Age-related differences in symptoms in older emergency department patients with COVID-19: Prevalence and outcomes in a multicenter cohort

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Abstract

Background: Older adults represent a disproportionate share of severe COVID-19 presentations and fatalities, but we have limited understanding of the differences in presentation by age and the association between less typical emergency department (ED) presentations and clinical outcomes.

Methods: This retrospective cohort study used the RECOVER Network registry, a research collaboration of 86 EDs in 27 U.S. states. We focused on encounters with a positive nasopharyngeal swab for SARS-CoV-2, and described their demographics, clinical presentation, and outcomes. Sequential multivariable logistic regressions examined the strength of association between age cohort and outcomes.

Results: Of 4536 encounters, median patient age was 55 years, 49% were women, and 34% were non-Hispanic Black persons. Cough was the most common presenting complaint across age groups (18–64, 65–74, and 75+): 71%, 67%, and 59%, respectively ($p < 0.001$). Neurological symptoms, particularly altered mental status, were more common in older adults (2%, 11%, 26%; $p < 0.001$). Patients 75+ had the greatest odds of ED index visit admission of all age groups (adjusted odds ratio [aOR] 6.66; 95% CI 5.23–8.56), 30-day hospitalization (aOR 7.44; 95% CI 5.63–9.99), and severe COVID-19 (aOR 4.26; 95% CI 3.45–5.27). Compared to individuals with alternate presentations and adjusting for age, patients with typical symptoms (fever, cough and/or shortness of breath) had similar odds of ED index visit admission (aOR 1.01; 95% CI 0.81–1.24), potentially higher odds of 30-day hospitalization (aOR 1.23; 95% CI 1.00–1.53), and greater odds of severe COVID-19 (aOR 1.46; 95% CI 1.12–1.90).

Conclusions: Older patients with COVID-19 are more likely to have presentations without the most common symptoms. However, alternate presentations of COVID-19 in older ED patients are not associated with greater odds of mechanical ventilation and/or death. Our data highlights the importance of a liberal COVID-19 testing strategy among older ED patients to facilitate accurate diagnoses and timely treatment and prophylaxis.

INTRODUCTION

Adults aged 65 years and older are 8.7 times more likely to require hospitalization for SARS-CoV-2 infection, and have accounted for 22% of cases and 78% of deaths related to COVID-19 in the United States.[1] Older adults are thought to have unique vulnerability to COVID-19 due to a higher comorbidity burden,[2–4] greater clinical frailty,[5] access to care challenges,[6] and immunosenescence,[5,7] all which could explain their greater likelihood of morbidity and mortality. Another possible explanation is that diagnoses of COVID-19 could be missed in older adults due to less common presenting symptoms leading to treatment delay. Treatment delay is associated with poorer treatment efficacy,[8] potentially leading to higher mortality rates.[9] Most SARS-CoV-2-positive patients present to U.S. emergency departments (EDs) with fever, cough, and dyspnea.[10–12] However, older adults with COVID-19 can present "atypically" or with alternate presentations such as falls or syncope,[13] drowsiness,[14] or acute mental status changes.[15,16]

While the link between age and worse clinical outcomes in older patients with SARS-CoV-2 infection has been well-established,[2,17] few studies in the United States have explored the ED presentation of older adults with COVID-19 and its impact on clinical outcomes in this population. It is largely unknown how common it is for older adult ED patients to present with alternate or uncommon symptoms and whether there is an association between alternate presentation and worse clinical outcomes in older patients compared to younger adults. A small, retrospective cohort study of 375 COVID-positive patients of all ages admitted from the BronxCare Health System ED in New York City cited an overall mortality of 43% and showed that increased age correlated with higher odds of death.[18] However, this study was completed in a single urban center and did not stratify patients into age groups or examine associations between ED presentations and outcomes. Additional studies based out of New York City evaluated the need for intensive care unit (ICU)-level care following ED presentation and concluded there was an association between dyspnea and low oxygen saturation and ICU admission.[19,20] However, outcome analysis based on age (i.e., ages 18–64 compared to ages 65 and greater) was not reported. As such, more multisite research is needed to understand the clinical presentation of older adults and subsequent outcomes following SARS-CoV-2 infection.

Key points

- Younger patients (<65 years old) with COVID-19 present to emergency departments with symptoms more typical of respiratory illness (fever, cough, and/or shortness of breath) than older adults.
- Older adults have worse clinical outcomes including greater odds of ED index visit and 30-day hospitalization, and mechanical ventilation and/or death (severe COVID-19).
- Lack of cough, fever, and/or shortness of breath in older ED patients was not associated with greater odds of severe COVID-19, but could challenge timely diagnosis without widely available, timely testing.

Why does this paper matter?

A liberal COVID-19 testing strategy among older ED patients is necessary to facilitate accurate diagnoses, timely treatment, and prophylaxis.

The objective of this study was to determine how the symptoms, laboratory results, and chest radiograph findings in older ED patients differ from younger adults, in a pre-vaccination cohort. We hypothesized that older adults were more likely to lack the typical features of acute respiratory infections. The secondary aim was to examine short-term and longer term (30-day) clinical outcomes of adults with SARS-CoV-2 by age and phenotype (typical vs alternate presentation). We hypothesized that older patients would have worse clinical outcomes overall, and older adults with alternate presentations would have worse short and long-term outcomes due to later or missed diagnoses.

METHODS

Population and data source

Data for this study was collected as part of a retrospective observational multicenter cohort study of U.S. ED patients with suspected COVID-19 as part of the REgistry of COVid-19 patients in emERgency care (RECOVER) Network.[21,22] RECOVER is a research collaboration of

EDs from 86 hospitals in 27 U.S. states, and detailed methods of the study are previously published.[20] Data were collected at each site using a centralized data abstraction form by automated download or manually. Data extractors were blinded to the study goals. Any discrepancies or missing data were addressed in quality checks of the data by the lead research coordinator. Symptoms not charted as present were presumed to be absent. The database was closed to new entries and uploads on October 16, 2020 and included data from patients March 2020–September 2020. Adult patients (aged 18 years or older) with a positive nasopharyngeal swab for SARS-CoV-2 by polymerase chain reaction (PCR) on the index ED visit or within 14 days prior to the ED visit were included in this analysis.

Patients were excluded if there was a high degree of certainty that the visit was not related to a viral infection such as presentations due to trauma, alcohol or drug intoxication, poisoning, suicidality, suspected rape or other domestic violence, involuntary commitment, or other isolated chief complaint clearly not related to COVID-19 (e.g., suture removal). The rationale was that these patients did not have an ED visit for COVID-19 symptoms, and could skew the data evaluation as symptoms are our exposure. Furthermore, patients who incidentally tested positive as a result of institutional routine screening, but who displayed no COVID-19 or other viral symptoms, were also excluded. All cases were reviewed a minimum of 30 days after the ED encounter to capture outcomes. Symptoms were abstracted from electronic health records and categorized as "typical" (cough, fever, or shortness of breath) or "alternate symptoms" based on existing literature.[10]

This reporting complies with the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) for observational cohort studies (see Supplementary Table S5).

Institutional review board approval

The local hospital IRB approved the study (IRB # 1586472-1), and informed consent was waived for this minimal risk study.

Measurement

Demographics

Patient demographics included: age in cohorts, sex, and race/ethnicity. As the study objective was to evaluate the association between age and alternate presentations, age cohorts were derived from a continuous age variable into
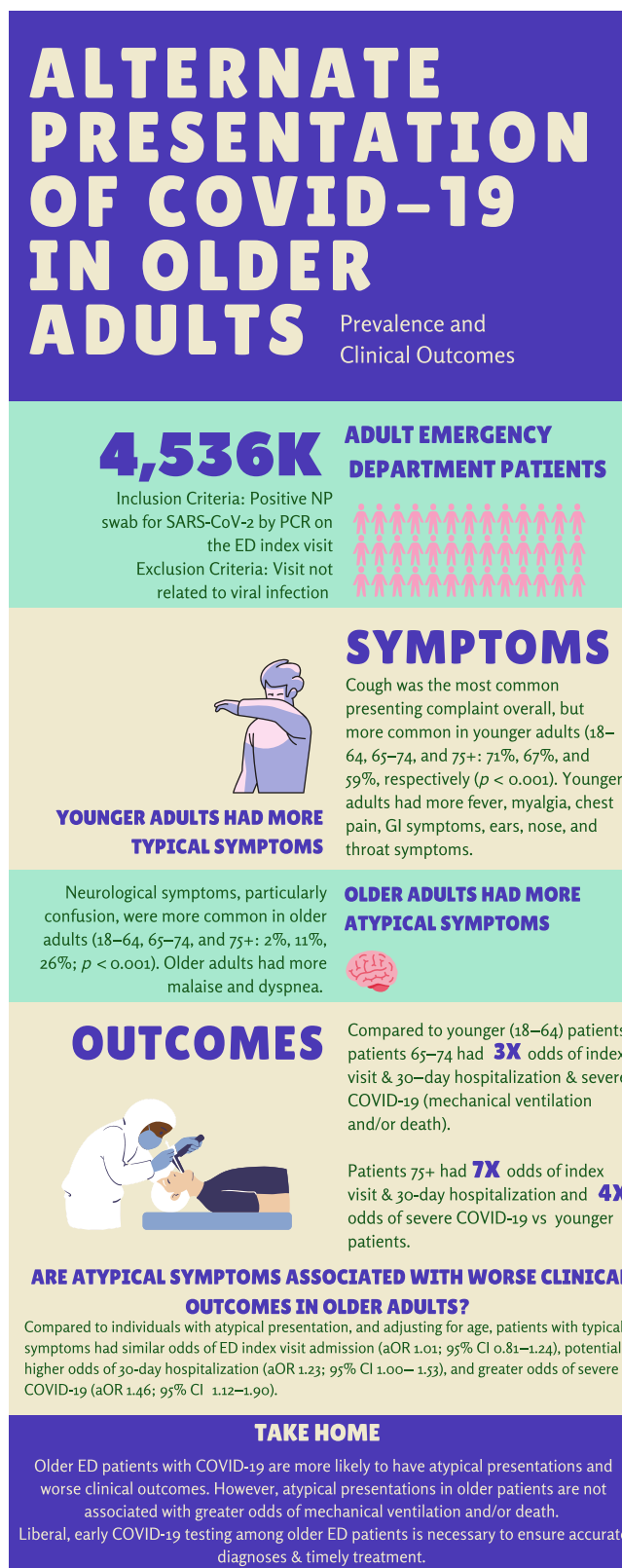

FIGURE 1 Visual abstract. An overview of the manuscript in visual abstract format, including the methods and findings

three age categories with "18–64 years," "65–74 years," and "75 and older" options. Sex was categorized with "Male" and "Female" options. Race/ethnicity was categorized with

"Black, non-Hispanic," "White, non-Hispanic," "Hispanic," and "Other" options.

Phenotype

We developed a phenotype variable that discerned typical and alternate COVID-19 symptoms to assess the association with each outcome measure. Fever, cough, and shortness of breath were considered typical symptoms due to frequent occurrence across all age groups in our study and literature search.[10–12] Any other symptoms experienced by patients pertaining to COVID-19 were considered alternate symptoms. Phenotype was coded into a three-level categorical variable with options of "2 or more typical symptoms," "any single typical symptom," and "no typical symptoms."

Outcome measures

There were three outcome measures which included: (1) need for hospitalization at the index ED visit, (2) any hospitalization within 30 days of the index ED visit, and (3) severe COVID-19, which was defined as intubation with mechanical ventilation and/or death within 30 days.[21,22] All three outcome measures were categorized with "Yes" and "No" response options.

Statistical analysis

We generated descriptive statistics to identify baseline patient characteristics (sex and race/ethnicity) and clinical presentation at the index ED visit (at least one of cough, fever, or shortness of breath is a typical presentation, laboratory testing, and radiographic findings) stratified by age (18–64, 65–74, and aged 75+). We also developed a pyramid plot with adjusted age bins to cohort younger patients together with similar rates of outcomes stratifying patients with COVID-19 by age and race/ethnicity.

We performed sequential multivariable logistic regression to examine the strength of association between age cohort and each clinical outcome after incrementally adjusting for phenotype (typical vs alternate presentation), demographic characteristics (age, sex, race/ethnicity), and comorbidities (base model (unadjusted), model 1 (adjusted for phenotype only), model 2 (model 1 and demographics), model 3 (model 2 and comorbidities). In the full model, we adjusted for 10 potential confounders—age, sex, race/ethnicity, hypertension, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), other chronic lung diseases, obesity, diabetes, and cancer, based on a priori knowledge.[23] Other chronic lung disease was defined by pulmonary fibrosis, cystic fibrosis, bronchiectasis, or pulmonary hypertension.

To assess for moderators of the outcomes, we performed an interaction analysis between phenotype and race/ethnicity and between phenotype and sex. We also performed an interaction assessment between race/ethnicity and age and race/ethnicity and sex. For these interaction analyses, we assessed two models, model 1 (adjusted for phenotype, race and the interaction between phenotype and race) and model 2 (model 1 and age cohorts). Effect moderators were identified with a significant interaction term where p-value <0.05. All data analyses were conducted using the statistical software package RStudio, version 1.4.1717-3.

A subgroup analysis of the oldest old (85+) compared to younger cohorts (65–74 and 75–84) was performed with similar methods.

RESULTS

Figure 1 provides an overview of the results. After exclusion of records from seven sites that used different inclusion criteria ($n = 9364$) (chief complaints or reason for visit were omitted), incomplete records ($n = 8069$),

TABLE 1 Patient demographics

Characteristics	All age groups $N = 4536$ n (%)	Age 18–64 $n = 3161$ n (%)	Age 65–74 $n = 745$ n (%)	Age 75+ $n = 630$ n (%)
Age (years), median, (IQR)	55 (40–67)	47 (34–56)	69 (67–72)	81 (78–86)
Female sex	2243 (49.44)	1573 (49.8)	343 (46)	327 (51.9)
Race/ethnicity				
Black, non-Hispanic	1558 (34.3)	1082 (34.2)	280 (37.6)	196 (31.1)
White, non-Hispanic	1212 (26.7)	676 (21.4)	247 (33.2)	289 (45.9)
Hispanic	1138 (25.1)	977 (30.9)	102 (13.7)	59 (9.2)
Other	627 (13.8)	425 (13.3)	116 (15.6)	86 (13.7)

TABLE 2 Clinical, laboratory, and radiographic characteristics

Clinical presentation	All age groups N = 4536 n (%)	Age 18–64 n = 3161 n (%)	Age 65–74 n = 745 n (%)	Age 75+ n = 630 n (%)
Respiratory symptoms				
Cough (wet and dry)	3121 (68.8)	2248 (71.1)	500 (67.1)	373 (59.2)
Cough—wet	573 (12.6)	413 (13.1)	85 (11.4)	75 (11.9)
Cough—dry	2615 (57.6)	1891 (59.8)	423 (56.8)	301 (47.8)
Fever	2748 (60.6)	2013 (63.7)	424 (56.9)	311 (49.4)
Shortness of breath	2444 (53.9)	1666 (52.7)	439 (58.9)	339 (53.8)
Chest pain	707 (15.6)	590 (18.7)	87 (11.7)	30 (4.8)
Respiratory distress	158 (3.5)	71 (2.2)	39 (5.2)	48 (7.6)
Arthralgia	110 (2.4)	87 (2.8)	11 (1.5)	12 (1.9)
Wheezing	88 (1.9)	58 (1.8)	19 (2.6)	11 (1.7)
Hemoptysis	31 (0.7)	25 (0.8)	1 (0.1)	5 (0.8)
Cardiac arrest	13 (0.3)	3 (0.1)	7 (0.9)	4 (0.6)
Non-respiratory symptoms				
Malaise	1401 (30.9)	927 (29.3)	250 (33.6)	224 (35.6)
Myalgia	1349 (29.7)	1123 (35.5)	147 (19.7)	79 (12.5)
GI (abdominal pain, nausea, vomiting, diarrhea)	1634 (36.0)	1189 (37.6)	278 (37.3)	167 (26.5)
Nausea/vomiting	995 (21.9)	746 (23.6)	156 (21)	93 (14.8)
Diarrhea	898 (19.8)	640 (20.2)	167 (22.4)	91 (14.4)
Abdominal pain	442 (9.7)	315 (10)	75 (10.1)	52 (8.3)
ENT (conjunctivitis, rhinorrhea, ear pain, sore throat, olfactory/taste disturbances)	1098 (24.2)	919 (29.1)	119 (16.0)	60 (9.5)
Sore throat	602 (13.3)	523 (16.5)	51 (6.8)	28 (4.4)
Rhinorrhea	391 (8.6)	311 (9.8)	49 (6.6)	31 (4.9)
Olfactory/taste disturbances	304 (6.7)	264 (8.4)	30 (4.0)	10 (1.6)
Ear pain	33 (0.7)	26 (0.8)	6 (0.8)	1 (0.2)
Conjunctivitis	8 (0.2)	6 (0.2)	2 (0.3)	0 (0.0)
Neuro (headache, altered mental status, seizures, syncope)	1231 (27.1)	840 (26.6)	184 (24.7)	207 (32.9)
Headache	849 (18.7)	726 (23.0)	87 (11.7)	36 (5.7)
Altered mental status	319 (7.0)	76 (2.4)	82 (11)	161 (25.6)
Syncope	99 (2.2)	52 (1.6)	30 (4.0)	17 (2.7)
Seizures	18 (0.4)	10 (0.3)	6 (0.8)	2 (0.3)
Cutaneous (skin rash and ulcers, lymphadenopathy)	25 (0.6)	19 (0.6)	3 (0.4)	3 (0.5)
Skin rash	21 (0.5)	16 (0.5)	3 (0.4)	2 (0.3)
Lymphadenopathy	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)
Skin ulcers	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Laboratory findings				
WBC, median, (IQR)	6.2 (4.7–8.3)	6.1 (4.7–8.0)	6.2(4.8–8.5)	6.6(5.0–8.9)
Lymphocyte count, median, (IQR)	1.3 (0.8–2.4)	1.3 (0.9–2.4)	1.1(0.7–2.1)	1.1(0.7–5.0)
Troponin				
First troponin, median, (IQR)	0.02 (0.01–0.03)	0.01(0.01–0.02)	0.02(0.01–0.03)	0.03(0.02–0.06)
High-sensitivity troponin, median, (IQR)	15 (6.0–38.0)	8.0(5.0–21.0)	23.5(11.0–61.3)	33.0(16.0–78.0)
Procalcitonin, median, (IQR)	0.12 (0.06–0.3)	0.1(0.05–0.2)	0.15(0.08–0.4)	0.15(0.08–0.4)

TABLE 2 (Continued)

| Clinical presentation	All age groups N = 4536 n (%)	Age 18–64 n = 3161 n (%)	Age 65–74 n = 745 n (%)	Age 75+ n = 630 n (%)
CXR findings				
Nonspecific infiltrate	1510 (33.3)	905 (28.6)	322 (43.2)	283 (44.9)
Normal	1064 (23.5)	828 (26.2)	125 (16.8)	111 (17.6)
Other	706 (15.6)	426 (13.5)	150 (20.1)	130 (20.6)
Atelectasis	405 (8.9)	223 (7.1)	87 (11.7)	95 (15.1)
Cardiomegaly	204 (4.5)	101 (3.2)	49 (6.6)	54 (8.6)
Ground glass infiltrate	195 (4.3)	128 (4.0)	44 (5.9)	23 (3.7)
Effusion	179 (3.9)	84 (2.7)	44 (5.9)	51 (8.1)
Interstitial or interlobular thickening	159 (3.5)	95 (3.0)	34 (4.6)	30 (4.8)
Pneumothorax	4 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
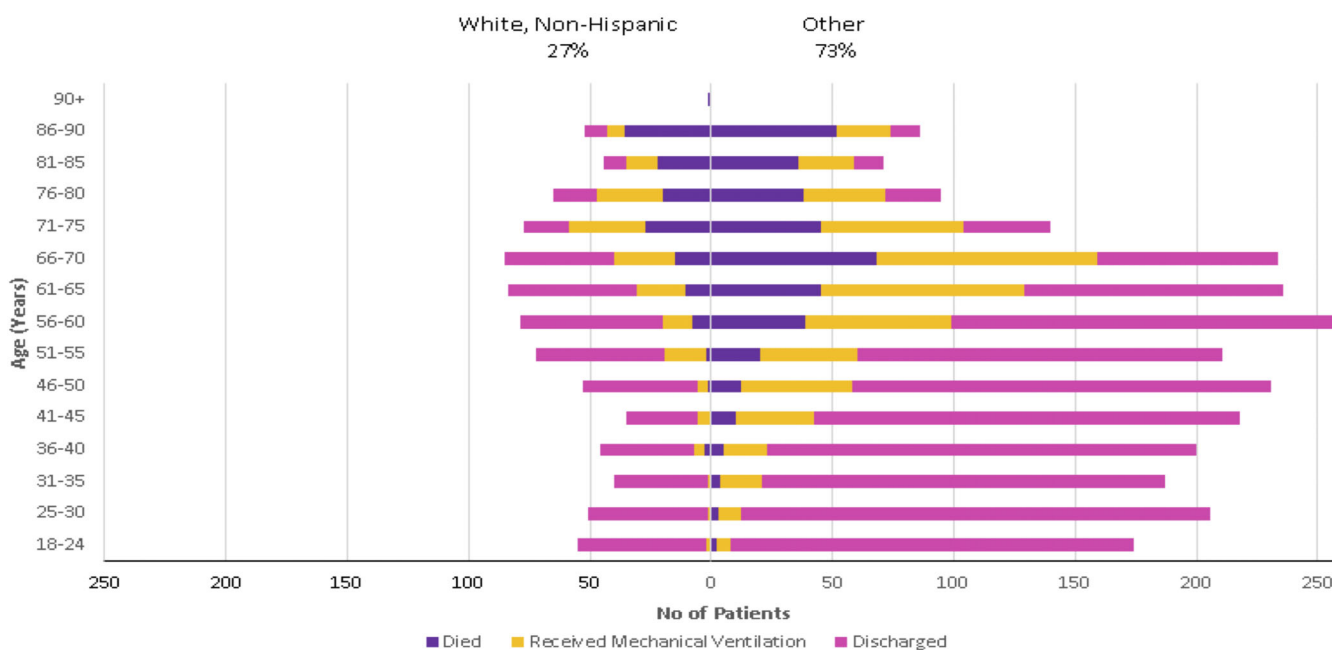
FIGURE 2 Pyramid plot of outcomes by patient age and race. The pyramid plot shows patients with COVID-19 stratified by age and race. With increasing age, particularly after age 60, severe COVID-19, requiring mechanical ventilation or experiencing mortality, correspondingly increased. Compared to White, non-Hispanics other racial and ethnic groups of the same age included in our study experienced a higher proportion of mechanical ventilation and death.

children (n = 426), and encounters without positive SARS-CoV-2 viral testing results (n = 9725), our analytic sample included 4536 patient encounters (see Supplementary Figure S1). Patient demographic information is provided in Table 1.

The median age was 55 (IQR 40–67) with 49% being women. Thirty-four percent were Black, non-Hispanic persons, 27% were White, non-Hispanic, and 25% were Hispanic. There were significant differences in age (p < 0.001) and race/ethnicity (p < 0.001) between age

cohorts, with the oldest cohort (75+) having the most White, non-Hispanic patients (46%).

Do older ED patients with COVID-19 present differently than younger adults?

Table 2 summarizes the clinical presentation of patients by age cohort. Cough was the most common symptom described on presentation in all age groups but was most

TABLE 3 Clinical outcomes by age cohorts among 4536 patients presenting to EDs for COVID-19

Outcomes	Base model (unadjusted) OR (95% CI)	p-Value	Model 1 (adjusted for phenotype) OR (95% CI)	p-Value	Model 2 (model 1 + sociodemographic features) OR (95% CI)	p-Value	Model 3 (model 2 + comorbidities) OR (95% CI)	p-Value
Hospitalization at ED index visit								
Age 18–64	Reference							
Age 65–74	3.92 (3.29–4.69)	<0.001	3.96 (3.32–4.74)	<0.001	3.89 (3.25–4.67)	<0.001	3.01 (2.49–3.64)	<0.001
Age 75+	8.30 (6.62–10.51)	<0.001	8.95 (7.11–11.38)	<0.001	9.09 (7.19–11.62)	<0.001	6.66 (5.23–8.56)	<0.001
Any hospitalization within 30 days[a]								
Age 18–64	Reference							
Age 65–74	4.19 (3.46–5.10)	<0.001	4.27 (3.52–5.21)	<0.001	4.21 (3.46–5.14)	<0.001	3.17 (2.59–3.91)	<0.001
Age 75+	9.44 (7.25–12.49)	<0.001	10.34 (7.92–13.72)	<0.001	10.59 (8.08–14.12)	<0.001	7.44 (5.63–9.99)	<0.001
Severe COVID-19 (mechanical ventilation and/or death)[b]								
Age 18–64	Reference							
Age 65–74	3.74 (3.10–4.51)	<0.001	3.78 (3.13–4.56)	<0.001	3.70 (3.05–4.48)	<0.001	2.94 (2.41–3.58)	<0.001
Age 75+	5.20 (4.29–6.31)	<0.001	5.46 (4.50–6.64)	<0.001	5.68 (4.64–6.97)	<0.001	4.26 (3.45–5.27)	<0.001

[a]Hospitalization immediately after the index ED visit or within 30 days from the index ED visit.

[b]Intubation with mechanical ventilation and/or death within 30 days from the index ED visit.

common in patients aged 18–64 (71%), versus older ages (ages 65–74 (67%), aged 75+ (59%), $p < 0.001$). Myalgias and chest pain were commonly described in younger patients, while older cohorts (65+) were more likely to present with malaise or respiratory distress. Gastrointestinal (GI) symptoms were more often reported by younger patients (18–64 (38%) 65–74 (37%), aged 75+ (27%), $p < 0.001$). Ears, nose, and throat (ENT) symptoms were similarly more frequent in younger patients (18–64 (29%), 65–74 (16%), aged 75+ (10%), $p < 0.001$).

Conversely, neurological symptoms, particularly altered mental status, were more common in older adults (18–64 (2%), 65–74 (11%), 75+ (26%), $p < 0.001$). Additionally, median white blood cell count and first troponin values were significantly higher in the older age cohorts ($p = 0.023$ and $p = 0.043$, respectively). Chest radiographs were more likely to be normal in younger patients (18–64 (26%), 65–74 (17%), 75+ (18%), $p < 0.001$), and show nonspecific infiltrates in older patients (18–64 (27%), 65–74 (43%), 75+ (45%), $p < 0.001$).

Do older adults with COVID-19 have worse clinical outcomes?

The pyramid plot (Figure 2) shows patients with COVID-19 stratified by age and race. With increasing age, particularly after age 60, severe COVID-19, requiring mechanical ventilation or experiencing mortality, correspondingly increased. Compared to White, non-Hispanics other racial and ethnic groups of the same age included in our study experienced a higher proportion of mechanical ventilation and death. These differences in the incidence of severe COVID-19 are significant for both Black patients ($p < 0.001$) and Hispanic and other ethnicities ($p = 0.003$) when compared to White, non-Hispanic patients, see Supplementary Table S1.

Odds ratios for clinical outcomes (hospitalization at index ED visit, hospitalization within 30 days, or severe SARS-CoV-2 infection characterized by mechanical ventilation and/or death) are summarized in Table 3. In the unadjusted base model, patients 75+ had 8.30 the odds of hospitalization at the index ED visit (95% CI 6.62–10.51), 9.44 the odds of hospitalization within 30 days (95% CI 7.25–12.49), and 5.20 the odds of severe COVID-19 (95% CI 4.29–6.31) compared to patients aged 18–64. After adjusting for phenotype (number of typical symptoms at presentation), sex, race/ethnicity, and comorbidities (hypertension, cardiovascular disease, COPD, other chronic lung disease, obesity, diabetes, and cancer) patients 75+ had 6.66 greater odds of ED index visit hospitalization (95% CI 5.23–8.56), 7.44 greater odds of admission within 30 days (95% CI 5.63–9.99), and 4.26 greater odds of severe COVID-19 (95% CI

3.45–5.27). Overall, with increasing age there was greater odds of undesirable clinical outcomes even after adjusting for potential confounders.

Do older adults with alternate symptoms have worse outcomes?

When evaluating the association between phenotype and clinical outcomes, those with two or more typical symptoms were significantly more likely than those without typical symptoms to experience severe COVID-19 (adjusted Odds Ratio (aOR) 1.46 (95% CI 1.12–1.90); however, no significant differences were seen in the odds of hospitalization at the ED index visit (aOR 0.01 (95% CI 0.81–1.24) or within 30 days of the ED index visit (aOR 1.23 (95% CI 1.00–1.53) when adjusting for age (Supplementary Table S2). We did not find significant interactions between phenotype and race/ethnicity or sex (Supplementary Table S3).

Are the oldest adults more likely to present without typical symptoms?

Among the oldest age group of 75+ ($n = 630$), there were 205 patients that were part of the oldest old, 85+ and 425 patients that were part of the younger age group, 75–84. There were no significant differences between the two age groups for gender ($p = 0.659$) and race/ethnicity ($p = 0.078$). Compared to 75–84 years group, the oldest adults (85+) were more likely to present with altered mental status (34.2% vs 21.4%, $p < 0.001$) and less likely to experience myalgias (5.9% vs 15.8%, $p < 0.001$), abdominal pain (3.9% vs 10.4%, $p < 0.001$), and headaches (1.5% vs 7.8%, $p < 0.001$). The other presenting symptoms did not differ significantly within these two age groups. Finally, there were no significant differences in laboratory and radiographic findings between the two oldest age groups (Supplementary Table S4).

DISCUSSION

In this large national retrospective cohort study of prevaccination COVID-19 patients, we found that older ED patients have worse clinical outcomes overall and are more likely to present with less typical COVID-19 symptoms compared to younger adults. Second, patients of all ages with alternate presentations had decreased odds of experiencing severe COVID-19, contrary to our hypothesis that failed recognition of the disease due to alternate presentation could explain the higher rates of severe

disease in older adults. These data do suggest that emergency physicians should consider testing for COVID-19 in older adults who present without fever, cough, or shortness of breath. Upper respiratory symptoms or other alternate symptoms only may be a sign of milder illness phenotype which potentially could sway decisions on treatments, especially during times of treatment scarcity. It also could inform the American College of Emergency Physicians (ACEP) COVID-19 management tool (https://www.acep.org/corona/COVID-19-alert/covid-19-articles/covid-19-ED-management-tool-now-available/), which relies on symptoms to categorize COVID severity, but does not include in their acuity criteria neurologic symptoms that were more prominent in older adults, such as syncope (4% of older adults) and altered mental status (11%, 26%, and 34% in ages 65–74, 75–84, and 85+). The outcome data from this study could potentially help refine the ACEP tool.

Several studies have shown that socially disadvantaged populations including older adults, Black, and Hispanic populations are at higher risk of hospitalization and death from COVID-19.[24] Our data also show that Black and Hispanic ED patients are more likely to experience mechanical ventilation and death from COVID-19. This observed disparity has been attributed to lower socioeconomic status (e.g., causing greater housing density),[25] differences in access to resources,[26] and structural racism.[27] Excess all-cause deaths and COVID-19 related deaths early in the pandemic have also been attributed to fears of seeking care and poor access to care.[28] Our retrospective cohort could not account for these or other unmeasured confounders such as frailty and social determinants of health, which are not routinely assessed in current ED practice. We suspect that prospective studies that include these confounders would nullify the interactions found between phenotype, race/ethnicity, and sex in this study. Including frailty status could also potentially modify the effects of age on mortality and hospitalization outcomes.

These data are important because rapid testing currently has a substantial false negative rate and PCR testing for COVID-19 is still not accessible, fast, or cheap enough. Relying on symptoms alone to diagnose COVID-19 is problematic as cases could be missed, particularly in older adults[29] with alternate symptoms. This is still critical. In the United States, the December 2021 to January 2022 wave of COVID from variant B1.1.529 resulted in lack of testing availability in many places, including some of the EDs in which these authors work clinically. Rapid diagnosis is critical because available COVID-19 treatments (e.g., monoclonal antibodies, intravenous and oral antiviral treatments) must be initiated early in the course of the illness to be effective. Additionally, delays to diagnosis increase transmission particularly in congregate setting where predominantly older adults reside and in communities with a high prevalence of vulnerable individuals due to age or immunosuppression (such as the state of Florida). Prophylaxis with monoclonal antibodies is effective in nursing homes if cases can be identified with liberal facility testing strategies.[30]

While this cohort is a pre-vaccination cohort, this data is still apropos to many areas and hypothesis generating for future variants. Despite widespread access to a safe, well-tolerated, effective vaccine,[31,32] vaccine uptake remains low in many areas of the country. Additionally, new variants have been shown to partially evade vaccination and reinfection with different strains is possible.

Diagnosing the older ED patient is often challenging due to cognitive impairment, hearing loss, poor recall of medical information,[33] and incomplete transfer documentation[34] and therefore ED clinicians often rely on caregiver report and laboratory/imaging findings. This study underscores that relying on history alone to make a diagnosis of COVID-19 in older ED patients is problematic. In a study by Kennedy et al. of 817 older ED patients with COVID-19, 28% had delirium on presentation.[16] Among those with delirium 37% had no typical symptoms.[16] Our multicenter findings are comparable. Delirium has been identified as an independent risk factor for severe disease[16,35] and death[16,35] and should be considered an important marker to identify patients at risk of developing poor COVID-19 outcomes. Patients with dementia more often present with delirium and should therefore be considered a particularly high risk population.[36] Vrillon et al. examined 76 patients older than 85 in France and found similarly that neurological symptoms including confusion and asthenia were common presenting complaints of COVID-19 in older patients.[37] In addition to presenting with confusion, older adults with COVID-19 may be afebrile[38] and may lack cough or chest discomfort, thus any change in their clinical status from baseline warrants COVID-19 testing.[39] In addition to delirium and atypical presentations of disease, several mechanisms could explain increased susceptibility to severe COVID-19 including age-related immunosenescence,[5] chronic inflammatory states due to dementia or other comorbidities,[40–42] less aggressive treatment due to age bias or preexisting code status, and greater avoidance of EDs during the pandemic.[6] The original study variables did not include DNR/DNI status, which is more frequent in older adults and could also confound the association between age and illness severity.

While few studies have evaluated associations between typical presentations and severe COVID-19, most, including ours, have concluded that alternate presentations are not associated with worse clinical

outcomes. In a study by Gan et al. in a single center in the United Kingdom, 122 older individuals with atypical symptoms versus typical symptoms (defined by fever, dry cough, dypsnea) had no significant differences in intubation with mechanical ventilation ($p = 0.76$) or mortality ($p = 0.68$).[43] In a study by Marzillano et al. among 4961 older inpatients in New York individuals with typical symptoms had greater odds (OR 1.39; 95% CI 1.15–1.67) of requiring ICU level care. These studies were both performed in March and April 2020. Unlike these studies, our data draws from ED encounters throughout the United States from February to October 2020 and supports these findings that atypical ED presentations, while more frequent in older adults, are not associated with worse clinical outcomes and may represent milder disease phenotype.

LIMITATIONS

Although this is a large national cohort study including encounters from 86 different EDs, there are several limitations. These include site-variability in testing standards: not all patients were tested upon ED arrival and the rate of alternate symptoms should be considered a lower limit of the actual incidence of alternate presentations. This would bias our findings toward the null. Secondly, asymptomatic cases of COVID-19 are common and patients included in the study may be experiencing symptoms in part due to coinfection[44] or other unrelated medical conditions. This could bias the study toward atypical cases having a milder disease course. The use of a nasopharyngeal PCR swab also could have missed patients with COVID, as it has a sensitivity of 0.73. However, as this is the most sensitive test used in EDs, this increases generalizability of our findings to our target population. Finally, available treatments for COVID-19, response to treatment by different variants, and mortality rates have changed rapidly during the course of the pandemic and these data reflect only the first several months of the pandemic in the United States, therefore replication of this study is encouraged. For instance, findings may differ with the Omicron variant, or among vaccinated versus unvaccinated individuals.

CONCLUSIONS

We found typical symptoms, including cough, fever, and shortness of breath were more common presenting complaints in younger ED patients with COVID-19, while older patients had higher rates of altered mental status. Therefore, cases in older adults may be missed when a symptom-only diagnostic strategy is used for testing or quarantine. Contrary to our hypothesis we found that patients presenting with alternate symptoms were less likely to experience severe COVID-19 when adjusting for age, and therefore alternate presentation is not associated with worse clinical outcomes. These data suggest that clinicians should maintain a high suspicion of COVID-19 in older adults and a liberal testing strategy should be used to correctly identify patients presenting without typical features of the disease.

CONFLICT OF INTEREST
The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS
Elizabeth M. Goldberg, Carlos A. Camargo, Jeffrey A. Kline, and Lauren T. Southerland designed the study. All authors reviewed the statistical analysis. Ryan Hoopes and Elizabeth M. Goldberg performed data abstraction and reviewed discrepancies. All authors contributed ideas to improve the design of the study. All authors contributed to the writing and editing of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix S1 The Supplemental Material contains additional information pertinent to the study topic. We include an inclusion flow diagram of the study. Additionally, we include tables that show interaction analyses and a subgroup analysis of the oldest old (85+) compared to younger cohorts (65–74 and 75–84).

Supplementary Figure S1. Inclusion flow diagram. This figure shows how we obtained our analytic sample. We

excluded records from seven sites that used different inclusion criteria ($n = 9364$). These sites did not report chief complaints or reason for visit limiting our ability to ensure patients were presenting with symptoms of COVID-19 rather than for other complaints. We also excluded records that were incomplete for other reasons ($n = 8069$). As our analysis focused on adults, we excluded records of children ($n = 426$). We also excluded encounters without positive SARS-CoV-2 viral testing results ($n = 9725$). Our analytic sample included 4536 patient encounters.

Supplementary Table S1. Outcomes by race/ethnicity, unadjusted and adjusted by age

Supplementary Table S2. Outcomes by phenotype, unadjusted and adjusted for age

Supplementary Table S3. Interaction assessments

Supplementary Table S4a and b. Subgroup analysis for the two oldest age groups (75–84 vs 85+)

Supplementary Table S5. STROBE checklist. We followed STROBE guidelines in the reporting of this manuscript. The checklist which shows compliance with each rubric and the location in the text can be reviewed in the STROBE checklist document.