Special issue on Infectious Disease: From Prevention to Management

Comorbidities predict 30-day hospital mortality of older adults with COVID-19

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ABSTRACT

We evaluated whether comorbidities predict disease severity and mortality in a cohort of 147 older adults with COVID-19. Patients were divided into three groups according to the Charlson Comorbidity Index (CCI) score. Groups 2 (CCI $4 − 5$) and 3 (CCI ≥ 6) had higher 30-day mortality rate as compared to group 1 (CCI ≤ 3). Cox regression showed that even after adding sex, National Early Warning Score (NEWS) 2 score and the need for intensive care unit admission to the model, no significant changes were found in the mortality risk predicted by the CCI score, showing that chronic pathologies are key determinants of short-term survival in COVID-19. This work is important for the geriatric nursing field as it demonstrates that alternative approaches for clinical decision-making that consider the comorbidities, rather than only chronological age, can be especially significant for the management of COVID-19 patients' hospitalization.

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Introduction

Over one year has passed since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first described, and yet only a slight improvement in controlling the viral spread has been reported.[1] With more than 100 million reported cases of infection, the coronavirus 2019 disease (COVID-19) reached pandemic status in March 2020, imposing an extensive burden on public life and health care worldwide.[2]

After a relatively short period of incubation, most SARS-CoV-2 infected individuals develop mild to moderate influenza-like symptoms and about 20% of them develop a severe inflammatory-mediated hypoxemic disease that resembles a cytokine-storm syndrome.[3] Most cases involve men, aging between 30 and 79 years, with one or more coexisting medical conditions.[4−8] According to a systematic review, the most prevalent associated diseases are hypertension (32%), obesity (25%), diabetes (18%), and cardiovascular disease (16%), whereas COVID-19 patients with chronic kidney or other renal diseases (51%, 44%), cerebrovascular accident (43%, 44%), and cardiovascular disease (44%, 40%) had more severity and mortality respectively. Additionally, substantial variation in the prevalence of comorbidities and associated disease severity and mortality in different geographic regions was observed, with the highest mortality in Latin American and European patients with any medical condition, mostly male older adults.[9]

Moreover, studies have also shown that older adults are more likely to develop severe respiratory disease that requires hospitalization or even die.[6] However, we frequently observe in clinical practice that the disease become more intense depending upon the number of clinically significant comorbidities, rather than age itself.[10] Thus, considering that older adults face a greater number and severity of different chronic diseases, as well as immune disfunction,[11] the purpose of the present study was to determine whether a Charlson Comorbidity Index (CCI) would reflect disease severity and all-cause 30-day mortality in a cohort of older adults with COVID-19.

Methods

Study design, participants and setting

This is an ongoing observational study conducted at the University Hospital of the Federal University of São Carlos (HU-UFSCar). In this report, 147 patients with 60 years and older admitted for COVID-19 to the respiratory ward were included in the analysis. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the UFSCar's Research Ethics Committee (Number: 30184220.8.0000.5504). Written informed consent was obtained from all subjects. Data were collected through in-person interviews of the study population, and there were no exclusion criteria that were explicitly listed. In this analysis, we used only patients with 60 years and older with complete follow-up information. Cases with missing values were list-wise deleted.

Study assessments

Patients were assessed daily from day 0 up to hospital discharge or 30 days of hospitalization (if not discharged). Sociodemographic, clinical characteristics, and baseline National Early Warning Score (NEWS) 2 and Sequential Organ Failure Assessment (SOFA) for clinical deterioration were obtained at hospital admission. For each patient, we evaluated Charlson Comorbidity Index (CCI) as an ordinal variable with three classes: group 1 (CCI score ≤ 3), group 2 (CCI score 4 − 5), and group 3 (CCI score ≥ 6). Pre-hospital frailty, measured by Clinical Frailty Scale (CFS), was defined as a score ≥ 5 according to this scale.[12] Clinical and laboratory data were also reviewed. Patients were categorized as mild, moderate, and severe and received standard of care treatment for COVID-19 as the latest recommendations set forth by the WHO's COVID-19 Clinical management living guidance.[2]

Sample size and statistical analysis

Based on previous studies on the association between CCI score and mortality in COVID-19 patients, we calculated a sample size of at least 40 participants per group assuming a hazard risk (HR) for mortality of at least 1.85 in the CCI score > 3 groups as compared to the CCI score ≤ 3 groups, with 80% of power and an alpha error of 5%.[13]

Continuous data are presented as mean ± standard deviation or median [1st, 3rd quartile] according to the Shapiro-Wilk test of normality. Categorical variables are presented as counts (percentages). Comparisons between groups were performed using Kruskal-Wallis test followed by Bonferroni-Dunn's Post Hoc test for continuous variables, and Fisher test followed by Bonferroni correction for categorical variables. The overall survival probability was estimated by Kaplan-Meier analysis and compared between the groups by log rank's test. The hazard risk (HR) and 95% confidence interval (CI) of mortality as a function of sex, NEWS2 at hospital admission, need for ICU admission during hospitalization and CCI score was estimated using Cox proportional hazards regression models. Statistical significance was assessed at a two-sided p value < 0.05. All analyses were conducted using R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) in R-Studio 1.3.1093 (RStudio Inc., Boston, USA).

Results

A total of 147 adults were included in this study. Mean age was 74.9 years old (range, 60−99 years) and half of the subjects were females (50.3%). Most of the subjects were hypertensive (61.2%) and frail (64.6%), but not diabetic (40.1%) nor they had cardiovascular diseases (23.8%), nor chronic lung diseases (17.7%), nor they were affected by dementia (11.6%). Table 1 summarizes overall baseline demographic and clinical characteristics of the study sample.

The median time from symptom onset to hospital admission was 7.5 [5, 11] days, and more than a half of the patients were classified as having a severe disease on admission. Almost a half (44.2%) of the patients were admitted to the intensive care unit, and about a fifth (21.1%) died. The median number of comorbidities was 2 [1, 3], as shown in Fig. 1. The median CCI was 2 [0 - 4], and almost a half (44.9%) of the subjects presented high comorbidity index (≥ 5).

Table 2 lists overall 30-day hospital outcomes and by CCI group. The patients' distribution into the CCI groups was 27.9%, 27.2%, and 44.9%, respectively. Groups were rather similar, except for age and 30-day mortality. The primary outcome of interest, defined as all-cause 30-day mortality, was observed in 7.3% of the patients in group 1, 22.5% in group 2, and 28.8% in group 3. A significant difference in mortality was noted only between the group 1 and the others (p = 0.06 and p = 0.007 in pairwise comparisons with group 2 and 3, respectively). (Fig. 2).

Table 1
Baseline demographic and clinical characteristics of the study sample.

Feature	Overall (N=147)
Age, years	74.9 ± 9.9
Female sex	74 (50.3)
Charlson Comorbidity Index (CCI)	4 [3, 6]
CCI score ≤ 3	41 (27.9)
CCI score 4 − 5	40 (27.2)
CCI score ≥ 6	66 (44.9)
Comorbidities	
Arterial hypertension	90 (61.2)
Cardiovascular disease	35 (23.8)
Diabetes	59 (40.1)
Chronic lung diseases	26 (17.7)
Dementia	17 (11.6)
Clinical Frailty Scale	5 [4, 7]
Frail	95 (64.6)
Time from symptom onset to hospital admission, days	7.5 [5, 11]
NEWS2 on admission	5 [3, 7]
SOFA on admission	3 [2, 3]
Disease severity on admission	
Mild	9 (6.1)
Moderate	58 (39.5)
Severe	80 (54.4)
Laboratory tests on admission	
AST (U/L)	35 [28, 51]
ALT (U/L)	25 [18, 40.5]
Alkaline phosphatase (U/L)	65.5 [50, 81]
Gamma-Glutamyl Transferase (U/L)	49 [31, 106]
Total bilirubin (mg/dL)	0.6 ± 0.3
Albumin (g/L)	3.2 ± 0.5
Lymphocyte count (x10^9/L)	0.963 [0.661, 1.396]
Platelets (x10^9/L)	215 [168.5, 276]
D−dimer (μg/mL)	1620 [700, 2890]
Lactate dehydrogenase (U/L)	321 [245, 456]
C-reactive protein	9.6 [4.0, 18.1]
Albumin to Globulin ratio	1.13 [0.97, 1.29]
Neutrophil to Lymphocyte ratio	6.75 [4.06, 9.84]

Continuous data are presented as mean ± standard deviation or median [1st, 3rd quartile]. Categorical variables are presented as counts (percentages).

The Kaplan-Meier curves for survival probability are shown in Fig. 3. Patients from groups 2 and 3 presented a lower survival rate with faster time-to-event as compared to group 1 (p = 0.009 at overall log-rank test). Subgroup analysis showed a significant difference between groups 1 and 2 (p = 0.03) and groups 1 and 3 (p = 0.005). No significant difference in survival rate was found between groups 2 and 3. Cox regression model showed that the CCI score predicts 30-day mortality among older adults with COVID-19 (HR = 1.27, 95% CI 1.01 to 1.60; p = 0.03). We also estimated the HR adjusted (aHR) for sex, NEWS2 score at hospital admission and the need for ICU admission during hospitalization (Table 3). Adding these variables to the model, since they are not included in CCI and could influence the outcome, resulted in no significant changes in the hazard risk predicted by the model (aHR = 1.33, 95% CI 1.04 to 1.70; p = 0.01).

Discussion

This retrospective study demonstrated that a high comorbidity index is independently associated with 30-day hospital mortality rate, implying that chronic pathologies and less functional reserve are key determinants of short-term survival in COVID-19 patients.

Some epidemiological studies have shown that the mortality pattern of COVID-19 patients has strong associations with age, besides pre-existing comorbidities and male-sex,[14,15] while others report that older age, severity of respiratory failure and renal impairment at presentation, but not comorbidities, are predictors of 28-day mortality in these patients.[16] Notably, a recent study showed that an age-adjusted CCI (aCCI) threshold > 3.5 yielded the best cut-off point for
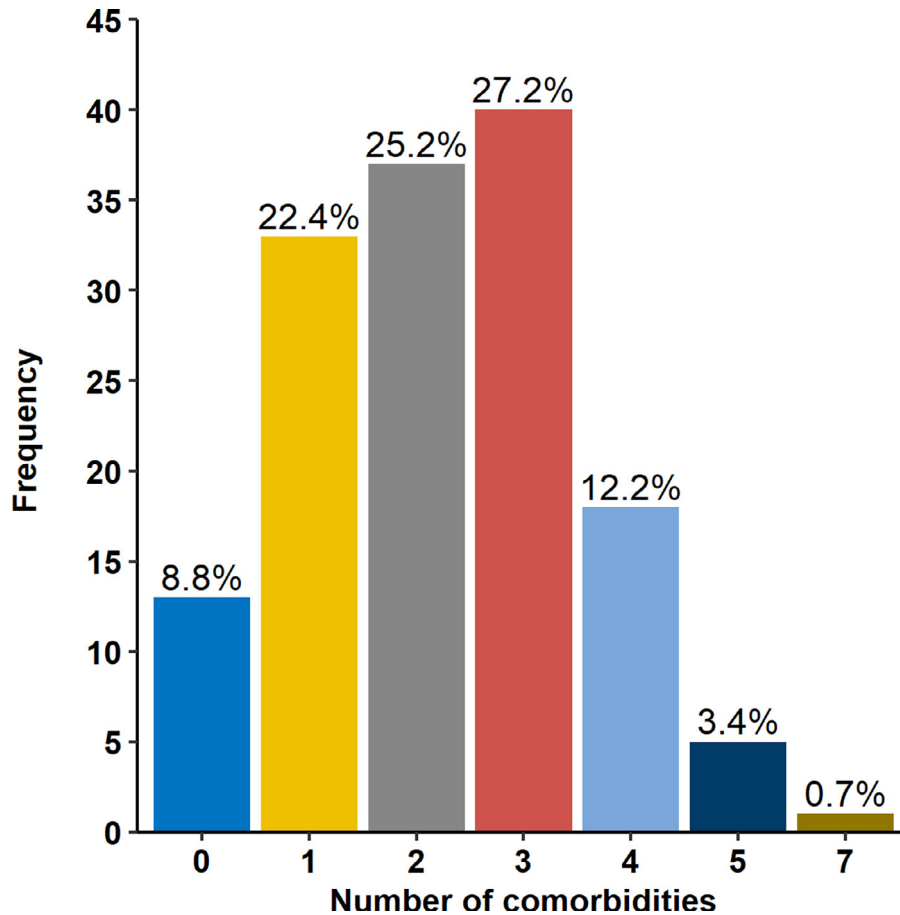
Fig. 1. Observed frequency of comorbidities in the study sample.

Table 2
Characteristics of the 30-day hospital outcomes by CCI group.

Feature	CCI score ≤ 3(n=41)	CCI score 4 − 5(n=40)	CCI score ≥ 6(n=66)	p
Age, years	66.4 ± 4.8	74.1 ± 9	80.7 ± 8.8	<0.001[abc]
Female sex	19 (46.3)	20 (50)	35 (53)	0.8
Disease severity				0.6
Mild	4 (9.8)	1 (2.5)	4 (6.1)	
Moderate	14 (34.1)	18 (45)	26 (39.4)	
Severe	23 (56.1)	21 (52.5)	36 (54.5)	
Time from symptom onset to hospital admission, days	8 [6, 10]	8 [5, 10]	7 [5, 12]	0.8
Length of hospital stay, days	16 [7, 26]	11 [5, 17.5]	10 [5, 19]	0.3
Need for ICU admission during hospitalization	21 (51.2)	18 (45)	26 (39.4)	0.5
30−day mortality	3 (7.3)	9 (22.5)	19 (28.8)	0.02[c]
Admission to ICU or death	21 (51.2)	19 (47.5)	33 (50)	0.9

Continuous data are presented as mean ± standard deviation or median [1st, 3rd quartile]. Categorical variables are presented as counts (percentages)

predicting mortality in COVID-19 patients,[17] whereas other studies have shown that neither comorbidities nor chronological age were powerful predictors of disease prognosis and outcomes.[18] All these findings can result from different study designs and/or populations, or due to the influence of confounding factors. Nevertheless, they point out to the vast outcomes heterogeneity among persons infected with SARS-CoV-2 and highlight how much we still need to understand from this complex disease.

Aging and comorbidities are characterized by a higher basal proinflammatory status (*inflammaging*) linked with a progressive failure of the immune system to initiate proper responses (*immunosenescence*).[19] An age-related gut dysbiosis has also been reported as cause of an imbalanced immune response and overreactive inflammatory phenotype in SARS-CoV-2 infection.[20] Moreover, other factors such as age-related increase in endothelial damage and changes in clotting function; higher density, increased affinity and different distribution of angiotensin converting enzyme 2 (ACE2) receptors and transmembrane serine protease 2; lower vitamin D levels;[21] and mitochondrial disfunction are also proposed as conditions that increase the severity of the disease in older adults.[22]

Having in mind that the age of COVID-19 patients has been proposed as a way to determine who will receive intensive care admission when critical care resources are limited,[23] this work provides evidence that an alternative approach may be adopted, considering the comorbidities of the patients, rather than only their age and arguing against the idea that few-sizes-fit-all decision-making resolutions. This observation can be especially important in aged but healthy older adults, who have been described as having much lower
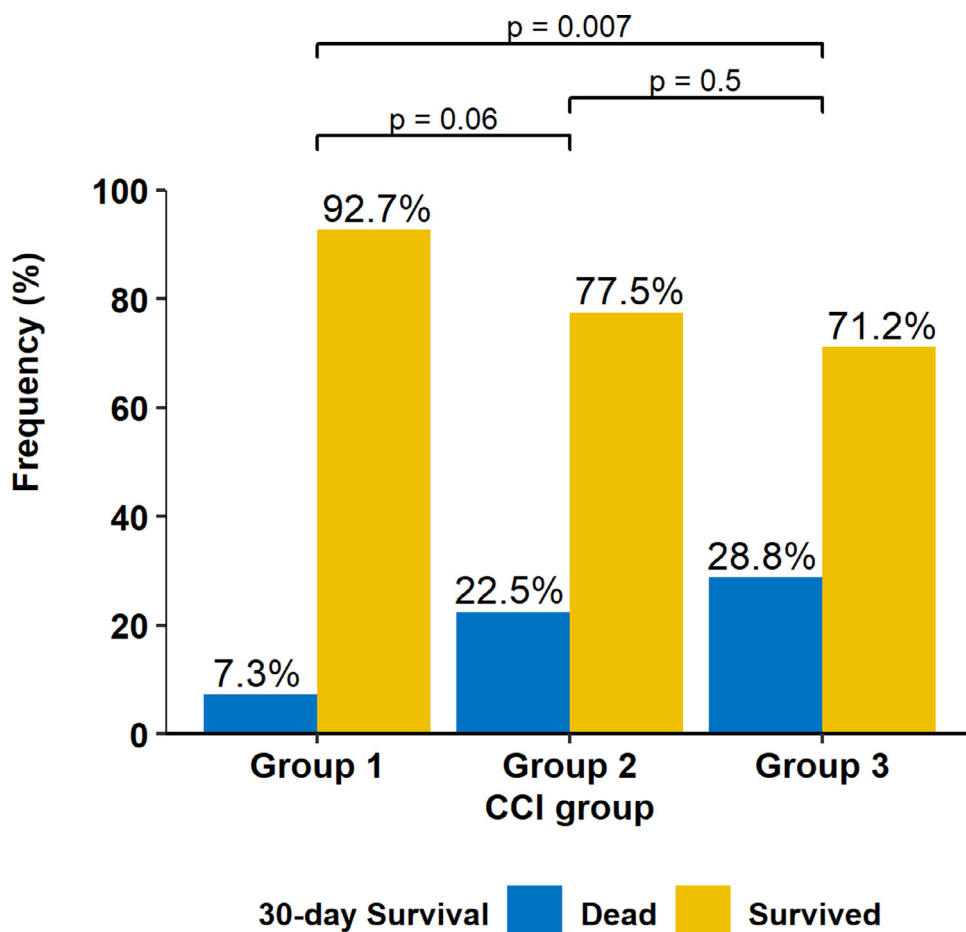
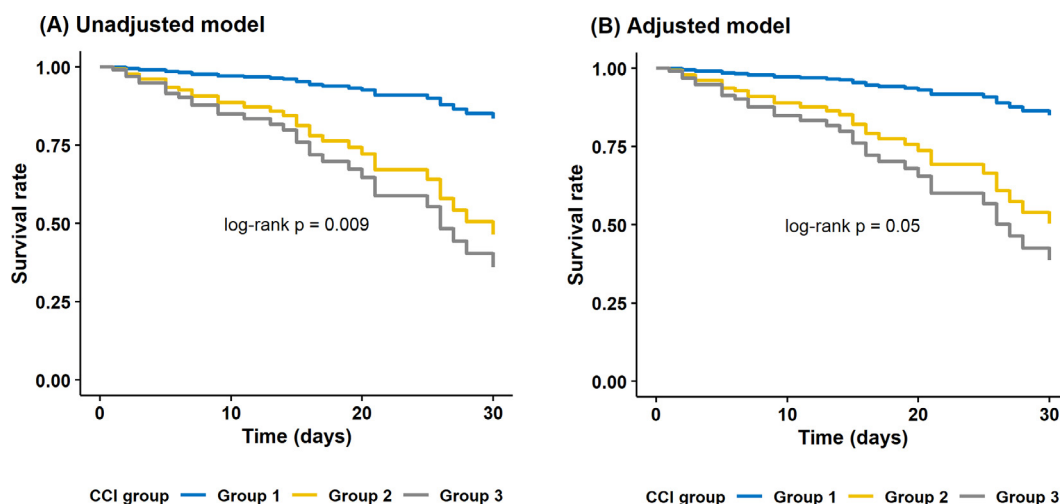**Fig. 2.** Distribution of 30-day mortality depending on CCI group.

Fig. 3. Kaplan-Meier analysis for survival probability: (A) unadjusted curve; (B) adjusted curve for age and disease severity on hospital admission.

risk of COVID-19 mortality.[24] Accordingly, in older adults without comorbidities, age was not a predictor of disease severity with structural factors, such as poverty and low socioeconomic status, playing a larger role. Notably, in the same study, mortality prediction in individuals without comorbidities improved only marginally when considering chronological age added to structural factors.[25]

Our results can contribute to avoid negative age stereotypes associated with older persons' rejection of COVID-19 hospitalization.[26]

This is in strong agreement with previous works,[25,27] showing that age alone is not enough to drive decisions to limited health-care resources during COVID-19 pandemic.

There are some limitations in this study, which include its single-centered characteristic and the relatively small sample size, which may limit the interpretation of the results. In addition, information on medical history, symptom onset, severity of each comorbidity, socioeconomic status, as well as specific treatment received before

Table 3
Cox regression for modeling the 30-day mortality risk.

Feature	aHR	95% CI	p
Sex			
Female	Reference	-	-
Male	1.09	0.51 – 2.35	0.8
NEWS2 at hospital admission	0.93	0.82 – 1.07	0.3
Need for ICU admission during hospitalization	1.62	0.63 – 4.14	0.3
Charlson Comorbidity Index (CCI)	1.33	1.04 – 1.70	0.01

Abbreviations: aHR, Adjusted Hazard Ratio; 95% CI, 95% Confidence Interval.

admission to hospital reported by the patients are susceptible to bias. Despite these limitations, the use of appropriate statistical tools allowed to identify comorbidity as an independent factor associated with 30-day hospital mortality in COVID-19 patients.

Conclusion

Chronic pathologies and less functional reserve are key determinants of short-term survival in COVID-19, rather than age itself. Taken together, these findings suggest that not all older patients have the same prognosis, and point to the importance to consider comorbidities, rather than only their age for clinical decision-making regarding COVID-19. This can be especially important for healthy older adults and contribute to avoid negative age stereotypes associated with rejection of COVID-19 hospitalization.

Funding

Declaration of Competing Interest

None.

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