Unvaccinated Non-Elderly Adult Population Hospitalized for COVID-19: Risk for Severe Disease and Poor Outcomes

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Abstract

Introduction: Vaccination offers significant protection against hospitalization and death due to severe COVID-19. However, a significant portion of the nonelderly U.S. adult population remains unvaccinated. **Methods:** This retrospective analysis of adult patients aged under 65 years hospitalized with PCR-confirmed SARS-CoV-2 between March and November 2021 assessed the age-biased risk for severe disease and outcome in non-elderly unvaccinated adults hospitalized for COVID-19. Main measures included predisposing risk factors, disease severity and progression, and outcomes in non-elderly adults compared between (1) vaccinated and unvaccinated individuals and (2) unvaccinated individuals grouped by 10-year age increment. **Results:** Two hundred nineteen non-elderly adults were included; of whom, 82.6% were unvaccinated. Overall, unvaccinated patients were more likely to be obese (60% vs 29%, $P < .001$) while vaccinated patients were more likely to have cardiovascular disease (50% vs 29%, $P = .03$). Unvaccinated individuals had prolonged ICU stay (11 vs 2 days, $P = .002$) and overall length of stay (6 vs 5 days, $P < .0001$), and higher proportion requiring oxygen at discharge (54% vs 29%, $P < .0001$). An age-stratified analysis of the unvaccinated cohort found that the time to discharge increased with age ($P = .003$). Compared to unvaccinated patients aged <46 years, unvaccinated patients aged ≥ 46 years demonstrated 1.47- and 3.49-times higher likelihood of oxygen dependency upon discharge ($P = .002$) and requiring higher level of care or worse at discharge ($P = .004$), respectively. **Conclusion:** Results from our non-elderly cohort affirm the benefit of vaccination despite a subset requiring hospitalization for breakthrough infection. In unvaccinated non-elderly adults, risk for worse outcomes and severe disease increased substantially from middle age onward and provides strong support for vaccination efforts in this population.

Keywords

SARS-CoV-2, unvaccinated, non-elderly, hospitalization, mortality

Introduction

The SARS-CoV-2 virus has infected nearly 50 million Americans and resulted in the death of over 800 000 persons. Mass vaccination efforts in the U.S. with the SARS-CoV-2 mRNA vaccines (tozinameran, Pfizer and mRNA-1273, Moderna) and the Johnson & Johnson's Janssen adenovirus vaccine have prevented an estimated 1.1 million COVID-19 deaths and 10.3 million additional COVID-19 hospitalizations through November 2021.[1] Among those fully vaccinated, the overall rate of breakthrough infections has been reported at $<0.1\%$ in the U.S.; of those, less than 5% required hospitalization.[2,3] A large multi-center study

reported that those hospitalized with breakthrough infections had the expected risk factors such as advanced age, multiple comorbidities, and immunosuppressive conditions but that the unvaccinated cohort was typically younger with fewer comorbid conditions.[4] Notably, vaccinated patients with breakthrough infections experienced a lower risk of

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progression to severe disease or death.[4] Despite data supporting vaccination, nearly a quarter of the adult population in the United States remains unvaccinated, leaving room for virus variant development and breakthrough infection among vaccinated individuals.[5] Vaccination rates vary by age and remain lower in non-elderly adults compared to elderly adults.[6] Prevalence of comorbid conditions associated with the risk of severe disease also varies by age in non-elderly adults, with typical manifestation of these chronic conditions around middle age.[7-10] Advanced age defined as ≥65 years along with comorbid conditions, functional status, and severity of acute illness have been shown to significantly predict prognosis of COVID-19 in the hospitalized elderly population.[11,12] However, the impact of age on the risk for severe disease and poor outcomes in the non-elderly cohort has not been well studied. Therefore, our study objectives are to compare risk factors, the severity of disease presentation, and outcomes (1) between unvaccinated and vaccinated adults with breakthrough infections and (2) between age groups among the unvaccinated non-elderly cohort hospitalized for severe COVID-19.

Methods

Design and Setting

This study was conducted retrospectively on adult patients with PCR-confirmed SARS-CoV-2 hospitalized for COVID-19 at 2 hospitals in Los Angeles County. Patients were identified through microbiology and medical records from March to November 2021 and included if they were: aged 18 to 64 years old, hospitalized for symptoms consistent with COVID-19, and had a PCR-positive detection of SARS-CoV-2. Exclusion criteria were absence of classic COVID-19 symptoms despite testing positive for SARS-CoV-2 on routine screening and hospitalized for other reasons or incomplete or lack of documentation of vaccination status.

Electronic medical records were reviewed and relevant demographic, laboratory, radiographic, and clinical data were recorded into HIPAA-compliant database REDCap v9.1.24.: age, body mass index, race, ethnicity, residence prior to admission, vaccination details (fully/partially/unvaccinated), comorbidities, time interval between symptom onset and hospitalization, oxygenation requirements upon admission and discharge, presence and duration of high flow oxygen and non-invasive and invasive ventilatory support, time to achieve clinical improvement, total hospital and intensive care unit (ICU) length of stay, receipt of in-hospital treatments for COVID-19, and in-hospital mortality.

Study Definitions

Patients were classified as fully vaccinated if there was documentation of receipt of both doses of a 2-dose series or one dose of a single-dose series before presentation to the hospital. During the time of study, the tozinameran vaccination booster was authorized on September 22, 2021 for those age ≥65 years, adults at high risk of severe COVID-19, or adults with frequent institutional or occupational exposure to SARS-CoV-2. Expansion of booster eligibility occurred on November 19, 2021 to include all adults who received a full schedule of any COVID-19 vaccines available in the U.S. Boosted patients were not classified in this study due to the short time frame of authorization to the end of the study period. Patients were classified as unvaccinated if they had received no vaccine dose prior to admission or only 1 dose of a 2-dose vaccination series. Patients grouped in the vaccinated cohort required documentation of vaccination (eg, vaccination card or California Immunization Registry).

Disease severity was classified by: (1) disease progression requiring invasive mechanical ventilation with or without organ support or death (severe disease) or not severe and (2) the World Health Organization (WHO) COVID-19 Clinical Progression Scale of 4 to 9 since our analysis included only hospitalized patients where 4 corresponds to mild disease without oxygen supplementation, 5 moderate disease requiring standard supplemental oxygen, 6 to 8 severe disease requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation, and 9 in-hospital mortality.

The WHO Clinical Progression Scale was also used to assess time to clinical improvement regarding oxygenation and oxygen requirements based on ≥1 point deduction from time of admission. Patients who did not require oxygen for the entirety of admission were classified as having 0 day for time to clinical improvement whereas those who had no improvement in oxygen status during admission (eg, requiring supplemental oxygen for the entirety of admission), time to clinical improvement was classified as the length of stay, with improvement defined as achieving clinical stability for hospital discharge. Only survivors who were discharged to an equivalent or lower level of care prior to admission were assessed.

Statistical Analysis

Patients were grouped by vaccination status and compared for demographics, comorbid conditions, clinical presentation, and outcomes. To assess the age-biased risk of severe disease and outcomes in the unvaccinated cohort, patients were stratified by age in decades from 25 to 64 years for comparison. Continuous variables were analyzed by Student's *t*-test (or Wilcoxon-Mann Whitney test), or one-way ANOVA (or Kruskal Wallis test) and categorical variables with Chi-square or Fisher's exact test where appropriate. Logistic regression was used to calculate odds ratio to identify the incremental likelihood of poor

outcomes with every decade increase in age. A receiver operating characteristics (ROC) analysis and Youden Index were utilized to estimate the age cutoffs for predicting poor outcomes. Propensity score was calculated, based on several comorbid conditions including cardiovascular disease, pulmonary disease, diabetes, immunocompromised, and obesity (BMI > 30), to balance the unvaccinated and vaccinated groups. The second propensity score was also calculated based on the same comorbid conditions to balance the groups of persons aged ≥46 years and <46 years old in the unvaccinated sample. Propensity score weights, also referred to as the inverse probability weighting (IPW), were calculated as reversed propensity score for in the unvaccinated group (or aged ≥46 years), and reversion of 1 minus propensity score for the vaccinated group (or aged <46 years). The propensity score weighted logistic regression models were then fitted to compare the outcomes. Time to discharge was analyzed by a cumulative incidence curve. Statistical significance was indicated by a 2-tailed *P*-value < .05. GraphPad Prism v9.0 (San Diego, CA, USA) and SAS software v9.4 (SAS Institute Inc., Cary, NC, USA) were used for statistical analysis.

Results

Patient Characteristics

Of the 495 adult patients admitted with a positive SARS-CoV-2 PCR test during the 9-month study, 276 were excluded for the following reasons: advanced age ≥65 years (n = 132), absence of classic COVID-19 symptoms (n = 109), and incomplete documentation of vaccination (n = 35). A total of 219 non-elderly patients with symptomatic COVID-19 were included in the study. Our non-elderly cohort hospitalized for COVID-19 were mostly unvaccinated (87%, 191/219), with the remaining 13% (28/219) admitted for breakthrough infections despite full vaccination. The median time between receipt of last dose of vaccination and hospitalization was 149 days [IQR 109-189]. Nearly all patients (208/219, 95%) were admitted from home regardless of vaccination status.

The study cohort had a median age of 49 years [IQR 39-57] and was similar between unvaccinated and vaccinated patients. Majority were Hispanic (45%, 98/219), followed by White non-Hispanic (24%, 52/219), and Black non-Hispanic (14%, 31/219) (Table 1). Unvaccinated patients included more White non-Hispanic (25% vs 18%) and Black non-Hispanic patients (15% vs 11%) and fewer Hispanic patients (43% vs 53%) compared to the vaccinated cohort, respectively. Overall, the 3 most commonly occurring comorbidities were obesity (56%, 122/219), followed by cardiovascular disease (32%, 70/219,), and diabetes (22%, 48/219). Unvaccinated patients were more likely to be obese (60% vs 29%, *P* < .001) than vaccinated patients

but the latter group had a higher proportion of cardiovascular disease (50% vs 29%, *P* = .03); the proportion with diabetes was similar between groups (29% vs 21%).

Clinical Presentation and Outcomes of Unvaccinated and Vaccinated Patients

More non-vaccinated patients numerically required supplemental oxygen within the first 24 hours of hospitalization compared to the vaccinated group (80%, 153/191 vs 68%, 19/28, *P* = .15) (Table 1). During hospitalization, a significantly higher proportion of unvaccinated patients required the use of high-flow nasal cannula compared to the vaccinated population (22% vs 14%, *P* = .005) (Table 2). However, the proportions of unvaccinated and vaccinated patients were similar in their requirement for non-invasive mechanical ventilation (16%, 31/191 vs 14%, 4/28) at any point during hospitalization or in severity according to the WHO Ordinal Scale (Table 2). Despite similar proportions of patients in both groups (18% vs 14%) requiring intensive care unit (ICU) level of care, the ICU length of stay was significantly prolonged in the 35 non-vaccinated patients compared to the 4 vaccinated patients [median 11 (IQR 4-18) vs 2 days (IQR 2-4), *P* = .002]. Of those who survived, the unvaccinated cohort had a prolonged hospital stay (median 6 [IQR 4-10] vs 5 [IQR3-6] days, *P* < .0001) and were less likely to be discharged on room air when compared to vaccinated patients (46% vs 71%, *P* < .0001). In-hospital mortality was 5% (10/191) in the unvaccinated cohort compared to none who died in the vaccinated group (Table 2).

Notably, 9% (17/191) of unvaccinated patients decompensated to requiring invasive mechanical ventilation following admission as compared to none of the vaccinated patients. Among those who decompensated, 82% (14/17) were at least 44 years of age or older and had an average of 2 comorbidities. The most frequent comorbid condition in this subgroup was obesity, followed by cardiovascular disease and diabetes (65%, 24%, and 48%, respectively). All 17 decompensated patients required ICU-level care with more than half dying (59%, 10/17). Of those who survived after invasive mechanical ventilation, only 3 were discharged home after a lengthy hospital stay (median 17 days) with the remaining 3 patients discharged with home health care, to acute rehabilitation, or to a skilled nursing facility. One patient left against medical advice.

Age-related Analysis of the Unvaccinated Cohort

Only 2 unvaccinated patients hospitalized were aged 18 to <25 years. Thus, we combined this subset with those aged 25 to 34 into the <35-year age bracket. The distribution of unvaccinated patients hospitalized for COVID-19 increased incrementally with each age bracket: <35 (18%), 35 to 44

Table 1. Baseline Patient Characteristics.

	All patients (n = 219)	Unvaccinated (n = 191)	Vaccinated (n = 28)	*P*-value*
Age, median [IQR]	49 [39-57]	49 [38-57]	49.5 [45-59]	.25
Age, years				
<35	35 (16)	34 (18)	1 (4)	.18
35-44	39 (18)	35 (18)	4 (14)	
45-54	75 (34)	62 (33)	13 (46)	
55-64	70 (32)	60 (31)	10 (36)	
Sex				
Female	93 (42)	84 (43.97)	9 (32)	.31
Race and ethnicity				
White, non-Hispanic	52 (24)	47 (25)	5 (18)	.95
Hispanic	98 (45)	83 (43)	15 (53)	
Black, non-Hispanic	31 (14)	28 (15)	3 (11)	
Asian	17 (8)	15 (8)	2 (7)	
Other	21 (9)	18 (9)	3 (11)	
Location PTA				
Home	208 (95)	183 (96)	25 (89)	
SNF/LTAC/rehabilitation	1 (1)	1 (1)	0 (0)	–
Other/homeless	10 (4)	7 (3)	3 (11)	
No. of chronic medical conditions	2 [1-3]	1 [1-3]	2 [1-3]	.30
Cardiovascular disease	70 (32)	56 (29)	14 (50)	.03
Pulmonary disease	24 (11)	16 (8)	8 (29)	<.01
Diabetes	48 (22)	40 (21)	8 (29)	.34
Immunocompromised	18 (8)	14 (7)	4 (14)	.26
Obesity (BMI > 30)	122 (56)	114 (60)	8 (29)	<.001
Median days of admission from last vaccine dose	–	–	149 [109-189]	–
Symptom duration PTA	7 [5-10]	7 [15-10]	7 [2.8-10]	.43
Required oxygen support within 24 h from admission	172 (79)	153 (80)	19 (68)	.15

Abbreviations: PTA, prior to admission; SNF, skilled nursing facility; LTAC, long-term acute care facility.
Data are presented as frequency (column percentage) or Median [interquartile range].
P-value < .05 denotes statistical significance .

(18%), 45 to 54 (32%) and 55 to 64 years (31%). Of note, age 45 appeared to be the point at which the proportion of unvaccinated patients hospitalized for COVID-19 increased nearly 2-fold which appeared to coincide with the age at which an increase in the prevalence of cardiovascular disease with or without diabetes was observed (Table 1). Age 45 was also the median age among patients that only reported obesity as their only comorbidity. Interestingly, obesity was highly prevalent in the younger cohort, particularly among unvaccinated patients aged <35 years (73.5%) (Figure 1).

An age-biased risk in disease severity and outcome was observed. Among unvaccinated patients, moderate and severe disease including death occurred most frequently in the 55 to 64 age group (90%). Time to discharge increased with age and was the longest in those 55 to 64 years (median 8 vs 6 vs 5 vs 5 days, *P* = .003) (Figure 2).

Additionally, a significantly greater proportion of unvaccinated patients aged 55 to 64 years required supplemental oxygen at discharge compared to the younger age brackets (72% vs 55% vs 57% vs 21%, *P* < .0001) (Table 3). Death occurred at the highest rate (10%) in those aged 55 to 64 years, two-fold higher than deaths occurring in those aged 45 to 54 years (5%) and over three-fold higher in those aged 35 to 44 years (3%). Medical records indicated that the 10 patients who died [median age 57 (IQR 49-60)] were survived by at least 23 children, collectively.

Age 46 years or older appeared to be the cutoff age most predictive of oxygen dependency and poor disposition status (HLOC or worse) based on ROC analysis. Following propensity score weighting by comorbid conditions, unvaccinated patients aged ≥46 years demonstrated 1.47 and 3.49 times higher likelihood of requiring oxygen (OR 2.47, 95% CI 1.38-4.42, *P* = .002) and higher level of care or worse at discharge (OR 4.49, 95% CI 1.60-12.62, *P* = .004), respectively, compared to patients age <46 years.

Table 2. Comparison of Outcomes Between Unvaccinated and Vaccinated Cohorts.

Characteristic	All patients (n = 219)	Unvaccinated (n = 191)	Vaccinated (n = 28)	aOR (CI 95%) or Parameter Est. (SE)	P-value*
ICU	39 (17)	35 (18)	4 (14)	2.14 (0.95-4.80)	.07
ICU durationa (n = 39), days[a]	9 [3-17]	11 [4-18]	2 [2-4]	10.4 (3.18)	.002
HFNC	46 (21)	42 (22)	4 (14)	3.35 (1.45-7.72)	.005
Non-invasive MV	34 (16)	31 (16)	4 (14)	0.64 (0.33-1.27)	.20
Invasive MV	17 (8)	17 (9)	0 (0)	-	-
Severity (WHO Scale)[b]					
Mild (4)	41 (20)	34 (19)	7 (25)	0.98 (0.59-1.64)	.94
Moderate (5)	116 (55)	102 (56)	14 (50)		
Severe (6-8)	52 (25)	45 (25)	7 (25)		
Death	10 (5)	10 (5)	0 (0)	-	-
Time to discharge, days[c]	6 [4-9]	6 [4-10]	5 [3-6]	4.2 (0.99)	<.0001
O2 on Discharge					
NC or worse	112 (51)	104 (54)	8 (29)	3.59 (2.03-6.34)	<.0001
Disposition					
HLOC or worse, including death	30 (14)	28 (15)	2 (7)	6.77 (1.90-24.07)	.003

Abbreviations: ICU, intensive care unit; HFNC, high flow nasal cannula; MV, mechanical ventilation; WHO, World Health Organization; O$_2$, oxygen; HLOC, higher level of care; aOR, adjusted odds ratio; CI, confidence interval; SE, standard error.
Data are presented as frequency (column percentage) or Median [interquartile range]; Odds ratios (95% CI) were used for categorical variables and parameter estimate (standard error) were used for continuous variables.
*P-value < .05 denotes statistical significance. P-values were obtained from multiple logistic regressions using inverse probability weighting (IPW) estimated by 5 types of comorbid conditions in Table 1.
[a]Only considers patients who were admitted to the ICU.
[b]n = 209, excluded deceased.
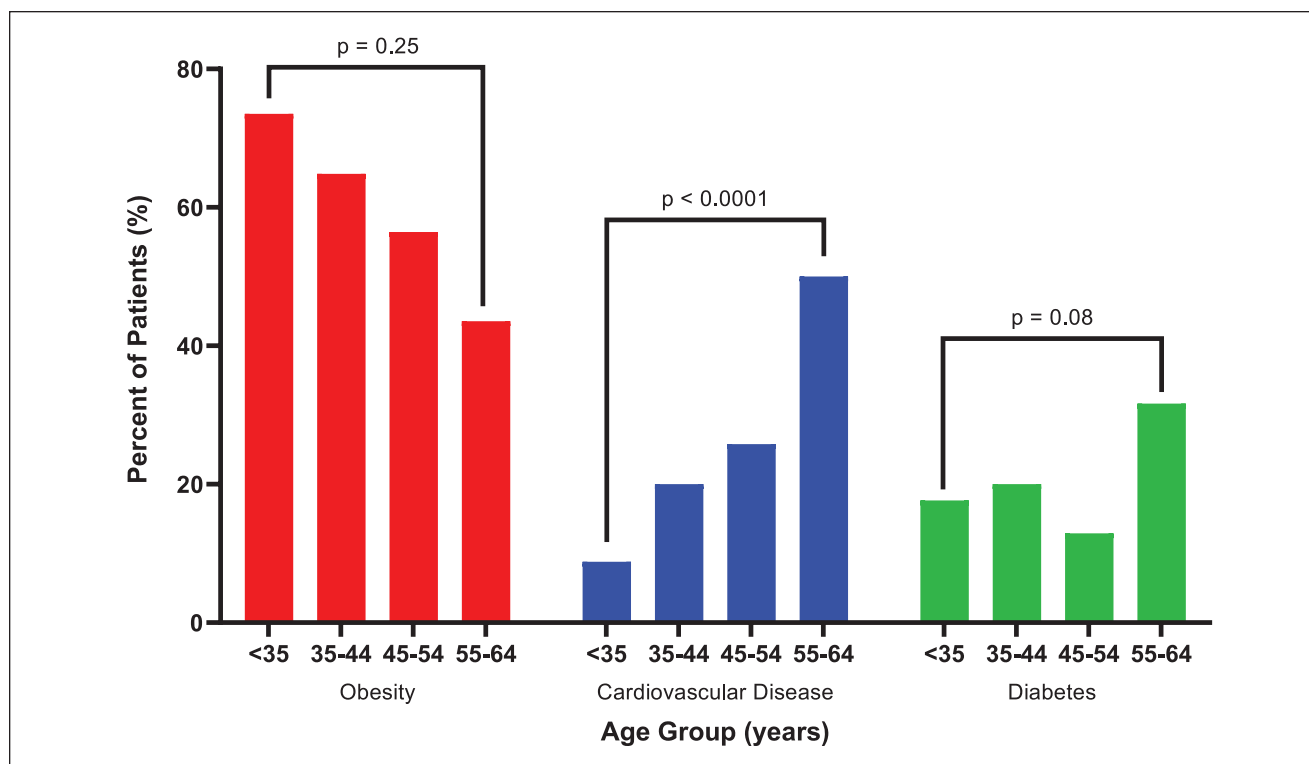[c]Only considers survivors discharged home or to lower level of care prior to admission.

Figure 1. Age-biased comorbid conditions and prevalence in unvaccinated cohort. Prevalence of obesity, cardiovascular disease, and diabetes among the different age groups is shown. Obesity (red) was more prevalent among the younger cohort and decreased with age. Cardiovascular disease (blue) and diabetes (green) demonstrate increased prevalence with age.
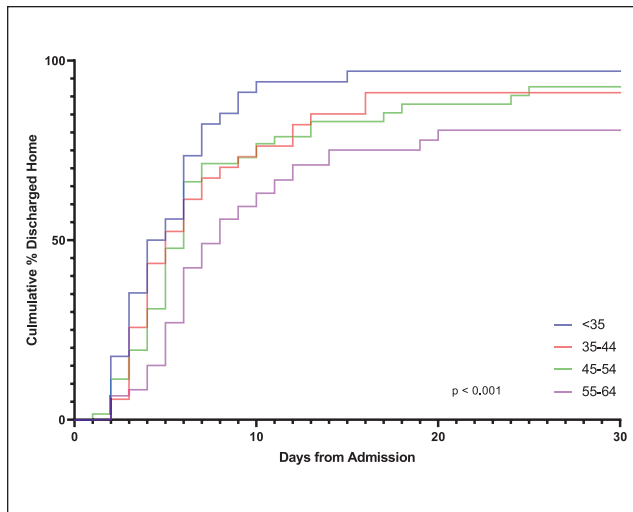
Figure 2. Time to discharge home comparing age groups in unvaccinated cohort. Cumulative incidence of hospital discharge by age group is shown. The event of interest was discharge from the hospital to home or lower level of care compared to prior to admission (eg, admitted from acute rehabilitation facility and discharged to skilled nursing facility). Patients who remained hospitalized for more than 60 days were censored at 60 days.

Discussion

In this study, we performed a detailed analysis of non-elderly adults hospitalized with COVID-19 between March to November 2021 to identify age differentiated characteristics and outcomes between unvaccinated and vaccinated non-elderly population during 2 different waves of the pandemic: the original Alpha variant and the more severe Delta variant. Our overall patient characteristics with regards to age, sex, and underlying comorbidities for the vaccinated and unvaccinated cohorts were similar to those reported in the study by Tenforde et al; however, we examined the clinical outcomes in our patient cohort in addition to presentation.[4] We found that both unvaccinated and vaccinated patients presented with similar oxygen requirements upon admission and during hospitalization. However, it is notable that 9% of unvaccinated patients in our study progressed to severe disease following admission requiring more intensive oxygen support compared to none in the vaccinated group. Importantly, our study demonstrated that vaccinated patients experienced a significantly shorter duration of ICU stay and overall length of stay. We also observed lower risk of decompensating to critical illness and a higher proportion of being discharged home without the need for supplemental oxygen which affirms that, despite breakthrough infection, vaccination offers protection against unfavorable hospital course and outcomes. Tenforde et al found a strong association of hospitalization among those aged ≥65 years without vaccination; however, the association was not as significant in those aged 18 to 64 years, which prompted a more in-depth evaluation of the non-elderly adult population.[4]

Data from the CDC shows lower vaccination rates among non-elderly adults particularly those aged 35 to 64 compared to elderly aged ≥65 years (70% vs 88%), respectively.[13] Notably, we found the age cutoff of 48 years or older to be strongly predictive of mortality and oxygen requirement at discharge in our unvaccinated cohort. The high prevalence of diabetes and cardiovascular disease in this age group predisposes them to poor immune response likely contributing to the high risk for severe disease.[14,15] A meta-analysis assessing the impact of these comorbidities on the severity of disease found that patients having a history of cardiovascular disease had nearly 50% greater odds of progressing to severe disease than a history of diabetes.[16] In line with those results, the oldest strata of unvaccinated patients had the highest proportion of having cardiovascular disease (with or without obesity and metabolic disease) which alone could have placed them at increased risk for progression to severe disease.

On the other hand, obesity was found to be the most prevalent comorbidity in our younger patient cohort (50%-75%). Our younger cohort demonstrated more favorable outcomes despite previous reports of the association of morbid obesity with severe COVID-19 progression and death in younger patients.[17,18] Gao et al demonstrated a linearly increased risk of death due to COVID-19 in patients with BMI > 23 kg/m^2.[19] Similar to our study, they also noted a low incidence of severe COVID-19 in their <40-year aged cohort, thus increased BMI as a risk factor was more attributable to those of middle age (40-60) years.[18] Consistent with our data, 45 years was the median age among those with obesity which coincided with the age group (>45 years) in which hospitalizations for COVID-19 doubled compared to the younger unvaccinated cohort. Additionally, this is also the age cohort in which we see a significant likelihood of oxygen dependency at discharge and poor disposition after hospitalization among the unvaccinated patients regardless of comorbidities. Taken together, intense vaccination efforts should target middle-aged adults with obesity even in the absence of other comorbidities.

Considering the high numbers of unprotected non-elderly individuals due to the low rate of vaccination, the risk for severe COVID-19 and death appears to be underappreciated in this cohort. Despite being younger and having fewer comorbid conditions, the unvaccinated cohort was more likely to experience unfavorable outcomes and morbidity than their vaccinated counterparts as more than half compared to less than 30% required supplemental oxygen upon discharge. Importantly, the hidden impact beyond those directly affected by COVID-19 infection on the dependent children is profound and particularly relevant in the non-elderly cohort evaluated in this study. Of those who died, 80% were documented to have had children, though

Table 3. Age-stratified Clinical Presentation and Outcomes of Unvaccinated Cohort (N = 191).

Characteristic	<35 (n = 34)	35-44 (n = 35)	45-54 (n = 62)	55-64 (n = 60)	P-value
ICU	3 (9)	7 (20)	15 (24)	10 (17)	.30
ICU duration, days[a]	7 [1-18]	9 [3-34]	8 [3-17]	13 [11-19]	.35
HFNC	3 (9)	11 (31)	12 (19)	16 (27)	.09
Non-invasive MV	1 (3)	7 (20)	10 (16)	13 (22)	.07
Invasive MV	2 (6)	1 (3)	7 (11)	7 (12)	.43
Severity[b]					
Mild	8 (23)	7 (21)	13 (22)	6 (11)	.61
Moderate	20 (59)	17 (50)	33 (56)	32 (59)	
Severe	6 (18)	10 (29)	13 (22)	16 (30)	
Death	0 (0.0)	1 (3)	3 (5)	6 (10)	.20
Time to discharge, days[c]	5 [3-7]	5 [3-10]	6 [4-9]	8 [5-12]	.003*
O2 on discharge					
NC or worse	7 (21)	20 (57)	34 (55)	43 (72)	<.0001*
Disposition					
HLOC or worse, including death	0 (0)	4 (11)	9 (15)	15 (25)	<.01*

Abbreviations used: ICU, intensive care unit; HFNC, high flow nasal cannula; MV, mechanical ventilation; WHO, World Health Organization; O_2, oxygen; NC, nasal cannula; HLOC, higher level of care.
Data are presented as frequency (column percentage) or Median [interquartile range].
*P-value < .05 denotes statistical significance.
[a]Only includes patients who were admitted to the ICU.
[b]n = 181, excluded non-survivors.
[c]Only includes survivors discharged home or to lower level of care prior to admission.

their dependency status was inconsistently documented. Adult caregivers with lingering health issues from severe COVID-19 infection can leave a toll on the household income and food security for the family. It is estimated that over 220 000 children under 18 years have been orphaned by the loss of one or both parents to COVID-19.[20] Furthermore, 65% of the children facing orphanhood as a result of COVID-19 belong to families of racial and ethnic minorities.[21] It has been shown that children with loss of a parental figure are at risk for mental health problems, shorter schooling, lower self-esteem, sexual risk behaviors, and increased risk of substance abuse, suicide, violence, sexual abuse, and exploitation.[22] Considering the broad and profound impact that COVID-19 has on the morbidity and mortality of the non-elderly populations, particularly those with children aged <18 years, the choice to get vaccinated has far-reaching health and social consequences on their immediate families.

Study Limitations

This study has several limitations. First, the small sample size and geographical limitations preclude generalizability to the populations across the country. Nonetheless, our patient characteristics were similar to those reported in the multicenter nationwide study by Tenforde et al. Notably, the distribution of race and ethnicity in our study indicating higher proportion of non-white Hispanics and Blacks uncover health inequities specific to the Los Angeles County area that need to be addressed with high priority. Second, this study did not differentiate those who received a vaccination booster due to the timing of approval of booster administration and thus the impact of booster dose on outcome was not explored. Regardless, the average time from last vaccination dose to hospitalization in our cohort demonstrated waning immunity from vaccination at 6 months and further supported the recommended waiting period of 5 months for the COVID-19 mRNA vaccine booster.[23] Additionally, while the exclusion of patients with incomplete vaccination information allows us to establish the protective effect of vaccination, it limits real-world generalizability by missing individuals who were vaccinated but unable to provide documentation. Finally, the retrospective nature of this study precludes exploration of the reasons why some patients who are at risk for severe COVID-19 remain unvaccinated.

Conclusion

Unvaccinated non-elderly adults, especially those in the age range upwards of 45 years, demonstrated notable vulnerability for severe COVID-19 infection and morbidity at discharge. Significant morbidity and mortality especially in the middle-aged cohort resulting from COVID-19 infection are being observed but likely underappreciated in this cohort given the lower rate of vaccination compared to elderly individuals. Vaccination efforts should be prioritized to protect these individuals while SARS-CoV-2

remains in circulation and to mitigate the collateral impact on family members particularly dependent children of infected individuals.

Ethics Declaration

This study was approved by the Institutional Review Boards at the University of Southern California and at Huntington Memorial Hospital, respectively.

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