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ORIGINAL RESEARCH

Infectious Disease

Predictors of hospitalization and severe disease due to breakthrough SARS-CoV-2 infection in fully vaccinated individuals

Steven Johnson DO[1] 🄳 | **Nicholas Mielke BS**[2] | **Trini Mathew MD**[3] |
Gabriel N Maine PhD[4] | **Nai-Wei Chen PhD**[5] | **Amit Bahl MD**[1]

[1]Department of Emergency Medicine, Beaumont Hospital, Royal Oak, USA

[2]Oakland University, William Beaumont School of Medicine, Royal Oak, USA

[3]Department of Infectious Disease, Beaumont Hospital, Royal Oak, USA

[4]Histocompatibility Laboratory, Beaumont Hospital, Royal Oak, USA

[5]Beaumont Hospital, Royal Oak, USA

Correspondence
Steven Johnson, DO, Department of Emergency Medicine, Beaumont Hospital, Royal Oak, 3601 13 Mile Rd, Royal Oak, MI 48073, USA.
Email: Steven.johnson.e@gmail.com

Funding information
Moderna

Abstract

Objective: We aimed to identify risk factors for hospital admission and severe disease among fully vaccinated (FV) individuals with COVID-19. Further, we investigated if risk factors for hospitalization and severe disease are similar between unvaccinated (UV) and vaccinated individuals.

Methods: This was a multicenter, observational cohort analysis from a large regional healthcare system in metro Detroit using electronic health record data to evaluate risk factors for hospitalization and severe COVID-19 disease. Vaccination data were retrieved using electronic medical records linked to our statewide immunization database. Consecutive adult FV and UV patients with a primary admission diagnosis of COVID-19 were included in the comparative analysis. Partially vaccinated patients and patients who had received a booster dose were excluded. The primary outcome of this study was hospital admission and severe disease inclusive of intensive care unit (ICU) admission, mechanical ventilation, or death.

Results: Between December 15, 2020 and December 19, 2021, 20,584 emergency department visits met our inclusion criteria. Among these, 2005 (9.7%) visits consisted of FV individuals, 18,579 (90.3%) were UV, and 40.3% of UV and 52.7% of FV required hospitalization with similar (12.7% and 12.6%, respectively) rates of severe disease. Hospitalized UV patients with severe disease were younger than their FV counterparts (49.5% <65 years vs. 13.5% $p < 0.001$). Risk factors for severe disease on UV and FV included age ≥65 years (UV: adjusted odds ratio [aOR] 1.49, 95% confidence interval [CI] 1.28–1.73, $p < 0.001$ and FV: aOR 2.50, 95% CI 1.44–4.36 $p = 0.001$) and weighted Elixhauser score >10 (UV: aOR 9.11, 95% CI 6.92–12.00, $p < 0.001$ and FV: aOR 6.04, 95% CI 2.68–13.26, $p < 0.001$). However, only on UV status, body mass index (BMI) ≥30 kg/m^2 was associated with increased odds of severe disease (aOR 2.59, 95% CI 2.09–3.22, $p < 0.001$).

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Conclusions: FV patients with breakthrough SARS-CoV-2 infection who require hospitalization and have severe disease are older and have more medical comorbidities compared to UV patients. When comparing risk factors for severe disease between UV and FV individuals, FV status is particularly associated with reduced risk among patients with a BMI ≥30 kg/m^2 and a moderate number of medical comorbidities, regardless of age, highlighting the importance of vaccination in these particularly vulnerable groups.

KEYWORDS
COVID-19, hospitalization, immunization, mortality, risk factors, severe disease, vaccination, SARS-CoV-2

1 | INTRODUCTION

1.1 | Background

Although current data demonstrate the COVID-19 vaccine's effectiveness in reducing SARS-CoV-2 infections and severe disease, there are limited real-world data regarding which characteristics place a vaccinated individual with COVID-19 at risk for hospitalization and severe disease.[1–5] Multiple studies early in the pandemic demonstrated various risk factors, such as specific medical conditions, socioeconomic status, and race to be significant predictors of severe disease or need for hospitalization.[6–9] However, larger studies looking at broader populations have concluded that age and comorbidity burden are likely the most predictive risk factors for hospitalization among the unvaccinated (UV), whereas body mass index (BMI) and individual comorbidities contribute more to a patient's risk of severe disease.[9,10] To date, there are minimal data evaluating if vaccination has shifted these individual risk factors. One study identified male sex, multiple comorbidities, and immunosuppression as key predictors for hospitalization among fully vaccinated (FV) individuals with breakthrough SARS-CoV-2 infection among a sample from Israel.[11] Another study demonstrated that chronic kidney disease, especially history of renal transplant, as well as a history of Down's syndrome, had a significant impact on the risk of hospitalization and severe disease among vaccinated patients with breakthrough infection among a population in the United Kingdom.[12]

1.2 | Importance

As more of the US population becomes FV, it is imperative that we understand which individuals are at the highest risk for hospitalization and severe disease in breakthrough COVID-19. In a recent investigation, we found that FV patients had a substantially reduced risk of requiring hospital-based treatment compared to UV patients.[2] However, we also observed that among elderly individuals with multiple comorbidities requiring hospitalization for COVID-19, outcomes were similar regardless of vaccination status. As frustrations grow regarding isolation and social distancing policies that have come about during the COVID-19 pandemic, it is important to better characterize the population at the highest risk for severe disease despite vaccination. This information would facilitate a more accurate and informed discussion among families, physicians, and patients regarding individual risk. However, current data are mixed regarding what specific features place a vaccinated individual at risk for hospitalization, especially among a US-based cohort.

1.3 | Goals of this investigation

In this investigation, we aim to identify historical, demographic, and socioeconomic data that may help to predict which vaccinated individuals are at the highest risk for hospitalization and severe disease after breakthrough SARS-CoV-2 infection. Further, we seek to determine if risk factors for hospitalization and severe disease are similar between UV and vaccinated individuals.

2 | METHODS

2.1 | Study design and setting

This multicenter, observational retrospective cohort analysis used electronic health record (EHR; Epic Systems, Verona, WI, USA) data to evaluate risk factors for hospitalization and severe disease among FV individuals with breakthrough SARS-CoV-2 infection.

The study was conducted at Beaumont Health, an 8-hospital acute care regional health system caring for 2.2 million people across the communities within the Metro Detroit area. The hospitals range from a large tertiary care academic center to intermediate-sized and smaller community hospitals.

2.2 | Selection of participants

Consecutive patients 18 years and older who presented to one of Beaumont Health's emergency departments between December 15, 2020

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and December 19, 2021 who had a principal diagnosis of COVID-19 (U07.1) were included. Patients were excluded if they tested positive for SARS-CoV-2 >28 days before their ED encounter, had COVID-19 (U07.1) as a secondary diagnosis, were partially vaccinated, or had received an additional booster vaccine dose. The Beaumont Institutional Review Board approved this investigation. Written informed consent was waived due to the retrospective nature of this study.

2.3 | Exposures and measurements

Included patients were identified as either UV or FV. UV individuals were defined as having positive laboratory SARS-CoV-2 testing with no record of immunization against the SARS-CoV-2 virus. FV individuals were defined as having positive laboratory testing for SARS-CoV-2 ≥14 days since the administration of a second dose of either mRNA vaccine, or ≥14 days since the administration of a viral vector vaccine (Janssen).

Partially vaccinated individuals were defined as having positive laboratory SARS-CoV-2 testing after a single dose of either mRNA (Pfizer, Moderna) vaccine, or <14 days after the second dose of either mRNA vaccine (Pfizer, Moderna) or <14 days after the administration of the single dose of viral vector vaccine (Janssen). FV and boosted individuals had received either 3 doses of an mRNA vaccine (Pfizer, Moderna), 1 dose of a viral vector vaccine (Janssen) and 1 dose of the mRNA, 1 dose of a viral vector vaccine and 2 doses of the mRNA, or 2 doses of a viral vector vaccine.

EHR data were used to confirm SARS-CoV-2 vaccination status. These data were available through our EHR and linked to the Michigan Care Improvement Registry (MCIR) and, therefore, captured patients who had been vaccinated outside of the Beaumont Health System.[13] MCIR contains all SARS-CoV-2 immunization data for patients who received their vaccine within the state of Michigan. The data included vaccine type as well as the date of administration.

Patients were classified as immunocompromised if their clinical medical records contained any historical *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes consistent with immunocompromised state as defined by the Agency for Healthcare Research and Quality (AHRQ) at the time of their ED presentation.[14] Preexisting end-stage renal disease (ESRD) was defined as any ICD-10-CM code consistent with chronic need for dialysis or a preexisting diagnosis of chronic kidney failure, as defined by AHRQ.[15]

Demographics included age, race, zip code, and gender. Clinical data included comorbidities, BMI, and the number of previous ED visits within the past 6 months. ICD-10-CM codes for comorbidities were used to calculate the weighted Elixhauser comorbidity scores as described by the AHRQ.[16] Median household income data were estimated based on the patient's zip code extracted from the EHR and data available from American Community Survey released by the US Census Bureau.[17]

The Bottom Line

A study of more than 20,000 patients with COVID-19 found factors associated with hospitalization and severe illness. Unvaccinated people were younger and had a higher body mass index, whereas those vaccinated were older with more comorbidities.

2.4 | Outcomes

COVID-19 hospitalization was defined as a principal admission and or discharge diagnosis of COVID-19 (U07.1). Severe disease was defined as a composite outcome of ICU admission any time during hospitalization, need for mechanical ventilation, or in-hospital death.

The primary outcome of this study was hospital admission and the secondary outcome was severity of illness. We examined demographic, epidemiologic, and clinical variables among UV and FV patients to identify risk factors that were unique to our FV population.

2.5 | Analysis

Descriptive analysis was used to summarize patient characteristics stratified by vaccination status. Categorical variables were expressed frequencies (percentages) and compared using chi-square test. To investigate the association of risk factors (patient characteristics) with hospitalization and severe disease, respectively, across vaccination status (UV, FV), the multivariable logistic regression model with the interactions between risk factors and vaccination status was used for this overall analysis. Regardless of the significance of the interactions, the interactions were included in the model. The adjusted odds ratios (aORs) on risk factors for hospitalization and severe disease, respectively, by vaccination status were estimated from this model. Similarly, the adjusted risk ratios (relative risk) of risk factors associated with hospitalization and severe disease, respectively, were also estimated via Poisson regression with the robust variance estimation.[18]

Moreover, we used the saturated log-linear model to examine the homogeneous association between individual comorbidity and hospitalization and severe disease, respectively, across vaccination status.

Subsequently, the risk factors were identified separately on the basis of vaccination status. After a univariable analysis, variables with a p value < 0.2 or variables determined by clinicians based on clinical rationale were subjected to a multivariable modeling strategy. The corresponding c-statistic and a bootstrap cross-validation with 1000 resamples were used to evaluate the performance of modeling in multivariable analysis. In multivariable regression analysis, there was potential collinearity on race and household income and only race was included in regression models. In addition, for a set of all risk factors,

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we used recursive partitioning with conditional inference tree algorithm to explore the subgroups each with a different characteristics profile for hospitalization and severe disease, respectively.[19] With the goal of reaching an unbiased tree, the procedure repeats until 2 stopping criteria: (1) 5% level of significance and (2) minimum sample size of 900, 300, 100, and 100 for all UV patients, UV hospitalized patients, all FV patients, and FV hospitalized patients, respectively, at terminal nodes. All tests with $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed with R-4.0.2 (R Foundation for Statistical Computing), Stata 15.1 (StataCorp), and SAS v9.4 (SAS Institute, Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics on study cohort

During the period between December 15, 2020 and December 19, 2021, there were 20,584 ED visits that met our inclusion criteria. Among these, 2005 (9.7%) visits consisted of FV individuals and 18,579 (90.3%) were UV. **Table 1** shows that among all 20,584 ED visits, characteristics of UV and FV patients were notably different. With regard to age, 78.8% of the UV patients were 18–64 years old compared to only 48.6% in the FV patients ($p < 0.001$). Compared to the UV group, the FV group had a higher proportion of patients with preexisting ESRD (1.2% vs. 3.4% $p < 0.001$), immunocompromised status (6.7% vs. 12.1% $p < 0.001$), and a weighted Elixhauser score >10 (20.6% vs. 30.9% $p < 0.001$), respectively.

Among all ED visits during our study period, 52.7% (1056) of the FV patients and 40.3% (7494) of the UV patients required hospitalization. With regard to age, 71.1% of FV patients requiring hospitalization were older than ≥65 versus only 37.3% of UV patients ($p < 0.001$). Additionally, when comparing UV to FV patients requiring hospitalization, FV patients had higher rates of preexisting ESRD (2.5% vs. 6% $p < 0.001$), immunocompromised status (11.4% vs. 17.2% $p < 0.001$), and weighted Elixhauser score >10 (39.2% vs. 50% $p < 0.001$).

Among hospitalized patients during our study period, severe disease occurred in 12.6% (133) of the FV patients and 12.7% (954) of the UV. At baseline, the only difference between these 2 groups was age, with patients being younger than their FV counterparts (49.5% <65 years vs. 13.5% $p < 0.001$).

3.2 | Hospitalization

3.2.1 | Association between risk factors and hospitalization across vaccination status

In an overall analysis, the multivariable regression models with the interactions between risk factors and vaccination status were used to evaluate the mutually adjusted effects of risk factors on vaccination status (UV, FV). Results were illustrated and summarized in **Table 2** and **Table 3**. *On UV status*, age ≥65 years (aOR 3.76, 95% confidence interval [CI] 3.45–4.10, $p < 0.001$), BMI ≥30 kg/m^2 compared with normal weight (18.5 to 25.0 kg/m^2) (aOR 2.06, 95% CI 1.86–2.27, $p < 0.001$), preexisting ESRD (aOR 1.90, 95% CI 1.26–2.86, $p = 0.002$), immunocompromised status (aOR 2.34, 95% CI 2.01–2.72, $p < 0.001$), and weighted Elixhauser score of >10 compared with <0 (aOR 3.40, 95% CI 3.06–3.79, $p < 0.001$) were all associated with increased odds of hospitalization. Female sex (aOR 0.76, 95% CI 0.71–0.82, $p < 0.001$) and African American race compared with White (aOR 0.65, 95% CI 0.60–0.70, $p < 0.001$) were associated with the decreased odds of hospitalization. *On FV status*, age ≥65 years (aOR 4.44, 95% CI 3.57–5.52, $p < 0.001$), BMI ≥30 kg/m^2 compared with normal weight (18.5 to 25.0 kg/m^2) (aOR 1.71, 95% CI 1.28–2.28, $p < 0.001$), preexisting ESRD (aOR 4.21, 95% CI 1.62–10.94, $p = 0.003$), immunocompromised status (aOR 1.67, 95% CI 1.13–2.46, $p = 0.01$), and weighted Elixhauser score >10 compared with <0 (aOR 6.27, 95% CI 4.52–8.69, $p < 0.001$) were associated with increased odds of hospitalization. Female sex (aOR 0.73, 95% CI 0.59–0.91, $p = 0.004$) was associated with the decreased odds of hospitalization. Similarly, the risk ratios (relative risk) of risk factors associated with the probability of hospitalization were also estimated via Poisson regression approach (**Table S1**).

3.2.2 | Internal bootstrap validation and tree analysis on UV patients for hospitalization

When analysis of hospitalization was separately performed among UV individuals, the multivariable logistic model with an internal bootstrap validation (c-statistic 0.78, 95% CI 0.77–0.79) revealed that age, sex, race, BMI, preexisting ESRD, immunocompromised status, and weighted Elixhauser score of 0–10 and >10 were significantly associated with the odds of hospitalization (**Table S2**). Similarly, the risk ratios (relative risk) of risk factors associated with the probability of hospitalization were also estimated via Poisson regression approach (**Table S3**). Through the exploration of a tree analysis, we observed that in UV patients the highest rate of hospitalization (89%) was among patients ≥65 years with a weighted Elixhauser score >10 (node 25) and the lowest rate of hospitalization (10%) was among African Americans <65 years with a BMI <30 kg/m^2 and a weighted Elixhauser score ≤10 (node 12) (**Figure 1**).

3.2.3 | Internal bootstrap validation and tree analysis on FV patients for hospitalization

When analysis of hospitalization was separately performed among FV individuals, results of the identified risk factors in the multivariable logistic model with an internal bootstrap validation (c-statistic 0.81, 95% CI 0.79–0.83) revealed that age, sex, preexisting ESRD, immunocompromised status, and weighted Elixhauser score >10 were significantly associated with the odds of hospitalization (**Table S2**). Similarly, the risk ratios (relative risk) of risk factors associated with the probability of hospitalization were also estimated via Poisson regression approach (**Table S3**). In a tree analysis of the FV group, the highest

TABLE 1 Patient characteristics by vaccination status on all patients, hospitalized patients, and hospitalized patients with severity of illness

Variables	All patients (ED visits)			Hospitalized patients			Hospitalized patients with severity of illness		
	Unvaccinated	Fully vaccinated	p value	Unvaccinated	Fully vaccinated	p value	Unvaccinated	Fully vaccinated	p value
N	18,579	2005		7494	1056		954	133	
Age, years									
18 to 64	14,640 (78.8%)	975 (48.6%)	< 0.001	4697 (62.7%)	305 (28.9%)	< 0.001	472 (49.5%)	18 (13.5%)	< 0.001
≥65	3939 (21.2%)	1030 (51.4%)		2797 (37.3%)	751 (71.1%)		482 (50.5%)	115 (86.5%)	
Sex									
Male	8511 (45.8%)	957 (47.7%)	0.10	3689 (49.2%)	566 (53.6%)	0.008	552 (57.9%)	80 (60.2%)	0.62
Female	10,068 (54.2%)	1048 (52.3%)		3805 (50.8%)	490 (46.4%)		402 (42.1%)	53 (39.8%)	
Race									
White/Caucasian	10,916 (58.8%)	1536 (76.6%)	< 0.001	4948 (66.0%)	861 (81.5%)	< 0.001	670 (70.2%)	107 (80.4%)	0.05
Black/African American	6167 (33.2%)	356 (17.8%)		1919 (25.6%)	150 (14.2%)		197 (20.7%)	17 (12.8%)	
Other	1496 (8.0%)	113 (5.6%)		627 (8.4%)	45 (4.3%)		87 (9.1%)	9 (6.8%)	
Household income[a]									
<40,000	4475 (24.1%)	290 (14.5%)	< 0.001	1518 (20.3%)	139 (13.2%)	< 0.001	189 (19.8%)	14 (10.5%)	0.06
40,000 to 60,000-	6610 (35.6%)	652 (32.5%)		2729 (36.4%)	359 (34.0%)		361 (37.8%)	51 (38.4%)	
60,000 to 80,000-	4692 (25.2%)	623 (31.1%)		2022 (27.0%)	347 (32.9%)		274 (28.7%)	45 (33.8%)	
≥80,000	2802 (15.1%)	440 (21.9%)		1225 (16.3%)	211 (20.0%)		130 (13.6%)	23 (17.3%)	
BMI, kg/m^2									
<18.5	260 (1.4%)	30 (1.5%)	0.003	136 (1.8%)	18 (1.7%)	< 0.001	22 (2.3%)	1 (0.8%)	0.007
18.5 to 25.0-	3357 (18.1%)	418 (20.8%)		1196 (16.0%)	222 (21.0%)		133 (13.9%)	31 (23.3%)	
25.0 to 30.0-	5170 (27.8%)	581 (29.0%)		2049 (27.3%)	319 (30.2%)		237 (24.8%)	39 (29.3%)	
≥30.0	9792 (52.7%)	976 (48.7%)		4113 (54.9%)	497 (47.1%)		562 (58.9%)	62 (46.6%)	
Preexisting ESRD									
No	18,351 (98.8%)	1936 (96.6%)	< 0.001	7304 (97.5%)	993 (94.0%)	< 0.001	921 (96.5%)	123 (92.5%)	0.02
Yes	228 (1.2%)	69 (3.4%)		190 (2.5%)	63 (6.0%)		33 (3.5%)	10 (7.5%)	
Immunocompromised									
No	17,331 (93.3%)	1763 (87.9%)	< 0.001	6639 (88.6%)	874 (82.8%)	< 0.001	812 (85.1%)	106 (79.7%)	0.11
Yes	1248 (6.7%)	242 (12.1%)		855 (11.4%)	182 (17.2%)		142 (14.9%)	27 (20.3%)	
Elixhauser weighted score									
< 0	3771 (20.3%)	421 (21.0%)	< 0.001	1688 (22.5%)	169 (16.0%)	< 0.001	64 (6.7%)	7 (5.3%)	0.06
0 to 10	10,972 (59.1%)	965 (48.1%)		2865 (38.2%)	359 (34.0%)		216 (22.6%)	19 (14.3%)	
>10	3836 (20.6%)	619 (30.9%)		2941 (39.2%)	528 (50.0 %)		674 (70.7%)	107 (80.4%)	
ED visits before 6 months									
No	13,630 (73.4%)	1348 (67.2%)	< 0.001	5357 (71.5%)	667 (63.2%)	< 0.001	683 (71.6%)	89 (66.9%)	0.27
Yes	4949 (26.6%)	657 (32.8%)		2137 (28.5%)	389 (36.8%)		271 (28.4%)	44 (33.1%)	
Vaccine manufacturer									
Pfizer		1123 (56.0%)			551 (52.2%)			68 (51.1%)	
Moderna		592 (29.5%)			358 (33.9%)			49 (36.8%)	
Janssen		290 (14.5%)			147 (13.9%)			16 (12.0%)	

(Continues)

TABLE 1   (Continued)

Variables	All patients (ED visits)			Hospitalized patients			Hospitalized patients with severity of illness		
	Unvaccinated	Fully vaccinated	p value	Unvaccinated	Fully vaccinated	p value	Unvaccinated	Fully vaccinated	p value
Time from complete injection to ED arrival, days									
<90		285 (14.2%)			155 (14.7%)			15 (11.3%)	
90 to 180-		516 (25.7%)			265 (25.1%)			42(31.6%)	
180 to 240-		832 (41.5%)			442 (41.9%)			52 (39.1%)	
≥240		372 (18.6%)			194 (18.4%)			24 (18.0%)	

Abbreviations: BMI, body mass index; ED, emergency department; ESRD, end-stage renal disease.
[a]Household median income for ZIP code areas was obtained from new 5-year estimates from the 2014–2018 American Community Survey released by the U.S. Census Bureau.

TABLE 2   Estimated odds ratio on patient characteristics for hospitalization and severity of illness by vaccination status in logistic regression models with the interactions between patient characteristics and vaccination status[a]

Variables	Hospitalization (n = 20,584 patients)				Severity of illness (n = 8550 hospitalized patients)			
	Unvaccinated		Fully vaccinated		Unvaccinated		Fully vaccinated	
	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value
Age, years								
≥65 versus 18 to 64	3.76 (3.45–4.10)	< 0.001	4.44 (3.57–5.52)	< 0.001	1.49 (1.28–1.73)	< 0.001	2.50 (1.44–4.36)	0.001
Sex								
Female versus male	0.76 (0.71–0.82)	< 0.001	0.73 (0.59–0.91)	0.004	0.64 (0.56–0.74)	< 0.001	0.81 (0.55–1.20)	0.29
Race								
Black/African American versus White/Caucasian	0.65 (0.60–0.70)	< 0.001	0.78 (0.59–1.04)	0.10	0.79 (0.66–0.95)	0.01	1.06 (0.59–1.90)	0.85
Other versus White/Caucasian	1.07 (0.95–1.21)	0.28	0.74 (0.46–1.17)	0.20	1.15 (0.89–1.48)	0.30	1.97 (0.87–4.49)	0.11
BMI, kg/m²								
<18.5 versus 18.5 to 25.0–	1.28 (0.92–1.77)	0.14	1.32 (0.51–3.43)	0.57	1.22 (0.74–2.03)	0.43	0.37 (0.05–2.93)	0.34
25.0 to 30.0– versus 18.5 to 25.0–	1.35 (1.21–1.50)	< 0.001	1.29 (0.95–1.77)	0.10	1.23 (0.98–1.55)	0.08	0.89 (0.53–1.51)	0.67
≥30.0 versus 18.5 to 25.0–	2.06 (1.86–2.27)	< 0.001	1.71 (1.28–2.28)	< 0.001	2.59 (2.09–3.22)	< 0.001	1.48 (0.90–2.42)	0.12
Preexisting ESRD								
Yes versus No	1.90 (1.26–2.86)	0.002	4.21 (1.62–10.94)	0.003	0.89 (0.58–1.37)	0.60	1.03 (0.44–2.40)	0.95
Immunocompromised								
Yes versus No	2.34 (2.01–2.72)	< 0.001	1.67 (1.13–2.46)	0.01	1.16 (0.92–1.45)	0.21	1.05 (0.60–1.84)	0.85
Elixhauser weighted score								
0 to 10 versus <0	0.49 (0.45–0.53)	< 0.001	0.98 (0.76–1.26)	0.86	2.27 (1.70–3.03)	< 0.001	1.30 (0.53–3.18)	0.57
>10 versus <0	3.40 (3.06–3.79)	< 0.001	6.27 (4.52–8.69)	< 0.001	9.11 (6.92–12.00)	< 0.001	6.04 (2.68–13.62)	< 0.001
ED visits before 6 months								
Yes versus No	1.05 (0.97–1.14)	0.19	1.09 (0.87–1.37)	0.46	0.88 (0.75–1.03)	0.11	0.68 (0.45–1.02)	0.06

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ED, emergency department; ESRD, end-stage renal disease.
[a]The interactions between patient characteristics (risk factors) and vaccination status were considered in multivariable logistic regression models. In this overall analysis, regardless of the significance of interactions, the interactions were included in the model. There was potential collinearity on race and household income and household income was not included in analysis.

TABLE 3 Summary table demonstrating which features increased odds of outcome in each cohort

	Fully vaccinated	Unvaccinated
Age ≥65 years	Hospitalization and severe disease	Hospitalization and severe disease
Preexisting ESRD	Hospitalization only	Hospitalization only
Immunocompromised	Hospitalization only	Hospitalization only
Elixhauser weighted score 0–10	-	Severe disease only
Elixhauser weighted score >10	Hospitalization and severe disease	Hospitalization and severe disease
BMI ≥30 kg/m^2	Hospitalization only	Hospitalization and severe disease
Male sex	Hospitalization only	Hospitalization and severe disease
White race	-	Hospitalization and severe disease

Severe disease defined as hospitalized patients who: required mechanical ventilation, were admitted to an intensive care unit, or death.
Abbreviations: BMI, body mass index; ESRD, end-stage renal disease.
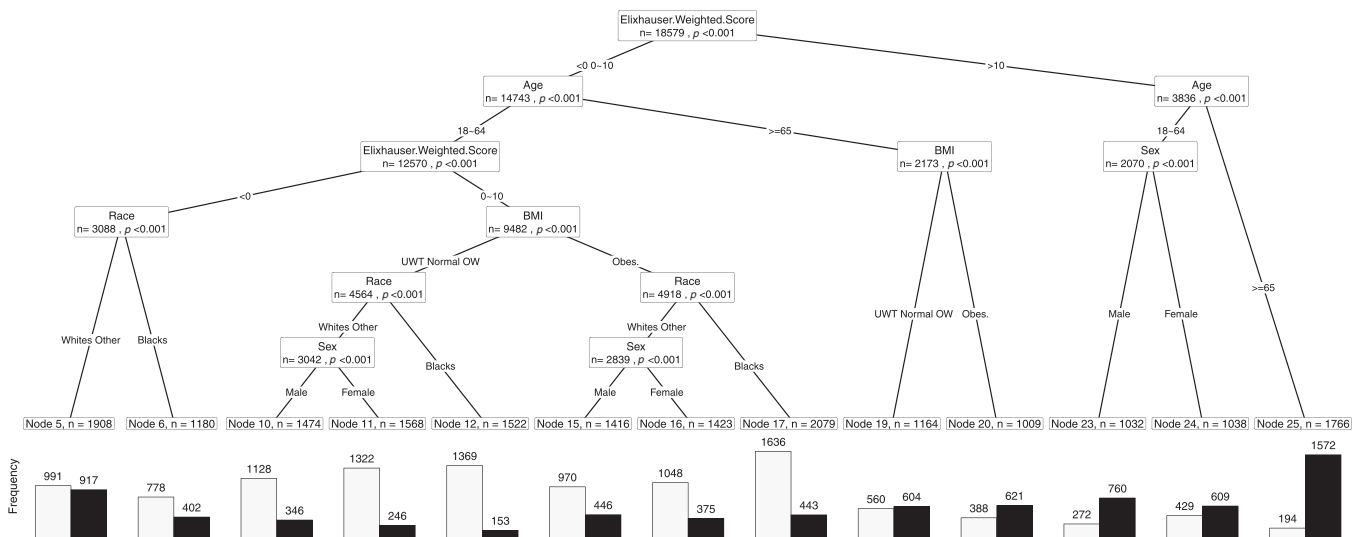
FIGURE 1 Exploration of the subgroups with different characteristics profiles on 18579 unvaccinated patients for hospitalization (black bars). BMI, body mass index; Normal, normal weight; Obes., obesity; OW, overweight; UWT, underweight

rate of hospitalization (88% and 95%) was seen among patients ≥65 years with a weighted Elixhauser score of >10, who had received the vaccine (node 16 and 17) and the lowest rate of hospitalization (11%) was seen in females <64 years with a BMI <30 kg/m^2 and a weighted Elixhauser score ≤10 (node 6) (**Figure S1**).

3.2.4 | Effects of individual comorbidities on hospitalization

Additionally, as shown in **Table S4**, when evaluating the association of individual comorbidity and hospitalization between UV and FV, the saturated log-linear models indicated that there was a heterogeneous association when examining: cardiac arrhythmia ($p = 0.001$), hypertension ($p = 0.05$), drug abuse ($p = 0.01$), uncomplicated diabetes ($p < 0.001$), and obesity ($p = 0.003$). Other comorbidity groups showed a homogeneous association when examining rates of hospitalization across FV and UV patients.

3.3 | Severe disease

3.3.1 | Association between risk factors and severe disease across vaccination status

As shown in **Table 2** and **Table 3**, with regard to an overall analysis for severe disease, on *UV status*, age ≥65 years (aOR 1.49, 95% CI 1.28–1.73, $p < 0.001$), BMI ≥30 kg/m^2 compared with normal weight (aOR 2.59, 95% CI 2.09–3.22, $p < 0.001$), and weighted Elixhauser score of 1–10 as well as >10 compared with <0 (aOR 2.27, 95% CI 1.70–3.03, $p < 0.001$), (aOR 9.11, 95% CI 6.92–12.00, $p < 0.001$) were associated with the increased odds of severe illness. Female sex (aOR 0.64, 95% CI 0.56–0.74, $p < 0.001$) and African American race (aOR 0.79, 95% CI 0.66–0.95, $p = 0.01$) were associated with the decreased odds of severe illness.

On *FV status*, only age ≥65 years (aOR 2.50, 95% CI 1.44–4.36 $p = 0.001$) and weighted Elixhauser score >10 compared with <0 (aOR 6.04, 95% CI 2.68–13.62, $p < 0.001$) were associated with increased

odds of severe disease. Similarly, the risk ratios (relative risk) of risk factors associated with the probability of severity of illness were also estimated via Poisson regression approach (**Table S1**).

3.3.2 | Internal bootstrap validation and tree analysis on UV patients for severe disease

When analysis of severe disease was separately performed among UV hospitalized individuals, results of the identified risk factors in the multivariable logistic model with an internal bootstrap validation (c-statistic 0.75, 95% CI 0.73–0.76) further identified that age, sex, race (African American), BMI ($\geq$30 kg/m^2), and weighted Elixhauser score of 0–10 and >10 were significantly associated with the odds of severity of illness (**Table S5**). Similarly, the risk ratios (relative risk) of risk factors associated with the probability of severity of illness were also estimated via Poisson regression approach (**Table S6**). In a tree analysis, the highest rate of severe disease (40%) was among male non-African Americans who had a BMI $\geq$30 kg/m^2 and had a weighted Elixhauser score $\geq$10 in a tree analysis (node 17) (**Figure S2**).

3.3.3 | Internal bootstrap validation and tree analysis on FV patients for severe disease

When analysis of severe disease was separately performed among FV hospitalized individuals, results of the identified risk factors in the multivariable logistic model with an internal bootstrap validation (c-statistic 0.74, 95% CI 0.69–0.78) revealed that age and weighted Elixhauser score (>10) were significantly associated with the odds of severity of illness (Table S5). Similarly, the risk ratios (relative risk) of risk factors associated with the probability of severity of illness were also estimated via Poisson regression approach (**Table S6**). An exploration of tree analysis indicates that the highest rate of severe disease (27%) was among patients $\geq$65 years with a weighted Elixhauser comorbidity score >10 and no previous ED visits in the past 6 months (node 6) (**Figure S3**).

3.3.4 | Effects of individual comorbidities on severe disease

When looking at the association of individual comorbidity and severe disease between hospitalized UV and FV individuals shown in **Table S7**, we observed a heterogeneous association on other neurologic disorders ($p < 0.001$). All other comorbidity groups demonstrated a homogeneous association when comparing across hospitalized FV and UV patients.

4 | LIMITATIONS

This study had some limitations. Given its retrospective design, multiple potential confounding variables were unable to be controlled

for. However, given the prolonged duration of our study period and the large size of our cohort, these confounding variables were likely less contributory to our results. It is possible that some hospitalized patients with COVID-19 were incidentally excluded during our screening despite careful review and validation of our EHR extraction method. Additionally, during our initial data validation period the authors manually reviewed charts to confirm that those who met our inclusion criteria but lacked available polymerase chain reaction testing in our system had reference to a positive laboratory test in their clinical note. However, after manual review of these cases we concluded that less than 1% of included individuals lacked reference to a positive laboratory test in their clinical note and therefore chose to discontinue this manual review process and accept this small rate of error. Similarly, inaccurate data from MCIR may have caused misclassification of some patients regarding vaccination status, including missed doses for patients who received immunization in another state. Also, prior SARS-CoV-2 infection is a confounder that may not have been captured for all patients. It is possible that prior infection may affected impacted immunity and outcomes in this subgroup. Given the relatively small number of patients who had received a booster dose during our study period, the decision was made to exclude them from the analysis. This decision somewhat limits the generalizability of this analysis given the increasing number of patients who have received a booster dose. Therefore, risks related to this particular group warrant additional inquiry. Additionally, patients who subsequently presented to an outside health system after their initial ED visit would have been misclassified as not requiring admission. Finally, given that we did not have patient-level data on specific SARS-CoV-2 variant strains, we were unable to draw any conclusions on how variant disease affected patient outcomes; this may be especially relevant given the high amounts of variant disease present during our study period.

5 | DISCUSSION

In this large multicenter investigation of hospitalization and severe disease associated with COVID-19, the overwhelming majority of patients (90.3%) who presented to the ED with COVID-19 were UV, as defined in our study methods. Although FV individuals had a higher rate of hospitalization compared to UV individuals (40.3% vs. 52.7%), the rate of severe illness between the groups of hospitalized patients was similar (12.7% vs. 12.6%). However, UV patients were significantly younger, with 78.8% of UV patients being less than 65 years old compared to 48.6% of FV patients ($p < 0.001$), highlighting the effectiveness of vaccination among younger patients. In terms of outcomes, previous studies suggest there is minimal difference in the rate of severe disease among older FV and UV individuals after hospitalization for COVID-19.[20] Although we know that vaccination is effective at preventing hospitalization and severe disease, factors that put FV individuals at risk of these outcomes are poorly understood.

In both overall and separate analyses, we found the majority of risk factors for hospitalization (age $\geq$65 years, male sex, preexisting ESRD, immunocompromised status, or a weighted Elixhauser comorbidity

score of >10) were similar between FV and UV individuals. These findings support what has been reported in previous studies.[11,12] However, we identified several interesting differences in risk factors for severe disease when comparing FV and UV patients. When examining the occurrence of severe disease among hospitalized patients, both groups exhibited a higher likelihood for severe disease if they were ≥65 years old or had a weighted Elixhauser score of >10. However, in FV individuals, BMI ≥30 kg/m^2, weighted Elixhauser score of 0–10, male sex, and White race all demonstrated no significant association with severe disease, unlike what was observed in the UV group. Specifically looking at BMI, we were able to find only 1 small study that previously reported the association between BMI and admission among FV patients, but this study did indeed demonstrate this same finding.[11] Additionally, when looking at individual comorbidities, among FV patients, the risk of severe disease equalized in patients with and without uncomplicated diabetes and converged among those with a documented history of obesity. These same findings were not observed among UV patients in our cohort. Overall, these are all interesting and unexpected observations. Previously, diseases associated with metabolic syndrome (obesity, diabetes, hypertension, and hyperlipidemia) have demonstrated an increased risk of severe disease among UV patients with COVID-19.[21,22] However, our data demonstrate that when comparing UV and FV individuals, obesity and diabetes did not show this same increased risk. Therefore, our findings suggest that vaccination may eliminate the increased risk of severe disease among patients with a history of metabolic syndrome, thus highlighting the particular importance of vaccination in this group.

As the pandemic has progressed, it appears as though younger individuals are less likely to comply with guidelines to reduce the risk of infection.[23] Although our data have shown that severe disease among younger patients hospitalized with COVID-19 are less common than among older individuals, UV younger adults are still at risk for the worst outcomes. In our exploration of tree analyses, we found that the highest rate of severe disease among UV patients was seen in White males with BMI ≥30 kg/m^2 and a higher weighted comorbidity score, regardless of age. Comparatively, among FV individuals, the highest rate of severe disease was in patients older than 65 years with a higher weighted comorbidity score. These differences highlight the importance of vaccination in individuals with underlying metabolic syndrome and emphasize the value of this intervention even among younger patients. Given the reduced enthusiasm for preventative measures along with obesity rates of 40% or higher among younger individuals in the United States,[24] it is imperative that we continue to encourage vaccination, especially among younger people who likely perceive themselves as low risk of severe disease. Unfortunately, it does appear that older individuals with multiple comorbidities are still at risk of severe disease despite vaccination if a breakthrough SARS-CoV-2 infection occurs that requires them to seek emergency care. However, our prior analysis demonstrated a substantial reduction in the rate of breakthrough SARS-CoV-2 that was severe enough to require emergency care even among these elderly patients.[20] Therefore, vaccination is likely still the best primary defense against severe disease even in elderly patients with multiple comorbidities. Additionally, as more SARS-CoV-2 variants continue to emerge, it is imperative that future research include variant testing to better understand how vaccination status affects outcomes among patients infected with specific variant viral strains. As we continue to adapt to living with COVID-19, data such as these should help to facilitate a more accurate and informed discussion among families, physicians, and patients regarding individual risk and may also help shape public health guidelines.

FV patients with breakthrough SARS-CoV-2 infection who require hospitalization and have severe disease are older and have more medical comorbidities compared to UV patients. When comparing risk factors between UV and FV individuals, FV status is associated with reduced risk among patients with a BMI ≥30 kg/m^2, weighted Elixhauser score of 0–10, and those with a history of diabetes. These results highlight the importance of vaccination in these particularly vulnerable groups. Additionally, given the large proportion of obese younger individuals in the U.S., our results demonstrate the importance of vaccination even amongst those who may not perceive themselves to be at high risk for a severe outcome.

CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

Amit Bahl, Nicholas Mielke, and Steven Johnson designed the study, had full access to the data, and take responsibility for the integrity and accuracy of the data analysis. Amit Bahl, Nicholas Mielke, and Steven Johnson contributed to data collection and initial manuscript drafting. Trini Mathew and Gabriel N Maine contributed to manuscript editing and assisted with initial study design. Nai-Wei Chen performed all statistical analyses. All authors contributed to the writing and editing of the manuscript. As the corresponding author, Steven Johnson attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT

ETHICS COMMITTEE APPROVAL

ORCID

Steven Johnson DO https://orcid.org/0000-0002-2829-8350

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REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383:2603–2615. https://doi.org/10.1056/nejmoa2034577
2. Bahl A, Johnson S, Gabriel M, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. *Lancet*. 2021;4:100065.
3. Daniel W, Nivet M, Warner J, Podolsky DK. Early evidence of the effect of SARS-CoV-2 vaccine at one medical center. *N Engl J Med*. 2021;384:1962–1963. https://doi.org/10.1056/NEJMc2102153
4. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384:1412–1423. https://doi.org/10.1056/nejmoa2101765
5. Amit S, Regev-Yochay G, Afek A, et al. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet North Am Ed*. 2021;397:875–877. https://doi.org/10.1016/S0140-6736(21)00448-7
6. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21:335–337. https://doi.org/10.1016/S1470-2045(20)30096-6
7. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)*. 2020;28:1195–1199. https://doi.org/10.1002/oby.22831
8. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:458–464. https://doi.org/10.15585/mmwr.mm6915e3
9. Ioannou GN, Locke E, Green P, et al. Risk factors for hospitalization, mechanical ventilation, or death among 10 131 US veterans with SARS-CoV-2 infection. *JAMA Netw Open*. 2020;3:e2022310. https://doi.org/10.1001/jamanetworkopen.2020.22310
10. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93:1449–1458. https://doi.org/10.1002/jmv.26424
11. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*. 2021;27:1652–1657. https://doi.org/10.1016/j.cmi.2021.06.036
12. Hippisley-Cox J, Coupland CA, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ*. 2020;374:n2244. https://doi.org/10.1136/bmj.n2244
13. Michigan Care Improvement Registry. *Michigan Immunization Portal for Citizens 18 Years and Older*. Michigan Care Improvement Registry; https://mcir.org/2021/12/01/michigan-immunization-portal-for-citizens-18-years-and-older/. Accessed Dec 23, 2021.
14. Agency for Healthcare Research and Quality. *Specification v2019*. Agency for Healthcare Research and Quality; 2019. https://qualityindicators.ahrq.gov/Downloads/Modules/PSI/V2019/TechSpecs/PSI_Appendix_I.pdf. Accessed Dec 21, 2021.
15. Agency for Healthcare Research and Quality. AHRQ QI™ ICD-10-CM/PCS specification v2020. In: *Patient Safety Indicator*. Agency for Healthcare Research and Quality; 2020;10(PSI 10). https://qualityindicators.ahrq.gov/Downloads/Modules/PSI/V2020/TechSpecs/PSI_10_Postoperative_Acute_Kidney_Injury_Requiring_Dialysis_Rate.pdf. Accessed Jan 21, 2022.
16. Agency for Healthcare Research and Quality. *Elixhauser Comorbidity Software Refined for ICD-10-CM*. Agency for Healthcare Research and Quality; 2021. https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp. Accessed Jan 5, 2021.
17. US Census Bureau. *United States Census Bureau (2022) 2020 Data Release*. American Community Survey (ACS).
18. McNutt L-A. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol*. 2003;157:940–943. https://doi.org/10.1093/aje/kwg074
19. Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graph Stat*. 2006;15:651–674. https://doi.org/10.1198/106186006%D7;133933
20. Bahl A, Johnson S, Maine G, et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. *Lancet Reg Health Am*. 2020;4:100065. https://doi.org/10.1016/j.lana.2021.100065
21. Denson JL, Gillet AS, Zu Y, et al. Metabolic syndrome and acute respiratory distress syndrome in hospitalized patients with COVID-19. *JAMA Netw Open*. 2021;4:e2140568. https://doi.org/10.1001/jamanetworkopen.2021.40568
22. Soares R de CM, Mattos LR, Raposo LM. Risk factors for hospitalization and mortality due to COVID-19 in Espírito Santo State, Brazil. *Am J Trop Med Hyg*. 2020;103:1184–1190. https://doi.org/10.4269/ajtmh.20-0483
23. Kim JK, Crimmins EM. How does age affect personal and social reactions to COVID-19: results from the national Understanding America Study. *PLoS One*. 2020;15:e0241950. https://doi.org/10.1371/journal.pone.0241950
24. Hales C, Carroll M, Fryar C, Ogden C. *Prevalence of Obesity and Severe Obesity among Adults: United States, 2017–2018*. NCHS Data Brief No. 360. National Center for Health Statistics. 2020. https://www.cdc.gov/nchs/products/databriefs/db360.htm. Accessed Feb 19, 2022.

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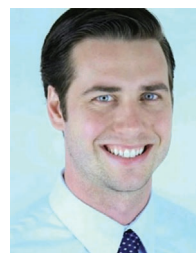
Steven Johnson, DO, is an Emergency Physician and Critical Care Fellow at Keck Medicine of University of Southern California in Los Angeles, California.

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