Title

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Journal

Medicine, 101(51)

Authors

Lee, Yoon
Motwani, Yash
Brook, Jenny
et al.

Publication Date

2022-12-23

DOI

10.1097/MD.0000000000032343

Peer reviewed

Observational Study

Medicine

OPEN

Predictors of COVID-19 outcomes

Interplay of frailty, comorbidity, and age in COVID-19 prognosis

Yoon Kyung Lee, BS[a,*], Yash Motwani, BS[b], Jenny Brook, MS[b], Emily Martin, MD, MS[c], Benjamin Seligman, MD, PhD[b,d], Joanna Schaenman, MD, PhD[b,c]

Abstract

Prior research has identified frailty, comorbidity, and age as predictors of outcomes for patients with coronavirus disease 2019 (COVID-19), including mortality. However, it remains unclear how these factors play different roles in COVID-19 prognosis. This study focused on correlations between frailty, comorbidity and age, and their correlations to discharge outcome and length-of-stay in hospitalized patients with COVID-19.

Clinical data was collected from 56 patients who were ≥50 years old and admitted from March 2020 to June 2020 primarily for COVID-19. Frailty Risk Score (FRS) and the Charlson Comorbidity Index (CCI) were used for assessment of frailty and comorbidity burden, respectively.

Age had significant positive correlation with FRS and CCI ($P < .001$, $P < .001$, respectively). There was also significant positive correlation between FRS and CCI ($P < .001$). For mortality, patients who died during their hospitalization had significantly higher FRS and CCI ($P = .01$ and $P < .001$, respectively) but were not significantly older than patients who did not. FRS, CCI, and age were all significantly associated when looking at overall adverse discharge outcome (transfer to other facility or death) ($P < .001$, $P = .005$, and $P = .009$, respectively). However, none of the 3 variables were significantly correlated with length-of-stay. Multivariate analysis showed FRS ($P = .007$) but not patient age ($P = .967$) was significantly associated with death.

We find that frailty is associated with adverse outcomes from COVID-19 and supplants age in multivariable analysis. Frailty should be part of risk assessment of older adults with COVID-19.

Abbreviations: CCI = Charlson Comorbidity Index, COVID-19 = coronavirus disease 2019, FRS = frailty risk score, IQR = interquartile range, LOS = length-of-stay, UCLA = University of California, Los Angeles.

Keywords: age, comorbidity, covid, frailty, geriatrics

1. Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, there have been various methods implemented to determine the best prognostic factors for COVID-19 outcomes. One of these prognostic factors has been age, with early studies showing that COVID-19 outcomes are age-related.[1,2]

Retrospective study of COVID-19 patients ≥65 years old at a hospital in Wuhan, China showed these patients had a mortality rate of 34.5%, significantly higher than the mortality rate of 4.7% for those <65 years.[1] These older patients also had more initial comorbidities, worse symptoms, and greater likelihood of multi-organ involvement than those younger.[1] Likewise, another study of 221 patients with COVID-19 showed that those who were ≥60 years had prolonged disease course and higher rate of respiratory failure than those who were <60 years.[3]

Current research remains equivocal, however, as to how strong of a predictor age alone is for COVID-19 outcomes. For instance, in their sample of 235 Caucasian patients who were ≥65 years, Mendes et al saw no significant difference in age between COVID-19 survivors and nonsurvivors, but saw greater frailty and comorbidity in nonsurvivors.[4] On the other hand, of 81 COVID-19 patients at a Belgian hospital, nonsurvivors were older and frailer, but when performing a bivariate model involving age and frailty, only frailty remained significantly associated with mortality whereas age did not.[2] The European COVID-19 in Older PEople study as well as the Brazilian CO-FRAIL study are 2 large prospective studies, both showing that in-hospital mortality was higher for frailer patients with COVID-19 after adjustment for age and comorbidities.[5,6] These studies, among others,[7] suggest that incorporating frailty may improve prognosis potential more than using age alone and demonstrate that further research is still needed

The authors have no funding to disclose.

The authors have no conflicts of interest to disclose.The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

[a] UCLA David Geffen School of Medicine, Los Angeles, CA, [b] UCLA Division of General Internal Medicine and Health Services Research, Los Angeles, CA, [c] UCLA Division of Infectious Diseases, Los Angeles, CA, [d] West LA VA Geriatric Medicine, Los Angeles, CA.

** Correspondence: Yoon Kyung Lee, UCLA David Geffen School of Medicine, Los Angeles, CA 90024 (e-mail: ylee014@ucla.edu).*

How to cite this article: Lee YK, Motwani Y, Brook J, Martin E, Seligman B, Schaenman J. Predictors of COVID-19 outcomes: Interplay of frailty, comorbidity, and age in COVID-19 prognosis. Medicine 2022;101:51(e32343).

Received: 16 September 2022 / Received in final form: 29 November 2022 / Accepted: 30 November 2022

http://dx.doi.org/10.1097/MD.0000000000032343

to elucidate the role of frailty, comorbidity, and age in patients with COVID-19.

Frailty is defined as a decline in physiologic function and increased vulnerability to stressors.[8] It has been shown to predict negative clinical outcomes for a variety of conditions, independent from age.[9] The Frailty Risk Score (FRS) from Lekan et al takes a biopsychosocial chart-based approach to evaluating frailty retrospectively.[10] The FRS has been shown to be an effective assessment of frailty for older adults and has been used to predict outcomes in older populations such as the older transplant population.[11,12]

We additionally assessed multimorbidity, or the burden of multiple chronic conditions. This was done using the Charlson Comorbidity Index (CCI).[13] Like frailty, comorbidity, through use of the CCI, has previously been shown to be a potential predictor for COVID-19 mortality after adjusting for age and sex.[14]

In this study, we use the FRS and CCI to determine if these chart-based assessments can indeed serve as predictors of COVID-19 outcomes and to further investigate how frailty and comorbidity compares to age in predictive power.

2. Methods

2.1. COVID-19 patient sampling selection

This retrospective study involved 56 patients who were ≥50 years old and primarily hospitalized for COVID-19 at the onset of the pandemic, admitted from March 2020 to June 2020. These patients were a part of the University of California, Los Angeles (UCLA) REDCap web-based data collection tool for COVID-19 patients. Inclusion criteria was hospital admission at UCLA (Ronald Reagan UCLA Medical Center and UCLA Santa Monica Medical Center) with a diagnosis of COVID infection and age ≥50 years.[15] No patients were excluded due to data availability, and the first 56 patients admitted to our center meeting these criteria were reviewed. Therefore, exclusion of patients should not have introduced bias to the results reported. COVID-19 cases were determined by positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction or antibody test in unvaccinated patients presenting with symptoms consistent with COVID-19. The 2 tests had a 92.9% proportion of observed agreement.[16,17]

2.2. FRS and CCI data collection

FRS was determined by chart review using a modified version from Lekan et al, looking at 15 different biopsychosocial frailty risk factors: nutritional issues (malnutrition or obesity), history of falls or fall risk (such as use of assistive device), weakness, vision impairment, dyspnea, fatigue, chronic pain, incontinence, smoking, depression, cognitive impairment, limited social support, low albumin (<3.9 g/dL), low hemoglobin (female <11.6 g/dL, male <13.5 g/dL), and abnormal white blood cell count (<4.16 × 10^3/uL or >9.95 × 10^3/uL).[10] To these 15 factors, we added sleep issues (such as insomnia), activities of daily living dependence, and hearing impairment to include a broader range of impairing conditions common in the older population. Our modified FRS is on a scale of 0 to 18, with 18 being the frailest. Chart review was manually completed using notes from history and physical examinations and consults as well as through automatic data collection for lab results. CCI components were determined based on an online calculator[18] using the past medical history from notes as well as the patients' problem lists. Modifications to CCI for our study were: paraplegia was included with hemiplegia, stage 4 or greater chronic kidney disease was considered moderate or severe renal disease, and lymphoma and leukemia were combined as 1 variable. Our modified CCI is on a scale of 0 to 35, 35 indicating the greatest comorbidity burden.

2.3. Outcomes

Mortality was defined by death any time during initial COVID-19 associated hospitalization. Adverse discharge outcome was defined as either discharge to another facility or death during initial hospitalization. Length-of-stay (LOS) was determined from initial hospital admission and discharge dates.

2.4. Data analysis

Statistical analysis was performed via JMP Pro 15 (SAS Institute Inc., Cary, NC) and R version 4.1.2 (The R Project for Statistical Computing). Linear regression was used to assess associations of age with FRS and CCI as well as associations of frailty and age with COVID-19 patients' outcomes. *t* test was used for comparisons of mortality and to compare between patients discharged alive and with adverse discharge outcome. The univariable and bivariable associations of age and FRS with the outcome of death or facility discharge were assessed by logistic regression. The association with age in the regression models used a categorical definition of age high/low < or ≥65 years based on COVID-19 literature using age 65 as a cutoff for worse clinical outcomes.[19,20] *P* value of <.05 was considered statistically significant.

2.5. Ethics declaration

This study was approved by the Institutional Review Board of UCLA.

3. Results

3.1. Demographic characteristics, comorbidities, and outcomes

Table 1 shows the characteristics of the 56 COVID-19 patients. The median interquartile range (IQR) age was 70 (61–77) years, 36 (64%) were male, and 28 (50%) were non-Hispanic White. Hypertension and diabetes were the most common comorbidities and remdesivir the most common COVID-19 treatment administered. Shown in Table 2, 46% were admitted to the ICU, and 23% were intubated at some point during their hospitalization. Median (IQR) length of stay was 11.5 (3–19) days. 56% of patients were discharged home, 33% were discharged to an acute rehabilitation or skilled nursing facility, and 11% of patients died during their hospitalization.

3.2. FRS and CCI score and patient age

As shown in Table 1, median FRS was 5 (IQR 3–7) and median CCI was 4 (IQR 2–7). Forty-four out of 56 (79%) of the patients had low albumin, making this the most prevalent frailty risk factor in this cohort (Table S1, Supplemental Digital Content, http://links.lww.com/MD/I165). Following low albumin, the most prevalent conditions were anemia (50%), current or former smoking status (39%), activities of daily living dependence (37.5%), and nutritional issues (37.5%). In Figure 1, age showed a significant correlation with both FRS ($P < .001$) and CCI ($P < .001$). FRS and CCI also showed a significant correlation with each other ($P < .001$) (Fig. 2).

3.3. Association between FRS and CCI scores and death

FRS and CCI scores were significantly higher in patients who died during their COVID-19-related hospitalization than patients who did not ($P = .01$ and $P < .001$, respectively)

Table 1

Clinical features of patient cohort.

Clinical feature	n = 56
Age (yr)	
Median (interquartile range)	70 (61–77)
Sex, male, n (%)	36 (64)
Race/ethnicity, n, (%)	
White (non-Hispanic)	28 (50)
Hispanic (White + non-White)	15 (27)
Black	4 (7)
Asian	3 (5)
Other	6 (11)
Comorbidities	
Hypertension, n, (%)	39 (70)
Diabetes, n, (%)	22 (39)
Congestive heart failure, n, (%)	9 (16)
Active cancer, n, (%)	4 (7)
Dementia/chronic cognitive deficit, n, (%)	11 (20)
Smoking status	
Current smoker, n, (%)	4 (7)
Former smoker, n, (%)	22 (39)
COVID treatment therapy, n, (%)	
Remdesivir	7 (13)
Prednisone	3 (5)
Prednisolone	0
Methylprednisolone	4 (7)
Dexamethasone	1 (2)
Hydrocortisone	2 (4)
Convalescent plasma	0
Frailty Risk Score (FRS)	
Median (interquartile range)	5 (3–7)
Charlson Comorbidity Index (CCI)	
Median (interquartile range)	4 (2–7)

COVID = coronavirus disease 2019.

Table 2

Outcomes of patient cohort.

Outcomes	n = 56
Intubated, n, (%)	13 (23)
Admitted to ICU, n, (%)	26 (46)
Length-of-stay (d)	
Mean (standard deviation)	15 (15)
Median (interquartile range)	11.5 (3–19)
Facility discharge, n (%)	18 (33)
Deceased, n (%)	6 (11)

ICU = intensive care unit.

(Fig. 3). Median FRS score was 7 for patients who died compared with 4 for patients who were discharged alive. For CCI, median score was 8.5 for patients who died compared with 3.5 for patients who were discharged alive. There was no significant difference in age between patients who died and those who did not ($P = .054$) (Fig. 3).

3.4. Higher FRS, CCI, and age are associated with adverse discharge outcome

Figure 4 compares FRS and CCI in patients who were discharged alive versus those who had either of a combined endpoint of death or facility discharge. FRS and CCI were significantly higher for patients who had an overall adverse discharge outcome (either discharged to other facility or died during hospital stay) than patients who were discharged alive ($P < .001$ and $P = .005$, respectively). We also found a significant association between age and discharge alive rather than death or facility discharge ($P = .009$) (Fig. 4). However, FRS, CCI, and age did not significantly correlate with LOS of initial COVID-19 hospitalization (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I166).

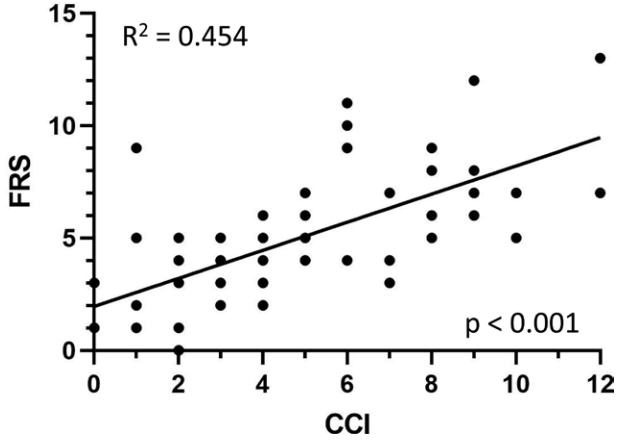

Figure 2. Association between FRS versus CCI, depicted by line. *P* values are indicated, $P < .05$ in bold. CCI = Charlson Comorbidity Index, FRS = Frailty Risk Score.

3.5. Frailty is a risk factor independent of age for adverse outcomes

Table 3 shows the results of logistic regression for adverse discharge outcome. Association with age in the regression models used a categorical definition of age high/low < or ≥65 years old. When run separately, both age and FRS were significantly associated with death. However, both were included in logistic regression, only FRS was significantly associated (OR [95% CI] 1.56 [1.15–2.29]).

4. Discussion and future directions

COVID-19 continues to affect health and healthcare globally, with older adults at an increased risk of severe illness.[21] Ongoing research has sought to elucidate the relationship of frailty, co-morbidly, and age with COVID-19 outcomes. This study looked at how frailty, assessed using FRS, co-morbidity assessed by CCI, and age predicted outcomes for patients with COVID-19.

Both FRS and CCI were associated with adverse outcomes from COVID-19. By contrast, age was not significantly associated with adverse outcomes once adjustment was made for frailty. These findings suggest that age alone may not be an adequate predictor of outcomes following infection from COVID-19 among older adults and assessment of frailty or comorbidity should be part of any risk assessment.

Other research also supports the use of frailty as a risk-stratification tool for older adults with COVID-19. The Clinical Frailty Scale, developed as a tool for rapid assessment of frailty, has been used extensively in research on frailty during the pandemic.[5,6,22,23] In addition, the UK's National Institute for Health and Care Excellence recommended frailty assessment with Clinical Frailty Scale in their COVID-19 guidelines. The Hospital FRS, was developed as an electronic measure of frailty to risk-stratify older patients.[24] Studies of this measure have been more mixed, finding no association with mortality in a Swedish cohort, whereas other studies have found associations with ICU admission, mechanical ventilation, and LOS.[25,26]

Advantages of the FRS include the ability to assess frailty electronically or by chart review, rather than through direct patient contact. This is useful both for automating assessment and minimizing contact with patients who may require isolation.

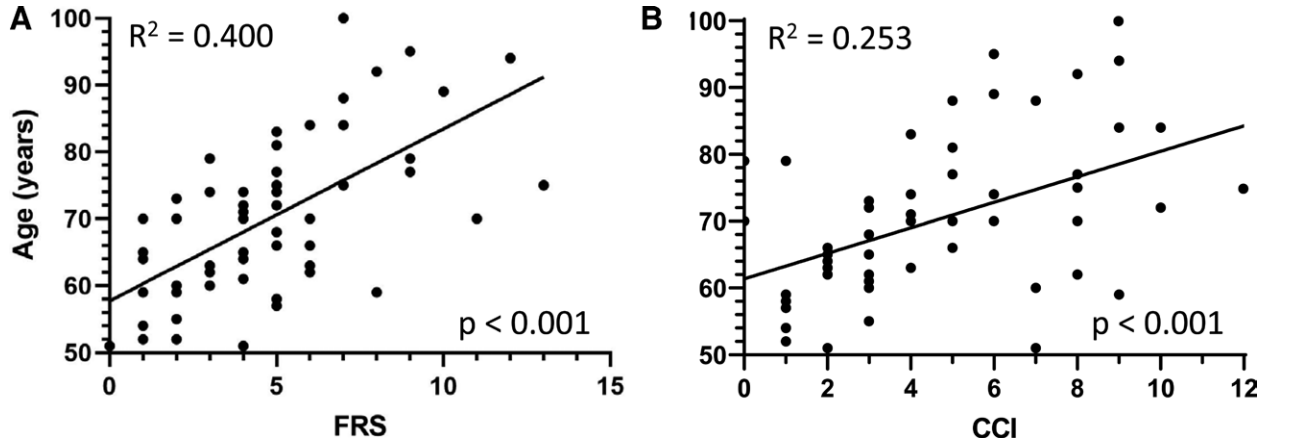

Figure 1. Association between age versus (A) FRS or (B) CCI, depicted by line. *P* values are indicated, *P* < .05 in bold. CCI = Charlson Comorbidity Index, FRS = Frailty Risk Score.

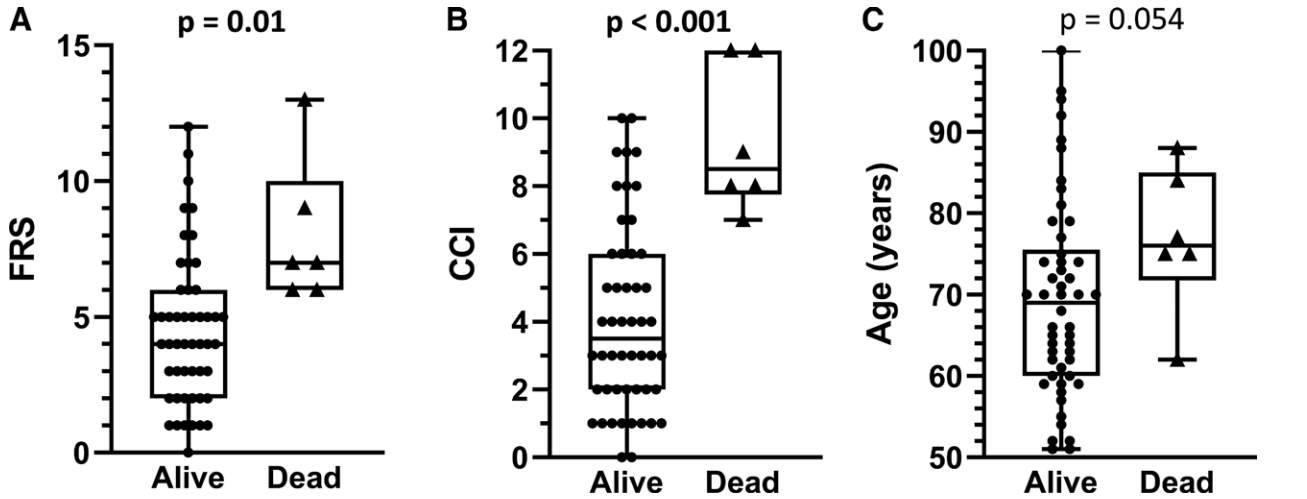

Figure 3. Box and whisker plots showing differences in (A) FRS, (B) CCI, and (C) age by mortality. Median at central line and range at whiskers. Statistical analysis by *t* test. *P* values are indicated, *P* < .05 in bold. CCI = Charlson Comorbidity Index, FRS = Frailty Risk Score.

In addition, in our study, rather than looking at individual comorbidities, we used CCI which offers the strength of integrating multiple co-morbidities, with prior meta-analysis revealing that comorbidity using CCI associates with higher mortality in COVID-19 patients.[27] Since CCI correlated with FRS in our study, CCI also presents as a potential tool for risk stratification. However, the potential interplay between comorbidity and frailty, specifically the role of comorbidity in FRS, needs additional exploration.

Limitations to this study include multifactorial elements in the discharge process that may have impacted transfer to another facility or LOS and may have led to a nonsignificant correlation between LOS and FRS, CCI, and age (Figure S1, Supplementary Digital Content, http://links.lww.com/MD/I166). We recognize the potential for other confounding variables in this study when analyzing the relationship between frailty and clinical outcomes such as the severity of COVID-19 or the time from symptom onset to hospitalization. However, information regarding severity as defined by WHO was not available in this dataset. Time from symptom onset to hospitalization is less likely to be a determining factor based on prior studies showing no significant association between time from symptom onset to hospitalization and COVID-19 severity or worsening outcome.[19,28] In addition, these patients were admitted early in the pandemic, so the impact of vaccination and infection with severe acute respiratory syndrome coronavirus 2 variant strains remains to be determined. Given the many cases of breakthrough infection in older individuals with comorbidities, we anticipate that a similar pattern will be observed.

The study was also limited by a small sample size, making it difficult to evaluate for all potential confounders present. However, despite the small size, there were still statistically significant associations. Future studies can incorporate a larger cohort size to validate these primary results for this pilot study.

Overall, frailty, comorbidity burden, and age significantly correlate with overall adverse COVID-19 discharge outcome but may have different potentials as prognostic factors when specifically looking at mortality during hospitalization. Further research with a larger cohort will elucidate which factors are the most important influencers when it comes to different COVID-19 outcomes.

Author contributions

Conceptualization: Yoon Kyung Lee, Joanna Schaenman.
Data curation: Yoon Kyung Lee, Yash Motwani, Jenny Brook, Emily Martin.
Formal analysis: Yoon Kyung Lee, Joanna Schaenman.
Project administration: Yoon Kyung Lee, Joanna Schaenman.
Supervision: Joanna Schaenman.
Writing – original draft: Yoon Kyung Lee, Joanna Schaenman.
Writing – review & editing: Yoon Kyung Lee, Yash Motwani, Emily Martin, Benjamin Seligman, Joanna Schaenman.

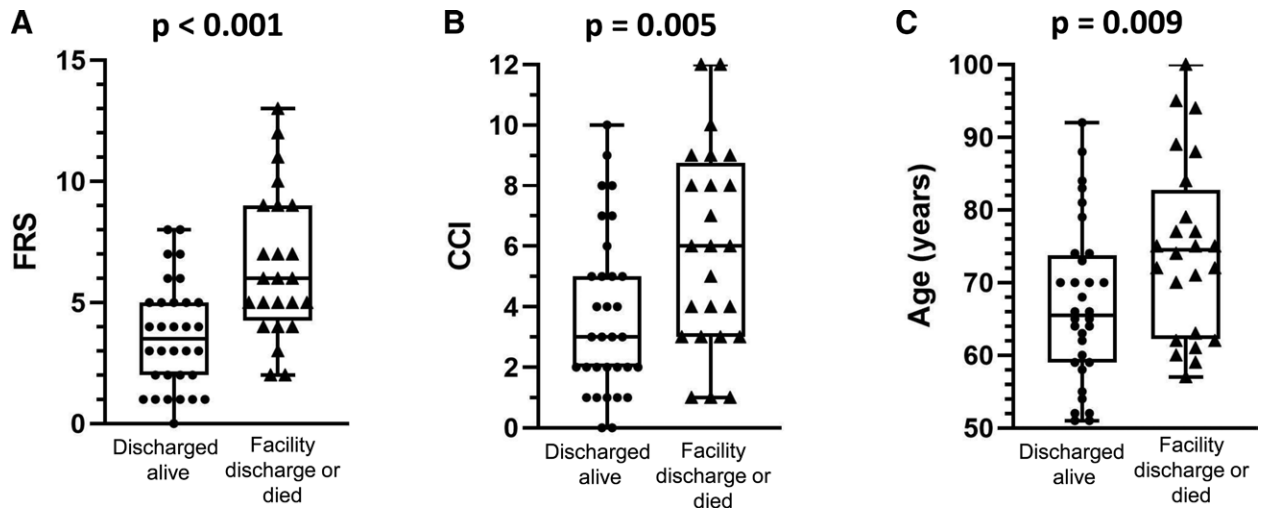

Figure 4. Box and whisker plots showing differences in (A) FRS, (B) CCI, and (C) age by adverse discharge outcome. Median at central line and range at whiskers. Statistical analysis by *t* test. *P* values are indicated, *P* < .05 in bold. CCI = Charlson Comorbidity Index, FRS = Frailty Risk Score.

Table 3

Results of univariable and multivariable regression of death/facility discharge on age and FRS among 56 hospitalized COVID-19 patients.

Univariable regression	OR (95% CI)	*P* value
Age	1.06 (1.01–1.12)	.023
FRS	1.56 (1.22–2.13)	<.01
Multivariable regression	OR (95% CI)	*P* value
Age	1.00 (0.93–1.07)	.99
FRS	1.56 (1.15–2.29)	.01

CI = confidence interval, FRS = Frailty Risk Score, OR = odds ratio.

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