Critical Care

RESEARCH Open Access

Frailty and long-term mortality in cardiogenic shock: a binational multicentre cohort study

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Abstract

Background Frailty is increasingly recognised as a prognostic marker in cardiovascular disease, but its role in cardiogenic shock is less defined.

Methods In this retrospective cohort study across 188 intensive care units (ICUs), we analysed data from the Australia and New Zealand Intensive Care Society Adult Patient Database on adults (≥ 16 years) with admitted with cardiogenic shock between 2017–2023, and a documented Clinical Frailty Scale (CFS). The primary outcome was death at up to four years using an adjusted Cox proportional hazards model, which we also assessed using a time-varying model. We conducted subgroup analyses based on age, sex, aetiology of cardiogenic shock, and a landmark survival analysis at ICU discharge.

Results We included 71,359 patients (median age 68.6 years, 70.0% males); 11,087 had frailty. Frailty was associated with a higher hazard of death (adjusted Hazard ratio [aHR]: 2.27, 95% confidence interval [CI]: 2.05–2.51) in a non-linear incremental fashion; this was consistent across sensitivity analyses. Time-varying analysis found that frailty demonstrated the highest hazard for death at approximately six months post-ICU admission (HR: 3.71, 95%-CI: 3.29–4.18). Frailty was more strongly associated with death in patients with ischaemic than non-ischaemic cardiogenic shock, and in males more than females. Frailty was also associated with death in a landmark survival analysis at ICU discharge (aHR: 3.13, 95%-CI: 2.82–3.48).

Conclusions Frailty is associated with mortality beyond ICU discharge in cardiogenic shock in a non-linear, stepwise fashion. These findings support the integration of frailty assessment into ICU risk stratification and post-discharge care planning.

Keywords Frailty, Cardiogenic shock, Clinical Frailty Scale, CFS, Survival, ANZICS

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Introduction

As global demographics shift towards an ageing population, the burden of cardiovascular diseases is projected to rise substantially [1]. Frailty is an age-related state characterised by diminished physiological reserves, multisystem dysregulation, and increased vulnerability to external stressors [2]. Its relationship with cardiovascular diseases is multi-faceted and bidirectional through shared pathophysiological mechanisms such as chronic inflammation, metabolic dysregulation, cellular changes and immune activation [3]. These overlapping pathways create a vicious cycle in which frailty accelerates cardiovascular decline and cardiovascular disease, in turn, promotes the progression of frailty.

While most existing evidence has focused on frailty and chronic cardiovascular disease, emerging data suggest that frailty significantly modifies the presentation and outcomes of acute cardiovascular syndromes, including cardiogenic shock [4–6]. Although acute myocardial infarction (AMI) was historically the predominant aetiology, there is a growing proportion of cardiogenic shock attributable to non-ischaemic aetiologies [4, 6–9]. In this evolving clinical context, frailty is both a risk factor for developing cardiogenic shock and a key determinant in its management [10]. Patients with frailty are less likely to receive invasive interventions such as revascularisation or mechanical circulatory support, and more likely to experience early treatment limitations and in-hospital complications [11–13]. Additionally, frailty doubles the likelihood of inpatient mortality and is associated with more in-hospital complications including delirium and acute kidney injury [10, 14].

Nonetheless, several critical knowledge gaps remain. Most studies of frailty in cardiogenic shock have focussed on ischaemic aetiologies, and insufficiently explore non-ischaemic and post-cardiac surgical cardiogenic shock, which now form majority of cases. In addition, existing studies are limited by sample size and short follow-up, with virtually no data on the trajectory of frailty-associated mortality beyond hospital discharge. Third, whether the association between frailty and death remains constant or varies over time (as observed in prior surgical populations) has not been investigated in cardiogenic shock; this may reveal windows of vulnerabilities that could inform the timing of targeted interventions. Finally, in the incremental impact of increasing frailty on outcomes remains poorly characterised, yet has direct implications for risk stratification and shared decision-making at the bedside. To address these gaps, we analysed data from the binational Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) to evaluate the association between frailty, assessed using the Clinical Frailty Scale (CFS), and both short- and long-term survival among patients with cardiogenic shock in a large, unselected ICU population. We further aimed to characterise the temporal dynamics of this association, assess the incremental impact of frailty severity, and explore whether the frailty-mortality relationship varied by cardiogenic shock aetiology, sex and age. We hypothesised that frailty is associated with poorer short-term and long-term mortality; the association would be strongest in the early- to medium-term, before plateauing in the longer-term period.

Methods

Study design and participants

In this retrospective multi-centre cohort study, we pooled data from 188 intensive care units (ICU) across Australia and New Zealand. We included all patients aged ≥ 16 years admitted to an ICU between 1 January 2017 and 30 June 2023 with cardiogenic shock. We then linked ICU admission records to the respective national death index registers using an encoded linkage key to record the patient's date of death, if present. We excluded patients transferred between ICUs, readmitted to an ICU within the same hospitalisation admitted for palliative care or organ donation, patients who did not have their frailty status documented in the registry, or patients where linkage with national death index registers were unsuccessful resulting in inaccurate survival times. This study was approved by the Alfred Hospital Ethics Committee (Reference 305/24) and the ANZICS Centre for Outcome and Resource Evaluation Management Committee.

Data sources, definition, and collection

Data were extracted from the ANZICS Adult Patient Database (APD), a binational clinical quality registry dataset that collects deidentified information on all admissions to 98% of adult ICUs in Australia, and 67% of ICUs in New Zealand. Data collectors receive regular training and quality assurance reviews and data are collected using a standardised data dictionary [15]. In addition, regular automated data checks further ensure the validity of recorded data. We extracted data on age, sex, comorbidities (as defined by the APACHE II and IV scoring systems), ICU admission source, admission diagnosis, acute illness severity (using the Sequential Organ Failure Assessment [SOFA], APACHE II and III, or Australian and New Zealand Risk of Death [ANZROD] scores), treatment limitations at admission to ICU, frailty status using the Clinical Frailty Scale (CFS), ICU organ supports (mechanical ventilation, non-invasive ventilation, vasopressors, extracorporeal membrane oxygenation, renal replacement therapy), ICU and hospital mortality, ICU and hospital length of stay, and discharge destinations (home, new 24-h long-term care or rehabilitation).

For the purposes of this study, patients were deemed to have cardiogenic shock if they: (A) had a principal diagnosis during their ICU admission of cardiogenic shock (diagnostic code APACHE III-J diagnostic code 101), or (B) had a cardiovascular diagnosis (see Supplementary Methods) and met at least two of the following three criteria: (1) a mean arterial pressure of < 65 mmHg within the first 24 h of ICU admission, (2) received vasopressors or inotropes, or (3) had a serum lactate of ≥ 2 mmol/l. This was chosen in broad adherence with inclusion criteria of prior trials in cardiogenic shock [16], and to broaden the potential population for inclusion in our study, given that some patients with cardiogenic shock may have been inadvertently excluded despite generally meeting the diagnostic criteria of cardiogenic shock.

In the ANZICS-APD, frailty is measured using a modified version of the Canadian Study of Health and Aging Clinical Frailty Scale (CFS), categorising patients as not frail (1 = very fit; 2 = well; 3 = managing well; 4 = vulnerable) or frail (5 = mild; 6 = moderate; 7 = severe; 8 = very severe; 9 = terminally ill) [17], which has demonstrated good inter-rater variability and high correlation with other frailty scales [18–20]. The CFS was assigned at the time of index ICU admission by local clinicians working in the admitting ICU based on the patient's level of function in the 2 months preceding admission. These data were collected in a standardised manner using patient progress notes, medical history and corroborative history from the patient's next-of-kin. In the ANZICS-APD, the CFS is modified to eight categories without a CFS of 9 (terminally ill) [21].

Outcomes

The primary outcome was survival time up to 4 years after ICU admission. Secondary outcomes were analysed descriptively and included survival at 1, 2, 3, and 4 years of follow-up, ICU and hospital mortality, ICU and hospital length of stays, ICU complications (delirium and pressure injury, defined based on the ANZICS-APD data dictionary, see Supplementary Methods), and discharge destination at hospital discharge. The ANZICS-APD collects data on outcomes surrounding the patient's admission (mortality, length of stay, complications, and discharge destination). We linked the ANZICS-APD to the National Death Indexes of each country and derived the death date of each patient, if present. We then estimated their overall survival time, and censored time-to-event data on 1st July 2023, at four-years of follow up, or at their death date, whichever was earliest. Survival at annual follow-up was then derived based on whether each patient was alive or not at the point of follow-up in our analysis.

Statistical analysis

We summarised categorical data using counts and percentages, and continuous data using mean (standard deviation) or median (inter-quartile range [IQR]) as appropriate depending on the distribution. We compared between groups using the $\chi 2$ test, Student t-test, or log-rank tests as appropriate. As in previous studies of the ANZICS-APD [22], we created a separate category "unknown" for patients in which the data field was not recorded or not known (see Table 1 for missingness of each demographic variable).

We estimated the association between frailty (defined as a CFS of ≥ 5) and survival time up to 4 years using a Cox proportional hazards model and reported the results of the analysis using adjusted hazards ratios (aHR) and 95% confidence intervals (95% CI). As with previous studies of the ANZICS registry [23, 24], it is likely that estimates cluster within centres and vary between them, we used robust sandwich-type estimators to estimate the standard errors. In this model, we adjusted for the following covariates, based on previous studies of the ANZICS registry: sex, chronic comorbidities (respiratory, cardiovascular, liver, and renal disease, metastatic cancer, immunosuppression, and diabetes mellitus), and the risk of malnutrition as defined by the modified Nutrition Risk in Critically Ill (mNUTRIC score, see Supplementary Methods) [25], which has been validated in more recent studies [26]. Given that acute illness severity is causally posterior to the presence of frailty, we did not adjust for it in our primary analysis. We also estimated adjusted mortality based on the Cox model using g-computation. To better understand the association between frailty and death over time, we estimated the variance-weighted transformation of the Schoenfeld residuals (or scaled Schoenfeld residuals) for frailty [27, 28]. These are then added to the time-variant coefficient of frailty from the primary Cox regression model. We then modelled these residuals against time in a non-linear fashion using restricted cubic splines, which we iteratively tested with two, three, four, and five knots, and selected the model with four knots based on the Akaike Information Criterion.

We conducted several exploratory sensitivity analyses to assess the robustness of the primary analyses. First, we modelled frailty as an ordinal, eight-level variable (with CFS 1 as the reference group) to explore the association between an increase in frailty status and outcomes. Second, with the updated frailty definition that defined CFS 4 as very mildly frail (rather than vulnerable)[29], we categorised the frailty into three levels (not frail [CFS 1–3], mildly frail [CFS 4–5], and moderately to severely frail [CFS 6–8]). Third, we conducted an analysis focusing only on patients with a principal diagnosis of "cardiogenic shock", excluding other patients with

Table 1 Baseline characteristics of patients with cardiogenic shock, stratified based on frailty status

Demographic variable	Patients without frailty (CFS 1–4)	Patients with frailty (CFS 5–8)	ASD	Missing
Number	60,272 (84.5%)	11,087 (15.5%)		0
Male sex	43,540 (72.2%)	6,378 (57.5%)	0.312	0
Indigenous status*	3,054 (5.2%)	618 (5.8%)	0.026	2,199
Age (years) **	67.7 (58.3, 74.7)	74.1 (65.4, 80.9)	0.541	0
Body mass index	28.1 (24.8–32)	28.1 (24.2–33.6)	0.000	19,672
ICU admission source				
- Emergency Department	10,035 (16.6%)	3,631 (32.8%)	1.08	0
- General Ward	6,505 (10.8%)	3,581 (32.3%)		
- Other hospital	1,807 (3.0%)	461 (4.2%)		
- Other hospital ICU	191 (0.3%)	53 (0.4%)		
- Operating theatre	41,647 (69.1%)	3,337 (30.1%)		
- Direct admit	87 (0.1%)	24 (0.2%)		
Hospital classification				
- Public Tertiary	36,103 (59.9%)	5,314 (47.9%)	0.339	0
- Public Metropolitan	4,481 (7.4%)	2,002 (18.1%)		
- Public Rural/Regional	2,605 (4.3%)	1,554 (14.0%)		
- Private	17,083 (28.3%)	2,217 (20.0%)		
Documented co-morbidities				
- Chronic respiratory condition	2,476 (4.1%)	1,655 (14.9%)	0.375	13
- Chronic cardiovascular condition	8,555 (14.2%)	3,487 (31.5%)	0.421	13
- Chronic liver disease	380 (0.6%)	263 (2.4%)	0.148	14
- Chronic renal failure	1,647 (2.7%)	1,245 (11.2%)	0.339	13
- Metastatic cancer	582 (1.0%)	360 (3.2%)	0.154	4
- Lymphoma	332 (0.6%)	117 (1.1%)	0.054	4
- Leukaemia	298(0.5%)	155 (1.4%)	0.093	4
- Diabetes mellitus	16,985 (28.2%)	4,376 (39.5%)	0.241	4,492
- Immunosuppression	1,365 (2.3%)	533 (4.8%)	0.135	4
- COVID-19 pneumonitis	388 (0.6%)	181 (1.6%)	0.096	0
Miscellaneous				
- Treatment limitations at ICU admission	2,033 (3.4%)	2,981 (26.9%)	0.694	0
- Cardiac arrest	7,336 (12.4%)	2,086 (19.3%)	0.190	1,390
- ICU following rapid response team review	5,565 (9.4%)	3,141 (28.8%)	0.509	1,092
- Pre-ICU hospital stay	24.8 (7.9, 74.3)	20.5 (4.9, 72.1)	0.087	31
Acute Illness Severity scores				
- APACHE-II	16 (13, 21)	22 (17, 29)	0.794	4
- APACHE-III	54 (43, 67)	70 (56, 91)	0.720	4
- ANZROD (%)	10.5 [21.2]	28.0 [29.9]	0.675	0
- SOFA	5 (4, 7)	6 (4, 8)	0.382	0
Organ supports* **				
- Mechanical ventilation	51,516 (85.5%)	6,203 (55.9%)	0.688	795
- Mechanically ventilated from day one	49,049 (95.2%)	5,883 (94.8%)	0.018	312
- Non-invasive ventilation	6,626 (11.0%)	2,152 (19.4%)	0.236	4,440
- Vasopressor and inotropes	55,580 (92.2%)	9,632 (86.9%)	0.174	1,099
- Renal replacement therapy	3,252 (5.4%)	1,245 (11.2%)	0.211	4,669
- Extracorporeal membrane oxygenation	600 (1.0%)	69 (0.6%)	0.045	4,705
- Tracheostomy	566 (0.9%)	137 (1.2%)	0.029	4,755

ASD – Absolute standardised difference, ANZROD – Australia New Zealand Risk of Death, APACHE – Acute Physiology and Chronic Health Evaluation, BMI – body mass index, CFS – clinical frailty scale, ICU – intensive care unit, SOFA – sequential organ failure assessment

* In Australia, those identified as Aboriginal/Torres Strait Islander were coded as Indigenous

** BMI missing in 4,500 patients with frailty, and 15,172 patients without frailty

Data are n (%), mean [standard deviation] or median (interquartile range)

*** Organ supports were added over time as the ANZICS-APD developed. Reporting of the organ supports was only made mandatory from 2019. As such, missingness is mostly attributable to participants admitted prior to 2019

cardiovascular diagnoses who may have otherwise presented with hypotension and signs of hypoperfusion. We did this to increase specificity, and assess the robustness of our inclusion criteria. Fourth, we conducted the analysis adjusting for a different basket of covariates in line with previous literature [30]. Fifth, we noted that approximately 30% of the population (30,000 out of 100,000 patients) had missing frailty status across the study period. While we excluded these patients in our primary analysis, we conducted a sensitivity analysis, using multiple imputation with chain equations to impute for frailty status, using a polytomous regression. We created 10 datasets with 50 iterations, using the 50th iteration as the iteration of datasets for imputation. Thereafter we estimated the hazards of mortality associated with frailty in each dataset, and then pooled the results together.

We then conducted several pre-defined exploratory subgroup analyses by introducing a multiplicative interaction term between the variable of interest and frailty, including aetiology of cardiogenic shock (ischaemic, non-ischaemic, and post-cardiac surgical, see Supplementary Methods for more details), age (< 65 and ≥ 65 years), and sex (male and female). Finally, we performed a landmark survival analysis at ICU discharge as an additional analysis to assess whether the association between frailty and mortality persisted beyond the acute admission. We conducted the data analysis using R 4.4.1 using the *survival, survminer, dplyr, ggplot2,* and *data.table* packages [31–35], and IBM SPSS Version 30 (Armonk, NY, USA), and used a p-value of < 0.005 to indicate statistical significance, given the potential size of our cohort.

Post-hoc analyses

We did two additional sensitivity analyses, including patients with missing frailty, missing frailty as a separate category. Second, we did a landmark analysis excluding patients with ICU stays of < 24 h. We also did two additional subgroup analyses – stratifying by body mass index (BMI < 25, BMI 25–30, BMI > 30), and based on nutritional status (mNUTRIC ≥ 5 vs. mNUTRIC < 5).

Results

Within the study period, 310,694 patients were admitted to ICU with an acute cardiovascular diagnosis. After applying our inclusion and exclusion criteria, we included 71,359 patients (median follow up 21.4 months [IQR: 6.6–39.6]) with cardiogenic shock (23%) in our analysis. Of these, 11,087 (15.5%) patients had a CFS ≥ 5 (Figure S1). A comparison between patients with a recorded vs. missing frailty status is found in Table S1, and a comparison between patients with and without frailty is found in Table 1. Figure S2 summarises the distribution of frailty status in our study.

A total of 12,858 patients (18.0%) did not survive up to four-year follow up. Adjusted mortality, after accounting for potential confounders was 18.2% (95%-CI: 17.9%-18.5%) in patients without frailty and 50.2% (95%-CI; 49.3%-51.1%) with frailty (aHR: 2.27, 95%-CI: 2.05–2.51, Fig. 1). The time-varying adjusted association between frailty and death is shown in Fig. 2; there was a non-linear relationship between frailty and death over time. The maximum association between frailty and death occurred approximately six months after ICU admission (HR: 3.71, 95%-CI: 3.29–4.18). This association was consistent when modelling frailty as an eight-level ordinal variable (from CFS 4 onwards, Figure S3), as a three-level variable (mild frailty aHR: 1.72, 95%-CI: 1.51–1.96, moderate-to-severe frailty aHR: 3.03, 95%-CI: 2.60–3.54, Figure S4), and when analysing a subset of patients who had a principal diagnosis of cardiogenic shock (aHR: 1.63, 95%-CI: 1.50–1.78). We also found similar results when adjusting for a different basket of covariates (aHR: 1.84, 95%-CI: 1.73–1.96) and when imputing for frailty status (aHR: 2.24, 95%-CI: 2.14–2.35). Patients with missing frailty status demonstrated a similar risk profile to those without frailty (aHR: 1.09, 95%-CI: 0.92–1.30).

Our subgroup analysis found that frailty was more strongly associated with mortality patients with ischaemic cardiogenic shock (aHR: 2.00, 95%-CI: 1.60–2.49) than non-ischaemic cardiogenic shock (aHR: 1.47, 95%-CI: 1.37–1.56, p-interaction = 0.0033), but not significantly differently when compared to patients with post-cardiac surgical cardiogenic shock (HR: 2.07, 95%-CI: 1.84–2.33, p = 0.028, Fig. 3). Compared to females (aHR: 2.04, 95%-CI: 1.82–2.28), frailty was more strongly associated with mortality in males (HR: 2.43, 95%-CI: 2.17–2.71, p-interaction < 0.0001, Figure S5). Compared to patients not malnourished (HR: 3.32, 95%-CI: 2.92–3.79), frailty was associated with smaller increases in death among patients with malnutrition (HR: 1.78, 95%-CI: 1.62–1.97, Figure S7). However, there was no association between frailty and outcomes when stratified based on age groups (p-interaction = 0.51, Figure S6) or BMI categories (p-interaction > 0.05, Figure S8). Finally, the landmark survival analysis at ICU discharge (aHR: 3.13, 95%-CI: 2.82–3.48, Figure S9) and excluding patients with ICU stays < 24 h (aHR: 2.37, 95%-CI: 2.13–2.63, Figure S10) showed frailty was also associated with poorer survival. Table 2 summarises the results of the primary and subgroup analyses.

Patients with frailty had higher ICU (21.2% vs. 7.8%) and hospital (29.0% vs. 9.4%) mortality rates, and lower survival rates in the long term. They also had longer ICU and hospital lengths of stay, had a higher rate of delirium and pressure injury, and were less likely to be discharged home. Table 3 summarises the results of the secondary outcomes.

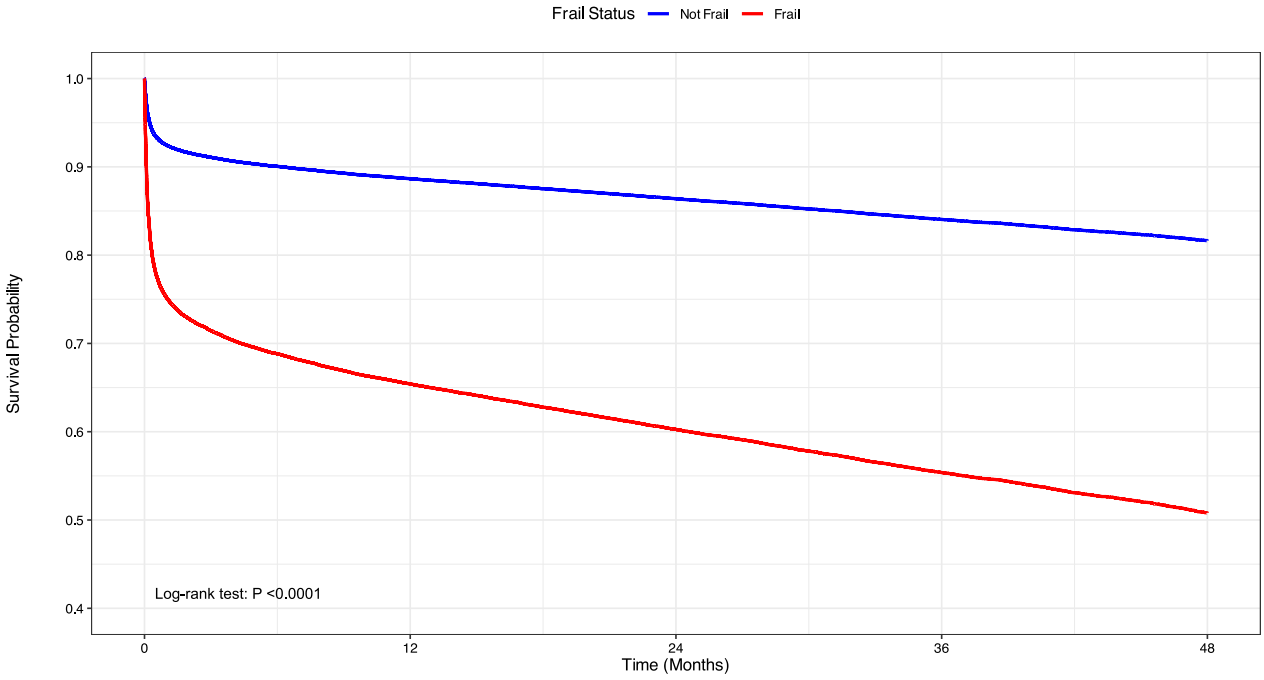

Fig. 1 Adjusted mortality rates in patients with cardiogenic shock, stratified by frailty status

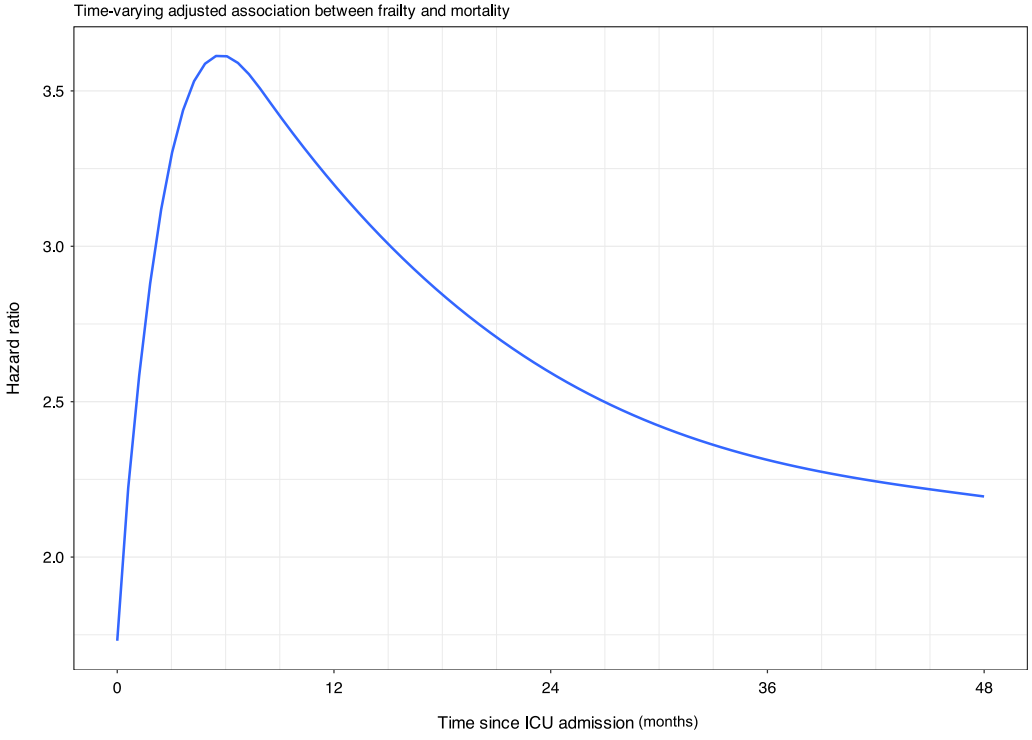

Fig. 2 Time-varying adjusted hazards of mortality in patients with frailty compared to patients without frailty using restricted cubic splines with four knots. Of note, the hazards of death rapidly increase and peak at 6 months, before gradually decreasing over time

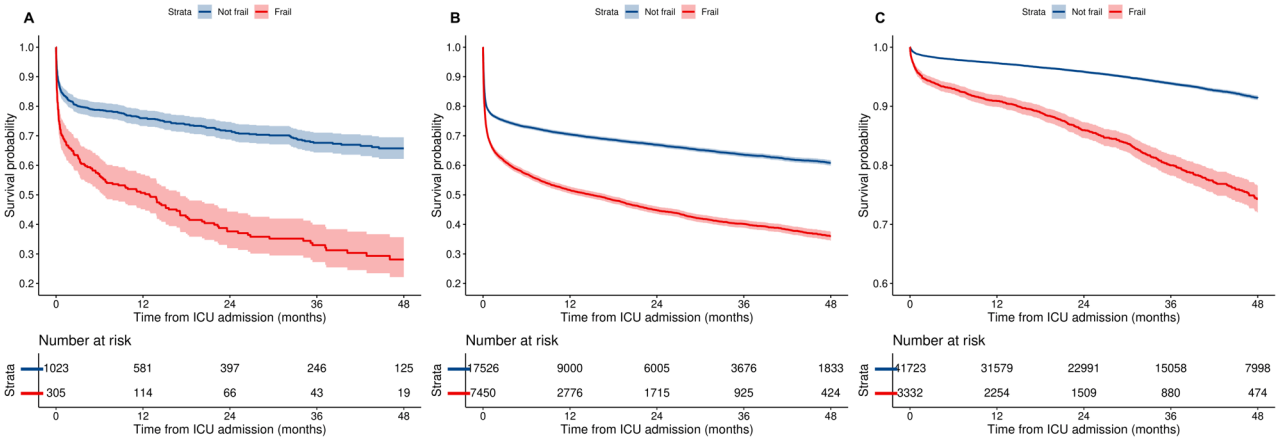

Fig. 3 Unadjusted mortality of patients with and without frailty, in patients with (**A**) ischaemic cardiogenic shock, (**B**) non-ischaemic cardiogenic shock, and (**C**) post-cardiac surgical cardiogenic shock

Discussion

In this binational, multicentre cohort study, frailty was associated with worse short- and long-term outcomes in cardiogenic shock. We also observed a non-linear incremental relationship between the severity of frailty and outcomes. From a CFS of 4, we found that each subsequent increase in frailty was associated with a progressively larger increase in mortality. In addition, the association between frailty and death gradually increased with time, peaked at around 6 months of follow up, before gradually decreasing over time. Finally, the association between frailty and death remained consistent across multiple subgroup analyses and was also evident among ICU survivors, suggesting that frailty may contribute to poor survival beyond the acute phase of illness.

The association between frailty and death in cardiogenic shock is likely mediated through several interconnected pathways. First, "inflammaging", the chronic low-grade inflammation characteristic of frailty, is compounded by the acute inflammatory surge with cardiogenic shock[38]. Patients with frailty may also have impaired resolution of inflammation, resulting in persistent inflammation, immunosuppression, and catabolism. Second, mitochondrial dysfunction results in bioenergetic failure in both skeletal and cardiac muscle, which is further exacerbated by the tissue hypoperfusion of cardiogenic shock [37]. Third, neuroendocrine dysregulation promotes muscle proteolysis via the ubiquitin–proteasome pathway and suppresses anabolic recovery [36]. These mechanisms form a bidirectional "vicious cycle" in which cardiac dysfunction drives sarcopenia and metabolic failure, which in turn impairs cardiovascular recovery.

Frailty is prevalent in cardiogenic shock [10, 14]. The association between frailty and death may be explained by the underlying pathophysiology, including impaired immune response, reduced metabolic reserve, and musculoskeletal decline [36]. As frailty fundamentally aims to measure functional reserve, acute physiological stressors such as cardiogenic shock may unmask compensatory mechanisms at baseline. These may include "inflammaging", where subacute inflammation may result in dysregulated immune responses during periods of stress, and resolution of acute inflammation as the stressor is resolved [37]. Other potential mechanisms include reduced metabolic reserve and mitochondrial myopathy, resulting in impaired oxidative phosphorylation and skeletal muscular capacity [38].

Our study found that 16% of patients admitted to ICU were frail, though frailty may also influence clinical decision-making, leading to less aggressive management strategies, potential underutilisation of life-sustaining therapies, and ICU admission [11–13]. To better capture frailty in cardiogenic shock, future studies may consider an all-inclusive cardiogenic shock registry comprising patients of all acuity levels. Incorporating frailty screening into triage and referral pathways may help in early recognition of frailty institute appropriate care plans. Nonetheless, our findings echo previous research demonstrating that frailty, even at low levels, is incrementally associated with mortality and morbidity in cardiogenic shock [39]. We found a novel finding that the association between frailty and death varied over time, peaking at approximately six months before gradually decreasing thereafter. This is slightly different than in patients who receive surgery [22, 30]. We postulate that the severity of cardiogenic shock dominates in the acute phase irrespective of baseline frailty. As patients enter recovery, the relative contribution of frailty becomes more apparent through the mechanisms outlined above. The subsequent attenuation beyond six months may reflect survivorship bias, leaving behind a surviving population enriched for relative resilience. This six-month vulnerability has direct implications, and may suggest that survivors with frailty

Table 2 Summary of results of primary outcome*, sensitivity analyses, and subgroup analyses

Analysis	HR of frailty (95%-CI)
Primary analysis	2.27 (2.05–2.51)
Sensitivity analyses	
Frailty as a three-level categorical variable:	
CFS 1–3 (No frailty)	Reference
CFS 4–5 (Mild frailty)	1.72 (1.51–1.96)
CFS 6–8 (Moderate to severe frailty	3.03 (2.60–3.54)
Frailty as an ordinal variable:	
CFS 1	Reference
CFS 2	0.83 (0.69–0.99)
CFS 3	0.95 (0.74–1.23)
CFS 4	1.39 (1.03–1.87)
CFS 5	2.15 (1.58–2.92)
CFS 6	2.67 (1.96–3.64)
CFS 7	3.30 (2.35–4.64)
CFS 8	3.47 (2.37–5.07)
Frailty in patients with a principal diagnosis of cardiogenic shock	1.63 (1.50–1.78)
Frailty after adjusting for a different basket of covariates**	1.84 (1.73–1.96)
Multiple imputation for patients with missing frailty status	2.24 (2.14–2.35)
Subgroup analyses	
Aetiology of cardiogenic shock	
Ischaemic	2.00 (1.60–2.49)
Non-ischaemic	1.47 (1.37–1.56)
Post-cardiac surgical	2.07 (1.84–2.33)
Sex	
Male	2.04 (1.82–2.28)
Female	2.43 (2.17–2.71)
Age	
< 65 years	2.11 (1.83–2.44)
≥ 65 years	2.44 (2.20–2.69)
Patients who survived their initial ICU stay	3.13 (2.82–3.48)

*Covariates adjusted for in the above analyses: Male sex, chronic comorbidities including respiratory, cardiovascular, liver, and renal disease based on the APACHE-III score, metastatic cancer, immunosuppression, and diabetes mellitus, and the risk of malnutrition based on the mNUTRIC score

** New basket of covariates includes: Age, male sex, admission principal diagnosis, and year of ICU admission

Table 3 Unadjusted outcomes

Demographic variable*	Patients without frailty (CFS 1–4) 60,272 (84.5%)	Patients with frailty (CFS 5–8) 11,087 (15.5%)	p-value
Primary Outcome			
Survival months	23.3 (8.3, 41.0)	10.0 (0.8, 27.9)	< 0.001
Survival at 1 year, % (95%CI)	89.2% (88.9%-89.4%)	63.5% (62.5%-64.4%)	
Survival at 2 years, % (95%CI)	87.1% (86.8%-87.4%)	57.1% (56.1%-58.1%)	
Survival at 3 years, % (95%CI)	84.8% (84.4%-85.1%)	52.0% (50.9%-53.1%)	
Survival at 4 years, % (95%CI)	82.3% (81.9%-82.7%)	47.4% (46.1%-48.7%)	
In-Hospital Mortality			
ICU mortality	4,720 (7.8%)	2,345 (21.2%)	< 0.001
Hospital mortality	5,632 (9.4%)	3,210 (29.0%)	< 0.001
Length of stay (days)			
ICU length of stay	2.1 (1.3, 4.0)	3.0 (1.7, 5.3)	< 0.001
Hospital length of stay	9.9 (7.0, 15.0)	11.1 (6.0, 19.7)	< 0.001
Discharge destination *(excluding in-hospital mortality)*			
Home	44,448 (73.8%)	5,095 (46.0%)	< 0.001
Transfer to other acute ICU/hospital	6,321 (10.5%)	1,552 (14.0%)	
Rehabilitation facility	3,225 (5.4%)	851 (7.7%)	
Nursing home/Palliative/Chronic care	387 (0.6%)	317 (2.9%)	
Other	206 (0.4%)	47 (0.4%)	
ICU Complications			
Delirium	2,924 (4.9%)	980 (8.8%)	< 0.001
Pressure Injury	896 (1.5%)	292 (2.6%)	< 0.001

may derive the greatest benefit from targeted rehabilitation and structured post-discharge follow-up during this period.

We observed that the association between frailty and mortality was stronger in ischaemic than non-ischaemic or post-cardiac surgical cardiogenic shock. Ischaemic cardiogenic shock typically involves sudden, large-vessel obstruction and extensive myocardial necrosis. In patients with frailty, recovery from such an abrupt and profound insult is likely severely compromised. Conversely, non-ischaemic cardiogenic shock often arises from chronic conditions such as progressive heart failure, where physiological adaptation may afford more buffering. Selection bias by surgeons may also explain the relatively smaller association of frailty with mortality in post-cardiac surgical cardiogenic shock. For example, patients with severe frailty may not receive surgical interventions, and perioperative optimisation could mitigate potential complications of frailty peri-operatively [30].

There are several strengths to this study. The study is based on a binational registry with substantial granularity of data and a validated, clinically-relevant frailty tool, allowing for comprehensive overall assessment and robust stratified analyses. The linkage to the national death indices was successful, which helped facilitate the assessment of long-term mortality outcomes. More importantly, the granularity of the registry with regards to the first 24 h of ICU admission allowed us to include more patients who would otherwise have been excluded strictly based on diagnostic codes. However, our study also has several limitations. First, the analysis was based on retrospective data, which cannot estimate causal effects. Missing data and erroneous data entry in the

registry may limit the precision or introduce biases to the analysis, although imputation of frailty found similar results. As the ANZICS-APD was first devised as a clinical quality and benchmarking registry, it does not collect data beyond the first 24 h of admission. In addition, the APD has evolved with clinical practice, and newer variables (including frailty) were only introduced in 2018, which partially explains the missingness in data. Second, we lack data on long-term functional recovery and health-related quality of life, which are important patient-reported outcomes. This will become part of data collected by ANZICS-APD in the future [40]. In addition, the ANZICS-APD does not capture data on interventions for cardiogenic shock, for example, revascularisation, and other mechanical circulatory support devices other than ECMO. These are important data which may have an impact on our findings. Third, our study may have inadvertently excluded patients who developed cardiogenic shock after the first 24 h of ICU admission or developed cardiogenic shock with a non-cardiovascular principal diagnosis. Fourth, in Australia and New Zealand, a large proportion of patients with cardiogenic shock, particularly of ischaemic pathologies, may be admitted to the Coronary Care Unit (which can manage patients receiving inotropes and vasopressors, but not invasive mechanical ventilation nor ECMO), and not the ICU (which can manage patients receiving invasive mechanical ventilation or ECMO). We were unable to capture the outcomes or characteristics of these patients. Finally, these findings are only generalisable to patients in Australia and New Zealand and may not be representative of patients in other countries, where resources, clinical workflows, and patient characteristics may differ.

In conclusion, frailty is strongly and consistently associated with mortality in cardiogenic shock in an incremental fashion, particularly in the post-acute phase at six months after ICU admission. Its influence varies by aetiology and sex, underscoring the need for personalized management approaches in the ICU stratified by frailty and other key prognostic variables status. Importantly, the association with mortality was larger in patients with ischaemic cardiogenic shock compared to non-ischaemic cardiogenic shock. These findings advance our understanding of long-term outcomes in cardiogenic shock and highlight frailty as a key target for future clinical and research efforts.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-026-05962-6.

Additional file 1.

Acknowledgements

The authors acknowledge the following contributing sites: Albury Wodonga Health, Alfred Hospital, Alice Springs Hospital, Angliss Hospital, Armadale Health Service, Ashford Community Hospital, Auckland City Hospital CV, Auckland City Hospital DCCM Austin Hospital, Bankstown-Lidcombe Hospital, Bathurst Base Hospital, Bendigo Health Care Group, Blacktown Hospital, Bowral Hospital HDU Box Hill Hospital, Braemar Hospital SCU Brisbane Private Hospital, Broken Hill Base Hospital & Health Services, Buderim Private Hospital, Bunbury Regional Hospital, Bundaberg Base Hospital, Caboolture Hospital, Cabrini Hospital, Cairns Hospital, Calvary Adelaide Hospital, Calvary John James Hospital, Calvary Mater Newcastle, Calvary North Adelaide Hospital, Campbelltown Hospital, Canberra Hospital, Casey Hospital, Central Gippsland Health Service (Sale), Christchurch Hospital, Coffs Harbour Health Campus, Concord Hospital (Sydney), Dandenong Hospital, Echuca Regional Hospital HDU Epworth Eastern Private Hospital, Epworth Freemasons Hospital, Epworth Geelong, Epworth Hospital (Richmond), Fairfield Hospital, Fiona Stanley Hospital, Flinders Medical Centre, Flinders Private Hospital, Footscray Hospital, Frankston Hospital, Gold Coast Private Hospital, Gold Coast University Hospital, Gosford Hospital, Gosford Private Hospital, Goulburn Base Hospital, Goulburn Valley Health, Grafton Base Hospital, Grampians Health Ballarat , Grampians Health Horsham, Greenslopes Private Hospital, Griffith Base Hospital, Hawkes Bay Hospital, Hervey Bay Hospital, Hollywood Private Hospital, Holmesglen Private Hospital , Hornsby Ku-ring-gai Hospital, Hurstville Private Hospital, Hutt Hospital, Ipswich Hospital, John Flynn Private Hospital, John Hunter Hospital, Joondalup Health Campus, Kareena Private Hospital, Knox Private Hospital, Latrobe Regional Hospital, Launceston General Hospital, Lingard Private Hospital, Lismore Base Hospital, Liverpool Hospital, Logan Hospital, Lyell McEwin Hospital, Mackay Base Hospital, Macquarie University Private Hospital, Maitland Hospital, Maitland Private Hospital, Manly Hospital & Community Health, Manning Rural Referral Hospital, Maroondah Hospital, Mater Adults Hospital (Brisbane), Mater Private Hospital (Brisbane), Mater Private Hospital (Sydney), Mater Private Hospital (Townsville), Melbourne Private Hospital, Middlemore Hospital, Mildura Base Public Hospital, Monash Medical Centre-Clayton Campus, Mount Hospital, Mount Isa Hospital, Mulgrave Private Hospital, National Capital Private Hospital, Nelson Hospital, Nepean Hospital, Nepean Private Hospital, Newcastle Private Hospital, Noosa Hospital, North Canberra Hospital, North Shore Hospital, North Shore Private Hospital, North West Private Hospital, Northeast Health Wangaratta, Northern Beaches Hospital, Norwest Private Hospital, Orange Base Hospital, Peninsula Private Hospital, Pindara Private Hospital, Port Macquarie Base Hospital, Prince of Wales Hospital (Sydney), Prince of Wales Private Hospital (Sydney), Princess Alexandra Hospital, Queen Elizabeth II Jubilee Hospital, Redcliffe Hospital, Robina Hospital, Rockhampton Hospital, Rockingham General Hospital, Rotorua Hospital, Royal Brisbane and Women's Hospital, Royal Darwin Hospital, Royal Hobart Hospital, Royal Melbourne Hospital, Royal North Shore Hospital, Royal Perth Hospital, Royal Prince Alfred Hospital, Ryde Hospital and Community Health Services, Shoalhaven Hospital, Sir Charles Gairdner Hospital, South East Regional Hospital, South West Healthcare (Warrnambool), St Andrew's Hospital Toowoomba, St Andrew's Private Hospital (Ipswich), St Andrew's War Memorial Hospital, St George Hospital (Sydney), St George Private Hospital (Sydney), St John Of God Hospital (Ballarat), St John of God Hospital (Bendigo), St John of God Hospital (Berwick), St John Of God Hospital (Geelong), St John Of God Hospital (Murdoch), St John of God Midland Public & Private, St Vincent's Private Hospital Northside, St Vincent's Hospital (Melbourne), St Vincent's Hospital (Sydney), St Vincent's Hospital (Toowoomba), St Vincent's Private Hospital (Sydney), St Vincent's Private Hospital Fitzroy, Sunnybank Hospital, Sunshine Coast University Hospital, Sunshine Coast University Private Hospital, Sunshine Hospital, Sutherland Hospital & Community Health Services, Sydney Adventist Hospital, Sydney Southwest Private Hospital, Tamworth Base Hospital, Taranaki Health, Tauranga Hospital, The Bays Hospital, The Chris O'Brien Lifehouse , The Memorial Hospital (Adelaide), The Northern Hospital, The Prince Charles Hospital, The Queen Elizabeth (Adelaide), The Wesley Hospital, Timaru Hospital, Toowoomba Hospital, Townsville University Hospital, Tweed Valley Hospital, University Hospital Geelong, Victorian Heart Hospital, Wagga Wagga Base Hospital & District Health, Waikato Hospital, Wairau Hospital, Warringal Private Hospital, Wellington Hospital, Werribee Mercy Hospital, Western District Health Service (Hamilton), Western Hospital (SA), Westmead Hospital, Westmead Private Hospital, Whangarei Area Hospital—Northland Health Ltd, Wollongong Hospital, Wollongong Private Hospital, Wyong Hospital.

Author contributions
Study conception: RRL, SLL, KR, AS Study design: RRL, SLL, DP, KR, AS Data collection: RRL, DP Data analysis and interpretation: RRL, AS Tables and figures: RRL, AS Writing of original draft: RRL, SLL **All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft. RRL, DP, and AS have accessed and verified the data. RRL and SLL were responsible for the final decision to submit the manuscript.**

Funding
There was no funding source for this study.

Data availability
The ANZICS-APD data dictionary and policies are available online at (https://www.anzics.org/adult-patient-database-apd). The participant data collected for this study are available to member centres conditional on approval from the Australia and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation, but it is not publicly available.

Declarations

Ethics approval and consent to participate
This study received approval from the Alfred Hospital Ethics Committee, Melbourne, Australia (Project No. 305/24). The study data were received after review and approval by the Australia and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation.

Consent for publication
Consent for publication was waived in view of the deidentified nature of the data.

Competing interests
RRL receives research support from the Clinician Scientist Development Unit, Yong Loo Lin School of Medicine, National University of Singapore. He serves as a fellow of the Extracorporeal Life Support Organisation (ELSO) Scientific Overesight Committee, and is an editorial board member of Critical Care. SLL is supposed by the National Medical Research Council Transitional Award. She has received research grants from National University Health System, National Kidney Foundation of Singapore and Singapore Heart Foundation. She is an Associate Editor for Resuscitation and serves on the editorial board of Resuscitation Plus. GM is the Past President of ELSO. KS serves on the Scientific Committee and Network Committee of the International ECMO Network (ECMONet). He reports receiving lecture honoraria outside of the submitted work from Getinge and Abiomed. DP is the chairman of the Australia and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation, and serves as an associate editor for Critical Care and Resuscitation. KR is the chair of the ELSO Publications Committee, and serves as a member and the past-chair of the ELSO Scientific Oversight Committee. AS serves as an associate editor for Critical Care and Resuscitation, and is the Intensive Care Medicine subspecialty editor for Internal Medicine Journal.

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Received: 13 January 2026 / Accepted: 16 March 2026
Published online: 25 March 2026

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