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Original Article

Estimating the Causal Effect of Two-Dose COVID-19 Vaccination on Hospitalization Rates

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Abstract

Background and aims: COVID-19 remains a global health challenge, with vaccination crucial for reducing severe cases. This study evaluated a two-dose COVID-19 vaccine's effectiveness in lowering hospitalization rates using advanced statistical techniques. This study evaluated the efficacy of a two-dose COVID-19 vaccination regimen in reducing hospitalization rates by employing advanced statistical techniques to control confounding variables in the observational data.

Methods: A retrospective cohort study was conducted among individuals tested for COVID-19 at Mashhad University of Medical Sciences from March 21, 2021, to March 20, 2022. The study population comprised all individuals who underwent polymerase chain reaction testing for COVID-19 during this period. A census sampling method was employed, resulting in a final sample size of 306 630 individuals. The participants were classified as "vaccinated" if they received both doses and "unvaccinated" if they received none. Hospitalization was defined as COVID-19-related admissions occurring at least two weeks post-vaccination. The required data were collected from three databases, including the Sina Health Information System, the Healthcare Services Monitoring System, and the Hospital Information System. To create comparable groups, propensity score (PS) matching and weighting were utilized, and a logistic regression model was utilized to estimate the average treatment effect (ATE) of vaccination on hospitalization outcomes.

Results: Among the 306 630 patients included in the study, 104 115 (33.95%) were unvaccinated, while 202 515 (66.05%) were vaccinated. Overall, 29 458 patients (9.61%) were hospitalized, comprising 28,244 unvaccinated and 1214 vaccinated individuals. Vaccinated individuals exhibited significantly lower odds of hospitalization. The adjusted odds ratio for hospitalization was 0.72 (95% confidence interval [CI]: 0.68–0.76) when using PS weighting, 0.32 (95% CI: 0.30–0.34) with matching, and 0.34 (95% CI: 0.33–0.35) after adjusting for extreme weights.

Conclusion: The findings underscore the protective effects associated with a two-dose COVID-19 vaccination regimen and emphasize the significance of employing robust statistical methods in evaluating real-world data.

Keywords: Propensity score matching, Propensity score weighting, Causal effect, Observational study, Logistic regression

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Introduction

In the protracted global fight against COVID-19, vaccines have emerged as essential instruments for safeguarding public health and preventing widespread alarm. However, accurately assessing their effectiveness in real-world settings presents significant challenges, particularly within the framework of observational studies. Unlike randomized clinical trials, which feature systematic assignment of treatments, observational studies are inherently susceptible to confounding variables that can obscure the true effects of vaccination.[1,2]

Propensity score (PS) analysis has emerged as a powerful statistical tool for addressing the challenges posed by confounding variables in observational studies. This method calculates the probability of receiving a treatment, such as vaccination, based on observable characteristics. By creating comparable groups, PS analysis mitigates the impact of confounders, thereby facilitating more accurate assessments of vaccine effectiveness (VE) on hospitalization outcomes [3]. This study has focused on employing PS weighting and PS matching (PSM) to investigate the causal relationship between vaccination and hospitalization, with hospitalization following vaccination regarded as the outcome. By rigorously adjusting for potential confounders, it is aimed to provide precise estimates of the effects of vaccination, thus contributing to the development of more effective COVID-19 strategies.[1,4]

Our approach is grounded in a meticulous methodological framework and thorough data examination to expand the existing body of knowledge regarding the effectiveness of COVID-19 vaccines. The findings of this study are intended to support policymakers in formulating informed strategies to mitigate the transmission of COVID-19 and alleviate the health burdens associated with the virus. Through this detailed analysis, the study seeks to understand the impact of vaccines and strengthen the evidence base that informs public health decisions during the ongoing pandemic.

Materials and Methods

Data

This cohort study estimates the effect of COVID-19 vaccination on hospitalization rates, utilizing data from 306 630 individuals who received exactly two doses of the vaccine between March 21, 2021, and March 20, 2022, with the study commencing on February 9, 2021. The data were sourced from the Medical Care Monitoring Center, the National Infectious Disease Surveillance System, and imaging centers, with individual-level information linked through national identification numbers. The participants were categorized as “exposed” if they received both vaccine doses and “unexposed” if they received no vaccination during this period.

The timing of vaccination varied among the participants, but all were followed until the end of the study to monitor hospitalization outcomes. Hospitalization is defined as instances where individuals who tested positive for COVID-19 via polymerase chain reaction and were vaccinated at least two weeks prior were admitted to a hospital due to complications from the virus. The analysis only considers hospitalizations directly attributable to COVID-19 infection, excluding those that occurred prior to vaccination. It should be noted that individuals who had been hospitalized before receiving the vaccine were not included in the study.

The average interval between vaccination and hospitalization was 119 days (SD = 90), with a range from 19 to 300 days. Key variables included hospitalization due to COVID-19, the number of COVID-19 infections prior to vaccination, body mass index, age, gender, vaccination status, educational level, occupation, marital status, number of comorbidities, residence, and vaccination status. These variables were utilized to assess the impact of vaccination on hospitalization while accounting for potential confounding factors.

Study Design and Inclusion/Exclusion Criteria

For this cohort study, the inclusion criterion included participants who had undergone at least one COVID-19 test. On the other hand, the exclusion criteria applied to individuals residing outside the university’s jurisdiction or those vaccinated outside the specified timeframe. Subjects with an interval of less than two weeks between vaccination and outcome assessment were excluded as well. The participants were classified as “exposed” if they received two doses of the COVID-19 vaccine between March 21, 2021, and March 20, 2022, and as “unexposed” if they did not receive any vaccination during this period.

Statistical Methods

In this study, PS methods were utilized to control confounding factors and estimate treatment effects. Specifically, the logistic regression was employed to estimate the PS, which reflects the likelihood of receiving the treatment based on baseline characteristics.[5,6] The covariates included in the model were selected based on their relevance to treatment decisions and outcomes, ensuring alignment with our analytical objectives. The backdoor criterion was applied to identify and adjust for all potential confounders. Furthermore, variables were chosen based on prior studies, with a focus on those directly related to outcomes or associated with both outcomes and treatment decisions.[1] According to Austin, only confounders and variables related to the outcome, but not the treatment itself, should be included in the PS model. This approach enhances the accuracy of treatment effect estimates.[7] The calculation of the PS incorporated several variables, including age, gender, body mass index, marital status, education level, occupation, place of residence, number of comorbidities, number of clinical symptoms, and history of previous COVID-19 infections. Two key methodologies were used, including PSM and inverse probability of treatment weighting (IPTW). For PSM, matching was conducted based on PS values using full optimal matching with replacement, allowing each unvaccinated individual to be matched with multiple vaccinated individuals who had similar PSs. This approach maximizes the utilization of available data while ensuring a balance between the groups.[8] IPTW was utilized to create a pseudo-randomized sample by assigning weights to participants that are inversely proportional to their likelihood of receiving the treatment.[9]

In our study, in addition to the standard application of IPTW, the truncation of extreme weights was also implemented to enhance the robustness and reliability of the analysis.[9,10] This modification involved truncating the weights at the 1st and 99th percentiles. Specifically, weights exceeding the 99th percentile and those below the 1st percentile were capped. This approach was adopted to mitigate the influence of extreme weights, which can disproportionately affect the estimation process and potentially lead to biased results.[11,12]

Before estimating the average treatment effect (ATE), rigorous balance checks were conducted using absolute standardized differences. Any significant imbalance, defined as greater than 0.10, prompted a re-evaluation and adjustment of our matching or weighting strategies.[1,13] Subsequently, the ATE was estimated to assess the overall impact of the two-dose vaccination on the population. A logistic regression model was employed to analyze the specific effect of vaccination on hospitalization, which was essential for determining the vaccine's efficacy in preventing severe outcomes.[14,15] Although conditional logistic regression is typically preferred for matched data, we opted for standard logistic regression due to its ease of interpretation regarding ATEs and its widespread use in PS analyses. This approach, while assuming independence between groups, is justified by our matching strategy that incorporates replacement, ensuring robust comparisons between the treated and control groups.[7] All statistical analyses were conducted using R software (version 4.2.3), with a significance threshold set at 0.05. PS analysis was performed utilizing the MatchIt and WeightIt packages, which facilitated our matching and weighting strategies effectively.

Results

Of the total participants, 104 115 (33.95%) were unvaccinated, while 202 515 (66.05%) were vaccinated. Among the unvaccinated group, 28 244 individuals (27.12%) were hospitalized in contrast to 1214 individuals (0.60%) in the vaccinated group. Overall, 29 458 patients (9.61%) were hospitalized, whereas 277 172 of them (90.39%) were not hospitalized. Table 1 presents the baseline characteristics of vaccinated and unvaccinated groups prior to PSM. As anticipated, there were significant differences between the groups, highlighting the necessity of employing PS methods to achieve better comparability.

It is important to clarify that our analysis focused exclusively on patients who received the vaccine before their hospitalization status was recorded. Consequently, our data do not include individuals who were hospitalized prior to receiving the vaccine, ensuring that the assessment of the vaccine's impact is based solely on those who were vaccinated first.

After applying PSM with replacement, the absolute standardized mean differences (ASMD) were found to be below 0.1, indicating a favorable balance between the groups. The analysis included a total of 46,686 pairs in

Table 1. Baseline Characteristics of the Vaccinated and Unvaccinated Population

Parameters	Category	All (N = 306630)	Vaccinated (n = 104115)	Unvaccinated (n = 202515)	*P*-value
Age		33.77 ± 18.34	35.89 ± 14.46	29.67 ± 23.64	< 0.001
Body mass index		23.92 ± 10.90	25.10 ± 5.38	21.63 ± 16.91	
Gender	Female	159768 (52.10)	107127 (52.90)	52641 (50.56)	< 0.001
	Male	146862 (47.90)	95388 (47.10)	51471 (49.44)	
Marital status	Single	112073 (36.55)	53895 (26.60)	58214 (50.51)	< 0.001
	Married	194557 (63.45)	148656 (73.40)	45901 (44.09)	
Education	Cycle & below	169548 (55.29)	95142 (46.98)	74406 (71.47)	< 0.001
	Diploma & BA	127670 (41.64)	100547 (49.65)	27123 (26.05)	
	Master & PhD	5984 (1.95)	4905 (2.42)	1079 (1.04)	
	Others	3428 (1.12)	1921 (0.95)	1507 (1.45)	
Occupation	Unemployed	172226 (56.17)	100717 (49.73)	71509 (68.68)	< 0.001
	Employee	14292 (4.66)	12442 (6.14)	1850 (1.78)	
	Laborer	30112 (9.82)	24465 (12.08)	5647 (5.42)	
	Freelancer	44682 (14.57)	32859 (16.23)	11823 (11.36)	
	Others	45318 (14.78)	32032 (15.82)	13286 (12.76)	
Place of residence	Rural	65789 (21.46)	46520 (22.97)	19269 (18.51)	< 0.001
	Urban	240841 (78.54)	84846 (77.03)	202515 (81.49)	
Number of comorbidities	0	270559 (88.24)	183131 (90.43)	87428 (83.97)	< 0.001
	1	23671 (7.72)	14289 (7.06)	9382 (9.01)	
	2	10277 (3.35)	4664 (2.30)	5613 (5.39)	
	3 and more	2123 (0.69)	431 (0.21)	1692 (1.63)	
Number of clinical symptoms	0	278008 (90.67)	201333 (99.42)	76675 (73.64)	< 0.001
	1	12905 (4.21)	533 (0.26)	12372 (11.88)	
	2	10144 (3.31)	453 (0.22)	9691 (9.31)	
	3 and more	5573 (1.82)	196 (0.10)	5377(5.16)	
Number of COVID-19 infections	0	167441 (54.61)	116208 (57.38)	51233 (49.21)	< 0.001
	1	117133 (38.20)	74152 (36.62)	42981 (41.28)	
	2	15282 (4.98)	10115 (4.99)	5167 (4.96)	
	3	5205 (1.70)	1438 (0.71)	3767 (3.62)	
	4 and more	1569 (0.51)	602 (0.30)	967 (0.93)	

the vaccinated group and 26 871 pairs in the unvaccinated group. In contrast, IPTW demonstrated less balance, with ASMD values exceeding 0.1 for several covariates. Following the trimming of extreme weights in the IPTW analysis, the ASMD improved, with many values falling below 0.1, signifying a reduction in bias and an enhancement in balance (Table 2).

Average Treatment Effect on the Population

The logistic regression model was developed as the outcome model, with the estimation of the average vaccine effect in the population presented in Table 3.

Furthermore, the effect of vaccination was evaluated using both the ATE methodologies of PSM and IPTW. The results indicated that vaccinated patients had significantly lower odds of hospitalization compared to their unvaccinated counterparts, with an odds ratio (OR) of 0.32 (95% confidence interval [CI]: 0.30–0.34) and $P<0.001$, as determined by PSM. Similarly, in the IPTW analysis, vaccinated individuals also demonstrated significantly reduced odds of hospitalization, with an OR of 0.72 (95% CI: 0.68–0.76) and $P<0.001$.

Upon truncating extreme weights in the IPTW method, a significant change in the OR was observed, shifting to 0.34 (95% CI: 0.33–0.35) with $P<0.001$. This adjustment mitigates the influence of extreme weights on the outcome, thereby enhancing the reliability of the analysis.

Discussion

In this study, both PSM and IPTW were employed to assess the effectiveness of two-dose COVID-19 vaccinations in reducing hospitalizations. Initially, PSM demonstrated a superior covariate balance, indicating a VE of 68%. This result reflects PSM's capacity to approximate randomized trial conditions by ensuring comparability among matched individuals regarding observed covariates. In contrast, the initial VE estimate from IPTW was lower at 28%, primarily due to the influence of extreme weights. However, after truncating weights above the 99th percentile and below the 1st percentile, the effectiveness estimate from IPTW significantly improved to 66%, aligning more closely with the PSM findings. These results underscore the effectiveness of vaccination in mitigating the risk of hospitalization due to COVID-19 when analyzed through both PSM and IPTW methods. The consistent findings from both analyses, particularly after adjusting for extreme weights in the IPTW method, robustly indicate the protective effect of vaccination against COVID-19-related hospitalization, thereby affirming the public health benefits of widespread vaccination campaigns.

A study conducted in the United States underscores the critical need to monitor VE, particularly as variants such as Delta emerge. While the BNT162b2 vaccine continues to demonstrate high effectiveness against hospitalizations up to six months post-vaccination, a significant decline in effectiveness against infections over time has been observed, likely attributable to waning immunity. These findings suggest the potential necessity of booster doses to sustain elevated levels of protection. Furthermore, the application of standard logistic regression, supported by the matching strategy employed, yielded clear and interpretable estimates of ATEs.[16]

Based on the findings of another study performed in Germany, vaccination could protect against severe disease for at least six months, with a VE of 90% for individuals receiving two doses and 99% for those receiving three doses. Notably, the VE was significantly lower among adults with three or more pre-existing comorbidities compared to those with fewer comorbidities; however, this reduction in effectiveness was mitigated following the administration of a third dose.[17]

The findings revealed a significant decline in the effectiveness of the BNT162b2 vaccine against infections over time, despite its continued strong protection against hospitalizations. This observation underscores the necessity of booster doses to sustain elevated levels of protection. Additionally, logistic regression analysis provides reliable estimates of treatment effects, emphasizing the importance of adjusting vaccination strategies to address waning immunity and the emergence of new variants.[18]

Moreover, a study conducted in Canada reported that the effectiveness of a two-dose vaccination regimen against severe acute respiratory syndrome coronavirus

Table 2. ASMD Values Before and After Propensity Score Matching and Propensity Score Weighting

Variable	Before Matching	After Matching	After IPTW	After Truncating IPTW
Age	0.13	0.031	1.35	0.23
Gender	0.01	0.003	0.38	0.02
Occupation	0.25	0.042	0.88	0.18
Education	0.36	0.002	0.96	0.30
Marital status	0.21	0.005	0.70	0.21
Place of residence	0.04	0.008	0.22	0.04
Body mass index	0.19	0.005	0.22	0.20
Number of comorbidities	0.31	0.081	0.23	0.17
Number of clinical symptoms	0.68	0.075	0.01	0.54
Number of COVID-19 infections	0.12	0.053	0.55	0.20

Note. ASMD: Absolute standardized mean difference; IPTW: Inverse probability of treatment weighting.

Table 3. Comparative Analysis of IPTW and PSM Results for Hospitalization

Propensity Score Method	OR (95% CI)	*P*-value
PSM	0.32 (0.30–0.34)	<0.001
IPTW	0.72 (0.68–0.76)	<0.001
IPTW after truncating	0.34 (0.33–0.35)	<0.001

Note. PSM: Propensity score matching; IPTW: Inverse probability of treatment weighting; OR: Odds ratio; CI: Confidence interval.

2 hospitalization was 93% during the period of Delta variant dominance. However, among adolescents, the effectiveness was notably lower at 40% during the same period, potentially attributable to vaccine waning and the earlier vaccination dates observed in the United States compared to Ontario.[19]

A multistate analysis involving over 34000 cases of hospitalization for COVID-19–like illness among adults with immunocompromising conditions demonstrated that two doses of the monovalent mRNA COVID-19 vaccine had an effectiveness of 36% against COVID-19–associated hospitalization during a period of Omicron predominance.[20]

While our study highlights the efficacy of vaccination in reducing hospitalization rates, several limitations warrant consideration. Most notably, the absence of data on anti-spike antibody titers, oxygen saturation levels, and specific vaccine types restricts a comprehensive analysis of their impact on hospitalization outcomes. Additionally, the variability in VE, timing of vaccination, and host immune responses underscores the complexity of managing breakthrough infections. A significant limitation of our study is the lack of consideration for the specific COVID-19 variants affecting patients. Different variants may exhibit varying levels of virulence and resistance to vaccines, which could influence hospitalization rates. Future studies should incorporate variant-specific data to provide a more nuanced understanding of VE against distinct strains.

Furthermore, it is important to acknowledge the potential for unmeasured confounding factors in our analysis. While we accounted for several significant demographic and clinical variables, there may be additional unmeasured factors that could have influenced the observed outcomes. These factors might include socioeconomic status, access to healthcare, adherence to public health measures, and genetic factors that could affect susceptibility to or severity of COVID-19.

Conclusion

Our findings underscore the pivotal role of vaccination in mitigating COVID-19 hospitalization. PSM provides a robust methodological framework for assessing the impact of vaccination, emphasizing its significance in pandemic control efforts. Future research should prioritize the examination of vaccine characteristics, specific COVID-19 variants, and potential unmeasured confounding factors to optimize public health strategies in combating COVID-19. Additionally, efforts should be directed toward the collection and analysis of data on specific vaccine types and their effectiveness against various variants to facilitate more targeted vaccination strategies.

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Authors' Contribution

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Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

Ethical considerations for this study included obtaining approval from the Ethics Committee of Mashhad University of Medical Sciences (approval No. IR.MUMS.FHMPM.REC.1401.164).

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