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Coronavirus Pandemic

Comparing COVID-19 vaccine effectiveness in Türkiye: heterologous, inactivated, and mRNA vaccines

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Abstract

Introduction: This study investigates the effectiveness of different coronavirus disease (COVID-19) vaccines in preventing hospitalization, ICU admissions, and mortality in Türkiye, upon comparing the responses to heterologous, inactivated, and mRNA vaccines.
Methodology: Data were gathered from 24,538 individuals, aged ≥ 18 years, whose COVID-19 status was confirmed through PCR testing. An analysis of the survival distributions for six vaccine types showed significant differences in severe disease outcomes, with distinct patterns observed for individuals older and younger than 65 years.
Results: Vaccines, including two-dose mRNA, both heterologous and homologous, showed the most protective and durable vaccine effectiveness. Homologous and heterologous inactivated vaccines demonstrated statistically significant reductions in severe COVID-19 outcomes for individuals aged > 65 years compared to unvaccinated individuals.
Conclusions: The results suggest that an early deployment of inactivated vaccines, despite being less advanced, may have played an important role in providing timely protection, mitigating severe outcomes, especially in countries with limited access to novel vaccine technologies. This study provides key insights for shaping future vaccine strategies and public health policies, particularly in regions with varying access to healthcare resources.

Key words: protective effectiveness; public health; severe disease outcomes; vaccine strategy, COVID-19; pandemic.

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Introduction

Coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, emerged in late 2019 and rapidly became a global pandemic, impacting millions of lives and transforming public health policies worldwide [1]. The virus primarily spreads through respiratory droplets, leading to a range of symptoms from mild respiratory illness to severe complications, especially in high-risk populations [2]. Governments and health organizations mobilized unprecedented resources to develop vaccines and therapeutic strategies to control its spread. Despite widespread vaccination efforts, variants such as Delta and Omicron posed ongoing challenges, making COVID-19 a continued focus of medical research and public health initiatives [3]. Vaccination programs are among the most effective tools for preventing disease and managing public health crises. On January 13, 2021, the Türkiye Medicines and Medical Devices Agency of Türkiye granted emergency-use authorization for the CoronaVac/Sinovac COVID-19 vaccine. Following this approval, the Ministry of Health launched the national vaccination campaign on January 14, 2021, beginning with high-risk groups such as healthcare workers, older adults, and individuals with underlying health conditions, before gradually expanding to cover the broader population [4,5]. While the campaign initially relied on inactivated virus vaccines, namely Sinovac and the domestically developed Turkovac, Pfizer's BNT162b2 (Pfizer-BioNTech) vaccine was introduced in April 2021 to enhance immunity across different age groups and health conditions as the program progressed [6].

Access to vaccines is a challenge, particularly in countries with low socioeconomic status [7-10]. In countries where vaccination is accessible, one significant challenge has been managing the diversity of available vaccines, which has led to controversies and confusion among the public and policymakers [11-14]. The vaccination efforts typically began with inactivated vaccines and were subsequently followed by vector and mRNA vaccines. However, because the choice of vaccine was often left to individuals, a large portion of the population received different types of

vaccines (heterologous) rather than a single type (homologous). As most vaccine studies have focused on homologous profiles, there are limited data on the effects of heterologous vaccination schemes, with only a few studies providing insights [15-17]. Although the World Health Organization made early recommendations on heterologous vaccination schedules (commonly referred to as a "mix-and-match" vaccination), they were primarily based on the best clinical practices rather than solid scientific evidence [18]. Understanding the impact of mixed vaccination profiles on the population and determining the duration of effective protective immunity will offer valuable insights, not only for assessing the current situation but also for preparing for future pandemics.

The objective of this study is to evaluate the relative protective effectiveness of approved COVID-19 vaccines in preventing severe outcomes, including hospitalization, intensive care unit (ICU) admissions, and mortality due to SARS-CoV-2 in Türkiye. A comprehensive analysis was conducted on the patient responses to different vaccine types, including homologous and heterologous inactivated and mRNA vaccines. This research provides insights into the vaccine efficacy in real-world settings, helping to inform public health strategies and vaccination policies for better protection against COVID-19, particularly for vulnerable populations.

Methodology

The study protocol was approved by the local institution's ethics committee and the Ministry of Health in Türkiye (Protocol No. 2022/55; approval date: March 7, 2022). This manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

Data Sources

This study includes data collected at the University of Health Sciences Izmir Bozyaka Training and Research Hospital in Türkiye, between April 1, 2021, and January 31, 2022. Data were gathered from 24,538 individuals, aged ≥ 18 years, whose COVID-19 status was confirmed through PCR testing. The study was conducted retrospectively as a cohort study at the University of Health Sciences, Izmir Bozyaka Training and Research Hospital. Polymerase chain reaction (PCR) test results for COVID-19 were obtained from the hospital's internal information system, which is accessible by the authorized hospital personnel. Additional data on hospitalization and outpatient follow-up were retrieved from the Public Health Management System, which provides access exclusively for patients registered at the study hospital. Vaccination histories were obtained through the National Vaccine Tracking System, available to authorized healthcare personnel.

Inclusion Criteria

The study included patients aged ≥ 18 years who had received at least one of the approved COVID-19 vaccinations in Türkiye. Repeated positive test results within 15 days were treated as a single episode.

Exclusion Criteria

A gap exceeding 3 months between repeated positive tests from the same individual was treated as a reinfection, and only the first episode within the study period was included. Since the Omicron variant has been predominant in Türkiye since December 2021, the reinfection threshold for a positive test after this date was defined as 1 month. All cases of reinfection were excluded from the study.

Vaccine Classification

In this study, an mRNA vaccine refers specifically to individuals who received the Pfizer-BioNTech COVID-19 vaccine, while the inactivated vaccine refers to Sinovac Biotech Ltd and Turkovac. In this study, recipients of the Turkovac vaccine represent a negligible portion of the sample, totalling

Table 1. Classification system used in this study to categorize participants based on their COVID-19 vaccination status.

Unvaccinated	**Individuals who have not received any COVID-19 vaccination.**
Inactivated (1 dose only)	Recipients who received a single dose of an inactivated vaccine, such as Sinovac or Turkovac.
mRNA (1 dose only)	Individuals who received only one dose of the Pfizer-BioNTech mRNA vaccine
Homologous mRNA (minimum 2 doses)	Recipients of at least two doses of the Pfizer-BioNTech mRNA vaccine, completing the recommended vaccination series.
Homologous inactivated (minimum 2 doses)	Individuals who have received two or more doses of an inactivated vaccine, such as Sinovac or Turkovac, as part of their vaccination schedule.
Heterologous 1 (minimum 2 Doses, 2 mRNA +)	Individuals who received a minimum of two doses, including at least two doses of mRNA vaccines, representing a mixed vaccination approach combining different vaccine types.
Heterologous 2 (minimum 2 Doses, 1 mRNA +)	Individuals who received a minimum of two doses, including at least one dose of an mRNA vaccine and one or more doses of an inactivated vaccine, reflecting a mixed vaccination strategy that combines different vaccine types.

approximately 70 individuals. Table 1 provides a detailed description of each vaccine category analyzed in this study.

Protective Effectiveness

In this study, three key indicators were defined to evaluate the protective effectiveness of vaccination against severe outcomes, including the need for hospitalization, the necessity for intensive care monitoring, and patient mortality rates.

Data Analysis

To analyse the survival outcomes, the vaccination type was categorized into six levels: single-dose inactivated, single-dose mRNA, homologous inactivated (inactivated-only series, ≥ 2 doses), homologous mRNA (mRNA-only series, ≥ 2 doses), heterologous 1 (mixed series – mRNA-dominant (≥ 2 mRNA + inactivated)), and heterologous 2 (mixed series – single mRNA dose + inactivated). Subgroup analyses were conducted by age. Preliminary chi-square tests were used to demonstrate that vaccinated individuals experienced fewer severe outcomes, such as hospitalization, ICU admissions, and mortality, compared with that in those who were not vaccinated. Following this validation, survival analyses were conducted because vaccine effectiveness is time-dependent, and its ability to prevent events like hospitalization, ICU admission, or mortality may vary over time. The survival outcomes were analyzed using the log-rank test for univariate comparisons and Kaplan–Meier curves for all categorical predictors. In this study, the events of interest were hospitalization, ICU admission, or mortality. Observation began at each individual's first positive SARS-CoV-2 PCR test and ended on January 31, 2022. The individuals were right-censored if: (1) they did not experience the event by the end of the study, (2) the outcome data were incomplete or missing, or (3) they were transferred or lost to follow-up with no subsequent record in the hospital system. The survival-time dataset was structured using the time between the first positive SARS-CoV-2 PCR test and the occurrence of each outcome or censoring. Right-censoring was used in the statistical analysis as it is the most appropriate method for handling incomplete follow-up data in retrospective cohorts, where the event occurrence may be unknown due to system limitations or the absence of outcomes within the observation period [20]. Right-censoring enables the inclusion of all individuals up to their last point of reliable follow-up, without assuming that missing data imply the absence of an event. This approach preserves the validity of time-to-event analysis and reduces the bias from incomplete outcome capture. It also accounts for staggered cohort entry, as the patients were included based on the date of their first positive PCR test, allowing the survival analysis to reflect each individual's actual observation time. Given the real-world nature of the dataset, absence of intervention, and limitations of hospital-based health information systems in a developing-country context, right-censoring offers a statistically appropriate and context-sensitive method for modelling clinical outcomes.

To assess the association between vaccine profiles and adverse clinical outcomes (hospitalization, ICU admission, and mortality), Cox proportional hazards models with time-varying covariates were conducted. Residual-based diagnostics involving Schoenfeld residuals were conducted to test the proportional hazards [21]. Cox proportional hazards regression model tests showed significant violations of the proportional hazards assumption for certain vaccine groups, namely homologous mRNA and homologous inactivated vaccine types, as well as heterologous vaccines across all outcomes in both age-adjusted and unadjusted models. These violations indicate that the effects of the vaccination status may change over time. While Cox models remain informative, constant hazard ratios should be interpreted with caution. To account for potential violations of the proportional hazards assumption, time-dependent effects were considered by incorporating the interactions between the key covariates and time [22]. The *stcox* command with time-varying covariates was used to evaluate the potential violations of the proportional hazards assumption by introducing interactions between vaccine categories and time for each outcome [22]. Each model included vaccine profile (categorical), age group (≥ 65 *vs* < 65 years), and their interactions with time. The inclusion of time-varying covariates enabled the modelling of potential waning vaccine effectiveness over time. The use of this framework allowed the capturing of both the baseline association of the vaccination status with clinical outcomes and the dynamic changes in risk as time progressed after infection. Kaplan–Meier curves remain valid as descriptive tools.

To reduce the risk of Type I error from multiple comparisons in the survival analysis, a Bonferroni correction was applied based on 15 tests (5 regimens × 3 outcomes), yielding an adjusted significance threshold of $p < 0.003$. This more conservative threshold reduces the likelihood that reported associations occurred by chance [23]. All statistical

tests were conducted using STATA BE 17.

Results

Study Population

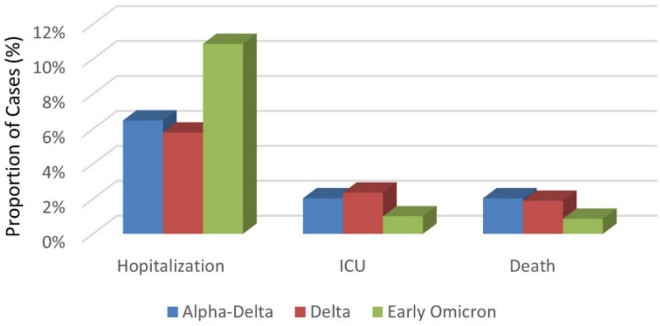
A total of 25,616 disease episodes were recorded. The data for 136 of these episodes could not be accessed because the patients were either foreign nationals or outside the scope of the study. Among the remaining 25,480 disease episodes, 942 were reinfection episodes and therefore eliminated from analysis. The remaining episodes included in the analysis were 24,538, which also represents the number of patients included in the study, as only the first disease episode per patient was evaluated. Overall, the median age of the study population was 40 years (IQR: 29–53). Among those hospitalized, the median age was 65 years (IQR: 52–77); for patients admitted to the ICU, it was 72 years (IQR: 60–81); and for mortality, it was 74 years (IQR: 62–82). The distribution of men and women was relatively balanced, with a male-to-female ratio of 0.93. Table 2 shows the characteristics of the study population by vaccine product received.

Descriptive Characteristics and Outcomes by Variant Period

The breakdown of severe outcomes and pairwise chi-square tests indicates temporal shifts in the disease severity and clinical outcomes associated with dominant SARS-CoV-2 variants (Figure 1). A total of 24,538 confirmed COVID-19 cases were recorded across three variant-dominant periods: Alpha–Delta (n = 4,286), Delta (n = 9,682), and Early Omicron (n = 10,570). The hospitalization rates varied, with 6.5% of Alpha–Delta cases (n = 278), 5.8% of Delta cases (n = 561), and 10.9% of Early Omicron cases (n = 1,149) requiring admission. The ICU admission rates were highest during the Delta period (2.4%, n = 228), followed by the Alpha–Delta (2.0%, n = 87) and Early Omicron (1.0%, n = 106) period. Mortality followed a similar trend, with death rates of 1.5% (n = 65), 1.9% (n = 183), and 0.9% (n = 91) for Alpha–Delta, Delta, and Early Omicron, respectively.

ICU admissions differed significantly between Alpha–Delta and Early Omicron cases ($\chi^2 = 24.29$, $p < 0.001$). ICU admissions were substantially lower during the early Omicron period compared to the Alpha-Delta period ($\chi^2 = 56.12$, $p < 0.001$). In terms of mortality,

Figure 1. Proportion of COVID-19 cases resulting in hospitalization, ICU admission, or mortality during periods dominated by the Alpha–Delta (April–June 2021), Delta (July–November 2021), and early Omicron (December 2021–January 2022) variants.



ICU Admission: *Early Omicron vs Alpha–Delta*: χ^2 (1, N = 13,856) = 24.29, $p < 0.001$; *Early Omicron vs Delta*: χ^2 (1, N = 20,252) = 85.29, $p < 0.001$. Death: *Early Omicron vs Alpha–Delta*: χ^2 (1, N = 14,856) = 5.10, $p = 0.024$; *Early Omicron vs Delta*: χ^2 (1, N = 20,252) = 26.11, $p < 0.001$.

Table 2. Characteristics of the study population by vaccine product received.

	Unvaccinated	One-dose		Two-dose			
		Inactivated	mRNA	mRNA	Inactivated	Heterologous 1*	Heterologous 2*
N	8.369	581	1.753	8.426	3.777	480	1.152
Age							
18-64	8.049	511	1.718	8.301	2.437	299	643
%	96.18	87.95	98	98.52	64.52	62.29	55.82
≥ 65	320	70	35	125	1.340	181	509
%	3.82	12.05	2	1.48	35.48	37.71	44.18
Gender							
Male	4.227	274	907	4.019	1.680	218	502
%	50.51	47.16	51.74	47.70	44.48	45.42	43.58
Female	4.142	307	846	4.407	2.097	262	650
%	49.49	52.84	48.26	52.30	55.52	54.58	56.42
Outcome							
Hospitalization	494	57	28	77	414	9	70
%	5.91	9.81	1.60	0.92	10.97	1.88	6.11
ICU admission	173	20	9	11	176	1	31
%	2.07	3.44	0.52	0.13	4.67	0.21	2.71
Mortality	143	18	6	9	136	1	26
%	1.71	3.10	0.34	0.11	3.61	0.21	2.27

Heterologous 1*: At least two doses, including two or more mRNA vaccines, in a mixed vaccination approach. Heterologous 2**: At least two doses, including one mRNA and one or more inactivated vaccines, in a mixed strategy.

there was a statistically significant difference between the early Omicron and Alpha–Delta variants (χ^2 = 11.99, $p < 0.001$), with a lower proportion of deaths during early Omicron. A similar pattern was observed when comparing the early Omicron to the Delta variant, where the difference was even more pronounced (χ^2 = 39.34, $p < 0.001$). The early Omicron variant was linked to significantly lower mortality than both the Alpha–Delta and Delta variants, reflecting a decline in the clinical severity as shown by reduced ICU admissions and mortality. Despite this, hospitalizations peaked during the early Omicron wave with 1,149 recorded cases.

Comparison of unvaccinated and vaccinated populations

Table 3 presents a comparison of hospitalization rates, ICU admissions, and mortality across age groups and vaccination statuses. Among individuals aged ≥ 65 years, homologous mRNA vaccines were associated with significantly lower rates of ICU admission (χ^2 = 23.01, $p < 0.001$) and mortality (χ^2 = 19.48, $p < 0.001$) compared to no vaccination status. Similarly, homologous inactivated vaccines were significantly associated with fewer ICU admissions (χ^2 = 38.82, $p < 0.001$) and mortality (χ^2 = 47.64, $p < 0.001$). Heterologous ≥ 2 mRNA vaccines were also associated with fewer ICU admissions (χ^2 = 50.19, p < 0.001) and mortality (χ^2 = 44.74, p < 0.001) when compared with those in the unvaccinated group. Finally, heterologous single-dose mRNA vaccines were linked to significantly fewer ICU admissions (χ^2 = 65.82, $p < 0.001$) and deaths (χ^2 = 60.35, $p < 0.001$) compared with those in the unvaccinated.

For those individuals aged < 65 years, a similar pattern can be seen with homologous mRNA vaccines, which were associated with a significantly lesser number of ICU admissions (χ^2 = 83.22, $p < 0.001$) and mortality (χ^2 = 64.84, $p < 0.001$) when compared with that in the no vaccination group. Among individuals in this age group, vaccine regimens containing two mRNA doses were consistently associated with lower mortality compared to the unvaccinated (mortality rate for homologous mRNA: 0.74%). No deaths were recorded in the heterologous ≥ 2 mRNA group; however, this difference did not reach statistical significance, likely due to the relatively small sample size in this subgroup.

Comparison Between Vaccination Profiles

Among individuals aged < 65 years, the homologous inactivated vaccine was overall less effective than homologous mRNA and heterologous mRNA-containing vaccines. For example, homologous two-dose mRNA vaccines provided significantly fewer hospitalizations than homologous inactivated vaccines (χ^2 = 135.67, $p < 0.001$). Hospitalization was also significantly less common in the heterologous ≥ 2-dose mRNA group, suggesting higher effectiveness compared to the homologous inactivated group (χ^2 = 9.74, $p = 0.002$). Receiving a single dose of mRNA in addition to the inactivated vaccines demonstrated fewer hospitalizations, suggesting higher effectiveness compared to the homologous inactivated group (χ^2 = 10.50, $p = 0.001$). For the same age group, homologous inactivated vaccination was not significantly different from the unvaccinated group for ICU admission (χ^2 = 0.34, $p = 0.56$) or mortality (χ^2 = 2.31, $p = 0.13$). ICU admissions were significantly lower in the homologous mRNA group compared to the heterologous single-dose mRNA group (χ^2 = 18.84, $p < 0.001$). Vaccination profiles containing two mRNA doses, whether homologous or heterologous, showed lower overall mortality compared to other groups. For example, the mortality was significantly lower in the homologous mRNA group compared to the heterologous single-dose mRNA group (χ^2 = 8.12, $p = 0.004$).

In patients aged > 65 years, homologous inactivated vaccines demonstrated fewer ICU admissions and mortality (χ^2 = 47.64, $p < 0.001$) compared to the no vaccination group (χ^2 = 38.82, $p < 0.001$). Among this

Table 3. Comparison of Hospitalization, ICU Admission, and Death by Age and Vaccination Status.

Category (N (%))		Unvaccinated	Single dose inactive vaccine	Single dose mRNA vaccine	Homologous ≥ two dose mRNA vaccines	Homologous ≥ two dose Inactive vaccines	Heterologous ≥ two dose mRNA vaccines	Heterologous ≥ single dose mRNA vaccines	Total
Total population	**≥ 65**	**320**	**70**	**35**	**125**	**1338**	**181**	**507**	**2576**
	< 65	**8041**	**511**	**1711**	**8285**	**2435**	**299**	**639**	**21921**
Hospitalization	**≥ 65**	**142 (44.4)**	**27 (38.6)**	**9 (25.7)***	**21 (16.8)*****	**321 (24)*****	**8 (4.42)*****	**62 (12.2)*****	**590 (22.9)**
	< 65	**352 (4.4)**	**30 (5.9)**	**19 (1.11)*****	**56 (0.7)*****	**93 (3.8)**	**1 (0.3)*****	**8 (1.25)*****	**559 (2.5)**
ICU admission	**≥ 65**	**79 (24.7)**	**13 (18.6)**	**4 (11.4)**	**6 (4.8)*****	**151 (11.3)*****	**1 (0.55)*****	**27 (5.33)*****	**281 (10.9)**
	< 65	**94 (1.2)**	**7 (1.4)**	**5 (0.29)*****	**5 (0.06)*****	**25 (1.03)**	**0 (0) NA$^+$**	**4 (0.6)**	**140 (0.6)**
Death	**≥ 65**	**72 (22.5)**	**13 (18.6)**	**3 (8.6)**	**6 (4.8)*****	**118 (8.9)*****	**1 (0.55)*****	**24 (4.7)*****	**237 (9.2)**
	< 65	**71 (0.9)**	**5 (1)**	**3 (0.18)*****	**3 (0.04)*****	**18 (0.74)**	**0 (0) NA$^+$**	**2 (0.3)**	**102 (0.5)**

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. p calculated using chi-square tests to compare the unvaccinated group with each of the vaccinated groups. + NA: Statistical calculations were not performed because the observed value is zero.

age group, the most effective vaccination profile was the heterologous regimen containing two doses of an mRNA vaccine. For ICU admission, the heterologous ≥ two-dose mRNA group suggested fewer events than the homologous mRNA group ($\chi^2 = 5.97$, $p = 0.015$), the homologous inactivated group ($\chi^2 = 20.40$, $p < 0.001$), and the heterologous single-dose mRNA group ($\chi^2 = 7.78$, $p = 0.005$). Similar results were also observed for mortality for the age group > 65 years, with heterologous ≥ two-dose mRNA being associated with fewer events compared to the homologous mRNA group ($\chi^2 = 5.97$, $p = 0.015$), the homologous inactivated group ($\chi^2 = 15.09$, $p < 0.001$), and the heterologous single-dose mRNA group ($\chi^2 = 6.66$, $p = 0.01$).

Durability of Protective Effectiveness

Vaccine effectiveness is time-dependent; therefore, the survival probabilities were subsequently analyzed for hospitalization, ICU admission, and mortality for both homologous and heterologous vaccines. Age was the most significant demographic factor associated with severe outcomes in this study, with marked differences between individuals younger and older than 65 years. Consequently, statistical analyses were conducted separately for each age group. This approach aligns with several previous studies that have also analyzed individuals aged ≥ 65 years as a distinct group [2,3,24,25].

Patients Aged ≥ 65 Years

In Cox models, including time-varying covariates, strong protective associations were observed between several vaccine combinations and risk of hospitalization, ICU admission, and mortality among individuals aged ≥ 65 years. Compared to the reference group (single dose inactivated), most vaccination categories were significantly associated with lower ICU admission risk in this age group. For example, receiving two or more doses of an mRNA vaccine was associated with a 99% reduction in the risk of ICU admission (HR = 0.010; 95% CI: 0.003–0.042, $p < 0.001$), while the mixed profile with only one mRNA dose also substantially reduced risk (HR = 0.026; 95% CI: 0.009–0.078, $p < 0.001$). Time-varying covariates suggested modest but statistically significant increases in the ICU risk over time for the homologous inactivated vaccine profile (HR = 1.011, 95% CI: 1.004–1.018, $p = 0.002$) and the mixed profile with only one mRNA dose, (HR = 1.017, 95% CI: 1.008–1.026, $p < 0.001$), suggesting possible waning of vaccine protection. In terms of mortality, receiving at least two doses of only mRNA vaccines was associated with the greatest reduction in mortality compared to the reference group (HR = 0.009, 95% CI: 0.002–0.040, $p < 0.001$). Other vaccine profiles, such as mixed regimen with one mRNA (HR = 0.030, 95% CI: 0.009– 0.094, $p < 0.001$) and homologous inactivated regimens (HR = 0.064, 95% CI: 0.027–0.150, $p < 0.001$), also showed significant protective effects, though to a lesser degree. Time-varying covariates suggest small but statistically significant increases in mortality over time for the mixed vaccine profile with one mRNA (HR = 1.014, 95% CI: 1.005–1.024, $p = 0.002$). The time-varying effect for the homologous inactivated regimen (HR = 1.011, 95% CI: 1.004–1.018, $p = 0.003$) was at the Bonferroni threshold and thus not statistically significant after correction.

Patients Younger Than 65 Years

Among individuals aged < 65 years, receiving at least two doses of the mRNA vaccine was associated with the lowest risk of hospitalization, indicating the highest level of protection among all vaccine profiles. Time-varying covariates suggest a gradual increase in the hospitalization risk over time for those who received homologous mRNA vaccines (HR = 1.015, 95% CI: 1.001–1.021 $p < 0.001$), homologous inactivated vaccines (HR = 1.012, 95% CI: 1.007–1.016, $p < 0.001$), and mixed regimen including only one mRNA dose (HR = 1.014, 95% CI: 1.008–1.0201, $p < 0.001$), suggesting a possible waning effect in these groups. Receiving at least two doses of mRNA was associated with the lowest risk for ICU admission (HR = 0.010, 95% CI: 0.003–0.042, $p < 0.001$). Time-varying covariates showed a modest but statistically significant increase in the ICU risk over time for those who received homologous inactivated vaccines (HR = 1.011, 95% CI: 1.004–1.018, $p = 0.002$), and mixed regimens including only one mRNA dose (HR = 1.017, 95% CI: 1.008–1.0257, $p < 0.001$), suggesting a potential waning of protection over time.

Among individuals aged < 65 years, the lowest risk of mortality was observed in those who received at least two doses of mRNA vaccines (HR = 0.009, 95% CI: 0.002–0.041, $p < 0.001$), indicating the highest level of protection against mortality. Similarly, those in the mixed vaccine group, including only one mRNA dose, and those who received at least two inactivated doses also showed a significantly reduced risk of death (HR = 0.030, 95% CI: 0.009–0.0941, and HR = 0.064, 95% CI: 0.027–0.150, respectively; both $p < 0.001$). Time-varying covariates indicated a small but statistically significant increase in the mortality risk over time for

recipients of a mixed regimen, including only one mRNA dose (HR = 1.014, 95% CI: 1.005–1.024, p = 0.002).

Table 4 presents the survival probabilities by vaccine type and age for hospitalization, ICU admission, and mortality, based on two-dose regimens at the 100-, 200-, 300-, and 400-day intervals. Survival probabilities remain higher for individuals aged < 65 years across all vaccine types, with individuals aged ≥ 65 years exhibiting more significant declines, particularly in ICU admissions and hospitalization. The mortality risk for individuals aged < 65 years with the mRNA vaccine slightly decreased over time; however, the probability of survival remained high throughout the 400 days. In particular, the mortality and ICU admission rates for individuals aged ≥ 65 years decreased substantially at the 300-day mark, dropping from 96% at 200 days to 79%. For the inactivated vaccine, individuals aged < 65 years also showed high survival rates, with some declining over time for all outcomes, especially for hospitalization. In contrast, in dividuals aged > 65 years experienced more pronounced declines in survival probabilities. Mortality rates dropped below 90% by 200 days and below 70% by 300 days. Similarly, survival probabilities for ICU admission fell below 85% at 200 days and declined further to below 60% by 300 days. While the data for the heterologous vaccines are limited, the available data suggest that the Heterologous 1 vaccine (containing a single dose of mRNA) maintained high survival

Figure 2. Kaplan–Meier curves illustrating the cumulative probability of hospitalization, ICU admission, and mortality for homologous and heterologous vaccine profiles. mRNA (blue line), inactivated (red line), Heterologous 1 (green line), and Heterologous 2 (yellow line).

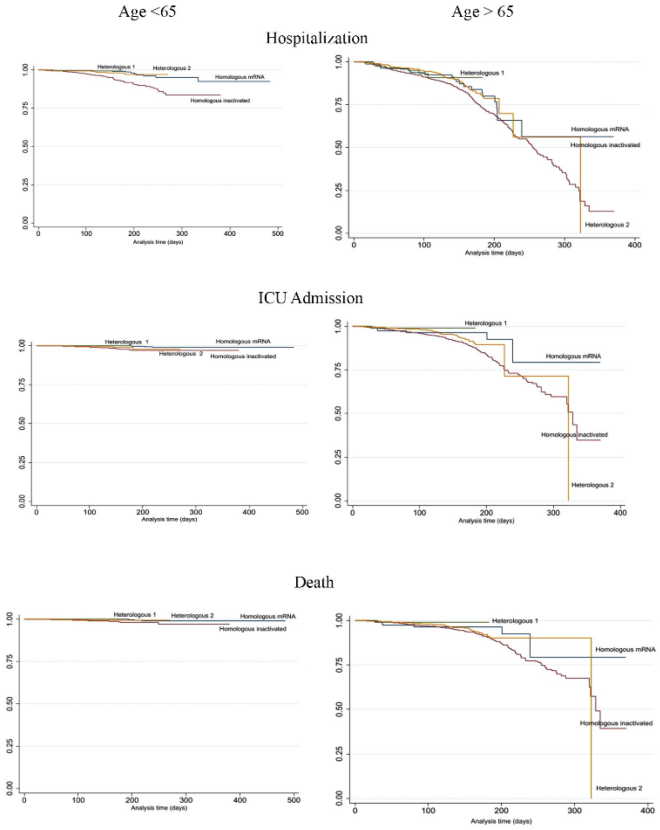


Table 4. Survival probabilities by vaccine group and outcome for two-dose regimens.

Vaccine Group	Outcome	Age Group	100 Days	200 Days	300 Days	400 Days
Homologous mRNA	Mortality	< 65	1.0000	0.9984	0.9917	0.9917
		> 65	0.9643	0.9643	**0.7935**	.
	ICU	< 65	0.9999	0.9989	0.9922	0.9922
		> 65	0.9643	0.9643	**0.7935**	.
	Hospitalization	< 65	0.9980	0.9819	0.9535	0.9255
		> 65	0.9373	**0.7994**	**0.5651**	.
Homologous inactivated	Mortality	< 65	0.9940	0.9814	0.9716	.
		> 65	0.9706	**0.8697**	**0.6750**	.
	ICU	< 65	0.9934	0.9726	0.9726	.
		> 65	0.9605	**0.8374**	**0.5963**	.
	Hospitalization	< 65	0.9763	0.9045	**0.8379**	.
		> 65	0.9141	**0.6913**	**0.3532**	.
Heterologous 1*	Mortality	< 65	1.0000	.	.	.
		> 65	0.9922	.	.	.
	ICU	< 65	1.0000	.	.	.
		> 65	0.9928	.	.	.
	Hospitalization	< 65	0.9961	.	.	.
		> 65	0.9322	.	.	.
Heterologous 2**	Mortality	< 65	0.9982	0.9953		.
		> 65	0.9823	**0.9024**	**0.9024**	.
	ICU	< 65	0.9982	0.9796	.	.
		> 65	0.9848	**0.8961**	**0.7169**	.
	Hospitalization	< 65	0.9966	0.9706		.
		> 65	0.9496	**0.7872**	**0.5598**	.

Missing values (denoted by ".") indicate that the survival data was not available for that time point. Heterologous 1*: At least two doses, including two or more mRNA vaccines, in a mixed vaccination approach. Heterologous 2**: At least two doses, including one mRNA and one or more inactivated vaccines, in a mixed strategy. The bolded text highlights a substantial decline in protective effectiveness against severe disease outcomes.

probabilities for individuals aged < 65 years across all outcomes for 100 days. For individuals aged > 65 years, the mortality and ICU survival rates remained high (> 99%), though hospitalization rates showed a slight decline (< 93%). The Heterologous 2 vaccine (containing two doses of mRNA), on the other hand, exhibited a gradual decline in the survival probabilities over time for both age groups, with more significant reductions observed in individuals aged > 65 years, particularly in hospitalization outcomes. The mortality for individuals aged < 65 years remained above 99% during the first 200 days. Meanwhile, the ICU and hospitalization survival probabilities decreased from 99% to 97% between 100 and 200 days. For individuals aged > 65 years, mortality started at approximately 98%, but declined to 92% by 200 days, while the ICU survival dropped to 89%. For individuals aged > 65 years, the protective effectiveness against ICU admission declined more sharply by 200 and 300 days.

Figure 2 displays the Kaplan–Meier curves for hospitalization, ICU admission, and mortality over time, comparing individuals above and below 65 years of age.

Discussion

This study uses real-life data from a comprehensive cohort of patients to evaluate the effectiveness of different COVID-19 vaccines in reducing severe outcomes (hospitalization, ICU admissions, and mortality). Examining vaccine protective effectiveness using real-world data has important implications to inform vaccine policy [26]. While controlled clinical trials operate under tightly regulated conditions, this study did not exclude individuals with underlying medical conditions, pregnant individuals, or others who may have been at higher risk. This broader inclusion enhances the study's generalizability [27] and offers valuable evidence to inform public health strategies and vaccination policies.

Overall, in both age groups (< 65 and ≥ 65 years), receiving at least two doses of an mRNA vaccine was consistently linked to the greatest protection against hospitalizations, ICU admissions, and mortality. Mixed regimens with only one mRNA dose and homologous inactivated regimens also reduced risk, but to a lesser extent. For those younger than 65 years of age, homologous inactivated vaccines offered little to no protection compared to the no vaccination group for this age group and were less effective than all mRNA-containing regimens. Two-dose mRNA regimens, whether homologous or heterologous, offered the greatest protection, while single-dose mRNA regimens were less effective. Among adults over 65 years of age, inactivated vaccines were associated with fewer ICU admissions and mortality compared to no vaccination, but offered less protection than mRNA regimens. Heterologous ≥ 2-dose mRNA yielded the best outcomes, outperforming all other profiles for both ICU admission and mortality for this age group.

Time-dependent modelling suggested that vaccine protection can wane over time, particularly for homologous inactivated regimens and mixed regimens with a single mRNA dose. While protection against severe outcomes remained substantial, these findings highlight the potential benefit of booster strategies, particularly for regimens not based solely on mRNA doses. A similar pattern was observed for mortality: individuals with full mRNA regimens consistently had the lowest risk of death, whereas other vaccine profiles, though still protective, were less effective. The gradual increase in risk over time for certain regimens highlights the need to consider the durability of immune protection when shaping vaccination policies.

As a general guideline, at least two doses of the inactivated and Pfizer-BioNTech vaccine profiles are recommended for vaccination to ensure effectiveness. An analysis of incomplete vaccinations shows that a single dose of an inactivated vaccine does not provide any substantial protective effect. While a single dose of an mRNA vaccine demonstrates effectiveness in the population of age < 65 years, this protection diminishes rapidly over time [28]. In the population aged > 65 years, homologous inactivated vaccination was found to reduce severe disease outcomes. However, the effectiveness of inactivated vaccines in this age group was lower compared to mRNA-based vaccination profiles, a result supported by findings in various other studies [29]. The protective effect of inactivated vaccines was not observed in the population aged < 65 years, where the outcomes were comparable to those in unvaccinated individuals. This finding differs from several other studies and may be partly due to the low number of severe cases observed in younger participants in our cohort [3,30]. Differences in the population characteristics across studies may also contribute to these contrasting results [31,32]. Nevertheless, the large sample size for the under-65 group in this study supports the reliability of these findings, even if the group is not perfectly homogeneous.

The protective effectiveness of inactivated vaccine profiles increases when they are combined with mRNA vaccines in heterologous vaccination protocols. Notably, heterologous regimens combining inactivated

vaccines with two doses of mRNA vaccines demonstrated high effectiveness across all populations, with the highest effectiveness observed in those aged 65 and older. It would be reasonable to attribute this increase primarily to the contribution of mRNA vaccines. When analysing protective effectiveness, heterologous regimens containing two doses of mRNA vaccines were found to be more effective than those with only one dose. The effects of heterologous vaccinations, which were of particular interest in this study, showed varying outcomes. For instance, in the population aged < 65 years, homologous regimens with two mRNA vaccines appeared more effective than heterologous regimens containing two mRNA vaccines. In contrast, heterologous vaccination was found to be more effective in the population aged ≥ 65 years. The most significant finding of our study is that both heterologous and homologous mRNA-based vaccinations were more successful and durable in possibly preventing severe forms of COVID-19 compared to inactivated vaccination profiles. This is likely attributable to the longer-lasting effects of immunological memory induced by mRNA-based vaccines [33,34].

In general, the protective effectiveness of the COVID-19 vaccine against severe outcomes is known to wane after 6 months [14,24,28]. The current study illustrates similar results, with the population aged ≥ 65 years being the most significantly affected by waning immunity. Across all age groups, protection persisted longest with homologous mRNA and heterologous regimens, while homologous inactivated vaccines showed a steeper and earlier decline in effectiveness [35].

Implications for practice

These findings highlight the importance of vaccination, especially full mRNA regimens, in reducing severe outcomes among older adults, the group most at risk. Complete vaccine types were associated with substantial risk reductions in this age group, highlighting the robust protection vaccination offers against the most serious complications of COVID-19. Examining the global chronology of the pandemic, the widespread adoption of inactivated vaccines as the first readily available option in several countries proved to be a strategic and beneficial decision. By prioritizing immediate deployment rather than delaying in anticipation of newer vaccine technologies, numerous nations were able to provide early protection to their populations and reduce the severity of cases. However, to enhance the immune response, expand coverage more rapidly, and ensure longer-lasting protection, improving the production and distribution of mRNA-based vaccines will be essential for managing future pandemics. A critical issue moving forward is determining the most effective strategy for vaccination efforts to continue protecting public health. Specifically, routine vaccination schedules and the impact of mixed vaccine regimens (heterologous vaccination) remain unclear due to differing policies across countries. As a result, understanding how individuals with heterologous vaccine profiles respond to COVID-19 infection is crucial.

Limitations

Several limitations should be mentioned. First, the current study is a real-world observational study; therefore, patients were not randomly assigned to receive a vaccine. This limitation is common to all real-world, population-based studies of vaccine effectiveness, as the individuals who received the vaccine may differ from those who did not [36]. Second, our study lacks detailed information on the participants' underlying health conditions. Therefore, it is difficult to fully account for how pre-existing conditions may have influenced the severity of COVID-19 outcomes or the effectiveness of different vaccines. As a result, the findings may not fully capture the impact of comorbidities on hospitalization, ICU admissions, or mortality rates, potentially limiting the generalizability of the results to all populations. It is also important to note that this study focused on evaluating the effectiveness of protection against severe disease outcomes, not protection against disease transmission. Therefore, the results and recommendations should be interpreted within this context.

This study was conducted using the data obtained from hospital-level health information systems, which inherently limits the availability of certain clinical and epidemiological variables. Specifically, data on comorbidities, prior SARS-CoV-2 infection, and variant-specific sequencing results were not accessible. Additionally, while variant-dominant timeframes were known at the population level, individual-level variant data were unavailable, limiting the ability to perform variant-specific analyses. These constraints reflect broader challenges in data infrastructure and interoperability in resource-limited settings and should be considered when interpreting the generalizability and precision of the study's findings. Additionally, due to small sample sizes in several vaccine subgroups, especially those representing mixed or partial

schedules, we were unable to conduct detailed stratified analyses by biologically distinct vaccination sequences. To preserve statistical validity, we retained broader vaccine categories for the main analyses. Finally, it is important to note that age ≥ 65 years was used as a stratification threshold in this study, reflecting the national public health policy in Türkiye at the time of the pandemic, which classified individuals in this age group as high-risk for severe COVID-19. In accordance with this policy, confirmed COVID-19 cases aged ≥ 65 years were prioritized for hospitalization. Therefore, the hospitalization criteria during the pandemic were less stringent than for ICU admissions or death and often included precautionary admissions for high-risk patients, such as those aged ≥ 65 years. This broader admission threshold likely inflated the hospitalization counts, making the measure less directly comparable to ICU admission and mortality for those aged ≥ 65 years.

Conclusions

The current study provides important insights into the effectiveness of different COVID-19 vaccines in preventing severe disease outcomes, including hospitalization, ICU admissions, and mortality, within the Turkish population. The COVID-19 pandemic highlighted an important question regarding the impact of mixed vaccine regimens, or heterologous vaccination, which involves combining different types of vaccines, such as inactivated and mRNA vaccines. These regimens have been implemented in some countries as a response to vaccine availability or supply constraints; however, the long-term effects on immunity and protection are not fully understood. Given that the vaccination policies and strategies vary significantly across countries, it is crucial to assess the effectiveness of heterologous vaccination in real-world settings, particularly for individuals who may have received different vaccine combinations based on the local guidelines or availability. Overall, the findings highlight the importance of tailored vaccination strategies that consider both age and vaccine type to maximize protection against severe disease.

By analysing the data from 25,481 individuals, the study highlights the protective benefits of mRNA-based vaccines as well as the effectiveness of homologous and heterologous inactivated vaccines, particularly in individuals over 65 years. The findings highlight the critical role of early vaccine deployment, especially in regions with limited access to newer technologies, and the importance of tailoring vaccine strategies to specific demographic groups. As countries continue to face evolving health challenges, these results will help guide future vaccination policies and public health responses, with an emphasis on equity and accessibility in vaccine distribution. A key challenge moving forward is determining the most effective vaccination strategies to ensure long-term protection against COVID-19, especially as new variants continue to emerge. This involves the need for standardized and routine vaccination schedules that can be adapted to both current and future epidemiological conditions. Countries must evaluate the timing and frequency of booster doses, taking into account evolving immunity levels, variant characteristics, and demographic factors.

Understanding how individuals with heterologous vaccine profiles respond to COVID-19 infection is essential for informing future public health policies. This includes analysing the durability of immunity, likelihood of breakthrough infections, and severity of disease in vaccinated individuals compared to those with homologous vaccination profiles. Identifying the most effective vaccine combinations and tailoring strategies to specific populations allows public health authorities to maximize protection. These insights are also critical for shaping future global vaccination efforts, particularly in low- and middle-income countries with limited access, and for reducing the risk of future outbreaks or emerging variants.

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Conflict of interest

No conflict of interest is declared.

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