Impact of frailty on clinical outcomes in patients with and without COVID-19 pneumonitis admitted to intensive care units in Australia and New Zealand: A retrospective registry data analysis

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Research Article

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Abstract

Background

It is unclear if the impact of frailty on mortality differs between patients with viral pneumonitis due to COVID-19 or other causes. We aimed to determine if a difference exists between patients with and without COVID-19 pneumonitis.

Methods

This multicenter, retrospective, cohort study using the Australian and New Zealand Intensive Care Society Adult Patient Database included patients aged ≥ 16 years admitted to 153 ICUs between 01/012020 and 12/31/2021 with admission diagnostic codes for viral pneumonia or acute respiratory distress syndrome, and clinical frailty scale (CFS). The primary outcome was hospital mortality.

Results

4,620 patients were studied, 3,077 (66.6%) had COVID-19. The patients with COVID-19 were younger (median [IQR] 57.0 [44.7–68.3] vs. 66.1 [52.0-76.2]; p < 0.001) and less frail (median [IQR] CFS 3 [2–4] vs. 4 [3–5]; p < 0.001), than non-COVID-19 patients. The overall hospital mortality was similar between the patients with and without COVID-19 (14.7% vs. 14.9%; p = 0.82). Frailty alone as a predictor of mortality showed only moderate discrimination in differentiating survivors from those who died but was similar between patients with and without COVID-19 (AUROC 0.68 vs 0.66; p = 0.42). Increasing frailty scores were associated with hospital mortality, after adjusting for Australian and New Zealand Risk-of-Death score and sex. However, the effect of frailty was similar in patients with and without COVID-19 (OR = 1.29; 95%CI 1.19–1.41 vs. OR = 1.24; 95%CI 1.11–1.37).

Conclusion

The presence of frailty was an independent risk factor for mortality. However, the impact of frailty on outcomes was similar in COVID-19 patients compared to other causes of viral pneumonitis.

Trial Registration:

Not applicable

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating global impact. The clinical spectrum ranges widely from asymptomatic to severe respiratory failure, multiorgan failure, and death [1, 2]. Evidence suggests that older people with frailty are unequally affected [3], and that higher degrees of frailty along with cumulative comorbidities are linked with higher mortality in patients with COVID-19 [3–7].

Healthcare in many parts of the world has been severely strained due to insufficient intensive care unit (ICU) beds and workforce capacity [8]. This pressure resulted in triage systems to maximize efficient resource use [9–14]. Frailty assessment tools, such as the clinical frailty scale (CFS), have been proposed as an adjunct to age-based criteria for critical care triage decisions (The National Institute for Health and Care Excellence, NICE triage guidelines) [15]. This

guideline suggested that patients older than 65 years with a CFS score ≥ 5 might not benefit from ICU admission [10, 12, 16] and such patients were encouraged to establish goals of care documentation [9, 12, 13, 17]. Despite this, frail patients with COVID-19 were admitted to ICU, and had greater mortality but spent relatively fewer days in ICU compared with non-frail patients [18].

Pre-pandemic, patients with frailty were also common among patients admitted to ICU. These patients had more than double the risk of death and functional dependence than patients without frailty [19–21]. A study in Australia and New Zealand found that a third of non-COVID-19 patients admitted to the ICU with pneumonia were frail and were associated with poor outcomes [22]. Frail patients with COVID-19 had a higher case fatality rate. It is, however, unclear if the impact of frailty on outcomes differs between patients with and without COVID-19. With the geographic isolation and very strict public health measures, the Australian and New Zealand healthcare system was not overwhelmed in 2020 [23], allowing improved access to ICU earlier to all patients, including those with frailty. This was however not the case in 2021 when a higher volume of cases put significant strain on the healthcare system in parts of Australia [24]. Consequently, we hypothesized that the presence of frailty in patients admitted to ICU with COVID-19 would be associated with worse outcomes than in patients with other 'non-COVID-19' causes of viral pneumonitis. We aimed to determine whether the impact of frailty differed between patients with viral pneumonitis due to COVID-19 or other causes. Australia and New Zealand were uniquely placed to test this hypothesis because our health systems were not stretched as they were in other parts of the world and resource issues are less of a confounder.

Methods

Study design and setting

This was a retrospective multicenter cohort study, which analysed ICU admissions reported to the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) between 1st January 2020 to 31st December 2021.

ANZICS-APD

The ANZICS-APD is a binational database, that prospectively collects high-quality de-identified patient information, including demographics (such as age and sex), chronic health status, physiological and biochemical variables within the first 24 hours of admission required for the Acute Physiology and Chronic Health Evaluation (APACHE)-III-j and IV illness severity scores and Australian and New Zealand Risk of Death (ANZROD), as well as ICU and hospital outcomes. Each patient is allocated a single diagnosis which reflects the primary cause of admission to ICU using the ANZICS modification of the APACHE-IV diagnosis coding system [25].

Patient Identification

Adult patients (age ≥ 16 years), with a documented CFS score, admitted to Australian and New Zealand ICUs with an ICU admission diagnosis of Viral Pneumonia or Acute Respiratory Distress Syndrome (ARDS) were included. Patients were further classified using a subcode of "suspected or confirmed pandemic infection" to indicate which were highly likely to have COVID-19 (Supplementary Table 1). Readmission episodes during the same hospitalization and admissions for organ donation or palliative care were excluded, as were patients with no primary outcome (hospital mortality) listed.

Data extraction

Data included patient demographics (age, sex, comorbidities, ethnicity, ICU admission source, smoking status), CFS, ICU organ supports (need for mechanical ventilation, non-invasive ventilation, vasopressors, tracheostomy, extracorporeal membrane oxygenation [ECMO] and/or renal replacement therapies), treatment limitation order, ICU and hospital mortality, and respective length of stays.

Frailty assessment

Frailty was identified using the Canadian Study of Health and Aging Clinical Frailty Scale, a nine-point assessment tool to quantify frailty based on the deficit accumulation approach [26]. This scale ranges from CFS = 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail) to 9 (terminally ill). This measurement has been validated among critically ill patients [19, 20] with good inter-rater reliability [19, 27], and reported to be correlated with the other comprehensive frailty scales [28, 29]. In the ANZICS-APD, the CFS is modified to eight categories without a CFS-9 (terminally ill) [30]. The CFS represented the patient's status in the two months preceding ICU admission [30]. For this study, we further grouped CFS scores according to five groups, CFS-1-3, CFS-4, CFS-5, CFS-6, and CFS-7-8 as reported in recent studies [31, 32].

Exposure and confounding variables

The exposure variable was frailty status based on CFS categories in patients with and without COVID-19. The confounding variables were illness severity (measured with ANZROD), and sex.

Study aims and outcomes

We aimed to investigate whether the impact of frailty on mortality differed between patients with and without COVID-19. The primary outcome was hospital mortality. Secondary outcomes included ICU mortality, ICU and hospital length of stays and discharge destination.

Subgroup analysis

Predefined subgroup analyses based on age ($\geq$ 65 years), and those needing mechanical ventilation were performed.

Statistical Analysis

The group comparisons between patients with and without COVID-19 were made using chi-square tests for proportions, student t-tests for normally distributed data and Mann-Whitney U or Kruskal-Wallis tests for non-parametric data depending on the number of categories examined. Data are reported as frequencies (%), means (standard deviations [SD]) or medians (interquartile range [IQR] 25%-75%) respectively. Illness severity was determined using ANZROD, a highly discriminatory, locally derived, and well-calibrated mortality prediction model used for benchmarking ICU performance in Australia and New Zealand which combines age, chronic illnesses, acute physiological disturbance, and diagnosis [33, 34]. The association of CFS with hospital mortality in patients with and without COVID-19 was investigated using multivariable logistic regression with results reported as odds ratio (OR) and 95% confidence interval (CI). Model discrimination was assessed using the area under the receiver operating characteristic (AUROC) plots with the comparison between models assessed using chi-square tests [35]. Sensitivity analysis was performed with CFS treated as a continuous variable. Further sensitivity subgroup analyses were performed which separately examined patients admitted in 2020 and 2021 (when there was a higher burden of COVID-19 admissions). Analyses were performed using SPSS software (version 27), and a two-sided p-value of < 0.05 was used to indicate statistical significance.

Ethics approval:

The Alfred Hospital Ethics Committee (Project No: 176/21) approved this study. ANZICS Centre for Outcome and Resource Evaluation Management Committee granted access to the ANZICS-APD in accordance with standing protocols.

Results

During the study period, a total of 5,735 patients were admitted to 153 Australian and New Zealand ICUs with admission diagnoses of either viral pneumonia or ARDS, that were reported to the ANZICS-APD. Of these, 4,620 patients had a documented CFS and were included in the study. There were no differences in age, sex, the proportion of treatment limitations, or hospitalization prior to ICU or pre-ICU hours between the 4,620 patients and 1,115 patients without a documented CFS. However, a lower proportion of those with missing frailty data had COVID-19 and these patients had higher illness severity scores (Supplementary Table 2).

Baseline characteristics are presented in Table 1. Patients with COVID-19 were younger (median age 57.0 [IQR 44.7–68.3] vs. 66.1 [IQR 52.0-76.2]; $p < 0.001$) and less frail (median CFS 3 [IQR 2–4] vs. 4 [IQR 3–5]; $p < 0.001$), than patients without COVID-19. A higher proportion of patients with COVID-19 were male (61.3% vs. 51.3%; $p < 0.001$). Patients with COVID-19 had lower APACHE-III scores and less frequently had chronic comorbidities such as respiratory, cardiovascular, renal, liver, immunosuppressive conditions, and metastatic cancer, but were more likely to be obese and have delirium, than patients without COVID-19. Admissions to ICU following a rapid response team review were less frequent for patients with COVID-19 (36.2% vs. 39.3%; $p = 0.045$). More patients with COVID-19 needed mechanical ventilation, tracheostomies, ECMO therapies and vasoactive agents, whereas fewer patients needed non-invasive ventilation or renal replacement therapy than patients without COVID-19 (Supplementary Fig. 1). Further categorization by age and CFS categories is provided in Supplementary Fig. 2; and Supplementary Tables 3a and 3b.

Table 1
Baseline characteristics of patients with and without COVID-19.

Variable	Patients with COVID-19	Patients without COVID-19	p-value
Number	3,077	1,543	-
Frailty status, n (%)			
- CFS-1-3	2,298 (74.7%)	620 (40.2%)	< 0.001
- CFS-4	410 (13.3%)	408 (26.4%)	
- CFS-5	157 (5.1%)	206 (13.4%)	
- CFS-6	144 (4.7%)	203 (13.2%)	
- CFS-7-8	68 (2.2%)	106 (6.9%)	
CFS - Frailty score (median [IQR])	3 (2, 4)	4 (3, 5)	< 0.001
Age (years) (median (IQR))	57.0 (44.7, 68.3)	66.1 (52.0, 76.2)	< 0.001
Male sex, n (%)	1887 (61.3%)	792 (51.3%)	< 0.001
Indigenous status, n (%)	79 (2.7%)	139 (9.3%)	< 0.001
Jurisdiction, n (%)			
- New South Wales	1,486 (48.3%)	466 (30.2%)	< 0.001
- Victoria	1,387 (45.1%)	396 (25.7%)	
- Queensland	37 (1.2%)	257 (16.7%)	
- Western Australia	37 (1.2%)	117 (7.6%)	
- South Australia	2 (0.1%)	62 (4.0%)	
- Tasmania	2 (0.1%)	25 (1.6%)	
- Australian Capital Territory	60 (1.9%)	62 (4.0%)	
- Northern Territory	4 (0.1%)	49 (3.2%)	
- New Zealand, n. (%)	62 (2.0%)	109 (7.1%)	
Admission source, n (%)			
- Home	2,483 (80.7%)	1,199 (77.7%)	< 0.001
- Other acute hospital	280 (8.4%)	251 (16.3%)	
- Nursing home or chronic care	15 (0.5%)	21 (1.4%)	
- Other hospital ICU	260 (8.4%)	52 (3.4%)	
- Rehabilitation	3 (0.1%)	6 (0.4%)	
- Missing	36 (1.2%)	14 (0.9%)	
ICU admission source, n (%)			
- Emergency department (ED)	1,198 (38.9%)	660 (42.8%)	< 0.001

Variable	Patients with COVID-19	Patients without COVID-19	p-value
- Ward	1,486 (48.3%)	714 (46.3%)	
- Other hospital (ED and ICU)	378 (12.2%)	161 (10.4%)	
- Operating theatre / Recovery	1 (0.0%)	2 (0.1%)	
- Direct admit	14 (0.5%)	6 (0.4%)	
Documented co-morbidities, n (%)			
- Chronic respiratory condition	201 (6.5%)	305 (19.8%)	< 0.001
- Chronic cardiovascular condition	180 (5.8%)	189 (12.2%)	< 0.001
- Chronic renal failure	74 (2.4%)	183 (11.9%)	< 0.001
- Chronic liver disease	22 (0.7%)	37 (2.4%)	< 0.001
- Diabetes mellitus	866 (29.3%)	415 (28.4%)	0.019
- Immune suppressive therapy	147 (4.8%)	182 (11.8%)	< 0.001
- Lymphoma	13 (0.4%)	29 (1.9%)	< 0.001
- Leukaemia	26 (0.8%)	77 (5.0%)	< 0.001
- Metastatic cancer	25 (0.8%)	59 (3.8%)	< 0.001
- Obese (BMI $\geq$ 30 $kg.m^{-2}$)	1,061 (34.5%)	412 (26.7%)	< 0.001
- Delirium	261 (8.5%)	116 (7.5%)	< 0.001
- Pregnancy status	72 (2.3%)	13 (0.8%)	< 0.001
Pre-ICU (days) (median [IQR])	0.35 (0.13, 1.63)	0.38 (0.14, 1.39)	0.90
Organ failure scores			
- APACHE III (mean [SD])	50.1 (20.0)	58.4 (21.7)	< 0.001
- ANZROD (%) (mean [SD])	9.6 (12.3)	16.0 (18.2)	< 0.001
ICU admission post MET call	1,107 (36.2%)	603 (39.3%)	0.045
Treatment limitations	248 (8.1%)	299 (19.4%)	< 0.001
Cardiac arrest, n (%)	6 (0.2%)	8 (0.5%)	0.08
ICU Supports			
Mechanical ventilation (MV), n (%)	1,314 (43.2%)	328 (22.1%)	< 0.001
MV duration (hours), median (IQR)	178.0 (68.0, 348.8)	92.0 (37.0, 204.5)	< 0.001
Non-invasive ventilation (NIV), n (%)	1268 (41.9%)	750 (50.0%)	< 0.001
NIV duration (hours), median (IQR)	21.0 (4.3, 66.0)	11.0 (3.0, 30.0)	< 0.001
Vasopressor and inotropes, n (%)	1,197 (39.3%)	461 (30.8%)	< 0.001
Renal replacement therapy, n (%)	182 (6.0%)	162 (10.9%)	< 0.001

Variable	Patients with COVID-19	Patients without COVID-19	p-value
Extracorporeal membrane oxygenation	106 (3.5%)	25 (1.7%)	< 0.001
Tracheostomy, n (%)	190 (6.3%)	38 (2.6%)	< 0.001

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, ED – emergency department, ICU – intensive care unit, ROD – risk of death, ANZROD – Australia New Zealand risk of death.

Please refer to Supplementary Tables 3a and 3b for baseline characteristics based on CFS categories.

Primary Outcome:

Overall hospital mortality was similar between patients with and without COVID-19 (14.7% [441/3,006] vs. 14.9% [280/1,541]; p = 0.82). Higher hospital mortality was observed in COVID-19 patients compared to those without COVID-19 at equivalent frailty levels (p = 0.024; Table 2; Fig. 1). Frailty alone as a predictor of mortality showed only moderate discrimination in differentiating survivors from those who died. This effect was similar between patients with and without COVID-19 (AUROC 0.68 vs 0.66; p = 0.42, Fig. 2).

Table 2
Unadjusted hospital mortality in patients with and without COVID-19 (overall and at different levels of frailty). (Also refer to Fig. 2).

	Patients with COVID-19 (n = 3,006)	Patients without COVID-19 (n = 1,541)	p-value
Hospital mortality overall, n (%)	441 (14.7%)	230 (14.9%)	0.82
Hospital mortality by CFS categories, n (%)			
- CFS-1-3	238/2,241 (10.6%)	53/620 (8.5%)	0.024
- CFS-4	88/405 (21.7%)	52/407 (12.8%)	
- CFS-5	43/154 (27.9%)	41/206 (19.9%)	
- CFS-6	42/140 (30.0%)	54/203 (26.6%)	
- CFS-7-8	30/66 (45.5%)	30/105 (28.6%)	
CFS – clinical frailty scale			

After adjusting for baseline illness severity (ANZROD) and sex, higher frailty scores were independently associated with mortality in patients with and without COVID-19 (Supplementary Table 4). The presence of frailty (assessed as CFS categories) added little to the discriminatory capacity of the logistic regression model to predict death which already included ANZROD and sex. The impact of frailty on mortality prediction was also no different between patients with and without COVID-19 (AUROC 0.80 vs 0.81; p = 0.82; Fig. 2).

In a sensitivity analysis where frailty was assessed using CFS as a continuous variable, increasing frailty scores were associated with mortality, after adjusting for ANZROD and sex. This effect was similar in patients with and without COVID-19 (OR = 1.29; 95%CI 1.19–1.41 vs. OR = 1.24; 95%CI 1.11–1.37; Supplementary Table 4).

Secondary Outcomes:

The unadjusted ICU mortality rates were higher only for non-frail patients with COVID-19 for CFS categories CFS-1-3 (8.6% vs. 5.8%; p = 0.023) and CFS-4 (17.1% vs. 8.9%; p < 0.001), compared to patients without COVID-19 (Supplementary Table 5). Patients with COVID-19 had a longer median length of stay in ICU than patients without COVID-19 (5.0 [IQR 2.1–10.9] vs. 3.0 [IQR 1.6–5.6] days; p < 0.001; Supplementary Fig. 3), especially for CFS categories CFS-1-3, CFS-4, and CFS-5. The median hospital length of stay was no different for patients with COVID-19 (12.9 [IQR 7.4–21.7] vs. 10.1 [IQR 5.4–18.8] days; p < 0.001) for CFS categories, than those without COVID-19 (p = 0.91). The ICU readmissions were lower in patients with COVID-19 for CFS categories CFS-1-3, CFS-4, and CFS-6, than in those without COVID-19 (p < 0.001). Overall, the patients with COVID-19 were less likely to be discharged home or to a nursing home, when compared to patients without COVID-19 (both p < 0.001 respectively.

Subgroup analysis

Patients ≥ 65 years

Of the 1,861, a lower proportion of patients with COVID-19 were ≥ 65 years, than those without COVID-19 (33.6% vs. 53.7%). Their median age was similar between the 2 groups (Supplementary Table 6). When compared to patients without COVID-19, the unadjusted hospital mortality was higher for patients with COVID-19 across all CFS categories, (p < 0.001). In patients aged ≥ 65 years, although the increasing frailty scores were associated with mortality, after adjusting for ANZROD and sex, the effect of frailty was similar in patients with and without COVID-19 (Fig. 3; Supplementary Table 10).

Patients needing mechanical ventilation

1,642 patients (35.5%) were mechanically ventilated. Although more patients with COVID-19 received mechanical ventilation overall, (42.7% vs. 21.3%; Supplementary Table 7), the number of patients with frailty was lower than those without COVID-19 (9.5% vs. 24.1%). The raw mortality was higher for patients with COVID-19 for CFS categories CFS-1-3, CFS-4, and CFS-7-8, when compared to patients without COVID-19 (p < 0.001). Although the increasing frailty scores were associated with mortality, after adjusting for ANZROD and sex, the effect of frailty was similar in patients with and without COVID-19 (Fig. 3; Supplementary Table 10).

Patients admitted in 2020

Of the 1,163 patients (25.2%) admitted, 38.1% (n = 444) had COVID-19 (Supplementary Table 8). The raw hospital mortality was higher for patients with COVID-19 for all CFS categories except CFS-7-8 when compared to patients without COVID-19 (p < 0.001). Despite the increasing frailty scores were associated with mortality, after adjusting for ANZROD and sex, the effect of frailty was similar in both groups (Fig. 3; Supplementary Table 10).

Patients admitted in 2021

Of the 3,457 patients (74.8%) admitted, 85.1% (n = 2,942) were patients with COVID-19 (Supplementary Table 9). Of these, most were non-frail (75.2%, 2,212/2,942) when compared to patients without COVID-19 (69.4%, 675/972). The raw hospital mortality was higher for patients with COVID-19 for all CFS categories (p < 0.001). Although the increasing frailty scores were associated with mortality, after adjusting for ANZROD and sex, the effect of frailty was similar in patients with and without COVID-19 (Fig. 3; Supplementary Table 10).

Discussion

Summary of key findings

This multicenter retrospective observational study that compared viral pneumonia patients with and without COVID-19 admitted to ICU in Australia and New Zealand revealed that: firstly, the mortality increased with increasing frailty, but the impact of frailty was similar in patients with and without COVID-19 pneumonitis. Secondly, patients with COVID-19 were less frail and younger than patients without COVID-19. Thirdly, the CFS independently predicted hospital mortality in both patients with and without COVID-19 pneumonitis but had a low discriminatory capacity. Fourthly, only one in ten patients with frailty with COVID-19 received mechanical ventilation. Finally, the mortality was higher in patients ≥65 years of age and those requiring mechanical ventilation, especially with increasing frailty.

Relationship to previous findings

Our key study finding was that although the risk of death increased with frailty, the impact of frailty on hospital mortality was comparable between patients with and without COVID-19 pneumonitis. It is important to note that the Australian experience of the COVID-19 pandemic has differed from that internationally [36]. Our mortality rates were considerably lower than in other parts of the world. Importantly, we observed that the patients with COVID-19 were not only younger and less frail but also the overall proportion of patients with frailty was smaller when compared with those without COVID-19. This was similar to a recent study that compared the characteristics and outcomes of very old patients with COVID-19 with historical controls and found that patients with COVID-19 were relatively less frail and had lower illness severity scores [37]. There was a higher proportion of patients with frailty in the non-COVID-19 group. Although outcomes in patients with frailty are bad [20, 22], the outcomes related to COVID-19 pneumonitis are worse. These two factors trade off against each other, explaining why the overall hospital mortality was similar between the two groups.

It is well established that higher degrees of frailty have been associated with poor outcomes and higher mortality rates during and after ICU admission [38, 39]. Similarly, we observed that hospital mortality increased with increasing frailty in both patients with and without COVID-19. A recent large prospective multinational study (COVIP) identified that frailty was independently associated with lower survival [11]. Our study found that although the CFS independently predicted hospital mortality but had a low discriminatory capacity. Furthermore, the CFS was unable to clinically improve upon the predictability provided by baseline patient illness severity.

Patients with frailty were associated with lower use of mechanical ventilation [11, 40]. A recent systematic review observed that patients with frailty with COVID-19 were less commonly admitted to ICU or receive mechanical ventilation [41]. However, among those admitted to the ICU, almost two-thirds of patients with frailty with COVID-19 died in the hospital, with a greater risk of death for those receiving mechanical ventilation, when compared with patients without frailty [40]. Hospital mortality was relatively lower in these patients when compared to the published literature [11, 37, 40-42]. We observed that only 10% of patients with frailty with COVID-19 needed mechanical ventilation, which was lower than recently published in patients with COVID-19 [37, 41]. However, although the hospital mortality was higher, it was comparable in patients without COVID-19. This may indicate that frailty status was adopted as one of the triaging factors to screen patients for ICU admission and/or appropriate critical care interventions. These in turn may reinforce the importance of prudent selection and appropriate management of older patients with frailty amidst the pandemic, as previously observed [41].

Study Implications

Our study found that frailty independently predicted mortality in both patients with and without COVID-19 pneumonitis, but the impact of frailty was similar in patients with and without COVID-19 pneumonitis. This implies that, regardless of COVID-19 status, the patients' care was no different. This may at least in part reflect intensive care resource availability owing to stringent public health measures in Australia and New Zealand.

Strengths And Limitations

Our study has several notable strengths. Firstly, the multicenter design, incorporating high-quality data Australia and New Zealand wide, as well as a larger sample size than many other studies. Secondly, the CFS, which is the most used frailty assessment tool for critically ill patients. Thirdly, we incorporated pre-specified several secondary analyses, to assess the impact of frailty on several important patient-centered ICU outcomes. To our knowledge, this is the only study to compare the impact of frailty among patients with and without COVID-19 pneumonitis. There are a few limitations to this study. Firstly, the retrospective study design meant that data collection was reliant on existing datasets and medical records. Secondly, despite the submitted information data to the ANZICS-APD being validated to protect the integrity of the collated dataset, there is an expected degree of a possible administrative issue with misinformation, as there could be human errors from manual data entry, misinterpretation of information received, or potentially incorrect source of information retrieved. Thirdly, the CFS was adopted in the assessment of frailty in ICUs across Australia and New Zealand. Despite being an attractive tool to distinguish the different grades of frailty, the reliability of a single assessment tool may be inadequate, especially when it comes to justifying the rationing of medical treatment. Fourthly, the patients with COVID-19 admitted to the ICUs with an alternate diagnosis could have been missed. Finally, the Australia and New Zealand healthcare system has been very fortunate with the magnitude of COVID-19 infections being largely under control, therefore the results may not be generalizable in resource-constrained healthcare systems.

Conclusion

This multicenter retrospective study that compared viral pneumonitis in patients with and without COVID-19 admitted to ICU in Australia and New Zealand found that patients with COVID-19 were younger and less frail than patients without COVID-19. The frailty independently predicted hospital mortality in both patients with and without COVID-19 pneumonitis but had low discriminatory capacity. The impact of frailty, however, was no different in patients with and without COVID-19.

Abbreviations

COPD - chronic obstructive pulmonary disease

COVID-19 – coronavirus disease 2019

IQR - interquartile range

LOS - length of stay

MI – myocardial infarction

n - number

RRT - renal replacement therapy

SD - standard deviation

Declarations

Ethics approval and consent to participate

- All experimental protocols were approved by The Alfred Hospital Ethics Committee (Project No: 176/21) approved this study with a waiver of informed consent.
- ANZICS Centre for Outcome and Resource Evaluation Management Committee granted access to the ANZICS-APD in accordance with standing protocols.
- All methods were carried out in accordance with the relevant guidelines and regulations of theDeclaration of Helsinki.

Consent for publication

- Not applicable

Availability of data and materials

- The datasets generated and/or analysed during the current study are not publicly available as these are linked from three registries (ANZICS, VAED and VDI), but are available from the corresponding author on reasonable request.

Competing interests

- All authors declare no support from any organization for the submitted work.
- All authors declare no financial or non-financial competing interests with regards to the submitted work.

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Author contributions:

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Prof	Kiran Shekar	Methodology, Supervision, Writing - review and editing
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All authors critically reviewed the manuscript and approved the final version before submission.

All authors have agreed both to be personally accountable for the author's own contributions and ensured that questions related to the accuracy or integrity of any part of the work.

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X *et al*: **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study**. Lancet 2020, **395**(10229):1054–1062.
2. He F, Deng Y, Li W: **Coronavirus disease 2019: What we know?** J Med Virol 2020, **92**(7):719–725.
3. Hagg S, Jylhava J, Wang Y, Xu H, Metzner C, Annetorp M, Garcia-Ptacek S, Khedri M, Bostrom AM, Kadir A *et al*: **Age, Frailty, and Comorbidity as Prognostic Factors for Short-Term Outcomes in Patients With Coronavirus Disease 2019 in Geriatric Care**. J Am Med Dir Assoc 2020, **21**(11):1555–1559 e1552.

4. Davis P, Gibson R, Wright E, Bryan A, Ingram J, Lee RP, Godwin J, Evans T, Burleigh E, Wishart S *et al*: **Atypical presentations in the hospitalised older adult testing positive for SARS-CoV-2: a retrospective observational study in Glasgow, Scotland**. Scott Med J 2020:36933020962891.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al*: **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China**. *JAMA* 2020.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC *et al*: **Clinical Characteristics of Coronavirus Disease 2019 in China**. N Engl J Med 2020.
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y *et al*: **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study**. Lancet 2020, **395**(10223):507–513.
8. Kramer DB, Lo B, Dickert NW: **CPR in the Covid-19 Era - An Ethical Framework**. N Engl J Med 2020, **383**(2):e6.
9. Chase J: **Caring for Frail Older Adults During COVID-19: Integrating Public Health Ethics into Clinical Practice**. J Am Geriatr Soc 2020, **68**(8):1666–1670.
10. Hubbard RE, Maier AB, Hilmer SN, Naganathan V, Etherton-Beer C, Rockwood K: **Frailty in the face of COVID-19**. Age Ageing 2020, **49**(4):499–500.
11. Jung C, Flaatten H, Fjølner J, Bruno RR, Wernly B, Artigas A, Bollen Pinto B, Schefold JC, Wolff G, Kelm M *et al*: **The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study**. Critical Care 2021, **25**(1):149.
12. Lewis EG, Breckons M, Lee RP, Dotchin C, Walker R: **Rationing care by frailty during the COVID-19 pandemic**. Age Ageing 2021, **50**(1):7–10.
13. O'Mara L SS, Orkaby AR, Ouchi K, Bernacki R: **A Framework to Triage Older Adults with Covid-19 to Provide Patient-Centered Care**. NEJM Catalyst 2020:1–11.
14. Straw S, McGinlay M, Drozd M, Slater TA, Cowley A, Kamalathasan S, Maxwell N, Bird RA, Koshy AO, Prica M *et al*: **Advanced care planning during the COVID-19 pandemic: ceiling of care decisions and their implications for observational data**. BMC Palliative Care 2021, **20**(1):10.
15. Excellence NIfHaC: **COVID-19 rapid guideline: critical care in adults**. 2020.
16. Smithard DG, Abdelhameed N, Han T, Pieris A: **Age, Frailty, Resuscitation and Intensive Care: With Reference to COVID-19**. *Geriatrics (Basel)* 2021, **6**(2).
17. Maltese G, Corsonello A, Di Rosa M, Soraci L, Vitale C, Corica F, Lattanzio F: **Frailty and COVID-19: A Systematic Scoping Review**. J Clin Med 2020, **9**(7).
18. Okahara S, Subramaniam A, Darvall JN, Ueno R, Bailey M, Pilcher DV: **The Relationship between Frailty and Mechanical Ventilation: A Population-based Cohort Study**. Ann Am Thorac Soc 2021.
19. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, Artiuch B, Ibrahim Q, Stollery DE, Rokosh E *et al*: **Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study**. CMAJ 2014, **186**(2):E95-102.
20. Darvall JN, Bellomo R, Paul E, Subramaniam A, Santamaria JD, Bagshaw SM, Rai S, Hubbard RE, Pilcher D: **Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study**. Med J Aust 2019, **211**(7):318–323.
21. Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, Sibley S, Rockwood K: **The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis**. Intensive Care Med 2017, **43**(8):1105–1122.

22. Darvall JN, Bellomo R, Bailey M, Paul E, Young PJ, Rockwood K, Pilcher D: **Frailty and outcomes from pneumonia in critical illness: a population-based cohort study**. Br J Anaesth 2020, **125**(5):730–738.
23. Chin KL, Ofori-Asenso R, Jordan KA, Jones D, Liew D: **Early signs that COVID-19 is being contained in Australia**. J Infect 2020, **81**(2):318–356.
24. **ANZICS CORE**: **Report on COVID-19 admissions to Intensive Care in Australia 01 January 2021–31 December 2021**. In. Melbourne; 2022: 15
25. **APD** Data Dictionary **ANZICS CORE - ADULT PATIENT DATABASE** [https://
26. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A: **A global clinical measure of fitness and frailty in elderly people**. CMAJ 2005, **173**(5):489–495.
27. Bagshaw SM, Stelfox HT, Johnson JA, McDermid RC, Rolfson DB, Tsuyuki RT, Ibrahim Q, Majumdar SR: **Long-term association between frailty and health-related quality of life among survivors of critical illness: a prospective multicenter cohort study**. Crit Care Med 2015, **43**(5):973–982.
28. Tipping CJ, Hodgson CL, Harrold M, Chan T, Holland AE: **Frailty in Patients With Trauma Who Are Critically Ill: A Prospective Observational Study to Determine Feasibility, Concordance, and Construct and Predictive Validity of 2 Frailty Measures**. Phys Ther 2019, **99**(8):1089–1097.
29. Darvall JN, Greentree K, Braat MS, Story DA, Lim WK: **Contributors to frailty in critical illness: Multi-dimensional analysis of the Clinical Frailty Scale**. J Crit Care 2019, **52**:193–199.
30. Bagshaw M, Majumdar SR, Rolfson DB, Ibrahim Q, McDermid RC, Stelfox HT: **A prospective multicenter cohort study of frailty in younger critically ill patients**. Crit Care 2016, **20**(1):175.
31. Aliberti MJR, Szlejf C, Avelino-Silva VI, Suemoto CK, Apolinario D, Dias MB, Garcez FB, Trindade CB, Amaral J, de Melo LR *et al*: **COVID-19 is not over and age is not enough: Using frailty for prognostication in hospitalized patients**. J Am Geriatr Soc 2021, **69**(5):1116–1127.
32. Aw D, Woodrow L, Ogliari G, Harwood R: **Association of frailty with mortality in older inpatients with Covid-19: a cohort study**. Age Ageing 2020, **49**(6):915–922.
33. Paul E, Bailey M, Kasza J, Pilcher D: **The ANZROD model: better benchmarking of ICU outcomes and detection of outliers**. Crit Care Resusc 2016, **18**(1):25–36.
34. Pilcher D, Paul E, Bailey M, Huckson S: **The Australian and New Zealand Risk of Death (ANZROD) model: getting mortality prediction right for intensive care units**. Crit Care Resusc 2014, **16**(1):3–4.
35. DeLong ER, DeLong DM, Clarke-Pearson DL: **Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach**. Biometrics 1988, **44**(3):837–845.
36. **Tracking outcomes during the COVID-19 pandemic (August 2020) – Divergence within Australia** [https://csrm.cass.anu.edu.au/sites/default/files/docs/2020/9/Tracking_wellbeing_outcomes_during_the_COVID-19_pandemic_February_to_August_2020.pdf]
37. Guidet B, Jung C, Flaatten H, Fjolner J, Artigas A, Pinto BB, Schefold JC, Beil M, Sigal S, van Heerden PV *et al*: **Increased 30-day mortality in very old ICU patients with COVID-19 compared to patients with respiratory failure without COVID-19**. Intensive Care Med 2022.
38. Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A: **Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones**. BMC Geriatrics 2021, **21**(1):389.
39. Rottler M, Ocskay K, Sipos Z, Görbe A, Virág M, Hegyi P, Molnár T, Erőss B, Leiner T, Molnár Z: **Clinical Frailty Scale (CFS) indicated frailty is associated with increased in-hospital and 30-day mortality in COVID-19 patients: a systematic review and meta-analysis**. Annals of Intensive Care 2022, **12**(1):17.

40. Subramaniam A, Anstey C, Curtis JR, Ashwin S, Ponnapa Reddy M, Aliberti MJR, Avelino-Silva TJ, Welch C, Koduri G, Prowle JR *et al*: **Characteristics and Outcomes of Patients With Frailty Admitted to ICU With Coronavirus Disease 2019: An Individual Patient Data Meta-Analysis**. Crit Care Explor 2022, **4**(1):e0616.
41. Subramaniam A, Shekar K, Afroz A, Ashwin S, Billah B, Brown H, Kundi H, Lim ZJ, Ponnapa Reddy M, Curtis JR: **Frailty and mortality associations in patients with COVID-19: A Systematic Review and Meta-analysis**. Intern Med J 2022.
42. Lim ZJ, Subramaniam A, Reddy MP, Blecher G, Kadam U, Afroz A, Billah B, Ashwin S, Kubicki M, Bilotta F *et al*: **Case Fatality Rates for COVID-19 Patients Requiring Invasive Mechanical Ventilation: A Meta-analysis**. Am J Respir Crit Care Med 2020.

Figures

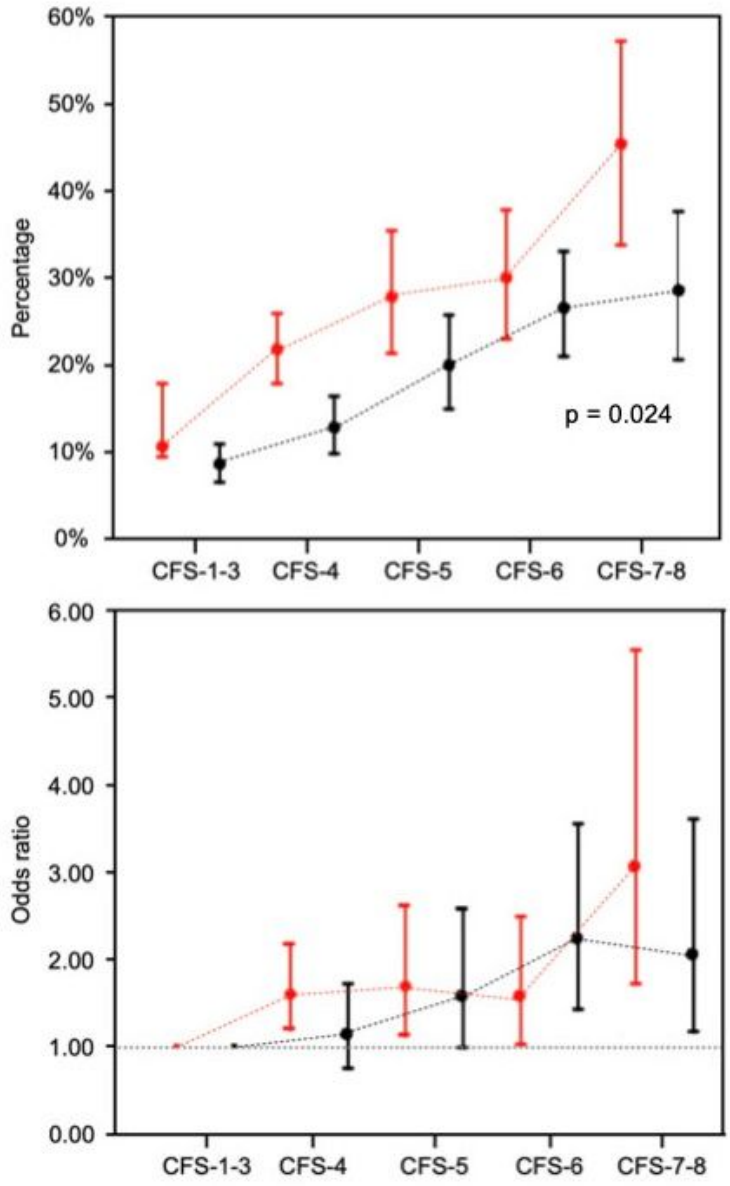

Figure 1

Area under the receiver operating curve with the Clinical Frailty Scale (CFS) treated as categories (CFS-1-3, CFS-4, CFS-5, CFS-6 and CFS-7-8). The comparison between models was assessed using chi-square tests and presented as p-values.

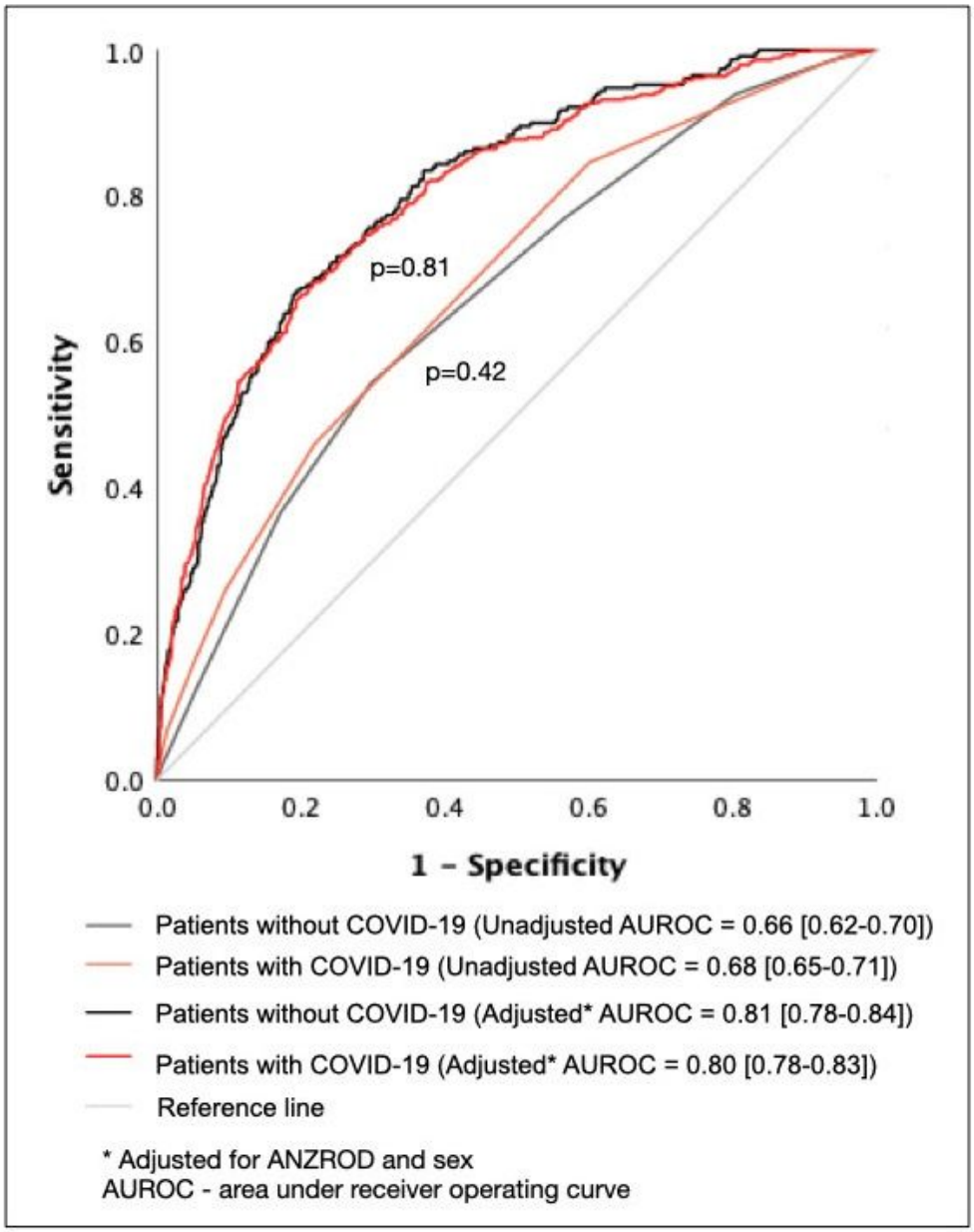

Figure 2

Hospital mortality according to Clinical Frailty Scale (CFS) score for all patients with (red lines) with and without (black lines) COVID-19. The top panel is unadjusted hospital mortality, while the bottom panel is adjusted for ANZROD and sex.

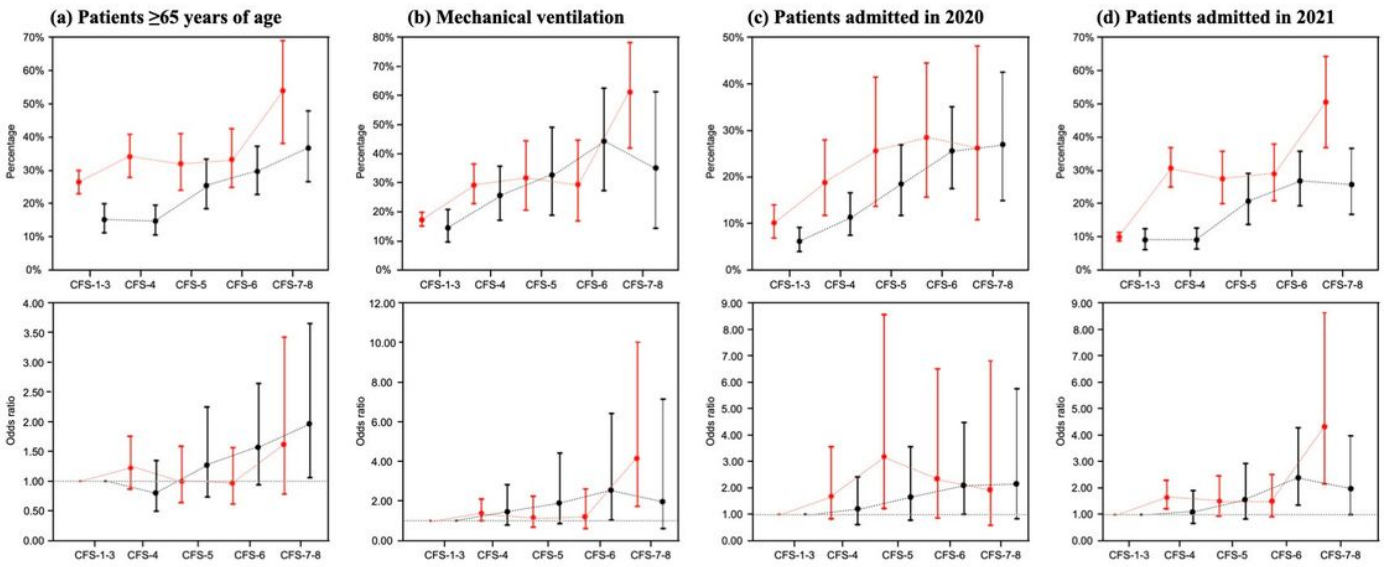

Figure 3

Hospital mortality according to Clinical Frailty Scale (CFS) categories for patients with (red) and without (black) COVID-19: (a) ≥65 years of age, (b) those needing mechanical ventilation, and (c) patients admitted in 2020 and (d) 2021. The top panel is unadjusted hospital mortality, while the bottom panel is adjusted for ANZROD and sex.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FrailtyCCSupplementaryMaterials.docx