COVID-19 is not over and age is not enough: Using frailty for prognostication in hospitalized patients

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Abstract

Background: Frailty screening using the Clinical Frailty Scale (CFS) has been proposed to guide resource allocation in acute care settings during the pandemic. However, the association between frailty and coronavirus disease 2019 (COVID-19) prognosis remains unclear.

Objectives: To investigate the association between frailty and mortality over 6 months in middle-aged and older patients hospitalized with COVID-19 and the association between acute morbidity severity and mortality across frailty strata.

Design: Observational cohort study.

Setting: Large academic medical center in Brazil.

Participants: A total of 1830 patients aged ≥50 years hospitalized with COVID-19 (March–July 2020).

Measurements: We screened baseline frailty using the CFS (1–9) and classified patients as fit to managing well (1–3), vulnerable (4), mildly (5), moderately (6), or severely frail to terminally ill (7–9). We also computed a frailty index (0–1; frail >0.25), a well-known frailty measure. We used Cox
proportional hazards models to estimate the association between frailty and time to death within 30 days and 6 months of admission. We also examined whether frailty identified different mortality risk levels within strata of similar age and acute morbidity as measured by the Sequential Organ Failure Assessment (SOFA) score.

**Results:** Median age was 66 years, 58% were male, and 27% were frail to some degree. Compared with fit-to-managing-well patients, the adjusted hazard ratios (95% confidence interval [CI]) for 30-day and 6-month mortality were, respectively, 1.4 (1.1–1.7) and 1.4 (1.1–1.7) for vulnerable patients; 1.5 (1.1–1.9) and 1.5 (1.1–1.8) for mild frailty; 1.8 (1.4–2.3) and 1.9 (1.5–2.4) for moderate frailty; and 2.1 (1.6–2.7) and 2.3 (1.8–2.9) for severe frailty to terminally ill. The CFS achieved outstanding accuracy to identify frailty compared with the Frailty Index (area under the curve = 0.94; 95% CI = 0.93–0.95) and predicted different mortality risks within age and acute morbidity groups.

**Conclusions:** Our results encourage the use of frailty, alongside measures of acute morbidity, to guide clinicians in prognostication and resource allocation in hospitalized patients with COVID-19. 

**KEYWORDS**
COVID-19, triage, frailty, resource allocation, prognosis

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### INTRODUCTION

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic, it was clear that age was associated with disease severity and prognosis. Early observational studies also pointed to an increased risk of hospitalization, need for mechanical ventilation, and mortality in older adults. As the pandemic progressed, age, as an objective and easily obtained characteristic, started to be used as a primary factor to estimate prognosis and decide how to allocate patient care. However, age does not account for the enormous heterogeneity of the older population, and, applied alone, it is not a reliable, or even ethical, criterion to complete judicious medical decisions. Therefore, a more comprehensive approach to prognostication is necessary and should include other factors such as comorbidities, extent of organ dysfunction, functional status, and frailty.

Previous studies and guidelines have proposed frailty among the measures to guide resource allocation in geriatric care. This syndrome reflects a state of vulnerability resulting from a lifetime accumulation of physiological deficits that leads to a limited capacity to respond to organic stressors. Frailty has been associated with several adverse outcomes (i.e., disability, hospitalization, and death) in older adults. Although recent studies have suggested that frailty can predict short-term mortality and length of hospital stay in older adults...
admitted for COVID-19, some controversies remain. Knopp et al. investigated clinical features associated with mortality in older adults admitted for COVID-19 and found that frailty was not independently associated with the outcome. In another study on hospitalized older adults, frailty was only associated with increased mortality in participants without COVID-19. Moreover, it is still unclear the prognostic value of frailty in middle-aged patients (50 to 64 years), a population also at higher risk of COVID-19-related adverse outcomes.

Therefore, we aimed to investigate in middle-aged and older adults admitted to the hospital with COVID-19: (1) the association between frailty and 30-day and 6-month mortality; (2) the association between acute morbidity severity and 30-day and 6-month mortality, across frailty strata; and (3) the concurrent validity of the Clinical Frailty Scale (CFS) with a well-validated frailty measurement (Frailty Index) of the same population.

METHODS

Study design and population

This cohort study is part of the CO-FRAIL Study, an ongoing research project designed to investigate the association between frailty and adverse outcomes in middle-aged and older patients admitted to hospital due to COVID-19. The work is conducted at Hospital das Clinicas, the largest academic medical center in Latin America. On March 30, 2020, the main hospital building was converted to a COVID-19-only facility—with 900 hospital beds (200 for intensive care units)—becoming a major center for COVID-19 treatment in Sao Paulo, the epicenter of the pandemic in Brazil. Hospital admissions were centrally managed by the Regulatory Center of the State of Sao Paulo, which prioritized severely ill patients referred from 85 cities and 278 secondary hospitals statewide, although mostly supporting the metropolitan area of Sao Paulo (Figure S1). A thorough description of the study setting was described in previous studies. We screened all individuals aged ≥50 years consecutively admitted to the hospital between March 30 and July 7, 2020. We included confirmed cases of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using reverse transcription-polymerase chain reactions or serological testing if the former were negative. We excluded patients discharged from the emergency department in less than 24 h of arrival and those with missing data on our main variables.

The Research Ethics Committee of the University of Sao Paulo Medical School approved the study and authorized researchers to secure verbal consent in the study’s follow-up interviews. We managed our data using the online platform Research Electronic Data Capture (REDCap).

Data collection

A trained research team composed of medical investigators collected the study data using structured electronic case report forms. These were completed after a detailed review of electronic medical records, nursing records, consulting notes, laboratory tests, and radiologic examinations. These records included detailed information regarding COVID-19 infection, documented by frontline health professionals using standardized forms specially designed for the pandemic. Medical investigators also conducted structured telephone interviews with participants or their proxy (i.e., family member or caregiver) to gather complementary information to that retrieved from the electronic hospital records. We were thus able to obtain extensive information on sociodemographic factors, acute symptoms of the disease (types and duration), comorbidities, vital signs, level of consciousness, need for supplemental oxygen, laboratory examinations, and image findings on admission.

Sociodemographic factors included age, sex, race or ethnicity, and education (less vs. more or equal to 8 years [middle school]). Patients were classified as having a course duration of COVID-19 symptoms of >7 or ≤7 days prior to admission. Comorbidities were assessed according to the Charlson Comorbidity Index (0–33), with higher scores indicating a greater burden of disease. We also evaluated the smoking status (never, former, current). The C-reactive protein (mg/L) served as a readily available biomarker of inflammation, with values ≤10, 11–100, and >100 defining normal, high, and very high levels of inflammation, respectively. Data on six additional systems were collected, including (1) respiratory (the partial pressure of arterial oxygen to the percentage of inspired oxygen [PaO2/FiO2] ratio), (2) neurological (Glasgow Coma Scale), (3) cardiovascular (mean arterial blood pressure and use of vasopressors), (4) hepatic (serum total bilirubin levels), (5) coagulation (platelet count), and (6) renal (serum creatinine levels) systems. These data were used to compute the Sequential Organ Failure Assessment (SOFA) score (0–24; higher = worse) based on the worst value of each parameter within the first 24 h of admission. For analysis purposes, we opted to categorize the SOFA score and Charlson Comorbidity Index according to quartiles because these measures do not have standard cutoff values.
Frailty assessment

Frailty was assessed using the CFS\textsuperscript{18} in a process that involved information on (a) frequency of physical activity per week (<1; 1–2; or ≥3), (b) report on symptoms that limit activities (e.g., being “slowed up” or tired), (c) level of independence to perform basic and instrumental activities of daily living,\textsuperscript{30} and (d) cognition. Because CFS-specific information is rarely available in chart reviews, we achieved characterization of frailty according to our participants’ baseline health conditions, its assessment was based on information referring to the period before (2–4 weeks) the acute disease onset. Following existing guidelines on the subject,\textsuperscript{33,34} medical investigators trained in geriatric medicine ranked the CFS, a nine-level global frailty rating scale with scores ranging from 1 (“very fit”) to 9 (“terminally ill”), based on their clinical judgment. As stated in prior work,\textsuperscript{13} we further combined CFS scores according to five groups, 1–3 (“very fit” to “managing well”), 4 (“vulnerable”), 5 (“mildly frail”), 6 (“moderately frail”), and 7–9 (“severely frail to terminally ill”).

To further validate our method, we employed the well-known concept of accumulation of deficits to define a frailty index (0–1)\textsuperscript{19,35} that could serve as an alternate frailty measure in our population. It described the proportion of impaired items across 40 age-related health conditions.\textsuperscript{36} We used electronic case report forms combined with data from the telephone interviews to systematically retrieve our frailty index items, which are fully detailed in Table S1. We defined frailty for Frailty Index values >0.25, as proposed in previous studies.\textsuperscript{37,38}

Outcome measures

Our primary outcomes were time to death within 30 days and 6 months of hospital admission. We registered dates of admission and discharge, or hospital death, and then followed discharged participants for at least 6 months after their admission. A research team blinded to the baseline data performed a series of follow-up telephone interviews to assess all-cause mortality. Patients who were alive at the end of the 6-month follow-up were censored.

Statistical analysis

We reported baseline characteristics as counts and frequencies for categorical variables and medians and interquartile ranges (IQR) for interval variables. We computed Spearman’s rank correlation between the CFS and the Frailty Index to investigate their concurrent validity, defining a strong correlation for values ≥0.70 and a negligible correlation for values ≤0.30.\textsuperscript{39} We also determined the accuracy of the CFS to discriminate between frail and nonfrail patients defined by the Frailty Index using areas under the receiving operating characteristic curves (AUCs). We further stratified this analysis according to age (<65 or ≥65 years old) to verify whether the CFS had adequate performance in middle-aged adults, comparing its accuracy with that observed for older adults. Hosmeret al. proposed that AUCs of 0.80 to 0.90 are “excellent,” and 0.90 or above, “outstanding”.\textsuperscript{40} Finally, we calculated sensitivity, specificity, likelihood ratios, and predictive values for each CFS score. The Youden Index (sensitivity + specificity – 1) indicated the threshold with the best discriminative performance.

We used Cox proportional hazards models to estimate the association between frailty and time to death within 30 days and 6 months, using the CFS groups as our primary independent variable. We also explored categories of age, sex, race or ethnicity, education, Charlson Comorbidity Index, smoking status, duration of COVID-19 symptoms, C-reactive protein, and SOFA score as predictors of time to death. We reported the cumulative incidence of outcomes, and the crude and adjusted hazards ratios (HR), with their 95% confidence intervals (95% CIs), for each variable of interest.

Because frailty may have different meanings depending on patients’ age,\textsuperscript{14} we conducted sensitivity analyses stratifying the sample based on conventional age ranges (middle-aged = 50–64 years, older adults = 65–79 years, and very old adults ≥80 years). First, we computed Kaplan–Meier survival curves over 6 months to estimate whether frailty improved the risk stratification of death across age groups. Next, we run crude and adjusted Cox proportional hazards models for 30-day and 6-month mortality. In these analyses, we used the Youden Index to define the cutoff for frailty per CFS scores (“primary variable of interest”) and incorporated the same pattern of covariates described above (except for age that was defined in years) into the adjusted models.

We also estimated Spearman’s rank correlations between CFS scores and SOFA scores to explore the divergent validity of frailty measures with acute morbidity, illustrating the analysis with a scatter plot. Then, we investigated the interaction between frailty and acute morbidity for 6-month mortality. We stratified the Kaplan–Meier survival curves and Cox proportional hazards models based on frailty status if the P-value for interaction achieved significance. In addition to frailty and acute morbidity, the adjusted Cox proportional hazards models included age, sex, race or ethnicity, education, Charlson Comorbidity Index, smoking status, duration of COVID-19 symptoms, and C-reactive protein.
All statistical tests were two-tailed, with a significance level set at 0.05. The analyses were conducted using Stata (version 15.1; StataCorp, College Station, TX).

### RESULTS

We assessed the eligibility of 2463 admissions between March 30 and July 7, 2020. We excluded individuals without a laboratory-confirmed diagnosis of COVID-19 \( (N = 396) \), those discharged from the emergency department in less than 24 h \( (N = 84) \), and those with missing data on our frailty assessment \( (N = 37) \) or main covariates \( (N = 55) \). We also excluded the readmissions of patients already included in the study \( (N = 61) \). Our final sample reached 1830 SARS-CoV-2–infected patients.

During the 6-month follow-up, 841 (46%) patients died: 724 (40%) in the hospital and 117 (6%) after discharge. The median length of hospital stay was 13 days \( (IQR = 7–21 \text{ days}) \). Of the 1106 patients discharged from the hospital, 920 (83%) returned home, and 186 (17%)...
were transferred to postacute care settings. Only four patients discharged from the hospital were lost before completing the 6-month follow-up.

The cumulative incidence of 30-day and 6-month mortality ranged from 28% to 36% for patients with CFS scores 1–3 and from 58% to 76% for those with CFS scores 7–9 (Table 2). We observed that higher CFS scores were significantly associated with mortality within 30 days and 6 months, even after adjusting for age, sex, race or ethnicity, education, Charlson Comorbidity Index, smoking status, duration of COVID-19 symptoms, C-reactive protein levels, and SOFA scores. Older age, male sex, multimorbidity (Charlson Comorbidity Index scores ≥ 2), very high C-reactive protein levels (>100 mg/L), and higher levels of acute morbidity (SOFA scores ≥ 4) were also independent predictors of mortality within 30 days and 6 months (Table 2). Of note, survival over 6 months varied significantly among patients in the same age group, depending on their frailty level (Figure 1). Frailty was associated with 30-day and 6-month mortality in each age stratum (50–64 years, 65–79 years, and ≥ 80 years) even after adjusting for the covariates (Table S3).

We verified that CFS and SOFA scores were not correlated (Spearman’s coefficient = 0.02; 95% CI = −0.03–0.06) (Figure S4). Furthermore, frailty modified the association between SOFA quartiles and 6-month mortality, with a p-value for interaction = 0.01 (Table S4). Figure 2 shows that frailty status predicted higher incidences of mortality within each stratum of SOFA scores. The prediction of different levels of 6-month mortality risk according to frailty status within each stratum of SOFA scores remained significant even in the adjusted analysis (Table 3).

**DISCUSSION**

The CO-FRAIL Study, a cohort designed to investigate the prognostic effect of frailty on severe forms of COVID-19 found that baseline frailty is a strong predictor of 30-day and 6-month all-cause mortality in middle-aged and older adults hospitalized for the disease. Frailty was observed in about 1 out of 3 patients aged over 65 years admitted with COVID-19. The CFS achieved outstanding accuracy to identify frailty on admission. This frailty measure provided valuable prognostic information for COVID-19 by capturing risks apart from those already associated with age, comorbidities, and acute morbidity of disease. Our results suggest that a triage process contemplating frailty assessment might support frontline health providers to get a more accurate prognosis of SARS-CoV-2 infection.

The fact that COVID-19 disproportionately affects older adults has led health providers, administrators, and governments to overemphasize age as the core element of vulnerability to the disease. However, previous studies have demonstrated how older adults can run divergent courses of COVID-19. In reality, the prognosis of the geriatric population generally depends on a broader concept of vulnerability that captures age-related accumulation of deficits (“biological age”) rather than chronological age itself. This aspect should be considered during the current scenario of public health crisis as several countries have proposed recommendations for triage and resource allocation. Despite some consensus on topics such as the importance of prognostic assessment and transparency of the decision-making process, other areas are more controversial. Triage tiebreakers are one such area. They range from age to luck (i.e., random allocation) and are often disputed. Our results suggest that frailty assessment might be valuable in distinguishing COVID-19 patients’ prognosis.

Most studies that assessed the effect of frailty on COVID-19 mortality have been completed in Europe, particularly in the United Kingdom, encouraged by the National Institute of Clinical Excellence (NICE) recommendation for using the CFS to guide the care of older adults hospitalized with COVID-19. In these studies, the prevalence of frailty ranged between 30% and 70%, similar to what we observed in patients over 65 (36%) and what was reported in Americans over 65 admitted to the hospital from the emergency department (36%). Although the CFS was not a strong predictor of mortality across all studies, those with larger sample sizes and enough power to adjust for potential confounders were able to find an association between CFS-defined frailty and short-term mortality, an assumption supported by the results from our sample based on a diverse population living in the epicenter of the pandemic in a low-to-middle-income country.

Our study advances the findings from prior work on frailty in the context of COVID-19. First, we determined the CFS concurrent validity against the Frailty Index in a population composed of patients admitted due to COVID-19. Moreover, we verified the excellent accuracy of this tool to identify frailty in middle-aged SARS-CoV-2–infected patients, showing that the CFS may also be valid in younger populations. Second, to the extent of our knowledge, no studies had been able to assess frailty as a predictor of mortality beyond 60 days, an outcome that could be related to the long-term complications of the viral infection. We explored all-cause mortality in a longer follow-up of 6 months. This is a relevant aspect since frailty, as a measure of preadmission health status, might be a more powerful predictor of long-term...
| Age | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|-----|-----------------|-----------------------|------------------|----------------------|
|     | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| 50–64 years old | 216/831 (26) | (reference) | (reference) | 293/831 (35) | (reference) | (reference) |
| 65–79 years old | 315/758 (42) | 1.8 (1.5–2.1) | 1.6 (1.3–1.9) | 389/758 (51) | 1.7 (1.4–2.0) | 1.5 (1.3–1.7) |
| ≥80 years old | 135/241 (56) | 2.9 (2.3–3.6) | 2.5 (2.0–3.1) | 159/241 (66) | 2.7 (2.2–3.2) | 2.2 (1.8–2.8) |

| Sex | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|-----|-----------------|-----------------------|------------------|----------------------|
|     | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| Female | 258/769 (34) | (reference) | (reference) | 258/769 (42) | (reference) | (reference) |
| Male | 408/1061 (38) | 1.2 (1.0–1.4) | 1.2 (1.0–1.4) | 408/1061 (49) | 1.2 (1.1–1.4) | 1.3 (1.1–1.5) |

| Race or ethnicity | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|------------------|-----------------|-----------------------|------------------|----------------------|
|                 | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| White | 422/1172 (36) | (reference) | (reference) | 422/1172 (47) | (reference) | (reference) |
| Black | 60/154 (39) | 1.1 (0.9–1.5) | 1.2 (0.9–1.6) | 60/154 (48) | 1.1 (0.8–1.4) | 1.2 (0.9–1.5) |
| Mixed | 165/460 (36) | 1.0 (0.8–1.2) | 1.0 (0.9–1.2) | 165/460 (43) | 0.9 (0.8–1.1) | 0.9 (0.8–1.1) |
| Other | 19/44 (43) | 1.3 (0.8–2.1) | 1.1 (0.7–1.7) | 19/44 (55) | 1.3 (0.9–1.9) | 1.0 (0.6–1.5) |

| Education | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|-----------|-----------------|-----------------------|------------------|----------------------|
|           | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| Middle school or higher | 245/682 (36) | (reference) | (reference) | 245/682 (44) | (reference) | (reference) |
| Less than middle school | 421/1148 (37) | 1.0 (0.9–1.2) | 0.8 (0.7–1.0) | 421/1148 (47) | 1.1 (1.0–1.3) | 0.9 (0.8–1.1) |

| Charlson score | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|----------------|-----------------|-----------------------|------------------|----------------------|
|               | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| 0 points | 124/487 (25) | (reference) | (reference) | 124/487 (33) | (reference) | (reference) |
| 1 point | 136/428 (32) | 1.3 (1.1–1.7) | 1.2 (0.9–1.5) | 136/428 (38) | 1.2 (1.0–1.6) | 1.1 (0.9–1.4) |
| 2–3 points | 169/440 (39) | 1.7 (1.4–2.2) | 1.5 (1.2–1.9) | 169/440 (50) | 1.8 (1.4–2.2) | 1.5 (1.2–1.8) |
| ≥4 points | 237/475 (50) | 2.4 (2.0–3.0) | 1.8 (1.5–2.4) | 237/475 (63) | 2.5 (2.1–3.0) | 1.9 (1.5–2.3) |

| Smoking status | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|----------------|-----------------|-----------------------|------------------|----------------------|
|               | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| Never | 472/1257 (38) | (reference) | (reference) | 472/1257 (47) | (reference) | (reference) |
| Former | 158/478 (33) | 0.8 (0.7–1.0) | 0.8 (0.7–1.0) | 158/478 (41) | 0.8 (0.7–1.0) | 0.8 (0.7–1.0) |
| Current | 36/95 (38) | 1.0 (0.7–1.4) | 0.9 (0.7–1.3) | 36/95 (53) | 1.1 (0.8–1.5) | 1.0 (0.8–1.4) |

| Days of symptom | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|-----------------|-----------------|-----------------------|------------------|----------------------|
|                 | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| 0–7 days | 386/978 (39) | (reference) | (reference) | 386/978 (51) | (reference) | (reference) |
| >7 days | 280/852 (33) | 0.8 (0.7–0.9) | 0.9 (0.8–1.1) | 280/852 (41) | 0.7 (0.6–0.9) | 0.9 (0.8–1.0) |

| C-reactive protein | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|--------------------|-----------------|-----------------------|------------------|----------------------|
|                   | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| 0–10 mg/L | 7/50 (14) | (reference) | (reference) | 7/50 (24) | (reference) | (reference) |
| 11–100 mg/L | 179/645 (28) | 2.2 (1.0–4.6) | 1.8 (0.9–3.9) | 179/645 (37) | 1.7 (1.0–3.1) | 1.5 (0.8–2.7) |
| >100 mg/L | 480/1135 (42) | 3.7 (1.7–7.8) | 2.4 (1.1–5.1) | 480/1135 (52) | 2.8 (1.6–4.9) | 1.9 (1.1–3.5) |

| SOFA score | 30-day mortality | Hazard ratio (95% CI) | 6-month mortality | Hazard ratio (95% CI) |
|------------|-----------------|-----------------------|------------------|----------------------|
|            | N died/N total (%) | Crude | Adjusted | N died/N total (%) | Crude | Adjusted |
| 0–3 points | 43/450 (9) | (reference) | (reference) | 43/450 (17) | (reference) | (reference) |
| 4–5 points | 137/463 (30) | 3.5 (2.5–4.9) | 2.8 (2.0–4.0) | 137/463 (39) | 2.7 (2.1–3.5) | 2.3 (1.7–3.0) |
| 6–9 points | 195/454 (43) | 5.6 (4.0–7.9) | 4.5 (3.2–6.3) | 195/454 (55) | 4.4 (3.4–5.7) | 3.7 (2.8–4.8) |
| ≥10 points | 291/463 (63) | 9.4 (6.8–13.0) | 8.6 (6.2–11.9) | 291/463 (73) | 7.0 (5.5–9.1) | 6.9 (5.3–8.9) |
prognosis than measures of organ dysfunction, which would arguably be better predictors of short-term outcomes. Finally, our results contribute to understanding the impact of acute morbidity measures on COVID-19 prognosis by showing that frailty intensifies the effect of SOFA on mortality.34,47

Although our results indicate the relevance of the early recognition of frailty in the prognostication of COVID-19 patients, no measure should be used in isolated manner to determine the allocation of medical resources.21 On the contrary, our study highlights the importance of sociodemographic factors, multimorbidity, and, particularly, acute disease morbidity to stratify risks in hospitalized middle-aged and older adults with COVID-19. These routinely assessed measures are essential to help health providers delineate a fuller picture of

### Table 2 (Continued)

| Clinical Frailty Scale | 30-day mortality | 6-month mortality |
|------------------------|------------------|------------------|
|                        | N died/N total (%) | Hazard ratio (95% CI) | N died/N total (%) | Hazard ratio (95% CI) |
|                        | Crude | Adjusted | Crude | Adjusted |
| 1–3 points             | 297/1042 (28) | (reference) | (reference) | 297/1042 (36) | (reference) | (reference) |
| 4 points               | 114/294 (39) | 1.5 (1.2–1.9) | 1.4 (1.1–1.7) | 114/294 (49) | 1.5 (1.2–1.8) | 1.4 (1.1–1.7) |
| 5 points               | 98/207 (47) | 1.9 (1.5–2.4) | 1.5 (1.1–1.9) | 98/207 (57) | 1.9 (1.6–2.4) | 1.5 (1.1–1.8) |
| 6 points               | 77/148 (52) | 2.3 (1.8–2.9) | 1.8 (1.4–2.3) | 77/148 (65) | 2.3 (1.8–2.9) | 1.9 (1.5–2.4) |
| 7–9 points             | 80/139 (58) | 2.6 (2.1–3.4) | 2.1 (1.6–2.7) | 80/139 (76) | 2.9 (2.4–3.6) | 2.3 (1.8–2.9) |

**Note:** Estimates were calculated using Cox proportional hazards models. Quartiles defined the categories of Charlson and SOFA scores. Abbreviations: CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

**Figure 1** Kaplan–Meier survival curves over 6 months, according to age group and frailty status. Frailty was assessed using the Clinical Frailty Scale (0–9), with a cutoff of five defining patients as frail. All pairwise comparisons between frail versus nonfrail patients within the same stratum of age resulted in a log-rank test with a *p*-value of ≤0.001 [Color figure can be viewed at wileyonlinelibrary.com]
COVID-19 prognosis in acute care settings, combined with baseline frailty. The accuracy of such a comprehensive approach in the prediction of adverse outcomes can be instrumental for both providers and fitter patients to choose more aggressive treatments when they are affected by more severe infections. Likewise, such
assessments can support decisions on avoiding burdensome interventions and prioritizing proportionate interventions, including palliative care and rehabilitation services, in frailer patients.\textsuperscript{48,49}

Our study should be interpreted in light of its limitations. First, although our findings are based on a large sample of patients with minimum missing data, they result from a study completed in a single reference hospital for severe cases of COVID-19. Therefore, our results might have limited generalizability to other levels of care (e.g., community hospitals) and settings (e.g., nursing homes). Second, we acknowledge that our method of assessing baseline frailty in an acute care setting using hospital records complemented with telephone interviews is subject to recall bias depending on the patient’s illnesses and social support. However, medical investigators trained in geriatric medicine collected such information in parallel with the admissions, followed guidelines, and used an approach documented in previous studies.\textsuperscript{31-33} This strategy was instrumental for our study’s feasibility, given the visiting restrictions and respiratory isolation measures implemented during the pandemic. Third, we did not account for differences in treatments (i.e., admission to intensive care, need for mechanical ventilation) in our analyses. Although we recognize that this decision might have introduced biases in our estimates, we find this possibility unlikely because we incorporated a widely used measure of acute disease morbidity (SOFA) in our models. In addition, managing clinicians were unaware of patients’ frailty status when making decisions on medical interventions as they had no access to our study protocol. Finally, other outcomes such as disability and quality of life are essential to understand the pandemic’s overall impact on older adults. We intend to explore these measures as we complete our long-term follow-up interviews. These discussions become even more interesting in the context of middle-aged people living with long-lasting disabilities, for whom some experts propose that the CFS criteria have adjustments.\textsuperscript{50}

In conclusion, frailty is a key predictor of COVID-19 prognosis, and its detection should not be neglected. Regardless of the challenges faced by health providers during the pandemic, they should examine baseline frailty, rather than age alone, to accurately estimate the vulnerability of SARS-CoV-2–infected patients. We believe that such an approach can be valuable in guiding evidence-based discussions on realistic goals of care and resource allocation for middle-aged and older adults hospitalized with COVID-19.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest, including financial and personal, in this study.

AUTHOR CONTRIBUTIONS
Aliberti, J. Avelino-Silva: study concept and design, acquisition of data, data analysis, data interpretation, and manuscript preparation.
Szlejf, I. Avelino-Silva, Suemoto, Apolinario, Jacob-Filho: study concept and design, data interpretation, and manuscript preparation.
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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**Data S1 Figure S1:** Distribution of the study population in the metropolitan area of Sao Paulo, according to postal code.

**Figure S2:** Scatter plots showing the correlation between Clinical Frailty Scale and Frailty Index scores.

**Figure S3:** Accuracy of the Clinical Frailty Scale (CFS) to identify frailty according to the Frailty Index. A, total sample; B, middle-aged patients; C, older patients

**Figure S4:** Scatter plots showing the correlation between frailty (CFS) and acute morbidity (SOFA)

**Table S1.** Variables and scoring of the Frailty Index.

**Table S2.** Performance of different Clinical Frailty Scale (CFS) scores to identify frailty according to the Frailty Index.

**Table S3.** Association between frailty and mortality in patients hospitalized with COVID-19 according to age groups.

**Table S4.** Interaction between frailty and acute morbidity for 6-month mortality

Members of the COVID HCFMUSP Study Group.

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