

# Frailty, delirium and hospital mortality of older adults admitted to intensive care, a mediation analysis: the Delirium (Deli) in ICU study.

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## Research

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# Abstract

## Background

As the population ages clinical frailty among older adults admitted to intensive care has been proposed as an important determinant of patient outcomes. Among this group of frail patients an acute episode of delirium is also common, and both frailty and delirium increase the risk of mortality. However, the complex relationship between frailty, delirium and mortality has not been extensively explored in the intensive care setting. Therefore, the aim of this study was to explore the relationship between clinical frailty, acute delirium and hospital mortality of older adults admitted to intensive care.

## Methods

This study is part of a Delirium in Intensive Care (Deli) study that is being conducted across the South Western Sydney Local Health District, between May 2019 and April 2020. During the initial 6-month baseline period, clinical frailty status on admission to ICU, among adults aged 50-years or more, acute episodes of delirium, and the outcomes of ICU and hospital stay will be described. Mediation analysis was used to assess the relationship between frailty, delirium and risk of hospital death.

## Results

During the 6-month baseline period 997 patients, aged 50-years or more, were included in this study. The average age was 71-years (IQR, 63–79), 55% were male ( $n = 537$ ). Among these patients 39.2% (95% CI 36.1–42.3%,  $n = 396$ ) had a Clinical Frailty Score (CFS) of 5 or more, and 13.0% ( $n = 127$ ) had at least one acute episode of delirium. Frail patients were at greater risk of an episode of delirium (17% versus 10%, adjusted Rate Ratio ( $_{adj}RR$ ) = 1.61, 95% Confidence Interval (CI) 1.14–2.28,  $p = 0.007$ ), had a longer hospital stay (2.6 days, 95% CI 1–7 days,  $p = 0.009$ ), and higher risk of hospital mortality (19% versus 7%,  $_{adj}RR = 2.43$ , 95% CI 1.68–3.57,  $p < 0.001$ ), when compared to non-frail patients. Patients who were frail and experienced an acute episode of delirium in the ICU had a 35% rate of hospital mortality, versus 10% among non-frail patients who also experienced delirium in the ICU ( $p = 0.034$ , for interaction between frailty, delirium and hospital mortality). The proportion of the effect of frailty and risk of hospital mortality mediated by an acute episode of delirium in the ICU was estimated to 9.4% (95% CI 2–24%).

## Conclusion

This study has been able to show that clinical frailty on admission increases the risk of delirium by approximately 60%, and both increase the risk of hospital mortality. One in three frail patients who experienced an acute episode of delirium during their stay in the ICU did not survive to hospital discharge. These results suggest the importance of recognising clinical frailty in the ICU setting, not just to improve

the prediction of outcomes from critical illness, but to identify patients at the greatest risk of adverse events such as delirium, and institute measures to reduce risk, and, importantly to discuss these issues in an open and empathetic way with the patient and their families.

## Introduction

The population is ageing worldwide, the 841 million people older than 60-years in 2013, is estimated to more than double to 2 billion by 2050 (United Nations, 2013). This increase in life expectancy has been influential in changing the characteristics of older patients admitted to the intensive care, and has highlighted frailty as an important emerging clinical problem (Clegg et al., 2013) (Bagshaw et al., 2014, Darvall et al., 2019, Duke et al., 2014, Athari et al., 2019).

Among these older frail patients admitted to ICU, an acute episode of delirium is also common, and has been suggested as a sign of brain frailty (Foster and Kelly, 2013, Moon and Lee, 2015, Salluh et al., 2010, Inouye et al., 2014), and some groups have suggested that frailty is not exclusively a physical state, but also has a cognitive impairment component (Avila-Funes et al., 2009, Rothman et al., 2008). Importantly, both frailty and delirium increase the risk of mortality (Dani et al., 2018, Eeles et al., 2012, Quinlan et al., 2011). Even though it has been explored among older acute admissions to hospital, the complex relationship between frailty, delirium and risk of mortality has not been extensively explored in the intensive care setting.

If frailty is considered a causal factor in terms of the risk of mortality, then an acute episode of delirium in the intensive care unit (ICU) could be considered a potential mediating factor, due to its association with both frailty and mortality. This hypothesis can then be framed on the following question: *Is the relationship between frailty and mortality mediated by delirium, if so, to what extent?* Therefore, the aim of this study was to explore the relationship between clinical frailty on admission, an episode of delirium and hospital mortality of older adults admitted to intensive care.

## Methods

This study of the relationship between clinical frailty, delirium and hospital mortality is part of a larger nurse-led interventional study to reduce the burden of delirium in the adult ICU setting, which has been described previously (Lynch et al., 2020). In brief, the Delirium in ICU (Deli) Study in a randomised stepped-wedge intervention trial, including the four adult intensive care units across the South Western Sydney Local Health District. The intervention is a nurse-led non-pharmacological bundle of care, to reduce the incidence of delirium among adults admitted to the ICU. The data for this specific study of the relationship between frailty, delirium and hospital mortality, is based on the baseline period (pre-intervention phase) of the larger *Deli Study*.

## Subjects and setting

The South Western Sydney Local Health District (SWSLHD) provides public hospital services for around a million residents, with five acute care hospitals, with approximately 230,000 separations each year. There are four adult intensive care units (ICU) (one tertiary referral and three metropolitan), with between 80 to 250 admissions each per month.

## Ethical Considerations

This project was considered by the **South Western Sydney Local Health District Human Research Ethics Committee** and was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007). Due to the use of routinely collected hospital separation data, the need for individual patient consent was waived (HREC ref: HE18/169). Australian New Zealand Clinical Trials Registry (ANZCTR) (ref no. ACTRN12618000411246p).

## Inclusion and exclusion criteria

Consecutive patients admitted during the study period were enrolled in the study, excluding patients with delirium on admission, or those among which delirium assessment was impractical. This includes: (1) patients at the end-of-life, and not expected to survive 24-hours; (2) patients not expected to stay in the ICU for at least 24-hours; (3) patients with acute or chronic neurological conditions that may prevent assessment of delirium (traumatic brain injury, intra-cerebral haemorrhage, ischaemic stroke, central nervous system infection, hypoxic brain injury, hepatic encephalopathy, severe mental disability, serious receptive aphasia, severe dementia).

## Data collection

Specific data collected for the study included age, sex, admission date and discharge from ICU and hospital, ICU and hospital outcome, and clinical frailty status on admission to intensive care, along with identification of an acute episodes of delirium. Other general characteristics of the patients on admission to ICU were collected from the Hospital Health Information Exchange (HIE), and the Australian and New Zealand Adult ICU data collection. History of comorbid conditions was obtained using ICD-10-AM codes, a Charlson Index was calculated, using the method suggested by Quan *et al* (Quan et al., 2011).

## Assessment of clinical frailty

Clinical frailty status, on admission to the ICU was collected using Rockwood's Clinical Frailty Score (Rockwood et al., 2005). Frailty status was based on the patient's level of physical function in the 2-months prior to their admission to hospital for the index ICU stay. Admissions with a Clinical Frailty Score (CFS) of five or more were classified as frail (Bagshaw et al., 2014, Rockwood et al., 2005).

## Identification of delirium

The *Confusion Assessment Method* (CAM) was used to identify acute episodes of delirium among any patient who appears to be disorientated or confused, or who has any change in behaviour, or level of consciousness (Inouye et al., 1990) during an ICU stay. The CAM is based on four main area of assessment: (1) *acute onset and fluctuating course* (Is there evidence of an acute change in mental

status from baseline? If so, did the abnormal behaviour fluctuate during the day?); (2) *Inattention* (did the patient have difficulty focussing attention during the interview?); (3) *Disorganised thinking* (was the patient's thinking disorganised?); and, (4) *Altered level of consciousness* (overall, how would you rate the patient's level of consciousness?) (Inouye et al., 1990). Patients who were rousable (Richmond Agitation and Sedation Scale  $\geq$  -3) were assessed for the presence of delirium using the CAM (Inouye et al., 1990) or CAM-ICU (Ely et al., 2001). Both versions have been validated as a reliable (kappa = 0.96; 95% CI 0.91–0.99) and valid (sensitivity 0.81–0.82 and specificity 0.99) tool for diagnosing delirium in the ICU setting (Ely et al., 2001) (Shi et al., 2013).

Delirium status was assessed each shift by nursing and/or medical staff (shifts range from 8 to 12-hours in duration), or when there was an acute change in mental status. On each morning of admission during an ICU stay (up to maximum of 21-days) patients were recorded as delirium yes, if at least one episode was recognized by clinical staff during that last 24-hour period, or delirium free. Each recorded delirium event were further categorised to be of a hypoactive, hyperactive, or mixed nature (Ely et al., 2001).

## Primary outcomes of interest

The primary outcomes of interest for our analysis were: (1) clinical frailty status on admission to ICU; (2) rates of acute episodes of delirium in the ICU; (3) rates of ICU mortality; (4) length of stay in the ICU and Hospital; and (5) Hospital mortality.

## Sample size

The sample size planned for the overall baseline and intervention phase of the Deli study was based on monthly admissions between 80 and 125 (adults, aged 16-years or more) patients from the four ICUs included in the 12-month study (Lynch et al., 2020). Our, local health district ICU data estimated approximately 80% of admissions was among patients aged 50-year or more, and that after application of the inclusion and exclusion criteria, approximately 70% of admissions would be included in our study. Using the baseline (6-month) period of the Deli study, we estimated approximately 1,008 patients (aged 50-years or more) would be included in our analysis of the relationship between frailty, delirium and hospital mortality. Therefore, based on a 15% rate of hospital mortality among non-frail patients, and a 33% rate of frailty (Bagshaw et al., 2014), our estimated sample size of 1,008 would have a power of 0.79 to detect an 50% increase in risk of hospital mortality among frail patients compared to non-frail patients.

## Statistical analysis

Characteristics of patients admitted to the four adult ICUs during the baseline 6-month period of the Deli study are presented using descriptive statistics. Risk of hospital mortality based on delirium and frailty status, was estimated using all ICU admissions, taking into account multiple admissions among some patients. Crude and adjusted Rate Ratios (RR), and 95% confidence intervals (95% CI), were estimated using a generalised linear mixed-effect model (Poisson error), clustered at the patient level (Pinheiro and Bates, 2000). Due to the potential complex relationship between frailty, delirium and subsequent risk of mortality, the role of delirium as a potential mediator of the effect of frailty and risk of death was

assessed using a model based approach to assess direct and indirect effects, while adjusting for age and sex (Greenland et al., 1999, Pearl, 2010, Pearl, 2012, Pearl, 2014). By assessing the extent of direct and indirect (via delirium) effects of frailty, the estimated mediated effect of frailty and risk of hospital mortality due to delirium can be presented as a proportion, and associated 95% CI confidence intervals can be also estimated (*Imai et al., 2010*). This analysis was undertaken using the R mediation package (Tingley, 2013). All data management and analyses were performed using the R-statistical language (R Core Team, 2018).

## Results

The total numbers of admissions to the four adult ICUs during the baseline period, and the number of patients included in the study aged 50-years or more, once inclusion and exclusion criteria were applied are presented in **Fig. 1**. Based on clinical frailty status on admission to ICU, the characteristics and outcomes of the 997 patients included in this study are presented in Table 1. For example, 39.2% (95% CI 36.1–42.3%, n = 396) had a Clinical Frailty Score (CFS) of 5 or more on admission to ICU, frail patients were older (77 versus 67 years,  $p < 0.001$ ), were more likely female (50% versus 42%,  $p = 0.021$ ), and had a higher rate of multiple admissions to ICU during the study period (6% versus 4%,  $p = 0.017$ ). Delirium was more common among the frail (17% versus 10%,  $p = 0.002$ ) compared to the non-frail, length of stay in the ICU and hospital were longer, 3 versus 2 days for ICU stay ( $p < 0.001$ ) and 11 versus 9 days for hospital stay ( $p < 0.001$ ). And, frail patients had higher rates ICU and hospital mortality, 10% versus 3% for ICU death ( $p < 0.001$ ), and 19% versus 7% for hospital death ( $p < 0.001$ ). Based on age group, frailty status, rates of delirium, ICU and hospital length of stay, and mortality are presented in Table 2. Older patients had higher rates of frailty, delirium, mortality, and stayed in the ICU and hospital longer (all  $p$ -values for trend  $< 0.01$ ).

Table 1

Characteristics of admissions, aged 50 years or more, to intensive care during baseline study period, based on frailty status.

<b>Clinical Frailty Score of 5 or more on admission to intensive care</b>				
	<b>Yes</b>	<b>No</b>	combined	<i>p</i> -value
	(n = 383)	(n = 594)	(n = 977)	
Age (yrs), median (IQR)	77 (69–83)	67 (60–75)	71 (63–79)	< 0.001
Males, n (%)	193 (50)	344 (58)	537 (55)	0.021
Single admission to ICU, n (%)	361 (94)	572 (96)	933 (95)	0.017
Delirium, n (%)	66 (17)	61 (10)	127 (13)	0.002
Charlson index, median (IQR)	2 (1–3)	1 (0–2)	1 (1–3)	< 0.001
No. of comorbidities, median (IQR)	2 (1–3)	1 (1–2)	1 (1–2)	< 0.001
Dementia, n (%)	15 (4)	3 (1)	18 (2)	< 0.001
Admitted from ED, n (%)	172 (45)	218 (37)	390 (40)	0.011
Planned surgery, n (%)	22 (6)	84 (14)	106 (11)	< 0.001
APACHE III, median (IQR)	64 (51–81)	50 (38–66)	56 (42–71)	< 0.001
mechanical ventilation, n (%)	53 (14)	97 (16)	150 (15)	0.292
ICU Death, n (%)	39 (10)	17 (3)	56 (6)	< 0.001
Hospital Death, n (%)	72 (19)	41 (7)	113 (12)	< 0.001
ICU LOS (days), median (IQR)	3 (2–5)	2 (1–4)	2 (1–5)	0.001
Hospital LOS (days), median (IQR)	11 (6–24)	9 (5–16)	10 (5–19)	< 0.001

**Note:** Characteristics of ICU stay are from first admission to ICU during study period.

Table 2  
 Characteristics of admissions, to intensive care during baseline study period, based on age group.

Age group (yrs)	50–64	65–79	80+	<i>p</i> -value <sup>a</sup>
	(n = 298)	(n = 443)	(n = 236)	
Frail, n (%)	62 (21)	164 (37)	157 (67)	< 0.001
Delirium, n (%)	26 (9)	56 (13)	45 (19)	< 0.001
Males, n (%)	168 (56)	344 (58)	537 (55)	0.021
ICU LOS (days), median (IQR)	2 (1–4)	3 (2–5)	2 (1–4)	0.284
ICU Death, n (%)	9 (3)	24 (5)	43 (18)	0.001
Hospital Death, n (%)	72 (19)	24 (7)	113 (12)	< 0.001
Hospital LOS (days), median (IQR)	8 (4–15)	10 (6–20)	11 (6–24)	0.004

**note:** <sup>a</sup> *p*-value for trend

Based on frailty status, risks of delirium and hospital mortality are presented in Table 3. Frail patients were at greater risk of an episode of delirium (17% versus 10%, adjusted Rate Ratio (<sub>adj</sub>RR) = 1.61, 95% Confidence Interval (CI) 1.14–2.28, *p* = 0.007), and higher risk of hospital mortality (19% versus 7%, <sub>adj</sub>RR = 2.43, 95% CI 1.68–3.57, *p* < 0.001), when compared to non-frail patients. Patients who were frail on admission to ICU and experienced an acute episode of delirium in the ICU had a 35% rate of hospital mortality, versus 10% among non-frail admissions who also experienced delirium in the ICU (*p* = 0.034, for interaction between frailty, delirium and hospital mortality). The graphical presentation of the relationship between frailty, delirium and hospital mortality are presented in **Fig. 2**. The estimated proportion of the effect of frailty and risk of hospital mortality mediated by an acute episode of delirium in the ICU was 9.4% (95% CI 2–24%) (Table 3).

Table 3  
Clinical frailty at the time of admission to ICU, risk of delirium and hospital mortality.

	<b>Risk of delirium in ICU</b>		<b>p-value</b>
	Crude Rate Ratio (95%CI)	Adjusted Rate Ratio (95%CI)	
Frailty (17%) versus non-frail (10%)	1.57 (1.12–2.22)	1.61 (1.14–2.28)	0.007
Age (each 10-year increase)	1.02 (0.96–1.05)	1.01 (0.94 – 1.04)	0.639
Males (14.7%) versus females (10.3%)	1.41 (0.99–2.02)	1.46 (1.14–2.28)	0.035
	<b>Risk of hospital death</b>		
	Crude Rate Ratio (95%CI)	Adjusted Rate Ratio (95%CI)	
Frail (19%) versus non-frail (7%)	2.60 (1.77–3.70)	2.40 (1.66–3.52)	< 0.001
Delirium (23%) versus no-delirium (10%)	2.28 (1.47–3.40)	2.01 (1.29–3.02)	0.001
Age (each 10-year increase)	1.02 (0.98–1.06)	1.01 (0.92–1.06)	0.767
Males (11%) versus females (12%)	0.93 (0.65–1.33)	0.95 (0.66–1.37)	0.773
	<b>Mediation analysis of risk of hospital death due to delirium</b>		
	Estimate	95% CI	
Proportion mediated (non-frail)	1.6%	-2%, 9%	0.460
Proportion mediated (frail)	9.4%	2%, 24%	0.008
Total proportion mediated (average)	5.5%	1%, 15%	0.010
Interaction term (frailty x delirium)			< 0.001

## Discussion

This study among adults, aged 50-years or more, admitted to ICU has been able to show that clinical frailty on admission increases the risk of delirium, resulted in a longer ICU and hospital stay, and increases the risk of in-hospital mortality. Importantly, our study suggests that a proportion (approximately 10%) of the effect of frailty on increased risk of hospital mortality is mediated by delirium, and one in three frail patients who experienced an acute episode of delirium in the ICU, did not survive to hospital discharge. These results suggest the importance of recognising clinical frailty in the ICU setting, not just to improve the prediction of outcomes from critical illness, but to identify patients at the greatest risk of adverse events such as delirium, and institute measures to reduce risk, and hopefully improve outcomes. The presence of frailty on admission to the ICU may also be considered as a marker of someone nearing the

end of their life. This prognostic information together with inherent uncertainty should be shared with the patient and their families in an honest and empathetic way.

The prevalence of clinical frailty among adults admitted to ICU has been previously described (Bagshaw et al., 2014, Darvall et al., 2019, Flaatten et al., 2017). And, along with the results of our study show longer lengths of stay and increased risk of mortality. The relationship between frailty and delirium has been previously explored in acute hospital admissions among the elderly (Dani et al., 2018, Eeles et al., 2012, Quinlan et al., 2011). Being frail and experiencing an acute episode of delirium during an index hospital admission was shown to be a strong risk factors mortality (Dani et al., 2018, Eeles et al., 2012). However, our study may be one of the first to specifically explore the relationship between frailty, delirium and risk of death among adults admitted to intensive care, and approaching this complex relationship from a causal-mediated framework (Pearl, 2014).

The prevalence of frailty among adults aged 50-years or more, admitted to intensive care has been reported to be 32.8% (95% CI 28.3–37.5%), in Alberta, Canada (Bagshaw et al., 2014), from six hospitals, and is similar to our rate of 39.2% (95% CI 36.1–42.3%). Frailty among the very elderly (aged 80 + years) admitted to the ICU has also been extensively explored, in terms of ICU and hospital outcomes (Darvall et al., 2019, Flaatten et al., 2017) (Guidet et al., 2020), and the increased prevalence in this very elderly group, has highlighted frailty as an important predictor of short-term mortality. Importantly, this study has explored the potential mediating effect of delirium in the relationship between frailty and increased risk of hospital mortality. In the extreme case of delirium mediating all the increased risk of hospital death due to frailty, adjusting for delirium would remove any effect of frailty. However, in our study having observed an interaction of frailty and delirium, in terms of the risk of hospital death, we have estimated that approximately 10% of the proportion of the relationship between frailty and risk of hospital death is mediated by delirium.

The results of our study need to be considered in the context of some potential weaknesses and strengths. Firstly, the classification of frailty in the clinical setting, especially among critically ill patients, is difficult – however, the work by Kenneth Rockwood, in developing the Clinical Frailty Score (CFS) has made this task easier. For instance, the CFS used in this study, has demonstrated a similar concordance to the more detailed cumulative deficit method in predicting 28-day mortality, among study participants in the Canadian Health and Ageing Cohort (Rockwood et al., 2005). And given, the impracticality of using a Comprehensive Geriatric Assessment in the ICU setting to identify frailty, the risk of our study participants being misclassified, is a potential weakness.

Another obvious problem is the identification of delirium in the ICU setting is often subject to some error. However, the majority of this error is related to false negatives (sensitivity of 0.81) when the CAM and ICU-CAM had been compared to a more exhaustive assessment of delirium using the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (Shi et al., 2013). Importantly, false positives rates have been estimated to be low (1%) when also compared to DSM IV (Shi et al., 2013). The consequences of this would be that delirium rates may be under estimated, and using the method suggested by Kelsey

(Kelsey et al., 1986) (using the above estimates of sensitivity and specificity of 0.81 and 0.99, respectively), the overall observed rate of 12.5% would increase to approximately 14.6%. A strength of this study is that it has been conducted across a number of adult ICUs, and that both frailty and delirium status were purposely collected as part of our larger study.

The implications of our finding are two-fold: (1) Frailty in the ICU setting is common, and needs to be routinely identified as part of the characteristics of patients admitted to the ICU; and, (2) frail patients in the ICU are at greater risk of adverse events, such as delirium, and have worse hospital and long term outcomes. Further work in this area, needs to identify modifiable risk factors to reduce the risk of adverse events, such as delirium, among this vulnerable group of patients cared for in the ICU, and explore more extensive outcomes of those who are frail and survive an ICU and hospital stay - for instance: functional outcomes (both at discharge and at 6- and 12-months follow-up); quality of life; and, longer-term mortality in the months following discharge from hospital.

## Conclusion

This study among adults, aged 50-years or more, admitted to ICU has been able to show that clinical frailty on admission increases the risk of delirium by 60%. Approximately 10% of the effect of frailty on the increased risk of hospital mortality is mediated by delirium, and one in three frail patients who experience an acute episode of delirium during their stay in the ICU did not survive to hospital discharge. These results suggest the importance of recognising clinical frailty in the ICU setting, not just to improve the prediction of outcomes from critical illness, but to identify patients at the greatest risk of adverse events such as delirium, and institute measures to reduce risk, improve health outcomes where possible and share prognostic information in a genuine way with the patient and their carer.

## Declarations

**Ethics approval and consent to participate:** This project was considered by the **South Western Sydney Local Health District Human Research Ethics Committee** and was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007). Due to the use of routinely collected hospital separation data, the need for individual patient consent was waived (HREC ref: HE18/169). Australian New Zealand Clinical Trials Registry (ANZCTR) (ref no. ACTRN12618000411246p).

**Consent for publication:** Consent for publication of the results of this study are implied from HREC permission to commence.

**Availability of data and material:** Reasonable request for access to data and material can be organised through the last author.

**Competing interests:** The Authors declare they have no competing or financial interests.

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**Authors' contributions:** All authors contributed to the conceptualisation, planning and conduct of the study. YH and SH were project officers for the study. SF and DN undertook the analysis and presentation of the results. DS, SF AA, DN and KM drafted the initial manuscript, and all authors contributed to the interpretation of results and editing of subsequent versions of the manuscript. All authors agree on the final version of the manuscript submitted for peer review.

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## References

- ATHARI, F., HILLMAN, K. M. & FROST, S. A. 2019. The concept of frailty in intensive care. *Aust Crit Care*, 32, 175-178.
- AVILA-FUNES, J. A., AMIEVA, H., BARBERGER-GATEAU, P., LE GOFF, M., RAOUX, N., RITCHIE, K., CARRIERE, I., TAVERNIER, B., TZOURIO, C., GUTIERREZ-ROBLEDO, L. M. & DARTIGUES, J. F. 2009. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *J Am Geriatr Soc*, 57, 453-61.
- BAGSHAW, S. M., STELFOX, H. T., MCDERMID, R. C., ROLFSON, D. B., TSUYUKI, R. T., BAIG, N., ARTIUCH, B., IBRAHIM, Q., STOLLERY, D. E., ROKOSH, E. & MAJUMDAR, S. R. 2014. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ*, 186, E95-102.
- CLEGG, A., YOUNG, J., ILIFFE, S., RIKKERT, M. O. & ROCKWOOD, K. 2013. Frailty in elderly people. *Lancet*, 381 North American Edition, 752-762 11p.
- DANI, M., OWEN, L. H., JACKSON, T. A., ROCKWOOD, K., SAMPSON, E. L. & DAVIS, D. 2018. Delirium, Frailty, and Mortality: Interactions in a Prospective Study of Hospitalized Older People. *J Gerontol A Biol Sci Med Sci*, 73, 415-418.
- DARVALL, J. N., BELLOMO, R., PAUL, E., SUBRAMANIAM, A., SANTAMARIA, J. D., BAGSHAW, S. M., RAI, S., HUBBARD, R. E. & PILCHER, D. 2019. Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study. *Med J Aust*, 211, 318-323.
- DUKE, G. J., BARKER, A., KNOTT, C. I. & SANTAMARIA, J. D. 2014. Outcomes of older people receiving intensive care in Victoria. *Med J Aust*, 200, 323-6.
- EELES, E. M., WHITE, S. V., O'MAHONY, S. M., BAYER, A. J. & HUBBARD, R. E. 2012. The impact of frailty and delirium on mortality in older inpatients. *Age Ageing*, 41, 412-6.

ELY, E. W., INOUE, S. K., BERNARD, G. R., GORDON, S., FRANCIS, J., MAY, L., TRUMAN, B., SPEROFF, T., GAUTAM, S., MARGOLIN, R., HART, R. P., DITTUS, R., ELY, E. W., INOUE, S. K., BERNARD, G. R., GORDON, S., FRANCIS, J., MAY, L., TRUMAN, B. & SPEROFF, T. 2001. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA: Journal of the American Medical Association*, 286, 2703-2746.

FLAATTEN, H., DE LANGE, D. W., MORANDI, A., ANDERSEN, F. H., ARTIGAS, A., BERTOLINI, G., BOUMENDIL, A., CECCONI, M., CHRISTENSEN, S., FARALDI, L., FJOLNER, J., JUNG, C., MARSH, B., MORENO, R., OEYEN, S., OHMAN, C. A., PINTO, B. B., SOLIMAN, I. W., SZCZEKLIK, W., VALENTIN, A., WATSON, X., ZAFERIDIS, T., GUIDET, B. & GROUP, V. I. P. S. 2017. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients ( $\geq 80$  years). *Intensive Care Med*, 43, 1820-1828.

FOSTER, J. & KELLY, M. 2013. A pilot study to test the feasibility and effectiveness of a nonpharmacologic intervention for prevention of delirium in medical intensive care unit. *Clinical Nurse Specialist: The Journal for Advanced Nursing Practice*, 27, 231-8.

GREENLAND, S., PEARL, J. & ROBINS, J. M. 1999. Causal diagrams for epidemiologic research. *Epidemiology*, 10, 37-48.

GUIDET, B., DE LANGE, D. W., BOUMENDIL, A., LEAVER, S., WATSON, X., BOULANGER, C., SZCZEKLIK, W., ARTIGAS, A., MORANDI, A., ANDERSEN, F., ZAFERIDIS, T., JUNG, C., MORENO, R., WALTHER, S., OEYEN, S., SCHEFOLD, J. C., CECCONI, M., MARSH, B., JOANNIDIS, M., NALAPKO, Y., ELHADI, M., FJOLNER, J., FLAATTEN, H. & GROUP, V. I. P. S. 2020. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med*, 46, 57-69.

IMAI, K., KEELE, L. & TINGLEY, D. 2010. A general approach to causal mediation analysis. *Psychol Methods*, 15, 309-34.

INOUE, S. K., VAN DYCK, C. H., ALESSI, C. A., BALKIN, S., SIEGAL, A. P. & HORWITZ, R. I. 1990. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*, 113, 941-8.

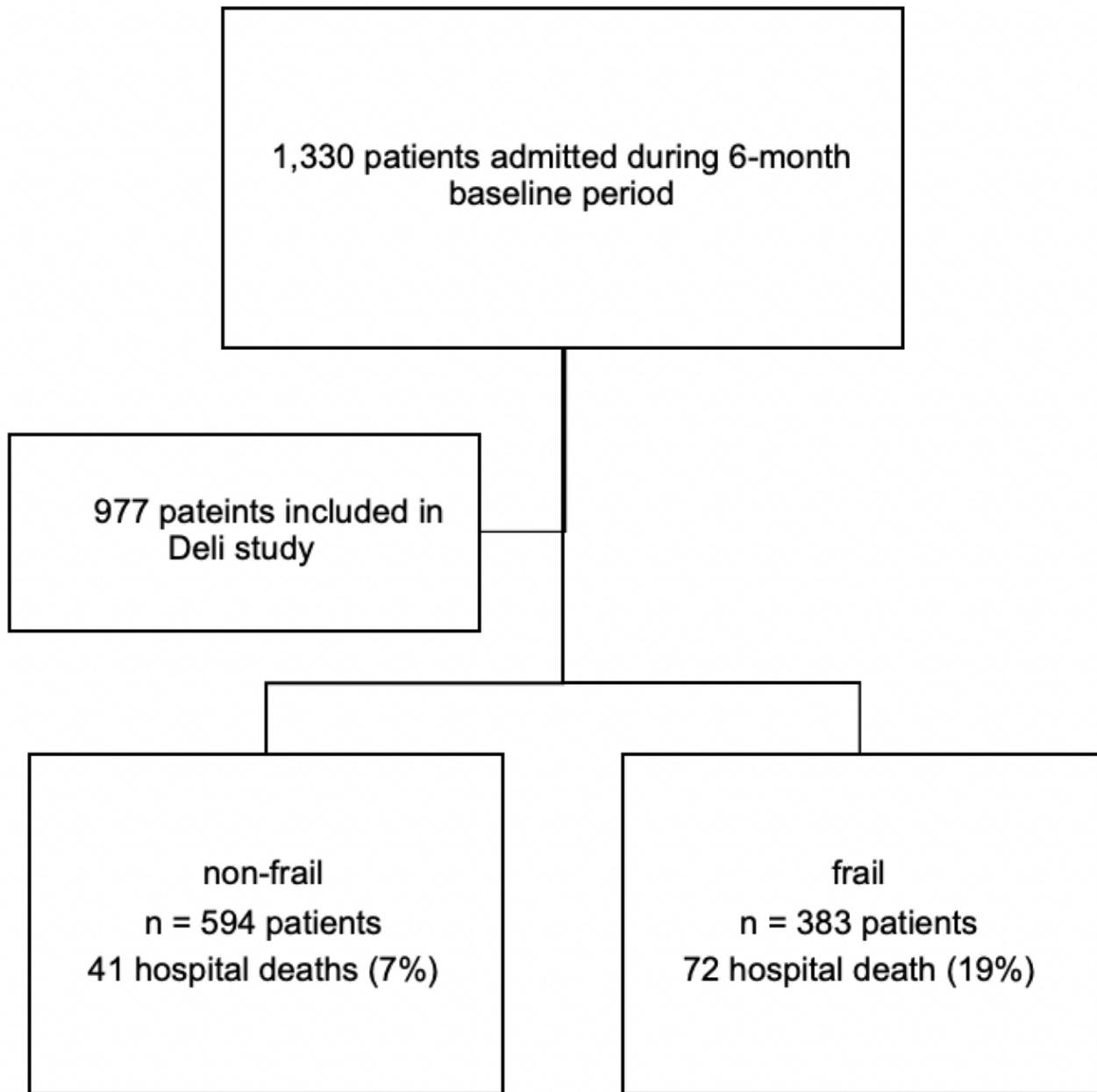
INOUE, S. K., WESTENDORP, R. G. & SACZYNSKI, J. S. 2014. Delirium in elderly people. *Lancet*, 383, 911-22.

KELSEY, J. L., THOMPSON, W. D. & EVANS, A. S. 1986. *Methods in observational epidemiology*, New York, Oxford University Press.

LYNCH, J., ROLLS, K., HOU, Y. C., HEDGES, S., AL SAYFE, M., SHUNKER, S. A., BRENNAN, K., SANCHEZ, D., BOGDANOVSKI, T., HUNT, L., ALEXANDROU, E. & FROST, S. A. 2020. Delirium in intensive care: A stepped-wedge cluster randomised controlled trial for a nurse-led intervention to reduce the incidence and duration of delirium among adults admitted to the intensive care unit (protocol). *Aust Crit Care*.

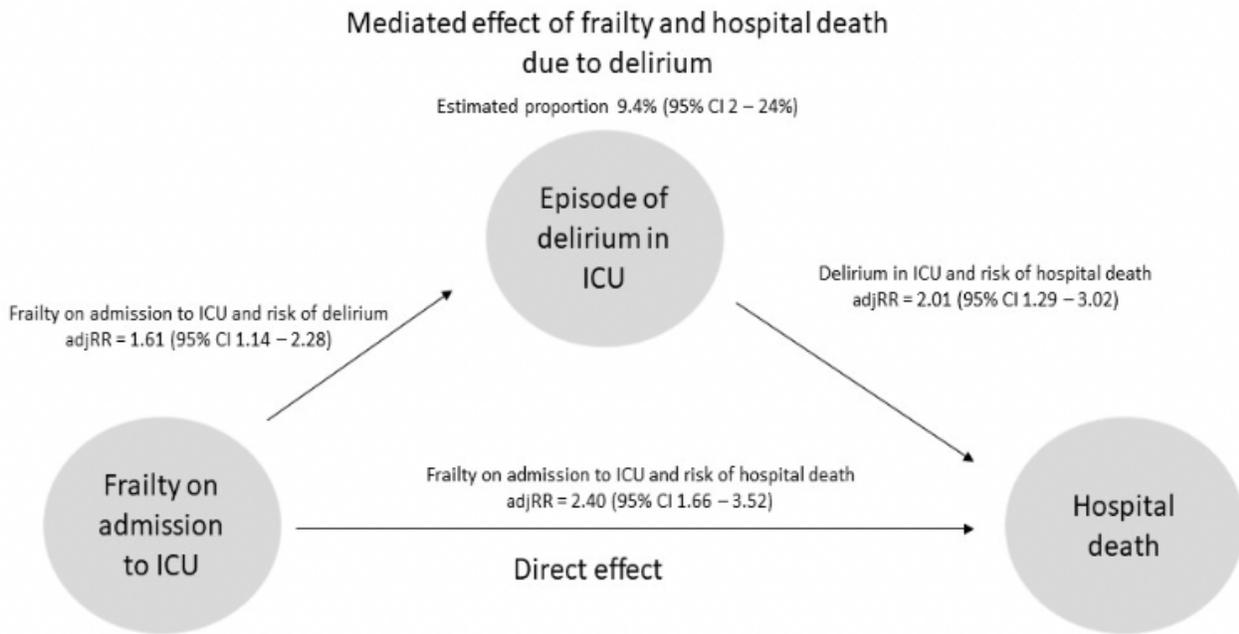
- MOON, K. J. & LEE, S. M. 2015. The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial. *Int J Nurs Stud*, 52, 1423-32.
- PEARL, J. 2010. An introduction to causal inference. *Int J Biostat*, 6, Article 7.
- PEARL, J. 2012. The causal mediation formula—a guide to the assessment of pathways and mechanisms. *Prev Sci*, 13, 426-36.
- PEARL, J. 2014. Interpretation and identification of causal mediation. *Psychol Methods*, 19, 459-81.
- PINHEIRO, J. C. & BATES, D. M. 2000. *Mixed effects models in S and S-PLUS*, New York, Springer.
- QUAN, H., LI, B., COURIS, C. M., FUSHIMI, K., GRAHAM, P., HIDER, P., JANUEL, J. M. & SUNDARARAJAN, V. 2011. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*, 173, 676-82.
- QUINLAN, N., MARCANTONIO, E. R., INOUE, S. K., GILL, T. M., KAMHOLZ, B. & RUDOLPH, J. L. 2011. Vulnerability: the crossroads of frailty and delirium. *J Am Geriatr Soc*, 59 Suppl 2, S262-8.
- ROCKWOOD, K., SONG, X., MACKNIGHT, C., BERGMAN, H., HOGAN, D. B., MCDOWELL, I. & MITNITSKI, A. 2005. A global clinical measure of fitness and frailty in elderly people. *CMAJ*, 173, 489-95.
- ROTHMAN, M. D., LEO-SUMMERS, L. & GILL, T. M. 2008. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc*, 56, 2211-16.
- SALLUH, J. I., SOARES, M., TELES, J. M., CERASO, D., RAIMONDI, N., NAVA, V. S., BLASQUEZ, P., UGARTE, S., IBANEZ-GUZMAN, C., CENTENO, J. V., LACA, M., GRECCO, G., JIMENEZ, E., ARIAS-RIVERA, S., DUENAS, C., ROCHA, M. G. & DELIRIUM EPIDEMIOLOGY IN CRITICAL CARE STUDY, G. 2010. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care*, 14, R210.
- SHI, Q., WARREN, L., SAPOSNIK, G. & MACDERMID, J. C. 2013. Confusion assessment method: a systematic review and meta-analysis of diagnostic accuracy. *Neuropsychiatr Dis Treat*, 9, 1359-70.
- TINGLEY, D. Y., T.; HIROSE, K.; KEELE, L; IMAI, K. 2013. mediation: R Package for Causal Mediation Analysis. R package version 4.4.2.
- UNITED NATIONS 2013. World population ageing 2013. *New York: Department of Economic and Social Affairs*.

## Figures



**Figure 1**

Flow diagram of participants included in stud, frailty status and hospital mortality.



**Figure 2**

Flow diagram of the relationship between frailty on admission to ICU, delirium and the risk of hospital mortality. Rate Ratios (RR) were adjusted for age, sex, delirium and frailty alternatively for the relationship between frailty and hospital death, and delirium and hospital death, respectively.