Boosters reduce in-hospital mortality in patients with COVID-19: An observational cohort analysis

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Summary

Background Real-world data on the effectiveness of boosters against COVID-19, especially as new variants continue to emerge, is limited. Our objective was to assess demographic, clinical, and outcome variables of patients requiring hospitalization for severe SARS-CoV-2 infection comparing fully vaccinated and boosted (FV&B), fully vaccinated (FV), and unvaccinated (UV) patients.

Methods This multicenter observational cohort analysis compared demographic, clinical, and outcome variables in FV&B, FV, and UV adults hospitalized for COVID-19. Partially vaccinated (PV) and individuals still hospitalized beyond the designated follow-up date of February 1, 2022 were excluded. The primary endpoint was in-hospital mortality. Secondary endpoints included characteristics and outcomes in subpopulations of intensive care and geriatric (age >65) patients.

Findings Between August 12th, 2021 and January 20th, 2022, 8232 patient encounters had a primary diagnosis of COVID-19 and required inpatient treatment. Of the 8232 encounters requiring hospitalization, 448 (5.8%) were FV&B, 2257 (29.2%) were FV, and 5023 (65.0%) were UV; 357 PV and 147 still hospitalized were excluded. The median age of FV&B cohort was 73 (IQR 62, 82) compared to 70 (IQR 59, 80) for FV and 59 (IQR 45, 71) for UV (0.001). Most patients were female in both the FB&V and UV groups with 51.1% and 51.8%, respectively, while the FV group had a majority of males (51.3%). The median Elixhauser weighted score was 12 (IQR 3, 22) for FV&B, 10 (IQR 2, 20) for FV, and 9 (IQR 0, 17) for UV groups ($p < 0.001$). In-hospital mortality was 7.1% in the FV&B, 10.3% in the FV group, and 12.8% in the UV group ($p < 0.001$). The FV&B group had lower in-hospital mortality than both FV and UV groups ($p = 0.045$ and $p = 0.001$, respectively). The FV group had lower in-hospital mortality than the UV group ($p = 0.004$).

Interpretation Fully vaccinated and boosted patients requiring hospital-level care for breakthrough COVID-19 have lower in-hospital mortality than fully vaccinated and unvaccinated patients despite being older and higher risk at baseline. Boosters offer added protection beyond full vaccination in preventing death. As COVID-19 continues to spread, larger expansive trials are needed to further identify risk factors for severe outcomes among the FV&B population.

Funding This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors.

Keywords: COVID-19; SARS-CoV-2; Booster dose; Vaccination; Severe illness; Mortality; Hospitalization; Death

Introduction

The Coronavirus Disease (COVID-19) pandemic landscape has changed dramatically since it began.[1] In just one year, scientists, industry, and governments were able to develop and distribute safe and effective vaccinations that offer protection against the SARS-CoV-2 virus.[2−4]

However, despite these advances, the death toll has been substantial, with nearly 1 in 100 Americans over the age of 65 succumbing to this deadly virus.[5] As SARS-CoV-2 infection continues to spread around the globe, one critical challenge is the continued viral mutation leading to new and potentially dangerous viral variants that may decrease the efficacy of current vaccines. Fortunately, studies on the B.1.351, B.1.1.7 (alpha), and B.1.617.2 (delta) variants revealed no major decrease in effectiveness with

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Research in context

Evidence before this study

We searched PubMed on December 1, 2021 for evidence surrounding breakthrough COVID-19 in vaccinated and boosted patients leading to hospital or emergency care encounters using the search terms (booster OR booster shot OR third dose) AND (SARS-CoV-2 OR novel coronavirus OR COVID-19) AND (vaccination OR immunization) AND (hospitalization OR emergency visit) with no language or time restrictions. Vaccine efficacy has been established by pharmaceutical trials and has triggered the availability of vaccines across the globe. However, effectiveness of booster shots at preventing hospital-based treatment for COVID-19 in fully immunized patients in a real-world population is poorly understood with limited prior publications. Further, it is unclear if boosters offer an advantage over full vaccination for severe outcomes associated with COVID-19.

Added value of this study

This study is one of the first large, real world investigations in the United States addressing the impact of booster shots on in-hospital mortality. We found that fully vaccinated and boosted individuals were at baseline older and at higher risk of in-hospital mortality based on comorbidities compared to fully vaccinated and unvaccinated individuals. Despite the increased baseline risk, fully vaccinated and boosted individuals had a reduced in-hospital mortality compared to fully vaccinated and unvaccinated groups ($p = 0.045$ and $p = 0.001$, respectively).

Implications of all the available evidence

While vaccination provides a layer of protection against mortality compared to no vaccination, the booster dose enhances this defense and confers an additional mortality benefit.

the Pfizer-BioNTech vaccine.[6,7] However, as new variants continue to emerge, breakthrough SARS-CoV-2 infections in vaccinated individuals remain a significant concern. Smaller studies on fully vaccinated healthcare workers who subsequently developed SARS-CoV-2 infections demonstrated rates of breakthrough infection between 0.05% and 11.6%.[8–11]

Early data from Israel and the United Kingdom also demonstrated that the effectiveness of the vaccine for preventing breakthrough infection and severe disease waned as time from vaccination increased.[12,13] In order to combat this potential for waning immunity, the United States Food and Drug Administration authorized booster vaccinations in all individuals who completed the primary vaccination series at least six months after receiving the Moderna or Pfizer-BioNTech SARS-CoV-2 vaccine or at least two months after being

vaccinated with the Janssen SARS-CoV-2 vaccine.[14,15] To date, there is minimal data regarding the effectiveness of a booster dose in preventing breakthrough COVID-19 and progression to severe disease and death, especially in areas with a high concentration of viral variants. It is our objective to assess shared characteristics and outcomes of patients requiring hospitalization for severe SARS-CoV-2 infection comparing fully vaccinated and boosted (FV&B), fully vaccinated (FV) and unvaccinated (UV) patients.

Materials and methods

Study design, setting, and participants

We conducted a multicenter observational cohort analysis evaluating adult patients requiring hospital admission for COVID-19. We compared demographic, clinical, and outcomes data among patients who had completed a SARS-CoV-2 primary vaccination series and received a booster dose (FV&B), completed primary vaccination series (FV), and unvaccinated (UV) patients who required hospitalization for COVID-19 during the same time period. Patients were identified through analysis of electronic health records (EHR; Epic Systems, Verona, WI, USA). This study was conducted at Beaumont Health, an eight-hospital acute care hospital system in southeastern Michigan.

Consecutive adult patients greater than or equal to 18 years of age presenting to the ED and requiring hospital admission with a discharge diagnosis indicating active COVID-19 disease were eligible for inclusion. Patients who had laboratory-confirmed SARS-CoV-2 infection during a previous hospitalization, pediatrics, partially vaccinated, and those still admitted at the designated follow-up date of February 1, 2022 were excluded. The study was approved by the home organization's Institutional Review Board. The written informed consent requirement was waived due to the retrospective nature of the study.

Study definitions

Patients were categorized as FV&B, FV, or UV. Current Centers for Disease Control and Prevention (CDC) guidelines were used for classification.[16] FV&B individuals had received either three doses of an mRNA vaccine (Pfizer, Moderna), one dose of a viral vector vaccine (Janssen) and one dose of the mRNA, one dose of a viral vector vaccine and two doses of the mRNA, or two doses of a viral vector vaccine. FV individuals had received either two doses of an mRNA vaccine (Pfizer, Moderna) or one dose of viral vector (Janssen).

UV individuals had no record of immunization against SARS-CoV-2 available in our EHR or within the Michigan Care Improvement Registry (MCIR), which tracks all vaccinations from any source across the state

of Michigan.[17] All individuals who received the correct number and combination of doses were included in the analysis irrespective of the timeline of dose administration. In-hospital mortality included death during the hospital stay as well as death within ten days of being discharged to hospice.

Data sources/measurement

All data were extracted from the EHR. This data included demographic, clinical, laboratory, and outcomes variables. Additionally, data included comorbidities, number of ED visits in the past six months, and body mass index (BMI) was extracted from the EHR after our cohort was identified. Comorbidities were assessed using the Agency for Healthcare Research and Quality (AHRQ) Elixhauser Comorbidity Index[18] (Appendix A). Specific to the FV&B group, we extracted initial ED vital signs and laboratory values. A manual chart review was performed to identify the time from symptom onset to ED presentation for FV&B individuals that received ICU level of care or expired. For all cohorts, we evaluated hospital treatment and outcomes data. These variables included: need for supplemental oxygen stratified by level of support including mechanical ventilation, highest level of care, need for renal replacement therapy, vasopressor use, extracorporeal membrane oxygenation (ECMO) use, hospital length of stay, and hospital disposition.

Data from the MCIR included dates of vaccine administration as well as vaccine type and brand.

Immunocompromised individuals were identified using the AHRQ list of ICD-10 diagnoses and procedure codes that they have listed as defining an immunocompromised state (IMMUNID).[19] All available EHR data were used to screen for these conditions and procedures and codes that were deemed active during the current hospitalization were included.

Outcome measures

The primary outcome of this study was in-hospital mortality. Secondary endpoints included characteristics and outcomes in ICU and elderly (age >65) subpopulations including mechanical ventilation, vasopressors, renal replacement therapy, ECMO, supplemental oxygen (none, low flow therapy, high flow therapy), and hospital length of stay.

Statistical analysis

All data were summarized through descriptive statistics. Numerical results are reported as means and standard deviation or medians and interquartile ranges. Categorical variables are reported as counts and percentages. The Chi-square or Fisher's exact test was used for categorical variables and the Kruskal-Wallis (exact) test was used for numerical variables. When comparing FVB, FV, and UV, the multiple comparison method was applied; the post hoc Holm-Bonferonni procedure was used for categorical variables and the Tukey-Kramer method was used for numerical variables.[20] All tests performed in this analysis were two-sided tests, with $p < 0.05$ or a confidence interval of 95% indicating statistical significance. Analysis was performed using R software, version 4.1.2 (R Foundation for Statistical Computing) and Excel (Microsoft).

Ethics committee approval

This study was approved by the Beaumont Health Institutional Review Board.

Role of the funding source

This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors.

Results

Between August 12th, 2021 and January 20th, 2022, there were 18,728 ED encounters with a primary diagnosis of COVID-19 (ICD 10: U07.1). After excluding 10,496 encounters that were discharged from the ED, 147 encounters that remained hospitalized at our designated follow-up date, and 357 partially vaccinated encounters, a total of 7728 encounters remained in the final analysis. Of these encounters, 448 (5.8%) were FV&B, 2257 (29.2%) were FV, and 5023 (65.0%) were UV (Figure 1).

The median age of FV&B patients was 73 (Interquartile range (IQR) 62, 82) compared to 70 (IQR 59, 80) for FV and 59 (IQR 45, 71) for UV ($p < 0.001$). The majority of patients were female in both the FB&V and UV groups with 51.1% and 51.8%, respectively, and male in the FV group (51.3%) ($p = 0.049$). FV&B had a lower median BMI of 28.3 (IQR 24.2, 34.0), compared to FV (29.2 (IQR 24.9, 34.7)), and UV (30.0 (IQR 25.7, 35.9)) ($p < 0.001$). The proportion of immunocompromised and pre-existing end-stage renal disease (ESRD) in the FV&B cohort were 29.5% and 13.6%, respectively, compared to 17.9% and 6.2% in the FV cohort, respectively, and 11.3% and 2.3% in the UV cohort, respectively ($p < 0.001$ for both). The median Elixhauser weighted score was 12 (IQR 3, 22) for FV&B, 10 (IQR 2, 20) for FV, and 9 (IQR 0, 17) for UV groups ($p < 0.001$). 4.9% of FV&B individuals required mechanical ventilation compared to 6.5% of FV, both of which were lower than the UV group (10.2%) ($p < 0.001$). In-hospital mortality was 7.1% in the FV&B, which was significantly lower than the FV group (10.3%; $p = 0.045$) and UV group (12.8%; $p = 0.001$) (Table 1 and *Supplementary Table* 1).
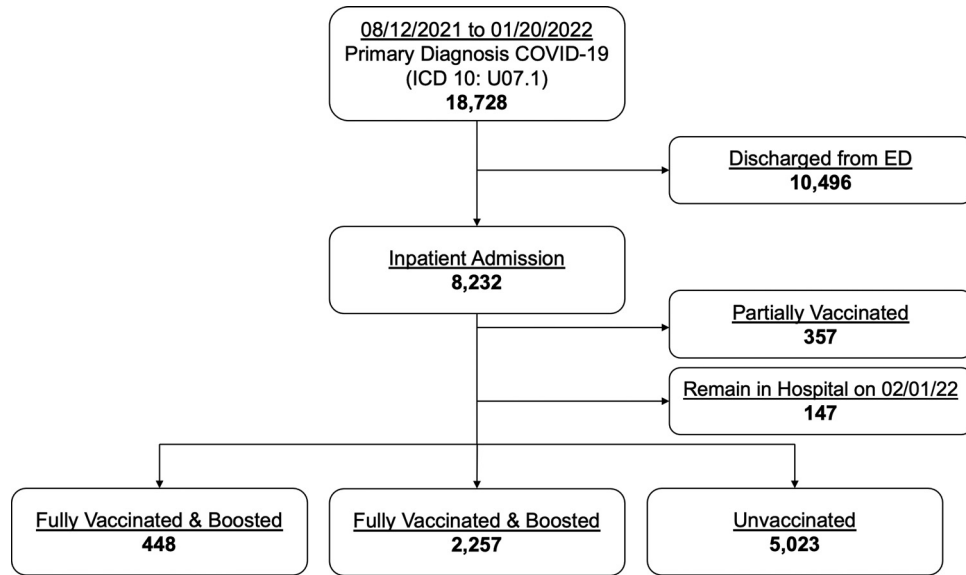
Figure 1. Enrollment profile of COVID-19 emergency and inpatient encounters.

In a sub-analysis comparing FV&B (n = 320), FV (n = 1449), and UV (n = 1885) patients >65 years old, outcome differences between groups were more apparent. Specifically, in-hospital mortality was 9.1% in FV&B, which was significantly lower than both the FV group (13.6%; p = 0.035) and UV group (21.2%; p < 0.001). (Table 2 and *Supplementary Table* 1)

A second sub-analysis was performed on patients requiring ICU-level care including FV&B group (n = 56), FV group (n = 271), and UV group (n = 757). The FV&B group had a higher proportion of immunocompromised individuals (41.1%) compared to the FV group (25.1%; p = 0.024) and UV group (12.4%; p < 0.001). There was no difference in median Elixhauser weighted comorbidity between the FV&B (22.5 (IQR 11, 31)) and FV (22 (IQR 11, 31)) (p = 0.999), although both were higher than the UV group (17 (IQR 7,26)) (p = 0.050 and p < 0.001, respectively). There was no difference in in-hospital mortality between the FV&B (37.5%) and FV (52.4%) (p = 0.119) or the FV and UV (58.5%) (p = 0.119), however, in-hospital mortality was significantly lower among the FV&B compared to the UV (p = 0.010) (Table 3 and *Supplementary Table* 1).

There were 32 (7.1%) patients in the FV&B cohort that died. Among these patients, three had received a mix of mRNA vaccine types (Pfizer and Moderna), 13 received three doses of the Pfizer vaccine and 15 received three doses of the Moderna vaccine, while one patient had received two doses of the viral vector vaccine (Janssen). The median number of days from booster vaccination to symptom onset was 38 (IQR 7.8, 66) with 10 subjects (31.3%) experiencing COVID-19 symptoms less than 12 days from booster administration (Figure 2).

Discussion

Our study is one of the first investigations of the real-world effectiveness of the SARS-CoV-2 booster vaccine in preventing severe disease among hospitalized COVID-19 patients in the United States. Despite their older age (median 73 vs 70 years old (p = 0.018)), higher rate of pre-existing ESRD (13.6% vs 6.2% (p < 0.001)), higher proportion of immunocompromised state (29.5% vs 17.9% (p < 0.001)), and a higher risk of in-hospital death (Elixhauser weighted score 12 vs 10 (p < 0.026)), in-hospital mortality was lower in the FV&B compared to the FV group (7.1% vs 10.3% (p = 0.045)). While it is unsurprising that our FV&B cohort was older and had more immunocompromised individuals given the staged rollout of the booster vaccine by age and risk factors, it is notable that they experienced a lower rate of in-hospital mortality despite being higher risk for death at baseline. Previous evidence suggested that amongst elderly individuals with multiple comorbidities, vaccination status did not provide a significant mortality benefit once breakthrough infection requiring hospitalization had occurred.[21] However, in our current analysis, among the subgroup of individuals over the age of 65, we found that not only did FV individuals have a lower incidence of in-hospital death when compared to UV individuals (9.1% vs 21.2% (p < 0.001)), FV&B individuals saw a further reduction in death when compared to FV patients (9.1% vs 13.6% (p = 0.035)). These findings suggest that even among elderly patients with significant comorbidities, a booster vaccine may provide additional protection against the progression toward severe disease despite breakthrough infection requiring hospitalization. This current analysis suggests an additional

Variables[‡]	All	Vaccination Status			p value
		FV&B	FV	UV	
N	7728	448 (5.80%)	2257 (29.21%)	5023 (65.00%)	
Demographics					
Age, years					
Mean (SD)	61.87 (17.64)	70.90 (14.40)[*,‡‡]	68.53 (15.78)[*,§]	58.07 (17.52)[§,‡‡]	<0.001[¶]
Median (IQRs)	63.00 (50.00, 75.00)	73.00 (62.00, 82.00)	70.00 (59.00, 80.00)	59.00 (45.00, 71.00)	
Gender					
Female	3933 (50.89%)	229 (51.12%)	1100 (48.74%)[§]	2604 (51.84%)[§]	0.049[†]
Male	3795 (49.11%)	219 (48.88%)	1157 (51.26%)	2419 (48.16%)	
Race (n = 7713/448/2255/5010)					
Black or African American	1921 (24.91%)	84 (18.75%)[‡‡]	464 (20.58%)[§]	1373 (27.41%)[§,‡‡]	<0.001[†]
White or Caucasian	5335 (69.17%)	337 (75.22%)	1667 (73.92%)	3331 (66.49%)	
Other	457 (5.93%)	27 (6.03%)	124 (5.50%)	306 (6.11%)	
BMI, kg/m^2 (n = 7509/438/2184/4887)					
Mean	31.17 (8.67)	29.27 (7.37)[*,‡‡]	30.63 (8.31)[*,§]	31.58 (8.90)[§,‡‡]	<0.001[¶]
Median	29.63 (25.28, 35.44)	28.25 (24.17, 34.01)	29.22 (24.90, 34.70)	29.95 (25.69, 35.94)	
Pre-existing comorbidities					
ESRD	315 (4.08%)	61 (13.62%)[*,‡‡]	140 (6.20%)[*,§]	114 (2.27%)[§,‡‡]	<0.001[†]
Immunocompromised	1105 (14.30%)	132 (29.46%)[*,‡‡]	404 (17.90%)[*,§]	569 (11.33%)[§,‡‡]	<0.001[†]
Elixhauser weighted score					
Mean	10.54 (12.18)	13.53 (12.96)[*,‡‡]	11.90 (12.86)[*,§]	9.66 (11.69)[§,‡‡]	<0.001[¶]
Median	10.00 (1.00, 18.00)	12.00 (3.00, 22.00)	10.00 (2.00, 20.00)	9.00 (0.00, 17.00)	
In-hospital therapies					
O$_2$ therapy	5529 (71.55%)	269 (60.04%)[‡‡]	1463 (64.82%)[§]	3797 (75.59%)[§,‡‡]	<0.001[†]
Nasal cannula/non-rebreather	3080 (39.86%)	180 (40.18%)	917 (40.63%)	1983 (39.48%)	0.644[†]
High flow O$_2$	1138 (14.73%)	30 (6.70%)[‡‡]	202 (8.95%)[§]	906 (18.04%)[§,‡‡]	<0.001[†]
Non-invasive ventilation	633 (8.19%)	37 (8.26%)	198 (8.77%)	398 (7.92%)	0.473[†]
Mechanical ventilation	678 (8.77%)	22 (4.91%)[‡‡]	146 (6.47%)[§]	510 (10.15%)[§,‡‡]	<0.001[†]
Vasopressor	694 (8.98%)	33 (7.37%)	168 (7.44%)[§]	493 (9.81%)[§]	0.002[†]
ICU-level care	1084 (14.03%)	56 (12.50%)	271 (12.01%)[§]	757 (15.07%)[§]	0.001[†]
Length of stay, hours					
Mean	184.13 (183.16)	164.31 (169.23)[‡‡]	171.15 (158.81)[§]	191.73 (193.83)[§,‡‡]	<0.001[¶]
Median	128.00 (72.00, 234.00)	113.50 (62.00, 207.50)	126.00 (71.00, 213.00)	134.00 (74.00, 241.50)	
Outcomes					
Death	908 (11.75%)	32 (7.14%)[*,‡‡]	232 (10.28%)[*,§]	644 (12.82%)[§,‡‡]	<0.001[†]
Discharge disposition location (n = 6820/416/2025/4379)					
Home	5846 (85.72%)	319 (76.68%)	1620 (80.00%)	3907 (89.22%)	
Rehab	100 (1.47%)	13 (3.12%)	36 (1.78%)	51 (1.16%)	
SNF	786 (11.52%)	72 (17.31%)	342 (16.89%)	372 (8.50%)	
Hospice	50 (0.73%)	11 (2.64%)	17 (0.84%)	22 (0.50%)	
Other	38 (0.55%)	1 (0.24%)	10 (0.49%)	27 (0.62%)	

Table 1: Demographics, pre-existing comorbidities, in-hospital therapies, and outcomes among FV&B, FV, and UV individuals.

Abbreviations: FV&B=fully vaccinated and boosted; FV=fully vaccinated; UV=unvaccinated; BMI=body mass index; ESRD=end-stage renal disease; ICU=intensive care unit; Rehab=rehabilitation; SNF=skilled nursing facility.

[‡]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented.

[¶]Kruskal-Wallis test.

[†]Chi-squared or Fisher's exact test.

[*]$p < 0.05$ between FV&B and FV[¶¶].

[§]$p < 0.05$ between FV and UV[¶¶].

[‡‡]$p < 0.05$ between FV&B and UV[¶¶].

[¶¶]In multiple comparisons test, post hoc Holm-Bonferroni procedure and the Tukey-Kramer method was used for categorical and numerical variables, respectively. P-values are available in Supplementary Table 1.

Variables[‡]	All, Age 65+	Vaccination Status			p value
		FV&B, Age 65+	FV, Age 65+	UV, Age 65+	
N	3654	320 (8.76%)	1449 (39.66%)	1885 (51.59%)	
Demographics					
Age, years					
Mean (SD)	76.97 (8.47)	78.21 (8.27)[‡‡]	77.97 (8.65)[§]	75.99 (8.25)[§,‡‡]	<0.001[¶]
Median (IQRs)	76.00 (70.00, 83.00)	78.00 (71.00, 84.25)	77.00 (71.00, 85.00)	74.00 (69.00, 82.00)	
Gender					
Female	1939 (53.07%)	162 (50.62%)	710 (49.00%)[§]	1067 (56.60%)[§]	<0.001[†]
Male	1715 (46.93%)	158 (49.38%)	739 (51.00%)	818 (43.40%)	
Race (n = 3652/320/1448/1884)					
Black or African American	628 (17.20%)	51 (15.94%)	212 (14.64%)[§]	365 (19.37%)[§]	<0.003[†]
White or Caucasian	2838 (77.71%)	249 (77.81%)	1170 (80.80%)	1419 (75.32%)	
Other	186 (5.09%)	20 (6.25%)	66 (4.56%)	100 (5.31%)	
BMI, kg/m^2 (n = 3540/312/1398/1830)					
Mean	28.91 (7.22)	28.30 (6.99)	29.15 (7.12)	28.84 (7.33)	0.108[¶]
Median	27.80 (24.11, 32.49)	27.12 (23.49, 33.14)	28.22 (24.21, 32.90)	27.53 (24.13, 32.28)	
Pre-existing comorbidities					
ESRD	174 (4.76%)	43 (13.44%)[*,‡‡]	84 (5.80%)[*,§]	47 (2.49%)[§,‡‡]	<0.001[†]
Immunocompromised	555 (15.19%)	89 (27.81%)[*,‡‡]	233 (16.08%)[*,§]	233 (12.36%)[§,‡‡]	<0.001[†]
Elixhauser weighted score					
Mean	14.24 (12.70)	15.62 (13.25)	14.25 (13.00)	13.99 (12.36)	0.093[¶]
Median	13.00 (5.00, 22.00)	16.00 (5.00, 25.00)	13.00 (5.00, 23.00)	13.00 (5.00, 22.00)	
In-hospital therapies					
O$_2$ therapy	2735 (74.85%)	213 (66.56%)[‡‡]	1023 (70.60%)[§]	1499 (79.52%)[§,‡‡]	<0.001[†]
Nasal cannula/non-rebreather	1508 (41.27%)	144 (45.00%)	628 (43.34%)[§]	736 (39.05%)[§]	0.016[†]
High flow O$_2$	502 (13.74%)	21 (6.56%)[*,‡‡]	150 (10.35%)[*,§]	331 (17.56%)[§,‡‡]	<0.001[†]
Non-invasive ventilation	373 (10.21%)	29 (9.06%)	139 (9.59%)	205 (10.88%)	0.373[†]
Mechanical ventilation	352 (9.63%)	19 (5.94%)[‡‡]	106 (7.32%)[§]	227 (12.04%)[§,‡‡]	<0.001[†]
Vasopressor	380 (10.40%)	25 (7.81%)[‡‡]	119 (8.21%)[§]	236 (12.52%)[§,‡‡]	<0.001[†]
ICU-level care	551 (15.08%)	44 (13.75%)	192 (13.25%)[§]	315 (16.71%)[§]	0.017[†]
Length of stay, hours					
Mean	204.63 (181.11)	185.23 (177.25)[‡‡]	187.16 (161.96)[§]	221.35 (193.75)[§,‡‡]	<0.001[¶]
Median	148.00 (91.00, 266.75)	133.50 (76.00, 242.00)	144.00 (85.00, 240.00)	159.00 (96.00, 292.00)	
Outcomes					
Death	626 (17.13%)	29 (9.06%)[*,‡‡]	197 (13.60%)[*,§]	400 (21.22%)[§,‡‡]	<0.001[†]
Discharge disposition location					
(n = 3028/291/1252/1485)					
Home	2257 (74.54%)	201 (69.07%)	904 (72.20%)	1152 (77.58%)	
Rehab	73 (2.41%)	13 (4.47%)	28 (2.24%)	32 (2.15%)	
SNF	641 (21.17%)	66 (22.68%)	302 (24.12%)	273 (18.38%)	
Hospice	45 (1.49%)	11 (3.78%)	14 (1.12%)	20 (1.35%)	
Other	12 (0.40%)	0 (0.00%)	4 (0.32%)	8 (0.54%)	

Table 2: Demographics, pre-existing comorbidities, in-hospital therapies, and outcomes among FV&B, FV, and UV individuals age 65 and older.

Abbreviations: FV&B=fully vaccinated and boosted; FV=fully vaccinated; UV=unvaccinated; BMI=body mass index; ESRD=end-stage renal disease; ICU=intensive care unit; Rehab=rehabilitation; SNF=skilled nursing facility.

[‡]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented.

[¶]Kruskal-Wallis test.

[†]Chi-squared or Fisher's exact test.

[*]$p < 0.05$ between FV&B and FV[¶].

[§]$p < 0.05$ between FV and UV[¶].

[‡‡]$p < 0.05$ between FV&B and UV[¶].

[¶]In multiple comparisons test, post hoc Holm-Bonferroni procedure and the Tukey-Kramer method was used for categorical and numerical variables, respectively. P-values are available in Supplementary Table 1.

Variables[‡]	All, ICU	Vaccination Status			p value
		FV&B, ICU	FV, ICU	UV, ICU	
n	1084	56 (5.17%)	271 (25.00%)	757 (69.83%)	
Demographics					
Age, years					
Mean (SD)	63.07 (15.79)	72.05 (13.17)[‡‡]	70.09 (12.60)[§]	59.89 (15.94)[§,‡‡]	<0.001[¶]
Median (IQRs)	65.00 (53.00, 74.00)	73.50 (66.00, 81.25)	71.00 (63.00, 79.50)	61.00 (49.00, 71.00)	
Gender					
Female	463 (42.71%)	32 (57.14%)	110 (40.59%)	329 (43.46%)	0.714[†]
Male	621 (57.29%)	24 (42.86%)	161 (59.41%)	428 (56.54%)	
Race (n = 1081/56/270/755)					
Black or African American	222 (20.54%)	6 (10.71%)	47 (17.41%)	169 (22.38%)	0.155[†]
White or Caucasian	796 (73.64%)	47 (83.93%)	206 (76.30%)	543 (71.92%)	
Other	63 (5.83%)	3 (5.36%)	17 (6.30%)	43 (5.70%)	
BMI, kg/m^2 (n = 1068/56/266/746)					
Mean	32.96 (9.66)	29.37 (5.82)[‡‡]	31.67 (9.25)[§]	33.69 (9.93)[§,‡‡]	<0.001[¶]
Median	31.41 (26.32, 37.59)	28.87 (25.45, 33.72)	30.51 (24.99, 36.29)	31.91 (27.14, 38.61)	
Pre-existing comorbidities					
ESRD	60 (5.54%)	13 (23.21%)[*,‡‡]	27 (9.96%)[*,§]	20 (2.64%)[§,‡‡]	<0.001[†]
Immunocompromised	185 (17.07%)	23 (41.07%)[*,‡‡]	68 (25.09%)[*,§]	94 (12.42%)[§,‡‡]	<0.001[†]
Elixhauser weighted score					
Mean	18.94 (13.90)	22.09 (13.69)[‡‡]	21.99 (15.20)[§]	17.61 (13.22)[§,‡‡]	<0.001[¶]
Median	19.00 (9.00, 28.00)	22.50 (11.00, 31.25)	22.00 (11.00, 31.00)	17.00 (7.00, 26.00)	
In-hospital therapies					
O$_2$ therapy	1042 (96.13%)	49 (87.50%)[‡‡]	259 (95.57%)	734 (96.96%)[‡‡]	0.005[†]
Nasal cannula/non-rebreather	129 (11.90%)	10 (17.86%)	44 (16.24%)[§]	75 (9.91%)[§]	0.008[†]
High flow O$_2$	84 (7.75%)	3 (5.36%)	19 (7.01%)	62 (8.19%)	0.755[†]
Non-invasive ventilation	212 (19.56%)	14 (25.00%)	65 (23.99%)	133 (17.57%)	0.042[†]
Mechanical ventilation	617 (56.92%)	22 (39.29%)[‡‡]	131 (48.34%)[§]	464 (61.29%)[§,‡‡]	<0.001[†]
Vasopressor	623 (57.47%)	32 (57.14%)	146 (53.87%)	445 (58.78%)	0.373[†]
Length of stay, hours					
Mean	388.93 (297.27)	370.29 (291.23)	344.73 (239.55)[§]	406.13 (314.49)[§]	0.014[¶]
Median	323.50 (187.75, 514.50)	292.50 (142.75, 504.00)	299.00 (168.00, 454.00)	338.00 (201.00, 534.00)	
Outcomes					
Death	606 (55.90%)	21 (37.50%)[‡‡]	142 (52.40%)	443 (58.52%)[‡‡]	0.004[†]
Discharge disposition location (n = 478/35/129/314)					
Home	298 (62.34%)	18 (51.43%)	75 (58.14%)	205 (65.29%)	
Rehab	43 (9.00%)	6 (17.14%)	13 (10.08%)	24 (7.64%)	
SNF	111 (23.22%)	9 (25.71%)	36 (27.91%)	66 (21.02%)	
Hospice	9 (1.88%)	2 (5.71%)	3 (2.33%)	4 (1.27%)	
Other	17 (3.56%)	0 (0.00%)	2 (1.55%)	15 (4.78%)	

Table 3: Demographics, pre-existing comorbidities, in-hospital therapies, and outcomes among FV&B, FV, and UV individuals requiring intensive care.

Abbreviations: FV&B=fully vaccinated and boosted; FV=fully vaccinated; UV=unvaccinated; BMI=body mass index; ESRD=end-stage renal disease; ICU=intensive care unit; Rehab=rehabilitation; SNF=skilled nursing facility.

[‡]For continuous variables, medians (interquartile ranges, IQRs) and means (standard deviation, SD) were presented. For categorical variables, frequencies (percentage) were presented.

[¶]Kruskal-Wallis test.

[†]Chi-squared or Fisher's exact test.

[*]$p < 0.05$ between FV&B and FV[¶¶].

[§]$p < 0.05$ between FV and UV[¶¶].

[‡‡]$p < 0.05$ between FV&B and UV[¶¶].

[¶¶]In multiple comparisons test, post hoc Holm-Bonferroni procedure and the Tukey-Kramer method was used for categorical and numerical variables, respectively. *P*-values are available in Supplementary Table 1.
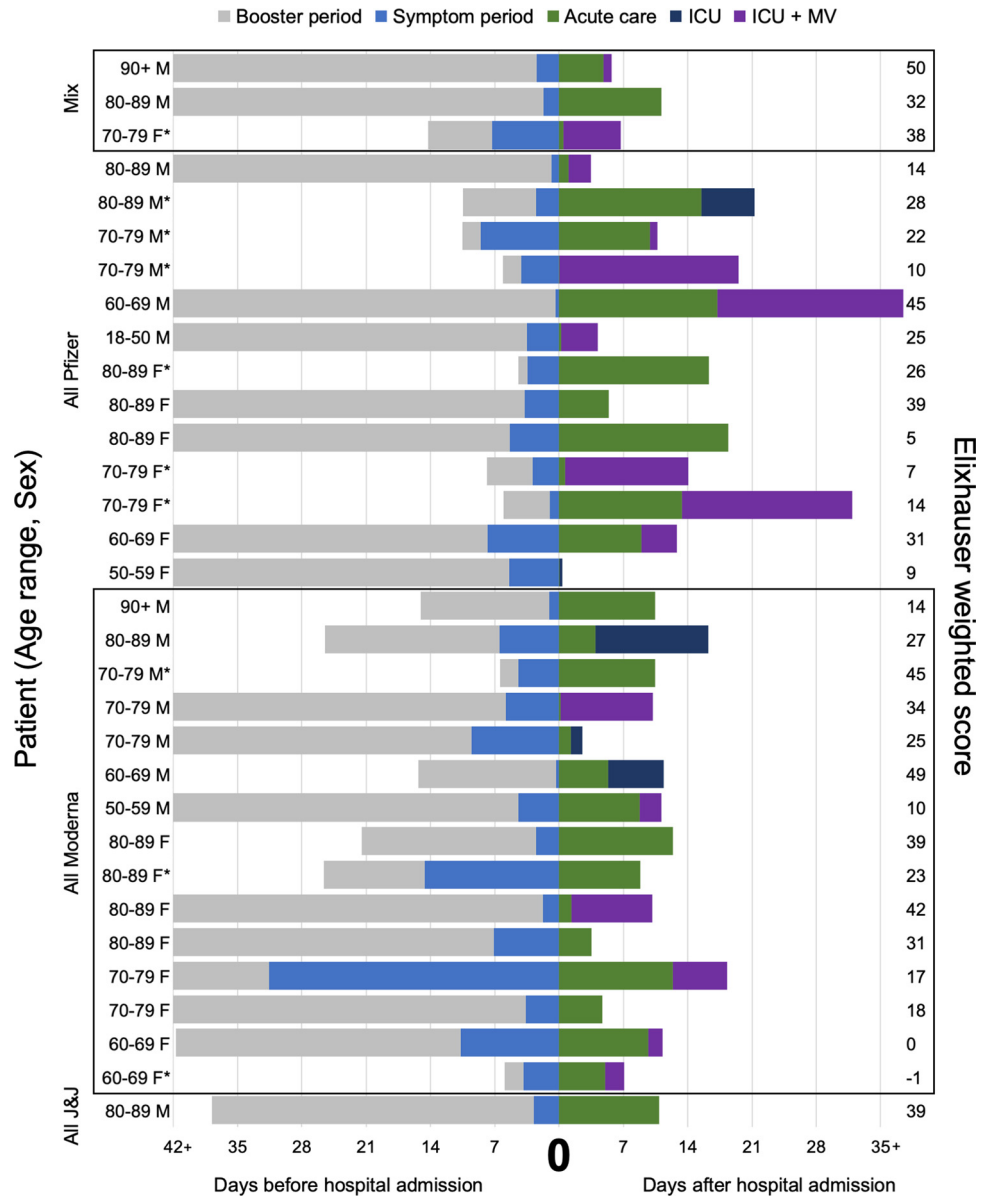
Figure 2. Characteristics and comorbidities of 32 fully vaccinated and boosted patients who expired from COVID-19.

Demographic/clinical data includes age range, sex, Elixhauser weighted score, vaccine type, timing of booster, and timing of symptom onset. Outcomes data includes mechanical ventilation and mortality.

Abbreviations: ICU=Intensive care unit; MV=Mechanical ventilation; J&J=Janssen.

* <12 days from booster vaccination to symptom onset. The median number of days from booster vaccination to symptom onset was 38 (IQR 7.8, 66).

value of the booster not seen in previous literature on fully vaccinated patients and severe disease.[21,22]

The relationship between the timing of booster administration and the onset of infectious symptoms is notable in the FV&B population that died. In general, COVID-19 was diagnosed in close proximity to receiving the dose. Specifically, 31.3% (10 out of 32) of the deceased group received the booster dose <12 days from onset of symptoms suggesting that FV&B

patients who required ICU care may not have had enough time since their booster dose to confer the full benefit of the additional vaccination. The relevance of the timing of booster administration is supported by data from an Israeli study assessing the benefit of BNT162b2 booster. In that analysis, the authors found that 12 days post-booster immunization, there was a significant decrease in the rate of breakthrough infection when compared to the control, un-boosted,

group.[23] Our data suggests that the mortality benefit for the FV&B group may be even greater as the full potency of the booster was likely unrecognized in a substantial minority of the deceased.

It is unclear if an immunocompromised state is an independent predictor of severe COVID-19 disease in boosted patients. In our study sample, the proportion of individuals who were identified as immunocompromised was much higher in the FV&B group compared to both the FV and UV groups, 29.5%, 17.9%, and 11.3%, respectively (all $p < 0.001$). Additionally, among patients who required ICU level care, this trend continued, with FV&B patients having the highest proportion of immunocompromised individuals (41.1%) when compared to FV (25.1% ($p = 0.024$)) and UV individuals (12.4% ($p < 0.001$)). Previous evidence has shown that immunocompromised patients may have a tempered immune response to vaccination.[24,25] However, additional doses may increase the likelihood of immune response.[26] Unfortunately, none of the deceased in the FV&B cohort had laboratory antibody testing results within their health records to explore this variable further.

This study has several limitations. First, the sample size of the FV&B group was small. This was due to a smaller proportion of the population that was eligible for the booster dose during the study period. Further, given that our study only evaluated patients who sought emergency care and subsequently required hospitalization, with presumed strengthened immunity from the additional dose, there are likely a number of breakthrough SARS-CoV-2 infections that were not captured in our cohort. Given the staged approval of the booster doses starting with high-risk individuals, our sample population was biased towards individuals $\geq$ 65 years old as well as those with a pre-existing immunocompromised state. As with all retrospective studies, we were unable to control for confounders that may have affected hospital outcomes when comparing FV&B, FV, and UV individuals. Lastly, given our small sample size and the heterogeneity of vaccination sequences we were unable to determine if one vaccine, or sequence of vaccines, has benefit over another.

Conclusions
In this study of hospitalized patients with COVID-19, we observed that the cohort of FV&B patients had a lower rate of in-hospital mortality compared to both FV and UV individuals, despite being higher risk for in-hospital mortality at baseline. While vaccination provides a layer of protection against mortality compared to no vaccination, the booster dose enhances this defense and confers an additional mortality benefit. As COVID-19 continues to spread, more extensive studies are needed to further identify risk factors for severe outcomes among the FV&B population.

Contributors
AB, NM, and SJ designed the study, had full access to the data, and take responsibility for the integrity and accuracy of the data analysis. AB, NM, and SJ contributed to subject enrollment, data collection, data and statistical analysis. All authors contributed to the writing and editing of the manuscript. All authors contributed to data acquisition, analysis and interpretation, and all reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement
The data that support the findings of this study are available via a data access agreement. Please contact the corresponding author (AB) for this request.

Declaration of interests
All authors declare no relevant conflicts of interest relevant to this work.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100227.

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