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Archives of Gerontology and Geriatrics 94 (2021) 104331

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Predictors for development of critical illness amongst older adults with COVID-19: Beyond age to age-associated factors

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ARTICLE INFO

Keywords:
Frailty
COVID-19
Geriatric assessment

ABSTRACT

Introduction: Older adults with COVID-19 have disproportionately higher rates of severe disease and mortality. It is unclear whether this is attributable to age or attendant age-associated risk factors. This retrospective cohort study aims to characterize hospitalized older adults and examine if comorbidities, frailty and acuity of clinical presentation exert an age-independent effect on COVID-19 severity.

Methods: We studied 275 patients admitted to the National Centre of Infectious Disease, Singapore. We measured: 1)Charlson Comorbidity Index(CCI) as burden of comorbidities; 2)Clinical Frailty Scale(CFS) and Frailty Index (FI); and 3)initial acuity. We studied characteristics and outcomes of critical illness, stratified by age groups (50–59,60–69 and ≥70). We conducted hierarchical logistic regression in primary model($N = 262$, excluding direct admissions to intensive care unit) and sensitivity analysis($N = 275$): age and gender in base model, entering CCI, frailty (CFS or FI) and initial acuity sequentially.

Results: The ≥70 age group had highest CCI($p<.001$), FI($p<.001$) and CFS($p<.001$), and prevalence of geriatric syndromes (polypharmacy,53.5%; urinary symptoms,37.5%; chronic pain,23.3% and malnutrition,23.3%). Thirty-two (11.6%) developed critical illness. In the primary regression model, age was not predictive for critical illness when a frailty predictor was added. Significant predictors in the final model (AUC 0.809) included male gender ($p=.012$), CFS ($p=.038$), and high initial acuity ($p=.021$) but not CCI or FI. In sensitivity analysis, FI ($p=.028$) but not CFS was significant.

Conclusions: In hospitalized older adults with COVID-19, geriatric syndromes are not uncommon. Acuity of clinical presentation and frailty are important age-independent predictors of disease severity. CFS and FI provide complimentary information in predicting interval disease progression and rapid disease progression respectively.

1. Introduction

The COVID-19 pandemic has infected 43.4 million people globally and caused over 1 million deaths(Organization, 2020). Reports across different regions consistently demonstrate disproportionately higher rates of severe disease and fatalities in older persons above 60 years old (ranging from 32.7% to 81.3% and 4.5% to 18.8%, respectively) (Bonanad et al., 2020; Livingston & Bucher, 2020; Richardson et al., 2020; Tomlins et al., 2020; Wang et al., 2020). Older adults are also more likely to exhibit greater disease acuity at presentation such as dyspnea and tachypnea (Niu et al., 2020). Whilst it is important to highlight the dangers of COVID-19 in the vulnerable elderly and the rationale behind public health measures to reduce the risk of exposure (Lim et al., 2020), over-emphasis of poor outcomes in elderly can have

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https://doi.org/10.1016/j.archger.2020.104331
Received 7 November 2020; Received in revised form 14 December 2020; Accepted 22 December 2020
Available online 24 December 2020
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unintended repercussions, including bias against the elderly population in receiving intensive care treatment (Le Couteur, Anderson, & Newman, 2020) or opportunities to be involved in clinical trials (Lithander et al., 2020).

Three gaps in the body of evidence about COVID-19 in older people stand out. Firstly, there is a relative paucity of studies which specifically focus on the older person. The few studies which characterize COVID-19 in older adults are descriptive studies, revealing the differences in clinical characteristics of younger and older patients with COVID-19 (Liu et al., 2020; Medetalibeyoglu et al., 2020), and the young-old and old-old (Guo et al., 2020).

Secondly, relevant variables in older adults such as functional ability and frailty are conspicuously missing. Frailty (Morley et al., 2013) increases with age and has been shown to predict adverse outcomes in inpatient and intensive care settings (Kojima, Iliffe, & Walters, 2018; Muscedere et al., 2017). Recently, published studies on frailty and COVID-19 had differing results. Frailty is associated with mortality in a study of patients ≥18 years with COVID-19 (Hewitt et al., 2020) while another study in patients ≥85 years old reported that frailty was only weakly associated with mortality, with majority of frail patients (72%) surviving the infection (De Smet et al., 2020). As such, it is still unclear if high severity rates and mortality rates in older adults are associated with age or a reflection of attendant age-associated risk factors of frailty, comorbidities and increased acuity of illness (Abbatecola & Antonelli-Incalzi, 2020).

Lastly, extant literature typically report an in-hospital mortality rate that is much higher than the case fatality rate (Sun et al., 2020; Zhao, Huang, & Huang, 2020). Because in-hospital mortality is a complex outcome in older adults that may reflect, inter alia, the influence of myriad factors such as medical management, healthcare resources and advance care planning, it is important to examine more proximal outcomes of disease progression (Guan et al., 2020; Hou et al., 2020) such as development of critical illness (Liang et al., 2020) beyond mortality per se for accurate delineation of prognosis.

Taken together, this highlights the need for specific studies using appropriate outcomes in older adults with COVID-19 to examine whether prognosis is determined by age or age-associated factors. Examining trends within each age stratum allows us to understand the reasons why some patients deteriorate whereas others of the same age group do not. Thus, the aims of this retrospective cohort study amongst older persons aged ≥ 50 years with laboratory-confirmed COVID-19 are two-fold: (i) to characterize co-morbidities, functional status, geriatric syndromes, acuity of clinical presentation and outcomes across age strata; and (ii) to examine if comorbidities, frailty and initial acuity exerted an age independent effect on disease severity of COVID-19. Greater understanding will guide management in a person-centered approach which takes into account three key biomedical factors: i) the degree of frailty, ii) severity of the presenting acute illness, iii) the likelihood of medical interventions being successful (Hubbard et al., 2020).

2. Methods

2.1. Study design and participants

We studied patients ≥ 50 years of age with confirmed COVID-19 infection who were admitted to the National Centre of Infectious Disease in Singapore between the period of 23 January to 15 April 2020. The outbreak response of the Ministry of Health during that period required all patients with newly confirmed COVID-19 infection to be admitted to hospital isolation facilities in hospitals for monitoring and stabilization, before transferring to community isolation facilities. Diagnosis was confirmed by means of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA of respiratory specimens (Young et al., 2020). Waiver of informed consent was granted by Ministry of Health (Singapore) under the Infectious Diseases Act as part of the COVID-19 outbreak investigation.

2.2. Data collection

Data from electronic health records was summarized using standardized data collection forms. Two researchers independently reviewed the data collection forms for accuracy. Demographic information, underlying comorbidities, symptoms, number of days of symptoms till presentation, vital signs, and laboratory findings were collected from medical and nursing records. In our study, functional assessment evaluated both basic activities of daily living (such as feeding, toileting, bathing, and mobility) as well as instrumental activities of daily living (such as ability to take one's medications). We also evaluated geriatric syndromes in terms of urinary symptoms, chronic pain, memory problems, dementia, nutrition, and polypharmacy. Nutritional data was routinely recorded using the Nutritional Screening Tool, which has been locally validated to identify malnourishment in hospitalized older adult patients (Y. P. Lim, Lim, Tan, & Daniels, 2008). These functional assessment and geriatric syndrome components form part of comprehensive geriatric assessment and were routinely assessed by the medical and nursing teams for all admissions. This allows early identification of needs so that a comprehensive care plan can be made for these patients.

We measured burden of comorbidities using the Charlson's Comorbidity Index (CCI) (Charlson, Pompei, Ales, & MacKenzie, 1987). High acuity of clinical presentation was defined as presence of any of the following: symptoms of dyspnea, temperature >38 °C, systolic blood pressure <100 mmHg, or heart rate > 100 beats per minute. Cutoffs for vital sign derangement were derived from the modified Severity of Illness Index, a validated 4-level burden of illness measure (Wong, Sahadevan, Ding, Tan, & Chan, 2010). The advantage of using vital signs and presenting symptom as a measure of illness acuity is that it can assessed quickly without the need for laboratory and radiological data.

2.3. Assessments of frailty

Prior studies reported significant variability between commonly used frailty scales. To achieve a comprehensive and complementary understanding of the impact of frailty on disease progression, we measured the Clinical Frailty Scale (CFS) and Frailty Index (FI), two complementary frailty assessment tools which showed good agreement from earlier studies (Theou, Brothers, Mitnitski, & Rockwood, 2013).

2.3.1. Clinical frailty scale

The CFS requires assessors to assign appropriate scores based on information from a comprehensive geriatric assessment about the level of functioning in activities of daily living (Rockwood et al., 2005). CFS afforded a global assessment of the overall frailty status. Because CFS in this study was scored retrospectively using information available in the electronic health records, this may exacerbate the inherent subjectivity in CFS scoring. To mitigate this, we assigned the CFS rating using a standardized algorithm (CFS-A) which was previously validated (Chong et al., 2019). The CFS-A was found to have excellent interrater reliability, as well as good diagnostic performance and predictive validity compared with standard CFS. Two raters independently assigned CFS based on the electronic health records. Discrepancies in CFS scoring were resolved through discussion, with adjudication by a third rater if necessary for unresolved discrepancies. All three raters were experienced in CFS scoring in their clinical practice. When scoring the CFS, the raters were blinded to the study hypotheses and FI score.

2.3.2. Frailty index

The FI is a multi-domain measure of frailty based on the deficit accumulation model (Jones, Song, & Rockwood, 2004), whereby the number of deficits accumulated is more important than the nature of deficit. FI is less influenced by missing variables in any one particular domain compared with physical performance-based models of frailty

(Theou et al., 2013), and has been used as the 'gold standard' in studies that compare frailty scales (Chong et al., 2019). We created a 32-item FI (Supplement: Table A1) in accordance with pre-specified criteria (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008) and modified from a prior FI construct developed for earlier studies in the acute geriatrics setting (Chew, Lim, Chong, Ding, & Tay, 2017; Chong et al., 2019). The FI comprised medical comorbidities, premorbid function in activities of daily living, laboratory markers (serum albumin and hemoglobin levels at admission) and geriatric syndromes such as malnutrition and impaired cognition. The items were further categorized into 3 domains: i) Functional (total 8 items), (ii) Medical (total 12 items), and (iii) Geriatric Syndromes (total 12 items). Each item was scored as present (1 point) or absent (0 point). We summed the items to obtain the respective domain scores and calculated the FI score by dividing the sum of all 3 domain scores by 32.

2.4. Outcome of critical illness

Case definition of critical illness is adopted from a previous study and refers to the development of any of the following outcomes: needing high flow oxygen, admission to intensive care unit (ICU), non-invasive or invasive mechanical ventilation, or death (Hou et al., 2020).

2.5. Statistical analysis

Continuous variables in our data were non-normally distributed and expressed as medians and inter-quartile ranges (IQR). Categorical variables were expressed as counts and percentages (n,%). Kruskal-Willis test to compare medians in non-normally distributed data and Chi-square test for categorical variables. We stratified participants into three age groups (50–59 years, 60–69 years and 70 years or greater) to analyze differences between age groups.

We determined a-priori to assess predictors of participant characteristics (age and gender), co-morbidity burden (CCI), frailty (CFS or frailty index) and acuity of initial clinical presentation, guided by previous literature of COVID-19 in the elderly.(Le Couteur et al., 2020; Lim et al., 2020; Lithander et al., 2020; Liu, Chen, Lin & Han, 2020) We conducted hierarchical logistic regression analysis to ascertain the comparative influence of these predictors on critical illness, with separate models for CFS and FI. We assessed these frailty scales in separate multi-variate logistic regression models in order to study their relative contribution to outcomes and to avoid multi-collinearity in the regression analysis. The base model (Model 1) comprised unmodifiable predictors of age and gender. Male gender has been consistently shown to predict worse outcomes in earlier studies (Jin et al., 2020; Meng et al., 2020). In Model 2, CCI was added. As patients with severe COVID-19 tend to have more co-morbidities (Yang et al., 2020), we used CCI, instead of individual comorbidities, to reflect comorbidity burden. In Model 3, we adjusted for frailty (either CFS or FI), whilst acuity of clinical presentation was added in the final model (Model 4). We reported the McFadden Pseudo-R^2 and area under curve (AUC) for each step. We also evaluated for the degree of multicollinearity of the predictor variables in the regression model by assessing the tolerance and variance inflation factor (VIF). Generally, if the value of tolerance is less than 0.1 and, simultaneously, the value of VIF 10 and above, then the multicollinearity is problematic.

We excluded patients who were intubated in Emergency Department (ED) or admitted directly to ICU at presentation from the primary model, as the rapid deterioration might indicate the outcome of critical illness at presentation. We conducted sensitivity analysis by repeating hierarchical logistic regression analysis without excluding these patients. We ascertained if there were differences in characteristics between excluded patients from those who developed interval deterioration in the general wards. Two sided tests of significance were used with level of significance at 5%. Statistical analysis was performed on STATA version 14.2.

3. Results

3.1. Characteristics and outcomes stratified by age-group (Table 1)

Amongst 275 patients who were recruited, the median age was 59 years (IQR 54–66 years), with the majority (50.5%) in the 50–59 age group, followed by 60–69 (33.8%) and ≥70 (15.6%) age groups. There was significant increase in co-morbidities across the age strata, with the highest CCI score in the ≥ 70 age group (median 1, $p<.001$). One hundred and twenty-six (45.82%) patients presented with high illness acuity. There was no difference in prevalence of high acuity at presentation across the age strata ($p=.945$). The ≥70 age group had the fewest days of symptoms to presentation (median 3, $p<.04$).

The patients were fairly robust with low CFS (median 3, IQR 2–3) and FI (median 0.031, IQR 0–0.094). CFS and FI scores increased across age strata, with highest scores for CFS (median 3, $p<0.001$) and FI (median 0.16, $p<0.001$) in the ≥70 age group. The majority of patients who needed assistance with activities of daily living such as feeding, toileting, bathing and transfers were in the ≥70 age group. The most common geriatric syndromes were polypharmacy (26.55%), presence of urinary symptoms (9.43%), chronic pain (7.64%) and risk of malnutrition (6.91%). The ≥ 70 age group had the highest prevalence rates of polypharmacy (53.4%), urinary symptoms (37.5%), chronic pain (23.26%), memory problems or dementia (13.95%), and risk of malnutrition (23.3%).

Thirty-two (11.64%) patients had critical illness. Compared with 50–59 age group, the prevalence of critical illness in the 60–69 age group (17.2%) increased by 5-fold while that in the ≥70 age group increased 7-fold (25.58%, $p<.001$).

3.2. Critical illness: primary model (Table 2)

We excluded 13 patients who were intubated in ED or admitted directly to ICU. They were older (median age 64, $p=.03$), had higher CCI scores (median 1, $p=.01$), and higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, and kidney disease. They also had higher FI (median 0.125, $p<.001$), contributed by higher medical domain score (median 3, $p<.001$). There was no difference in the functional nor geriatric syndrome domains (Supplement: Table A2).

In Model 1 (base model), both age (OR 1.09, 95% CI 1.04–1.14) and male gender (OR 3.46, 95% CI 1.28–10.60) predicted development of critical illness (Pseudo-R^2 0.124, AUC 0.785). In Model 2, age (OR 1.09, 95% CI 1.04–1.15) remained significant despite addition of CCI. Addition of a frailty predictor in Model 3, either CFS or FI, resulted in age no longer being a significant predictor for development of critical illness (AUC change 0.4–2%). CFS was a significant predictor for development of critical illness (OR 1.90, 95% CI 1.03–3.40) along with male gender (OR 5.94, 95% CI 1.47–23.95) and high acuity of clinical presentation (OR 3.61, 95% CI 1.22–10.74) in Model 4 (Pseudo-R^2 0.206, AUC 0.809). For FI, only male gender (OR 4.54, 95% CI 1.25–16.48) and high initial acuity (OR 3.28, 95% CI 1.10 – 9.80) remained significant. The values for tolerance and variance inflation factor of the CFS (0.73 and 1.37 respectively) and FI (0.59 and 1.70 respectively) models suggest low likelihood of multi-collinearity of the predictor variables.

3.3. Critical illness: sensitivity analyses (Table 3)

We included 275 patients in sensitivity analyses. In Model 1 (base model), both age (OR 1.08, 95% CI 1.04–1.12) and male gender (OR 3.69, 95% CI 1.50–9.08) predicted development of critical illness (Pseudo-R^2 0.127, AUC 0.774). In Model 2, age (OR 1.08, 95% CI 1.03–1.13) remained significant despite addition of CCI. The impact on age in subsequent models differed depending on the frailty measure used. For CFS, age (OR 1.07, 95% CI 1.02–1.13) remained significant along with male gender (OR 4.56, 95% CI 1.62–12.84) and high acuity

of clinical presentation (OR 6.50, 95% CI 2.58–17.04) in Model 4 (Pseudo-R^2 0.230, AUC 0.828). In contrast, for FI, age was no longer significant in Model 4 (Pseudo-R^2 0.244, AUC 0.833). Instead, FI (OR1.07, 95% CI 1.01–1.14), male gender (OR 4.16, 95% CI 1.50–11.56) and high initial acuity (OR 5.76, 95% CI 2.17–15.24) remained significant.

4. Discussion

Our study adds to the body of evidence by reporting the functional and frailty characteristics of older adults with COVID-19, examined across the age strata. Frailty and initial acuity, but not age nor burden of comorbidity, are important predictors of disease severity in older adults with COVID-19. Taken together, these results strongly suggest that age should not be the only consideration in decision making for management of the older patient with COVID-19, and that a holistic appraisal should also consider the frailty status and acuity of initial presentation (Cesari & Proietti, 2020).

The relatively low prevalence of dementia and functional issues in our population of older adults with COVID-19 may reflect the successful public health strategy in Singapore with specific measures targeted at frail older adults (Lee, Chiew, & Khong, 2020; Tan & Seetharaman, 2020). Despite a more robust older adult population, geriatric syndromes were common, especially in the oldest age group. This finding emphasizes the need for systematic evaluation and management of geriatric syndromes amongst hospitalized older adults with COVID-19 (Landi et al., 2020).

An added strength of our study is the application of two frailty tools. Multivariate analysis from primary models and sensitivity analyses corroborate earlier studies that CFS and FI are distinct but complementary frailty tools (Morley et al., 2013). The CFS, which is predominantly function based, has been shown to predict mortality and post-discharge outcomes in oldest-old adults (aged ≥80 years) admitted to acute wards and intensive care units, with the mildly frail having better outcomes than the moderately or severely frail (Chong, Chan, Tan, & Lim, 2020; Darvall et al., 2019). In our study, CFS predicted interval disease progression beyond the immediate phase. In contrast, the FI did not predict interval development of critical illness but was significantly associated with critical illness in the sensitivity analyses. The FI incorporates different variables across a range of health domains including co-morbidities, rendering it useful in predicting rapid disease progression in a subset of patients with high co-morbidity burden.

We further demonstrated that acuity of initial presentation is the strongest predictor of disease progression in development of critical illness, regardless of age. High acuity of initial illness presentation may be related to the pathogenesis of the SARS-CoV-2 virus (Vellas, Delobel, De Souto Barreto, & Izopet, 2020; Yuki, Fujiogi, & Koutsogiannaki, 2020), immunological responses (Qin et al., 2020) and viral dynamics (Liu et al., 2020). Taken together, the knowledge that frailty and acuity of initial presentation are important predictors of disease progression allows appropriate risk stratifications to guide right siting of care and to institute treatment in a timely manner. Our results suggest that older adults aged 50 years and older with COVID-19 who present with derangement of vital signs at triage or symptoms of dyspnea and are screened as frail using a validated assessment tool such as the CFS, should be considered as having increased risk of disease progression and warrant monitoring in an appropriate care setting.

We would like to highlight some study limitations. The assignment of CFS and FI was retrospective and based on electronic health records with potential for under-detection of clinical symptoms. However, many variables in the FI were routinely collected and we accessed both nursing and medical inputs for a more thorough assessment. Previous studies supported the validity of retrospective assignment of CFS and FI scores based on electronic health records (Clegg et al., 2016; Marincowitz et al., 2020). Generalizability of our results to other samples of older adults may be limited due to relatively fewer older adults aged ≥70 years and a predominantly non-frail to pre-frail cohort. In addition, as our cohort was a fairly homogenous cohort of older adults with COVID-19, the Charlson Comorbidity Index was less predictive of the outcome of critical illness (Tables 1–3).

Table 1
Baseline demographic, comorbidity and clinical presentation by age groups.

Characteristic	Total (*n* = 275)	50–59 years (*n* = 139)	60–69 years (*n* = 93)	≥ 70 years (*n* = 43)	*p*-value
Demographics					
Age	59 (54–66)	–	–	–	
Male, n (%)	148 (53.82)	76 (54.70)	50 (53.80)	22 (51.20)	.920
Chinese, n (%)	162 (58.91)	75 (53.20)	58 (62.40)	30 (69.80)	.077
Current/Ex-Smoker, n (%)	30 (11.49)	18 (13.90)	6 (6.74)	6 (14.30)	.220
Comorbidities					
Diabetes Mellitus, n (%)	62 (22.55)	18 (13.00)	30 (32.30)	14 (32.60)	.001
Hypertension, n (%)	105 (38.18)	33 (23.80)	42 (45.20)	30 (69.80)	<0.001
Hyperlipidaemia, n (%)	123 (44.73)	41 (29.50)	59 (63.40)	32 (74.40)	<0.001
Ischemic Heart Disease, n (%)	34 (12.36)	10 (7.19)	13 (14.00)	11 (25.60)	.005
Stroke disease, n (%)	6 (2.18)	1 (0.72)	1 (1.08)	4 (9.30)	.002
Kidney disease, n (%)	8 (2.91)	0 (0.00)	3(3.23)	5 (11.60)	<0.001
Asthma/COPD, n (%)	17 (6.18)	5 (3.60)	8 (8.60)	4 (9.30)	.196
Cancer, n (%)	9 (3.27)	1 (0.72)	3 (3.23)	5 (11.63)	.002
CCI	0 (0–1)	0 (0–0)	0 (0–1)	1 (0–2)	<0.001
Functional Difficulties					
Feeding, n (%)	3 (1.09)	0 (0.00)	0 (0.00)	3 (6.98)	<0.001
Toileting, n (%)	7 (2.55)	1 (0.72)	0 (0.00)	6 (13.95)	<0.001
Bathing, n (%)	8 (2.91)	1 (0.72)	0 (0.00)	7 (16.28)	<0.001
Mobility and transfer, n (%)	6 (2.18)	0 (0.00)	0 (0.00)	6 (13.95)	<0.001
Swallowing, n (%)	2 (0.73)	0 (0.00)	0 (0.00)	2 (4.65)	.004
Taking medications, n (%)	8 (2.91)	1 (0.72)	0 (0.00)	7 (16.28)	<0.001
Geriatric Syndromes					
Urinary symptoms, n (%)	25 (9.43)	4 (2.92)	6 (6.82)	15 (37.50)	<0.001
Chronic pain, n (%)	21 (7.64)	2 (1.44)	9 (9.68)	10 (23.26)	<0.001
Memory problems/ Dementia, n (%)	7 (2.55)	1 (0.72)	0 (0.00)	6 (13.95)	<0.001
Polypharmacy (≥4 medications), n (%)	73 (26.55)	19 (13.67)	31 (33.33)	23 (53.49)	<0.001
Nutritional risk, n (%)	19 (6.91)	5 (3.60)	4 (4.30)	10 (23.30)	<0.001
Clinical Frailty Scale	3 (2–3)	2 (2–3)	3 (2–3)	3 (3–4)	<0.001
Frailty Index	0.031 (0-0.094)	0.031 (0-0.031)	0.063 (0.031-0.093)	0.0160 (0.094-0.280)	<0.001
Initial presentation					
High acuity, n (%)	126 (45.82)	65 (46.76)	42 (45.16)	19 (44.19)	.945
Days of symptoms	5 (2–8)	5 (3–9)	5 (3–8)	3 (1–7)	.04
Outcome					
Critical illness, n (%)	32 (11.64)	5 (3.60)	16 (17.20)	11 (25.58)	<0.001

COPD, Chronic Obstructive Pulmonary Disease; CCI, Charlson Comorbidity Index.
Values are median (IQR), unless otherwise indicated.

Table 2
Hierarchical logistic regression for critical illness: Primary model ($N = 262$[a]).

Predictor variable	β-coefficient	Odds ratio	95% CI	*p*-value[b]	McFadden Pseudo R^2	AUC
CFS						
Model 1					0.124	0.785
Age	0.083	1.09	1.039 – 1.136	<0.000		
Male	1.240	3.46	1.128 – 10.597	.030		
Model 2					0.125	0.785
Age	0.086	1.09	1.036 – 1.147	.001		
Male	1.273	3.57	1.129 – 11.302	.030		
CCI	- 0.071	0.93	0.540 – 1.607	.799		
Model 3					0.163	0.789
Age	0.046	1.05	0.985 – 1.111	.140		
Male	1.843	6.31	1.540 – 25.896	.010		
CCI	- 0.264	0.77	0.421 – 1.401	.389		
CFS	0.717	2.05	1.110 – 3.778	.022		
Model 4[c]					0.206	0.809
Age	0.055	1.06	0.994 – 1.124	.079		
Male	1.782	5.94	1.473 – 23.951	.012		
CCI	- 0.192	0.83	0.444 – 1.534	.544		
CFS	0.641	1.90	1.034 – 3.485	.038		
Acuity [d]	1.284	3.61	1.215 – 10.738	.021		
FI						
Model 1					0.124	0.785
Age	0.083	1.09	1.039 – 1.136	<0.000		
Male	1.240	3.46	1.128 – 10.597	.030		
Model 2					0.125	0.785
Age	0.086	1.09	1.036 – 1.147	.001		
Male	1.273	3.57	1.129 – 11.302	.030		
CCI	- 0.071	0.93	0.540 – 1.607	.799		
Model 3					0.164	0.805
Age	0.033	1.03	0.965 – 1.107	.345		
Male	1.598	4.94	1.326- 18.435	.017		
CCI	- 0.425	0.65	0.335 – 1.275	.213		
FI [e]	0.086	1.09	1.012 – 1.173	.023		
Model 4[f]					0.200	0.809
Age	0.046	1.05	0.974 – 1.125	.211		
Male	1.512	4.54	1.249 – 16.482	.022		
CCI	- 0.308	0.73	0.373 – 1.449	.374		
FI[e]	0.071	1.07	0.996 – 1.158	.065		
Acuity [d]	1.187	3.28	1.096 – 9.798	.034		

CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; FI, Frailty Index; mSII, modified Severity of Illness Index.
[a] Excluded 13 patients intubated in ED or directly admitted to ICU.
[b] $P < 0.05$.
[c] Hosmer-Lemeshow chi$^2(8) = 2.58$, $p = .958$; mean Tolerance=0.73; mean VIF=1.37.
[d] High acuity at initial presentation.
[e] Odds ratio per 0.01 FI.
[f] Hosmer-Lemeshow chi$^2(8)$=5.83, $p = 0.666$; mean Tolerance=0.59; mean VIF=1.70.

5. Conclusion

In older adults aged ≥ 50 years admitted with confirmed COVID-19, age per se did not predict critical illnesses. Acuity of initial clinical presentation was a strong predictor of further deterioration. CFS predicted interval development of critical illness, whilst FI may be useful in predicting rapid progression in COVID-19. Frailty should be an integral part of routine assessment for hospitalized older adults with COVID-19, both to identify those at-risk of disease progression and to trigger comprehensive geriatrics assessment for evaluation and management of concomitant geriatric syndromes and functional issues.

Brief summary

Frailty and initial acuity, not age, are important predictors of disease severity in older adults with COVID-19. Clinical Frailty Scale and Frailty Index provide complimentary information in predicting disease progression.

Authors statement

JPL drafted the manuscript. All authors critically appraised and contributed to manuscript revision, approved the final version of the paper, and agree to be accountable for all aspects of the work.

Funding/Support

Recruitment of study participants and sample collection was funded by the Singapore National Medical Research Council (Ref: COVID19F-001).

Role of the funder/sponsor

The Singapore National Medical Research Council had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Competing Interest

One of the authors (Barnaby Edward Young) has received personal fees from Sanofi Pasteur and Roche, outside of the submitted work. Otherwise, the other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Table 3
Hierarchical logistic regression for critical illness: Sensitivity analysis ($n = 275$).

Predictor variable	β-coefficient	Odds ratio	95% CI	*p*-value[a]	McFadden Pseudo R^2	AUC
CFS						
Model 1					0.127	0.774
Age	0.080	1.08	1.044 – 1.124	<0.000		
Male	1.306	3.69	1.500 – 9.082	.004		
Model 2					0.128	0.777
Age	0.076	1.08	1.034 – 1.125	<0.000		
Male	1.263	3.54	1.408 – 8.884	.007		
CCI	0.086	1.09	0.714 – 1.662	.690		
Model 3					0.139	0.778
Age	0.055	1.06	1.005 – 1.111	.030		
Male	1.480	4.39	1.600 – 12.066	.004		
CCI	−0.002	1.00	0.642 – 1.551	.993		
CFS	0.386	1.47	0.892- 2.426	.131		
Model 4[b]					0.230	0.828
Age	0.067	1.07	1.015 – 1.125	.011		
Male	1.518	4.56	1.621 – 12.841	.004		
CCI	0.044	1.05	0.658 – 1.662	.851		
CFS	0.378	1.46	0.875 – 2.433	.147		
Acuity [c]	1.871	6.50	2.575 – 17.044	<0.000		
FI						
Model 1					0.127	0.774
Age	0.080	1.08	1.044 – 1.124	<0.000		
Male	1.306	3.69	1.500 – 9.082	.004		
Model 2					0.128	0.777
Age	0.076	1.08	1.034 – 1.125	<0.000		
Male	1.263	3.54	1.408 – 8.884	.007		
CCI	0.086	1.09	0.714 – 1.662	.690		
Model 3					0.168	0.802
Age	0.027	1.03	0.972 – 1.085	.340		
Male	1.481	4.40	1.584 – 12.195	.004		
CCI	- 0.255	0.78	0.468 – 1.283	.322		
FI [d]	0.088	1.09	1.025 – 1.163	.006		
Model 4 [e]					0.244	0.833
Age	0.045	1.05	0.987 – 1.108	.133		
Male	1.426	4.16	1.498 – 11.556	.006		
CCI	- 0.150	0.86	0.510 – 1.451	.573		
FI [d]	0.072	1.07	1.007 – 1.146	.028		
Acuity ‡	1.750	5.76	2.174 – 15.237	<0.000		

CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; FI, Frailty Index; mSII, modified Severity of Illness Index.
[a] $P < 0.05$.
[b] Hosmer-Lemeshow chi$^2(8) = 3.47$, $p = .902$; mean Tolerance=0.72; mean VIF=1.39.
[c] High acuity at initial presentation.
[d] Odds ratio per 0.01 FI.
[e] Hosmer-Lemeshow chi$^2(8) = 4.73$, $p = .786$; mean Tolerance= 0.59; mean VIF=1.69.

Acknowledgements

We thank all clinical and nursing staff who provided care for the patients at National Centre for Infectious Diseases. We would like to also thank Miss Tan Cai Ning from Institute of Geriatrics and Active Ageing for assisting in the referencing and formatting of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2020.104331.

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