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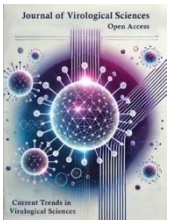

Review Article

Protection Conferred by Booster Vaccine Doses in Hospitalized Patients with COVID-19 during the SARS-CoV-2 Omicron BA.2 and BA.5 Epidemics from 2022 to 2023 in Greece

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Abstract

This review critically examines a study that evaluated the protective efficacy of coronavirus disease 2019 (COVID-19) vaccine booster doses in hospitalized patients amidst the dominance of the Omicron BA.2 and BA.5 subvariants in Greece, spanning from 2022 to 2023. The research meticulously employed multivariable logistic and negative binomial regression models to rigorously analyze the intricate associations between the number of vaccine doses administered, the incidence of adverse clinical outcomes, and the duration of hospital stay. The principal findings of this study compellingly demonstrate that patients who had received three or more vaccine doses exhibited significantly lower odds of experiencing adverse outcomes during their hospitalization and also benefited from a notably reduced length of hospital stay in comparison to their unvaccinated counterparts. This pivotal evidence underscores the crucial importance of booster doses in effectively mitigating the risk of severe COVID-19 outcomes among hospitalized patients, thereby alleviating the burden on healthcare facilities and improving patient prognosis.

Introduction

The global burden of COVID-19 on healthcare systems and societies worldwide remains a substantial concern, despite the observed decrease in morbidity and mortality rates since the initial emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019. The persistent impact of the disease can be largely attributed to the emergence of new, highly transmissible variants and subvariants, which possess the ability to evade the immunity conferred by both natural infection and existing vaccines, thereby posing a continued challenge to public health efforts. Furthermore, the suboptimal global vaccine uptake rates, even among individuals with high-risk comorbidities who stand to benefit the most from vaccination, contribute to the ongoing transmission and severity of COVID-19. In light of these evolving dynamics, real-world studies play a crucial role in continuously assessing the severity of COVID-19 and evaluating the effectiveness of booster vaccine doses in providing protection against emerging subvariants as they rise to dominance. The findings derived from such studies are of paramount importance as they directly inform the formulation of evidence-based vaccination policies and enable healthcare facilities to proactively develop preparedness strategies to effectively manage periods of peak healthcare demand and hospitalizations [1-3].

This review is focused on a study that meticulously investigated the clinical course of patients admitted to hospitals with COVID-19 and comprehensively evaluated the protection conferred by booster doses during the specific context of the Omicron BA.2 and BA.5 subvariant epidemics that occurred in Greece.

Literature Review

Previous research endeavors have consistently demonstrated the effectiveness of booster vaccine doses in conferring significant protection against severe COVID-19 outcomes, thereby playing a crucial role in mitigating the adverse consequences of the disease. A prior study conducted in Greece during the periods when the Delta and Omicron variants were dominant provided compelling evidence that booster doses offered substantial protection against a range of severe outcomes, including admission to an intensive care unit (ICU), the requirement for invasive mechanical ventilation, the occurrence of in-hospital death, and

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the experience of prolonged hospitalization. As SARS-CoV-2 continues to evolve and new subvariants emerge with altered transmissibility and virulence the continuous evaluation of vaccine effectiveness in real world settings becomes an indispensable component of public health surveillance Studies that specifically analyze the impact of booster doses during the periods of dominance of different subvariants provide invaluable insights that are essential for shaping and refining public health strategies, optimizing vaccination campaigns, and guiding clinical decision-making. The existing body of literature robustly emphasizes the critical need for ongoing research to continually inform and improve COVID-19 vaccination policies and healthcare management practices, ensuring that they remain responsive to the evolving challenges posed by the pandemic [4,5].

The study under review was meticulously designed as a prospective observational study, strategically conducted in Greece over a period from November 14, 2022, to May 28, 2023. This study design allowed for the systematic and longitudinal collection of data on patients admitted to hospitals with COVID-19, providing a comprehensive understanding of the disease's progression and the impact of vaccination. The study population comprised adult patients who were consecutively admitted to tertiary-care hospitals and had received a laboratory-confirmed diagnosis of COVID-19, ensuring the inclusion of a representative sample of hospitalized cases. To maintain the study's focus on community-acquired COVID-19 and to minimize confounding factors, specific exclusion criteria were applied. Patients younger than 18 years of age were excluded to concentrate on the adult population, those with asymptomatic SARS-CoV-2 infection were excluded as the study focused on symptomatic disease requiring hospitalization, and patients with healthcare-associated COVID-19 were excluded to isolate the impact of community-acquired infection. The data collection process was comprehensive, encompassing a wide range of variables relevant to the study objectives. These variables included:

- **Demographic characteristics:** Age and sex of the patients, providing essential context for understanding the study population.
- **Comorbidities:** The presence of chronic cardiovascular disease, diabetes mellitus, immunosuppression, malignancy, obesity, chronic neuromuscular disorder, chronic pulmonary disease, and chronic renal disease, all of which are known to influence COVID-19 severity.
- **COVID-19 vaccination history:** The number of vaccine doses received, the dates of administration, and the brand names of the vaccines, enabling the assessment of vaccine effectiveness.
- **History of SARS-CoV-2 infections:** Any prior confirmed SARS-CoV-2 infection before the current illness, allowing for the analysis of the impact of prior immunity.
- **Influenza vaccination history:** Vaccination status for seasonal influenza, considered as a potential confounding factor.
- **COVID-19-associated symptoms:** The date of onset, providing a timeline of the illness.
- **COVID-19 diagnosis:** The date of diagnosis, crucial for analyzing the time from diagnosis to admission.
- **Virus co-infection:** The presence of any concomitant infection with other respiratory viruses, which could affect the severity of COVID-19.

To ensure accuracy and reliability, the history of COVID-19 vaccination was retrieved from the national COVID-19 vaccination registry, a centralized and authoritative source of vaccination records. The statistical analysis involved a multi-faceted approach, employing a combination of descriptive and inferential statistics to comprehensively analyze the collected data.

- Descriptive analysis: This was conducted to characterize the overall study population and to provide a detailed description of the key variables of interest. Furthermore, the study population was stratified by the number of COVID-19 vaccine doses received at the time of the encounter (no vaccination, one to two doses, or three or more doses) to facilitate comparisons across vaccination groups. Similar descriptive analyses were also performed across all collected demographic, clinical, and contextual variables to separately assess unadjusted differences between individuals who experienced any adverse outcome and those who did not, as well as to examine differences in the average in-hospital length of stay.
- **Inferential statistics:** Chi-squared tests and analysis of variance (ANOVA) or Kruskal-Wallis tests were used, as appropriate, to assess statistically significant differences across subgroups for categorical and continuous variables, respectively. Univariate (unadjusted) and multivariable (adjusted) logistic regressions were then conducted to estimate the association between the occurrence of any adverse outcome during hospitalization (defined as ICU admission, invasive mechanical ventilation, or in-hospital mortality) and the number of COVID-19 vaccine doses at the time of admission. Similarly, univariate (unadjusted) and multivariable (adjusted) negative binomial regression models were employed to estimate the association between in-hospital length of stay (measured in days) and the number of COVID-19 vaccine doses at the time of admission, taking into account the expected right-skewed distribution of the length of stay data. To facilitate the interpretation of the negative binomial regression results, estimates were transformed using marginal effects to show differences in the average length of stay in days. Both multivariable models incorporated controls for a comprehensive set of potential confounding factors and characteristics, including age groups, sex, number of comorbidities, time from diagnosis to admission, influenza vaccination status, and past SARS-CoV-2 infection. Additionally, hospital and month fixed effects were included in the models to control for unobserved differences across hospitals and temporal variations. To account for potential correlations within hospitals, standard errors were clustered at the hospital level [6].

All data were meticulously collected and managed using Microsoft Excel, and all statistical analyses were performed using Stata version 18.0 (StataCorp, College Station, TX, USA), a robust statistical software package.

Results

During the 28-week study period, a total of 962 adult patients were consecutively admitted with laboratory-confirmed COVID-19 in the participating hospitals, providing a substantial dataset for analysis. The median age of these patients was 78 years, with an interquartile range (IQR) of 69-86 years, indicating that the study population comprised predominantly elderly individuals, a group particularly vulnerable to severe COVID-19. The mean length of hospital stay for all patients was 9.2 days, with a standard deviation (SD) of 8.4 days, reflecting the variability in the duration of hospitalization among individuals. The study meticulously documented the occurrence of adverse outcomes among the hospitalized patients, providing valuable insights into the severity of COVID-19 in this population [7,8].

- 39 patients (4.0%) required admission to the ICU, indicating the need for intensive care support.
- 44 patients (4.6%) received invasive mechanical ventilation, highlighting the occurrence of severe respiratory failure.
- 110 patients (11.4%) died in the hospital, underscoring the risk of mortality associated with severe COVID-19.
- Overall, 118 patients (12.3%) experienced at least one adverse outcome during their hospitalization, demonstrating the significant burden of severe illness in this population.

The study meticulously categorized the vaccination status of the patients, allowing for a detailed analysis of the impact of vaccination on clinical outcomes [9,10].

Discussion

The findings of this review highlight the protective effect of COVID-19 vaccine booster doses against adverse outcomes and prolonged hospitalization. The study indicates a shift in the profile of hospitalized COVID-19 patients, with older age and more comorbidities observed in the 2022-2023 period compared to the previous season. Despite this vulnerable patient profile, outcomes improved, suggesting the positive impact of vaccination. However, the study also identified delayed hospital admission as a risk factor for adverse outcomes, raising concerns about barriers to healthcare access. The study acknowledges limitations, including the small number of severe outcome cases and the lack of data on specific anti-COVID-19 treatments.

Conclusion

The reviewed study provides evidence that booster doses of COVID-19 vaccines offer significant protection against adverse outcomes and reduce the length of hospital stay for hospitalized patients. The changing profile of hospitalized patients, with increased age and comorbidities, underscores the importance of vaccination strategies. These findings can inform public health policies and healthcare practices to mitigate the impact of COVID-19.

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