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

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

Running title: Frailty and COVID-19 prognosis

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Impact Statement:

We certify that this work is novel and advances the findings from prior work on frailty and COVID-19 prognosis. First, we determined the concurrent validity of the Clinical Frailty Scale (CFS) against the Frailty Index, a well-known frailty measure. Second, we showed the utility of the CFS in middle-aged patients. Third, 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. Finally, we demonstrated that frailty works as an effect modifier on the association between acute morbidity (SOFA score) and mortality.

Key Points

- The Clinical Frailty Scale (CFS) achieved outstanding accuracy to identify frailty compared to the Frailty Index in middle-aged and older patients admitted to the hospital with COVID-19.
- Frailty assessment provided valuable prognostic information for COVID-19 by capturing risks apart from those already associated with age, comorbidities, and acute morbidity of disease.
- A triage process contemplating frailty alongside routinely measured factors in acute care settings might support clinicians to get a more comprehensive picture of COVID-19 prognosis.

Why does this paper matter?

Frailty is a key predictor of COVID-19 prognosis, and its assessment alongside measures of acute morbidity, rather than age alone, might help clinicians in offering realistic goals of care in hospitalized patients with COVID-19.

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 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 1,830 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%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; 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 as compared to 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.

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 increased risk of hospitalization, need for mechanical ventilation, and mortality in older adults.[1,2] 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.[3-7] 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.[8,9]

Previous studies and guidelines have proposed frailty among the measures to guide resource allocation in geriatric care.[10,11] 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.[12] 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.[13-15] 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.[16] In another study on hospitalized older adults, frailty was only associated with increased mortality in participants without COVID-19.[17] 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.[2,14]

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; (3) and the concurrent validity of the Clinical Frailty Scale (CFS)[18] with a well-validated frailty measurement (Frailty Index)[19] 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.[20] 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.[21,22]

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.[23] We excluded patients discharged from the emergency department in less than 24 hours 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).[24]

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 exams. 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 exams, 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]).[25] Patients were classified as having a course duration of COVID-19 symptoms of > or ≤7 days prior to admission.[26] Comorbidities were assessed according to the Charlson Comorbidity Index (0-37),[27] 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.[26,28] 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),[29] based on the worst value of each parameter within the first 24 hours of admission. For analysis purposes, we opted to categorize the SOFA score and Charlson Comorbidity Index according to quartiles since these measures do not have standard cut-off values.

Frailty assessment

Frailty was assessed using the Clinical Frailty Scale (CFS)[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 (ADL and IADL),[30] and (d) cognition. Since CFS-specific information is rarely available in chart reviews, we achieved completed data using the telephone interviews.[31,32] To characterize 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,[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,[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 develop a Frailty Index (0-1)[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.[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 **Supplementary Table S1**. We defined frailty for Frailty Index values >0.25, as proposed in previous studies.[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.[39] We also determined the accuracy of the CFS to discriminate between frail and non-frail patients defined by the Frailty Index using areas under the receiving operating characteristic curves (AUC). We further stratified this analysis according to age (< 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. Hosmer and Lemeshow et al. 2013 proposed that AUCs of 0.80 to 0.90 are "excellent", and 0.90 or above, "outstanding".[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% CI), for each variable of interest.

Because frailty may have different meanings depending on patients' age,[14] we conducted sensitivity analyses stratifying the sample based on conventional age ranges (middle-aged=50 to 64 years, older adults=65 to 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 cut-off 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. Besides 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 2,463 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 hours (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 1,830 SARS-CoV-2-infected patients.

Participants had a median age of 66 years (IQR=59-74 years; range=50-100 years), and 58% were male (**Table 1**). According to the CFS, 494 (27%) patients were identified as having some baseline degree of frailty (CFS scores 5-8) –16% of those aged 50 to 64 years, and 36% of those aged 65 or older. Only 5 (0.3%) patients were classified as terminally ill (CFS score 9). The median of Frailty Index was 0.17 (IQR=0.11-0.25; range=0.00-0.68). CFS scores were strongly correlated with Frailty Index scores (Spearman's coefficient=0.73; 95% CI=0.71-0.75) (**see Figure S2 in the Supplement**). Moreover, the CFS presented outstanding accuracy to discriminate between frail and non-frail patients defined by a Frailty Index score >0.25 (AUC=0.94; 95% CI=0.93-0.95), with similar performances in middle-aged and older patients (**see Figure S3 in the Supplement**). Sensitivity, specificity, likelihood ratios, and predictive values for the different CFS scores are detailed in **Supplementary Table S2**. CFS scores ≥5 had the best discriminative performance to detect frailty (sensitivity=83%, specificity=92%, positive likelihood ratio=10.1).

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 days). Of the 1,106 patients discharged from the hospital, 920 (83%) returned home, and 186 (17%) were transferred to post-acute care settings. Only 4 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 to 64 years, 65 to 79 years, and ≥80 years) even after adjusting for the covariates (**Supplementary Table S3**).

We verified that CFS and SOFA scores were not correlated (Spearman's coefficient=0.02; 95% CI=-0.03-0.06) (**Supplementary Figure S4**). Furthermore, frailty modified the association between SOFA quartiles and 6-month mortality, with a *P*-value for interaction=0.01 (**Supplementary 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 over 65 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.[9,21] However, previous studies have demonstrated how older adults can run divergent courses of COVID-19.[20,41] 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.[7,21] 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.[42] 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,[15-17, 43-45] 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.[33] 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%).[46] Although the CFS was not a strong predictor of mortality across all studies,[16,43] 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,[13,15,44] 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.[14,34] 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 pre-admission health status, might be a more powerful predictor of long-term 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 isolatedly 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 COVID-19 prognosis

in acute care settings, combined with baseline frailty.[15,43] 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.[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.[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. While we recognize that this decision might have introduced biases in our estimates, we find this possibility unlikely since 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 people living with disabilities, for whom some experts propose that the CFS criteria have adjustments.[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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Conflicts 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.

Dias, Garcez, Trindade, Amaral, Melo, Aguiar, Coelho, Hojaij, Saraiva, Silva: study concept and design, acquisition of data, and manuscript preparation.

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Figure Legends

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 cut-off of 5 defining patients as frail.

All pairwise comparisons between frail vs. non-frail patients within the same stratum of age resulted in a log-rank test with a *P*-value of ≤0.001.

Figure 2. Kaplan-Meier survival curves over 6 months, according to levels of acute morbidity and frailty status

SOFA = Sequential Organ Failure Assessment

Quartiles defined SOFA categories (0-24), which assessed COVID-19 acute morbidity. Frailty was evaluated using the Clinical Frailty Scale (0-9), with a cut-off of 5 defining patients as frail.

All pairwise comparisons between frail vs. non-frail patients within the same SOFA stratum resulted in a log-rank test with a *P*-value of <0.001.

Table 1. Baseline characteristics of middle-aged and older adults hospitalized with COVID-19 (N = 1,830)

Characteristics	N (%) or median (interquartile range)
Sociodemographic factors	
Age (years)	66 (59, 74)
Age	
50 - 64 years old	831 (45)
65 - 79 years old	758 (42)
≥ 80 years old	241 (13)
Men	1061 (58)
Race or Ethnicity	
White	1172 (64)
Black	154 (9)
Mixed	460 (25)
Other	44 (2)
Education less than 8 years	1148 (63)
Comorbidities	
Chronic obstructive pulmonary disease	146 (8)
Hypertension	1264 (69)
Heart failure	279 (15)
Coronary artery disease	261 (14)
Diabetes	802 (44)
Chronic kidney disease (moderate to severe)	295 (16)
Cerebrovascular disease	153 (8)
Dementia	92 (5)
Cancer	298 (16)
Charlson Comorbidity Index score (0-37)	1.5 (0, 4)
Behavior measure	
Smoking status	
Never	1257 (69)
Former	478 (26)
Current	95 (5)
Acute disease	
Days of symptoms	7 (5, 10)
C-reactive protein (mg/L)	133 (68, 223)
Sequential Organ Failure Assessment (SOFA; 0-24)	6 (4, 10)
Frailty	
Clinical Frailty Scale (1-9)	
Very Fit (1)	94 (5)
Fit (2)	291 (16)
Managing Well (3)	657 (36)
Vulnerable (4)	294 (16)
Mildly Frail (5)	207 (11)
Moderately Frail (6)	148 (8)
Severely Frail (7)	115 (6)
Very Severely Frail (8)	19 (1)
Terminally Ill (9)	5 (0)
Frailty Index (0-1)	0.17 (0.11, 0.25)

Table 2. Association between risk factors and mortality in middle-aged and older adults hospitalized with COVID-19

	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
Age						
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						
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						
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						
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						
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						
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						
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						
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						
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)
Clinical Frailty Scale						
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)

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

Table 3. Mortality in patients hospitalized with COVID-19 according to levels of acute morbidity and frailty status

	6-month mortality				
	N died / N total (%)	Hazard ratio (95% confidence interval)			
SOFA | CFS [a]		**Crude**	***P*-value** [b]	**Adjusted**	***P*-value** [b]
SOFA 0-3 | Non-frail	35/343 (10)	(reference)		(reference)	
SOFA 0-3 | Frail	40/107 (38)	4.4 (2.8-6.9)	<0.001	3.3 (2.1-5.2)	<0.001
SOFA 4-5 | Non-frail	104/328 (32)	3.6 (2.4-5.3)		3.2 (2.2-4.7)	
SOFA 4-5 | Frail	77/135 (57)	7.6 (5.1-11.3)	<0.001	4.7 (3.1-7.1)	<0.001
SOFA 6-9 | Non-frail	150/318 (47)	5.9 (4.1-8.6)		5.1 (3.5-7.4)	
SOFA 6-9 | Frail	99/136 (73)	12.5 (8.5-18.4)	<0.001	7.8 (5.2-11.6)	<0.001
SOFA ≥10 | Non-frail	233/347 (67)	10.3 (7.2-14.8)		9.7 (6.7-13.9)	
SOFA ≥10 | Frail	103/116 (89)	19.5 (13.3-28.7)	<0.001	13.6 (9.2-20.2)	<0.001

SOFA = the Sequential Organ Failure Assessment

Estimates were calculated using Cox proportional hazards models. The adjusted model included age, sex, race or ethnicity, education, Charlson Comorbidity Index, smoking status, days of COVID-19 symptoms, and C-reactive protein levels.

[a] Quartiles defined SOFA categories (0-24), which assessed COVID-19 acute morbidity. Frailty was evaluated using the Clinical Frailty Scale (0-9), with a cut-off of 5 defining patients as frail.

[b] Pairwise comparisons between frail vs. non-frail patients within the same stratum of SOFA.

Supporting Information

Additional Supporting Information may be found in the Supplementary Material available online:

Members of the COVID HCFMUSP Study Group

Figures

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

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

Supplementary 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

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

Tables

Supplementary Table S1. Variables and scoring of the Frailty Index

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

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

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