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Original Article

Impact of frailty on long-term survival in patients discharged alive from hospital after an ICU admission with COVID-19☆

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ABSTRACT

Objective: Though frailty is associated with mortality, its impact on long-term survival after an ICU admission with COVID-19 is unclear. We aimed to investigate the association between frailty and long-term survival in patients after an ICU admission with COVID-19.

Design, Setting and Participants: This registry-based multicentre, retrospective, cohort study included all patients ≥16 years discharged alive from the hospital following an ICU admission with COVID-19 and documented clinical frailty scale (CFS). Data from 118 ICUs between 01/01/2020 through 31/12/2020 in New Zealand and 31/12/2021 in Australia were reported in the Australian and New Zealand Intensive Care Society Adult Patient Database. The patients were categorised as 'not frail' (CFS 1-3), 'mildly frail' (CFS 4-5) and 'moderately-to-severely frail' (CFS 6-8).

Main Outcome Measures: The primary outcome was survival time up to two years, which we analysed using Cox regression models.

Results: We included 4028 patients with COVID-19 in the final analysis. 'Moderately-to-severely frail' patients were older (66.6 [56.3–75.8] vs. 69.9 [60.3–78.1]; $p < 0.001$) than those without frailty (median [interquartile range] 53.0 [40.1–64.6]), had higher sequential organ failure assessment scores ($p < 0.001$), and less likely to receive mechanical ventilation ($p < 0.001$) than patients without frailty or mild frailty. After adjusting for confounders, patients with mild frailty (adjusted hazards ratio: 2.31, 95%-CI: 1.75–3.05) and moderate-to-severe frailty (adjusted hazards ratio: 2.54, 95%-CI: 1.89–3.42) had higher mortality rates than those without frailty.

Conclusions: Frailty was independently associated with shorter survival times to two years in patients with severe COVID-19 in ANZ following hospital discharge. Recognising frailty provides individualised patient intervention in those with frailty admitted to ICUs with severe COVID-19.

Clinical trial registration: Not applicable.

Abbreviations: ANZ, Australia and New Zealand; ANZICS, Australia and New Zealand Intensive Care Society; ANZROD, Australia and New Zealand a risk of death; APACHE, Acute Physiology and Chronic Health Evaluation; APD, Adult Patient Database; aHR, adjusted hazard ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CFS, Clinical Frailty Scale; ECMO, extracorporeal membrane oxygenation; ED, emergency department; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MET, medical emergency team; MI, myocardial infarction; NIV, non-invasive ventilation; PerCI, persistent critical illness; RRT, renal replacement therapy; SD, standard deviation; SOFA, sequential organ failure assessment; USA, United States of America.

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THE KNOWN: Evidence suggests that older people with frailty are disproportionately affected by severe COVID-19. Frailty and comorbidities are linked with mortality in such patients.

THE NEW: A third of the population admitted to ANZ ICUs with COVID-19 were frail. Frailty was independently associated with shorter survival times to two years in patients in ANZ following hospital discharge.

IMPLICATIONS: Assessing frailty status better informs therapeutic choices and expectations regarding prognosis. Clinicians should discuss the expected outcomes with the patient and family when admitted to ICU and consider goals of care for those with multiple chronic conditions and if clinical frailty scale ≥4. This knowledge makes us better equipped in caring for patients with frailty the next frontier beyond COVID-19.

1. Introduction

Frailty is a multidimensional geriatric syndrome characterized by a decline of the physical, physiological, and cognitive reserves.[1] People with frailty require more assistance in daily activities and are more susceptible to adverse events and death.[2–4] A previous meta-analysis found that frailty was associated with mortality in the intensive care unit (ICU), and these patients are less likely to be discharged home.[3] While the clinical frailty scale (CFS) is used in younger populations,[5,6] it is far more widely used and validated in older patients age (≥65 years).[7]

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating global impact. Evidence suggests that older people with frailty are disproportionately affected[8] and that frailty and comorbidities are linked with mortality,[9,10] within and without COVID-19.[11,12] Although vaccination has minimized the impact of the severity and mortality of COVID-19, people can have symptoms that persist in the longer term ('long-COVID')[13] and potentially affect many organ systems.[13–15] The first studies translating 'long-COVID' into patient-centered outcomes (including frailty) found that long-term survival in patients with frailty with severe COVID-19 is poor.[16–18] Nonetheless, data reporting on this association in Australia and New Zealand (ANZ) is sparse. Therefore, we investigated the association between frailty and long-term survival of patients discharged alive from hospital after ICU admission with COVID-19. We hypothesized that after adjusting for confounders, increasing levels of frailty would be associated with poorer survival for up to two years.

2. Methods

2.1. Study design and setting

This is a retrospective multicentre cohort study, analysing the Australian and New Zealand Intensive Care Society (ANZICS) adult patient database (APD) between 1st January 2020 and 31st March 2022.

2.2. Patient identification

All adults ≥16 years discharged alive from their index hospitalisation following admission to ANZICUs with suspected or confirmed COVID-19 infection and a documented CFS were included. Patients transferred from another ICU were excluded. The CFS was assigned by trained data collectors working in the participating ICU, comprising of junior doctors, nurses, and administrative staff and was based on the patient's level of physical function in the two months preceding ICU admission.[19]

2.3. Data sources and measurement

We extracted data from the ANZICS-APD, a bi-national clinical quality registry dataset, collected by the ANZICS Centre for Outcomes and Resources Evaluation that contains information on all admissions to 98% of adult ICUs in Australia and 67% of ICUs in New Zealand. ICU admission records between 01/01/2020 through 31/12/2020 in New Zealand and 31/12/2021 in Australia were linked to the date of death recorded in the national death registers in each country using an encoded linkage key. There was at least a three-month follow-up for all patients. Data collectors receive regular training and quality assurance review, and data are collected using a standardized data dictionary.[19] In addition, regular automated data checks further ensure the recorded data are valid.[20] Apart from demographic details, the registry also captures diagnostic, biochemical, physiological, and chronic health parameters from the first 24 h of ICU admission as required to calculate illness severity scores.

2.4. Variables

We extracted data on patient demographics (age, sex, comorbidities, ethnicity, ICU admission source, smoking status), frailty status using the CFS, body mass index (based on patient's weight and height), ICU organ supports (mechanical ventilation, non-invasive ventilation, vasopressors, extracorporeal membrane oxygenation, and/or renal replacement therapy), ICU and hospital length of stay (LOS), and discharge destinations (home, nursing home, or rehabilitation).

2.5. Frailty

Frailty was measured using a modified version of the Canadian Study of Health and Aging CFS, which categorizes patients as not-frail (CFS 1–4) or frail (CFS 5–9),[7] which has been validated among patients with critical illness,[3] and correlates well with the other comprehensive frailty scales.[21,22] In the ANZICS-APD, the CFS represents the patient's status in the two months preceding ICU admission and is modified to eight categories without a CFS-9 (terminally ill). The CFS was updated at the start of the pandemic to aid with scarce resource allocation, where they revised level names (e.g., CFS 4 which was previously 'vulnerable' was revised to 'living with very mild frailty').[23] For this study, the patients were categorized as 'not frail' (CFS 1–3), 'mildly frail' (CFS 4–5), and 'moderately-to-severely frail' (CFS 6–8), and patients with CFS ≥4 are frail, based on the updated CFS tool.

2.6. Study outcomes

The primary outcome was survival time up to two years, and overall survival at one and two years after ICU admission. Secondary outcomes included ICU resource use, the prevalence of delirium, ICU and hospital LOS, and discharge destinations.

2.7. Subgroup analysis

We did prespecified subgroup analyses stratifying patients based on age (<65 vs. ≥65 years), the receipt of mechanical ventilation, and by waves (Wave-1: January to June 2020, Wave-2: July 2020 to June 2021 Wave-3: June 2021 to December 2021, with

Wave-2 as the reference period).[24] Given that patients from New Zealand in 2021 were excluded (Supplementary Figure 1), only patients from Australia were included in wave-3.

2.8. Statistical analysis

For categorical variables, we report percentages with counts and made comparisons using Chi-squared tests. For continuous variables, we report normally distributed data using means (standard deviation) and non-parametric data using median (interquartile range [IQR]). We made comparisons using the student's *t*-test for normally distributed data and the Mann–Whitney U test otherwise. As estimates can cluster around centres, we used a robust-variance sandwich-type estimator to derive the standard errors and account for this clustering.[25] Overall survival estimates are displayed using Kaplan–Meier curve plots by classifying CFS into three categories. We analysed the effect of frailty using a Cox proportional hazards model, adjusting for age, male sex, comorbidities (including chronic cardiovascular, respiratory, renal, and liver conditions, diabetes mellitus, and a composite of solid and hematologic malignancies), sequential organ failure assessment score, jurisdiction (Australian states and New Zealand), the presence of treatment limitations, and hospital type (tertiary, metropolitan, rural/regional, and private). We set CFS 1–3 as the reference group based on previous literature.[9] We report the results of the Cox models using adjusted hazard ratios (aHR, 95%CI). We conducted three sensitivity analyses. First, we treated CFS as a continuous variable and presented the relationship between CFS and survival time graphically. Second, we used another set of potential confounders including the Australia New Zealand Risk of Death (ANZROD, a highly predictive mortality prediction model benchmarking ICU performance in ANZ[26,27]) score, male sex, jurisdiction, and hospital type. Finally, we conducted another analysis to assess the impact of comorbidities on frailty and presented that as Kaplan Meier plots. We performed data analysis using R4.2.2 (The R Foundation, Boston, MA). We used a two-sided p value of <0.05 to indicate statistical significance.

2.9. Ethics approval

The Alfred Hospital Ethics Committee (reference: 87/22) approved this study and waived the requirement for informed consent by individual patients.

3. Results

5834 patients with COVID-19 were linked with the National Death Index during the study period. After applying the inclusion and exclusion criteria, the final study population comprised 4028 patients from 110 Australian and 8 New Zealand ICUs (Supplementary Figure 1). The comparison between patients with and without documented CFS is presented in Supplementary Table 1. Briefly, patients without a document CFS were more frequently admitted to a tertiary ICU, less likely to have comorbidities (chronic cardiovascular, respiratory, or renal conditions), and less likely to receive ICU organ supports including mechanical ventilation or inotropes, they had similar age, sequential organ failure assessment scores, and 2 year mortality after hospital discharge. Supplementary Table 2 summarizes the patient characteristics of those who died in the hospital (n = 605) when compared to those who survived hospitalisation.

Of 4028 patients, 65.1% (n = 2624) were 'not frail', 24.0% (n = 967) were 'mildly frail', and 10.9% (n = 437) were 'moderately-to-severely frail'. Patients with frailty were older than patients without frailty. Patients with moderate-to-severe frailty were more likely to be admitted to ICU from an emergency department and had a higher proportion of comorbidities, treatment limitations at ICU admission, non-invasive ventilatory supports, and illness severity scores at ICU admission than other frailty categories. Patients with moderate-to-severe frailty less frequently received invasive ventilatory, tracheostomy and extracorporeal membrane oxygenation support than the other two categories. No difference in the receipt of vasopressors or renal replacement therapies was observed. There was no difference in the prevalence of delirium between the groups. The baseline characteristics are summarised in Table 1.

3.1. Primary outcome

The overall 2-year survival for patients who were 'not frail' (2480/2624; 90.6%, 95%-CI: 88.8%–92.5%) were higher than those who were "mildly frail" (729/967; 58.7%, 95%-CI: 53.7%–64.1%) and 'moderately-to-severely frail' (274/437; 43.5%, 95%C–I: 36.4%–51.9%, p < 0.001) (Table 2 and Fig. 1). After adjusting for confounders, patients with mild frailty (aHR: 2.31, 95%-CI: 1.75–3.05) and moderate-to-severe frailty (HR: 2.54, 95%CI: 1.89–3.42) had shorter survival times than those without frailty (Table 3). Sensitivity analyses treating CFS as a continuous variable (Supplementary Table 4; Supplementary Figure 2) and with a different set of potential confounders yielded similar results (Supplementary Table 3). The sensitivity analysis based on comorbidities demonstrated lower survival up to 2 years in patients with comorbidities, however, for each comorbidity (0, 1, or ≥2) stratified by frailty demonstrated similar lower survival times for patients with any level of frailty (Supplementary Figure 3).

3.2. Subgroup analyses

3.2.1. Patients stratified by age (<65 vs. ≥65 years)

Using 65 years as an arbitrary threshold (Supplementary Figure 4), a total of 1433 patients (35.6%) were ≥65 years old. Compared to those <65 years, patients ≥65 years more frequently had some degree of frailty (CFS ≥4; 25.9% [672] vs. 56.0% [n = 803]; p < 0.001). After adjusting for confounders, the presence of frailty was associated with a shorter time to death in both subgroups (Supplementary Table 5, Fig. 2). The relationship between frailty and age for survival time up to 2 years remained significant, independent of confounders (p < 0.001; Supplementary Table 6).

3.2.2. Patients who received mechanical ventilation

1144 patients received mechanical ventilation, of which 25.7% (n = 294) were frail (CFS ≥4). The duration of mechanical ventilation was shorter in patients with frailty (p < 0.001; Table 1). Kaplan–Meier survival curves estimated that there was no difference in survival time up to 2 years in 'not frail' patients. The 'mildly frail' and 'moderately-to-severely frail' patients who did not receive mechanical ventilation had worse survival than those who received mechanical ventilation within the same frailty groups (Fig. 2). After adjusting for confounders, the presence of frailty was associated with a shorter time to death ('mildly frail' aHR = 2.13, 95%-CI: 1.32–3.46, and 'moderately-to-severely frail' aHR = 1.93, 95%-CI: 1.13–3.28, respectively; Supplementary Table 7). Both mildly frail and moderate-to-severely frail patients exerted no effect on death in those needing mechanical ventilation, independent of confounders (Supplementary Table 8).

3.2.3. COVID-19 waves

190/757 admitted in wave-1 died. Similarly, 198/829 patients in the wave-2, and 157/2442 patients in the third wave did not survive. Compared to the wave-2, patients admitted during wave-1

Table 1
Baseline characteristics, illness severity and ICU management of patients with COVID-19 based on the CFS categories.

Frailty categories	'Not frail' Patients (CFS 1–3)	'Mildly frail' Patients (CFS 4–5)	'Moderately-to-severely frail' Patients (CFS 6–8)	p-value
Number	2624 (65.1%)	967 (24.0%)	437 (10.9%)	–
Male sex	1538 (58.7%)	515 (53.3%)	213 (48.9%)	**<0.001**
Indigenous status	80 (3.2%)	52 (5.6%)	23 (5.6%)	**0.002**
Age (years)	53.0 (40.1, 64.6)	66.6 (56.3, 75.8)	69.9 (60.3, 78.1)	**<0.001**
Hospital classification				**<0.001**
- Public Tertiary	1452 (55.4%)	316 (32.7%)	95 (21.7%)	
- Public Metropolitan	822 (31.3%)	289 (29.9%)	128 (29.3%)	
- Public Rural/Regional	288 (11.0%)	309 (32.0%)	191 (43.7%)	
- Private	61 (2.3%)	53 (5.5%)	23 (5.3%)	
ICU admission source				**<0.001**
- Emergency Department	1342 (51.2%)	637 (65.9%)	314 (71.9%)	
- Ward	1156 (44.1%)	284 (29.4%)	100 (22.9%)	
- Other hospital	107 (4.1%)	44 (4.6%)	22 (5.0%)	
- Operating Theatre/Recovery	1 (0%)	1 (0.1%)	0 (0%)	
- Direct admit	17 (0.6%)	1 (0.1%)	1 (0.2%)	
Documented co-morbidities				
- Chronic respiratory condition	174 (6.6%)	224 (23.2%)	210 (48.1%)	**<0.001**
- Chronic cardiovascular condition	120 (4.6%)	151 (15.6%)	116 (26.5%)	**<0.001**
- Chronic renal failure	32 (1.2%)	56 (5.8%)	39 (8.9%)	**<0.001**
- Chronic liver disease	9 (0.3%)	12 (1.2%)	6 (1.4%)	**0.002**
- Diabetes mellitus	618 (24.5%)	432 (35.4%)	160 (37.5%)	**<0.001**
- Immunosuppression	80 (3.0%)	85 (8.8%)	35 (8.0%)	**<0.001**
- Cancer without metastasis	45 (1.7%)	48 (5.0%)	28 (6.4%)	**<0.001**
- Cancer with metastasis	20 (0.8%)	30 (3.1%)	13 (3.0%)	**<0.001**
- Leukaemia	14 (0.5%)	9 (0.9%)	10 (2.3%)	**<0.001**
- Lymphoma	12 (0.5%)	9 (0.9%)	6 (1.4%)	0.05
- BMI (kg/m^2)	31.1 (26.7, 36.8)	30.5 (25.1, 36.5)	29.7 (23.9, 38.2)	**0.004**
Miscellaneous				
- ICU admission post-MET call	846 (32.5%)	201 (20.9%)	202 (46.2%)	**<0.001**
- Cardiac arrest 24 h prior	16 (0.6%)	10 (1.1%)	2 (0.5%)	0.35
- Pre-ICU (hours)	10.4 (4.5, 43.6)	8.0 (4.6, 21.9)	7.1 (4.2, 14.9)	**<0.001**
- Treatment limitations at ICU admission	85 (3.2%)	137 (45.2%)	65 (48.5%)	**<0.001**
- Delirium	135 (7.4%)	74 (9.5%)	36 (10.6%)	0.05
Organ failure scores				
- APACHE-II	13.6 [5.9]	17.4 [6.3]	19.5 [6.0]	**<0.001**
- APACHE-III	45.6 [18.7]	54.5 [19.4]	58.1 [19.7]	**<0.001**
- ANZROD (%)	3.5 (1.8, 7.3)	6.1 (3.0, 13.2)	10.1 (5.1, 19.8)	**<0.001**
- ANZROD (%)	7.5 [10.6]	13.7 [16.0]	19.1 [18.7]	**<0.001**
- SOFA	3 (2, 4)	3 (2, 5)	3 (2, 5)	**<0.001**
Organ supports				
- Mechanical ventilation	850 (33.0%)	233 (25.0%)	61 (14.6%)	**<0.001**
- MV within 24 h of ICU admission	737/850 (86.7%)	230/233 (98.7%)	55/61 (90.1%)	**<0.001**
- MV duration (hours)	149 (51, 279)	78 (22, 210)	102 (37, 240)	**<0.001**
- Non-invasive ventilation	973 (38.0%)	356 (38.0%)	189 (44.9%)	**0.023**
- NIV duration (hours)	20 (4, 54)	35 (3, 40)	15 (6, 36)	0.11
- Vasopressor and inotropes	829 (32.2%)	310 (33.0%)	119 (28.3%)	0.20
- Renal replacement therapy	68 (2.7%)	33 (3.6%)	17 (4.1%)	0.15
- ECMO	49 (1.9%)	3 (0.3%)	0 (0%)	**<0.001**
- Tracheostomy	104 (4.1%)	21 (2.3%)	6 (1.4%)	**0.003**

Data are n (%), mean [SD] or median (IQR).
CFS – clinical frailty scale, SD – standard deviation, IQR – interquartile range, BMI – body mass index, MET – medical emergency team, APACHE – Acute Physiology and Chronic Health Evaluation, ICU – intensive care unit, ANZROD – Australia New Zealand Risk of death.

Table 2
Raw outcomes of patients with COVID-19 based on CFS categories.

Resource Use/Outcomes	'Not frail' Patients (CFS 1–3)	'Mildly frail' Patients (CFS 4–5)	'Moderately-to-severely frail' Patients (CFS 6–8)	p-value
Primary Outcome				
- Overall survival at one year	93.5% (92.2%–94.7%)	78.9% (76.0%–81.9%)	68.1% (63.4%–73.1%)	**<0.001**
- Overall survival at two years	90.6% (88.8%–92.5%)	58.% (53.7%–64.1%)	43.5% (36.4%–51.9%)	**<0.001**
Secondary Outcomes				
1. Length of stay				
- ICU length of stay	3.8 (1.8, 7.8)	2.8 (1.5, 5.7)	2.8 (1.5, 5.3)	**<0.001**
- Hospital length of stay	10.3 (6.0, 17.4)	9.4 (4.9, 18.0)	9.0 (5.5, 16.6)	**0.013**
2. Hospital outcomes				**<0.001**
- Discharged home	2018 (76.9%)	703 (72.7%)	307 (70.3%)	
- Transferred to other hospital	477 (18.2%)	198 (20.5%)	90 (20.6%)	
- Rehabilitation facility	108 (4.1%)	49 (5.1%)	14 (3.2%)	
- Nursing Home	11 (0.4%)	17 (1.8%)	23 (5.3%)	
- Other[a]	9 (0.4%)	0 (0%)	2 (0.5%)	

Data are n (%), mean [SD] or median (IQR).
COVID-19 – Coronavirus disease 2019, ICU – intensive care unit, IQR – interquartile range, MV – mechanical ventilation, NIV – non-invasive ventilation, ECMO – extra-corporeal membrane oxygenation.
[a] Includes discharge to a mental health facility or other.

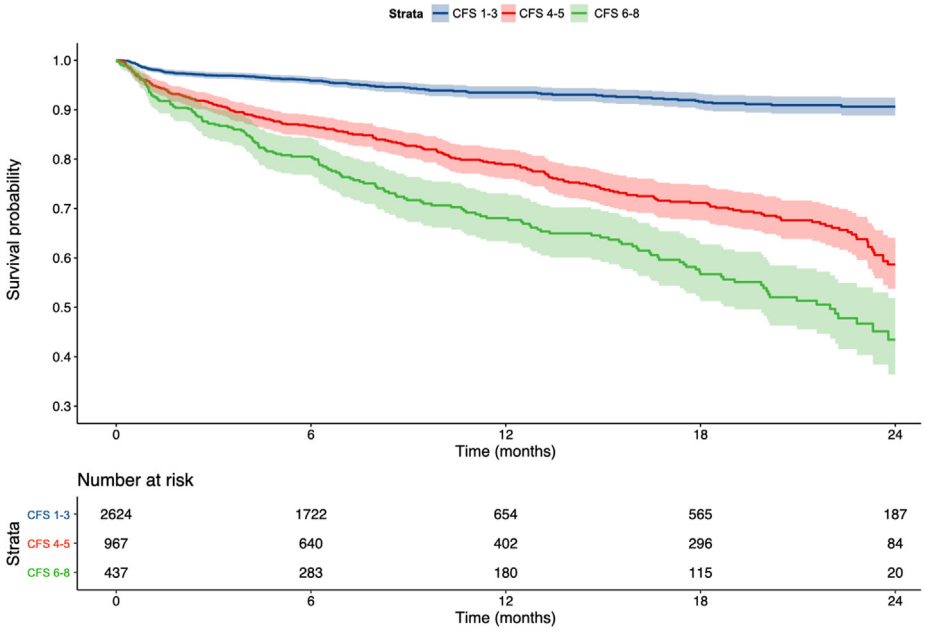

Fig. 1. Kaplan Meier up to 2-year survival curves based on CFS categories for all patients. CFS, clinical frailty scale.

early in the pandemic had similar outcomes (aHR: 0.93, 95%-CI: 0.57–1.51) while patients in the wave-3 later in the pandemic had poorer outcomes (aHR: 2.07, 95%-CI: 1.001–4.30; Supplementary Table 9). Although wave-3 had a higher mortality than the other 2 waves, which both had similar mortality, frailty did not have an effect regardless of the waves (Supplementary Table 10).

Table 3
Cox Proportional Hazards Regression Analysis, for up to 2-year survival, adjusted for SOFA, male sex, Comorbidities, hospital type and jurisdiction for all patients. The CFS was treated as a categorical variable.

Predictor	HR (95%CI)	p-value
CFS categories		
- CFS 1-3	Reference	
- CFS 4-5	2.31 (1.75–3.05)	**<0.001**
- CFS 6-8	2.54 (1.89–3.42)	**<0.001**
Demographics		
- Male sex	1.22 (1.04–1.44)	**0.016**
- Age	1.02 (1.01–1.02)	**<0.001**
Comorbidities		
- Chronic respiratory condition	1.30 (1.06–1.59)	**0.011**
- Chronic cardiovascular condition	1.08 (0.81–1.45)	0.59
- Chronic renal failure	1.16 (0.83–1.61)	0.40
- Chronic liver disease	1.33 (0.56–3.17)	0.51
- Diabetes mellitus	1.00 (0.83–1.20)	0.99
- Metastatic cancer or haematological malignancy	2.73 (2.09–3.57)	**<0.001**
Patient factors		
- SOFA score (per increase of 1)	1.07 (1.02–1.11)	**0.003**
- Treatment limitations at ICU admission	1.84 (1.52–2.23)	**<0.001**
Hospital classification		
- Metropolitan	Reference	
- Private	1.09 (0.81–1.47)	0.57
- Rural/Regional	0.98 (0.79–1.21)	0.85
- Tertiary	0.55 (0.37–0.83)	**0.004**
Jurisdiction		
- Australian Capital Territory	Reference	
- New South Wales	1.90 (1.45–2.50)	**<0.001**
- Northern Territory	1.73 (0.70–4.30)	0.24
- New Zealand	2.94 (0.35–24.86)	0.32
- Queensland	126 (0.74–2.13)	0.28
- South Australia	1.28 (0.82–2.00)	0.28
- Tasmania	0.00 (0.00–0.00)	**<0.001**
- Victoria	1.52 (1.16–2.00)	**<0.001**
- Western Australia	1.57 (0.64–3.86)	0.33

CFS – clinical frailty scale, SOFA – sequential organ failure assessment.

3.3. Secondary outcomes

The ICU LOS was lower for 'mildly frail' (median 2.8 [IQR 1.5–5.7] days) and 'moderately-to-severely frail' (median 2.8 [IQR 1.5–5.3] days) patients than 'not frail' (median 3.8 [IQR 1.8–7.8] days) patients. Persistent critical illness, defined as ICU LOS $\geq$10 days, was infrequent in patients with frailty ('mildly frail' 12.0% [n = 116], and 'moderately-to-severely frail' 7.3% [n = 32]) when compared to 'not frail' (18.3% [n = 481]) patients ($p < 0.001$). Similarly, the hospital LOS was lower for 'mildly frail' (median 9.4 [IQR 5.9–18.0] days) and 'moderately-to-severely frail' (median 9.0 [IQR 5.5–16.6] days) patients than 'not frail' (median 10.3 [IQR 6.0–17.4] days) patients. When compared to the 'not frail' patients, those with frailty were less commonly discharged home and more commonly discharged to nursing homes ($p < 0.001$). The raw secondary outcomes are summarised in Table 2.

4. Discussion

4.1. Key findings

This study found that patients with frailty (comprising one-third of the population) had poorer survival outcomes in most populations, including those of older age groups. However, the survival time of up to two years for 'moderately-to-severely frail' patients who received mechanical ventilation was better than those without frailty. Our findings suggest that frailty has a relevant prognostic value in patients with severe COVID-19.

4.2. Relationship to previous studies

Even after discharge, frailty increases the risk of patient-centred adverse outcomes in COVID-19 ICU survivors.[18] As such, investigating long-term survival and 'long-COVID' is pertinent. Previous studies have suggested that frailty is associated with in-hospital mortality[12,28] and patient-centred adverse outcomes after

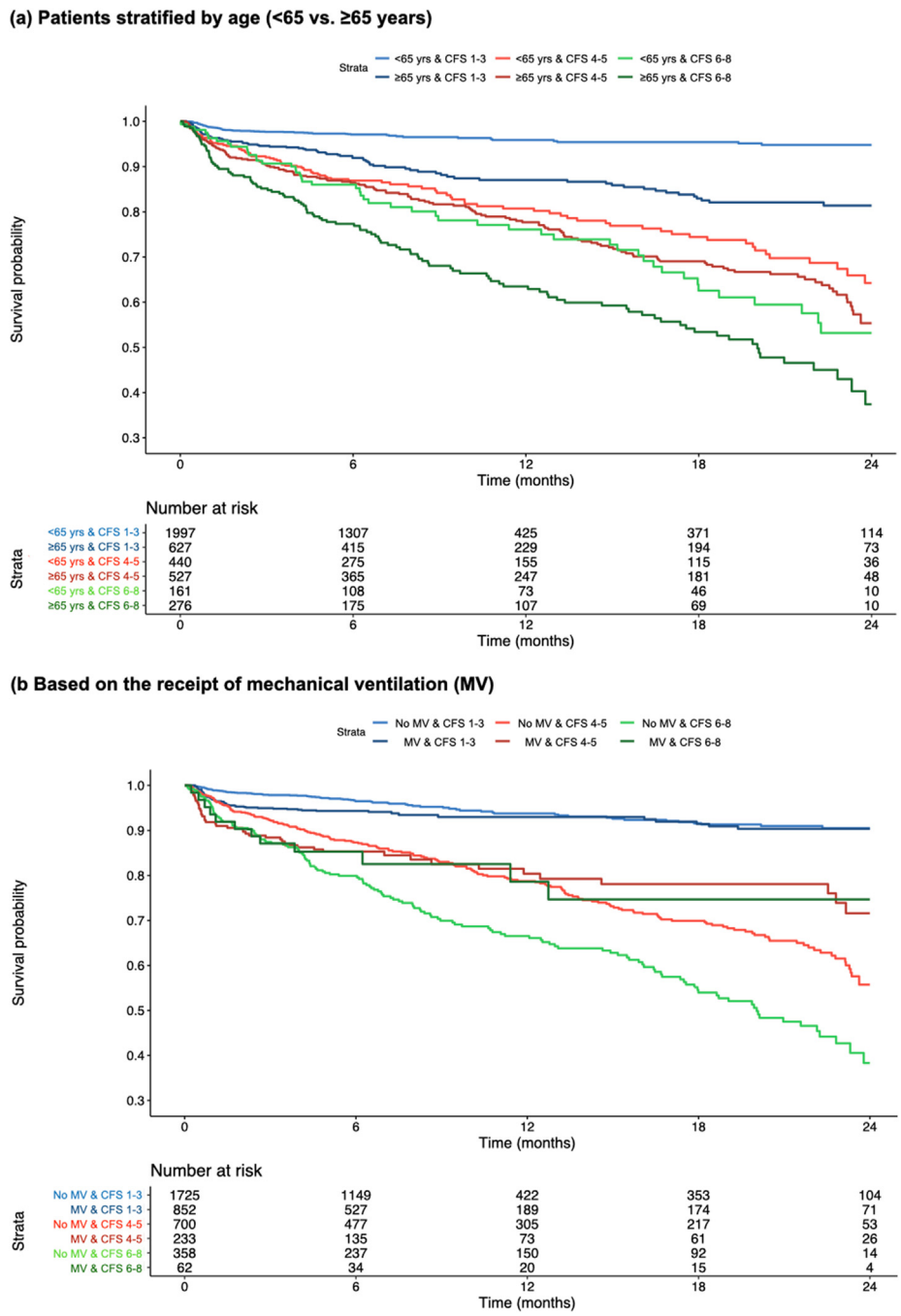

Fig. 2. Kaplan Meier curves up to 2-year survival curves based on the frailty status (**a**) within the same age group and (**b**) receipt of mechanical ventilation or not.

hospital discharge,[18] which formed the basis of our population. A recent study found that patients with CFS ≥4 had poorer six-month.[17] We found that patients with frailty (CFS ≥4) had poorer long-term survival. Although we did not collect the cause of death, this is likely multifactorial: critical illness is associated with systemic inflammation, which accelerates a decline in muscle mass, physical function, and frailty, especially in those with prolonged critical illness or who received mechanical ventilation.[29] The socio-demographic characteristics, comorbidities, severity of illness and disease burden can all be postulated.[30] Furthermore, the patients could have died of an unrelated cause.

The older population is heterogeneous, and it is controversial whether age is a predictor of mortality in COVID-19. While some have found that frailty was associated with mortality only among middle-aged patients,[16] others suggest that outcomes were poor regardless of age group.[28] This study found an independent association between frailty and death in patients ≥65 years of age. Although there is controversy in the validity of the CFS in younger patients, a study pre-pandemic found that prehospital frailty is common among younger critically ill patients (50–65 years) and was associated with higher 1-year mortality and rehospitalization.[5]

Patients with frailty are less likely to receive mechanical ventilation[28] and for shorter periods.[9] While others have reported that 50–80% of patients with severe COVID-19 required mechanical ventilation,[9,16,17] we found that only 30% of patients received mechanical ventilation, less so for patients with 'moderately-to-severely frail' patients. An individual patient data meta-analysis observed that in patients receiving mechanical ventilation, frailty

was associated with mortality,[9] of which were echoed by more recent studies.[12] However, a study reported that >50% of patients receiving mechanical ventilation for COVID-19 survived at 180 days.[15] Similarly, we found that patients with frailty who did not receive mechanical ventilation had higher mortality rates than those who did, suggesting appropriate patient selection. Nonetheless, we cannot exclude the possibility of survivor bias and inaccuracies in CFS recordings cannot be ruled out.

4.3. Implications of study findings

Our study found that a third of patients discharged after severe COVID-19 have frailty. Therefore, cautious, individualized, evidence-informed patient-centred care is of paramount importance. Our results support the assessment of frailty to better inform therapeutic choices and expectations regarding prognosis in severe COVID-19.3 Conversations about goals of care may be essential for those with multiple chronic conditions and greater baseline frailty levels.[17,31] Furthermore, it is essential for clinicians to discuss the expected outcomes with the patient and family when admitted to ICU. Our findings support the incorporation of frailty measurement in day-to-day ICU practice[17] and suggest developing international guidelines to consider frailty in clinical decision-making. Furthermore, this knowledge of frailty and critical care will make us better equipped in caring for patients with and without frailty in the next frontier beyond COVID-19.

4.4. Strengths and limitations

Our study has several notable strengths. First, this is based on a large sample of high-quality data, increasing the precision of our estimates. The pre-specified secondary analyses lend weight to the primary analysis. Furthermore, we are the first study to use the new updated CFS tool,[23] which better reflects the continuous nature of functional status, and more accurately predicts ICU outcomes.[32] There are a few limitations to this study. First, this is a retrospective study and causal inferences cannot be drawn. In addition, we had to exclude patients without a documented CFS. While we believe that our cohort is broadly representative of the larger population, this cannot be confirmed. In addition, we cannot rule out data coding inaccuracy, data misclassification and its effects on our findings. Second, the database did not capture patients who were referred for and denied ICU admission. Third, we did not longitudinally assess frailty to account for ongoing disability. As a result, it is challenging to determine the precise impact of frailty after discharge, and whether frailty during ICU admission is the only factor affecting long-term survival. Third, we did not collect data on patients' quality of life after hospital discharge. Fourth, although there is evidence that patients who failed non-invasive ventilation and required mechanical ventilation had poorer outcomes,[15] we did not collect that information. Fifth, we did not have any information about individual patients' vaccination status or if they developed long-COVID. Finally, as these data are limited to patients with critical illness in ANZ, the results may not be generalizable in other healthcare systems or non-critically ill populations.

5. Conclusion

In this retrospective study, frailty was associated with poorer outcomes in patients with severe COVID-19 in ANZ following hospital discharge. Recognizing frailty may provide individualized patient intervention in those with frailty admitted to ICUs with severe COVID-19.

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Author contributions

Study conception: AS.
Study design: AS, RRL, DP.
Data analysis and interpretation: RRL, AS, DP.
Tables and figures: RRL, AS.
Writing – original draft: AS.
Writing – review & editing: AS, RRL, DP.
Critical revision of the manuscript for intellectually important content:
All authors provided critical conceptual input, interpreted the data analysis, and read, and approved the final draft.
DP and AS have accessed and verified the data. AS was responsible for the decision to submit the manuscript.

Conflict of interest

All three authors declare no support from any organization for the submitted work.

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Macquarie Base Hospital ICU, Prince of Wales Hospital (Sydney) ICU, Redcliffe Hospital ICU, Rockingham General Hospital ICU, Royal Brisbane and Women's Hospital ICU, Royal Darwin Hospital ICU, Royal Hobart Hospital ICU, Royal Melbourne Hospital ICU, Royal North Shore Hospital ICU, Royal Prince Alfred Hospital ICU, Ryde Hospital and Community Health Services ICU, Shoalhaven Hospital ICU, Sir Charles Gairdner Hospital ICU, South East Regional Hospital ICU, South West Healthcare (Warrnambool) ICU, St Andrew's Hospital (Adelaide) ICU, St Andrew's Private Hospital (Ipswich) ICU, St George Hospital (Sydney) ICU, St John of God Hospital (Bendigo) ICU, St John Of God Hospital (Murdoch) ICU, St Vincent's Hospital (Sydney) ICU, St Vincent's Hospital (Toowoomba) ICU, St Vincent's Private Hospital Northside ICU, Sunshine Coast University Hospital ICU, Sunshine Hospital ICU, Sutherland Hospital & Community Health Services ICU, Sydney Adventist Hospital ICU, Tamworth Base Hospital ICU, The Bays Hospital ICU, The Chris O'Brien Lifehouse ICU, The Northern Hospital ICU, The Prince Charles Hospital ICU, The Valley Private Hospital ICU, Toowoomba Hospital ICU, Tweed Heads District Hospital ICU, University Hospital Geelong ICU, Wagga Base Hospital & District Health ICU, Waikato Hospital ICU, Wellington Hospital ICU, Werribee Mercy Hospital ICU, Western District Health Service (Hamilton) ICU, Westmead Hospital ICU, Whangarei Area Hospital, Northland Health Ltd ICU, Wimmera Health Care Group (Horsham) ICU, Wollongong Hospital ICU, and Wyong Hospital ICU.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.11.001.

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