Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Original Research

The Long-Term Impact of Frailty After an Intensive Care Unit Admission Due to Chronic Obstructive Pulmonary Disease

Matthew T. Donnan, BSc, MBBS[1,2] Shailesh Bihari, MBBS, FCICM, MD, PhD[3,4]
Ashwin Subramaniam, MBBS, MMED, FRACP, FCICM, PhD [5,7] Eli J. Dabscheck, MBBS, MClinEpi, FRACP[2,8]
Brooke Riley, BBioMedSc, MBBS, FCICM[1] David V. Pilcher, MBBS, MRCP[1,7,9]

Abstract

Rationale: Frailty is an increasingly recognized aspect of chronic obstructive pulmonary disease (COPD). The impact of frailty on long-term survival after admission to an intensive care unit (ICU) due to an exacerbation of COPD has not been described.

Objective: The objective was to quantify the impact of frailty on time to death up to 4 years after admission to the ICU in Australia and New Zealand for an exacerbation of COPD.

Methods: We performed a multicenter retrospective cohort study of adult patients admitted to 179 ICUs with a primary diagnosis of an exacerbation of COPD using the Australian and New Zealand Intensive Care Society Adult Patient Database from January 1, 2018, through December 31, 2020, in New Zealand, and March 31, 2022, in Australia. Frailty was measured using the clinical frailty scale (CFS). The primary outcome was survival up to 4 years after ICU admission. The secondary outcome was readmission to the ICU due to an exacerbation of COPD.

Measurements and Main Results: We examined 7126 patients of which 3859 (54.1%) were frail (CFS scores of 5–8). Mortality in not-frail individuals versus frail individuals at 1 and 4 years was 19.8% versus 40.4%, and 56.8% versus 77.3% respectively (both $p<0.001$). Frailty was independently associated with a shorter time to death (adjusted hazard ratio 1.66; 95% confidence interval 1.54–1.80). There was no difference in the proportion of survivors with or without frailty who were readmitted to the ICU during a subsequent hospitalization.

Conclusion: Frailty was independently associated with poorer long-term survival in patients admitted to the ICU with an exacerbation of COPD.

1. Department of Intensive Care, The Alfred Hospital, Melbourne, Australia
2. Department of Respiratory Medicine, The Alfred Hospital, Melbourne, Australia
3. College of Medicine and Public Health, Flinders University, South Australia
4. Department of Intensive and Critical Care, Finders Medical Centre, Adelaide, Australia
5. Intensive Care Unit, Peninsula Health, Melbourne, Australia
6. Peninsula Clinical School, Monash University, Frankston, Victoria, Australia
7. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
8. Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Australia
9. The Australian and New Zealand Intensive Care Society, Centre for Outcome and Resources Evaluation, Melbourne, Victoria, Australia

Abbreviations:

ANZICs=Australian and New Zealand Intensive Care Society; **ANZROD**=Australian and New Zealand Risk of Death; **APACHE**=Acute Physiology And Chronic Health Evaluation; **BMI**=body mass index; **CFS**=clinical frailty scale; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **F_IO_2**=fraction of inspired oxygen; **HR**=hazard ratio; **ICU**=intensive care unit; **IQR**=interquartile range; **NYHA**=New York Heart Association; **$PaCO_2$**=arterial partial pressure of carbon dioxide; **PaO_2**=arterial partial pressure of oxygen; **SOFA**=sequential organ failure assessment

Funding Support:

No funding.

Citation:

Donnan MT, Bihari S, Subramaniam A, Dabscheck EJ, Riley B, Pilcher DV. The long-term impact of frailty after an intensive care unit admission due to chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis.* 2024;11(1):83-94. doi: https://doi.org/10.15326/jcopdf.2023.0453

Publication Dates:

Date of Acceptance: October 18, 2023
Published Online Date: October 31, 2023

Keywords:

COPD; frailty; intensive care; mortality; readmission

Address correspondence to:

Professor Shailesh Bihari
Department of Intensive Care Unit
Flinders Medical Centre,
Bedford Park, Australia, 5042
Email: biharishailesh@gmail.com; biha0002@flinders.edu.au

This article has an online supplement.

Introduction

Frailty is a multidimensional geriatric syndrome defined by a reduction in physical, physiological, and cognitive reserves, characterized by an increased susceptibility to adverse health outcomes and mortality.[1-5] The incidence of frailty, in addition to the burden of other medical comorbidities, increases with advancing age.[6] Patients with frailty are more commonly admitted to the intensive care unit (ICU) and experience poorer outcomes including increased hospital length of stay, higher rate of discharge into supported care, and greater inpatient and long-term mortality.[7-11] As a result, frailty is becoming an increasingly recognized component of decision-making in critical care medicine.[10,12-14] There is a complex bidirectional interplay between frailty and chronic obstructive pulmonary disease (COPD),[14] with a significant overlap between the symptoms of COPD and the features of frailty.[15] Frailty and COPD share common pathophysiological pathways including systemic inflammation, skeletal muscle dysfunction, and endocrine dysregulation.[16,17] The reported prevalence of frailty among patients with COPD varies significantly according to the population studied and the frailty assessment tool used, but is at least twice that of those without, and appears to increase with the worsening severity of COPD.[18-22] Patients with both COPD and frailty experience more dyspnea and report a lower quality of life than those with either individual condition.[20] Frailty in those with COPD has been associated with an increased rate of exacerbations, hospital readmission, and all-cause mortality.[18-20, 23-31]

While frailty has been shown to be a predictor of inpatient mortality in patients admitted to the ICU with an exacerbation of COPD,[32] its impact on long-term outcomes has not been described. We aimed to quantify the effect of frailty on time to death up to 4 years following admission to ICUs in Australia and New Zealand. We hypothesized that frailty would be independently associated with poor long-term outcomes.

Methods

Study Design

We performed a retrospective multicenter study of all critically ill adult (age≥16 years) patients admitted to 179 ICUs in Australia and New Zealand with a primary diagnosis of an exacerbation of COPD. Only the first ICU admission per hospitalization was included. Subsequent hospitalizations with ICU admissions were excluded.

Data Sources

Data was extracted from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database, a binational quality registry dataset, containing information on all admissions to 98% of adult ICUs in Australia, and 67% of ICUs in New Zealand. An exacerbation of COPD was defined using the Acute Physiology And Chronic Health Evaluation (APACHE) IV diagnosis (ANZICS modified) list taking into account emergency department documentation, ICU admission documentation, ICU observation charts, and all other clinically relevant information.[33] The list comprises approximately 140 individual diagnoses of which the ICU clinician can select only one (with an associated subcode) to represent the primary cause of admission to the ICU. COPD is coded within the ANZICS database using the diagnostic code 206, with subcodes 206.01(emphysema/bronchitis) and 206.2(associated with suspected or confirmed pandemic infection) used to further define admissions. Admission records from January 1, 2018, through December 31 2020, in New Zealand, and March 31, 2022, in Australia, were matched to the date of death recorded in the national death registers of each country using an encoded linkage key. This provided a maximum follow-up period of 36 months for New Zealand ICUs and 51 months for Australian ICUs.

We extracted data on patient demographics, such as age, sex, comorbidities, goals of care, and biochemical and physiological parameters within the first 24 hours of admission.[33] Interventions including invasive mechanical ventilation, noninvasive ventilation, tracheostomy, vasopressors, and renal replacement therapy were also recorded. Frailty was measured using a modified version of the Canadian Study of Health and Aging Clinical Frailty Scale (CFS), which categorizes 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).[2] The CFS was assigned at the time of the index ICU admission by local clinicians working in the admitting ICU and based on the patient's level of function in the 2 months preceding the admission.[33] This data was collected in a standardized manner using patient progress notes and medical history.

Outcomes

The primary outcome was mortality up to 4 years after

ICU admission. The secondary outcome was readmission to the ICU due to COPD during a future hospitalization, considered only in those who survived to hospital discharge after the index ICU admission. Other outcomes reported included in-ICU and in-hospital mortality, length of stay, and discharge destination. The primary outcome was also examined in 2 predefined subgroups based on the requirement (or not) for invasive mechanical ventilation.

Statistical Analysis

Categorical data are reported as a percentage (*n* [%]); continuous data as mean (standard deviation) or median (interquartile range [IQR]) as appropriate depending on data distribution. Comparisons were made using Chi-square, student's *t*, or Log-rank tests as appropriate depending on the type and distribution of data. Overall survival estimates are displayed using Kaplan-Meier plots. After assessing proportionality, the effect of frailty on time to death was assessed using a Cox proportional hazards model, adjusting for age, sex, comorbidities, ICU admission source, treatment limitations on admission, time in hospital prior to ICU admission, COVID-19 status, acute illness severity at ICU admission assessed using the sequential organ failure assessment (SOFA) score, and hospital type, with results reported as hazard ratios (HRs), (95% confidence intervals [CI]). Time to readmission to the ICU during a future hospitalization was examined using a Fine and Gray proportional subhazards model with death considered as a competing event. A 2-sided *p*-value of <0.05 was used to indicate statistical significance. Analyses were undertaken using Stata 16.1(College Station, Texas).

Ethics Approval

The study was approved by the Alfred Hospital Ethics Committee (Reference 125/23).

Results

Demographics

Over the study period, 9223 individual patients had 11,542 ICU admissions for an exacerbation of COPD, at a total of 188 hospitals, representing 1.5% of all ICU admissions reported to the ANZICS Adult Patient Database (Appendix Figure 1 in the online supplement). After the exclusion of 157 patients in whom long-term follow-up data was unavailable and 1940 patients for whom there was no information about frailty, the final study population comprised 7126 patients with an index admission to 167 Australian and 12 New Zealand ICUs. A comparison of patients with and without frailty data is provided in Appendix Table 1 in the online supplement.

Of the total 7126 patients studied, 3859 (54.1%) were identified as frail (CFS scores 5-8). Patients with frailty were older, more likely to be female, and had a lower body mass index (BMI) (Table 1). Among patients with frailty, there was a significantly higher burden of comorbidities, with higher rates of severe chronic respiratory disease, chronic cardiovascular disease, and dialysis-dependent chronic kidney disease. Over 50% of patients with frailty had some form of treatment limitation in place at the time of admission to the ICU, compared to only 21.2% of patients without frailty (Table 1). When compared with their nonfrail counterparts, patients with frailty had worse oxygenation, lower pH, and a higher arterial partial pressure of carbon dioxide ($PaCO_2$). Patients with frailty had higher acute illness severity scores and a higher predicted risk of in-hospital death.[34] Patients with frailty less commonly received invasive mechanical ventilation but were more commonly treated with noninvasive ventilation and for a longer duration of time. Tracheostomies were rarely performed in both groups but were more common in patients without frailty (Table 1).

Primary Outcome: Long-term Mortality

Mortality in the not-frail compared with the frail group at 1, 2, 3, and 4 years was 19.8% versus 40.4%, 30.4% versus 53.5%, 40.1% versus 65.7%, and 56.8% versus 77.3% respectively ($p<0.001$) (Table 2 and Figure 1). The median survival of patients without frailty was 21.1 months (IQR 8.7–30.4) compared to 11.8 months (IQR 2.2–26.8) for patients with frailty ($p<0.001$). After adjusting for confounders including age, chronic comorbidities, treatment limitations on admission to the ICU, and acute illness severity, the presence of frailty was associated with a shorter time to death (adjusted HR 1.66; 95% CI 1.54–1.80) (Table 3). This finding was further established by a sensitivity analysis conducted using the CFS as a continuous variable which demonstrated a relationship between increasing frailty and time to death (Appendix Table 2 in the online supplement). Appendix Tables 6 and 7 in the online supplement show a sensitivity analysis (lifetable estimates) of increasing mortality with each individual level of the CFS up to 4 years.

Male sex, age, and the presence of treatment limitations on admission were all independently associated with increased long-term mortality, as were pre-existing chronic respiratory disease, chronic renal disease, and metastatic or hematological malignancy. The requirement for inotropic support (but not invasive or noninvasive ventilation) was also associated with an increased probability of mortality (Table 3).

In both of the examined subgroups, i.e., those who received invasive mechanical ventilation and those who

Table 1. Baseline Characteristics, Physiological Parameters, and Intensive Care Management

	Not Frail (CFS 1-4)	Frail (CFS 5-8)	*P* Value
Clinical Frailty Scale (1 very fit – 8 very severely frail), mean (SD)	3.4 (0.7)	6.0 (0.8)	<0.001
Demographics			
Age, years, mean (SD)	66.7 (11.5)	71.4 (10.3)	<0.001
Sex, male, n (%)	1686 (51.7)	1743 (45.2)	<0.001
BMI, kg/m^2, median (IQR)	28.1 (23.2–34.6)	27.0 (22.2–34.1)	<0.001
Hospital Type, n (%)			0.14
Public Tertiary	632 (19.3)	682 (17.7)	
Public Metropolitan	1254 (38.4)	1542 (40.0)	
Public Rural/Regional	1120 (34.3)	1295 (33.6)	
Private	261 (8.0)	340 (8.8)	
Source of Admission to ICU, n (%)			<0.001
Emergency Department	2248 (68.8)	2681 (69.5)	
General Ward	652 (20.0)	879 (22.8)	
Other Hospital	360 (11.0)	283 (7.3)	
Other[a]	7 (0.2)	16 (0.4)	
Time in Hospital Prior to ICU Admission, hours, n (%)	5.8 (2.3–12.1)	6.2 (3.1–14.8)	<0.001
Socioeconomic Decile, 1 lowest–10 highest, median (IQR)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.086
Treatment Limitation Present on Admission to ICU, n (%)	691 (21.2)	1945 (50.4)	<0.001
Comorbidities,[b] n (%)			
Diabetes	684 (20.9)	932 (24.2)	0.001
Respiratory	1648 (50.4)	2816 (73.0)	<0.001
Cardiovascular	411 (12.6)	635 (16.5)	<0.001
Renal	90 (2.8)	144 (3.7)	0.021
Liver	40 (1.2)	36 (0.9)	0.23
Immunosuppression	146 (4.5)	188 (4.9)	0.42
Metastatic cancer or haematological malignancy	67 (2.1)	88 (2.3)	0.51
Associated COVID-19 infection	180 (5.5)	176 (4.6)	0.067
Physiological and Biochemical Parameters[c]			
Worst F_IO_2,[d] mean (SD)	0.36 (0.16)	0.35 (0.15)	0.089
Lowest PaO_2 (mm Hg),[d] mean (SD)	72 (38)	68 (36)	<0.001
PaO_2/ FIO_2 ratio, mean (SD)	219 (86)	209 (79)	<0.001
Highest $PaCO_2$ (mm Hg),[d] mean (SD)	55.1 (17.3)	59.2 (19.1)	<0.001
Lowest pH,[d] mean (SD)	7.344 (0.092)	7.337 (0.095)	0.010
Highest White Cell Count, x10^9 L^{-1}, median (IQR)	11.4 (8.6–15.3)	11.1 (8.2—15.2)	0.011
Highest Core Temperature, °C, median (IQR)	37.0 (36.7–37.4)	37.0 (36.7–37.5)	0.72
Management			
Invasive Ventilation, n (%)	563 (17.2)	459 (11.9)	<0.001
Duration of Invasive Ventilation, hours,[e] median (IQR)	52 (22–110)	48 (25–115)	0.87
NIV, n (%)	1927 (63.0)	2618 (72.4)	<0.001
Duration of NIV, hours,[f] median (IQR)	14 (6–32)	16 (7–34)	0.002
Invasive Ventilation and NIV, n (%)	256 (7.8)	246 (6.4)	0.016
Tracheostomy,[g] n (%)	25 (0.8)	14 (0.4)	0.026
Inotropes,[h] n (%)	549 (18.3)	563 (16.3)	0.032
Renal Replacement Therapy,[h] n (%)	16 (0.5)	26 (0.8)	0.28
Severity of Illness			
SOFA Score, mean (SD)	3.3 (2.2)	3.6 (2.4)	<0.001
APACHE II Score, mean (SD)	17.3 (6.0)	20.1 (6.2)	<0.001
APACHE III Score, mean (SD)	50.3 (17.8)	56.5 (18.6)	<0.001
ANZROD percentage, mean (SD)	8.5 (9.7)	14.9 (14.2)	<0.001
ANZROD percentage, median (IQR)	4.9 (2.6–10.5)	10.4 (5.0–19.7)	<0.001

[a] Chronic care facility, rehabilitation facility, mental health facility, other; [b] APACHE II and III comorbidities[33]; [c] Recorded within the first 24 hours of ICU admission; [d] Recorded from the same arterial blood gas, data available for 1071 not frail and 1211 frail; [e] Duration of invasive ventilation available for 396 not frail and 327 frail; [f] Duration of noninvasive ventilation available for 1534 not frail and 2175 frail; [g] Information about tracheostomy available for 2948 not frail and 3410 frail; [h] Information about renal replacement therapy and inotropes available for 2942 not frail and 3409 frail

(continued on next page)

CFS=clinical frailty scale; SD=standard deviation; BMI = body mass index; IQR=interquartile range; ICU=intensive care unit; F_IO_2=fraction of inspired oxygen; PaO_2=arterial partial pressure of oxygen; $PaCO_2$=arterial partial pressure of carbon dioxide; NIV=noninvasive ventilation; SOFA=sequential organ function assessment; APACHE=Acute Physiology And Chronic Health Evaluation; ANZROD=Australian and New Zealand Risk of Death

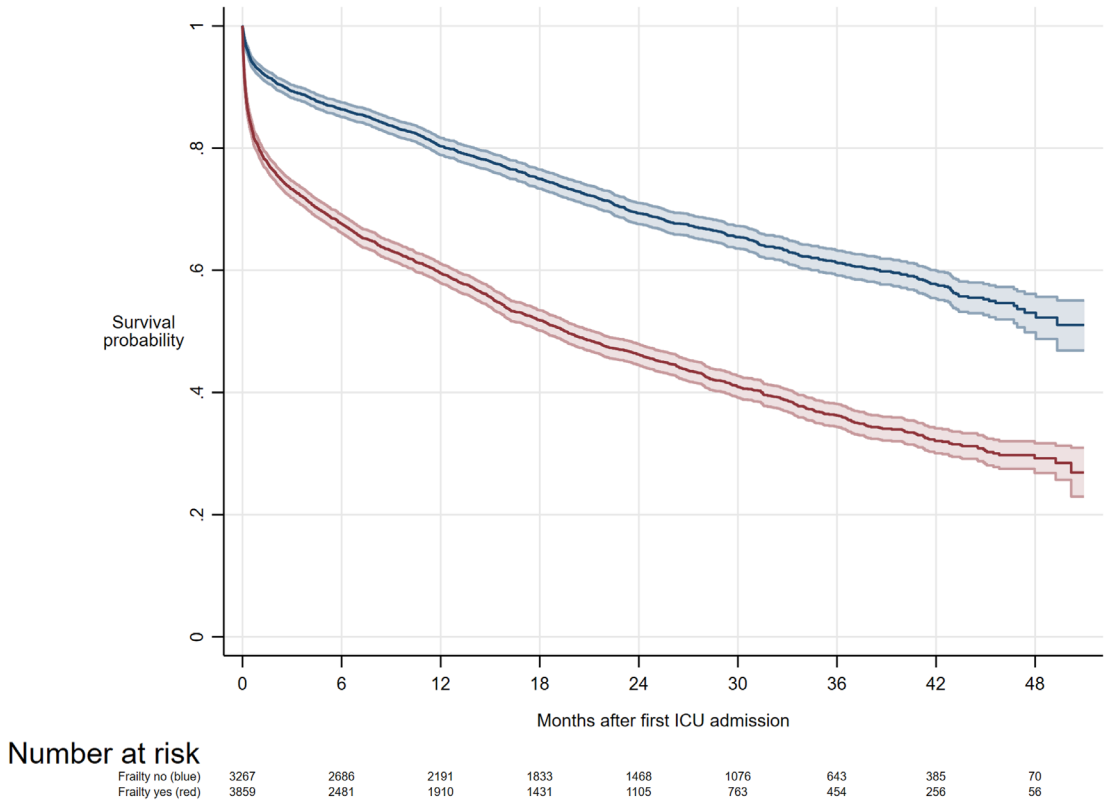
Table 2. Primary and Secondary Outcomes

	Not Frail (CFS 1-4)	Frail (CFS 5-8)	*P* Value
Primary Outcome:			
Mortality, n (%)			<0.001
Mortality at 1 year	535/2707 (19.8)	1287/3182 (40.4)	
Mortality at 2 years	631/2078 (30.4)	1263/2360 (53.5)	
Mortality at 3 years	409/1021 (40.1)	826/1257 (65.7)	
Mortality at 4 years	67/118 (56.8)	133/172 (77.3)	
Secondary Outcomes:			
In-ICU Mortality, n (%)	89 (2.7)	331 (8.6)	<0.001
Hospital Outcomes, n (%)			<0.001
Died in-hospital	177 (5.4)	617 (16.0)	
Discharged home	2589 (79.2)	2520 (65.3)	
Transferred to other hospital	327 (10.0)	375 (9.7)	
Rehabilitation facility	107 (3.3)	136 (3.5)	
Chronic care facility or nursing home	51 (1.6)	182 (4.7)	
Other[a]	16 (0.5)	29 (0.8)	
Length of ICU Stay, days, median (IQR)	2.4 (1.4–4.0)	2.4 (1.3–4.1)	0.92
Length of Hospital Stay, days, median (IQR)	6.9 (4.3–11.0)	7.8 (4.8–12.9)	<0.001
Readmitted to ICU During Hospitalization,[b] n (%)	82 (2.6)	120 (3.4)	0.050
Readmitted to ICU During Subsequent Hospitalization,[c] n (%)	510 (16.5)	567 (17.5)	0.29

[a]Includes discharge to mental health facility or other destination
[b]Expressed as a percentage of those who survived initial ICU admission (readmission to ICU for any reason)
[c]Expressed as a percentage of those who survived to hospital discharge (readmission to ICU for COPD only)

CFS=clinical frailty scale; ICU=intensive care unit; IQR=interquartile range

Figure 1. Kaplan Meier Survival Plot of Patients With and Without Frailty



ICU=intensive care unit

Table 3. Multivariable Cox-Proportional Hazards Model for Time to Death

	Hazard Ratio (95% CI)	*P* Value
Frailty Status		
Not Frail (CFS 1-4)	Reference Value	
Frail (CFS 5-8)	1.66 (1.53 to 1.79)	<0.001
Demographics		
Male	1.23 (1.14 to 1.32)	<0.001
Age, years	1.017 (1.014 to 1.021)	<0.001
Treatment Limitation on Admission	1.88 (1.74 to 2.03)	<0.001
Comorbidities[a] and Illness Severity		
Respiratory	1.22 (1.13 to 1.32)	<0.001
Cardiovascular (NYHA classification III/IV)	1.00 (0.90 to 1.10)	0.93
Renal (dialysis dependent)	1.23 (1.03 to 1.46)	0.022
Liver (cirrhosis)	1.37 (0.99 to 1.89)	0.06
Metastatic or Haematological Malignancy	1.93 (1.60 to 2.33)	<0.001
Associated COVID-19	0.91 (0.75 to 1.10)	0.32
SOFA Score	1.06 (1.05 to 1.08)	<0.001
Source of Admission to ICU		
Emergency Department	Reference Value	
General Ward	1.13 (1.04 to 1.23)	0.004
Other Hospital	0.92 (0.80 to 1.05)	0.21
Other[b]	1.30 (0.78 to 2.17)	0.31
Management		
Invasive Ventilation	0.99 (0.87 to 1.12)	0.89
Noninvasive Ventilation		
No NIV	Reference Value	
NIV Used	1.11 (0.89 to 1.37)	0.35
NIV Not Stated	1.16 (0.95 to 1.42)	0.13
Tracheostomy		
No Tracheostomy	Reference Value	
Tracheostomy	0.62 (0.33 to 1.17)	0.14
Tracheostomy Unknown	1.63 (0.85 to 3.14)	0.14
Renal Replacement Therapy		
No Renal Replacement Therapy	Reference Value	
Renal Replacement Performed	0.96 (0.61 to 1.53)	0.88
Renal Replacement Unknown	0.60 (0.32 to 1.16)	0.13
Inotropes/Vasopressors		
No Inotropes/Vasopressors	Reference Value	
Inotropes/Vasopressors Given	1.14 (1.02 to 1.28)	0.024
Inotropes/Vasopressors Unknown	1.26 (0.92 to 1.73)	0.16

[a]APACHE II and III comorbidities[33]
[b]Chronic care facility, rehabilitation facility, mental health facility, other

CI=confidence interval; CFS=clinical frailty scale; NYHA=New York Heart Association; SOFA=sequential organ function assessment; ICU=intensive care unit; NIV=noninvasive ventilation; APACHE=Acute Physiology And Chronic Health Evaluation

did not, patients with frailty had worse long-term mortality outcomes (Figure 2). Additional information regarding demographics and outcomes in each of these subgroups is provided in Appendix Tables 3 and 4 in the online supplement.

Secondary Outcome: Readmission to the Intensive Care Unit During a Future Hospitalization

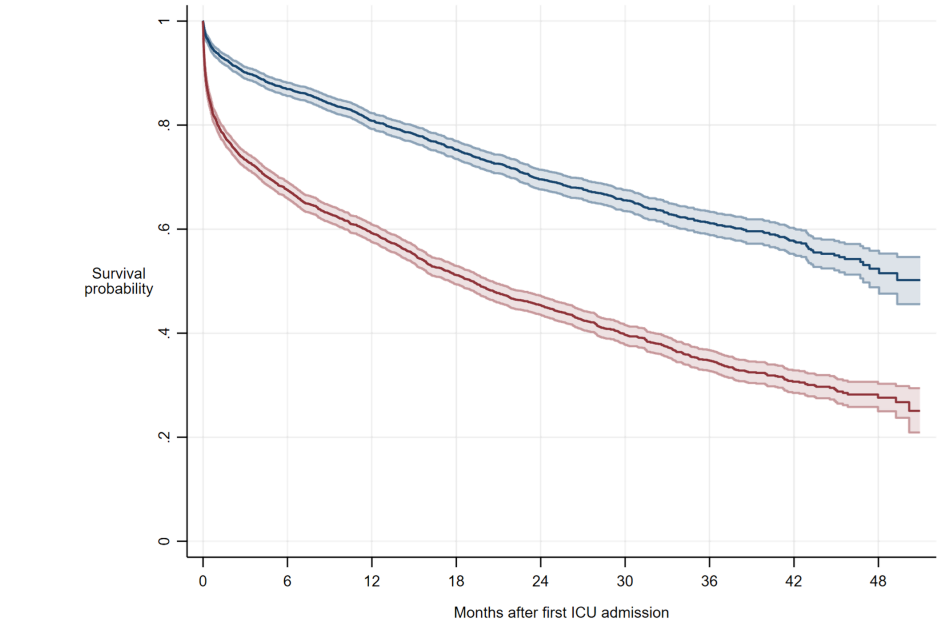
Readmission to an ICU at the same or any other hospital due to an exacerbation of COPD occurred in 17.0% of the 6332 patients who survived to be discharged alive after their initial ICU admission. There was no difference between patients with or without frailty. After accounting for confounders and for death as a competing event, frailty was not associated with an increase in the risk of readmission (subhazard ratio 1.14 [95%CI 0.99–1.3], p=0.06) (Appendix Table 5 in the online supplement).

Additional Outcomes

In-ICU and in-hospital mortality were higher among patients

Figure 2. Kaplan Meier Survival Plot of Patients With and Without Frailty Among Patients Who Did Not Receive Invasive Ventilation[a] and Patients Who Did[b]

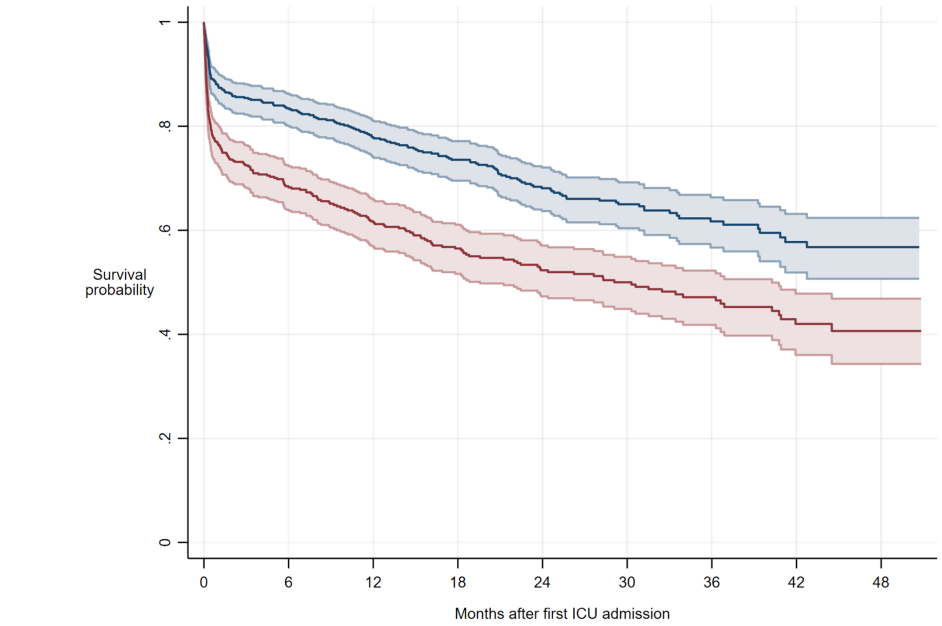
Panel A: Kaplan-Meier survival estimates
Patients who did not receive invasive ventilation



Number at risk

Frailty no (blue)	2704	2230	1823	1525	1225	896	539	322	61
Frailty yes (red)	3400	2182	1678	1239	957	647	377	210	45

Panel B: Kaplan-Meier survival estimates
Patients who received invasive ventilation



Number at risk

Frailty no (blue)	563	456	368	308	243	180	104	63	9
Frailty yes (red)	459	299	232	192	148	116	77	46	11

[a]Panel A
[b]Panel B

ICU=intensive care unit

with frailty (in-ICU: 2.7% versus 8.6%, $p<0.001$; in-hospital: 5.4% versus 16.0%, $p<0.001$). The in-hospital mortality for all patients within the ANZICS database, considering all ICU admissions for all conditions, was 6.9% during the study period. Patients with frailty had similar lengths of stay in the ICU, but longer lengths of stay in the hospital. Although discharge to home was the most common destination for survivors in both groups, discharge to a chronic care facility or nursing home was more common in patients with frailty (51/3172 [1.7%] versus 182/3524 [5.6%]; $p<0.001$) (Table 2). All-cause readmission to the ICU during the same hospitalization was higher among patients with frailty (2.6% versus 3.4%, $p=0.05$) although only just meeting the threshold for statistical significance for the study (Table 2).

Discussion

Executive Summary

This study of over 7000 patients across Australia and New Zealand demonstrated an association between frailty and long-term mortality after ICU admission for an exacerbation of COPD. More than half of the patients admitted to the ICU were frail. The median survival duration was shorter for patients with frailty, with less than a quarter of this group alive at 4 years. After adjusting for confounders including age, sex, and severity of illness, the presence of frailty was independently associated with a shorter time to death. The rate of readmission to the ICU due to COPD during a subsequent hospitalization was similar among patients with or without frailty.

Frailty and Long-term Mortality

Frailty is independently associated with increased long-term mortality in both the community setting,[4,21] and the critical care environment.[7-9] Among patients with COPD, there is also a strong correlation between frailty and long-term mortality.[23] Frailty has been shown to be an independent predictor of in-hospital mortality in the setting of an exacerbation of COPD,[32] however, few studies have examined the relationship between frailty and outcomes following an exacerbation requiring ICU admission,[32,35] and none have reported long-term mortality. Patients with both COPD and frailty who are admitted to the ICU have a high rate of in-hospital mortality when compared to all patients admitted to the ICU. In our study, twice as many patients with frailty had died 1 year after ICU discharge compared to those without, and a third of our total population was deceased. This is in keeping with contemporary local and international outcomes.[36-39] By 4 years, more than half of those without frailty and three-quarters of those with frailty had died. Given the large proportion of patients represented in this study who had frailty, this provides vital prognostic information for clinicians working both in the community and inpatient setting and allows for better informed, shared decision-making with patients and their families.

The link between frailty and COPD is well-established and is likely driven by overlapping pathophysiological mechanisms. COPD is associated with chronic dyspnea and fatigue, metabolic disruption, low-grade systemic inflammation, malnutrition, sarcopenia, and skeletal muscle dysfunction,[17,18,40,41] each of which can coexist with or contribute to the development of frailty. In our population, frailty was more common among patients with COPD admitted to the ICU than previously reported.[32] This may be reflective of a broader trend of increasing age and complexity of patients admitted to the ICU,[6,14] and highlights the need for a deeper understanding of the impact a critical illness may have on this patient cohort. Despite the high prevalence of frailty in our population, the in-hospital mortality rate was toward the lower range of that previously reported.[32,35,36,42-45]

Management of an exacerbation of COPD in the ICU setting may consist of potentially burdensome therapies for ventilatory support, either noninvasive ventilation or invasive mechanical ventilation. Exacerbations of COPD can be complicated by further organ dysfunction requiring the need for vasoactive or inotropic support, or renal replacement therapy. These interventions are not without risk or complications, and careful consideration of the suitability of intervention must be had. While a large number of patients in our study with frailty had documented treatment limitations in place prior to their index ICU admission, there remains a significant proportion in whom this was not the case. An understanding of the likely outcomes post-admission to the ICU can help frame treatment decisions and establish appropriate goals of care. Our study provides the clinician with valuable insights into potential outcomes in this patient group, however, individual patient values must be considered when determining treatment goals. We are agnostic as to the use of frailty in determining whether a patient should be admitted to the ICU. If a patient is admitted to the ICU, the results of this study could be used to inform discussions with family and other clinicians about expected outcomes.

While it appears likely that frailty does increase the risk of all-cause hospitalization, its impact on the rate of exacerbations of COPD is less clear.[20,25,26,28,31,46,47] We demonstrated an increased risk of all-cause ICU readmission during an index hospitalization among patients with frailty. However, the risk of readmission to the ICU during a future hospitalization for an exacerbation of COPD was similar among patients with and without frailty.

Given the poor, long-term outcomes seen in patients with frailty and COPD, it becomes a pertinent goal to reduce the risk of frailty itself. Pulmonary rehabilitation is a

mainstay of COPD management,[48] and has been shown to lead to improvements in dyspnea, fatigue, walking distance, and muscle strength, with results favoring frail patients.[49] Pulmonary rehabilitation has the potential to reverse a diagnosis of frailty,[49] although referral rates are low,[50] identifying an area of potential improvement that may have significant implications in a frail population.

Strengths

Our study included patients admitted to almost 180 ICUs in 2 countries over 4 years and is, thus, representative of practices and outcomes in both countries. The linkage success to the death registers was high, suggesting an accurate assessment of long-term survival. We used an established, large, high-quality dataset that increases the precision of our estimates.

Limitations

Our study does have several limitations due to its retrospective registry-based study design. Our analysis is reliant on pre-existing datasets and medical records. Thus, it is only possible to highlight associations, and no causality inferences can be drawn. The impact of data inaccuracies and misclassification of diagnostic codes, on our findings, is unknown. ANZICS does not specify how CFS is collected other than to state that this score should reflect the patient's status over the 2 months prior to the ICU admission. However, this score has been consistently shown to be related to patient-related outcomes[10,11] which provides internal validation. The degree of mistaken linkage (i.e., to another person's death date) cannot be determined from this study and we have no outcomes regarding those who moved out of each country. The categorization of patients into 2 cohorts, frail and not frail, results in an arbitrary but well-established dichotomization of a continuum from very fit through vulnerable and mildly frail, to extremely frail. The sensitivity analysis presented in Appendix Table 2 in the online supplement (multivariable Cox-proportional hazards model with clinical frailty scale entered as a continuous variable) and Appendix Tables 6 and 7 in the online supplement (raw mortality outcomes at individual CFS levels), demonstrated a relationship between progressively increasing levels of frailty and outcomes across the spectrum of frailty. Given that we have no data on all hospital readmissions, only those readmitted to the ICU, the lack of difference in the proportion of patients readmitted on a future hospitalization could be explained by other factors such as treatment limitations put in place on admission that precluded further ICU admission.

Baseline lung function data was unavailable. Thus, the presence and severity of airflow limitation is unknown. Patients' home medications and COPD-specific therapies provided in the ICU were not available. We had no information regarding patients referred for ICU admission but deemed unsuitable, due to frailty or otherwise. Finally, our results cannot be translated to a noncritically ill population.

Conclusion

In this large, bi-national cohort study, we demonstrated an independent relationship between frailty and long-term mortality after ICU admission for an exacerbation of COPD, with a 4-year survival rate of less than 1 in 4 among patients with frailty. Patients with frailty had similar rates of readmission to the ICU with an exacerbation of COPD compared with their nonfrail counterparts. Our findings have implications for discussions regarding suitable management and interventions for this vulnerable, at-risk population.

Acknowledgements

Author Contributions: MTD, SB, AS, and DVP were involved in the study design and preparation of the manuscript. DVP and MTD performed the statistical analysis. MTD, SB, AS, and DVP were responsible for the interpretation of the data. BR and ED provided supervision and revision of the manuscript. All authors approved the final manuscript.

The authors and the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation management committee thank clinicians, data collectors, and researchers at the contributing sites (see online supplement).

Availability of data and materials: The dataset can be requested through an application to ANZICS CORE.

Declaration of Interest

The authors have no conflicts of interest to declare.

References

1. 1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-156. https://doi.org/10.1093/gerona/56.3.M146

2. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005;173(5):489-495. https://doi.org/10.1503/cmaj.050051

3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* 2013;381(9868):752-762. https://doi.org/10.1016/S0140-6736(12)62167-9

4. Peng Y, Zhong GC, Zhou X, Guan L, Zhou L. Frailty and risks of all-cause and cause-specific death in community-dwelling adults: a systematic review and meta-analysis. *BMC Geriatr.* 2022;22(1):725. https://doi.org/10.1186/s12877-022-03404-w

5. Aguayo GA, Donneau AF, Vaillant MT, et al. Agreement between 35 published frailty scores in the general population. *Am J Epidemiol.* 2017;186(4):420-434. https://doi.org/10.1093/aje/kwx061

6. Fogg C, Fraser SDS, Roderick P, et al. The dynamics of frailty development and progression in older adults in primary care in England (2006-2017): a retrospective cohort profile. *BMC Geriatr.* 2022;22(1):30. https://doi.org/10.1186/s12877-021-02684-y

7. Turcotte LA, Zalucky AA, Stall NM, et al. Baseline frailty as a predictor of survival after critical care: a retrospective cohort study of older adults receiving home care in Ontario, Canada. *Chest.* 2021;160(6):2101-2111. https://doi.org/10.1016/j.chest.2021.06.009

8. Darvall JN, Bellomo R, Paul E, et al. Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study. *Med J Aust.* 2019;211(7):318-323. https://doi.org/10.5694/mja2.50329

9. Muscedere J, Waters B, Varambally A, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43(8):1105-1122. https://doi.org/10.1007/s00134-017-4867-0

10. Subramaniam A, Ueno R, Tiruvoipati R, Srikanth V, Bailey M, Pilcher D. Comparison of the predictive ability of clinical frailty scale and hospital frailty risk score to determine long-term survival in critically ill patients: a multicentre retrospective cohort study. *Crit Care.* 2022;26(1):121. https://doi.org/10.1186/s13054-022-03987-1

11. Subramaniam A, Anstey C, Curtis JR, et al. Characteristics and outcomes of patients with frailty admitted to ICU with coronavirus disease 2019: an individual patient data meta-analysis. *Crit Care Explor.* 2022;4(1):e0616. https://doi.org/10.1097/CCE.0000000000000616

12. Biasio JCD, Mittel AM, Mueller AL, Ferrante LE, Kim DH, Shaefi S. Frailty in critical care medicine: a review. *Anesth Analg.* 2020;130(6):1462-1473. https://doi.org/10.1213/ANE.0000000000004665

13. Brown H, Donnan M, McCafferty J, Collyer T, Tiruvoipati R, Gupta S. Association between frailty and clinical outcomes in hospitalised patients requiring code blue activation. *Intern Med J.* 2022;52(9):1602-1608. https://doi.org/10.1111/imj.15352

14. Athari F, Hillman KM, Frost SA. The changing nature of the population of intensive-care patients. *J Hosp Adm.* 2018;7(2):1. https://doi.org/10.5430/jha.v7n2p1

15. Fragoso CAV, Enright PL, McAvay G, Ness PHV, Gill TM. Frailty and respiratory impairment in older persons. *Am J Med.* 2012;125(1):79-86. https://doi.org/10.1016/j.amjmed.2011.06.024

16. Guan C, Niu H. Frailty assessment in older adults with chronic obstructive respiratory diseases. *Clin Interv Aging.* 2018;13:1513-1524. https://doi.org/10.2147/CIA.S173239

17. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease. *Chron Resp Dis.* 2017;14(1):85-99. https://doi.org/10.1177/1479972316679664

18. Roberts MH, Mapel DW, Ganvir N, Dodd MA. Frailty among older individuals with and without COPD: a cohort study of prevalence and association with adverse outcomes. *Int J Chron Obstruct Pulmon Dis.* 2022;17:701-717. https://doi.org/10.2147/COPD.S348714

19. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K. The relationship between COPD and frailty: a systematic review and meta-analysis of observational studies. *Chest.* 2018;154(1):21-40. https://doi.org/10.1016/j.chest.2018.02.014

20. Hanlon P, Guo X, McGhee E, Lewsey J, McAllister D, Mair FS. Systematic review and meta-analysis of prevalence, trajectories, and clinical outcomes for frailty in COPD. *NPJ Prim Care Respir Med.* 2023;33(1):1. https://doi.org/10.1038/s41533-022-00324-5

21. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health.* 2018;3(7):e323-e332. https://doi.org/10.1016/S2468-2667(18)30091-4

22. Lahousse L, Ziere G, Verlinden VJA, et al. Risk of frailty in elderly with COPD: a population-based study. *J Gerontol A Biol Sci Med Sci.* 2016;71(5):689-695. https://doi.org/10.1093/gerona/glv154

23. Hanlon P, Lewsey J, Quint JK, et al. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. *BMJ Open Respir Res.* 2022;9(1):e001314. https://doi.org/10.1136/bmjresp-2022-001314

24. Lee SY, Nyunt MSZ, Gao Q, et al. Co-occurrence of physical frailty and COPD and association with disability and mortality: Singapore Longitudinal Ageing Study. *Chest.* 2022;161(5):1225-1238. https://doi.org/10.1016/j.chest.2021.12.633

25. Zhang D, Tang W, Dou LY, Luo J, Sun Y. Four different frailty models predict health outcomes in older patients with stable chronic obstructive pulmonary disease. *BMC Geriatr.* 2022;22(1):57. https://doi.org/10.1186/s12877-022-02750-z

26. Luo J, Zhang D, Tang W, Dou LY, Sun Y. Impact of frailty on the risk of exacerbations and all-cause mortality in elderly patients with stable chronic obstructive pulmonary disease. *Clin Interv Aging.* 2021;16:593-601. https://doi.org/10.2147/CIA.S303852

27. Osadnik C, Kavanagh A, Macdonald M, Tran A, Haines T, Bardin P. Characteristics of frail patients with acute exacerbations of COPD who experience readmissions. *Eur Respir J.* 2019;54:Suppl. 63, OA3813. https://doi.org/10.1183/13993003.congress-2019.OA3813

28. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and clinical outcomes in chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* 2019;16(2):217-224. https://doi.org/10.1513/AnnalsATS.201803-175OC

29. Galizia G, Cacciatore F, Testa G, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clin Exp Res.* 2011;23(2):118-125. https://doi.org/10.1007/BF03351076

30. Bernabeu-Mora R, García-Guillamón G, Valera-Novella E, Giménez-Giménez LM, Escolar-Reina P, Medina-Mirapeix F. Frailty is a predictive factor of readmission within 90 days of hospitalization for acute exacerbations of chronic obstructive pulmonary disease: a longitudinal study. *Ther Adv Respir Dis.* 2017;11(10):383-392. https://doi.org/10.1177/1753465817726314

31. Gale NS, Albarrati AM, Munnery MM, et al. Frailty: a global measure of the multisystem impact of COPD. *Chron Resp Dis.* 2018;15(4):347-355. https://doi.org/10.1177/1479972317752763

32. Warwick M, Fernando SM, Aaron SD, et al. Outcomes and resource utilization among patients admitted to the intensive care unit following acute exacerbation of chronic obstructive pulmonary disease. *J Intensive Care Med.* 2020;36(9):1091-1097. https://doi.org/10.1177/0885066620944865

33. Australian and New Zealand Intensive Care Society (ANZICS). ANZICS APD Dictionary version 6.1 ANZICS website. Published April 2022. Accessed August 2023. https://www.anzics.com.au/wp-content/uploads/2021/03/ANZICS-APD-Dictionary-Version-6.1.pdf

34. Paul E, Bailey M, Pilcher D. Risk prediction of hospital mortality for adult patients admitted to Australian and New Zealand intensive care units: development and validation of the Australian and New Zealand risk of death model. *J Crit Care.* 2013;28(6):935-941. https://doi.org/10.1016/j.jcrc.2013.07.058

35. Berenyi F, Steinfort DP, Abdelhamid YA, et al. Characteristics and outcomes of critically ill patients with acute exacerbation of chronic obstructive pulmonary disease in Australia and New Zealand. *Ann Am Thorac Soc.* 2020;17(6):736-745. https://doi.org/10.1513/AnnalsATS.201911-821OC

36. Sivakumar S, McNally A, Tobin J, Williamson J, Aneman A. Observational cohort study of outcomes in patients admitted to the intensive care unit for acute exacerbation of chronic obstructive pulmonary disease. *Intern Med J.* 2018;48(8):944-950. https://doi.org/10.1111/imj.13805

37. Gungor S, Kargin F, Irmak I, et al. Severity of acidosis affects long-term survival in COPD patients with hypoxemia after intensive care unit discharge. *Int J Chron Obstruct Pulmon Dis.* 2018;13:1495-1506. https://doi.org/10.2147/COPD.S159504

38. Ho TW, Tsai YJ, Ruan SY, et al. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One.* 2014;9(12):e114866. https://doi.org/10.1371/journal.pone.0114866

39. Nyström H, Ekström M, Berkius J, Ström A, Walther S, Inghammar M. Prognosis after intensive care for COPD exacerbation in relation to long-term oxygen therapy: a nationwide cohort study. *COPD.* 2023;20(1):64-70. https://doi.org/10.1080/15412555.2022.2106840

40. Singer JP, Lederer DJ, Baldwin MR. Frailty in pulmonary and critical care medicine. *Ann Am Thorac Soc.* 2016;13(8):1394-1404. https://doi.org/10.1513/AnnalsATS.201512-833FR

41. Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Resp Crit Care Med.* 2014;189(9):e15-62. https://doi.org/10.1164/rccm.201402-0373ST

42. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA.* 1995;274(23):1852-1857. https://doi.org/10.1001/jama.1995.03530230038027

43. Breen D, Churches T, Hawker F, Torzillo PJ. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. *Thorax.* 2002;57(1):29-33. https://doi.org/10.1136/thorax.57.1.29

44. Alaithan AM, Memon JI, Rehmani RS, Qureshi AA, Salam A. Chronic obstructive pulmonary disease: hospital and intensive care unit outcomes in the kingdom of Saudi Arabia. *Int J Chron Obstruct Pulmon Dis.* 2012;7:819-823. https://doi.org/10.2147/COPD.S37611

45. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J.* 2005;26(2):234-241. https://doi.org/10.1183/09031936.05.00024804

46. Yee N, Locke ER, Pike KC, et al. Frailty in chronic obstructive pulmonary disease and risk of exacerbations and hospitalizations. *Int J Chron Obstruct Pulmon Dis.* 2020;15:1967-1976. https://doi.org/10.2147/COPD.S245505

47. de Souza Dias L, Ferreira ACG, da Silva, Jr JLR, Conte MB, Rabahi MF. Prevalence of frailty and evaluation of associated variables among COPD Patients. *Int J Chron Obstruct Pulmon Dis.* 2020;15:1349-1356. https://doi.org/10.2147/COPD.S250299

48. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;(2):CD003793. https://doi.org/10.1002/14651858.CD003793.pub3

49. Maddocks M, Kon SSC, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax*. 2016;71(11):988-995. https://doi.org/10.1136/thoraxjnl-2016-208460

50. Milner SC, Boruff JT, Beaurepaire C, Ahmed S, Janaudis-Ferreira T. Rate of, and barriers and enablers to, pulmonary rehabilitation referral in COPD: a systematic scoping review. *Resp Med*. 2018;137:103-114. https://doi.org/10.1016/j.rmed.2018.02.021