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ORIGINAL

# Frailty and invasive mechanical ventilation: association with outcomes, extubation failure, and tracheostomy

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## Abstract

**Purpose:** Invasive mechanical ventilation is a common form of life support provided to critically ill patients. Frailty is an emerging prognostic factor for poor outcome in the Intensive Care Unit (ICU); however, its association with adverse outcomes following invasive mechanical ventilation is unknown. We sought to evaluate the association between frailty, defined by the Clinical Frailty Scale (CFS), and outcomes of ICU patients receiving invasive mechanical ventilation.

**Methods:** We performed a retrospective analysis (2011–2016) of a prospectively collected registry from two hospitals of consecutive ICU patients ≥ 18 years of age receiving invasive mechanical ventilation. CFS scores were based on recorded pre-admission function at the time of hospital admission. The primary outcome was hospital mortality. Secondary outcomes included discharge to long-term care, extubation failure at time of first liberation attempt, and tracheostomy.

**Results:** We included 8110 patients, and 2529 (31.2%) had frailty (CFS ≥ 5). Frailty was associated with increased odds of hospital death (adjusted odds ratio [aOR]: 1.24 [95% confidence interval [CI] 1.10–1.40) and discharge to long-term care (aOR 1.21 [95% CI 1.13–1.35]). As compared to patients without frailty, patients with frailty had increased odds of extubation failure (aOR 1.17 [95% CI 1.04–1.37]), hospital death following extubation failure (aOR 1.18 [95% CI 1.07–1.28]), tracheostomy (aOR 1.17 [95% CI 1.01–1.36]), and hospital death following tracheostomy (aOR 1.14 [95% CI 1.03–1.25]).

**Conclusions:** The presence of frailty among patients receiving mechanical ventilation is associated with increased odds of hospital mortality, discharge to long-term care, extubation failure, and need for tracheostomy.

**Keywords:** Frailty, Mechanical ventilation, Extubation failure, Tracheostomy

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## Introduction

Invasive mechanical ventilation remains a mainstay of life support therapy among critically ill patients. Of all patients admitted to the Intensive Care Unit (ICU), between 35 and 50% will require mechanical ventilation at some point during their admission [1–3]. Of these patients, roughly 35–40% will die in-hospital [4], though survival in this population has improved gradually over time [5]. Mechanical ventilation is also associated with significant morbidity, including muscle atrophy, infection, and delirium [6]. Overall costs from mechanical ventilation remain significant [3], and it has been consistently demonstrated to be one of the biggest drivers of cost among critically ill patients [7].

Approximately 10–20% of patients will ultimately fail to be liberated from mechanical ventilation, and may fail extubation, thus requiring re-intubation. Such patients are at increased risk of death [8, 9]. Patients who fail extubation experience prolonged mechanical ventilation, and often require tracheostomy [10]. Therefore, there has been considerable focus on identification of prognostic factors associated with mortality and extubation failure in those receiving mechanical ventilation, to facilitate decision making with patients and their families regarding goals-of-care.

As a clinical state characterized by reduced physiologic reserve and increased vulnerability to physiological stresses [11], frailty has become recognized as an important prognostic indicator in critically ill patients [12]. In the ICU, screening for frailty is typically performed using the Clinical Frailty Scale (CFS) [13], which can be applied quickly and conveniently, and is associated with increased mortality and resource utilization in various ICU populations [14–18]. While the relationship between increasing age and poor outcomes among mechanically ventilated patients is well documented [19, 20], it is unclear whether this association is due to the higher prevalence of frailty in the elderly, or due to some other factor associated with aging. Importantly, frailty is not always synonymous with aging, and younger patients with significant comorbidities may also have frailty [21]. Overall, little is known regarding the association between frailty and outcomes following institution of invasive mechanical ventilation. Therefore, we sought to evaluate this relationship in ICU patients receiving mechanical ventilation, and in particular, to examine associations with hospital mortality, extubation failure, and tracheostomy.

## Methods

Ethics approval for this study was obtained from The Ottawa Health Science Network Research Ethics Board (Protocol 20160570-01H).

### Take-home message

Clinical frailty was associated with important outcomes following mechanical ventilation, including hospital mortality, disposition to long-term care, extubation failure, and tracheostomy. This prognostic factor may ultimately be useful in patient-provider discussions related to mechanical ventilation, and could be incorporated into future prediction models for clinical decision making.

### Study design, setting and subjects

We studied patients at two hospitals within The Ottawa Hospital network (Ottawa, ON). Combined, both hospitals have approximately 2500 total ICU admissions per year. We retrospectively examined prospectively collected data from The Ottawa Hospital Data Warehouse, a health administrative database used in previous studies [22–24]. During hospital admission, daily data are gathered from each patient and stored in The Ottawa Hospital Data Warehouse. Data quality assessments are executed routinely, and quality-assurance initiatives are conducted regularly to ensure completeness and accuracy.

We included all patients $\geq 18$ years of age, admitted between 2011 and 2016, who received invasive mechanical ventilation, defined as mechanical ventilation delivered via endotracheal tube or tracheostomy. We excluded patients who only received non-invasive mechanical ventilation or high flow nasal cannulae. We also excluded patients with chronic invasive ventilation requirements at the time of hospital admission (since there would be no expectation of liberation from mechanical ventilation), and those with existing goals-of-care that did not allow for mechanical ventilation. We excluded patients with missing data related to baseline function prior to admission. Importantly, hospital mortality data from 791 patients (9.8% of our study cohort) have been presented previously [18]. However, data related to extubation failure and tracheostomy among these patients have not been previously presented.

### Data collection

All data were obtained from The Ottawa Hospital Data Warehouse. We abstracted basic demographic data, comorbidities, Elixhauser Comorbidity Score [25], and Multiple Organ Dysfunction Score (MODS) [26] at the time of ICU admission. The Elixhauser Comorbidity Index is generated from comorbidities stored in the Data Warehouse, and the association between this index and mortality has been previously validated in our database [27]. The most responsible diagnosis was recorded at death or discharge, based upon International Classification of Diseases, Version 10 (ICD-10). Outcome data were collected from admission until either the point of discharge from hospital, or hospital death.

As there is no consensus definition, we followed existing standards in defining "extubation failure" [28]. Since successful liberation has been defined as the absence of invasive ventilatory support during the first 48 h after extubation [29], we considered re-initiation of invasive mechanical ventilation within the first 48 h of extubation (i.e., removal of an endotracheal tube) to indicate "extubation failure". In keeping with evidence that non-invasive ventilation following extubation does not prevent re-intubation [30], we did not include initiation of non-invasive ventilation as constituting extubation failure. In the analysis of extubation failure, we excluded patients who were extubated with a "do not re-intubate" order, patients who were extubated to facilitate palliation, and those who required re-intubation strictly for a planned procedure, as determined from patient records. Need for percutaneous or open tracheostomy was confirmed through patient records, and further validated by review of chest X-ray reports.

The primary outcome was hospital mortality. Secondary outcomes included discharge directly from hospital to long-term care (among survivors to hospital discharge originally from home), extubation failure, tracheostomy, ICU LOS, hospital LOS, and hospital readmission within 30 days.

### Screening for frailty

To identify the presence of frailty, we used the CFS, a 9-point global frailty scale which evaluates baseline mobility, energy, physical activity, and function (prior to hospital admission) [13]. We applied the CFS for each study patient as described previously [18]. Briefly, we evaluated patient pre-admission mobility and function assessments (prior to the acute illness), as completed by nursing staff or occupational therapy within 24 h of ICU admission. We used these staff assessments to retrospectively score each patient on the CFS, using a standardized abstraction tool (Supplemental Fig. 1). This method has been used previously in critically ill patients, and been shown to have comparable reliability to prospective assessment [18, 31]. Patients with a CFS of 9 were excluded, given their high likelihood of short-term mortality. We performed abstraction from charts according to accepted standards [32]. To evaluate reproducibility in abstraction, two independent investigators (SMF, CD), blinded to each other's scores, individually evaluated a random sample of 20% of patient records. As inter-rater reliability was excellent ($\kappa = 0.951$), a single investigator (SMF) completed the remaining records. Consistent with previous research, a CFS $\geq 5$ was used to identify the presence of frailty [15, 17].

### Statistical analysis

We performed all statistical analyses with R (Version 3.3.3) and IBM SPSS (Version 24.0). We present data as mean values, with standard deviation (SD), or medians, with interquartile range (IQR), where appropriate. The Student's $t$ test (parametric values), Mann–Whitney test (non-parametric values), and $\chi^2$ (for categorical values) were performed to determine between-group baseline differences. As recommended for observational studies in the critically ill [33], confounders were determined a priori, on the basis of their likelihood of influencing both the presence of frailty and associated outcomes, informed by clinical knowledge and existing studies evaluating the association between frailty and mortality in critically ill patients [14–16]. In accordance with the existing recommendations [33], we used multivariable logistic regression modeling to adjust for age, sex, illness severity [MODS], location of intubation and initiation of mechanical ventilation (ICU vs. non-ICU), most responsible diagnosis, and Elixhauser comorbidity index [25]. We present adjusted odds ratios (aOR) with 95% confidence intervals. To evaluate the robustness of our findings, we performed post hoc sensitivity analyses excluding patients with severe frailty (CFS 8), and patients with limitations on care, either at the time of ICU admission or extubation. Finally, we followed the Prognosis Research Strategy guidelines in developing a predictive model for in-hospital mortality [34]. These guidelines recommend a clinical hypothesis-driven approach for a priori selection of all model variables, as opposed to bivariate association testing methods. We ensured the recommended sample size threshold of at least 10 events per predictor was met [35]. One thousand bootstrap samples with the same size as the original cohort were generated without replacement. Where a CI did not include 1, the variable was considered to be a significant predictor.

For baseline characteristics, a $P$ value of $\leq 0.05$ was considered statistically significant. For outcomes, we applied a Bonferroni correction, and, therefore, a $P$ value of $< 0.01$ was considered significant.

## Results

A total of 17,173 patients were admitted to the participating ICUs from 2011 to 2016 (Supplemental Fig. 2). Of these, 8928 patients (52.0%) were excluded, as they did not receive invasive mechanical ventilation. A further 41 patients (0.5%) were excluded because of baseline chronic invasive ventilatory needs through permanent tracheostomy. Finally, 94 patients (1.1%) were excluded due to insufficient available data allowing for CFS scoring.

In total, we included 8110 patients in the analyses. Of these patients, 2529 (31.2%) had frailty (CFS $\geq$ 5).

**Table 1 Characteristics of non-frail and frail ICU patients requiring mechanical ventilation ($n = 8110$)**

| Characteristic | No frailty ($n = 5581$) | Frailty ($n = 2529$) | *P* value |
|---|---|---|---|
| Age (years), mean (SD) | 57.6 (18.1) | 69.2 (12.2) | < 0.001 |
| Male, *n* (%) | 3227 (57.8) | 1361 (53.8) | < 0.01 |
| ICU MODS, mean (SD) | 4.8 (2.6) | 5.2 (2.7) | < 0.001 |
| Comorbidities | | | |
| Congestive heart failure | 194 (3.5) | 468 (18.5) | < 0.001 |
| Atrial fibrillation | 590 (10.6) | 457 (18.1) | < 0.001 |
| Peripheral vascular disease | 222 (4.0) | 301 (11.9) | < 0.001 |
| Hypertension | 1382 (24.8) | 775 (30.7) | < 0.001 |
| Chronic obstructive pulmonary disease | 83 (1.5) | 891 (35.2) | < 0.001 |
| Diabetes mellitus | 1320 (23.7) | 912 (36.1) | < 0.001 |
| Chronic kidney disease | 182 (3.3) | 170 (6.8) | < 0.001 |
| Liver disease | 216 (3.9) | 232 (9.2) | < 0.001 |
| Malignancy | 413 (7.4) | 601 (23.8) | < 0.001 |
| Alcohol misuse | 329 (5.9) | 166 (6.6) | 0.24 |
| Psychosis | 81 (1.5) | 15 (0.6) | < 0.01 |
| Depression | 178 (3.2) | 44 (1.7) | < 0.01 |
| Elixhauser Comorbidity Score, mean (SD) | 3.5 (5.1) | 9.2 (7.1) | < 0.001 |
| Daytime ICU admission (0800-1700), *n* (%) | 3534 (63.3) | 1742 (68.9) | < 0.001 |
| Location prior to ICU admission, *n* (%) | | | < 0.001 |
| Emergency department | 2170 (38.9) | 834 (33.0) | |
| Hospital wards | 1885 (33.8) | 1090 (43.1) | |
| Operating room | 314 (5.6) | 199 (7.9) | |
| Peripheral hospital | 1212 (21.7) | 406 (16.0) | |
| Setting of intubation, *n* (%) | | | 0.24 |
| ICU | 3182 (57.0) | 1477 (58.4) | |
| Outside of ICU | 2399 (43.0) | 1052 (41.6) | |
| Previous ED visits, mean (SD)[a] | 2.2 (2.6) | 2.3 (1.8) | < 0.001 |
| Previous ICU admissions, mean (SD)[a] | 0.2 (0.6) | 0.5 (1.2) | < 0.001 |
| Previous ICU days, mean (SD)[a] | 1.3 (5.7) | 4.3 (15.0) | < 0.001 |
| No CPR directive at admission, *n* (%) | 692 (12.4) | 701 (27.7) | < 0.001 |
| Most responsible diagnosis, *n* (%) | | | < 0.001 |
| Infection/sepsis | 849 (15.2) | 421 (16.6) | |
| Respiratory failure | 460 (8.2) | 577 (22.8) | |
| Trauma | 821 (14.7) | 88 (3.5) | |
| Malignancy | 394 (7.1) | 248 (9.8) | |
| Spontaneous intracranial hemorrhage | 403 (7.3) | 46 (1.8) | |
| Stroke | 288 (5.2) | 61 (2.4) | |
| Overdose/poisoning | 242 (4.3) | 7 (0.3) | |
| Renal failure | 97 (1.7) | 46 (1.8) | |
| Gastrointestinal bleeding | 79 (1.4) | 34 (1.3) | |
| Congestive heart failure | 20 (0.4) | 67 (2.6) | |
| Cardiac arrest | 102 (1.8) | 23 (0.9) | |
| Seizures/status epilepticus | 114 (2.0) | 20 (0.8) | |
| Diabetic ketoacidosis | 51 (0.9) | 37 (1.5) | |
| Other | 1661 (29.8) | 854 (33.8) | |

*CPR* cardiopulmonary resuscitation, *ED* emergency department, *ICU* intensive care unit, *MODS* Multi-Organ Dysfunction Score, *SD* standard deviation

[a] Only including patients with previous visits to The Ottawa Hospital, and includes encounters prior to the index admission

Baseline characteristics of non-frail and frail patients are shown in Table 1. Patients with frailty were older (mean age 69.2 years vs. 57.6 years, $P < 0.001$), had higher severity of illness (mean MODS 5.2 vs. 4.8, $P < 0.001$), and higher comorbidity burden. No difference in setting of intubation was seen between the groups. Respiratory failure was more common as an admitting diagnosis among patients with frailty compared to without (22.8% vs. 8.2%, $P < 0.001$).

Comparisons of outcomes between groups by frailty status are depicted in Table 2. Fully specified multivariable logistic regression analyses examining in-hospital mortality, extubation failure, and tracheostomy are displayed in the appendix (Supplemental Tables 1–3, respectively) as suggested by existing recommendations [33]. Patients with frailty had higher odds of hospital mortality (adjusted OR 1.24 [95% CI 1.10–1.40]), extubation failure (adjusted OR 1.17 [95% CI 1.04–1.37]), and tracheostomy (adjusted OR 1.17 [95% CI 1.01–1.36]), as compared to people without frailty. The association between frailty and increased in-hospital mortality persisted in sensitivity analyses removing patients with the most severe frailty (CFS of 8), and those with limitations on care (Supplemental Tables 4, 5). With regard to disposition, patients with frailty had a higher likelihood of discharge to a long-term care facility, as compared to those without frailty (adjusted OR 1.21 [95% CI 1.13–1.35]). Finally, frailty was associated with longer median ICU LOS (7 days vs. 6 days, $P < 0.001$) and median total hospital LOS (15 days vs. 12 days, $P < 0.001$). Figure 1 depicts liberation of mechanical ventilation over the course of the first 14 days following initiation of mechanical ventilation. At all measured time points, a higher proportion of non-frail than frail patients had been successfully liberated from mechanical ventilation. Evaluation of patients stratified by duration of mechanical ventilation found that frailty was associated with increased odds of mortality, extubation failure, and tracheostomy in all subgroups (Supplemental Table 6). Frailty was also found to be a significant predictor of in-hospital mortality in our logistic regression model (Supplemental Table 7).

A total of 1243 patients (15.3%) in our cohort met criteria for extubation failure. Of these patients, 445 (35.8%) had frailty. Comparison of those with and without frailty experiencing extubation failure is shown in Table 3. Patients with frailty were significantly older than those without (mean 68.9 years vs. 57.6 years, $P < 0.001$) and had higher severity of illness (mean MODS 5.9 vs. 5.4, $P < 0.001$). Patients with frailty experiencing extubation failure had a higher likelihood of death in-hospital, as compared to those without frailty (adjusted OR 1.18 [95% CI 1.07-1.28]).

Finally, a total of 1470 (18.1%) patients in our cohort required tracheostomy. Of these, 554 (37.7%) had frailty. Comparison of patients receiving tracheostomy, by frailty status, is displayed in Table 4. A higher proportion of those with frailty underwent tracheostomy without prior attempt at extubation, as compared to patients without frailty (68.0% vs. 61.5%, $P < 0.01$), who were more likely to receive tracheostomy after extubation failure. No difference in timing of tracheostomy (relative to initiation of mechanical ventilation) was found between groups (median 9 days vs. 10 days, $P = 0.31$). Patients with frailty were more likely than those without frailty to die

**Table 2 Outcomes of non-frail and frail ICU patients requiring mechanical ventilation (*n* = 8110)**

| Characteristic | No frailty (*n* = 5581) | Frailty (*n* = 2529) | Adjusted odds ratio[c] (95% CI) | *P* value |
|---|---|---|---|---|
| In-hospital mortality, *n* (%) | 1617 (29.0) | 1021 (40.3) | 1.24 (1.10–1.40) | < 0.001 |
| Extubation failure, *n* (%)[a] | 798 (14.9) | 445 (19.9) | 1.17 (1.04–1.37) | < 0.001 |
| Tracheostomy, *n* (%) | 916 (17.1) | 544 (24.4) | 1.17 (1.01–1.36) | < 0.001 |
| Disposition, *n* (%)[b] | | | 1.21 (1.13–1.35) | < 0.001 |
| Home | 2280 (57.5) | 704 (46.7) | | |
| Long-term care center | 1684 (42.5) | 804 (53.3) | | |
| ICU length of stay (days), median (IQR) | 6 (2–12) | 7 (4–14) | | < 0.001 |
| Hospital length of stay, days, median (IQR) | 12 (4–28) | 15 (7–32) | | < 0.001 |
| Ventilator-free days, median (IQR) | 7 (1–19) | 6 (2–20) | | < 0.001 |
| Readmission to ICU during hospitalization, *n* (%) | 921 (16.5) | 463 (18.3) | 1.04 (0.98–1.11) | 0.07 |
| Readmission within 30 days from discharge, *n* (%)[b] | 1187 (29.9) | 416 (27.6) | 1.09 (0.87–1.21) | 0.19 |

*ICU* intensive care unit, *IQR* interquartile range, *MODS* Multi-Organ Dysfunction Score, *SD* standard deviation

[a] Excludes patients where extubation was performed only for palliation, or who died prior to attempt at extubation

[b] Only includes patients surviving to discharge

[c] Ratio of frail patients to non-frail patients

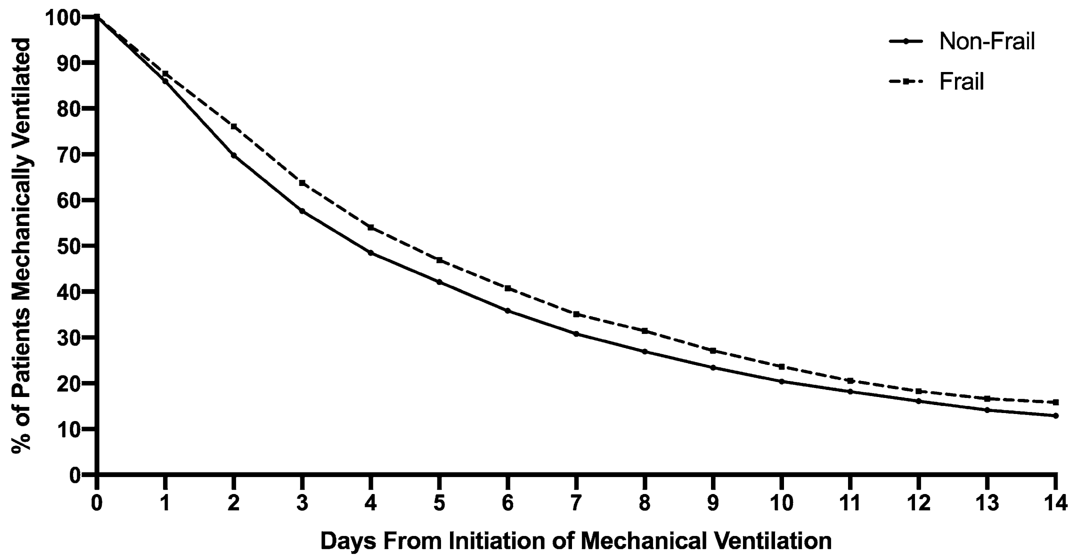


**Fig. 1** Liberation from invasive mechanical ventilation over the first 14 days between frail and non-frail patients. $P<0.05$ at all points

in-hospital following tracheostomy (adjusted OR 1.14 [95% CI 1.03–1.25]).

## Discussion

Among critically ill adults requiring mechanical ventilation, we found that the presence of pre-admission frailty was associated with increased odds of extubation failure, tracheostomy, and hospital mortality, even after adjustment for age and other clinically relevant confounders. Ventilated patients with frailty were also more likely to be discharged to long-term care facilities than those without frailty, and more likely to have prolonged ICU and total hospital LOS. Finally, following extubation failure or receipt of tracheostomy, frailty was associated with increased risk of in-hospital death. Importantly, the relationship between frailty and these outcomes was independent of chronological age. These findings provide novel insight into the prognostic significance of frailty in predicting outcomes among critically ill adults requiring invasive mechanical ventilation.

The initiation of mechanical ventilation in a critically ill patient is an important event, and prior to offering this treatment, clinicians often discuss prognosis with patients and families [36]. The goal for the clinician at this point is often to not only explain the possible complications that may arise from mechanical ventilation, but also to discuss the likelihood of survival and future quality of life, and to inform goals-of-care discussions. In the elderly population, a growing evidence base suggests that patients with respiratory failure, even when treated with mechanical ventilation, have high mortality [19, 20, 37]. It is also evident that younger patients with a high burden of comorbidity (especially liver failure and chronic obstructive pulmonary disease) who require mechanical ventilation have a similarly poor prognosis [38, 39]. This suggests that it may not simply be chronological age that determines outcome following critical illness and need for mechanical ventilation, but rather reduced physiologic reserve. Clinical frailty is aligned with this framework, and observational evidence to date strongly links frailty to worse outcomes in ICU patients, independent of age [14–18]. This study, specifically focusing on patients requiring mechanical ventilation, is consistent with these previous studies suggesting that the diagnosis of frailty may offer important prognostic information for patients, families, and clinicians to guide decision making and inform goals-of-care decisions [40].

These findings also place focus on the importance of frailty in predicting outcomes following extubation. Frailty was associated not only with extubation failure, but also predicted in-hospital death among patients experiencing extubation failure. Extubation failure is a critical event in ICU patients as, independent of illness severity, failing to wean from mechanical ventilation is associated with worse outcomes in critically ill patients [9, 28]. Therefore, there is a growing need to identify factors predictive of failed extubation. While increasing age has been shown to be an independent predictor of extubation failure [9, 41], there is likely an additional effect of comorbidity, with one study demonstrating a fourfold higher risk in those with significant comorbidities [9]. Our findings, which support pre-ICU frailty as an important predictor of extubation failure independent of age and comorbidity, are also supported by clinically

**Table 3 Extubation failure and outcomes following extubation failure in non-frail and frail ICU patients requiring mechanical ventilation ($n = 1243$)**

| Characteristic | No frailty ($n = 798$) | Frailty ($n = 445$) | Adjusted odds ratio (95% CI)[b] | *P* value |
|---|---|---|---|---|
| Age (years), mean (SD) | 57.6 (17.9) | 68.9 (12.4) | | < 0.001 |
| Male, *n* (%) | 442 (55.4) | 238 (53.5) | | 0.52 |
| ICU MODS, mean (SD) | 5.4 (2.2) | 5.9 (1.6) | | < 0.001 |
| Comorbidities | | | | |
| Congestive heart failure | 34 (4.3) | 92 (20.7) | | < 0.001 |
| Atrial fibrillation | 86 (10.8) | 80 (18.0) | | < 0.01 |
| Peripheral vascular disease | 26 (3.3) | 61 (13.7) | | < 0.001 |
| Hypertension | 179 (22.4) | 139 (31.2) | | < 0.001 |
| Chronic obstructive pulmonary disease | 19 (2.4) | 36 (8.1) | | < 0.001 |
| Diabetes mellitus | 194 (24.3) | 156 (35.1) | | < 0.001 |
| Chronic kidney disease | 29 (3.6) | 27 (6.1) | | 0.05 |
| Liver disease | 38 (4.8) | 48 (10.8) | | < 0.001 |
| Malignancy | 43 (5.4) | 99 (22.2) | | < 0.001 |
| Alcohol misuse | 59 (7.4) | 34 (7.6) | | 0.87 |
| Psychosis | 9 (1.1) | 2 (0.4) | | 0.22 |
| Depression | 19 (2.4) | 4 (0.9) | | 0.06 |
| Elixhauser Comorbidity Score, mean (SD) | 3.5 (5.2) | 9.6 (7.3) | | < 0.001 |
| Most responsible diagnosis, *n* (%) | | | | < 0.001 |
| Infection/sepsis | 140 (17.5) | 83 (18.7) | | |
| Respiratory failure | 74 (9.3) | 60 (13.5) | | |
| Trauma | 123 (15.4) | 58 (13.0) | | |
| Malignancy | 35 (4.4) | 38 (8.5) | | |
| Spontaneous intracranial hemorrhage | 66 (8.3) | 16 (3.6) | | |
| Stroke | 32 (4.0) | 8 (1.8) | | |
| Overdose/poisoning | 31 (3.9) | 0 (0) | | |
| Renal failure | 10 (1.3) | 9 (2.0) | | |
| Gastrointestinal bleeding | 9 (1.1) | 4 (0.9) | | |
| Congestive heart failure | 2 (0.3) | 19 (4.3) | | |
| Cardiac arrest | 19 (2.4) | 9 (2.0) | | |
| Seizures/status epilepticus | 8 (1.0) | 2 (0.4) | | |
| Diabetic ketoacidosis | 6 (0.8) | 5 (1.1) | | |
| Other | 243 (30.5) | 134 (30.1) | | |
| Outcomes following extubation failure, *n* (%) | | | | |
| Died in-hospital | 196 (24.6) | 147 (33.0) | 1.18 (1.07–1.28) | < 0.001 |
| Re-intubation, successful extubation, survival | 249 (31.2) | 124 (27.9) | 0.91 (0.80–1.15) | 0.47 |
| Re-intubation, tracheostomy, survival | 353 (44.2) | 174 (39.1) | 0.94 (0.85–1.07) | 0.32 |

*ICU* intensive care unit, *IQR* interquartile range, *MODS* Multi-Organ Dysfunction Score, *SD* standard deviation

[a] Excludes patients where extubation was performed only for palliation, or who died prior to attempt at extubation

[b] Ratio of frail patients to non-frail patients

plausible mechanisms. For example, frailty and sarcopenia often co-occur in older patients [42], and the muscle loss inherent in sarcopenia can impair the ability to take deep breaths and clear secretions. Whether frailty is associated with diaphragmatic dysfunction or puts patients at higher risk of ventilator-induced diaphragmatic dysfunction is unknown, but represents an avenue for future investigation. Finally, patients with frailty often have cognitive impairment and are at high risk of delirium [42] which may affect their ability to follow directions and expectorate effectively, and thereby contribute to extubation failure [28]. This suggests that frailty could act both as an important predictor, while also informing strategies to optimize extubation readiness.

**Table 4 Tracheostomy in non-frail and frail ICU patients requiring mechanical ventilation**

| Characteristic | No frailty ($n = 916$) | Frailty ($n = 544$) | Adjusted odds ratio (95% CI)[a] | *P* value |
|---|---|---|---|---|
| Age (years), mean (SD) | 56.8 (17.0) | 68.3 (12.3) | | < 0.001 |
| Male, *n* (%) | 527 (57.5) | 307 (56.4) | | 0.68 |
| ICU MODS, mean (SD) | 4.9 (2.3) | 5.3 (1.9) | | < 0.01 |
| Comorbidities | | | | |
| Congestive heart failure | 49 (5.3) | 115 (21.1) | | < 0.001 |
| Atrial fibrillation | 141 (15.4) | 114 (21.0) | | < 0.01 |
| Peripheral vascular disease | 38 (4.1) | 63 (11.6) | | < 0.001 |
| Hypertension | 249 (27.1) | 190 (34.9) | | < 0.001 |
| Chronic obstructive pulmonary disease | 22 (2.4) | 232 (42.6) | | < 0.001 |
| Diabetes mellitus | 230 (25.1) | 205 (37.7) | | < 0.001 |
| Chronic kidney disease | 37 (4.0) | 30 (5.5) | | 0.19 |
| Liver disease | 48 (5.2) | 47 (8.6) | | 0.01 |
| Malignancy | 53 (5.8) | 106 (19.5) | | < 0.001 |
| Alcohol misuse | 38 (4.1) | 34 (6.3) | | 0.07 |
| Psychosis | 10 (1.1) | 3 (0.6) | | 0.29 |
| Depression | 26 (2.8) | 5 (0.9) | | 0.01 |
| Elixhauser Comorbidity Score, mean (SD) | 4.2 (5.3) | 9.1 (7.0) | | < 0.001 |
| Most responsible diagnosis, *n* (%) | | | | < 0.001 |
| Infection/sepsis | 186 (20.3) | 105 (11.5) | | |
| Respiratory failure | 134 (14.6) | 107 (19.7) | | |
| Trauma | 155 (16.9) | 33 (6.1) | | |
| Malignancy | 48 (5.2) | 49 (9.0) | | |
| Spontaneous intracranial hemorrhage | 78 (8.5) | 35 (6.4) | | |
| Stroke | 38 (4.1) | 10 (1.1) | | |
| Overdose/poisoning | 11 (1.2) | 0 (0) | | |
| Renal failure | 7 (0.8) | 10 (1.8) | | |
| Gastrointestinal bleeding | 13 (1.4) | 4 (0.7) | | |
| Congestive heart failure | 3 (0.3) | 16 (2.9) | | |
| Cardiac arrest | 5 (0.5) | 3 (0.5) | | |
| Seizures/status epilepticus | 6 (0.7) | 3 (0.5) | | |
| Diabetic ketoacidosis | 6 (0.7) | 5 (0.9) | | |
| Other | 226 (24.7) | 144 (15.7) | | |
| Outcome | | | | |
| Tracheostomy following extubation, *n* (%) | 353 (44.2) | 174 (39.1) | | 0.01 |
| Tracheostomy without extubation attempt, *n* (%) | 563 (61.5) | 370 (68.0) | | |
| Time from initiation of mechanical ventilation to tracheostomy (days), median (IQR) | 10 (8–14) | 9 (7–14) | | 0.34 |
| In-hospital death following tracheostomy, *n* (%) | 280 (30.6) | 256 (47.0) | 1.14 (1.03–1.25) | < 0.01 |
| Tracheal infection, *n* (%) | 73 (8.0) | 52 (9.6) | 1.07 (0.89–1.19) | 0.31 |

*ICU* intensive care unit, *IQR* interquartile range, *MODS* Multi-Organ Dysfunction Score, *SD* standard deviation

[a] Ratio of frail patients to non-frail patients

Finally, we evaluated the association of frailty with incidence and outcomes following tracheostomy. In our cohort, roughly 18% of eligible patients underwent tracheostomy and ventilated patients with frailty were more likely to receive tracheostomy than non-frail counterparts. Additionally, frail patients were more likely to receive tracheostomy without an attempt at extubation. This may reflect a perceived higher risk of extubation failure among frail patients, which is supported by our findings. While tracheostomy is a necessary intervention in many patients requiring prolonged mechanical ventilation, it is also associated with important early and late complications, including infection, bleeding, fistulae, and tracheal stenosis [43]. Accordingly, in many situations, tracheostomy is a bridge to further therapy or recovery, and tracheostomy may be less likely to be pursued in situations of irreversible illness [10]. We found that frailty was associated with higher odds of in-hospital mortality following tracheostomy, again emphasizing the importance of considering this prognostic factor in discussion around patient-defined goals-of-care.

We used a large multicenter database of mechanically ventilated patients and identified patient- and health system-important associations between frailty and disease-specific outcomes. We also closely followed existing recommendations for control of confounding in observational studies [33]. However, our study has important limitations. Most importantly, decisions related to mechanical ventilation are made on the basis of patient-defined goals-of-care and may be influenced by indication bias. While data were available related to goals-of-care at the time of ICU admission, we do not have data on how these goals changed over the course of admission. Since patients living with frailty may be guided toward less aggressive treatments, this has the potential to bias our results. We performed a sensitivity analysis excluding patients with a pre-existing "No-CPR" order, and those extubated with a "Do-Not-Reintubate" order, which did not alter our conclusions. Second, we screened for frailty using the CFS in a retrospective fashion, although it was originally designed for prospective application [13]. While this has the potential to introduce bias, we used previously described methods [18], and followed best-practice recommendations for health record review methodology, through the use of multiple scorers and combined agreement [32]. These retrospective methods have been shown to have strong concordance with prospective CFS scoring in the ICU [31]. Third, with regard to extubation failure, data were not sufficiently granular to evaluate the association of frailty with other factors that may predict extubation failure. In particular, data related to weaning and physiotherapy protocols were unavailable. Such protocols may potentially have a greater relative effect upon patients with frailty than those without frailty, and as such, the absence of these data represents an important limitation to our work, particularly as it relates to associations between frailty, extubation failure, and tracheostomy. Furthermore, we lack data regarding the timing of initiation of mechanical ventilation relative to patient deterioration. Whether earlier ventilatory intervention among frail patients with respiratory failure is associated with outcomes is unknown. Finally, we did not have data related to long-term outcomes among survivors of mechanical ventilation. While frail patients may survive their admission, their long-term outcomes may be similarly poor. Addressing value in healthcare delivery is a major current focus of critical care [44, 45], and understanding the impact of frailty on long-term survival and quality of life will provide greater insight into whether provision of critical care in this population is truly beneficial. Future work should evaluate the association between frailty and long-term survival and disability following mechanical ventilation.

## Conclusions

We found that, among ICU patients requiring mechanical ventilation, the presence of frailty increased the likelihood of short-term mortality, discharge to long-term care, extubation failure, and tracheostomy, even after adjustment for potential confounders. These findings have important implications in the risk stratification of all patients requiring mechanical ventilation, and may have a role in informed shared decision making with patients and families prior to the provision of mechanical ventilation.

#### Electronic supplementary material

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#### Author contributions

SMF, DIM, BR, SMB, JM, and KK designed the study. SMF, CD, and KK gathered the data. SMF, DIM, BR, SMB, JM, LM, NDF, AJES, DJC, PT, and KK analyzed the data. All the authors wrote the manuscript.


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None.


#### Compliance with ethical standards

#### Conflicts of interest

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