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Changing Severity and Epidemiology of Adults Hospitalized With Coronavirus Disease 2019 (COVID-19) in the United States After Introduction of COVID-19 Vaccines, March 2021–August 2022

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(See the Editorial Commentary by Lundgren on pages 558–9.)

Introduction. Understanding the changing epidemiology of adults hospitalized with coronavirus disease 2019 (COVID-19) informs research priorities and public health policies.

Methods. Among adults (≥18 years) hospitalized with laboratory-confirmed, acute COVID-19 between 11 March 2021, and 31 August 2022 at 21 hospitals in 18 states, those hospitalized during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron-predominant period (BA.1, BA.2, BA.4/BA.5) were compared to those from earlier Alpha- and Delta-predominant periods. Demographic characteristics, biomarkers within 24 hours of admission, and outcomes, including oxygen support and death, were assessed.

Results. Among 9825 patients, median (interquartile range [IQR]) age was 60 years (47–72), 47% were women, and 21% non-Hispanic Black. From the Alpha-predominant period (Mar–Jul 2021; N = 1312) to the Omicron BA.4/BA.5 sublineage-predominant period (Jun–Aug 2022; N = 1307): the percentage of patients who had ≥4 categories of underlying medical conditions increased from 11% to 21%; those vaccinated with at least a primary COVID-19 vaccine series increased from 7% to 67%; those ≥75 years old increased from 11% to 33%; those who did not receive any supplemental oxygen increased from 18% to 42%. Median (IQR) highest C-reactive protein and D-dimer concentration decreased from 42.0 mg/L (9.9–122.0) to 11.5 mg/L (2.7–42.8) and 3.1 mcg/mL (0.8–640.0) to 1.0 mcg/mL (0.5–2.2), respectively. In-hospital death peaked at 12% in the Delta-predominant period and declined to 4% during the BA.4/BA.5-predominant period.

Conclusions. Compared to adults hospitalized during early COVID-19 variant periods, those hospitalized during Omicron-variant COVID-19 were older, had multiple co-morbidities, were more likely to be vaccinated, and less likely to experience severe respiratory disease, systemic inflammation, coagulopathy, and death.

Keywords. COVID-19; SARS-CoV-2; hospitalization; death; severe disease.

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The use of coronavirus disease 2019 (COVID-19) vaccines, beginning in December 2020 in the United States, has attenuated COVID-19 disease severity and conferred protection against critical outcomes such as respiratory failure and death [1–3]. Infection-acquired immunity from previous COVID-19 illness may also reduce the risk or severity of re-infection [4–6]. With a growing proportion of the US population having serologic evidence of previous infection and increased nationwide coverage of vaccination [7,8], the epidemiology of COVID-19 and patterns of immunity continue to shift over time [9]. When compared to earlier variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the infection caused by the SARS-CoV-2 Omicron variant and subsequent sublineages has been observed to cause less severe systemic inflammation [10], a major risk factor for COVID-19-associated death [11]. Furthermore, clinicians and patients now have access to therapies for acute COVID-19 that have been shown to improve clinical outcomes, including antiviral therapies for outpatient disease and corticosteroids for hospitalized patients with hypoxemia [12–14].

The emergence of the SARS-CoV-2 Omicron variants and sublineages heralded 2 key changes in the epidemiology of COVID-19 that have influenced disease prevention and control strategies. First, as compared with previous variants, Omicron variants are more transmissible and better evade immunity in the respiratory tract, resulting in a high incidence of repeat infections in vaccinated and unvaccinated persons [15, 16]. However, due to preserved memory T- and B-cell immune responses, and possibly lower pathogenicity, these breakthrough Omicron infections in immunized persons have been associated with lower rates of acute lung injury and systemic inflammation [10, 17]. Intrinsic viral factors, such as tropism of new variants for the upper respiratory tract, may also decrease the incidence of severe lower respiratory disease [18]. Second, although COVID-19 can be self-limiting in healthy populations, infections still lead to hospitalizations and death in medically frail populations with comorbidities such as heart disease, chronic obstructive pulmonary disease, or immunosuppression [19]. It has been observed that influenza and other respiratory disease can trigger sequelae such as myocardial infarction (MI), cerebrovascular accident, or other acute insults among people with multiple chronic conditions [20, 21]. As a consequence, even though a lower fraction of those infected with Omicron have progressed to severe disease and death, hospitalizations and deaths have remained high in medically frail patients [22].

Understanding the epidemiology of COVID-19 due to Omicron-variant viruses versus earlier variants can inform research and policies for prevention and control of the disease. In this analysis, we assessed changes in clinical characteristics and outcomes of hospitalized patients with COVID-19 during the Alpha-, Delta-, and Omicron-predominant periods of the pandemic in a multi-state sentinel surveillance network.

METHODS

Setting and Design

The Investigating Respiratory Viruses in the Acutely Ill (IVY) Network, a collaboration among 21 US hospitals in 18 states and the Centers for Disease Control and Prevention (CDC), conducted this prospective observational program [23, 24]. CDC reviewed these activities, which were consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq). CDC and each enrolling site determined the activities to be public health surveillance.

Participants

We prospectively enrolled hospitalized patients with laboratory-confirmed, symptomatic acute COVID-19 at 21 US hospitals from 11 March 2021, to 31 August 2022. This period was largely consistent with distribution and uptake of monovalent COVID-19 vaccination, beginning with widespread availability of the initial COVID-19 vaccines in the US and ending with the introduction of bivalent COVID-19 vaccines. Personnel screened hospitalized adults aged ≥18 years for eligibility through a review of hospital admission logs/reports and electronic medical records. All enrolled patients were hospitalized with COVID-19-like illness defined as ≥1 of the following symptoms and signs: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia. Additionally, patients had a positive nucleic acid amplification or antigen test result for SARS-CoV-2 within 14 days of symptom onset [25].

Sites attempted to include all patients admitted to the hospital during the surveillance period who met eligibility criteria (Supplementary Figure 1) [23]. Vaccination status was determined following patient enrollment. Among all patients receiving any number of vaccines, only those with an mRNA (BNT162b2 [Pfizer] and mRNA-1273 [Moderna]) or Ad26.COV2 (Janssen/Johnson and Johnson [J&J]) product administered were included. Exclusion criteria included receipt of a non-mRNA COVID-19 vaccine product, unknown vaccination status [2, 23], missing clinical outcomes data, or patient voluntary withdrawal.

Data Collection

Trained personnel collected demographic and clinical data through standardized participant (or proxy) interviews and medical record reviews using standardized procedures and data collection tools shared by all sites. The highest white blood cell counts, C-reactive protein (CRP), and D-dimer concentrations measured within the first 24 hours after hospital admission as part of routine clinical care were recorded from the medical record.

Laboratory Analysis

Upper respiratory specimens (nasal swabs or saliva) were collected from enrolled patients, frozen, and shipped to a central laboratory at Vanderbilt University Medical Center (Nashville, Tennessee, USA) [1]. These specimens were tested using reverse transcription–polymerase chain reaction for SARS-CoV-2 nucleocapsid gene targets with standardized methods and interpretive criteria [26]. Specimens positive for SARS-CoV-2 were shipped to the University of Michigan (Ann Arbor, Michigan, USA) for viral whole-genome sequencing. SARS-CoV-2 lineages were assigned with >80% coverage using Pangolin nomenclature [23, 27, 28].

Classification of SARS-CoV-2 Variant Period

We classified participants into SARS-CoV-2 variant periods based on the predominant circulating variant identified by viral genome sequencing. We defined the Alpha-predominant period as 11 March 2021, to 3 July 2021, the Delta-predominant period as 4 July 2021, to 25 December 2021, and the Omicron-predominant period as 26 December 2021 through the last date of enrollment (31 August 2022). We further divided the Omicron-predominant period into sublineages: BA.1 from 26 December 2021, to 26 March 2022, BA.2, which also included BA.2.12.1, from 27 March to 18 June 2022, and BA.4/BA.5 from 19 June to 31 August 2022.

Classification of COVID-19 Vaccination Status

Classification of vaccination status followed IVY network methods in alignment with CDC guidelines for the observation period, which included recommendations based on patient age, immunosuppression status, licensed COVID-19 vaccine product (mRNA or J&J), and timing of previous vaccination (Supplementary Table 1) [2, 29, 30]. Patients were classified into 6 mutually exclusive vaccination status groups: unvaccinated, partially vaccinated, completed primary series, and completed primary series plus 1, 2, or 3 monovalent booster doses. Participants were considered to have completed a primary series if the final dose was received ≥14 days prior to symptom onset; patients were considered to have received a booster dose if it was administered ≥7 days before symptom onset [2, 23].

COVID-19 Outcomes Classification

In-hospital outcomes were measured through the 28th day of hospitalization or the event of discharge or death, if one of those events occurred before the 28th day of hospitalization.

Highest oxygen support received in the hospital was ranked based on 5 categories, including: (1) no use of supplemental oxygen, (2) low flow oxygen (≤15 liters/minute by nasal cannula or face mask), (3) high-flow nasal canula (HFNC) or noninvasive positive pressure ventilation (NIPPV), (4) invasive mechanical ventilation (IMV), and (5) extracorporeal membrane oxygenation (ECMO).

Statistical Analysis

Demographics, as well as in-hospital interventions, treatments, and outcomes were reported using frequencies and proportions by SARS-CoV-2 variant periods. Continuous variables were presented as median with interquartile range (IQR). The Jonckheere–Terpstra test was used to test the trend over variant periods for continuous variables and ordered categorical variables with >2 groups. The Cochran-Armitage test was used to test the trend over variant periods for binary variables. Unordered categorical variables (race and ethnicity, primary series vaccine product, and last booster product) were treated as binary (yes/no) variables for each category and individual *P* values presented. Age group, categories of underlying medical conditions (ie, autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, kidney, neurologic, and pulmonary diseases), and highest level of oxygen support were plotted as proportion of participants by week beginning 11 March 2021. Laboratory values were treated as missing when tests were not performed. Interview data were missing for patients with cognitive impairment for whom surrogates were not available. Analyses were conducted among patients with non-missing data, with no imputation for missing datapoints; missing data were excluded. Analyses were completed using Stata SE Version 17.0 (StataCorp, College Station, Texas, USA).

RESULTS

From 11 March 2021, to 31 August 2022, 10 657 COVID-19 patients were enrolled. Among 9825 patients eligible for analysis (Supplementary Figure 1), median age was 60 years (IQR, 47–72 years), 47% were women, 21% were non-Hispanic Black, and 17% were Hispanic (Table 1). Patients had a median of 2 (IQR, 1–3) chronic medical conditions from separate categories; 22% had an immunocompromising condition. Overall, 52% were unvaccinated, 13% were partially vaccinated, 23% completed a primary series, and 13% completed a primary series with 1 or more booster doses. Twenty-five percent of patients did not receive any supplemental oxygen support, 40% received low flow oxygen (flow rate ≤15 liters/minute), and 36% received higher level oxygen support (Table 2).

Demographic Trends

Patients hospitalized for COVID-19 during the Omicron-predominant period were generally older than patients infected during earlier periods (Table 1). From the Alpha-predominant period to the Omicron BA.4/BA.5-predominant period, the percentage of patients aged ≥75 years increased from 11% to 33% (trend test $P < .001$; Table 1 and Figure 1*A*).

Percentages of patients with ≥4 categories of underlying medical conditions increased from 11% to 21% (trend test $P < .001$; Table 1 and Figure 1*B*) from the Alpha-predominant period to the Omicron BA.4/BA.5-predominant period.

During the Alpha-predominant period, 17% of hospitalized patients had an immunocompromising condition (Table 1). Over subsequent periods, the percentage of hospitalized patients with immunocompromising conditions increased: 17% during Delta; 27% during BA.1, 30% during BA.2, and 28% during BA.4/BA.5 (trend test $P < .001$).

Vaccination Trends

Percentages of adults hospitalized with COVID-19 who had completed a primary COVID-19 vaccine series, with or without additional ("booster") vaccine doses, increased from 7% during the Alpha-predominant period to 67% during the Omicron BA.4/BA.5-predominant period (trend test $P < .001$; Table 1 and Figure 1*C*).

In-Hospital Outcomes

Based on the pattern of supplemental oxygen use and in-hospital medications, the severity of lung disease likely decreased over time for adults hospitalized with COVID-19. From the Alpha-predominant period to the Omicron BA.4/BA.5-predominant period, the percentage of patients who did not receive any supplemental oxygen increased from 18% to 42% (trend test $P < .001$; Table 2 and Figure 1*D*). Use of corticosteroids peaked during the Delta-predominant period (80%) and declined throughout the Omicron periods to its lowest level in the Omicron BA.4/BA.5-predominant period (54%; trend test $P < .001$). Use of other in-hospital medicines for acute COVID-19, including remdesivir (trend test $P < .001$), tocilizumab (trend test $P < .001$), and baricitinib (trend test $P < .001$), also changed over time with lower use during the later Omicron periods compared to early variant periods. Similar trends were observed among unvaccinated patients and patients who had completed at least a primary vaccine series, for example, a decrease in the proportion with IMV or higher respiratory support across periods (trend test $P < .001$).

Over time, the percentage of adults hospitalized with COVID-19 with a documented MI (trend test $P = .020$; Table 2), acute pulmonary embolism (PE; trend test $P < .001$), and acute deep vein thrombosis (DVT; trend test $P < .001$) also changed, with the lowest percentage of patients with these outcomes during the later Omicron BA.2 and BA.4/BA.5-predominant periods.

Biomarkers of Systemic Inflammation and Coagulopathy

Based on peak results from clinically obtained serum CRP and D-Dimer concentrations measured within 24 hours hospital admission, the degree of systemic inflammation, and activation of the coagulation, respectively, decreased over time. From the Alpha-predominant period to the Omicron BA.4/BA.5-predominant period, the median CRP decreased from 42.0 mg/L (IQR, 9.9–122.0) to 11.5 mg/L (IQR, 2.7–42.8), and median D-dimer decreased from 3.1 mcg/mL (IQR, 0.8–640.0) to 1.0 mcg/mL (IQR, 0.5–2.2; trend test $P < .001$ for both comparisons; Table 2). Concentrations of CRP and D-dimer decreased over time among both unvaccinated patients and patients who had completed at least a primary vaccine series (all trend test $P < .001$).

Hospital Discharge and Mortality

The percentage of patients that were discharged alive from the hospital within 28 days (ie, did not experience an in-hospital death within 28 days and were not still an inpatient on day 28) was lowest during the Delta-predominant period (78%) and increased to its highest level in the Omicron BA.4/BA.5-predominant period (93%; trend test $P < .001$; Figure 1*E*). Among patients who were discharged, the median length of stay decreased from its highest point during the Delta and Omicron BA.1-predominant period of 6 days (IQR, 3–10) and decreased to its lowest level in the Omicron BA.4/BA.5-predominant period of 4 days (IQR, 3–10; trend test $P < .001$). In-hospital fatality peaked in the Delta-predominant period (12%) and declined throughout the Omicron periods to its lowest level in the Omicron BA.4/BA.5-predominant period (4%; trend test $P < .001$; Table 2).

DISCUSSION

Among adults hospitalized with COVID-19 in a multistate surveillance network, the epidemiology of COVID-19 changed markedly during the 18 months following widespread availability of COVID-19 vaccines in the US. As vaccination coverage has increased, vaccinated individuals continued to benefit from strong protection against COVID-19-associated death and severe disease [1]. However, with a larger proportion of the population vaccinated, coupled with emergence of more immune-evasive SARS-CoV-2 variants and waning effects of vaccination [31], vaccinated individuals also made up a larger proportion of hospitalized adults with COVID-19. Notably, after the emergence of Omicron variants, hospitalized patients were substantially more likely to have known risk factors for severe COVID-19, including age ≥75 years and multiple categories of underlying chronic medical conditions or immunocompromising conditions [1]. Despite these changes in patient characteristics, overall disease severity decreased over time, illustrated by lower levels of systemic inflammation and coagulopathy, a higher proportion discharged within 28 days of admission, and a lower proportion receiving treatment with supplemental oxygen or progressing to invasive mechanical ventilation and death.

As the epidemiology of COVID-19 continues to evolve [32], routine assessment of the epidemiology of patients hospitalized

Table 1. Demographics and Clinical Characteristics of Patients by Predominant SARS-CoV-2 Variant Period—IVY Network, United States, 11 March 2021 to 31 August 2022

	Total N = 9825	Alpha N = 1312	Delta N = 4466	Omicron – BA.1 N = 1649	Omicron – BA.2 N = 1091	Omicron – BA.4/BA.5 N = 1307	*P* value
Median (IQR) or n (%)							
Age in y	60 (47–72)	57 (44–66)	57 (44–69)	63 (51–73)	66 (54–78)	66 (53–78)	<.001[e]
Age category							<.001[e]
18–49	2847 (29%)	462 (35%)	1527 (34%)	361 (22%)	209 (19%)	288 (22%)	
50–64	3033 (31%)	487 (37%)	1415 (32%)	530 (32%)	282 (26%)	319 (24%)	
65–74	2025 (21%)	223 (17%)	864 (19%)	419 (25%)	244 (22%)	275 (21%)	
≥75	1920 (20%)	140 (11%)	660 (15%)	339 (21%)	356 (33%)	425 (33%)	
Sex							.019[f]
Female	4637 (47%)	625 (48%)	2056 (46%)	759 (46%)	543 (50%)	654 (50%)	
Race and ethnicity							
Non-Hispanic White	5375 (55%)	589 (45%)	2416 (54%)	929 (56%)	647 (59%)	794 (61%)	<.001[f]
Non-Hispanic Black	2107 (21%)	354 (27%)	971 (22%)	324 (20%)	200 (18%)	258 (20%)	<.001[f]
Hispanic, any race	1650 (17%)	263 (20%)	791 (18%)	276 (17%)	146 (13%)	174 (13%)	<.001[f]
Non-Hispanic, all other races	520 (5%)	82 (6%)	203 (5%)	92 (6%)	76 (7%)	67 (5%)	.417[f]
Unknown	173 (2%)	24 (2%)	85 (2%)	28 (2%)	22 (2%)	14 (1%)	.145[f]
Self-reported or EHR-confirmed prior SARS-CoV-2 infection							<.001[f]
Yes	603 (6%)	53 (4%)	138 (3%)	122 (7%)	118 (11%)	172 (13%)	
BMI, kg/m^2	30 (25–36)	31 (26–38)	31 (26–37)	29 (24–35)	27 (23–33)	27 (23–32)	<.001[e]
BMI category							<.001[e]
<30	4999 (51%)	566 (43%)	2076 (46%)	910 (55%)	663 (61%)	784 (60%)	
30–39	3165 (32%)	472 (36%)	1612 (36%)	497 (30%)	280 (26%)	304 (23%)	
≥40	1400 (14%)	256 (20%)	744 (17%)	213 (13%)	81 (7%)	106 (8%)	
Missing	261 (3%)	18 (1%)	34 (1%)	29 (2%)	67 (6%)	113 (9%)	
No. of categories of medical conditions[a]	2 (1–3)	2 (1–3)	1 (0–3)	2 (1–3)	2 (1–3)	2 (1–3)	<.001[e]
Categories of medical conditions[a]							<.001[e]
0	1855 (19%)	317 (24%)	1142 (26%)	206 (12%)	87 (8%)	103 (8%)	
1	2365 (24%)	326 (25%)	1112 (25%)	368 (22%)	249 (23%)	310 (24%)	
2	2332 (24%)	293 (22%)	992 (22%)	413 (25%)	299 (27%)	335 (26%)	
3	1747 (18%)	229 (17%)	676 (15%)	332 (20%)	223 (20%)	287 (22%)	
≥4	1526 (16%)	147 (11%)	544 (12%)	330 (20%)	233 (21%)	272 (21%)	
Immunocompromising condition[b]							<.001[f]
Yes	2116 (22%)	217 (17%)	770 (17%)	443 (27%)	325 (30%)	361 (28%)	
Vaccination status - 6 categories							<.001[e]
Unvaccinated	5133 (52%)	1007 (77%)	2930 (66%)	653 (40%)	218 (20%)	325 (25%)	
Partially vaccinated	1234 (13%)	213 (16%)	593 (13%)	219 (13%)	101 (9%)	108 (8%)	
Completed primary series	2270 (23%)	91 (7%)	899 (20%)	586 (36%)	352 (32%)	342 (26%)	
Completed primary series + received one booster dose	1035 (11%)	1 (0%)	44 (1%)	190 (12%)	378 (35%)	422 (32%)	
Completed primary series + received two booster doses	150 (2%)	0 (0%)	0 (0%)	1 (0%)	41 (4%)	108 (8%)	
Completed primary series + received three booster doses	3 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (0%)	
Vaccine product received for primary series[c]							
BNT162b2 (Pfizer-BioNTech)	1940 (56%)	50 (54%)	533 (57%)	444 (57%)	433 (56%)	480 (55%)	.541[f]
mRNA-1273 (Moderna)	1130 (33%)	23 (25%)	262 (28%)	239 (31%)	280 (36%)	326 (37%)	<.001[f]
Mixed mRNA	12 (0%)	0 (0%)	3 (0%)	4 (1%)	2 (0%)	3 (0%)	.968[f]
Johnson & Johnson (Janssen)	376 (11%)	19 (21%)	145 (15%)	90 (12%)	57 (7%)	65 (7%)	<.001[f]
Vaccine product received for last booster[d]							
BNT162b2 (Pfizer-BioNTech)	506 (43%)	0 (0%)	27 (61%)	98 (51%)	167 (40%)	214 (40%)	.002[f]
mRNA-1273 (Moderna)	656 (55%)	1 (100%)	14 (32%)	87 (46%)	249 (59%)	305 (57%)	.001[f]
Johnson and Johnson (Janssen)	26 (2%)	0 (0%)	3 (7%)	6 (3%)	4 (1%)	13 (2%)	.296[f]

Abbreviations: BMI, body mass index; EHR, electronic health record; IQR, interquartile range.

[a]Categories of medical conditions included autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, kidney, neurologic, and pulmonary diseases.

[b]Immunocompromising conditions included active solid organ cancer (defined as active treatment or newly diagnosed in past 6 months), active hematologic cancer (eg, leukemia, lymphoma, or myeloma), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection (without AIDS), congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, taking immunosuppressive drugs, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[c]Total with known information = 3458 overall; Alpha 92; Delta 943; BA.1 777; BA.2 772; BA.4/BA.5 874.

[d]Total with known information = 1188 overall; Alpha 1; Delta 44; BA.1 191; BA.2 420; BA.4/BA.5 532.

[e]Jonckheere–Terpstra test for trend was used for continuous variables and ordered categorical variables with >2 groups.

[f]Cochran–Armitage test for trend was used for binary variables. Categories of race and ethnicity, primary series vaccine product, and last booster product were treated as binary (yes/no) variables with individual *P*-values presented.

Table 2. In-hospital Interventions, Outcomes, and Biomarkers by Predominant SARS-CoV-2 Variant Period—IVY Network, United States, 11 March 2021 to 31 August 2022

	Total N = 9825	Alpha N = 1312	Delta N = 4466	Omicron – BA.1 N = 1649	Omicron – BA.2 N = 1091	Omicron – BA.4/ BA.5 N = 1307	*P* value
Median (IQR) or n (%)							
Hospital course							
Hospitalized at 28 d of admission							<.001[c]
No	8954 (91%)	1140 (87%)	4006 (90%)	1490 (90%)	1054 (97%)	1264 (97%)	
Yes	871 (9%)	172 (13%)	460 (10%)	159 (10%)	37 (3%)	43 (3%)	
Discharged within 28 d of admission							<.001[c]
No	1748 (18%)	273 (21%)	992 (22%)	306 (19%)	83 (8%)	94 (7%)	
Yes	8077 (82%)	1039 (79%)	3474 (78%)	1343 (81%)	1008 (92%)	1213 (93%)	
Hospital length of stay among discharged patients (in d)	5 (3–9)	5 (3–9)	6 (3–10)	6 (3–10)	4 (3–8)	4 (3–8)	<.001[c]
Death within 28 d of admission							<.001[c]
No	8948 (91%)	1211 (92%)	3934 (88%)	1502 (91%)	1045 (96%)	1256 (96%)	
Yes	877 (9%)	101 (8%)	532 (12%)	147 (9%)	46 (4%)	51 (4%)	
Admitted to ICU							<.001[c]
No	6670 (68%)	824 (63%)	2711 (61%)	1147 (70%)	908 (83%)	1080 (83%)	
Yes	3155 (32%)	488 (37%)	1755 (39%)	502 (30%)	183 (17%)	227 (17%)	
Oxygen support							
Any oxygen support							<.001[c]
No	2417 (25%)	240 (18%)	778 (17%)	408 (25%)	437 (40%)	554 (42%)	
Yes	7408 (75%)	1072 (82%)	3688 (83%)	1241 (75%)	654 (60%)	753 (58%)	
Highest O_2 support							<.001[d]
None	2417 (25%)	240 (18%)	778 (17%)	408 (25%)	437 (40%)	554 (42%)	
Low flow oxygen	3890 (40%)	529 (40%)	1673 (37%)	662 (40%)	488 (45%)	538 (41%)	
HFNC or NIPPV	1831 (19%)	273 (21%)	1034 (23%)	314 (19%)	90 (8%)	120 (9%)	
IMV	1513 (15%)	227 (17%)	873 (20%)	243 (15%)	76 (7%)	94 (7%)	
ECMO	174 (2%)	43 (3%)	108 (2%)	22 (1%)	0 (0%)	1 (0%)	
Therapies and outcomes[a]							
Vasopressor receipt							<.001[c]
No	8153 (83%)	1054 (80%)	3529 (79%)	1383 (84%)	1000 (92%)	1187 (91%)	
Yes	1672 (17%)	258 (20%)	937 (21%)	266 (16%)	91 (8%)	120 (9%)	
Renal therapy support							<.001[c]
No	9414 (96%)	1248 (95%)	4217 (94%)	1577 (96%)	1083 (99%)	1289 (99%)	
Yes	411 (4%)	64 (5%)	249 (6%)	72 (4%)	8 (1%)	18 (1%)	
Venous thromboembolic event							<.001[c]
No	9216 (94%)	1239 (94%)	4129 (92%)	1518 (92%)	1056 (97%)	1274 (97%)	
Yes	609 (6%)	73 (6%)	337 (8%)	131 (8%)	35 (3%)	33 (3%)	
Stroke							.086[c]
No	9692 (99%)	1290 (98%)	4404 (99%)	1624 (98%)	1079 (99%)	1295 (99%)	
Yes	133 (1%)	22 (2%)	62 (1%)	25 (2%)	12 (1%)	12 (1%)	
Myocardial infarction							.020[c]
No	9623 (98%)	1289 (98%)	4358 (98%)	1607 (97%)	1077 (99%)	1292 (99%)	
Yes	202 (2%)	23 (2%)	108 (2%)	42 (3%)	14 (1%)	15 (1%)	
Acute pulmonary embolism							<.001[c]
No	9498 (97%)	1269 (97%)	4291 (96%)	1579 (96%)	1073 (98%)	1286 (98%)	
Yes	327 (3%)	43 (3%)	175 (4%)	70 (4%)	18 (2%)	21 (2%)	
Acute deep vein thrombosis							<.001[c]
No	9471 (96%)	1273 (97%)	4267 (96%)	1568 (95%)	1070 (98%)	1293 (99%)	
Yes	354 (4%)	39 (3%)	199 (4%)	81 (5%)	21 (2%)	14 (1%)	
Corticosteroids[b]							<.001[c]
No	2762 (30%)	336 (26%)	860 (20%)	503 (33%)	498 (46%)	565 (46%)	
Yes	6573 (70%)	976 (74%)	3352 (80%)	1004 (67%)	580 (54%)	661 (54%)	
Remdesivir[b]							<.001[c]
No	4137 (44%)	543 (41%)	1691 (40%)	772 (51%)	514 (48%)	617 (50%)	

Table 2. Continued

	Total N = 9825	Alpha N = 1312	Delta N = 4466	Omicron – BA.1 N = 1649	Omicron – BA.2 N = 1091	Omicron – BA.4/ BA.5 N = 1307	*P* value
Yes	5198 (56%)	769 (59%)	2521 (60%)	735 (49%)	564 (52%)	609 (50%)	
Tocilizumab[b]							<.001[c]
No	8678 (93%)	1118 (85%)	3822 (91%)	1451 (96%)	1068 (99%)	1219 (99%)	
Yes	657 (7%)	194 (15%)	390 (9%)	56 (4%)	10 (1%)	7 (1%)	
Baricitinib[b]							<.001[c]
No	8821 (94%)	1306 (100%)	3828 (91%)	1395 (93%)	1076 (100%)	1216 (99%)	
Yes	514 (6%)	6 (0%)	384 (9%)	112 (7%)	2 (0%)	10 (1%)	
Monoclonal antibodies[b]							.012[c]
No	8843 (95%)	1256 (96%)	3930 (93%)	1461 (97%)	1010 (94%)	1186 (97%)	
Yes	492 (5%)	56 (4%)	282 (7%)	46 (3%)	68 (6%)	40 (3%)	
Biomarkers							
White blood cell count (1000 cells/ μL)							
Complete	9166 (93%)	1284 (98%)	4167 (93%)	1488 (90%)	1045 (96%)	1182 (90%)	
Median (IQR)	7.0 (5.1–10.1)	6.7 (4.9–9.5)	6.7 (4.9–9.6)	7.7 (5.3–10.8)	7.5 (5.3–10.4)	7.6 (5.2–10.6)	<.001[d]
C reactive protein (CRP) (mg/L)							
Complete	5275 (54%)	854 (65%)	2727 (61%)	777 (47%)	428 (39%)	489 (37%)	
Median (IQR)	22.3 (6.6–97.4)	42.0 (9.9–122.0)	28.4 (8.4–107.9)	16.6 (5.6–75.0)	7.2 (2.0–27.5)	11.5 (2.7–42.8)	<.001[d]
D-Dimer (μg/mL)							
Complete	4981 (51%)	825 (63%)	2551 (57%)	727 (44%)	414 (38%)	464 (36%)	
Median (IQR)	1.5 (0.7–20.0)	3.1 (0.8–640.0)	1.6 (0.7–352.0)	1.3 (0.6–3.7)	1.0 (0.5–2.0)	1.0 (0.5–2.2)	<.001[d]

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; ICU. intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation.

[a]Values represent those with documented outcomes (eg, IMV received). A patient without a documented outcome was assumed to not have the outcome ("no").

[b]Total with known information = 9335 overall; Alpha 1312; Delta 4212; BA.1 1507; BA.2 1078; BA.4/BA.5 1226.

[c]Cochran-Armitage test for trend was used for binary variables.

[d]Jonckheere-Terpstra test for trend was used for continuous variables and ordered categorical variables with >2 groups.

with COVID-19 can help inform strategic clinical and public health efforts. To do this effectively, it is necessary to differentiate the clinical phenotypes of patients hospitalized with COVID-19 by assessing markers of clinical severity, measurements of risk factors, and predictors of outcomes. For example, acute lung injury was more frequently observed during the pre-Omicron periods of the pandemic [33–35]. During the Omicron period, in contrast, patients were less likely to require advanced respiratory support despite being older and more chronically ill in general. Potential explanations for this trend include protection against critical illness from vaccination (which was more common in the Omicron period), the hospitalization of medically complex patients for less severe symptoms of COVID-19, or reduced virulence of Omicron variants.

Similar trends were observed in serum concentrations of biomarkers of systemic inflammation and coagulopathy obtained during the first 24 hours of hospitalization. Among those tested, CRP and D-dimer levels were lower during the Omicron-predominant period compared to Alpha- and Delta-predominant periods. Given that many of the current therapies for patients hospitalized for COVID-19 are potent anti-inflammatory agents with significant side-effects [36], the trends towards lower systemic inflammation and improved outcomes of adults hospitalized with COVID-19 suggest a potential need for iterative assessments of therapeutic agents as the COVID-19 pandemic evolves. The decreased percentage of patients diagnosed with MI, acute PE, and acute DVT also suggest lower rates of coagulopathy.

In the setting of competing public health priorities, results of this analysis suggest that focused attention on preventive measures and early treatment of COVID-19 in older adult patients and those with multiple comorbidities may have the greatest potential for preventing progression to severe disease. The emergence of the Omicron variant and its sublineages have highlighted that prevention of mild infection is challenging [15]. Although risk of severe disease after SARS-CoV-2 infection is lower in young, healthy adults, infections cause a substantial number of hospitalizations among the elderly, immunocompromised, and chronically ill [37].

These findings also have implications for evaluating COVID-19 vaccine effectiveness. Although COVID-19-associated hospitalization has traditionally been used as an outcome measure for severe COVID-19 [3], the severity of COVID-19 related illness among the

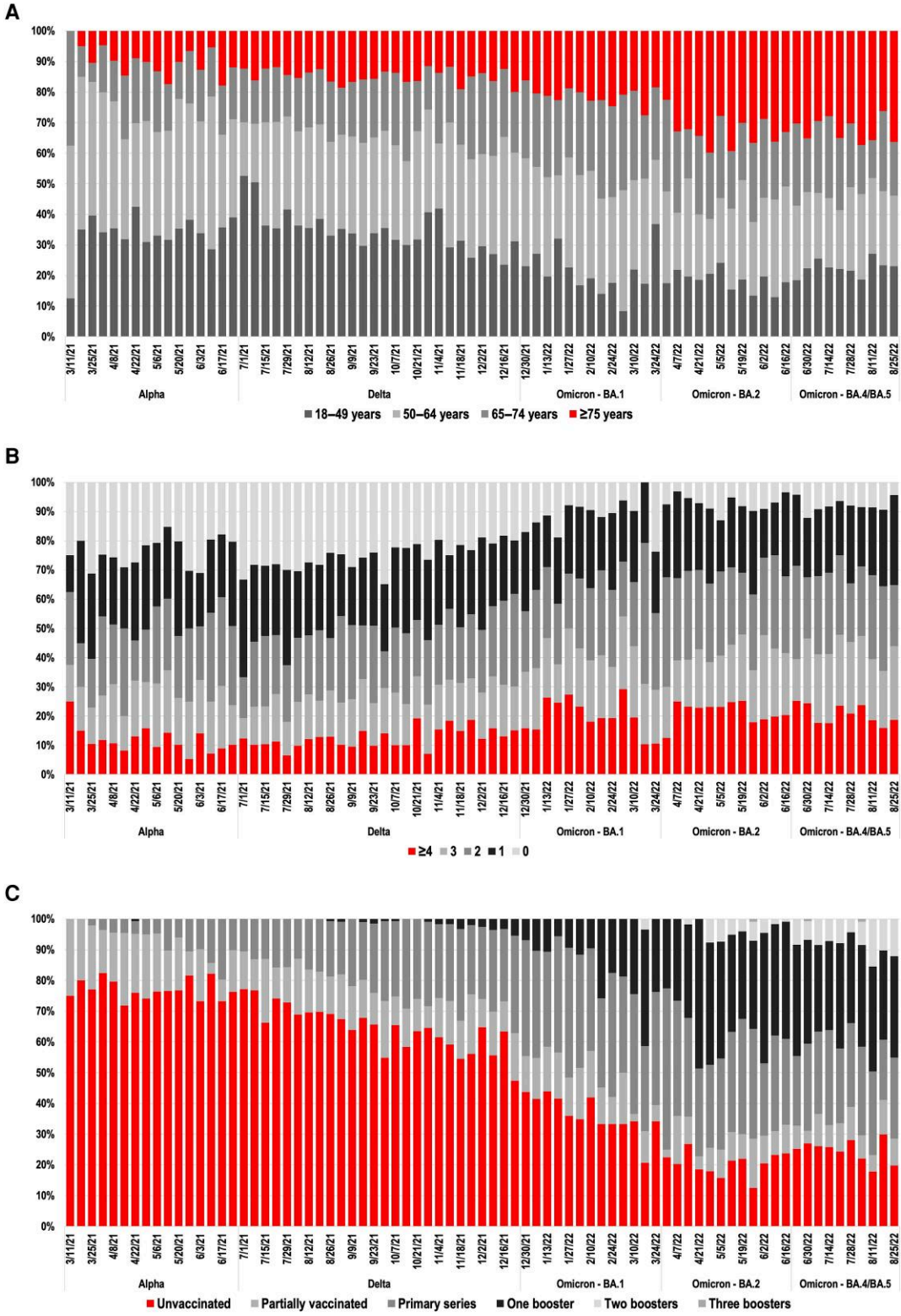

Figure 1. (*A*) Age group of hospitalized adults with acute COVID-19 by week and predominant SARS-CoV-2 variant period—IVY Network, United States, 11 March 2021–31 August 2022. (*B*) Number of categories of underlying medical conditions among hospitalized adults with acute COVID-19 by week and by predominant SARS-CoV-2 variant period. Categories of medical conditions included autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, kidney, neurologic, and pulmonary diseases. (*C*) Vaccination status of hospitalized adults with acute COVID-19 by week and by predominant SARS-CoV-2 variant period.

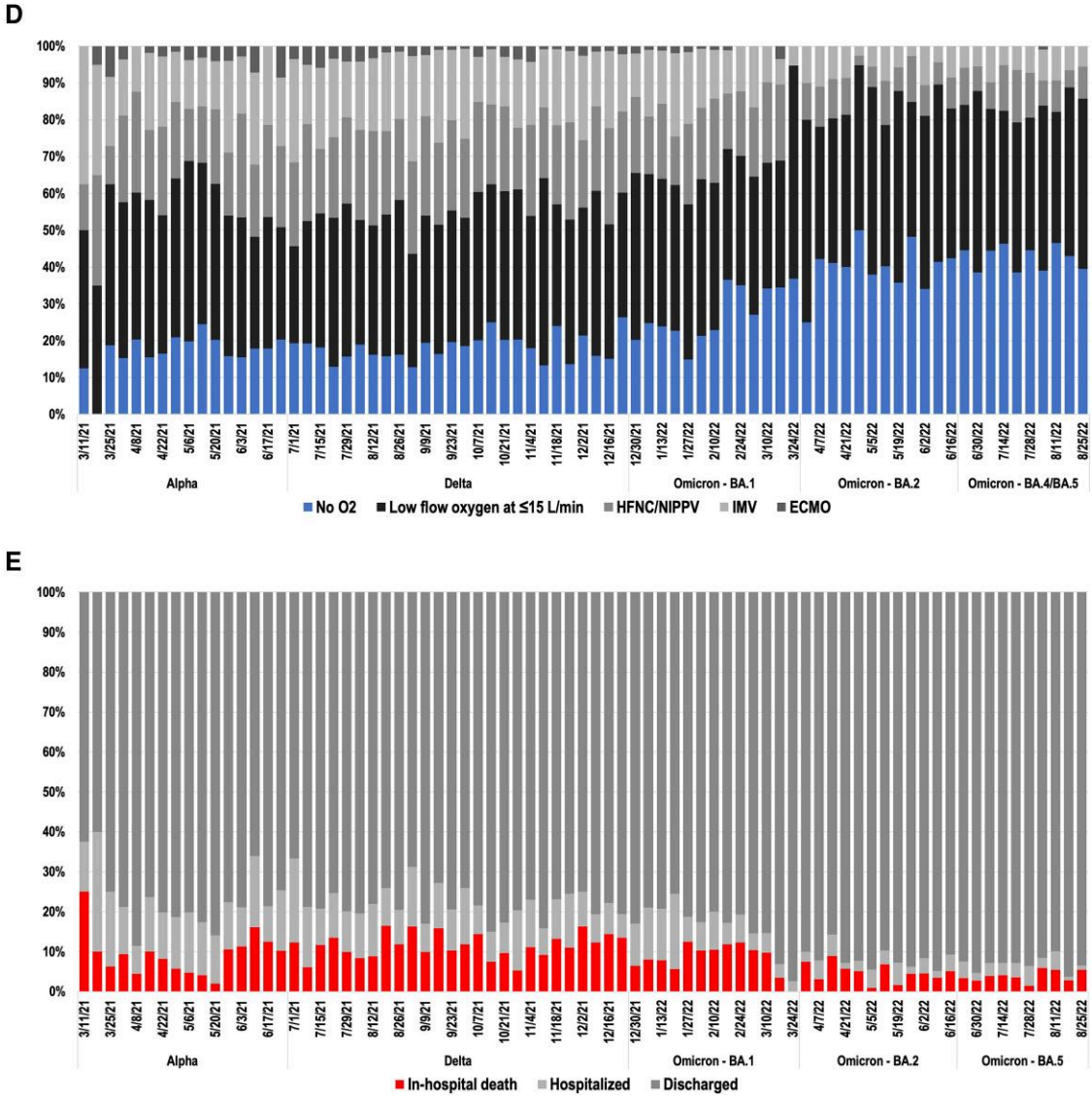

Figure 1. (*D*) Highest level of supplemental oxygen received among hospitalized adults with acute COVID-19 by week and predominant SARS-CoV-2 variant period. (*E*) Patient status (dead, still hospitalized, or discharged from the hospital) 28 days following hospital admission among hospitalized adults with acute COVID-19 by week and predominant SARS-CoV-2 variant period. Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; IMV. invasive mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; O_2, oxygen; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

hospitalized population declined over time. This can impact observed vaccine effectiveness against COVID-19-associated hospitalization as COVID-19 vaccines are more effective in preventing more severe outcomes, such as COVID-19-associated respiratory failure requiring IMV support [3, 28]. Thus, in addition to evaluating vaccine effectiveness against hospitalizations, other outcome measures, like hypoxemia, should be considered to stratify the severity and phenotype of disease of all patients admitted with a positive SARS-CoV-2 test to understand the protective benefit of COVID-19 vaccines.

This evaluation has several limitations. First, over time, clinical practice patterns for management of COVID-19 may have changed, including for patients admitted with similar disease severity. For example, it has been documented that clinician management strategies for COVID-19 shifted to increased use of high-flow nasal cannula and less early initiation of IMV and ECMO over the pandemic period [38]. Second, the cohort was largely limited to urban/metropolitan, academic hospitals which are not representative of hospitals nationally. Third, some of the analyses relied on clinically obtained data, which were subject to missingness based on local clinical practice patterns. Fourth, we excluded patients with an unknown COVID-19 vaccination status. Fifth, our study was unable to delineate the relative contributions of different factors in the decrease in COVID-19 severity over time; the reasons for this decline in severity may have been multi-factorial, including

changes in the virus, increasing vaccine coverage and increasing immunity from prior infection over time.

CONCLUSIONS

During the 18 months following widespread introduction of COVID-19 vaccines, the epidemiology of adults hospitalized in the United States with COVID-19 changed substantially. Compared to earlier periods in the pandemic, patients hospitalized during later Omicron sublineage periods were older and had more comorbidities, were more likely to be vaccinated, experienced less systemic inflammation and coagulopathy, received lower levels of oxygen support, and were less likely to die. The implications of these findings are that prevention and treatment strategies that are effective in this population will need to be advanced for optimal control of severe COVID-19-associated disease and death.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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