeseh Karimian⁴ , Koorosh Etemad²

¹Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Department of Epidemiology and Biostatistics, School of Public Health, Shahrekord University of Medical Sciences, Shahrekord, Iran

⁴Department of Medical Biotechnology, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran

Abstract

Introduction: COVID-19 vaccination and its associated complications have been a controversial issue worldwide. This study aimed to identify the determinants of infection leading to hospitalization following COVID-19 vaccination in Chaharmahal and Bakhtiari Province.

Methods: In this case-control study, after screening records from 47,001 individuals, 260 hospitalized vaccinated individuals were selected as cases, while 130 vaccinated outpatients and 130 healthy individuals were included as controls ($n=520$). Data were analyzed by Stata 17 using descriptive and inferential statistics, including univariate and multivariable analyses and ordinal logistic regression models.

Results: Multivariable analyses revealed older age (>55 years, $OR=11.08$, $P<0.001$), female gender ($OR=0.45$, $P=0.002$), prior infection ($OR=292.7$, $P=0.001$), and non-healthcare occupations ($OR=2.07$, $P=0.036$) as significant risk factors for hospitalization, while being male ($OR=0.45$, $P=0.002$) and a healthcare worker ($OR=0.22$, $P=0.006$) were protective. Moreover, the Sinopharm ($OR=2.40$, $P=0.012$) and other vaccines ($OR=2.54$, $P=0.036$) were associated with higher hospitalization risk compared to AstraZeneca. Additionally, the protective effect of vaccination and underlying disease decreased over time (underlying disease $HR=0.99$, $P=0.014$; homologous booster $HR=0.99$, $P<0.001$; heterologous booster $HR=0.99$, $P=0.025$).

Conclusion: Age, gender, comorbidities, recent hospitalization, and high-risk occupation influenced COVID-19 hospitalization, while prior infection and vaccination provided temporary protection, underscoring the need for targeted, time-sensitive interventions.

Keywords: COVID-19, COVID-19 vaccines, Risk factors, Hospitalization, Case-control studies

*Corresponding Author:

Seyed Saeed Hashemi Nazari,
Email: saeedh_1999@yahoo.com

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on daily life and the health system worldwide.¹ The rapid spread of the virus and its high transmission rate have overwhelmed healthcare systems, significantly burdening healthcare facilities and professionals.² Global trends indicate an increase in COVID-19 prevalence from 0.011 to 0.098, which is concurrent with higher mortality rates in low-income countries.³ Public health interventions, such as social distancing, mask-wearing, and vaccination campaigns, have been implemented to mitigate the effect of this virus on community health.⁴ However, the effectiveness of these measures varies across communities, underscoring the importance of understanding the specific factors that shape

the impact of COVID-19 on community health.⁵ Given that this disease can seriously damage vital organs (lungs, brain, and heart), increase the length of hospital stay, and increase costs, vaccination was proposed as a serious solution. In addition to limiting the disease's epidemics and pandemics, this prevention strategy led to reduced social restrictions and job losses but improved social support for individuals.⁶ Vaccination is crucial for reducing infections and deaths from COVID-19. First, vaccines help build immunity against the virus, decreasing the likelihood that individuals will contract the disease.⁷ After receiving a COVID-19 vaccine, individuals develop antibodies that can neutralize the virus upon subsequent exposure.⁸ As more people are vaccinated, the overall transmission rate decreases, resulting in fewer infections and ultimately saving lives.⁹ Despite the

effectiveness of COVID-19 vaccines in lowering the risk of severe illness, hospitalization, and death, hospitalization continues to pose a serious public health challenge^{10, 11} because no vaccine is 100% effective, and breakthrough infections can occur. Breakthrough infections refer to cases where vaccinated individuals contract COVID-19 despite being fully vaccinated.¹² Accordingly, knowing the characteristics of hospitalized patients after vaccination is crucial for several reasons. Firstly, it helps assess the vaccine's effectiveness in preventing severe COVID-19 and deaths.² Secondly, understanding the epidemiological characteristics of COVID-19 among vaccinated patients is essential for identifying potential vaccine-related adverse effects.¹³ Rudolph et al reported that receiving a COVID-19 vaccine prior to infection was associated with a reduced risk of developing post-COVID-19 conditions.¹⁴ Another study indicated that a considerable proportion of participants experienced at least one adverse effect after vaccination. The reported side effects were significantly associated with gender, age, drug use, job, and the type of vaccine dose received.¹⁵ Although several studies have examined vaccine effectiveness and post-vaccination outcomes, important knowledge gaps remain regarding the epidemiological and contextual factors related to COVID-19 hospitalization after vaccination. Therefore, it was necessary to conduct this research in order to better understand the determinants of post-vaccination hospitalization and provide evidence to support targeted prevention strategies, optimize healthcare planning, and reduce the burden of severe COVID-19 outcomes among vulnerable populations. Accordingly, serious attention should be paid to other related factors in order to reduce health risks for people by controlling these factors. Therefore, this study aims to determine the epidemiological profile of COVID-19 hospitalizations and analyze the relationship between relevant demographic, clinical, and contextual factors and hospitalization following COVID-19 vaccination in southwestern Iran.

Materials and Methods

Study Design and Setting

The present case-control study was conducted using data from hospitals and health centers in Chaharmahal and Bakhtiari Province in southwestern Iran. The dataset included demographic information on individuals residing in this province who referred to hospitals in this province between April 2020 and March 2022. The outcome considered in this study was the hospitalization status of individuals with COVID-19 who were admitted to hospitals in Chaharmahal and Bakhtiari Province.

Data Sources and Measurement

Vaccination data for all vaccinated individuals in Chaharmahal and Bakhtiari Province were extracted from the Integrated Health System (SIB) of the Ministry of Health and subsequently linked with the provincial medical care monitoring center (MCMC) database. Thus, the initial data obtained for the patient group included 14,364 vaccinated individuals, 3,537 of whom were outpatients and 10,840 of

whom were inpatients, from health centers in Chaharmahal and Bakhtiari Province. Moreover, data for healthy participants were collected using a structured checklist administered in person and based on self-reporting. The intended checklist consisted of demographic information, vaccination and infection history, occupational status, adherence to health protocols, and presence of underlying diseases. For hospitalized and outpatient participants, occupational information and adherence to protocols were obtained via telephone interviews using contact details from hospital medical records. Additionally, eligibility for checklist participation required residence in the province and self-reported absence of COVID-19 infection. All the classifications of healthy individuals were, therefore, based on checklist data.

Participants and Sampling

Initially, vaccination data were obtained from the national SIB health information system and subsequently linked with provincial MCMC hospital registry data to identify vaccinated individuals who developed COVID-19 infection following vaccination. After data cleaning and confirmation of vaccination status, 10,840 hospitalized patients and 3,537 outpatient cases met the eligibility criteria. From these groups, participants were selected by simple random sampling in order to minimize selection bias while enhancing representativeness.

This research was classified as a case-control study because participants were selected based on the presence or absence of the study outcome after vaccination. In addition, the primary outcome was severe COVID-19 infection resulting in hospitalization. Further, individuals experiencing this outcome were assigned to the case group, while those without hospitalization constituted the control group.

Participants were divided into cases, control group 1, and control group 2. Cases were vaccinated individuals who were hospitalized due to COVID-19 infection ($n=260$). Control group 1 included vaccinated individuals with outpatient COVID-19 infection who required no hospitalization ($n=130$), and control group 2 encompassed vaccinated individuals with no history of COVID-19 infection up to the time of data collection ($n=130$).

The primary comparison was between hospitalized and non-hospitalized vaccinated individuals to identify factors associated with severe COVID-19 outcomes following vaccination.

Moreover, the extensive cohort of vaccinated individuals identified through administrative databases constituted the source population for this study rather than the final analytical sample. Sample size reduction occurred in multiple phases to ensure data quality and adherence to eligibility criteria.

Initially, unvaccinated individuals and records with incomplete linkage between vaccination and hospitalization databases were excluded, and only those who met the predefined post-vaccination interval criteria were retained accordingly. From these eligible populations,

random samples of hospitalized and outpatient participants were selected for detailed data collection, which included telephone interviews to obtain information on occupation and adherence to preventive measures.

Furthermore, sample size estimation was based on the variable of adherence to health protocols, with an assumed 65% and 80% adherence among cases and controls, respectively, 80% statistical power, and a significance level of 0.05. The minimum required sample size was 139 individuals. However, the number of hospitalized cases was increased to 260 in order to enhance statistical power and allow for multivariable analyses.

Eligibility Criteria

Eligible participants were individuals who had received at least one dose of a COVID-19 vaccine, resided in Chaharmahal and Bakhtiari Province, and had passed a minimum of 14 days since the first vaccine dose or at least 7 days since the second or third dose at the time of infection or study entry.¹⁶ Additionally, participants were required to have accessible demographic and vaccination information. However, individuals whose vaccination status could not be verified through the integrated health information systems or whose infection occurred before the specified post-vaccination intervals were excluded from the study.

Risk of Bias

Multiple strategies were implemented to minimize potential sources of bias. In addition, misclassification bias was mitigated through deterministic linkage between the SIB integrated health system and the MCMC registry, enabling precise identification of vaccination and hospitalization status. Likewise, selection bias was differently managed among study groups; hospitalized and outpatient participants were chosen via simple random sampling from eligible registry populations in order to avoid convenience sampling, whereas healthy vaccinated individuals were enrolled through community-based convenience sampling owing to the lack of a centralized registry. To partially address this bias, recruitment was conducted across several healthcare facilities, and strict eligibility criteria were enforced. Further, non-response bias was minimized by employing a predefined substitution protocol, wherein participants who could not be contacted after five attempts were replaced by randomly selecting from the same eligible sampling frame within each study group; thus, substitutions were determined via random reselection rather than subjective judgment. Furthermore, information bias was reduced through using standardized questionnaires and trained interviewers, while analytical bias was addressed by applying penalized regression methods to accommodate sparse data and separation.

Data Collection Procedures

Data were collected in 2024 using linked administrative databases and supplementary checklist-based methods. Vaccination records were extracted from the national SIB database and linked with the provincial MCMC registry to

confirm vaccination status and identify COVID-19-related hospital admissions and outpatient visits.

Following the application of eligibility criteria and database cleaning, participants for the hospitalized and outpatient groups were selected by simple random sampling from eligible registry populations. Additionally, supplementary data not available in administrative records (e.g., occupational status and adherence to preventive health protocols) were collected through structured telephone interviews. Moreover, contact information was obtained from hospital medical records, and when necessary, direct contact numbers were requested from family members or companions. Likewise, participants unreachable after five telephone attempts were classified as non-responders and replaced through random reselection from the eligible sampling frame.

Similarly, healthy controls were separately recruited, as no centralized registry existed for vaccinated individuals without prior COVID-19 infection. Community-based convenience sampling was also employed to identify eligible participants from healthcare facilities across counties in Chaharmahal and Bakhtiari Province. For this group, data were collected using a structured checklist that was administered during face-to-face interviews, capturing demographic characteristics, vaccination and infection history, occupational exposures, adherence to preventive measures, and underlying medical conditions. In addition, eligibility criteria for the healthy control group included provincial residence, confirmed vaccination history, and self-reported absence of prior COVID-19 infection.

In Ardal and Lordegan, data were collected by a trained research assistant, while in the remaining counties, the principal investigator was responsible for this process. Ultimately, standardized procedures and instruments were implemented across all sites to ensure consistency and minimize information bias.

Statistical Methods

Statistical analyses were conducted using Stata, version 17. Descriptive statistics for continuous variables were presented as means and standard deviations, while categorical variables were summarized as frequencies and percentages across hospitalized patients, outpatients, and healthy individuals. In addition, the primary case group comprised hospitalized vaccinated patients ($n=260$), with two control groups consisting of outpatient vaccinated patients ($n=130$) and vaccinated healthy individuals without a history of COVID-19 infection ($n=130$). Moreover, binary analyses included comparisons between hospitalized and healthy individuals (390 participants), as well as between hospitalized and non-hospitalized individuals (520 participants, including both outpatients and healthy controls). Additionally, associations between study variables and hospitalization were evaluated using univariate and multivariable logistic regression models. Further, penalized logistic regression was employed in instances of sparse data or separation. Ordinal logistic regression was also utilized to assess associations with

the three-level outcome variable (healthy, outpatient, and hospitalized). Furthermore, Cox proportional hazards regression models were applied to evaluate infection-free survival time following vaccination. Likewise, Firth's penalized maximum likelihood logistic regression was used to address small-sample bias and separation caused by zero-cell counts in subgroups of the "previous infection" variable in the 390-participant dataset. Similarly, generalized ordinal logistic regression models were employed for ordinal regression analyses, allowing the estimation of partial proportional odds models when the proportional odds assumption was violated. For Cox regression, extended Cox models were utilized, and the proportional hazard assumption was assessed using Schoenfeld residuals. Variables that violated this assumption were modeled as time-varying covariates in order to permit interaction with time and ensure accurate hazard ratio estimation.

Results

Descriptive Analysis

The mean participant age was 42.9 ± 15.3 years, reflecting considerable age variability. Further, the gender distribution was nearly equal. Approximately 35% of participants resided in the provincial capital, with the remainder living in other cities. Furthermore, the majority of participants (87.9%) reported no prior history of COVID-19 infection (Table 1). The distribution of the main study variables is tabulated in Table 1.

Based on the findings (Figure 1-A), the mean interval between the last vaccine dose and subsequent infection was longer among hospitalized patients (170 days) compared to outpatients (120 days). Similarly, the mean interval between the first vaccine dose and infection was 288 days for hospitalized patients and 246 days for outpatients (Figure 1-B). In addition, increasing the number of vaccine doses was associated with longer infection-free intervals in both groups, with the most pronounced effects observed after the first and second doses and minimal differences following the third and fourth doses (Figures 1-A and 1-B).

Logistic Regression Analyses: Sample 1 (n = 390)

Univariate Analysis

Older age was associated with an increased likelihood of hospitalization, whereas individuals aged 30–54 years had lower odds than the 7–29-year reference cohort. Moreover, male gender was significantly linked to a reduced risk of hospitalization. Furthermore, homologous and heterologous booster vaccination regimens were related to diminished odds of hospitalization in univariate analysis. In comparison to AstraZeneca, Sinopharm, and other vaccine types were associated with greater odds of hospitalization. Finally, there was an association between an increase in the number of administered vaccine doses and a lower risk of hospitalization (Table 2).

Multivariable Analysis

After adjusting for potential confounders, age > 55 years remained substantially related to an increased risk of

hospitalization, while male gender continued to exhibit a protective effect. Additionally, healthcare workers demonstrated significantly lower odds of hospitalization compared to the reference occupational group. In the adjusted model, vaccine type, booster status, mask usage, alcohol consumption, and number of vaccine doses were not markedly associated with hospitalization. Likewise, estimates related to prior COVID-19 infection were unstable due to the absence of previous infection among healthy participants (Table 2).

Logistic Regression Analyses: Sample 2 (n = 520)

Univariate Analysis

Univariate analysis indicated that advancing age was associated with an increased risk of hospitalization, although individuals aged 30–54 years had lower odds of hospitalization compared to younger participants. Further, male gender, residence in the provincial center, and a history of previous COVID-19 infection were linked to reduced hospitalization risk. Similarly, booster vaccination and a greater number of vaccine doses were related to protective effects. When compared to recipients of the AstraZeneca vaccine, individuals vaccinated with Sinopharm or other vaccine types demonstrated higher odds of hospitalization. Likewise, within occupational categories, unemployed individuals with high exposure were at greater risk of hospitalization (Table 3).

Multivariable Analysis

In the multivariable model, being aged 30–54 years, male gender, and a history of previous COVID-19 infection remained significantly associated with reduced odds of hospitalization. In addition, vaccination with Sinopharm or other vaccines, compared with AstraZeneca, was related to substantially higher odds of hospitalization. High-exposure unemployed participants also exhibited increased risk of hospitalization. Nonetheless, no significant associations were observed for booster vaccination status, mask use, alcohol consumption, number of vaccine doses, or presence of comorbidities (Table 3).

Ordinal Logistic Regression

Ordinal logistic regression analysis was conducted with a three-level outcome variable (hospitalized, outpatient, and healthy). Individuals over 55 years of age exhibited remarkably greater odds of experiencing more severe disease, whereas those aged 30–54 years demonstrated reduced odds relative to the 7–29-year reference group. Moreover, male gender and employment in healthcare were associated with lower odds of hospitalization or outpatient infection. In the adjusted ordinal model, most vaccination-related variables were not significantly related to disease severity (Table 4).

Cox Regression (Time-to-Infection Analysis)

Cox regression has been used to assess the association of each variable with infection-free time. While the infection-free time was considered to be from the time of the last dose

Table 1. Descriptive Characteristics of Study Variables in Three Groups: Inpatient, Outpatient, and Healthy

Variable	Category	Healthy n = 130	Outpatient n = 130	Hospitalized n = 260	Total N = 520
		Mean ± SD/n (%)	Mean ± SD/n (%)	Mean ± SD/n (%)	Mean ± SD/n (%)
Age (years)	Mean ± SD	38.3 ± 8.8	43.5 ± 14.1	45.0 ± 17.8	42.9 ± 15.3
Gender	Female	48 (36.9)	62 (47.7)	149 (57.3)	259 (49.8)
	Male	82 (63.1)	68 (52.3)	111 (42.7)	261 (50.2)
Residence	Shahrekord (provincial capital)	53 (40.8)	52 (40.0)	75 (28.8)	180 (34.6)
	Other cities	77 (59.2)	78 (60.0)	185 (71.2)	340 (65.4)
History of COVID-19	No	130 (100.0)	76 (58.5)	251 (96.5)	457 (87.9)
	Yes	0 (0.0)	54 (41.5)	9 (3.5)	63 (12.1)
Vaccination status	Only doses 1 and 2	72 (55.4)	67 (51.5)	178 (68.5)	317 (61.0)
	Homologous boosters	45 (34.6)	40 (30.8)	65 (25.0)	150 (28.9)
	Heterologous boosters	13 (10.0)	23 (17.7)	17 (6.5)	53 (10.2)
Vaccine type	AstraZeneca	16 (12.3)	24 (18.5)	16 (6.2)	56 (10.8)
	Sinopharm	101 (77.7)	87 (66.9)	213 (81.9)	401 (77.1)
	Other	13 (10.0)	19 (14.6)	31 (11.9)	63 (12.1)
Number of doses	1 dose	13 (10.0)	15 (11.5)	19 (7.3)	47 (9.0)
	2 doses	59 (45.4)	52 (40.0)	159 (61.2)	270 (51.9)
	3 doses	47 (36.2)	47 (36.2)	72 (27.7)	166 (31.9)
	4 doses	11 (8.5)	16 (12.3)	10 (3.8)	37 (7.1)
Occupation/exposure	Unemployed, low exposure	20 (15.4)	22 (16.9)	33 (12.7)	75 (14.4)
	Unemployed, high exposure	19 (14.6)	23 (17.7)	62 (23.8)	104 (20.0)
	Healthcare workers	21 (16.2)	6 (4.6)	16 (6.2)	43 (8.3)
	Employed, high exposure	33 (25.4)	33 (25.4)	50 (19.2)	116 (22.3)
	Employed, low exposure	37 (28.5)	46 (35.4)	99 (38.1)	182 (35.0)
Mask use during the pandemic	Never	1 (0.8)	3 (2.3)	6 (2.3)	10 (1.9)
	Sometimes	15 (11.5)	20 (15.4)	43 (16.5)	78 (15.0)
	Often	45 (34.6)	47 (36.2)	68 (26.2)	160 (30.8)
	Always	69 (53.1)	60 (46.2)	143 (55.0)	272 (52.3)
Alcohol use during the pandemic	Never	4 (3.1)	11 (8.5)	14 (5.4)	29 (5.6)
	Sometimes	35 (26.9)	38 (29.2)	66 (25.4)	139 (26.7)
	Often	38 (29.2)	44 (33.8)	80 (30.8)	162 (31.2)
	Always	53 (40.8)	37 (28.5)	100 (38.5)	190 (36.5)
Comorbidities	No	120 (92.3)	104 (80.0)	238 (91.5)	462 (88.8)
	Yes	10 (7.7)	26 (20.0)	22 (8.5)	58 (11.2)

Note. SD: Standard deviation; COVID-19: Coronavirus disease 2019.

of vaccine, the hazard ratio in the variable of history of infection increased over time and changed from a variable with a protective effect to a variable with a risk factor effect ($P=0.000$, confidence interval [CI]: 0.00–0.99 $n=390$, Table 5). This trend has been decreasing and significant for the hazard ratio of the variables of the third and fourth dose status compared to the first and second doses and underlying diseases ($P=0.000$, CI: 0.00–1.99; $P=0.035$, CI: 0.00–1.99; $P=0.002$, CI: 0.00–1.98).

The same relationship was examined for a sample of 520, and the results (Table 6) revealed that the effect of the variable of underlying diseases and the status of the third and fourth doses was significant and decreasing over time ($P=0.014$, CI: 0.001–0.99; $P=0.000$, CI: 0.001–0.99; $P=0.025$, CI: 0.001–0.99). Due to the aforementioned reasons related to calculating the interval from vaccination

to the occurrence of infection and the cumulative effect of vaccines on the occurrence of the outcome, both of these analyses were performed using the Cox regression method and based on the time interval from the first vaccination to the occurrence of infection as an inpatient or an outpatient.

For the sample of 390, history of infection was transformed from a variable with a protective effect to a risk factor ($P=0.041$, CI: 1.00–1.01), and vaccine dose transformed into a nearly ineffective variable ($P=0.000$, CI: 1.00–1.01).

According to the data in Table 7, For the sample of 520 and based on the time free from infection since the first vaccine injection, only the vaccine dose transformed over time from a variable with a protective effect to a nearly ineffective variable ($P=0.000$, CI: 1.00–1.01, Table 8). In the Cox analysis, the median follow-up time was 275 and

Table 2. Association of Variables With the Incidence of Hospitalization due to COVID-19, Univariate and Multiple Logistic Regression in 390 People

Variables	Category	Univariate OR (95% CI)	P-Value	Multivariable OR (95% CI)	P-Value
Age (continuous)		1.03 (1.02-1.05)	<0.001	-	-
Age groups (7–29 years)	30–54 years	0.44 (0.24-0.80)	0.008	0.62 (0.32-1.20)	0.155
	> 55 years	4.40 (1.62-1.92)	0.004	11.08 (3.38-36.31)	<0.001
Gender (Female)		0.44 (0.28-0.67)	<0.001	0.45 (0.28-0.74)	0.002
Residence (other cities)		0.59 (0.38-0.92)	0.019	0.66 (0.39-1.10)	0.112
History of COVID-19 infection		9.86 (0.57-170.71)	0.116	292.71 (10.43-8215.16)	0.001
Booster status (only doses 1 and 2)	Homologous booster	0.61 (0.38-0.97)	0.036	0.48 (0.17-1.37)	0.171
	Heterologous booster	0.40 (0.18-0.91)	0.029	0.36 (0.08-1.59)	0.178
Vaccine type (AstraZeneca)	Sinopharm	2.38 (0.92-6.16)	0.073	1.29 (0.42-3.91)	0.656
	Other vaccines	2.11 (1.01-4.39)	0.046	2.02 (0.86-4.73)	0.104
Number of vaccine doses		0.74 (0.55-1.00)	0.048	1.03 (0.50-2.12)	0.928
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.98 (0.93-4.21)	0.077	1.69 (0.72-3.97)	0.231
	Healthcare workers	0.46 (0.20-1.09)	0.077	0.22 (0.07-0.64)	0.006
	Employed, high exposure	0.92 (0.45-1.86)	0.813	0.90 (0.40-2.01)	0.797
	Employed, low exposure	1.62 (0.83-3.17)	0.158	1.48 (0.69-3.17)	0.313
Mask use		0.99 (0.75-1.30)	0.926	0.95 (0.68-1.34)	0.785
Alcohol use		0.97 (0.76-1.23)	0.807	1.06 (0.78-1.44)	0.711
Comorbidities		1.11 (0.51-2.42)	0.794	0.24 (0.08-0.72)	0.011

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; OR: Odds ratio.

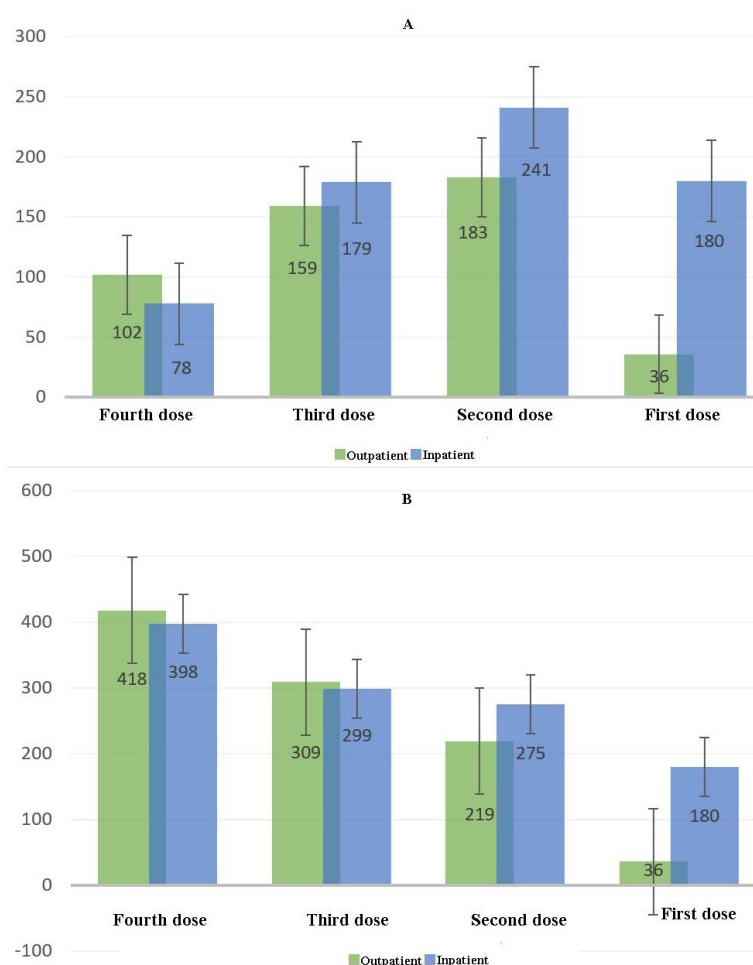


Figure. (1-A) Mean Time Interval From Last Dose of Vaccine to Disease Onset in Outpatient and Inpatient Groups (Days) and **(1-B)** Mean Time Interval From First Dose of Vaccine to Disease Onset in Outpatient and Inpatient Groups (Days)

Table 3. Relationship of Variables With Incidence of Hospitalization due to COVID-19, Univariate and Multiple Logistic Regression in 520 Individuals

Variables	Category	Univariate OR (95% CI)	P-Value	Multivariable OR (95% CI)	P-Value
Age		1.02 (1.01-1.03)	0.002	-	-
Age groups (7–29 years)	30–54 years	0.41 (0.24-0.67)	0.001	0.47 (0.27-0.83)	0.009
	> 55 years	0.32 (0.72-2.44)	0.370	1.60 (0.80-3.21)	0.184
Gender (Female)		0.55 (0.39-0.77)	0.001	0.49 (0.33-0.72)	<0.001
Residence (other cities)		0.60 (0.42-0.86)	0.006	0.75 (0.50-1.15)	0.186
History of COVID-19 infection		0.14 (0.07-0.28)	<0.001	0.13 (0.06-0.29)	<0.001
Booster status (only doses 1 and 2)	Homologous booster	0.60 (0.40-0.88)	0.010	0.56 (0.25-1.26)	0.159
	Heterologous booster	0.37 (0.20-0.68)	0.002	0.44 (0.15-1.30)	0.137
Vaccine type (AstraZeneca)	Sinopharm	2.83 (1.54-5.22)	0.001	2.40 (1.21-4.78)	0.012
	Other vaccines	2.42 (1.13-5.19)	0.023	2.54 (1.06-6.06)	0.036
Number of vaccine doses		0.72 (0.57-0.91)	0.006	1.06 (0.62-1.82)	0.823
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.88 (1.03-3.43)	0.040	2.07 (1.05-4.10)	0.036
	Healthcare workers	0.75 (0.35-1.63)	0.472	0.92 (0.39-2.15)	0.844
	Employed, high exposure (banking)	0.96 (0.54-1.73)	0.903	1.10 (0.57-2.13)	0.769
	Employed, low exposure	1.52 (0.88-2.61)	0.131	1.63 (0.89-3.00)	0.115
Mask use		1.01 (0.82-1.26)	0.913	0.88 (0.65-1.20)	0.429
Alcohol use		1.09 (0.90-1.31)	0.368	1.15 (0.88-1.50)	0.300
Comorbidities		0.58 (0.33-1.01)	0.053	0.82 (0.41-1.64)	0.580

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; OR: Odds ratio.

Table 4. Association of Variables With the Incidence of Hospitalization due to COVID-19, Ordinal Logistic Regression

Variable		OR	P-Value	95% CI
Age group (7–29 years)	30–54	0.58	0.044	0.35-0.99
	> 55	4.77	0.002	1.80-12.61
Gender		0.51	0.000	0.36-0.73
Residence (other cities)		0.74	0.100	0.51-1.06
History of COVID-19 infection		0.72	0.179	0.44-1.16
Booster status (only doses 1 and 2)	Homologous booster	0.55	0.098	0.27-1.12
	Heterologous booster	0.91	0.849	0.34-2.42
Vaccine type (AstraZeneca)				
Sinopharm		0.89	0.704	0.48-1.64
Other vaccines		1.99	0.069	0.95-4.18
Number of vaccine doses		1.12	0.643	0.70-1.77
Occupation/exposure (unemployed/low exposure)	Unemployed, high exposure	1.78	0.061	0.97-3.26
	Healthcare workers	0.43	0.037	0.19-0.95
	Employed, high exposure	1.11	0.728	0.63-1.96
	Employed, low exposure	1.56	0.104	0.91-2.66
Mask use		0.85	0.230	0.65-1.11
Alcohol use		0.88	0.330	0.67-1.14
Comorbidities		1.60	0.224	0.75-3.39

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; OR: Odds ratio.

354 days from the last and first injection, respectively, in the sample of 390 people, and 325 days from the last injection and 329 days from the first injection in the sample of 520 individuals. In general, the time interval from the last vaccine injection to the end of the study was 8–879 days, and the time interval from the first injection to the end of the study was 8–1110 days.

Discussion

In this study, increasing age was found to be a powerful predictor of hospitalization following COVID-19 vaccination in Chaharmahal and Bakhtiari Province. The mean age of hospitalized patients was 45.0 years, compared with 43.5 years among outpatients and 38.3 years among healthy individuals. This index was approximately 62 years in the study by Menni et al, reporting it among individuals

Table 5. The Relationship Between the Time Interval Between the Last Vaccine Injection and Hospitalization and the Incidence of Hospitalization due to COVID-19 in 390 Individuals

Variable		HR	P-Value	95% CI
Age group (7–29 years)	30–54	0.77	0.123	0.55-1.08
	> 55	2.53	0.000	1.72-3.71
Gender (Female)		0.71	0.009	0.54-0.92
Residence (other cities)		0.79	0.103	0.59-1.05
History of COVID-19 infection		0.20	0.155	0.02-1.82
Booster status (only doses 1 and 2)	Homologous booster	3.54	0.002	1.61-7.78
	Heterologous booster	3.43	0.062	0.94-12.51
Vaccine type (AstraZeneca)	Sinopharm	1.13	0.711	0.60-2.11
	Other vaccines	1.47	0.151	0.87-2.48
Number of vaccine doses		0.85	0.442	0.57-1.28
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.39	0.138	0.90-2.14
	Occupational therapy staff	0.50	0.044	0.26-0.98
	Employed, high exposure	1.14	0.560	0.73-1.78
	Employed, low exposure	1.29	0.217	0.86-1.93
Mask use		1.04	0.602	0.90-1.20
Alcohol use		0.97	0.719	0.81-1.16
Comorbidities		5.78	0.001	2.04-16.36
Variable (time-varying)	History of COVID-19 infection	1.02	0.001	1.01-1.03
	Comorbidities	0.99	0.002	0.98-1.00
Booster status (only doses 1 and 2)	Homologous booster	0.99	0.000	0.99-1.00
	Heterologous booster	0.99	0.035	0.99-1.00

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; HR: Hazard ratio.

Table 6. The Relationship Between the Variable Time Interval Between the Last Vaccine Injection and Hospitalization With the Incidence of Hospitalization due to COVID-19 in 520 People

Variable		HR	P- Value	95% CI
Age group (7–29 years)	30–54	0.74	0.081	0.53-1.04
	> 55	2.35	0.000	1.60-3.45
Gender (Female)		0.68	0.003	0.53-0.88
Residence (other cities)		0.86	0.299	0.65-1.14
History of COVID-19 infection (baseline)		0.49	0.054	0.24-1.01
Booster status (baseline, only doses 1 and 2)	Homologous booster	3.65	0.001	1.69-7.91
	Heterologous booster	3.47	0.032	1.11-10.85
Vaccine type (AstraZeneca)	Sinopharm	1.66	0.059	0.98-2.79
	Other vaccines	1.44	0.246	0.78-2.67
Number of vaccine doses		0.77	0.187	0.53-1.13
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.46	0.082	0.95-2.25
	Occupational therapy staff	0.78	0.436	0.42-1.45
	Employed, high exposure	1.19	0.435	0.76-1.86
	Employed, low exposure	1.40	0.097	0.94-2.09
Mask use		1.16	0.105	0.97-1.40
Alcohol use		0.80	0.031	0.65-0.98
Comorbidities (baseline)		3.75	0.002	1.61-8.73
Booster status (time-dependent, Ref.: only doses 1 and 2)	Homologous booster	0.99	0.000	0.99-1.00
	Heterologous booster	0.99	0.025	0.99-1.00
Comorbidities (time-dependent)		0.99	0.014	0.99-1.00

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; HR: Hazard ratio.

Table 7. The Relationship Between the Time Interval Between the First Dose of Vaccine and Hospitalization and the Incidence of Hospitalization due to COVID-19 in a Sample of 390

Variable		HR	P-Value	95% CI
Age group (7–29 years)	30–54	0.75	0.102	0.54-1.06
	>55	2.72	0.000	1.86-4.00
Gender (Female)		0.70	0.008	0.54-0.91
Residence (other cities)		0.78	0.094	0.58-1.04
History of COVID-19 infection (baseline)		0.74	0.814	0.06-8.69
Booster status (baseline, Ref.: only doses 1 and 2)	Homologous booster	0.89	0.684	0.52-1.54
	Heterologous booster	0.79	0.562	0.35-1.77
Vaccine type (AstraZeneca)	Sinopharm	1.51	0.211	0.79-2.90
	Other vaccines	1.91	0.023	1.10-3.33
Number of vaccine doses (baseline)		0.25	0.000	0.14-0.46
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.34	0.195	0.86-2.08
	Occupational therapy staff	0.59	0.110	0.31-1.13
	Employed, high exposure	1.16	0.517	0.74-1.81
	Employed, low exposure	1.34	0.154	0.90-2.02
Mask use		1.05	0.477	0.91-1.22
Alcohol use		0.91	0.287	0.76-1.08
Comorbidities (baseline)		0.76	0.372	0.41-1.39
History of COVID-19 infection (time-dependent)		1.01	0.041	1.00-1.01
Number of vaccine doses (time-dependent)		1.00	0.000	1.00-1.01

Note. CI: Confidence interval; COVID-19: Coronavirus disease 2019; HR: Hazard ratio.

Table 8. The Relationship Between the Variable Time Interval Between First Vaccine Injection and Hospitalization, and the Incidence of Hospitalization due to COVID-19 in 520 Individuals

Variable		HR	P-Value	95% CI
Age group (7–29 years)	30–54	0.72	0.060	0.51-1.01
	>55	2.34	0.000	1.59-3.45
Gender (Female)		0.67	0.002	0.52-0.87
Residence (other cities)		0.85	0.247	0.64-1.12
History of COVID-19 infection (baseline)		0.55	0.093	0.27-1.10
Booster status (baseline, ref: only doses 1 and 2)	Homologous booster	0.97	0.903	0.57-1.64
	Heterologous booster	0.77	0.502	0.36-1.65
Vaccine type (AstraZeneca)	Sinopharm	2.04	0.008	1.21-3.43
	Other vaccines	1.84	0.055	0.99-3.41
Number of vaccine doses (baseline)		0.20	0.000	0.11-0.35
Occupation/exposure (unemployed, low exposure)	Unemployed, high exposure	1.50	0.062	0.98-2.31
	Occupational therapy staff	0.83	0.550	0.45-1.53
	Employed, high exposure	1.23	0.363	0.79-1.92
	Employed, low exposure	1.43	0.081	0.96-2.13
Mask use		1.15	0.137	0.96-1.37
Alcohol use		0.81	0.037	0.66-0.99
Comorbidities (baseline)		1.16	0.520	0.73-1.85
Number of vaccine doses (time-dependent)		1.00	0.000	1.00-1.01

Note. COVID-19: Coronavirus disease 2019; CI: Confidence interval; HR: Hazard ratio.

who contracted COVID-19 only after vaccination, regardless of hospitalization status.¹⁷ In the study performed by Hippisley-Cox et al, this index was 77 years among hospitalized patients.¹⁸ A study conducted by Rzymiski et al, including people hospitalized for coronaviruses disease after receiving at least one dose of the vaccine, reported a mean age of 68 years.¹⁹ This is consistent with

the established mechanisms of immune aging, including reduced adaptive immune responsiveness, impaired memory B cell formation, and chronic mild inflammation, collectively reducing the durability of vaccine-induced protection. From a comparative perspective, despite differences in absolute age distributions across studies, the consistent direction and magnitude of associations

observed in multiple sources underscore that age-related immune decline remains a principal determinant of severe clinical outcomes, even in the post-vaccination era.

Male gender was consistently associated with a reduced risk of hospitalization across all analytical approaches. This observation contradicts the findings of the pre-vaccination period, when male gender was typically linked to poorer clinical outcomes, suggesting a possible alteration of gender-related risk gradients following widespread vaccination. One possible explanation is that vaccination may partially mitigate biological differences related to gender, or interact with behavioral and exposure patterns that vary by gender in the post-vaccination context. This finding contrasts with evidence from the pre-vaccination pandemic, where male gender was typically linked with worse COVID-19 outcomes, or some studies have reported a higher risk of hospitalization and death after vaccination in men.²⁰⁻²² These results suggest that gender-based risk stratification in the post-vaccination era may fundamentally differ from early pandemic models. The finding of several studies are consistent with those of our study, indicating a reduced risk of hospitalization and COVID-19 severity among males.^{23,24}

Moreover, there was an association between prior COVID-19 infection and hospitalization outcomes. However, this result should be interpreted with caution, as none of the healthy participants reported prior infection, resulting in complete separation and unstable odds ratio estimates in the regression models. As a result, the extremely high odds ratio does not provide a reliable measure of effect size. While prior infection may confer temporary immunity, the current data do not permit a stable estimation of its independent association with hospitalization risk. However, the durability of this protection and its interaction with vaccine-induced immunity appear to be highly contingent upon the interval since exposure and the specific circulating viral variants. According to investigations, the odds ratio of experiencing severe adverse events is higher among individuals with a history of COVID-19 before vaccination than among those without such a history.²⁵ Moreover, Li et al found that prior severe acute respiratory syndrome coronavirus 2 infection, independent of the administered vaccine platform, provided greater protective immunity against sudden infection after vaccination.²⁶

Moreover, our findings confirmed that increasing the vaccine dose reduces hospitalization for the disease, although this effect disappeared after controlling for confounders. This attenuation demonstrates that vaccine-induced protection exhibits temporal dynamics, with immunity waning over time rather than following a strictly cumulative dose-response pattern. In a comparative analysis of clinical outcomes during the early phase of the pandemic, COVID-19 vaccination status was found to be an important protective factor that was independently associated with the reduced risks of hospitalization and mortality.²⁷ As shown in the time-variable Cox models, vaccine dose changed from a protective variable to a nearly ineffective variable over time. These findings corroborate

the immunological evidence of a decline in neutralizing antibodies and a decrease in the memory response months after vaccination. This pattern provides strong epidemiological evidence of reduced vaccine-induced immunity, particularly against severe outcomes, supporting the interpretation that protection is temporally structured rather than simply dose-structured. One study revealed that vaccination decreased the risk of severe outcomes, including the need for invasive ventilation and in-hospital death, by about 50% within 12 months. Similarly, booster doses within six months provided comparable protection, sharply lowering the risk of in-hospital mortality.²⁸

Additionally, our study results indicated that people vaccinated with Sinopharm or other non-AstraZeneca vaccines consistently showed higher risks of hospitalization, with these effects being significant in the second sample and in the ordinal models. Nonetheless, these findings should be considered indicative rather than causal, as they may be subject to confounding by indication, temporal variations in vaccine deployment, and differences in population characteristics among vaccine groups.

Likewise, the results of a study demonstrated that COVID-19 vaccination reduced disease severity and hospitalization, and that the Pfizer/BioNTech vaccine had the highest effect on the B.1.1.7 and B.1.351 variants among other vaccines.⁷

The findings revealed that occupations with high public exposure (e.g., banking) were associated with a lower likelihood of COVID-19 hospitalization. Healthcare workers consistently indicated a protective effect in multivariate and ordinal models, likely reflecting higher vaccination coverage, better adherence to infection control protocols, and earlier access to protective resources. This could be due to their priority in the immunization and vaccination process and greater adherence to protocols among these individuals. In contrast, unemployed individuals with high exposure and employed individuals with low exposure displayed higher risks in some models, suggesting that informal exposure patterns and socioeconomic vulnerability may increase formal occupational risk classifications. Agrawal et al, examining high-risk occupations as a risk factor for COVID-19 hospitalization following vaccination, found that people in high-risk jobs who were tested frequently (≥ 10 times) had more than double the likelihood of COVID-19 infection than those tested less often, reflecting higher exposure or risk in these occupational settings.²⁹ Likewise, Bonde et al investigated the effect of occupation on hospitalization and concluded that some workers (e.g., physicians and laboratory workers) were at high risk of hospitalization, whereas midwives and physiotherapists did not face a comparable level of risk.³⁰

In this study, neither mask use nor alcohol consumption showed a consistent or significant association with the risk of hospitalization across models. However, some studies reported that mask use can significantly reduce the risk of infection, regardless of age. In general, to assess the status of masks and their impact on disease

transmission, a combination of factors, including population effects, transmission characteristics, source control, and sociological considerations, must be taken into consideration.^{31, 32} This issue likely reflects limitations in self-reported behavioral data, misclassification bias, and the inability to capture the quality, consistency, and context of preventive behaviors. Although these findings do not negate the protective value of masks at the population level, they highlight methodological challenges in accurately measuring behavioral exposures in observational studies. At the individual level, these measures are especially vulnerable to misclassification, potentially attenuating true associations, even when effectiveness at the population level is well established.

Comorbidities demonstrated inconsistent patterns across models. In some multivariate and Cox analyses, comorbidities were associated with increased hospitalization risk, whereas in other analyses, they appeared protective or neutral. Based on the findings of one study, patients with five or more comorbidities were 4.24 times more likely (95% CI: 3.34–5.39) to experience severe COVID-19 outcomes.²⁹ Research has shown that while comorbidity can be a determining factor in hospitalization and disease severity, the type of disease is an influential factor as well.³³ These inconsistencies suggest that comorbidities may act through complex mediating pathways, rather than as simple independent risk factors.

Limitations of the Study

This study is subject to several limitations. Although multivariable models were employed, residual confounding may persist due to unmeasured variables, such as smoking, detailed patterns of alcohol consumption, and socioeconomic status. Furthermore, potential confounding among correlated variables (e.g., occupation, vaccination type, and exposure level) cannot be entirely excluded. In addition, interaction effects between key variables (e.g., age, gender, vaccination status, and comorbidities) were not formally examined, owing to limited statistical power within certain strata; consequently, possible effect modification may be present but was not quantified in this study. Likewise, the study's restriction to a single province may have limited the generalizability of our findings. Additionally, migration or changes in residence were not comprehensively tracked, which could introduce information bias. Finally, the small number of participants with specific comorbidities precluded subgroup analyses by disease type, necessitating aggregation into a single variable.

Conclusion

The findings of this study indicated that post-vaccination COVID-19 hospitalization cannot be sufficiently attributed to isolated risk factors; instead, it results from a complex interplay among host susceptibility, exposure context, and the temporal dynamics of vaccine-induced immunity. The findings suggest that risk stratification following vaccination should move beyond static demographic

categorizations toward integrated models that account for time since vaccination, intensity of exposure, and baseline health status.

From a public health perspective, these findings reveal the necessity of dynamic rather than static prioritization strategies. Specifically, the waning of vaccine-induced protection over time indicates that immunity is not permanent and should be bolstered through timely booster programs targeted at high-risk populations, rather than based on uniform, population-wide assumptions. Additionally, the heterogeneity observed across occupational and clinical subgroups suggests that exposure classification based solely on job title is inadequate for informing prevention strategies, representing the need for more nuanced exposure assessment frameworks.

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Authors' Contribution

Conceptualization: Kosar Farhadi Babadi and Seyed Saeed Hashemi Nazari
Data Curation: Amir Kavousi
Formal Analysis: Amir Kavousi, Seyed Saeed Hashemi Nazari
Funding Acquisition: Seyed Saeed Hashemi Nazari, Koorosh Etemad
Investigation: Kosar Farhadi Babadi
Methodology: Ali Ahmadi
Project Administration: Kosar Farhadi Babadi
Resources: Seyed Saeed Hashemi Nazari
Software: Ali Ahmadi
Supervision: Seyed Saeed Hashemi Nazari
Validation: Kosar Farhadi Babadi
Visualization: Kosar Farhadi Babadi and Seyed Saeed Hashemi Nazari
Writing–Original Draft: Kosar Farhadi Babadi, Mohadeseh Karimian
Writing–Review & Editing: All authors

Competing Interests

The authors declared there is no conflict of interests.

Ethical Approval

None of the data were reported with the individual characteristics of participants. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1402.020).

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