Modulation of the Association Between Age and Death by Risk Factor Burden in Critically Ill Patients With COVID-19

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OBJECTIVES: Older age is a key risk factor for adverse outcomes in critically ill patients with COVID-19. However, few studies have investigated whether pre-existing comorbidities and acute physiologic ICU factors modify the association between age and death.

DESIGN: Multicenter cohort study.

SETTING: ICUs at 68 hospitals across the United States.

PATIENTS: A total of 5,037 critically ill adults with COVID-19 admitted to ICUs between March 1, 2020, and July 1, 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary exposure was age, modeled as a continuous variable. The primary outcome was 28-day inhospital mortality. Multivariable logistic regression tested the association between age and death. Effect modification by the number of risk factors was assessed through a multiplicative interaction term in the logistic regression model. Among the 5,037 patients included (mean age, 60.9 yr [± 14.7], 3,179 [63.1%] male), 1,786 (35.4%) died within 28 days. Age had a nonlinear association with 28-day mortality (p for nonlinearity <0.001) after adjustment for covariates that included demographics, preexisting comorbidities, acute physiologic ICU factors, number of ICU beds, and treatments for COVID-19. The number of preexisting comorbidities and acute physiologic ICU factors modified the association between age and 28-day mortality (p for interaction <0.001), but this effect modification was modest as age still had an exponential relationship with death in subgroups stratified by the number of risk factors.

CONCLUSIONS: In a large population of critically ill patients with COVID-19, age had an independent exponential association with death. The number of pre-existing comorbidities and acute physiologic ICU factors modified the association between age and death, but age still had an exponential association with death in subgroups according to the number of risk factors present. Additional studies are needed to identify the mechanisms underpinning why older age confers an increased risk of death in critically ill patients with COVID-19.

KEY WORDS: age; COVID-19; critical care; death; risk factors

Since the outbreak of the severe acute respiratory syndrome coronavirus 2 in December of 2019 in Wuhan, China, more than 219 million people worldwide have developed COVID-19, and more than 6 million people have died as of August 9, 2022 (1). Prior investigations identified several risk factors associated with adverse clinical outcomes in patients with COVID-19. Among these risk factors, older age consistently remains one of the strongest risk factors associated with adverse clinical outcomes in patients with COVID-19 (2–8).

Previous studies have demonstrated that older age is associated with more severe illness from COVID-19, including a higher risk of hospitalization, need for ICU admission, and death (9–15). Fewer studies demonstrated these associations in critically ill patients with COVID-19, a setting in which other patient characteristics and acute severity-of-illness might contribute to a greater degree of an individual's risk of death (3, 7, 16, 17). Furthermore, whether the number of preexisting comorbidities and acute physiologic ICU factors modifies the association between age and death in critically ill patients with COVID-19 is not well-described. Enhanced understanding of the association of age with mortality in the context of risk factors among critically ill patients may serve to generate hypotheses of potential mechanisms underlying the association between age and death.

Since multiple prior studies evaluated age in categories (18–20), which may not fully capture its association with death, our first aim was to determine whether age had an independent linear or nonlinear association with death. Our second aim was to determine whether the number of preexisting comorbidities and acute physiologic ICU factors serves as an effector modifier of the association between age and death. We used data from a large multicenter cohort study of critically ill patients with COVID-19 admitted to ICUs across the United States to investigate these aims. We hypothesized that age has a nonlinear association with death and that the association between age and death differs according to the number of preexisting comorbidities and acute physiologic ICU factors present within critically ill patients with COVID-19.

MATERIALS AND METHODS

Study Design, Oversight, and Patient Population

We used data from the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (16), a multicenter cohort study that enrolled consecutive adults (≥18 yr old) with laboratory confirmed COVID-19 admitted to ICUs at 68 geographically diverse hospitals across the United States. A complete list of participating sites is provided in the **Supplementary Appendix** (http://links.lww.com/CCX/B52). We included patients admitted to the ICU during their index admission between March 1, 2020, and July 1,

2020. We followed patients until the first of hospital discharge, death, or August 1, 2020, the date when the study database for the current analysis was locked (16). STOP-COVID was approved with a waiver of informed consent by the Institutional Review Board at Mass General Brigham (protocol number 2007000003) and Northwestern University (March 31, 2020) and is in accordance with the principles of the Declaration of Helsinki.

Data Collection

Study personnel at each site collected data by detailed chart review and used a standardized case report form to enter data into a secure online database (research electronic data capture [REDCap]) (21). Patient-level data included baseline demographic information, coexisting conditions, symptoms, medications before hospital admission, vital signs on ICU admission, and daily data for the 14 days after ICU admission on physiologic and laboratory values, pharmacologic and nonpharmacologic treatments administered, and organ injury and support, as previously described (16). Vital status was collected up to the time of hospital discharge. All data were validated through a series of automated verifications using REDCap's data quality module.

Exposure and Outcomes

The primary exposure was age, treated as a continuous variable. We also evaluated age in categories: less than 65, 65–79, and greater than or equal to 80 years as performed in prior studies (16, 18–20). The primary outcome was 28-day inhospital mortality. The secondary outcome was 90-day mortality. Patients discharged alive from the hospital before 28 or 90 days were considered to be alive at 28 or 90 days, respectively. The validity of this assumption was tested in a subset of patients, as previously described (16).

Statistical Analysis

Descriptive statistics were summarized as counts with percentages for categorical variables and mean ± sd or median with interquartile range for continuous variables. We used chi-square tests to compare frequency distributions of categorical variables by age group. For evaluations between continuous variables and age group, we used analysis of variance (for normally

distributed variables) and Kruskal-Wallis tests (for nonnormally distributed variables).

We used multivariable logistic regression to determine the association of age with death. We fitted a series of hierarchically adjusted models with prespecified covariates on the basis of clinical knowledge and our prior work (16). Model 1 was unadjusted; model 2 was adjusted for sex, race, current smoking status, body mass index (calculated as weight in kilograms divided by height in meters squared, and categorized as ≤25, 25–29.9, 30–34.9, 35–39.9, and ≥40), hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, and active malignancy; model 3 included all model 2 variables as well as symptom duration prior to ICU admission (≤3 vs >3 days), number of ICU beds at each hospital prior to the COVID-19 pandemic (<50, 50–99, and ≥100 beds), shock (simultaneous receipt of ≥2 vasopressors/inotropes), lymphocyte count (<1,000/uL vs ≥1,000/uL), degree of hypoxemia and respiratory support (categorized as no receipt of invasive mechanical ventilation, or receipt of invasive mechanical ventilation with a ratio of Pao_2 to Fio_2 ≥300, 200–299, 100–199, and <100), and the renal, liver, and coagulation components of the Sequential Organ Failure Assessment (SOFA) score (22); model 4 included all model 3 variables as well as treatments for COVID-19: remdesivir, tocilizumab, and corticosteroids. Acute physiologic ICU factors were assessed during the first 2 days following ICU admission, with the worst value used. The **Supplemental Methods** (http://links.lww.com/CCX/B52) provide additional details for the multivariable modeling strategy, including definitions of covariates. We examined the possible nonlinear relation between age and death with restricted cubic splines. Tests for nonlinearity used the likelihood ratio test, comparing each model with only the linear term to the analogous model with the linear and cubic-spline terms (23, 24). To evaluate for unmeasured confounding, we calculated an E-value based on the methodology of VanderWeele and Ding (25). This estimates what the odds ratio would have to be for any unmeasured confounder to overcome the observed association of age with death in this study.

To determine the number of risk factors for death present for each individual, we first identified pre-existing comorbidities and acute physiologic ICU factors that had a significant association with death in univariate logistic regression models. Next, we summed the number of risk factors present for each individual. We tested for interaction between age and the number of risk factors in multivariable logistic regression models with the use of a multiplicative interaction term.

To account for missing data, we used multiple imputation, for which we used a multiple regression procedure in IVEware 2.0 (26). We generated five imputed datasets and imputed values for missing data on the basis of the observed data with the assumption that the data were missing at random. Imputations were created through a sequence of multiple regression models (27). We combined the test results across the imputed datasets using the rules of Rubin (28). Statistical analyses were performed using the SAS software, Version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-sided, and $p < 0.05$ was considered significant.

RESULTS

Baseline Characteristics

Supplemental Table 1 (http://links.lww.com/CCX/B52) summarizes baseline characteristics of STOP-COVID patients ($n = 5,037$) by age categories. The mean age was 60.9 years (sd ± 14.7), and 3,179 (63.1%) were men. Compared with younger patients, older patients were more likely to be White, current smokers, and to have a lower body mass index. Older patients had a higher prevalence of congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, hypertension, active cancer, chronic kidney disease, and end-stage kidney disease compared with younger patients. On ICU admission, older patients were more likely to have higher renal and coagulation SOFA scores and to receive vasopressors and invasive mechanical ventilation compared with younger patients. Older patients were less likely to receive treatments such as remdesivir, corticosteroids, or tocilizumab within 2 days following ICU admission compared with younger patients. Older patients were more likely to be admitted to hospitals with less than 50 ICU beds.

Association of Age With Death

Within 28 days of ICU admission, 1,786 patients (35.5%) died, and 2,017 patients (40.0%) died within 90 days of admission. **Figure 1** shows the unadjusted and
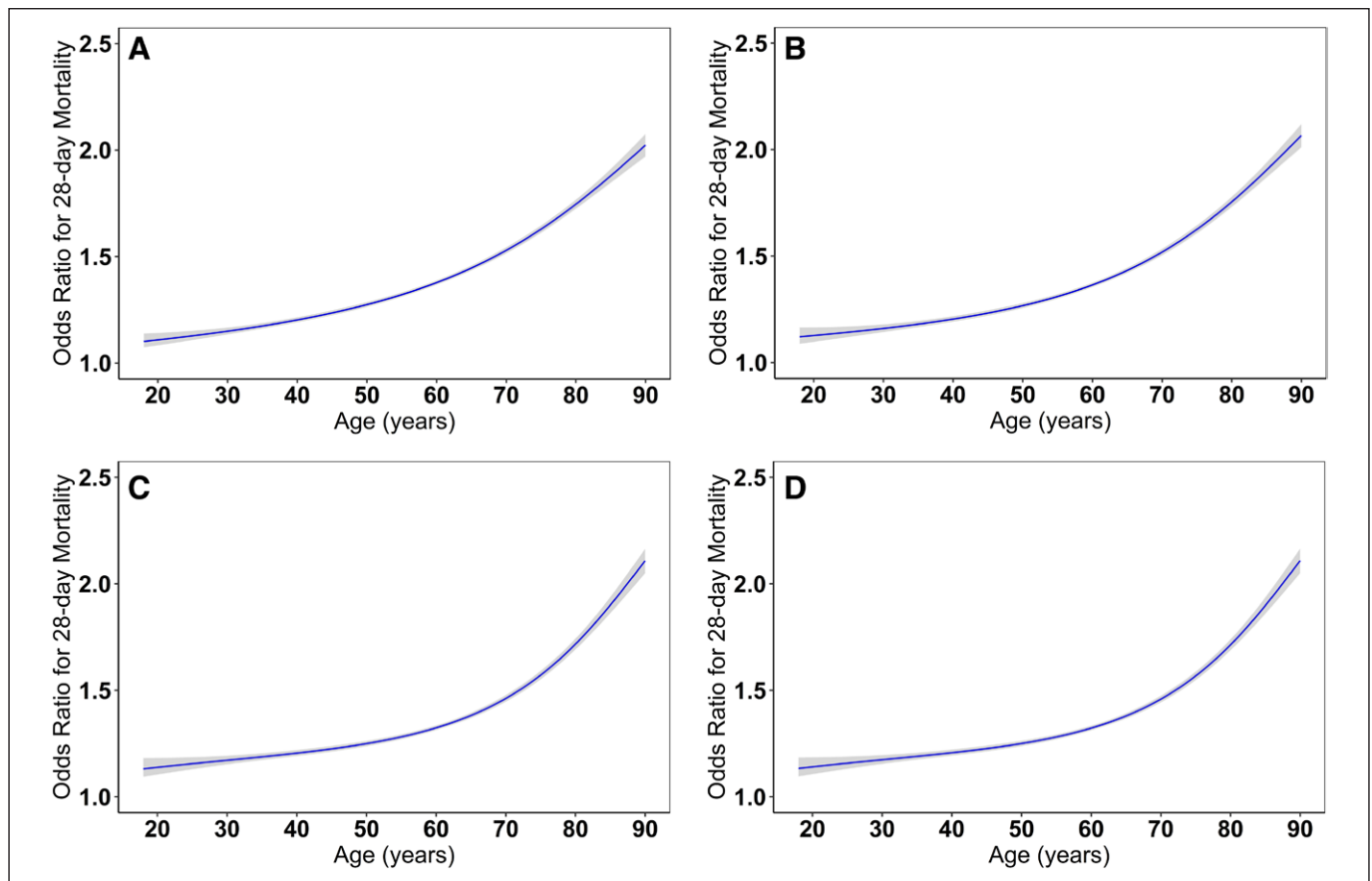
Figure 1. Nonlinear association between age and 28-day mortality. **A**, The model is unadjusted. Age-linear akaike information criterion (AIC): 30,713 versus age-spline AIC: 30,686, likelihood ratio test *p* value for AIC difference: < 0.001. **B**, This model is further adjusted for demographic characteristics, including male sex, and presence of hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and active cancer. Age-linear AIC: 30,218 versus Age-spline AIC: 30,160, likelihood ratio test *p* value for AIC difference: < 0.001. **C**, This model is further adjusted for acute ICU physiologic factors, including symptom onset less than or equal to 3 d prior to ICU admission, lymphocyte count less than 1,000/uL, degree of hypoxemia and respiratory support, shock, SOFA coagulation greater than 0, SOFA liver greater than 0, and SOFA renal greater than 0, and the number of ICU beds. Age-linear AIC 26,913 versus Age-spline AIC: 26,783, likelihood ratio test *p* value for AIC difference: < 0.001. **D**, This model is further adjusted for COVID-19 treatments, including: remdesivir, tocilizumab, and corticosteroids. Age-linear AIC: 26,778, Age-spline AIC 26,643, likelihood ratio test *p* value for AIC difference: < 0.001. SOFA = Sequential Organ Failure Assessment.

sequentially multivariable-adjusted restricted cubic-spline models between age and 28-day mortality. Age had a nonlinear association with 28-day mortality in each restricted cubic-spline models (*p* for nonlinear association <0.001), which had a better fit than modeling age as a linear term (**Fig. 1***A*–*D*). In the fully adjusted model, the Akaike Information Criterion (AIC) for age modeled as a continuous variable and as a spline was 26,778 and 26,643 (*p* value for AIC difference < 0.001), respectively. The association between age and 28-day mortality remained significant even after accounting for demographics, preexisting comorbidities, acute physiology ICU factors, number of ICU beds, and

treatments for COVID-19 (Fig. 1; and **Supplemental Table 2**, http://links.lww.com/CCX/B52). The results for 90-day mortality were similar (**Supplemental Fig. 1**, http://links.lww.com/CCX/B52; and Supplemental Table 2, http://links.lww.com/CCX/B52**).

The odds ratio for the association between age (modeled continuously per 10 yr) and death was 1.51 (95% CI, 1.42–1.60). The E-value (odds ratio) for the point estimate of age (modeled continuously per 10 yr) was 1.76. Using the suggested language of VanderWeele and Ding (25), the observed odds ratio of 1.51 for the association between age (per 10 yr) and death could be explained by an unmeasured confounder that was

associated with both the exposure (age) and the outcome (death) with an odds ratio of 1.76, above and beyond the measured confounders, but a weak confounder could not do so.

Preexisting Comorbidities and Acute Physiologic ICU Factors Associated With Death

To determine whether the association of age with death is modified according to the number of risk factors present, we identified preexisting comorbidities and acute physiologic ICU factors associated with 28-day mortality in univariate logistic regression models (**Supplemental Table 3**, http://links.lww.com/CCX/B52). Male sex, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, active cancer, symptom onset less than or equal to 3 days prior to ICU admission, lymphocyte count less than 1,000/uL, lower Pao_2 to Fio_2 ratio, shock, higher coagulation, liver, and renal SOFA scores, and admission to a hospital with fewer ICU beds were each associated with a higher odds of death (**Supplemental Table 4**, http://links.lww.com/CCX/B52). **Supplemental Figure 2** (http://links.lww.com/CCX/B52) shows the distribution of the number of preexisting comorbidities and acute physiologic ICU factors associated with 28-day mortality in the STOP-COVID participants.

Effect Modification of Age With 28-day Mortality by Number of Preexisting Comorbidities and Acute Physiologic ICU Factors

The number of preexisting comorbidities and acute physiologic ICU factors modified the association between age and death (p for interaction < 0.001). **Figure 2** shows the association of age with death stratified by tertiles of the number of preexisting comorbidities and acute physiologic ICU factors: 0–4, 5–6, and 7–13 risk factors, which corresponded to 35.9%%, 35.9%, and 28.2% of the study population, respectively. Although the number of preexisting comorbidities and acute physiologic ICU factors modified the association between age and death, this effect modification was modest as age had a nonlinear association with 28-day mortality in each of the risk factor subgroups. **Supplemental Table 5** (http://links.lww.com/CCX/B52) shows the association between ages modeled in categories with 28-day mortality in each of the risk
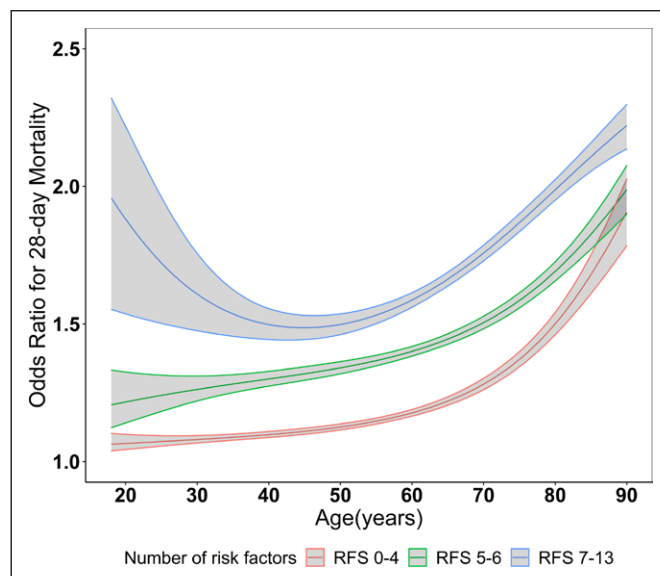
Figure 2. Nonlinear association between age and 28-day mortality stratified by number of risk factors. Nonlinear association of age (continuous) with 28-day mortality stratified by categories of the number of significant preexisting comorbidities and acute physiologic ICU factors. p for nonlinearity in each group less than 0.001. Risk factors: male sex, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, active cancer, symptom onset less than or equal to 3 d, lymphocyte count less than 1,000/μL, invasive mechanical ventilation, shock, SOFA Coagulation Score greater than 0, SOFA Renal Score greater than 0, SOFA Liver Score greater than 0, and number of ICU beds less than 100. Models are further adjusted for body mass index (in categories), White versus non-White, current smoker, remdesivir, tocilizumab, and corticosteroids. SOFA = Sequential Organ Failure Assessment.

factor subgroups. Patients who were in the older age categories had a higher odds of death compared with patients who were less than 65 years old, but the magnitude of association between older age and death was lower with increasing risk factor categories.

DISCUSSION

In this multicenter cohort study of over 5,000 critically ill patients with COVID-19 admitted to ICUs across the United States, we identified an exponential association between age and death even after multivariable adjustment for demographics, preexisting comorbidities, acute physiologic ICU factors, number of ICU beds, and treatments for COVID-19. We found that the relationship between age and death is modified by the number of preexisting comorbidities and acute physiologic ICU factors present, but this effect modification was modest, and age still had an exponential association with death

in subgroups based on the number of risk factors. Collectively, our findings demonstrate that age is an important risk factor for death in critically ill patients with COVID-19, even in subgroups of individuals who have a fewer or greater number of preexisting comorbidities or acute physiologic ICU factors. Future studies are warranted to identify mechanisms that may explain why older age is associated with a significantly increased risk of death in patients with COVID-19.

In our first STOP-COVID study that included 2,215 patients, we identified a graded association between age and 28-day mortality (16). In this study, we found that age has an exponential association with death. These findings are consistent with prior population-based studies of adults at risk for COVID-19 (20). and adults who tested positive for COVID-19 (29). Although these prior studies demonstrated a similar nonlinear association between age and death, our study extends these findings to critically ill patients from a large number of hospitals across the United States. Importantly, our findings were independent of demographics, preexisting comorbidities, and acute physiologic ICU factors, number of ICU beds, and treatments for COVID-19.

A prior study identified that the number of risk factors modified the association of age with COVID-19 mortality. The investigators found a higher magnitude of association between older age and death in patients with more risk factors compared with patients with fewer risk factors (20). Importantly, the prior study included participants in a large population-based cohort at risk for COVID-19 with a limited number of risk factors obtained years prior to the diagnosis of COVID-19. We found that the number of preexisting comorbidities and acute physiologic ICU factors modified the association between age and death. While we detected effect modification, this appeared to be modest since the association between age and death remained exponential in the same direction within each of the risk factor subgroups. Although we found a slightly lower magnitude of association between older age and death with increasing risk factor categories, these findings may suggest that the effect of age on death is slightly attenuated in populations enriched with a greater severity of illness. Our findings demonstrate that there may be subtle differences in the magnitudes of the association between age and death based on the number of risk factors present in an individual, but age still remained a strong risk factor for death.

The pathophysiologic link between age and death among patients with COVID-19 remains unclear, but a variety of mechanisms have been proposed. Aging induces a hypersecretory cellular state that leads to the release of inflammatory and tissue repair mediators, predisposing aged cells to damage (30). "Inflammaging," a chronic low-grade inflammation that occurs in response to endogenous signals during aging in the absence of infection (31), may further drive immune dysfunction and impaired antiviral responses. In older patients, CD3+ T-cells that mediate the antiviral immune response may increase production of interleukin 6 (32), neutrophils demonstrate impaired tissue migration (33), and B-cells show impaired antibody responses in older patients (34).

Although aging may have direct effects on the immune system, aging may encompass risk factors, known and unknown, that indirectly increase mortality in critically ill patients. Elderly patients are more likely to have preexisting comorbid conditions, but a number of comorbidities may remain underdiagnosed due to a subclinical presentation or a desire to reduce the burden of excessive testing (35–37). Prior studies demonstrated that elderly patients may have socioeconomic barriers to healthcare, which may delay their presentation until their health deteriorates significantly (38, 39). We previously reported that hospitals with fewer ICU beds were a risk factor for increased mortality (16), and our current data demonstrated that older patients were more likely to be treated in hospitals with fewer ICU beds. The reason why older patients were more likely to be treated in hospitals with fewer ICU beds remains unclear, but potential barriers may include distance from larger hospitals or transportation (40, 41). Limited resources and hospital strain likely enhanced these barriers during the pandemic (42, 43). Additionally, older patients who are treated in hospitals with fewer ICU beds may be less likely to be transferred to a larger medical center due to a perception of a lower likelihood of survival by healthcare providers or treatment allocation strategies favoring younger patients during times of treatment scarcity.

Although we demonstrated age is a strong independent risk factor for death after adjustment for a number of risk factors, unmeasured or undiagnosed risk factors may further explain the association between age and death. Our E-value analysis demonstrated that an unmeasured confounder of sufficient magnitude could attenuate the association between age and death.

Our multivariable-adjusted analyses demonstrated that most, but not all, of the covariates included in this study were under the threshold of the E-value, and therefore, we cannot exclude the possibility of an unmeasured covariate or a combination of unmeasured covariates that could explain the association of age with death. We must acknowledge that an important unmeasured confounder in this analysis is frailty (44–48), which has the potential to have a sufficiently high magnitude of association with both age and death. Prior investigations demonstrated that frailty was a powerful predictor of mortality in patients with COVID-19, with hazard ratios for death ranging from 2.5 to 4.4 and 1.5 to 2.7 in the COVID-19 in Older People (COPE) (18) and COMET (19) studies, respectively. Future studies in critically ill patients with COVID-19 should attempt to capture data on variables such as frailty, to comprehensively evaluate associations between risk factors and death in critically ill patients with COVID-19.

Strengths of this study include the use of a large cohort of geographically diverse, critically ill patients with COVID-19 across the United States. Data were obtained by detailed chart review rather than reliance on administrative or billing codes, allowing us to capture granular and reliable data. Our study also has limitations. Our models do not account for varying degrees of strain on the availability of resources across hospitals, which may affect clinical outcomes. Patients were followed for a maximum of 90 inhospital days in the current analyses, and some of the 90-day survivors may have died after 90 days. However, our prior analyses from the same cohort found that 28- and 90-day mortality rates differed only to a small extent, occurring in 34.5% and 39.6% of patients, respectively (49). Although we included a large number of critically ill patients with COVID-19, there were fewer patients in the younger subgroups, which may have limited our ability to detect a significant association with death. Although we adjusted for therapies against COVID-19, older patients may have been less likely to receive these treatments or other interventions (e.g., extracorporeal membrane oxygenation). We did not assign relative weights for each risk factor when constructing the number of preexisting and acute physiologic ICU factors for our effect modification analyses. The patients included in this study were admitted to ICUs prior to the advent of vaccines and antiviral treatments for COVID-19, which may reduce the generalizability of the results. Nevertheless, our findings still underscore the age-associated risks among the unvaccinated.

In conclusion, age had independent, exponential association with death, and this relationship was modified according to the number of preexisting comorbidities and acute physiologic ICU factors present in a large population of critically ill patients with COVID-19. However, the effect modification was modest as age still had an exponential associated with death in subgroups based on the number of preexisting comorbidities and acute physiologic ICU factors. Our finding of an association between age and COVID-19 mortality independent of risk factors should motivate further investigation into the direct and indirect impacts of age on patient health. Future clinical trials in critically ill patients with COVID-19 should assess whether treatment efficacy differs according to age and risk factor profile.

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