

Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study

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ABSTRACT

Background: Frailty is a multidimensional syndrome characterized by loss of physiologic and cognitive reserves that confers vulnerability to adverse outcomes. We determined the prevalence, correlates and outcomes associated with frailty among adults admitted to intensive care.

Methods: We prospectively enrolled 421 critically ill adults aged 50 or more at 6 hospitals across the province of Alberta. The primary exposure was frailty, defined by a score greater than 4 on the Clinical Frailty Scale. The primary outcome measure was in-hospital mortality. Secondary outcome measures included adverse events, 1-year mortality and quality of life.

Results: The prevalence of frailty was 32.8% (95% confidence interval [CI] 28.3%–37.5%). Frail patients were older, were more likely to be female, and had more comorbidities and greater functional dependence than those who were not frail. In-hospital mortality was

higher among frail patients than among non-frail patients (32% v. 16%; adjusted odds ratio [OR] 1.81, 95% CI 1.09–3.01) and remained higher at 1 year (48% v. 25%; adjusted hazard ratio 1.82, 95% CI 1.28–2.60). Major adverse events were more common among frail patients (39% v. 29%; OR 1.54, 95% CI 1.01–2.37). Compared with nonfrail survivors, frail survivors were more likely to become functionally dependent (71% v. 52%; OR 2.25, 95% CI 1.03–4.89), had significantly lower quality of life and were more often readmitted to hospital (56% v. 39%; OR 1.98, 95% CI 1.22–3.23) in the 12 months following enrolment.

Interpretation: Frailty was common among critically ill adults aged 50 and older and identified a population at increased risk of adverse events, morbidity and mortality. Diagnosis of frailty could improve prognostication and identify a vulnerable population that might benefit from follow-up and intervention.

Competing interests: Ross Tsuyuki has served on advisory boards for Bristol-Myers Squibb, PharmaSmart International and Abbott Laboratories, and a data monitoring board for dabigatran studies for Boehringer Ingelheim; he has received consultant fees from Merck; and his institution has received grants from Sanofi and AstraZeneca. No competing interests were declared by the other authors.

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Frailty is a term widely used to describe a multidimensional syndrome characterized by the loss of physiologic and cognitive reserves that gives rise to heightened vulnerability to adverse outcomes.^{1,2} Adverse events associated with frailty include incident falls, susceptibility to acute illness, perioperative complications, unplanned hospital admissions, disability, need for institutional care, and death.^{3–10} Frailty has substantial implications for quality of life, functional autonomy and health services utilization, but it has not been evaluated in critically ill patients.

The development of critical illness may lead to frailty in vulnerable patients. Critical illness may also be a key factor impeding recovery and functional autonomy in those already considered to be frail.¹¹ We hypothesized that frailty would identify vulnerable patients who are less likely to tolerate critical illness, who are more susceptible

to complications and death, and who are less likely to fully recover after critical illness over the short or long term. We further hypothesized that this information would translate into more accurate prognostication, which might improve decision-making for frail patients and their families. To test these hypotheses, we performed a prospective multi-centre study in an unselected cohort of critically ill patients.

Methods

Study design and population

This was a multicentre prospective cohort study. The study population comprised adults admitted to 1 of 6 participating intensive care units (ICUs) between Feb. 1, 2010, and July 31, 2011. The ICUs were located in 2 tertiary care academic hospitals and 4 community hospitals in the province of

Alberta (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130639/-/DC1). These hospitals were selected to represent the province and capture academic and community settings to minimize selection bias.

Patients were included if they were aged 50 years or more (based on the low prevalence of frailty among younger patients¹²), were admitted to a participating ICU and were able to provide consent. Patients were excluded if their expected ICU stay or survival was less than 24 hours or if they had previously been enrolled in the study. Consecutive participants were identified by daily screening of new ICU admissions.

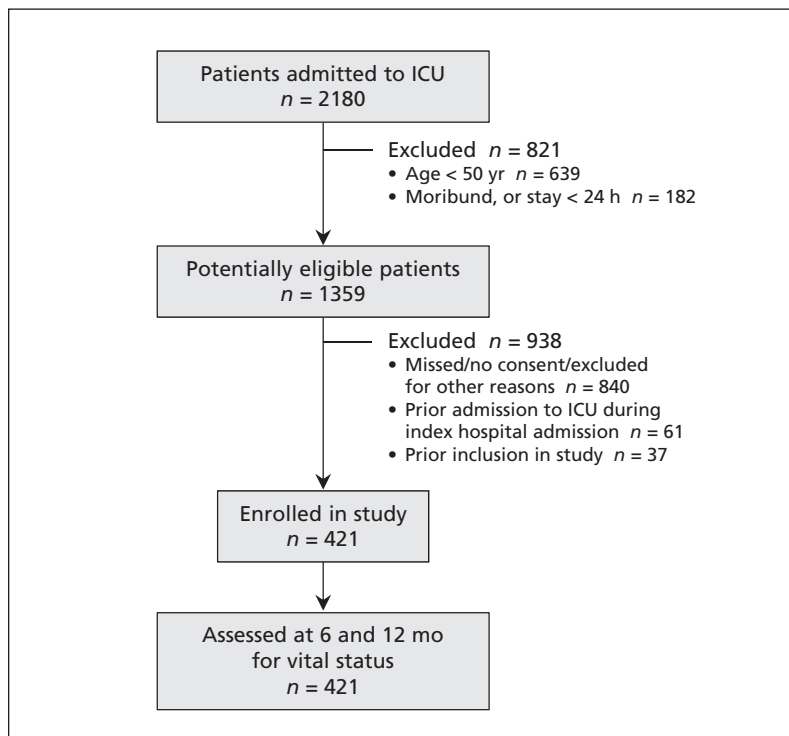


Figure 1: Selection of critically ill patients for the study cohort.

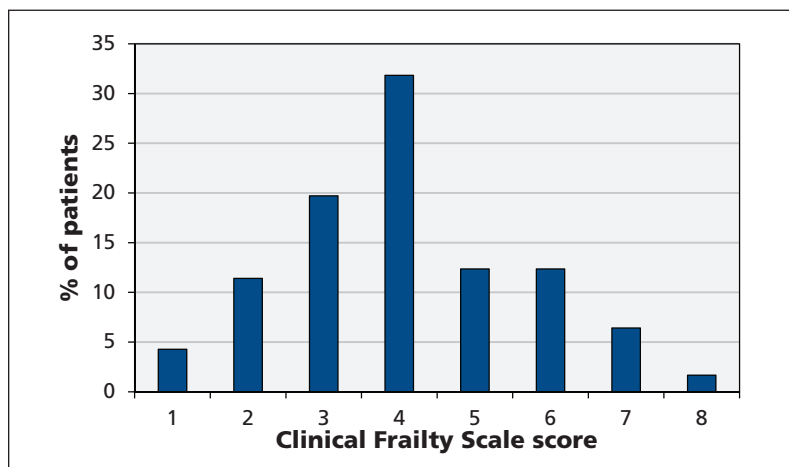


Figure 2: Distribution of Clinical Frailty Scale scores and prevalence of frailty (score > 4) among the participants.

All participants or their surrogates provided informed consent. The study was approved by the Health Research Ethics Board at the University of Alberta and the Conjoint Health Research Ethics Board at the University of Calgary.

Determination of frailty

Frailty was defined with the use of the Canadian Study on Health and Aging Clinical Frailty Scale, a well-validated 9-point assessment tool designed to quantify frailty (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130639/-/DC1).³ Trained research coordinators masked to the study hypotheses determined the Clinical Frailty Scale scores by interviewing participants or surrogates and reviewing each participant's medical record. We considered patients to be frail if they had a score greater than 4 (which represents mild, moderate, severe or very severe frailty³) immediately before the index hospital admission.

Outcome measures

The primary outcome measure was all-cause in-hospital mortality. Secondary outcome measures included the following: death in ICU, hospital or at 6 months; health-related quality of life at 6 and 12 months (as measured by the 12-item Short-Form Health Survey [SF-12]¹³ and the EuroQol Health Questionnaire [EQ-5D]);¹⁴ intensity of treatment in the ICU (as determined by whether vasoactive therapy, mechanical ventilation, renal replacement therapy or blood transfusion was provided); major adverse events (defined as a composite of serious medication errors, self-extubation or re-intubation, or nosocomial infection [e.g., catheter-related bloodstream infection] during the hospital stay); and health services utilization (as measured by durations of stay in ICU and hospital as well as readmission to hospital within 12 months after enrolment).

Other covariables

At enrolment, the trained research coordinators collected information through interviews with the participants (or surrogates) and chart reviews. The collected data included age, sex, race/ethnicity, education level, marital status, ability to perform instrumental and functional activities of daily living, comorbid conditions and degree of comorbidity (e.g., defined according to Elixhauser score^{15,16}), number of prescription medications,¹⁷ number of hospital and ICU admissions in the year before enrolment, source of transfer to ICU (e.g., ward, emergency department, other hospital, operating theatre), illness severity (e.g., defined according to Acute Physiology and Chronic Health Evaluation [APACHE] II score¹⁸), and presence and severity

of organ dysfunction (e.g., defined according to Sequential Organ Failure Assessment [SOFA] score¹⁹). In addition, the research coordinators determined whether limitations in the provision of ICU-specific, life-sustaining therapy (e.g., cardiopulmonary resuscitation, advanced cardiac life support, mechanical ventilation, use of vasoactives and renal replacement therapy) were documented in the medical record.

The research coordinators contacted surviving participants by telephone at 6 and 12 months after enrolment to determine vital status, disposition and health-related quality of life using a scripted text.^{20,21}

Data were captured on standardized case report forms and entered into an electronic database.

Statistical analysis

Based on data from a pilot study involving 50 patients, we expected a prevalence of frailty of 30% (unpublished data). To confirm this magnitude of prevalence within 5% binomial confidence limits, we required a sample of at least 400 participants. With an anticipated 1-year mortality of 40% (160 events), this sample size would permit up to 16 covariates in multivariable models of 1-year mortality with a 2-tailed α value of 0.05 and would have at least 80% power to detect 15% differences between frail and nonfrail participants.

Descriptive statistics according to frailty status were tabulated, and univariable comparisons of means, medians and proportions were performed. Kaplan–Meier survival curves were constructed, and multivariable logistic regression (in-hospital mortality) and Cox regression (1-yr mortality) analyses were used to determine the association between frailty and mortality. The models were adjusted for potential confounding factors, which were included based on their clinical importance, evidence from the literature or their significance at $p < 0.20$ in the univariable analysis.

For the logistic regression analysis, model fit and calibration were assessed with the Hosmer–Lemeshow goodness-of-fit test and the C statistic. For the Cox regression analysis, time-dependent covariates and log(–log) plots were used to test for violations of the proportional hazards assumptions; no violations were observed. Analogous analyses were undertaken for the other study outcomes.

Using the Student *t* test, we compared participants' health-related quality-of-life measures at 6 and 12 months against normative SF-12 and EQ-5D data for the general population in Alberta.²²

A *p* value of less than 0.05 was considered statistically significant for all comparisons. All analyses were performed with the use of Stata 11.2 (StataCorp).

Table 1: Baseline characteristics of patients admitted to intensive care unit (ICU), by frailty status

Characteristic	Group; no. (%) of patients*		<i>p</i> value†
	Frail <i>n</i> = 138	Not frail <i>n</i> = 283	
Age, yr, mean \pm SD	69 \pm 10	66 \pm 10	0.007
Sex, female	66 (47.8)	97 (34.3)	0.007
Race, white	114 (82.6)	240 (84.8)	0.6
Marital status			
Married or common law	87 (63.0)	189 (66.8)	0.45
Never married	4 (2.9)	23 (8.1)	0.03
Widowed	25 (18.1)	28 (9.9)	0.02
Less than high school education	39 (28.3)	54 (19.1)	0.03
Residence			
Living at home independently	58 (42.0)	244 (86.2)	< 0.001
Living at home with help	64 (46.4)	35 (12.4)	
Other‡	9 (6.5)	3 (1.2)	
Able to perform activity independently§			
Taking a bath	79 (57.2)	274 (96.8)	< 0.001
Walking	77 (55.8)	259 (91.5)	< 0.001
Taking medications	90 (65.2)	270 (95.4)	< 0.001
Managing own finances	102 (73.9)	273 (96.5)	< 0.001
Elixhauser comorbidity score, mean \pm SD	10 \pm 9	7 \pm 7	< 0.001
No. of prescription medications, mean \pm SD	8.9 \pm 5	5.5 \pm 4	< 0.001
Prior hospital admission¶	77 (55.8)	99 (35.0)	< 0.001
Prior ICU admission¶	37 (26.8)	63 (22.3)	0.3
Source of transfer to ICU			
Ward	72 (52.2)	167 (59.0)	
Emergency department	40 (29.0)	72 (25.4)	
Another hospital	24 (17.4)	39 (13.8)	
Other	2 (1.4)	5 (1.8)	
Postoperative ICU admission**	34 (24.6)	108 (38.2)	0.006
Cardiac arrest††	10 (7.2)	21 (7.4)	0.9
Rapid response team††	36 (26.1)	74 (26.1)	0.9
APACHE II score,†† mean \pm SD	21 \pm 7	19 \pm 7	< 0.001
SOFA score,†† mean \pm SD	8 \pm 4	7 \pm 4	0.1
Limitation of medical therapy‡‡	47 (34.1)	34 (12.0)	< 0.001

Note: APACHE = Acute Physiology and Chronic Health Evaluation, CSHA = Canadian Study of Health and Ageing, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

*Unless stated otherwise.

†† test for comparisons of continuous data and χ^2 test for comparisons of categorical data.

‡Continuing care facility, subacute care facility or other.

§Score of 0 on the CSHA Function Scale.

¶In the year before enrolment.

**Surgery within 48 hours before ICU admission.

††At time of ICU admission.

‡‡Limitation in the provision of ICU-specific life-sustaining therapy (e.g., cardiopulmonary resuscitation, advanced cardiac life support, mechanical ventilation, use of vasoactives, renal replacement therapy) documented in the medical record.

Results

A total of 421 patients were enrolled in our study (Figure 1). Their mean age (\pm standard deviation) was 67 ± 10 years; 163 (39%) were female, and 402 (95%) were living at home independently or with assistance. At the time of ICU admission, the mean APACHE II score was 20 ± 7 , the SOFA score was 7 ± 4 , and 142 (34%) of the participants had had surgery within 48 hours before

Table 2: Treatment intensity and use of resources associated with admission to intensive care unit, by frailty status

Variable	Group; no. (%) of patients		<i>p</i> value*
	Frail <i>n</i> = 138	Not frail <i>n</i> = 283	
Mechanical ventilation	122 (88.4)	240 (84.8)	0.3
Re-intubation	17 (12.3)	30 (10.6)	0.6
Tracheostomy	18 (13.0)	35 (12.4)	0.9
Vasoactive medications	83 (60.1)	146 (51.6)	0.1
Renal replacement therapy	14 (10.1)	33 (11.7)	0.6
Blood transfusion	57 (41.3)	113 (39.9)	0.8
Surgical procedure or re-operation	26 (18.8)	63 (22.3)	0.4

* χ^2 test.

Table 3: Clinical outcomes, by frailty status

Outcome	Group; no. (%) of patients*		Association, OR (95% CI) or difference in medians (<i>p</i> value)†
	Frail <i>n</i> = 138	Not frail <i>n</i> = 283	
Adverse event‡	54 (39.1)	83 (29.3)	1.54 (1.01–2.37)
Death			
In ICU	16 (11.6)	27 (9.5)	1.37 (0.72–2.62)
In hospital	44 (31.9)	45 (15.9)	1.81 (1.09–3.01)
Duration of stay, d, median (IQR)			
In ICU	7 (4–13)	6 (3–10)	1 d (0.02)
In hospital	30 (10–64)	18 (10–40)	12 d (0.02)
Discharge disposition§	<i>n</i> = 91	<i>n</i> = 235	
Home, living independently	20 (22.0)	104 (44.3)	0.35 (0.20–0.61)
Home, living with help	33 (36.3)	58 (24.7)	1.67 (1.00–2.81)
Other¶	38 (41.8)	73 (31.1)	1.51 (0.92–2.48)
Discharged newly dependent**	24 (70.6)	96 (51.6)	2.25 (1.03–4.89)
Hospital readmission§	51 (56.0)	92 (39.1)	1.98 (1.22–3.23)

Note: CI = confidence interval, ICU = intensive care unit, OR = odds ratio.

*Unless stated otherwise.

†Mann-Whitney test.

‡Composite of medication errors, self-extubation/reintubation, nosocomial infection, death.

§Among 91 frail and 235 nonfrail patients for whom data on discharge disposition and on hospital readmission within 12 mo after discharge could be ascertained (data missing, *n* = 1 per group; in hospital at end of follow-up, *n* = 2 per group).

¶Continuing care facility, subacute care facility or other.

**Among 34 frail and 186 nonfrail patients who were living independently at baseline.

the admission. There were no clinically important or statistically significant differences in baseline sociodemographic characteristics or illness severity between enrolled participants and patients who were eligible but were not enrolled (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130639/-/DC1).

Overall, 138 of the 421 participants were considered to be frail (Clinical Frailty Scale score > 4), for a frailty prevalence of 32.8% (95% confidence interval [CI] 28.3%–37.5%). The median frailty score was 4 (interquartile range 3–5) (Figure 2). Compared with nonfrail patients, frail patients were older, were more likely to be female, had more comorbid disease and greater functional dependence, and tended to have fewer social supports (Table 1).

Frail patients were more likely than nonfrail patients to be admitted for nonsurgical reasons and to have higher APACHE II scores, although baseline and daily SOFA scores were not significantly different between the two groups (Table 1). Irrespective of frailty, all patients received similar intensity of treatment (Table 2). Compared with nonfrail patients, those with frailty were more likely to have limitations of medical therapy at ICU admission (34% v. 12%; *p* < 0.001).

Mortality during the ICU stay did not differ according to frailty, but in-hospital mortality was higher among frail patients (32% v. 16%; adjusted odds ratio [OR] 1.81, 95% CI 1.09–3.01) (Table 3). In the multivariable analysis, over the 12-month follow-up period, frailty was independently associated with all-cause mortality (48% v. 25%; adjusted hazard ratio [HR] 1.82; 95% CI 1.28–2.60). In a dose-dependent manner, an increasing frailty score (rather than the cutpoint of 4 used in the primary analysis) was independently associated with incremental mortality in adjusted analyses (Figures 3 and 4).

Among the survivors, frailty was associated with significantly longer durations of stay in both ICU and hospital (Table 3). Frail patients also had a 1.5-fold higher odds of major adverse events during their hospital stay compared with their nonfrail counterparts (OR 1.54, 95% CI 1.01–2.37). In the 12 months after hospital discharge, frail patients had a greater rate of hospital readmission than nonfrail patients had (56% v. 39%; OR 1.98, 95% CI 1.22–3.23).

After hospital discharge, frail patients were less likely than nonfrail patients to be living at home independently (22% v. 44%; OR 0.35, 95% CI 0.20–0.61) (Table 3). This difference persisted at 6 months (28% v. 61%; OR 0.25, 95% CI 0.14–0.43) and at 12 months (31% v. 67%; OR 0.22, 95% CI 0.12–0.40). Among survivors who were living independently at baseline, frail

patients were more likely than nonfrail patients to become functionally dependent (71% v. 52%; OR 2.25, 95% CI 1.03–4.89) (Table 3). In a sensitivity analysis, this association was stronger when stratified by a baseline frailty score of more than 5 or of 3 or lower (78% v. 46%; OR 4.14, 95% CI 1.34–12.73). Health-related quality of life was generally lower among the frail patients than among the nonfrail patients at 6 and 12 months, and across all physical and mental health domains; however, both groups had lower health-related quality of life compared with the general population of Alberta²² (Table 4).

Interpretation

In this prospective multicentre study of a representative cohort of critically ill patients over the age of 50, we found that frailty was common, affecting one-third of the participants. Frail patients differed from nonfrail patients in many sociodemographic and clinical characteristics, including having a greater burden of comorbid illness and functional

impairment at ICU admission. Despite both groups having similar treatment intensity, frail patients were more likely to experience adverse events, had longer lengths of stay in ICU and hospital, and were more likely to die while in hospital and within 12 months after admission. Among survivors, frail patients were more likely than nonfrail patients to have new functional dependence at hospital discharge and had higher rates of hospital readmission. There was a similar disadvantage for frail patients for worse health-related quality of life across all domains measured. These associations were stronger with increasing severity of frailty and persisted even after adjustment for sociodemographic factors, premorbid health status, comorbidities and illness severity.

Our data suggest that frailty can be measured in patients admitted to the ICU using a simple bedside assessment tool and is an important prognostic factor in both the short and long term.²³ Similar to acute care hospital admission contributing to an increased likelihood of cognitive impairment, an episode of critical illness may have a sustained

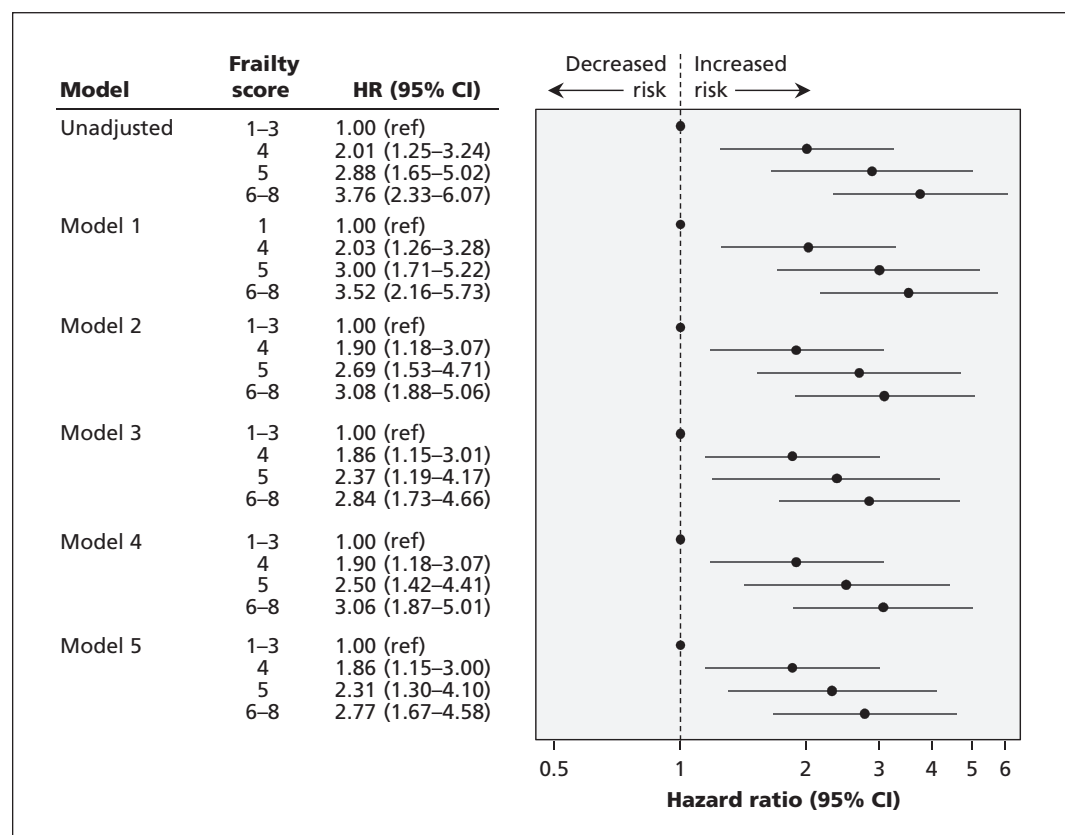


Figure 3: Adjusted hazard ratios for death within 12 months after admission to an intensive care unit, stratified by Clinical Frailty Scale score (score > 4 indicates frailty). Hazard ratios greater than 1.0 indicate an increased risk of death. The models were adjusted as follows: model 1 for age and sex; model 2 for age, sex and Elixhauser score (comorbidity indicator); model 3 for age, sex, Elixhauser score and non-age-specific Acute Physiology and Chronic Health Evaluation (APACHE) II score (illness severity); model 4 for age, sex, Elixhauser score and Sequential Organ Failure Assessment (SOFA) score (presence and severity of organ dysfunction); and model 5 for age, sex, Elixhauser score, non-age-specific APACHE II score and hospital type (tertiary care/academic v. community). CI = confidence interval, ref = reference group.

impact on the capacity for frail patients to recover and regain or maintain functional independence.^{24,25}

In the context of critical illness, a degree of frailty seems to identify a vulnerable population whose risk of poor outcomes is heightened. This risk may be further exacerbated by frail patients having fewer social supports, as shown in our study. The interplay of frailty and critical illness may provide an opportunity to target and evaluate interdisciplinary programs of care and rehabilitation, with the aim of improving recovery and avoiding mortality, functional dependence, reduced quality of life and added health service utilization.^{23,26,27} For frail critically ill patients, such an integrated program may have elements addressing the minimization of unnecessary sedation,²⁸ screening for delirium,²⁹ early assessment for weaning from mechanical ventilation, nutritional support,³⁰ medication reconciliation³¹ and early mobilization.^{32,33} In addition, the measurement and diagnosis of frailty could translate

into better informed decision-making for patients, their families and clinicians around issues related to the provision of advanced life support and designation of goals of care.

Frailty is generally viewed as an age-associated loss of reserve across multiple physiologic and cognitive systems that give rise to susceptibility to adverse events.^{1,2} A variety of operational definitions have been applied to encapsulate the frail state across clinical contexts; however, none has been used to describe frailty among a generalizable cohort with critical illness.³⁴ Similarly, other measures of performance status have been integrated into studies involving critically ill patients, generally for risk adjustment; however, they have not been evaluated in the context of frailty.^{35,36} Data from the Canadian National Population Health Survey showed that the prevalence of frailty was about 7% and that it increased exponentially with age.⁴ In a vulnerable cohort of older outpatients, the prevalence of frailty was 59%.³ We found frailty in 33% of the critically ill patients enrolled in our study, an estimate between the extremes of the general population and an older outpatient population. Notably, our cohort was relatively young compared with these cohorts, implying the susceptibility to critical illness may be “age-shifted” in those with frailty. This suggests that an episode of critical illness in a frail patient may herald a momentous transition toward greater homeostatic instability, disability and risk of death.¹¹

Frailty is a common state preceding death.³⁷ Two-thirds of frail patients have disabling trajectories at the end of life.³⁷ In a recent population-based study, 26.7% of deaths were associated with frailty.³⁸ Frailty is associated with high health service utilization, with most expenditures related to long-term care and in-patient care at the end of

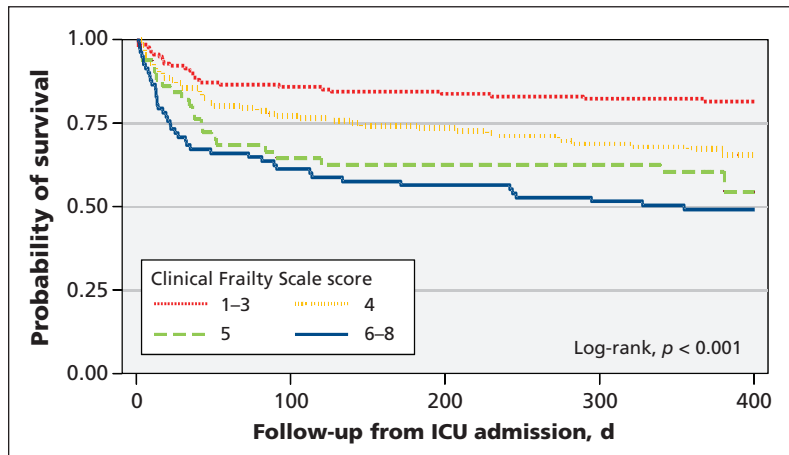


Figure 4: Kaplan–Meier survival curves stratified by Clinical Frailty Scale score.

Quality-of-life measure	Group; score, mean ± SD			p value*		
	Frail	Not frail	General population†	Frail v. not frail	Frail v. general population	Not frail v. general population
At 6 mo	n = 67	n = 195				
EQ VAS	52 ± 22	65 ± 19	79 ± 16	< 0.001	< 0.001	< 0.001
SF-12, physical health	35 ± 9	37 ± 7	52 ± 9	0.1	< 0.001	< 0.001
SF-12, mental health	33 ± 7	39 ± 8	48 ± 11	< 0.001	< 0.001	< 0.001
At 12 mo	n = 59	n = 170				
EQ VAS	54 ± 23	68 ± 18	79 ± 16	< 0.001	< 0.001	< 0.001
SF-12, physical health	35 ± 8	38 ± 7	52 ± 9	0.005	< 0.001	< 0.001
SF-12, mental health	34 ± 7	39 ± 8	48 ± 11	< 0.001	< 0.001	< 0.001

Note: EQ VAS = EuroQol visual analogue scale, SD = standard deviation, SF-12 = 12-item Short-Form Health Survey.
 *† test.
 †Normative EQ VAS and SF-12 data for a random sample of 4200 people in the general population of Alberta.²²

life.³⁸ Indeed, health expenditures for frail people increase 2.4-fold on average in the final 3 months of life.³⁸ Consistent with these observations, frail patients in our study had longer stays in ICU and hospital, had more acquired disability and had higher hospital readmission rates than their non-frail counterparts. Frail participants also had higher in-hospital and 12-month mortality. Moreover, we found graded increases in the risk of death associated with increasing severity of frailty.

We observed no differences between the frail and nonfrail patients in the intensity of treatment provided or in ICU mortality. These data suggest that frail patients, once admitted to ICU, received therapy commensurate with their illness severity, and perhaps only later had goals of care reassessed following a time-limited trial.³⁹

Limitations

Our study has several limitations. First, the Clinical Frailty Scale, although a well-validated bedside assessment tool,^{3,10} has an inherent element of informed subjectivity. However, we believe we mitigated this by ensuring all research personnel were trained to use it systematically and were masked to the study hypotheses. This was reinforced by patients classified as frail having numerous features consistent with the frail phenotype.^{1,23}

Second, we recruited participants after admission to ICU. Thus, we did not have reliable measures of health-related quality of life before admission, and all of our analyses were anchored to assessments that started in the ICU.

Third, we were unable to integrate dynamic functional measures such as mobility, grip strength and cognition before the development of critical illness that may have further informed on survival and trajectory relative to baseline. Similarly, we did not have markers of inflammation or nutritional status or other laboratory measures that might have helped with a mechanistic understanding of why frailty was associated with adverse events.

Conclusion

Frailty was common among critically ill adults aged 50 years or more and identified a vulnerable population at increased risk of adverse events, morbidity and mortality. Our findings suggest that routine assessment of frailty could provide more accurate prognostication and identify a vulnerable population that might benefit from follow-up and intervention.

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