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Major Article

Risk factors associated with mortality in hospitalized patients with laboratory confirmed SARS-CoV-2 infection during the period of omicron (B.1.1.529) variant predominance

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Background: SARS-CoV-2 Omicron variant has a high transmission rate. In December 2021, Omicron became the dominant variant and quickly accounted for majority of infections in the United States. Drug shortages have led to prioritization of patients for COVID-19 treatment based on risk factors for severe disease.

Methods: A retrospective analysis of hospitalized patients with COVID-19 infection at Veteran Affairs Healthcare System across the United States. The primary outcome was 14-day all-cause mortality after the first documented positive SARS-CoV-2 laboratory test. Odds ratios were generated from a multivariate logistic regression of significant factors.

Results: This study included 12,936 COVID-19 inpatients during a period of Omicron predominance. Age ≥ 65 years is a predictor of 14-day mortality among the vaccinated and unvaccinated population (OR 4.05, CI 3.06-5.45, $P \leq .0001$). Triple vaccinated patients demonstrated a 52% decreased risk of death with COVID-19 infection (OR 0.48, CI 0.37-0.61, $P \leq .0001$). Patients who were double vaccinated had a 39% decreased risk of death with COVID-19 infection (OR 0.61, CI 0.46-0.80, $P = .003$).

Conclusion: Advanced age ≥ 65 is the greatest risk factor for mortality in hospitalized COVID-19 patients. COVID-19 vaccination, especially booster doses, was associated with a decreased risk of 14-day mortality compared to double vaccinated or non-vaccinated patients. Results of this study suggest that advanced age should be considered first for prioritization of COVID-19 treatments for Omicron.

The Omicron variant of SARS-CoV-2 was first discovered in 4 fully vaccinated diplomats in South Africa in November 2021. In late December 2021, Omicron became the dominant strain of COVID and quickly accounted for majority of infections in the United States.[1]

Data supports that Omicron has a replication advantage over the Delta variant. Rapid replication in nasal epithelial cells and bronchial tissue supports Omicron's transmission advantage over other variants.[2] CDC data found that omicron was the most common variant in the United States by late December 2021.[3,4] An analysis conducted by the United Kingdom Health Security Agency found a higher risk associated with Omicron versus Delta for household secondary attack rate (21.6% with Omicron vs 10.7% with Delta).[5]

Additionally, Omicron evades vaccine induced humoral immunity to a greater extent than previous variants. It is associated with decreased susceptibility to neutralizing antibodies, including monoclonal antibodies for COVID-19 treatment.[6,7] Clinical data indicates that vaccination, particularly in those who received a booster dose, remains effective against prevention of severe disease with Omicron. However, vaccine efficacy is lower with Omicron compared to other variants.[6,7]

A case-control study from the United States analyzed over 12,000 individuals with either Omicron or Delta infection.[6] The 3-dose series mRNA COVID-19 vaccine, compared with receipt of the 2-dose series or unvaccinated status, was less likely among cases with symptomatic SARS-CoV-2 infection. These findings conclude that a booster dose is associated with greater protection against both the Omicron and Delta strains compared to a primary series alone. However, a

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lower risk reduction for infection with Omicron (OR 0.33) versus Delta (OR 0.065) was detected, thus suggesting that there is less protection with vaccination for Omicron compared to the Delta variant.

Similarly, a report from a South African private health system demonstrated that 2 doses of the Pfizer COVID-19 vaccine were associated with 33% effectiveness against any infection and 70% effectiveness against COVID-19 hospitalization during the Omicron surge.[7] This differs from vaccine effectiveness against hospitalization during the Delta surge which was approximately 93%. Despite a high transmission rate and evasion of the immune system, Omicron appears to be associated with lower severity of disease compared to prior variants. Animal studies demonstrate that lower viral levels in lung tissues may further support the rationale for Omicron causing intrinsically less severe disease than other strains.

Evidence supports that vaccination against SARS-CoV-2 is effective at preventing COVID-19 associated hospitalization and death with the Omicron variant. However, some vaccinated persons may still develop COVID-19 infection with severe outcomes. These risk factors include advanced age ≥65 years and patients who are immunosuppressed or have underlying health conditions.[8,9] The objective of this study is to utilize national data in patients hospitalized with COVID-19 during Omicron prevalence (December 2021-February 2022) to determine which risk factors were associated with increased mortality in hospitalized patients.

METHODS

Patient selection

Data was retrospectively obtained from The Corporate Data Warehouse (CDW) and analyzed in the Veterans Affair Informatics and Computing Infrastructure. Access of the CDW was approved by the Institutional Review Board of the VA Western New York Healthcare System. This study was deemed exempt and so informed consent was not required. Cases of COVID-19 were identified by the COVID-19 Shared Data Resource from December 25, 2021 to February 2, 2022. Cases included a timeframe of December 25, 2021 to February 16, 2022 and were retrospectively followed for the primary outcome until February 16, 2022. The primary outcome was 14-day all-cause mortality after the first documented positive SARS-CoV-2 laboratory PCR. COVID-19 and comorbidities were defined by the COVID Shared Data Resource using ICD-10 codes and natural language processing.

Patients were considered triple vaccinated against COVID-19 if they received 3 doses of any combination of Pfizer-BioNTech or Moderna MRNA vaccines or Johnson and Johnson. Patients were considered double vaccinated if they received 2 doses of Johnson and Johnson, 2 doses of Moderna, or 2 doses of Pfizer-BioNTech. Patients with 1 dose of any vaccine, including Johnson and Johnson, were included in the study, but were not analyzed separately. Mixing and matching of vaccine manufacturers was acceptable to be included in the study.

Statistics

A multivariate logistic regression was performed, accounting for factors that may be associated with increased risk of COVID-19 mortality. These variables include age, sex, vaccination status, body mass index (BMI), and comorbidities. In the regression model, significant factors were eliminated in a stepwise, backwards fashion. Odds ratios with 95% confidence intervals (CI) were produced to determine the odds of death at 14 days. One multivariable analysis was provided with patients who received 2 doses of vaccine and a second multivariable analysis as provided for patients who received 3 doses (compared to those who received 0, 1, or 2 doses).

A Sensitivity Analysis was performed on the subset of double vaccinated patients to determine the durability of results. A multivariable analysis to assess risk factors for death at 14 days.

RESULTS

Of the 12,936 participants, 563 died within 14 days of a positive COVID-19 test result (4.35% death rate). Of the 563 patients that experienced the primary outcome 549 were male (97.5%, $P = .0004$) and 507 were ≥ 65 years (90.1%, $P \leq .0001$). The multivariable logistic regression analysis predicting COVID-19 mortality at 14 days accounted for sex, race, age, comorbidities, vaccination status, BMI (Table 1). More than half of the population received 2 doses of vaccine (53.99% (n = 6,984). Nearly 20% received 3 doses of vaccine prior to COVID-19 (19.7%, (n = 2,548)).

Of the total veterans who died within 14 days of COVID-19 PCR (n = 563), 258 who died had received 2 doses of vaccine and 73 who died, had received 3 doses of vaccine. Percent of the total cohort who experienced mortality was 4.35%. Of the total cohort, 2.36% either were not vaccinated or only received 1 dose, 1.99% received 2 doses or 3 doses. Among the people who received 3 doses of vaccine 0.56% experienced mortality. Of those who died, 54.2% either were not vaccinated or only received 1 dose, 45.8% received 2 doses or 3 doses.

The multivariable logistic regression model demonstrates that age ≥ 65 years was a statistically significant predictor of 14-day mortality (OR 4.05, CI 3.06-5.45, $P \leq .0001$). The model also demonstrated that significant risk factors for mortality within 14 days include congestive heart failure (CHF) (OR 1.37, CI 1.13-1.66, $P = .0018$), cirrhosis (OR 1.55, CI 1.09-2.14, $P = .0146$), and chronic kidney disease (CKD) (OR 1.55, CI 1.29-1.86, $P = .0001$). Vaccination status (at least 2 vaccines compared to 0 or 1 vaccinations) reduced the odds of death by 0.55 95%CI (0.46-1.66) (Table 2).

In the same cohort of veterans, but substituting triple vaccinated veterans compared to patients who received 0, 1, or 2 vaccines, patients ≥ 65 years with a booster dose demonstrated significant risk for death within 14 days (OR 3.99, CI 3.02-5.37, $P \leq .0001$). Other significant predictors of 14-day mortality include CHF (OR 1.34, CI 1.10-1.63, $P = .0035$), cirrhosis (OR 1.50, CI 1.06-2.07, $P = .0242$), and CKD (OR 1.49, CI 1.24-1.79, $P \leq .0001$). Among triple vaccinated patients, there was a 52% decreased risk of death in COVID-19 infection (OR 0.48, CI 0.37-0.61, $P \leq .0001$) compared to those who received less than 3 vaccinations (Table 3).

In the sensitivity analysis including only patients who were double or triple vaccinated (n = 6,984), patients ≥ 65 years with 2 vaccinations demonstrated significant risk for death within 14 days (OR 4.82, CI 2.97-8.39, $P < .0001$). Other significant predictors of 14-day mortality include CHF (OR 1.41, CI 1.07-1.85, $P = .0135$), cirrhosis (OR 1.81, 1.17-2.70, $P = .0084$), and CKD (OR 1.51, 1.16-1.96, $P = .0025$). Patients who were triple vaccinated had a 39% decreased risk of death from COVID-19 infection (OR 0.61, CI 0.46-0.80, $P = .003$) compared to those who were double vaccinated (Table 4).

DISCUSSION

This study consisted of a largely elderly, veteran population, including 12,936 COVID-19 inpatients during a period of Omicron predominance. The purpose of the study was to determine risk factors that impact mortality rate in hospitalized patients with COVID-19. Treatments for COVID are often in short supply during times of surging COVID levels and therefore we chose to examine risk factors for death to prioritize patients for treatment.

The overall death rate was 4.35% within 14 days of a confirmed laboratory COVID-19 test. Although mortality rate is significantly

Table 1
Baseline characteristics and outcomes for the cohort (n = 12,936)

Variable	Death within 14 d (N = 563, 4.35%)	Survival (N = 12,373, 95.65%)	*P*-value
Male	549 (97.5%)	11,619 (93.9%)	.0004
Age	76.9 ± 10.03	68.1 ± 13.8	<.0001
Age ≥65	507 (90.1%)	8,238 (66.6%)	<.0001
Race			.0530
African American	139 (24.7%)	3,459 (28.0%)	
White	382 (67.9%)	7,781 (62.9%)	
Other	42 (7.5%)	1,133 (9.2%)	
Body mass index	26.8 ± 6.99	28.56 ± 7.21	<.0001
Charlson comorbidity Index			<.0001
0-5	357 (63.4%)	9,676 (78.2%)	
6-20	206 (36.6%)	2,697 (21.8%)	
CAHD	241 (42.8%)	4,178 (33.8%)	<.0001
Cancer	193 (34.3%)	3,544 (28.6%)	.0039
Cardiomyopathy	69 (12.3%)	1,115 (9.0%)	.0090
Cerebrovascular	31 (5.5%)	661 (5.3%)	.8657
Congestive heart failure	185 (32.9%)	2,772 (22.4%)	<.0001
Cirrhosis	42 (7.5%)	599 (4.8%)	.0051
Chronic kidney disease	252 (44.8%)	3,717 (30.0%)	<.0001
Chronic obstructive pulmonary disease	202 (35.9%)	3,609 (29.2%)	.0006
CVD	379 (67.3%)	7,103 (57.4%)	<.0001
Diabetes	291 (51.7%)	5,590 (45.2%)	.0024
HIV	4 (0.7%)	123 (1.0%)	.5044
Hypertension	475 (84.4%)	9,524 (77.0%)	<.0001
Dexamethasone	374 (66.4%)	5,028 (40.6%)	<.0001
Vaccinated (2 doses)	258 (45.8%)	6,726 (54.4%)	<.0001
Vaccinated (3 doses)	73 (13.0%)	2,475 (20.0%)	<.0001
Ventilator within 60 d	192 (34.1%)	723 (5.8%)	<.0001
Length of stay	6.12 ± 3.7	7.8 ± 7.97	<.0001
Death within 30 d	563 (100%)	437 (3.5%)	<.0001
Readmission within 30 d	23 (4.1%)	1,517 (12.3%)	<.0001
ICU within 60 d	384 (68.2%)	3,210 (25.9%)	<.0001

CAHD, coronary atherosclerotic heart disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; ICU, intensive care unit.

lower with Omicron than Alpha and Delta strains, increased risk of reinfection, higher transmissibility, and decreased vaccine effectiveness remain major issues related to Omicron and its subvariants. A retrospective, matched study from Ontario, Canada examined hospitalization and mortality associated with Omicron BA.1 sublineage compared to Delta.[10] The study identified 37,296 Omicron cases from November 22, 2021 to December 24, 202, of which 9,087 were matched 1:1 with Delta cases. There were 53 hospitalizations (0.6%) and 3 deaths (0.03%) among Omicron cases compared to 129 hospitalizations (1.4%) and 26 deaths (0.3%) among Delta cases. The hazard ratio for hospitalization or death among Omicron cases compared with Delta cases was 0.41 (95% CI, 0.30-0.55); 0.33 (95% CI, 0.19-0.56). The results of this study align with other findings from South Africa, Scotland, and England, in which they all demonstrate a lower risk for hospitalization and death with Omicron compared to Delta cases. Although severity of disease appears to be reduced with the Omicron variant, the number of hospitalizations and impact on health care systems are significant due to the overall high incidence rate.

The largest risk factor for death is age. Our study demonstrated that age ≥ 65 years is a statistically significant predictor of 14-day mortality among the vaccinated and unvaccinated population (OR 4.05, CI 3.06-5.45 $P < .0001$). Among triple vaccinated patients, there was a 52% decreased risk of death in COVID-19 infection (OR 0.48, CI 0.37-0.61, $P < .0001$). Double vaccinated patients had a 39% decreased risk of death in COVID-19 infection (OR 0.61, CI 0.46-0.80, $P = .0003$). This shows the importance of a booster dose of vaccination.

While our study demonstrated the benefits of a booster vaccine, other studies have also found a correlation between booster doses and decreased risk for severe disease with COVID-19.[11] Our study however differed from many previous studies in that it took place during the period of the Omicron variant, whereas the aforementioned study took place prior to detection of the Omicron variant.[12]

Table 2
Multivariable logistic regression model for odds of 14-day mortality (n = 12,936)

	Odds ratio	95% CI	*P*-value
Age ≥ 65 y	4.05	3.06-5.45	<.0001
Body mass index (per unit change in regressor)	0.97	0.96-0.99	<.0001
Congestive heart failure	1.37	1.13-1.66	.0018
Cirrhosis	1.55	1.09-2.14	.0146
Chronic kidney disease	1.55	1.29-1.86	<.0001
Vaccinated (2 doses)	0.55	0.46-0.66	<.0001

Table 3
Multivariable logistic regression model for odds of 14-day mortality with the inclusion of triple vaccinated patients (n = 12,936)

	Odds ratio	95% CI	*P*-value
Age ≥ 65 y	3.99	3.02-5.37	<.0001
Body mass index (per unit change in regressor)	0.97	0.96-0.99	<.0001
Congestive heart failure	1.34	1.10-1.63	.0035
Cirrhosis	1.50	1.06-2.07	.0242
Chronic kidney disease	1.49	1.24-1.79	<.0001
Vaccinated (3 doses compared to 0, 1, or 2 doses)	0.48	0.37-0.61	<.0001

Table 4
Sensitivity analysis: subgroup of double and triple vaccinated patients only

	Odds ratio	95% CI	*P*-value
Age ≥ 65 y	4.82	2.97-8.39	<.0001
Body mass index (per unit change in regressor)	0.97	0.95-0.99	.0015
Congestive heart failure	1.41	1.07-1.85	.0135
Cirrhosis	1.81	1.17-2.70	.0084
Chronic kidney disease	1.51	1.16-1.96	.0025
Vaccinated (3 doses: 2 doses)	0.61	0.46-0.80	.0003

Multivariable analysis for Odds of 14-day mortality (n = 6,984).

One study from England, however, evaluated vaccine effectiveness against symptomatic disease caused by the Omicron and Delta variants between November 27, 2021, and January 12, 2022.[13] Similar to our study, it also found increased vaccine effectiveness with booster doses. Our study however differed in that we did not examine primary efficacy against infection, but rather mortality outcomes as COVID-19 moves into the endemic phase. We also did not examine a timeframe from vaccination to infection to determine waning immunity.

Risk for mortality among hospitalized COVID-19 patients was highly influenced by congestive heart failure (CHF), cirrhosis, and chronic kidney disease (CKD). Although other comorbidities, such as diabetes and cancer, were found to be significant in the bivariate analysis but were not significant in the multivariate analysis. The CDC has conducted systematic reviews of evidence about associations between severe COVID-19 and underlying comorbidities. Higher risk for severe outcomes includes underlying conditions such as cancer, CKD, cirrhosis, diabetes mellitus type 1 and 2, HIV, obesity (>30 kg/m^2), current or former smoker, and immunocompromised patients.[9] Overall, we must be cognizant of patients with comorbidities when classifying high risk patients. Our study demonstrates that this is especially true for patients with CHF, CKD, and cirrhosis.

Many studies have revealed that age, comorbidities, and vaccination status have a large impact on patient survival rate. Prioritization of outpatient COVID-19 drugs administered within their appropriate time frames remains vital to prevent further hospitalizations and mortality. This study has demonstrated that age, regardless of vaccination status, should be considered a major risk factor when determining prioritization of COVID-19 drugs. Accessing monoclonal antibodies, which are effective against the circulating variant and oral antivirals, has been difficult due to shortages. Therefore, prioritizing patients based on age and comorbidities may be the most advantageous way to improve survival rate during the Omicron era.

Limitations of this study include results that may not be generalizable beyond our study population of predominantly older, male veterans. We did not examine concurrent medications that veterans may have been taking. The study was unable to account for timeframe after vaccination to infection, to determine if there is an exact timeframe of waning immunity. An additional limitation is the retrospective nature of the study and the way in which data was extracted, with high reliability placed on the accuracy of documentation and reporting in patient charts. The various types of vaccines were not broken up by manufacturer as this fragmented the data. The predominant vaccine type was the mRNA vaccine.

CONCLUSION

Advanced age ≥ 65 is the largest risk factor for disease progression and subsequent mortality in hospitalized COVID-19 patients. COVID-19 vaccination, especially booster doses, was associated with a decreased risk of 14-day mortality compared to double vaccinated or non-vaccinated patients. Results of this study suggest that advanced age should be considered first for prioritization of COVID-19 treatments for Omicron rather than a compilation of comorbidities. However, when prioritizing COVID-19 treatment, consideration of comorbidities such as CHF, CKD, and cirrhosis should be considered as major risk factors for 14-day mortality rate.

Disclosures

There is no conflict of interest to disclose concerning financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this article. The contents of this article do not reflect or represent the views of the Department of Veterans Affairs or the United States Government.

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