

Characteristics and Outcomes of Patients With Frailty Admitted to ICU With Coronavirus Disease 2019: An Individual Patient Data Meta-Analysis

OBJECTIVES: Frailty is often used in clinical decision-making for patients with coronavirus disease 2019, yet studies have found a variable influence of frailty on outcomes in those admitted to the ICU. In this individual patient data meta-analysis, we evaluated the characteristics and outcomes across the range of frailty in patients admitted to ICU with coronavirus disease 2019.

DATA SOURCES: We contacted the corresponding authors of 16 eligible studies published between December 1, 2019, and February 28, 2021, reporting on patients with confirmed coronavirus disease 2019 admitted to ICU with a documented Clinical Frailty Scale.

STUDY SELECTION: Individual patient data were obtained from seven studies with documented Clinical Frailty Scale were included. We classified patients as nonfrail (Clinical Frailty Scale = 1–4) or frail (Clinical Frailty Scale = 5–8).

DATA EXTRACTION: We collected patient demographics, Clinical Frailty Scale score, ICU organ supports, and clinically relevant outcomes (ICU and hospital mortality, ICU and hospital length of stays, and discharge destination). The primary outcome was hospital mortality.

DATA SYNTHESIS: Of the 2,001 patients admitted to ICU, 388 (19.4%) were frail. Increasing age and Sequential Organ Failure Assessment score, Clinical Frailty Scale score greater than or equal to 4, use of mechanical ventilation, vasopressors, renal replacement therapy, and hyperlactatemia were risk factors for death in a multivariable analysis. Hospital mortality was higher in patients with frailty (65.2% vs 41.8%; $p < 0.001$), with adjusted mortality increasing with a rising Clinical Frailty Scale score beyond 3. Younger and nonfrail patients were more likely to receive mechanical ventilation. Patients with frailty spent less time on mechanical ventilation (median days [interquartile range], 9 [5–16] vs 11 d [6–18 d]; $p = 0.012$) and accounted for only 12.3% of total ICU bed days.

CONCLUSIONS: Patients with frailty with coronavirus disease 2019 were commonly admitted to ICU and had greater hospital mortality but spent relatively fewer days in ICU when compared with nonfrail patients. Patients with frailty receiving mechanical ventilation were at greater risk of death than patients without frailty.

KEY WORDS: coronavirus disease 2019; clinical frailty scale; frailty; hospital-related mortality; individual patient data meta-analysis; invasive mechanical ventilation

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DOI: 10.1097/CCE.0000000000000616

BACKGROUND

Coronavirus disease 2019 (COVID-19) causes severe respiratory illness in about 13% of cases and can rapidly transform into a life-threatening illness in about 4% of cases, particularly in those with comorbidities. The life-threatening form of the disease is characterized by severe acute respiratory distress syndrome, cytokine release, metabolic acidosis, and venous thromboembolism and/or disseminated

intravascular coagulopathy (1). The surge in critically ill patients with respiratory failure has overwhelmed ICU capacity in many healthcare systems across the world (2, 3). Studies published during the early phase of the pandemic have shown poor outcomes in mechanically ventilated patients with COVID-19 (4), although some studies suggest survival has improved over time (5, 6). Older people, particularly patients with frailty, were unequally affected (7) with those with a higher degree of frailty, and cumulative comorbidities were linked with higher mortality in patients with COVID-19 (7–11). It was also postulated that patients with frailty have a compromised immune response to severe acute respiratory syndrome coronavirus 2, which led to higher short-term mortality, slower recovery, and further functional decline in patients (12). Given that healthcare resources worldwide were overstretched by the unprecedented COVID-19 pandemic, there has been interest in reliable assessment tools to inform patient prioritization for scarce intensive care resources.

Frailty tools, such as the Clinical Frailty Scale (CFS), have found clinical utility as an adjunct to age-based criteria for critical care triage decisions (The National Institute for Health and Care Excellence, NICE triage guidelines) (13). However, the guideline has been criticized as it was extrapolated from prepandemic data (14). Many studies have recently been published on the impact of frailty in patients with COVID-19 with some reporting on patients in the ICU. Due to these limitations in existing information, variations in study design, limitations of published data, and the heterogeneity in the measures of frailty, conventional meta-analyses based on these studies will have limited accuracy. We conducted an individual patient data meta-analysis to evaluate the characteristics and outcomes across the range of frailty in patients with COVID-19 admitted to ICU.

MATERIALS AND METHODS

The study was registered with The International Prospective Register of Systematic Reviews (CRD42020224255) and conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (15).

Search Strategy, Information Sources, and Study Selection

Two authors (A.S., S.A.) independently searched the publicly available COVID-19 living systematic review

(16). It is updated daily to provide a dynamic database of research papers related to COVID-19 that are indexed by PubMed, Excerpta Medica dataBASE, MedRxiv, and BioRxiv. Studies were extracted between December 1, 2019, and February 28, 2021, using the search terms “frail” and “frailty” within the title and the abstract columns of the systematic review list (**Supplementary Table 1**, <http://links.lww.com/CCX/A896>). Due to the rapidly evolving pandemic, preprint studies that were yet to be peer-reviewed were included to capture as much data as possible. These terms were combined with the Boolean operator “OR”.

Eligibility Criteria

The corresponding authors of eligible studies (17–33) (**Supplementary Table 2**, <http://links.lww.com/CCX/A896>) were invited to participate and share their original individual patient data. We included studies that reported on adults greater than or equal to 18 years old with laboratory-confirmed symptomatic COVID-19 patients, a documented CFS score, and admitted to ICU. Only the patients with hospital outcomes were included in the final analysis.

Data Extraction

Data collection included patient demographics (age, sex, comorbidities, ethnicity, ICU admission source, smoking status), CFS score, ICU organ supports, such as the need for mechanical ventilation (MV), noninvasive ventilation, vasopressors, and/or renal replacement therapy, medical treatment limitation order, ICU and hospital mortality, and ICU and hospital length of stay (LOS). The treatment limitation order implied that medical treatment would be constrained by either patient wishes or medical futility but not necessarily implying that the patient was expected to die during this ICU admission (34). These were independently extracted, tabulated, and verified by the two authors (A.S., S.A.).

Quality Assessment and Risk of Bias in Individual Studies

The quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) tool (35) by two authors (S.A., M.P.R.) independently assessed selected based on the predefined criteria for nonrandomized study selection,

comparability, and the ascertainment of the outcomes of interest. Any discrepancies from the NOS were reviewed and resolved by a third author (A.S.).

Explanatory Variable—Frailty

In the Canadian Study of Health and Aging, CFS based on a nine-point judgment-based categorical scale was used for frailty measurement (36). This scale has demonstrated validity and reliability in frailty assessment in ICU patients and other populations (36, 37). This scale includes CFS = 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill) (36). The modified eight-category CFS is the most used frailty assessment in the critically ill (38). Frailty scores were also dichotomized as non-frail (CFS = 1–4) or frail (CFS = 5–8) according to accepted definitions (37), with the frail cohort further considered in terms of mild/moderate frailty (CFS = 5–6) and severe/very severe frailty (CFS = 7–8).

Ethical Issues

The individual patient data meta-analysis was exempt from ethics approval because we obtained deidentified data from previously published and ethically approved individual studies.

Other Covariates

Exposure variables such as the CFS, age, sex, chronic respiratory disease, chronic kidney disease, ischemic heart disease, admission source, Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation (APACHE) 2 scores were investigated as risk factors for hospital mortality in patients with COVID-19.

Main Outcome(s)

This was a one-stage individual patient data meta-analysis to assess the ordinal approximation of continuous variable covariates (CFS and age) (39). The primary aim was to evaluate whether frailty scores predicted outcomes for patients with COVID-19 admitted to ICU, including ICU mortality, hospital mortality, and discharge destination after adjusting for age and gender. The primary outcome was hospital mortality.

We examined the following secondary outcomes: organ support within the ICU (MV, noninvasive ventilation, renal replacement therapy, vasoactive infusion, and extracorporeal membrane oxygenation); length of ICU and hospital stay; ICU bed days; and discharge destination.

Missing Data

There were minimal missing data for the primary outcome (0.2%). However, there were missing data with illness severity scores (42.9%), comorbidities (11.4%), presenting symptoms (8.2%), biochemistry within 24 hours of ICU admission (10.5%), use of noninvasive ventilation (37.8%), use of invasive MV (IMV, 32.9%), hospital LOS (0.7%), and discharge destination (31.3%). For the main predictors, the data were generally complete, and imputation was deemed not necessary.

Statistical Analysis

In this study, the data were initially checked for completeness and validity with queries directed back to the contributing institutions. Normality was assessed in continuous data by employing both normal quantile (probit) plots and the Shapiro-Wilk test. Normally distributed data were reported using the mean (SD). Nonnormal, categorical, and dichotomous data were reported using either the median (interquartile range [IQR]) or number (frequency [%]), respectively. The final dataset included 2,001 patients drawn from seven discrete institutions with data for 80 variables collected for each patient. All analyses were clustered by the institution. An initial analysis was conducted between survivors and nonsurvivors to identify the independent predictors of mortality in critically ill patients with COVID-19. The selection of predictors was based on the clinical experience of the investigators with comparisons conducted on demographic, comorbidity, symptomatology, illness severity score, and biochemical and hematological data that were available within the first 24 hours of admission. ICU and hospital mortality were examined using a logistic model. When specifically analyzing from a clinical frailty point of view, the binary CFS categories non-frail/frail, data were compared using either a standard *t* test for normally distributed data, the Wilcoxon rank-sum test for categorical data, or the Fisher exact test

for dichotomous data. Our primary analysis included the CFS scale (1–8) with subsequent adjustment for age and sex. Secondary multivariable logistic models were constructed to examine the effects of age, CFS, obesity measured as body mass index less or greater than 30 kg/m², presence or absence of comorbidities including active cancer, dementia, and the neutrophil-lymphocyte ratio as a marker of chronic inflammation on ICU mortality with the predictors selected from the results of the univariate analysis described above. Two-way interactions were also tested between the CFS and the significant predictors. Although overfitting was possible (40), we employed a sequential deletion of nonsignificant predictors using backward stepwise regression. Potential misspecification was tested using the linktest was conducted at each step of model development. Postestimation checks for model specification and presence of collinearity were conducted using the link test and variance inflation factor, respectively. Results were reported as the odds ratio of death with its 95% CI and *p* value. A competing risk analysis was performed next to examine the marginal probability of death using both the presence of ventilation and CFS. The method of Fine and Gray was used to generate the cumulative prevalence function (41). The significant predictors from the logistic model were used, and results were expressed as subhazard ratios and their 95% CIs. Youden's *Y* statistic was calculated for each CFS score thus yielding individual sensitivity and specificity results. All analyses were conducted using STATA (Version 16.0; StataCorp LLC, College Station, TX) with the level of significance set at α less than 0.05.

RESULTS

Of the 616 studies identified, 16 studies (17–31) (Supplementary Table 2, <http://links.lww.com/CCX/A896>) met all eligibility criteria. All 16 corresponding authors were invited to participate and share their original individual patient data. We included seven studies (17, 21, 24, 26, 27, 31, 32) that provided individual patient data on 9,332 hospitalizations (Supplementary Table 3, <http://links.lww.com/CCX/A896>; Supplementary Fig. 1, <http://links.lww.com/CCX/A896>); of these, 3,690 patients (39.5%) were deemed frail. Although considered, no non-English articles were included. One of the included studies was from the preprint server (24). All included studies were obser-

vational cohort studies: three prospective (17, 31, 32), whereas the other four were retrospective (21, 24, 27, 33). The CFS was documented prospectively by clinicians in six studies at hospitalization (17, 21, 24, 27, 31, 32), whereas one study retrospectively scored the CFS based on patient information found in electronic medical records (33). Based on the NOS criteria, two studies (17, 31) were good, three were fair (27, 32, 33), and two studies (21, 24) were of poor quality. There were a total of 2,804 patients from the excluded nine studies, of which 476 (17%) were admitted to ICU. It was unclear as to what proportion of these patients were frail. Of the 2,003 patients with CFS scores, two patients with CFS scores of 9 were removed. A total of 2,001 patients (21.4%; 2,001/9,332) admitted to the ICU were included in the final analysis.

Survivor Versus Nonsurvivor Analysis

The initial analysis identified that 54.1% of patients (1,083/2,001) admitted to the ICU died (Supplementary Table 4, <http://links.lww.com/CCX/A896>). The independent predictors that increase the probability of death in these patients with COVID-19 were increasing age, CFS greater than or equal to 4, increasing SOFA score, use of IMV, dialysis and vasopressors, and rising or high lactate; a history of hypertension was associated with a lower likelihood of death (Supplementary Tables 5 and 6, <http://links.lww.com/CCX/A896>; Supplementary Fig. 2, <http://links.lww.com/CCX/A896>).

Analysis Based on Frailty Status

One of the major predictors of mortality in patients with COVID-19 was their frailty status. Of the 2,001 included patients admitted to the ICU, 80.6% (1,613/2,001) were nonfrail and 19.4% (388/2,001) were frail. The baseline characteristics, presenting symptoms, biochemistry, and acid-base between frail and nonfrail patients are presented in Table 1. The demographics based on the CFS score are presented in Supplementary Table 7 (<http://links.lww.com/CCX/A896>). Frailty increased with advancing age (Supplementary Fig. 3, <http://links.lww.com/CCX/A896>). Nonfrail patients were more likely to have presenting symptoms such as fever and myalgia/lethargy, whereas patients with frailty were more likely to present with delirium. The time from symptoms to hospitalization was shorter for patients with frailty when

TABLE 1.
Demographics of Patients With Coronavirus Disease 2019 Admitted to ICU Based on Frailty Status

Characteristics	Nonfrail (CFS 1–4)	Frail (CFS 5–8)	<i>p</i> ^a
<i>n</i>	1,613	388	–
General demographics			
Male sex, <i>n</i> (%)	870 (54)	182 (47)	0.008
Age (yr), mean (SD)	62.5 (11.3)	70.1 (11.9)	< 0.001
Age categories, yr, <i>n</i> (%)			
< 50	164 (10.2)	17 (4.4)	< 0.001
50–64.9	731 (45.3)	91 (23.4)	< 0.001
65–74.9	516 (32.0)	150 (38.7)	0.001
≥ 75	202 (12.5)	130 (33.5)	< 0.001
Admission source, <i>n</i> (%)			
Home	506 (90.5)	81 (90.0)	0.85
24-hr long-term facility	11 (2.0)	8 (8.8)	0.002
Other	42 (7.5)	1 (1.1)	0.020
Smoking status, <i>n</i> (%)			
Current smoker	287 (28.9)	77 (26.3)	0.42
Ex or nonsmoker	707 (71.1)	215 (73.6)	
Documented comorbidities, <i>n</i> (%)			
Hypertension	693 (66.4)	220 (73.8)	0.017
Cardiovascular disease	241 (15.5)	141 (36.4)	< 0.001
Cerebrovascular accident	46 (4.4)	53 (17.7)	< 0.001
Active cancer	133 (8.6)	89 (23.0)	< 0.001
Chronic respiratory disease ^b	251 (15.7)	67 (17.2)	0.44
Obesity (body mass index ≥ 30 kg/m ²)	496 (35.1)	82 (23.0)	< 0.001
Chronic kidney disease	134 (13.7)	78 (26.2)	< 0.001
Diabetes mellitus	643 (40.1)	180 (46.4)	0.025
Dementia	11 (0.7)	41 (10.6)	< 0.001
Charlson Comorbidity Index, median (IQR)	1 (0–3)	3 (1, 6)	< 0.001
No comorbidities	237 (14.7)	71 (18.3)	0.002
Number of comorbidities ≤ 2	390 (24.2)	63 (16.2)	
Number of comorbidities > 2	986 (61.1)	254 (65.5)	
CFS, median (IQR)	3 (2–3)	6 (5–6)	< 0.001
Illness severity scores, median (IQR)			
APACHE 2	14 (6, 23)	14 (9–23)	0.07
APACHE 3	No data	No data	-
Simplified Acute Physiology Score 2	38 (24–56)	41 (30–57)	0.006
Sequential Organ Failure Scale	7 (5–12)	8 (5–12)	0.09

(Continued)

TABLE 1. (Continued).**Demographics of Patients With Coronavirus Disease 2019 Admitted to ICU Based on Frailty Status**

Characteristics	Nonfrail (CFS 1–4)	Frail (CFS 5–8)	<i>p</i> ^a
Symptoms, <i>n</i> (%)			
Respiratory	1,344 (91.7)	329 (89.9)	0.25
Sputum	35 (4.0)	14 (5.2)	0.39
Fever	921 (62.9)	183 (50.0)	< 0.001
Lethargy/myalgia	416 (45.9)	97 (35.0)	0.001
Delirium	126 (8.6)	72 (19.8)	< 0.001
Gastrointestinal	120 (13.3)	27 (9.8)	0.15
Symptom time (d)	8 (5–11)	7 (4–10)	0.001
Time to ICU (hr)	3 (1–5)	3 (2–5)	0.46
Pathology results (first 24 hr), median (IQR)			
Acid base status			
pH	7.41 (7.33–7.46)	7.39 (7.33–7.45)	0.20
Pao ₂ (mm Hg)	70 (60–84)	73 (59–90)	0.18
Paco ₂ (mm Hg)	38 (33–46)	38 (32–44)	0.42
Hco ₃ (mmol/L)	24 (21–26)	23 (20–27)	0.024
Arterial O ₂ saturation	93 (89–96)	94 (90–96)	0.023
L-lactate (mmol/L)	11 (2–16)	12 (7–18)	< 0.001
Biochemistry			
C-reactive protein	154 (78–248)	144 (52–260)	0.11
Urea	33 (9–66)	62 (25–103)	< 0.001
Creatinine	97 (71–164)	115 (79–195)	0.002
Lactate dehydrogenase	471 (365–629)	433 (316–551)	< 0.001
D-dimer	1,670 (784–5,193)	2,116 (1,023–5,861)	0.002
Troponin	0.08 (0.02–8.00)	0.05 (0.03–0.16)	0.044
Hematology			
Neutrophils	7.6 (5.0–11.4)	7.8 (5.0–11.5)	0.98
Lymphocytes	0.83 (0.57–1.19)	0.72 (0.47–1.1)	< 0.001
Neutrophil-lymphocyte ratio	8.8 (5.2–15.6)	10.0 (5.6–18.9)	0.015
Platelets	217 (159–300)	195 (131–260)	< 0.001
Radiology, <i>n</i> (%)			
Abnormal chest radiograph	1,237 (76.7)	285 (73.5)	0.102

APACHE = Acute Physiology and Chronic Health Evaluation, CFS = Clinical Frailty Scale, IQR = interquartile range.

^aSome of the results will be statistically significant because of the large sample size but may not be clinically significant.

^bChronic obstructive pulmonary disease and/or asthma.

Dashes indicate number of patients included in frail and nonfrail group.

compared with nonfrail patients (median [IQR] days, 7 [4–10] vs 8 [5–11]; $p = 0.001$). Patients with frailty were more likely to have an accompanying acute kidney injury. They were also more lymphopenic with a higher neutrophil-to-lymphocyte ratio than nonfrail patients.

A lower proportion of male patients were frail (47% vs 54%; $p < 0.001$). Although home residence was similar, there was a higher proportion of frail than nonfrail patients residing in a 24-hour long-term facility (8.8% vs 2.0%; $p = 0.002$) before the index hospitalization. The

patients classified as frail were older and had higher illness severity scores (Simplified Acute Physiology Score 2). The patients with frailty also had higher chronic comorbidities, particularly hypertension, cardiovascular disease, diabetes mellitus, active cancer, and dementia, but were less likely to be obese (body mass index [BMI] ≥ 30 kg/m²).

Primary Analyses of Primary Outcome

Patients with frailty were more likely to die in ICU (unadjusted mortality 26.8% vs 17.9%; $p = 0.044$) and in hospital (unadjusted mortality 65.2% vs 41.8%; $p < 0.001$). Frailty status, after adjusting for age and sex, was independently associated with hospital mortality but not ICU mortality (Table 2 and Fig. 1, A and B). In secondary analyses, the relationship between frailty and hospital mortality remained significant independent of age, BMI, and neutrophil-lymphocyte ratio (Table 3).

Secondary Outcomes

The raw outcomes are presented in Supplementary Table 8 (<http://links.lww.com/CCX/A896>) and based

on the CFS score in Supplementary Table 9 (<http://links.lww.com/CCX/A896>).

Mechanical Ventilation. Excluding the 658 patients (32.9%) with missing data, a total of 1,014 of the 1,343 patients (75.5%) received MV, most of them had a CFS score between 2 and 4 (Fig. 1C). Of these 1,014 patients who received MV, there was no difference between frail and non-frail patients (68.2% [199/292] vs 77.5% [815/1,051]; $p = 0.21$). However, patients with frailty spent a shorter median (IQR) duration on MV (9 d [5–16 d] vs 11 d [6–18 d]; $p = 0.012$). The unadjusted mortality rates were higher in patients requiring MV than those who did not (Supplementary Table 8, <http://links.lww.com/CCX/A896>; Supplementary Fig. 4, <http://links.lww.com/CCX/A896>). All patients with CFS score of 8 who were mechanically ventilated died. Figure 2 describes the cumulative risk of death over time among patients who received MV, which demonstrated that the cumulative risk of death decreases with more days on MV. Multivariable linear regression in ICU survivors indicated that the adjusted geometric mean duration of MV reduced significantly with increasing CFS score (from 9.5 d [8.3–10.7] for CFS 1 to 3.6 [2.3–5.0]

TABLE 2.
Unadjusted and Adjusted (for Age and Sex) for ICU and Hospital Mortality (Primary Outcome)

Clinical Frailty Scale	No. of Patients	ICU Mortality ^a , n (%)	Unadjusted ICU Mortality, OR (95% CI; p)	Adjusted ICU Mortality, OR (95% CI; p)	Hospital Mortality ^a , n (%)	Unadjusted Hospital Mortality, OR (95% CI; p)	Adjusted Hospital Mortality, OR (95% CI; p)
1	193	20 (10.4)	Reference	Reference	53 (27.5)	Reference	Reference
2	450	59 (13.1)	0.82 (0.44–1.51; $p = 0.52$)	0.90 (0.48–1.67; $p = 0.73$)	165 (37.6)	1.43 (0.98–2.06; $p = 0.06$)	1.37 (0.94–2.00; $p = 0.10$)
3	669	143 (21.4)	0.87 (0.48–1.52; $p = 0.58$)	0.92 (0.51–1.64; $p = 0.77$)	295 (44.1)	1.98 (1.40–2.81; $p < 0.001$)	1.57 (1.10–2.25; $p = 0.014$)
4	301	67 (22.3)	0.90 (0.49–1.65; $p = 0.74$)	0.88 (0.47–1.63; $p = 0.68$)	161 (53.5)	3.04 (2.06–4.48; $p < 0.001$)	2.21 (1.48–3.30; $p < 0.001$)
5	180	49 (27.2)	1.16 (0.61–2.19; $p = 0.65$)	0.99 (0.51–1.90; $p = 0.97$)	109 (60.6)	4.04 (2.62–6.24; $p < 0.001$)	2.70 (1.71–4.25; $p < 0.001$)
6	124	33 (26.6)	1.28 (0.64–2.55; $p = 0.48$)	1.15 (0.57–2.33; $p = 0.70$)	89 (64.5)	4.62 (2.85–7.51; $p < 0.001$)	3.16 (1.91–5.23; $p < 0.001$)
7	70	17 (24.3)	0.90 (0.41–1.97; $p = 0.80$)	0.80 (0.36–1.78; $p = 0.59$)	43 (61.4)	3.91 (2.20–6.94; $p < 0.001$)	2.61 (1.44–4.73; $p = 0.002$)
8	14	5 (35.7)	1.26 (0.36–4.35; $p = 0.72$)	1.05 (0.30–3.74; $p = 0.94$)	12 (85.7)	14.73 (3.19–67.9; $p = 0.001$)	14.20 (2.98–67.6; $p = 0.001$)

OR = odds ratio.

^aDichotomized unadjusted analysis for frail vs nonfrail patients: ICU mortality: 26.8% vs 17.9%; $p = 0.044$; hospital mortality: 65.2% vs 41.8%; $p < 0.001$.

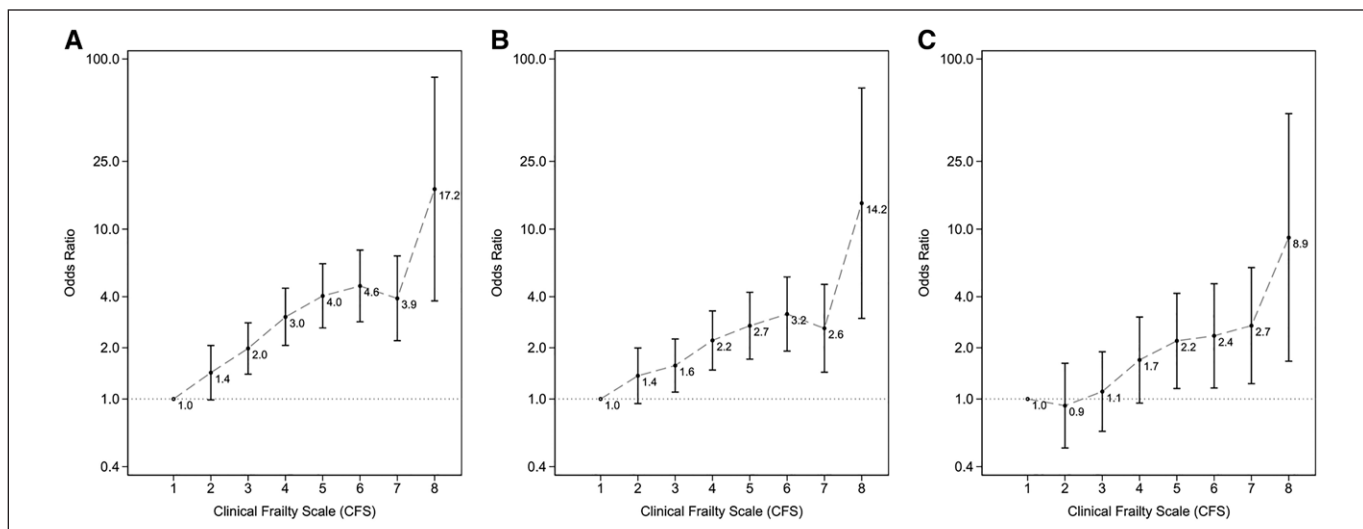


Figure 1. Hospital mortality according to Clinical Frailty Scale (CFS) score for all patients adjusted for age and sex. **A**, Is the raw (unadjusted) data by CFS. **B**, Is the data adjusted for age and sex. **C**, Is as for (B) with ventilation included.

for CFS 7 and 8 combined) (**Supplementary Table 10**, <http://links.lww.com/CCX/A896>).

ICU and Hospital LOS. Patients with frailty admitted to ICU were more likely to have shorter median (IQR) LOS in ICU (8 d [4–16 d] vs 11 d [5–20 d]; $p < 0.001$). Of the total $24.3 \times 1,000$ ICU bed days, patients with frailty only contribute 12.3% of the ICU bed days (**Supplementary Fig. 4**, <http://links.lww.com/CCX/A896>). Similar findings were observed when only survivors were analyzed. Patients with CFS score of 7 and 8 spent the shortest time in ICU ($0.6 \times 1,000$ ICU bed days, 2.5%). However, the ICU bed days occupied by patients with frailty who died were almost double that of survivors for CFS score of 5–7. Patients with frailty also had shorter median (IQR) hospital LOS (13 d

[8–23 d] vs 16 d [10–28 d]; $p < 0.001$) when compared with nonfrail patients (**Supplementary Table 8**, <http://links.lww.com/CCX/A896>). Heat map comparing age- and CFS-stratified data based on ICU survivors and ICU nonsurvivors demonstrated that most patients admitted to ICU were younger than 80 years old and CFS less than or equal to 6 (**Supplementary Fig. 5**, <http://links.lww.com/CCX/A896>).

Other Organ Support. Patients with frailty were less likely to receive noninvasive ventilation (27% vs 35%; $p = 0.011$) or renal replacement therapy (25% vs 32%; $p = 0.026$) when compared with nonfrail patients. There was no difference in vasopressor infusion use between frail and non-frail patients (**Supplementary Table 9**, <http://links.lww.com/CCX/A896>).

TABLE 3. Secondary Analysis of Primary Outcome With Multipredictor Modeling for Hospital Mortality

Variables	Multivariable Model			Interaction With CFS
	OR	95% CI	<i>p</i>	<i>p</i>
Age	1.04	1.02–1.06	< 0.001	0.65
CFS	1.23	1.12–1.35	< 0.001	-
Mechanical ventilation	4.45	3.20–6.18	< 0.001	0.07
Dialysis ^a	3.98	2.95–5.37	< 0.001	0.18
Obesity (body mass index ≥ 30 kg/m ²)	0.59	0.44–0.79	0.001	0.29
Active cancer	1.71	1.15–2.52	0.007	0.80

CFS = Clinical Frailty Scale.

^aDialysis and chronic kidney disease highly correlated.

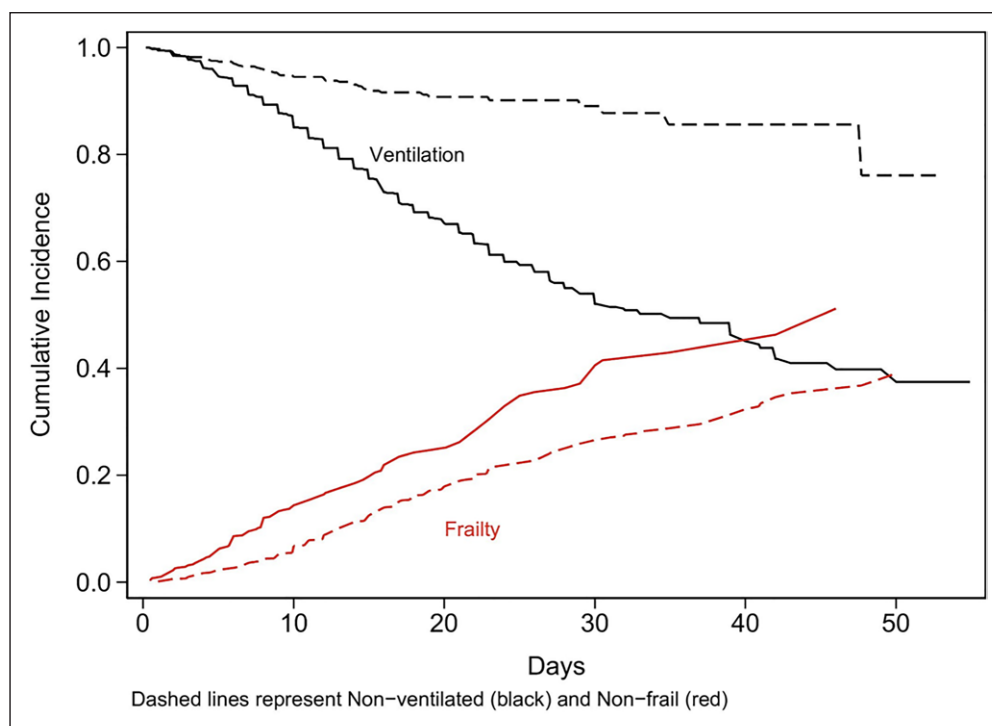


Figure 2. Graphical representation of cumulative incidence of death for frailty.

Discharge Destination. Patients with frailty were less likely to be discharged home (unadjusted 23% vs 45%; $p < 0.001$) and rehabilitation (unadjusted 23% vs 35%; $p < 0.001$). However, the unadjusted new discharges to 24-hour long-term facility discharge (1.5% vs 2.3%; $p = 0.17$) were similar between frail and non-frail patients (Supplementary Table 9, <http://links.lww.com/CCX/A896>).

DISCUSSION

This multinational, individual patient data meta-analysis included 2,001 patients with COVID-19 admitted to an ICU from seven studies identified the following five key findings. First, increasing age and SOFA score, CFS score greater than or equal to 4, use of MV, vasopressors, renal replacement therapy, and hyperlactatemia were independent predictors of mortality. Second, A fifth of the patients admitted to ICU were frail, with almost two-thirds of these patients with frailty dying in hospital. The odds of hospital mortality increased from a CFS score of 3 when compared with patients with scores less than or equal to 2. Multivariable analysis demonstrated that older age and increasing frailty were independently associated with hospital mortality. Third, the impact of frailty on the use of MV differed

with age, with younger and nonfrail patients being more likely to receive MV. Fourth, the frail ICU survivors received a shorter duration of MV and had a shorter ICU LOS. Fifth, the ICU bed days occupancy in patients with frailty was only 16% and spent a shorter time in ICU. This final finding may relate to decisions to limit invasive and burdensome treatments.

The hospital mortality of patients with COVID-19 admitted to ICU has ranged widely depending on the geographical location and the different levels of strain on the critical care

system (18, 22, 24, 25, 31, 42–50). A large cohort study of patients with COVID-19 treated in ICU during periods of peak COVID-19 found a two-fold increase in mortality compared with those treated during periods of low demand (42). Furthermore, several studies have demonstrated an association of higher mortality with an increased hospital or regional COVID-19 case-loads, regardless of whether the patients were frail or not (51). Having said that, hospital and ICU mortalities in patients with COVID-19 have improved over time (52). Although not specifically studied in patients with frailty, large-scale randomized trials identified treatments, such as dexamethasone and tocilizumab, have demonstrated improvements in overall mortality (53–55). Our study findings suggest the importance of caution in interpreting results from different time periods.

A single-center retrospective study from Italy of 105 patients observed that the frailty index was an independent predictor of both higher in-hospital mortality and lower proportions with ICU admission (56). A recent large prospective multinational study (Outcomes and Prognostic Factors in COVID-19) identified that frailty was independently associated with lower survival (57). Similarly, our individual patient data meta-analysis also observed that frailty was independently associated with hospital mortality among patients with

COVID-19 admitted to ICU. A nationwide Turkish study of patients 65 years old and older, using the hospital frailty risk score, observed that frailty was independently associated with hospital mortality, ICU admission, and use of MV (44). These studies may suggest that the high risk of mortality in older patients along with ICU resource constraints may raise the question of triaging ICU admissions. Even in times of nonconstrained resources, shared decision-making may be informed by the risk of mortality assessments, to allow patients and their caregivers to make informed choices about their care. A recent systematic review and meta-analysis recommended that frailty screening may be helpful to stratify high-risk groups (58).

Our study observed MV was used more often among younger and nonfrail patients. This was consistent with a recent study in non-COVID patients that investigated the impact of frailty on the duration of ventilation where they observed frail young patients had a longer duration of ventilation but not old patients with frailty (59). In a recent large systematic review, the reported mortality in mechanically ventilated patients was 45% and was significantly higher with increasing age and higher among those receiving MV (4). In our meta-analysis, patients with frailty, both survivors and nonsurvivors, spent a shorter time on MV. This finding implies that the patients with frailty may have died sooner or may have had treatment limitations.

We identified that nonfrail patients accounted for 85% of the ICU bed days. This is contrary to the findings of a recent study of older non-COVID-19 ICU patients with pneumonia which found a significantly higher ICU bed occupancy by patients with frailty (60). Furthermore, the findings that frail ICU survivors received a shorter duration of MV and had shorter ICU LOS are noteworthy and somewhat counterintuitive. This finding may be influenced by differing patterns of care for frail older adults between countries, resource constraints related to patient triage, and possibly earlier decisions to limit life-sustaining treatments in these patients.

Even before the COVID-19 pandemic began, frailty was recognized as a predictive factor for adverse outcomes, such as mortality (61), hospitalizations (62), and readmission (63). Consequently, frailty was proposed as an important aspect of patient assessment early in the pandemic. Despite the stringent guidelines, the patients with COVID-19 remained eligible for

ICU admission under the NICE guidelines, particularly following a ward deterioration. However, triaging patients just based on the frailty status is not justified by the current data (64, 65). Indeed, an odds ratio of ~ 2 by itself is not useful clinically. A patient-centered approach to triage that incorporates frailty screening could be developed to rapidly assess patients for the severity of the presenting acute illness and the likelihood of medical interventions being successful (66). An option of triage committee involvement to provide an ethical framework to guide clinicians to equitable rationing under crisis standards of care has been proposed (67, 68).

This individual patient data meta-analysis has several notable strengths. First, we had high-quality data from the seven included studies from diverse countries, both resource rich and limited, at their peak of the pandemic. Second, the CFS, which is the most used frailty assessment tool for critically ill patients, was reported in all of the included studies. Third, we incorporated prespecified several secondary analyses, including the competing risk analyses, to assess the impact of frailty on several important patient-centered ICU outcomes.

However, some of the limitations should be noted. First, the datasets from the seven included studies had missing data for a proportion of covariates, such as APACHE scores. This may introduce potential bias in parameter estimation and weaken the generalizability of the results. Second, it is important to acknowledge that the results may have been predominantly influenced by two main studies, one of which was a single-center study. This single-center study patients were from a single reference hospital that cared for the severe cases of COVID-19. As a result, this may not impact on generalizability. Third, the differences in the healthcare systems across the different studies included in this individual patient data meta-analysis may introduce variability that is difficult to address with clustering by institution. Fourth, although there is evidence that COVID-19 has a disproportionate impact on disease severity and mortality in minority racial and ethnic groups, we did not have adequate data on the patient's race or ethnicity (17). Fifth, although patients with frailty tend to have treatment limitations (do not resuscitate, do not intubate, etc.) (69) which may guide their management, we did not have data on treatment limitations or pre-ICU triage

decisions which undoubtedly influenced our results. Sixth, limitations of the NOS in terms of interrater reliability and external validation should be acknowledged (70). Finally, although imprecise CFS scoring is possible (71), there is evidence that the CFS has acceptable interindividual variation in the critically ill population and is validated to stratify older adults according to the level of vulnerability (36) and predict poor short- and long-term outcomes in critically ill patients (37, 72–74).

CONCLUSIONS

In this multinational individual patient data meta-analysis, almost two thirds of patients with frailty with COVID-19 who were admitted to ICU died in hospital. Patients with frailty spent a shorter amount of time in ICU suggesting decisions to limit life-sustaining treatments play a role in our findings. Frailty captures risks beyond other known risk factors in those with COVID-19 admitted to the ICU. Future studies should consider incorporating frailty into the patient assessment process alongside other commonly used measures (age, sex, comorbidities, illness acuity) to support clinicians in making better decisions for severe forms of COVID-19.

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The authors have disclosed that they do not have any potential conflicts of interest.

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A few authors provided individual patient data to conduct this meta-analysis.

This work was performed at Monash University.

Systematic review registration: Registration/protocol in The International Prospective Register of Systematic Reviews (CRD42020224255).

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