

## Online Supplement

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

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Regional Hospital ICU, Launceston General Hospital ICU, Lingard Private Hospital ICU, Lismore Base Hospital ICU, Liverpool Hospital ICU, Logan Hospital ICU, Lyell McEwin Hospital ICU, Mackay Base Hospital ICU, Macquarie University Private Hospital ICU, Maitland Hospital HDU/CCU, Maitland Private Hospital, Manly Hospital & Community Health ICU, Manning Rural Referral Hospital ICU, Maroondah Hospital ICU, Mater Adults Hospital (Brisbane) ICU, Mater Health Services North Queensland ICU, Mater Private Hospital (Brisbane) ICU, Mater Private Hospital (Sydney) ICU, Melbourne Private Hospital ICU, Middlemore Hospital ICU, Mildura Base Hospital ICU, Monash Medical Centre-Clayton Campus ICU, Mount Isa Hospital ICU, National Capital Private Hospital ICU, Nelson Hospital ICU, Nepean Hospital ICU, Nepean Private Hospital ICU, Noosa Hospital ICU, North Shore Hospital ICU, North Shore Private Hospital ICU, North West Private Hospital ICU, North West Regional Hospital (Burnie) ICU, Northeast Health Wangaratta ICU, Northern Beaches Hospital, Norwest Private Hospital ICU, Orange Base Hospital ICU, Peninsula Private Hospital ICU, Pindara Private Hospital ICU, Port Macquarie Base Hospital ICU, Prince of Wales Hospital (Sydney) ICU, Princess Alexandra Hospital ICU, Queen Elizabeth II Jubilee Hospital ICU, Redcliffe Hospital ICU, Robina Hospital ICU, Rockhampton Hospital ICU, Rockingham General Hospital ICU, Rotorua Hospital ICU, Royal Adelaide Hospital ICU, Royal Brisbane and Women's Hospital ICU, Royal Darwin Hospital ICU, Royal Hobart Hospital ICU, Royal Melbourne Hospital ICU, Royal North Shore Hospital ICU, Royal Perth Hospital ICU, Royal Prince Alfred Hospital ICU, Ryde Hospital & Community Health Services ICU, Shoalhaven Hospital ICU, Sir Charles Gairdner Hospital ICU, South East Regional Hospital ICU, South West Healthcare (Warrnambool) ICU, St Andrew's Hospital Toowoomba ICU, St Andrew's Private Hospital (Ipswich) ICU, St Andrew's War Memorial Hospital ICU, St George Hospital (Sydney) ICU, St George Private Hospital (Sydney) ICU, St John Of God Health Care (Subiaco) ICU, St John Of God Hospital (Ballarat) ICU, St John Of God Hospital (Geelong) ICU, St John Of God Hospital (Murdoch) ICU, St John of God (Berwick) ICU, St John of God Hospital (Bendigo) ICU, St John of God Midland Public & Private ICU, St Vincent's Hospital (Melbourne) ICU, St Vincent's Hospital (Sydney) ICU, St Vincent's Hospital (Toowoomba) ICU, St Vincent's Private Hospital Fitzroy ICU, Sunnybank Hospital ICU, Sunshine Coast University Hospital ICU, Sunshine Coast University Private Hospital ICU, Sunshine Hospital ICU, Sutherland Hospital & Community Health Services ICU, Sydney Adventist Hospital ICU, Sydney Southwest Private Hospital ICU, Tamworth Base Hospital ICU, The Bays Hospital ICU, The Chris O'Brien Lifehouse ICU, The Northern Hospital ICU, The Prince Charles Hospital ICU, The Queen Elizabeth (Adelaide) ICU, The Townsville Hospital ICU, The Valley Private Hospital ICU, The Wesley Hospital ICU, Timaru Hospital ICU, Toowoomba Hospital ICU, Tweed Heads District Hospital ICU, University Hospital Geelong ICU, Wagga Wagga Base Hospital & District Health ICU, Waikato Hospital ICU, Warrigal Private Hospital ICU, Wellington Hospital ICU, Werribee Mercy Hospital ICU, Western District Health Service (Hamilton) ICU, Western Hospital (SA) ICU, Westmead Hospital ICU, Whangarei Area Hospital, Northland Health Ltd ICU, Wimmera Health Care Group (Horsham) ICU, Wollongong Hospital ICU, Wollongong Private Hospital ICU, Wyong Hospital ICU

**Appendix Table 1: Comparison between patients with and without known frailty data**

	Frailty status known n = 7,126	Frailty status unknown n = 1,940	P Value
<b>Demographics</b>			
Age, years, mean (SD)	69.2 (11.1)	68.9 (11.2)	0.18
Sex, male, n (%)	3,429 (48.2)	1,004 (51.8)	0.005
BMI, kg/m <sup>2</sup> , median (IQR)	27.5 (22.6-34.5)	26.8 (22.0-32.4)	0.012
Hospital Type, n (%)			<0.001
Public tertiary	1,314 (18.4)	626 (32.3)	
Public metropolitan	2,796 (39.2)	381 (19.6)	
Public rural/regional	2,415 (33.9)	748 (38.6)	
Private	601 (8.4)	185 (9.5)	
Source of admission to ICU, n (%)			<0.001
Emergency department	4,929 (69.2)	1,249 (64.4)	
General ward	1,531 (21.5)	448 (23.1)	
Other hospital	643 (9.0)	228 (11.8)	
Other*	23 (0.3)	15 (0.8)	
Time hospital prior to ICU admission, hours, n (%)	6.0 (2.8-13.1)	5.6 (2.1-12.5)	0.005
Socio-economic decile, 1 low, 10 high, median (IQR)	4.0 (2.0-7.0)	5.0 (2.0-7.0)	0.022
Treatment limitation present on admission to ICU, n (%)	2,636 (37.0)	636 (32.8)	<0.001
<b>Co-morbidities<sup>†</sup>, n (%)</b>			
Diabetes	1,616 (22.7)	254 (13.1)	<0.001
Respiratory	4,464 (62.7)	932 (48.0)	<0.001
Cardiovascular	1,046 (14.7)	149 (7.7)	<0.001
Renal	234 (3.3)	42 (2.2)	0.011
Liver	76 (1.1)	17 (0.9)	0.46
Immunosuppression	334 (4.7)	109 (5.6)	0.092
Metastatic cancer or haematological malignancy	155 (2.2)	50 (2.6)	0.29
Associated COVID-19 infection	356 (5.0)	44 (2.3)	<0.001
<b>Physiological and biochemical parameters<sup>‡</sup></b>			
Worst F <sub>I</sub> O <sub>2</sub> <sup>§</sup> , mean (SD)	0.35 (0.16)	0.37 (0.16)	<0.001
Lowest PaO <sub>2</sub> (mm Hg) <sup>§</sup> , mean (SD)	70 (37)	69 (31)	0.34
PaO <sub>2</sub> / F <sub>I</sub> O <sub>2</sub> ratio, mean (SD)	214 (83)	205 (87)	<0.001
Highest PaCO <sub>2</sub> (mm Hg) <sup>§</sup> , mean (SD)	57.3 (18.4)	57.1 (19.1)	0.67
Lowest pH <sup>§</sup> , mean (SD)	7.340 (0.094)	7.334 (0.098)	0.023
Highest white cell count, x10 <sup>9</sup> L <sup>-1</sup> , median (IQR)	11.2 (8.4-15.2)	11.4 (8.5-15.5)	0.80
Highest core temperature, °C, median (IQR)	37.0 (36.7-37.4)	37.1 (36.8-37.5)	<0.001
<b>Management, n (%)</b>			
Invasive ventilation	1,022 (14.3)	447 (23.0)	<0.001
NIV	4,545 (68.1)	936 (62.6)	<0.001
Invasive ventilation and NIV	502 (7.0)	211 (10.9)	<0.001
Inotropes	1,112 (17.3)	281 (20.5)	0.004
Renal replacement therapy	42 (0.7)	13 (1.0)	0.18
<b>Severity of illness</b>			
SOFA score, mean (SD)	3.5 (2.3)	3.6 (2.5)	0.006
APACHE II score, mean (SD)	18.8 (6.3)	18.5 (6.5)	0.032
APACHE III score, mean (SD)	53.6 (18.5)	55.1 (19.3)	0.002
ANZROD percent, mean (SD)	11.9 (12.8)	12.1 (13.0)	0.61
ANZROD percent, median (IQR)	7.3 (3.5-15.7)	7.5 (3.5-16.0)	0.62
<b>Primary outcome: Mortality, n (%)</b>			
Mortality at one year	1822/5889 (30.9)	565/1785 (31.7)	
Mortality at two years	1894/4438 (42.7)	629/1471 (42.8)	
Mortality at three years	1235/2278 (54.2)	417/867 (48.1)	
Mortality at four years	200/290 (69)	130/217 (59.9)	
<b>Secondary outcomes:</b>			
In-ICU mortality, n (%)	420 (5.9)	126 (6.5)	0.31
Hospital outcome, n (%)			0.002
Died in-hospital	794 (11.1)	234 (12.1)	
Discharged home	5,109 (71.7)	1,313 (67.7)	
Transferred to other hospital	702 (9.9)	231 (11.9)	
Rehabilitation facility	243 (3.4)	58 (3.0)	
Chronic care facility or nursing home	233 (3.3)	87 (4.5)	
Other <sup>  </sup>	45 (0.6)	17 (0.9)	

Length of ICU stay, days, median (IQR)	2.4 (1.4-4.1)	2.4 (1.3-4.1)	0.47
Length of hospital stay, days, median (IQR)	7.3 (4.6-11.9)	7.2 (4.7-11.6)	0.67
Readmitted to ICU during hospitalisation, n (%)	202 (2.8)	51 (2.6)	0.63
Readmitted to ICU during subsequent hospitalisation, n (%)	1,111 (15.6)	134 (6.9)	<0.001

*Definition of abbreviations:* CFS = clinical frailty scale; ICU = intensive care unit; BMI = body mass index; COVID-19 = coronavirus; FiO<sub>2</sub> = fraction of inspired oxygen; PaO<sub>2</sub> = arterial partial pressure of oxygen; PaCO<sub>2</sub> = arterial partial pressure of carbon dioxide; SD = standard deviation, IQR = interquartile range; °C = degrees Celsius; NIV = non-invasive ventilation; SOFA = sequential organ function assessment; APACHE = acute physiology and chronic health evaluation; ANZROD = Australian and New Zealand Risk of Death.

\* Chronic care facility, rehabilitation facility, mental health facility, other

† APACHE II and III co-morbidities (33)

‡ Recorded within the first 24 hours of ICU admission

§ Recorded from the same arterial blood gas, data available for 1,071 not frail and 1,211 frail

|| Discharge to discharge to mental health facility or other destination

**Appendix Table 2: Multivariable cox-proportional hazards model for time to death (sensitivity analysis with clinical frailty scale entered as a continuous variable)**

	Hazard Ratio (95% confidence interval)	P Value
<b>Frailty status</b>		
Clinical Frailty Scale (CFS 1-8)	1.27 (1.24 to 1.31)	<0.001
<b>Demographics</b>		
Male	1.25 (1.16 to 1.34)	<0.001
Age, years	1.016 (1.01 to 1.02)	<0.001
Treatment limitation on admission	1.75 (1.62 to 1.89)	<0.001
<b>Comorbidities* and illness severity</b>		
Respiratory	1.17 (1.08 to 1.27)	<0.001
Cardiovascular	0.99 (0.90 to 1.09)	0.81
Renal	1.21 (1.02 to 1.45)	0.03
Liver	1.31 (0.95 to 1.81)	0.10
Metastatic or haematological cancer	1.93 (1.60 to 2.34)	<0.001
Associated COVID-19	0.92 (0.76 to 1.11)	0.38
SOFA Score	1.06 (1.04 to 1.08)	<0.001
<b>Source of admission to ICU</b>		
Emergency department	Reference value	.
General ward	1.13 (1.04 to 1.22)	0.005
Other hospital	0.92 (0.80 to 1.05)	0.20
Other†	1.16 (0.70 to 1.94)	0.56
<b>Management</b>		
Invasive ventilation	1.00 (0.88 to 1.13)	1.00
Non-invasive ventilation		
No NIV	Reference value	
NIV used	1.10 (0.89 to 1.36)	0.40
NIV not stated	1.14 (0.93 to 1.39)	0.20
Tracheostomy		
No tracheostomy	Reference value	
Tracheostomy	0.61 (0.33 to 1.15)	0.13
Tracheostomy unknown	1.64 (0.84 to 3.17)	0.14
Renal replacement therapy		
No renal replacement therapy	Reference value	
Renal replacement performed	0.95 (0.60 to 1.51)	0.82
Renal replacement unknown	0.60 (0.31 to 1.14)	0.12
Inotropes/vasopressors		
No inotropes/vasopressors	Reference value	
Inotropes/vasopressors given	1.15 (1.03 to 1.29)	0.017
Inotropes/vasopressors unknown	1.24 (0.9 to 1.71)	0.19

*Definition of abbreviations:* CFS = clinical frailty scale; COVID-19 = coronavirus; SOFA = sequential organ function assessment; ICU = intensive care unit; NIV = non-invasive ventilation

\* APACHE II and III co-morbidities (33)

† Chronic care facility, rehabilitation facility, mental health facility, other

**Appendix Table 3: Invasive ventilation vs no invasive ventilation outcomes**

<b>Primary outcome: Mortality, n (%)</b>	<b>Not frail (CFS 1-4)</b>	<b>Frail (CFS 5-8)</b>	<b>P Value</b>
<b>Patients who received invasive ventilation</b>	n = 563	n = 459	<0.001
Mortality at one year	103/469 (22%)	127/358 (35.5%)	
Mortality at two years	106/346 (30.6%)	125/271 (46.1%)	
Mortality at three years	58/158 (36.7%)	77/152 (50.7%)	
Mortality at four years	8/13 (61.5%)	13/21 (61.9%)	
<b>Patients who did not receive invasive ventilation</b>	n = 2,704	n = 3,400	<0.001
Mortality at one year	432/2238 (19.3%)	1160/2824 (41.1%)	
Mortality at two years	525/1732 (30.3%)	1138/2089 (54.5%)	
Mortality at three years	351/863 (40.7%)	749/1105 (67.8%)	
Mortality at four years	59/105 (56.2%)	120/151 (79.5%)	

*Definition of abbreviations:* CFS = clinical frailty scale

**Appendix Table 4: Multivariable cox-proportional hazards model for time to death in subgroups of patients who received invasive ventilation, and no invasive ventilation**

	Invasive ventilation n = 1,022		No invasive ventilation n = 6,104	
	Hazard Ratio (95% confidence interval)	P Value	Hazard Ratio (95% confidence interval)	P Value
<b>Frailty status</b>				
Not frail (CFS 1-4)	Reference value	.	Reference value	.
Frail (CFS 5-8)	1.51 (1.22 to 1.86)	<0.001	1.70 (1.56 to 1.85)	<0.001
<b>Demographics</b>				
Male	1.23 (1.01 to 1.5)	0.039	1.23 (1.14 to 1.33)	<0.001
Age, years	1.01 (1.00 to 1.02)	0.06	1.018 (1.01 to 1.02)	<0.001
Treatment limitation on admission	2.29 (1.78 to 2.94)	<0.001	1.83 (1.69 to 1.99)	<0.001
<b>Comorbidities* and illness severity</b>				
Respiratory	1.36 (1.09 to 1.7)	0.006	1.21 (1.11 to 1.32)	<0.001
Cardiovascular	1.25 (0.92 to 1.7)	0.16	0.97 (0.87 to 1.07)	0.54
Renal	1.07 (0.53 to 2.15)	0.86	1.27 (1.06 to 1.52)	0.01
Liver	1.83 (0.85 to 3.93)	0.12	1.30 (0.91 to 1.85)	0.16
Metastatic or haematological cancer	2.64 (1.23 to 5.65)	0.013	1.92 (1.58 to 2.34)	<0.001
Associated COVID-19	0.97 (0.55 to 1.70)	0.91	0.92 (0.75 to 1.12)	0.41
SOFA score	1.03 (0.99 to 1.07)	0.19	1.07 (1.05 to 1.09)	<0.001
<b>Source of admission to ICU</b>				
Emergency department	Reference value	.	Reference value	.
General ward	0.96 (0.73 to 1.26)	0.74	1.15 (1.06 to 1.26)	0.002
Other hospital	1.04 (0.81 to 1.34)	0.74	0.87 (0.74 to 1.02)	0.08
Other†	0.85 (0.12 to 6.26)	0.87	1.33 (0.78 to 2.25)	0.29
<b>Management</b>				
Non-invasive ventilation				
No NIV	Reference value	.	Reference value	.
NIV used	1.13 (0.62 to 2.05)	0.69	1.1 (0.88 to 1.39)	0.40
NIV not stated	0.9 (0.51 to 1.61)	0.73	1.21 (0.98 to 1.50)	0.08
Tracheostomy				
No tracheostomy	Reference value	.	Reference value	.
Tracheostomy	0.57 (0.30 to 1.09)	0.09	Not applicable	
Tracheostomy unknown	1.71 (0.54 to 5.43)	0.36	1.85 (0.76 to 4.48)	0.17
Renal replacement therapy				
No renal replacement therapy	Reference value	.	Reference value	.
Renal replacement performed	1.75 (0.99 to 3.11)	0.06	0.44 (0.19 to 1.01)	0.05
Renal replacement unknown	0.53 (0.18 to 1.59)	0.26	0.54 (0.22 to 1.32)	0.18
Inotropes/vasopressors				
No inotropes/vasopressors	Reference value	.	Reference value	.
Inotropes/vasopressors given	1.47 (1.16 to 1.85)	0.001	1.03 (0.89 to 1.19)	0.70
Inotropes/vasopressors unknown	1.41 (0.76 to 2.61)	0.27	1.27 (0.84 to 1.89)	0.25

*Definition of abbreviations:* CFS = clinical frailty scale; COVID-19 = coronavirus; SOFA = sequential organ function assessment; ICU = intensive care unit; NIV = non-invasive ventilation

\* APACHE II and III co-morbidities (33)

† Chronic care facility, rehabilitation facility, mental health facility, other

**Appendix Table 5: Fine and Gray proportional sub-hazards model for time to readmission to hospital in 6,322 patients who survived their first admission to ICU, with death as competing event.**

	Sub-hazard Ratio (95% Confidence Interval)	P Value
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<b>Frailty status</b>		
Not frail (CFS 1-4)	Reference value	
Frail (CFS 5-8)	1.14 (0.99 to 1.3)	0.06
<b>Demographics</b>		
Male	0.93 (0.83 to 1.05)	0.25
Age, years	0.98 (0.97 to 0.98)	<0.001
Treatment limitation on admission	1.06 (0.92 to 1.23)	0.41
<b>Comorbidities* and illness severity</b>		
Respiratory	1.17 (1.02 to 1.33)	0.021
Cardiovascular	0.92 (0.77 to 1.11)	0.40
Renal	1.05 (0.72 to 1.52)	0.80
Liver	0.69 (0.37 to 1.31)	0.26
Metastatic or haematological cancer	0.61 (0.35 to 1.06)	0.08
Associated COVID-19	0.87 (0.63 to 1.20)	0.40
SOFA Score	0.99 (0.96 to 1.02)	0.62
<b>Source of admission to ICU</b>		
Emergency department	Reference value	
General ward	0.55 (0.46 to 0.67)	<0.001
Other hospital	0.96 (0.78 to 1.17)	0.67
Other†	0.78 (0.26 to 2.35)	0.65
<b>Management</b>		
Invasive ventilation	1.25 (1.03 to 1.53)	0.027
Non-invasive ventilation		
No NIV	Reference value	
NIV used	1.03 (0.73 to 1.45)	0.87
NIV not stated	1.37 (1.0 to 1.88)	0.05
Tracheostomy		
No tracheostomy	Reference value	
Tracheostomy	0.9 (0.4 to 1.99)	0.79
Tracheostomy unknown	0.61 (0.26 to 1.44)	0.26
Renal replacement therapy		
No renal replacement therapy	Reference value	
Renal replacement performed	0.6 (0.18 to 1.93)	0.39
Renal replacement unknown	1.53 (0.6 to 3.9)	0.37
Inotropes/vasopressors		
No inotropes/vasopressors	Reference value	
Inotropes/vasopressors given	0.74 (0.59 to 0.93)	0.009
Inotropes/vasopressors unknown	1.67 (0.99 to 2.82)	0.053

*Definition of abbreviations:* CFS = clinical frailty scale; COVID-19 = coronavirus; SOFA = sequential organ function assessment; ICU = intensive care unit; NIV = non-invasive ventilation

\* APACHE II and III co-morbidities (33)

† Transfers from another ICU and other sources of ICU admission



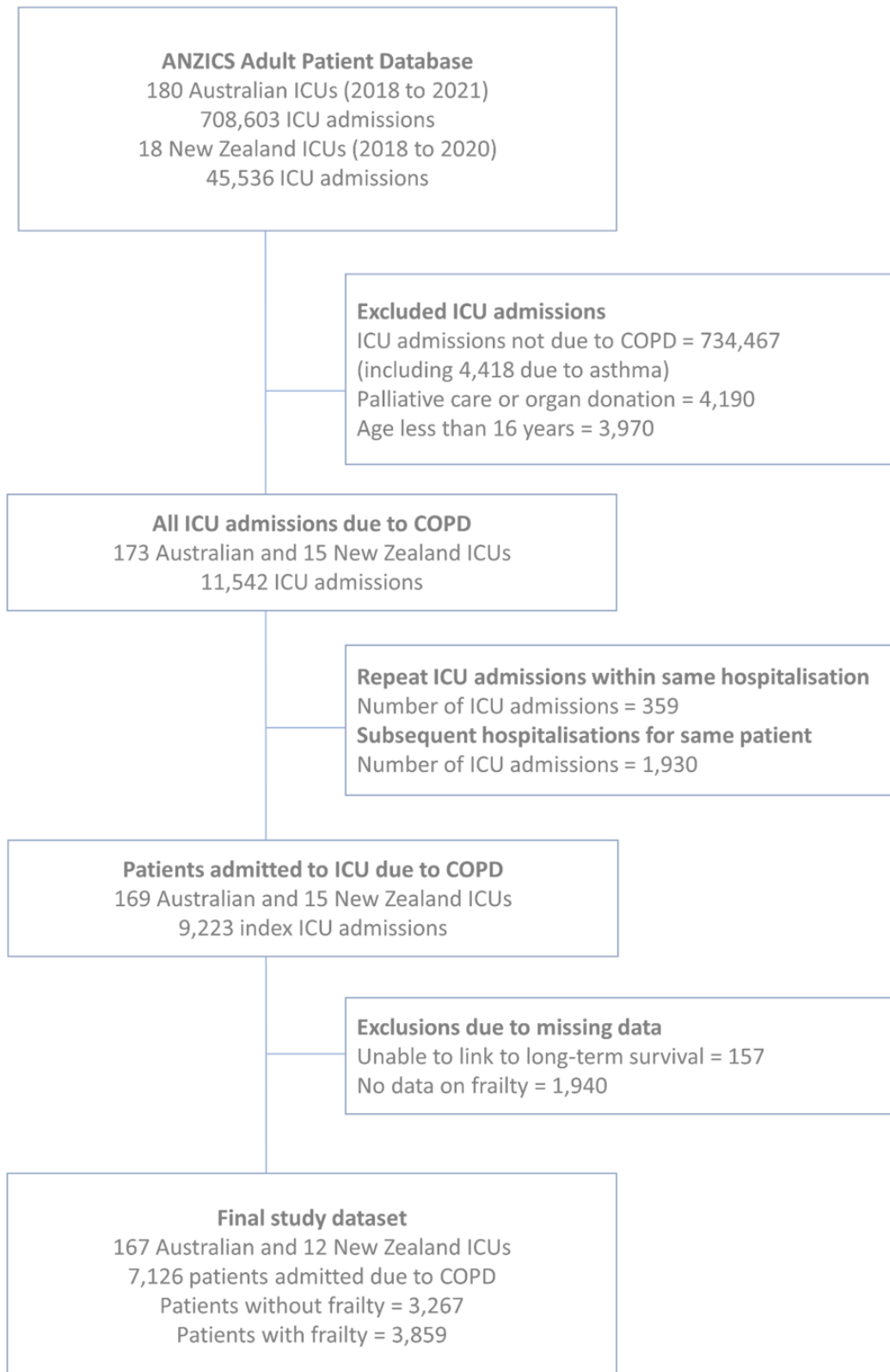
**Appendix Table 6: Sensitivity Analysis (Lifetable Estimates) of In-hospital Mortality with Individual Level of CFS**

Clinical Frailty Score	Number	Total Deaths	In-hospital Mortality (%)
1	12	1	8.3%
2	322	7	2.2%
3	1122	53	4.7%
4	1811	116	6.4%
5	1257	117	9.3%
6	1649	258	15.6%
7	807	189	23.4%
8	146	53	36.3%

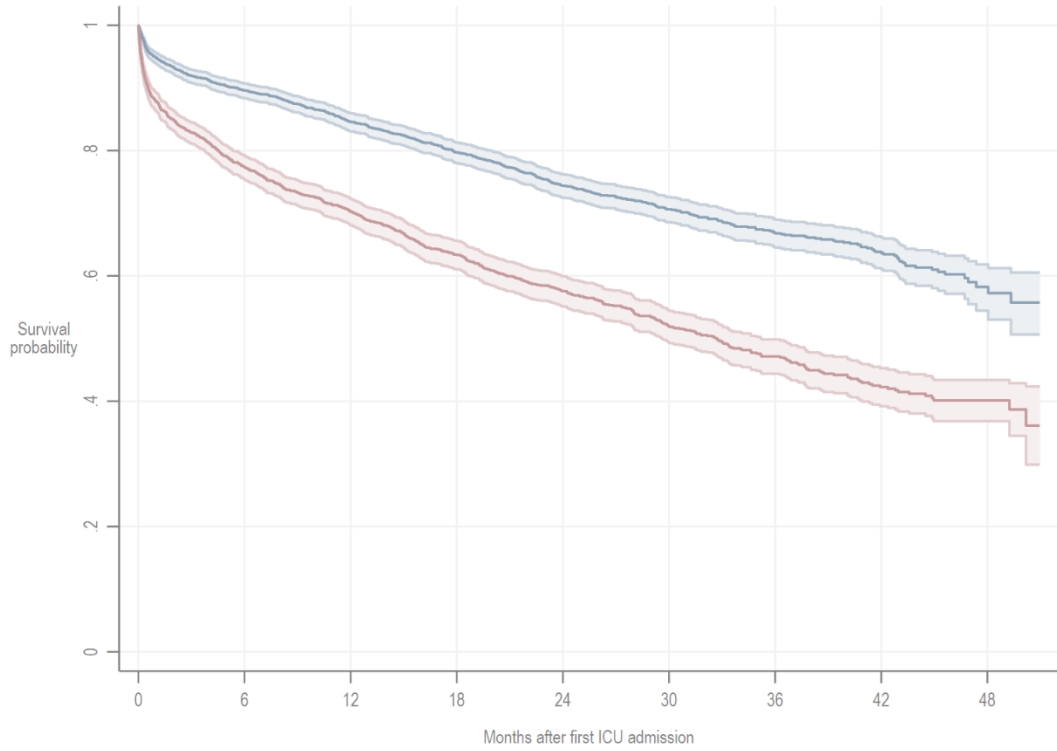
**Appendix Table 7: Sensitivity Analysis (Lifetable Estimates) of mortality up to 4 years with Individual Level of CFS**

Clinical Frailty Score	Number	In-hospital Mortality (%)	0 to 12 months	12 to 24 months	24 to 36 months	36 to 48 months
1	12	8.3%	8.3% (1.2%-46.1%)	8.3% (1.2%-46.1%)	8.3% (1.2%-46.1%)	8.3% (1.2%-46.1%)
2	322	2.2%	10.5% (7.5%-14.5%)	17% (13%-22%)	21.8% (17%-27.7%)	29.9% (22.5%-39%)
3	1122	4.7%	17.5% (15.3%-20%)	26.8% (24.1%-29.8%)	35% (31.8%-38.5%)	42.4% (38%-47.2%)
4	1811	6.4%	23.9% (22%-26%)	36.5% (34.1%-39%)	45% (42.3%-47.8%)	52.8% (49.3%-56.4%)
5	1257	9.3%	31.4% (28.8%-34.1%)	43.6% (40.7%-46.7%)	54.3% (51%-57.6%)	64.7% (60.4%-69%)
6	1649	15.6%	40.2% (37.8%-42.7%)	53.9% (51.3%-56.5%)	64.2% (61.4%-67%)	71.2% (67.9%-74.5%)
7	807	23.4%	54.8% (51.3%-58.3%)	67.9% (64.4%-71.4%)	76.6% (72.9%-80%)	79.3% (75.1%-83.2%)
8	146	36.3%	75.5% (68.3%-82.2%)	84.6% (77.8%-90.2%)	86.2% (79.2%-91.8%)	90.2% (80.5%-96.3%)

## Appendix Figure 1: Flow chart of inclusions and exclusions



## Appendix Figure 2: Survival Probability in Patients without Treatment Limitations

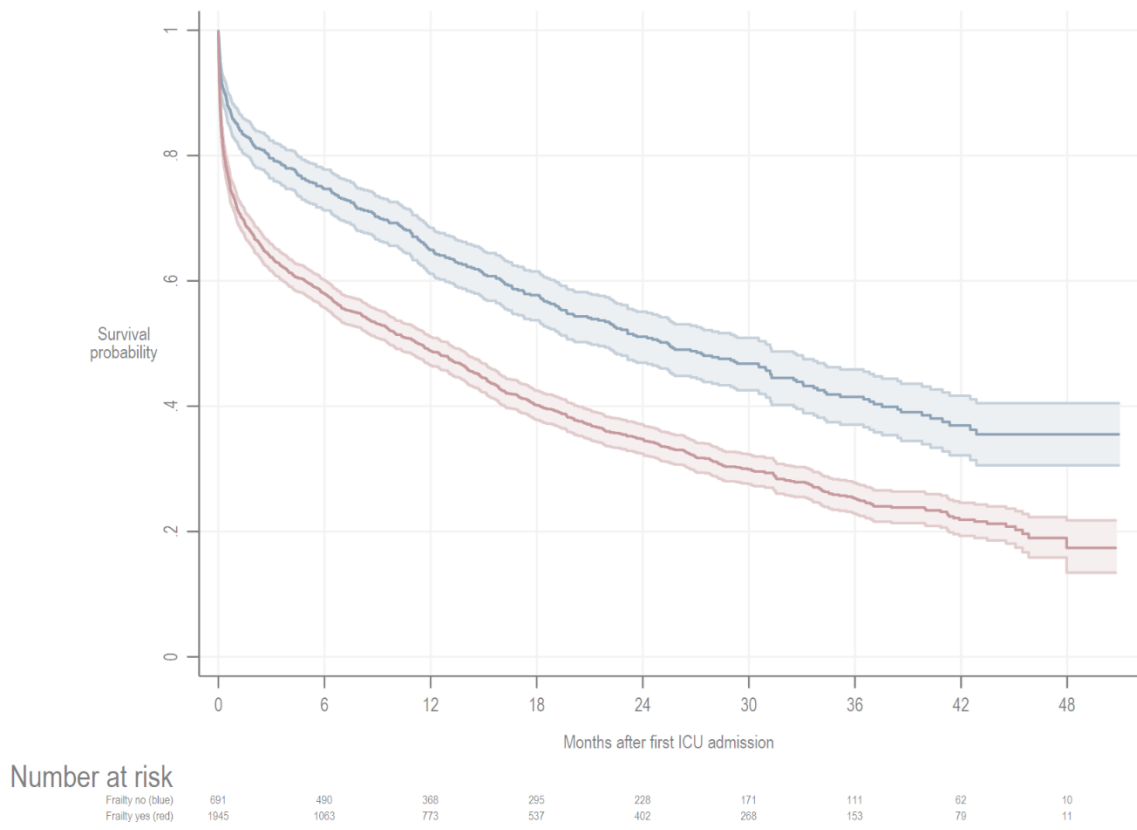


Number at risk

Frailty no (blue)	2564	2169	1818	1533	1237	902	532	323	60
Frailty yes (red)	1905	1410	1130	887	698	493	299	176	44

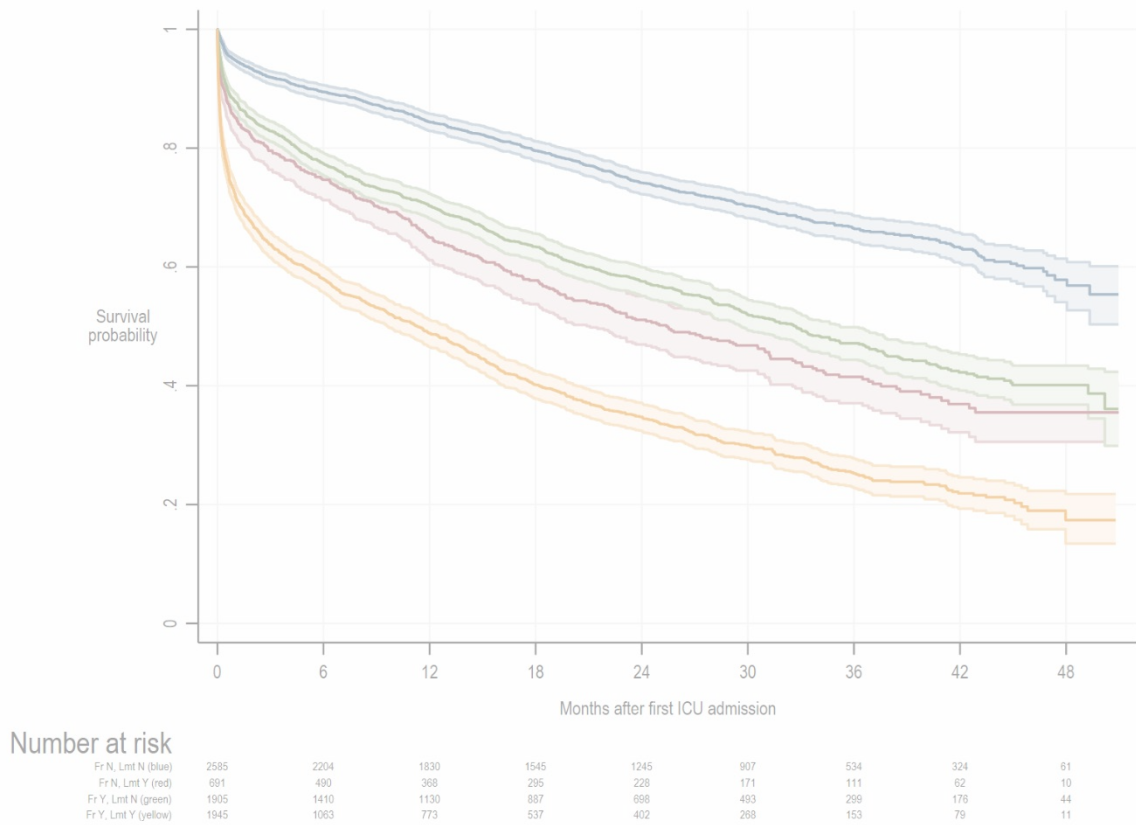
**Legend:** blue line represents patients without frailty, red line indicates patients with frailty

### Appendix Figure 3: Survival Probability in Patients with Treatment Limitations



Legend: blue line represents patients without frailty, red line indicates patients with frailty

## Appendix Figure 4: Survival Probability in Patients with and without Treatment Limitation



**Legend:** blue line represents patients without frailty and without treatment limitations, red line indicates patients without frailty but with treatment limitations, green line indicates patients with frailty but without treatment limitations, yellow line indicates patients with both frailty and treatment limitations.