

# Ageing Population

Lessons From the “Very Old Intensive Care Patients” (VIP) Project, *H. Flaatten, B. Guidet, D. deLange*

In Search of a Crystal Ball: Predicting Long-term Outcomes in Critically Ill Older Adults, *S. Jain, L. Ferrante*

Nutritional Management of the Critically Ill Older Adult, *O. Tatucu-Babet, K. Lambell, E. Ridley*

Unmasking the Triumphs, Tragedies, and Opportunities of the COVID-19 Pandemic, *J. Patel, D. Heyland*

What Intensivists Can Learn From Geriatric Medicine, *A. Reid, P. Young*

Ageing and Critical Illness: What Does Quality Care Look Like? *C. Subbe, C. Thorpe, R. Pugh*

Lessons from COVID-19: ICU Preparedness, Ethical Issues and Digital Congresses, *JL Vincent*

Predicament Prevention for Pandemics, *A. Michalsen*  
Challenges in the Management of Severe SARS-CoV2 Infection in Elderly Patients, *O. Perez-Nieto, E. Zamarron-Lopez, M. Guerrero-Gutierrez et al.*

Vitamin D in Critical Illness – Fifty Shades of VIOLET, *K. Amrein, P. Zajic, M. Hoffman et al.*

Angiotensin II in Post Cardiopulmonary Bypass Vasoplegia - The Experience So Far, *N. Cutler, J. Signorelli, P. Wieruszewski et al.*

Promising Techniques in Sepsis After Cardiac Surgery, *G. Paternoster, Á. Nagy*

Microtools to Identify and Resuscitate Microcirculatory Dysfunction in Critically Ill Patients, *M. Hilty, C. Ince*

The Future of Critical Care: The Human Capital, *S. Ho, A. Wong, A. Butnar, M. Malbrain*




**Snigdha Jain**

Post-doctoral Fellow in Geriatric Clinical Epidemiology and Aging-Related Research  
Fellow Physician  
Section of Pulmonary, Critical Care and Sleep Medicine  
Department of Internal Medicine  
Yale University School of Medicine  
New Haven, Connecticut  
USA

[Snigdha.Jain@yale.edu](mailto:Snigdha.Jain@yale.edu)

[@snigdhajain89](https://twitter.com/snigdhajain89)

# In Search of a Crystal Ball: Predicting Long-term Outcomes in Critically Ill Older Adults


**Lauren Ferrante**

Assistant Professor of Medicine  
Section of Pulmonary, Critical Care, & Sleep Medicine  
Department of Internal Medicine  
Yale School of Medicine  
New Haven, Connecticut  
USA

[Lauren.Ferrante@yale.edu](mailto:Lauren.Ferrante@yale.edu)

[@LFerranteMD](https://twitter.com/LFerranteMD)

Older adults who survive critical illness are at risk of adverse long-term outcomes, including long-term mortality and impairment in physical function, cognitive function, and mental health. In this article, we discuss the evidence behind prediction of these outcomes in older ICU survivors, and review risk factors that should be considered in future prediction modelling studies.

Older adults who survive a critical illness are at risk of a host of adverse long-term outcomes, including increased risk of death, readmission, and long-term impairments in physical, cognitive, and mental health domains (Hill et al. 2016; Iwashyna et al. 2010; Marra et al. 2018; Pandharipande et al. 2013; Wunsch et al. 2010). As increasing numbers of older adults are admitted to and survive the intensive care unit (ICU) around the world (Iwashyna et al. 2012; Jones et al. 2020), an understanding of factors that predict these outcomes is crucial to guide decision-making and to identify patients at risk of poor long-term outcomes.

Prediction modelling studies are investigations that utilise multiple known variables to construct a model that allows estimation of the likelihood of a particular outcome (Riley et al. 2013; Steyerberg et al. 2013). While knowledge of individual prognostic factors is useful, prediction models allow for a synthesis of multiple factors from several domains to provide actionable information about outcomes. A prediction modelling

study should 1) provide a model where information of independent variables is used to generate the probability of the outcome of interest, 2) be informed by predictors (factors) that are known before the outcome occurs, and 3) be generalisable (Leisman et al. 2020). In this article, we first review existing prediction modelling studies for long-term outcomes among older ICU survivors, followed by a discussion of factors that may inform future prediction modelling studies based on the current evidence supporting their association with long-term outcomes.

## Long-Term Mortality

Older adults who survive a critical illness hospitalisation are at risk of higher long-term mortality compared to their younger counterparts and older adults who are hospitalised for non-critical acute care illnesses (Baldwin et al. 2015; Fuchs et al. 2012; Seethala et al. 2017; Wunsch et al. 2010). This risk is highest in the first year after discharge, but persists for up to three years and possibly longer (Wunsch et al. 2010). For those who become chronically

critically ill (CCI), the risk is even greater; only one-third of CCI patients over the age of 65 were alive at one year in a large American study (Kahn et al. 2010).

Several prediction models have been developed for long-term mortality among older ICU survivors, though only a handful have also undergone external validation. Baldwin and colleagues developed and externally validated a prediction model to estimate 6-month mortality specifically for older adults who survive critical illness (Baldwin et al. 2013). This model included do-not-resuscitate order, older age, comorbidity burden, admission from or discharge to a skilled-care facility, hospital length of stay, principal diagnosis of sepsis and haematologic malignancy, and male sex (area under the curve [AUC] 0.80 in the derivation cohort, 0.71 in the validation cohort). In an older study, age, diagnosis, and physiologic severity of illness were predictive of 1-year mortality in older adults, with an AUC 0.75 in external validation (Djaiani and Ridley 1997; Jandziol and Ridley 2000). A prediction model developed using a multi-centre registry

of older patients in very old adults (age  $\geq 80$  years) in Finnish ICUs identified age, male sex, medical (vs surgical) admission, severity of illness, and poor pre-morbid functional status as independent predictors of 1-year mortality (AUC 0.79 in the derivation cohort), though the model was not validated (Pietilainen et al. 2018). Other prediction models in older adults have identified age, male sex, mechanical ventilation, renal replacement therapy, frailty, diagnosis, and organ dysfunction as predictors of 30-d mortality; however, whether these risk factors can predict long-term mortality remains to be determined (de Lange et al. 2019; Minne et al. 2011).

In addition to true prediction modelling studies, a breadth of studies have attempted to elucidate individual risk factors that may inform prognostication of long-term mortality in older adults. One of the most important factors is pre-ICU functional status, which has been associated with long term mortality in several studies (Chelluri et al. 2004; Haas and Wunsch 2016; Iwashyna et al. 2010; Pietilainen et al. 2018). In a longitudinal cohort study with monthly assessments of functional status, mild-to-moderate and severe pre-ICU functional trajectories were found to be associated with double and triple the risk of death within 1 year of ICU admission, respectively, relative to those with minimal pre-ICU disability (Ferrante et al. 2015).

The evidence base behind frailty and long-term mortality is equally strong. In the same cohort, frailty was found to be independently associated with 6-month mortality with double the risk of death for each one-point increase in frailty count on a scale of 0-5 (Ferrante et al. 2018). This association between frailty and long-term mortality has been observed across multiple studies with 6-month mortality (Le Maguet et al. 2014), 1-year mortality (Bagshaw et al. 2014), and 3-year mortality (Hope et al. 2015).

Characteristics associated with the ICU stay have also been shown to influence

long-term mortality. In a study of Medicare beneficiaries, mechanical ventilation was associated with substantially higher risk of long-term (up to 3-year) mortality after ICU discharge, though the risk was concentrated in the first 6 months after discharge (Wunsch et al. 2010). ICU length of stay and severity of illness have also been associated with increased mortality at 6 months and 1 year in an older critically ill population (Chelluri et al. 1993; de Rooij et al. 2005; Le Maguet et al. 2014; Pintado et al. 2016). Notably, the addition of ICU clinician estimates of outcomes may be helpful in improving the performance of prediction models, particularly for long-term mortality. In a prospective cohort study of adults aged 53-71 years in the ICU who were requiring either mechanical ventilation or vasopressors or both, Detsky and colleagues found that when added to an existing model of age, sex, functional comorbidity index, hospitalisations in the prior year, medical (vs surgical) ICU, and severity of illness score, physician and nurse predictions improved the model performance for outcomes of mortality and toileting at 6 months (AUC 0.88 vs 0.80, and 0.85 vs 0.77 respectively), though prediction estimates for ambulation and cognition were not significantly improved (Detsky et al. 2017a).

### Long-Term Physical Impairment and Disability

Up to 70% of patients who survive an ICU stay experience new or worsening disabilities (Hopkins et al. 2017; Pfoh et al. 2016). Disability is an important clinical outcome for patients and their families as it is associated with diminished quality of life, increased risk of rehospitalisation, and death (Covinsky et al. 2011; Gill et al. 2010). One study developed and internally validated a prediction model to predict the performance status of very old adults ( $\geq 80$  years of age) at one year after an ICU stay (Heyland et al. 2016). The model included being married, having a primary

diagnosis of emergency cardiac surgery or valve replacement, and higher baseline performance status as measured by the Palliative Performance Scale (PPS) to be predictive of a higher performance status (PPS  $\geq 60$ ). Being male, a primary diagnosis of stroke, higher severity of illness, Charlson comorbidity index, and higher score on the Clinical Frailty Scale were predictive of a low performance status ( $<60$ ) at 12-months assessed using the same scale (AUC 0.81 derivation, 0.79 internal validation; good calibration). Only two other studies have described models to predict the risk of physical disability after discharge from the ICU, but these were not specific to older adults. A multi-centre prospective cohort study of middle-aged male adults admitted to medical/surgical ICUs in the United States identified age, medical (vs. surgical) patient, non-white race, higher APACHE III score, hospitalisation in prior year, and past history of cancer, liver disease, neurologic condition, or any type of transplantation in the model as predictive of returning to baseline physical function at 6 months after discharge (AUC 0.78 derivation, 0.73 internal validation; good calibration) (Detsky et al. 2017b). Another single centre study in Europe followed 148 middle-aged adults for 2 months after ICU discharge and identified low educational level, impaired core stability, fractures, and an ICU length of stay of more than two days at discharge as predictive of new-onset physical disability (AUC 0.82 derivation, 0.80 internal validation, good calibration) (Schandl et al. 2014). A recent study developing and externally validating a risk prediction model (the PREDICT model) for persistent functional decline among older ICU survivors is currently under review (Ferrante et al. 2019).

Among older adults, several pre-ICU factors have been found to be strongly associated with post-ICU functional outcomes and should be candidates for inclusion in future prediction modelling studies. Functional disability prior to ICU admission has

been consistently associated with new or worsening disability in ICU survivors of all ages (Hopkins et al. 2017). Among older adults, a quarter of those with minimal pre-ICU disability and 40% of those with mild to moderate pre-ICU disability became severely disabled in the year following ICU stay (Ferrante et al. 2015). A prospective cohort study examining functional recovery 12 months after discharge from the ICU found functional status at discharge as measured by the Barthel Index to be associated with recovery measured by the same index (Sacanella et al. 2011).

Frailty has been consistently associated with post-ICU disability across multiple studies and should be a candidate for inclusion in future prediction modelling studies (Bagshaw et al. 2014; Ferrante et al. 2018; Muscedere et al. 2017). Notably, this strong association exists regardless of which frailty assessment tool is used; most ICU studies have used either the Clinical Frailty Scale (Rockwood et al. 2005) or the Fried frailty phenotype (Fried et al. 2001). Although the Fried frailty phenotype requires patient participation, Baldwin and colleagues successfully demonstrated the feasibility and usefulness of measuring frailty in older ICU survivors prior to hospital discharge (Baldwin et al., 2014). Pre-existing frailty and cognitive impairment have also been shown to interact to amplify the magnitude of post-ICU disability over the 6 months after discharge among older adults (Ferrante et al. 2019). Other pre-admission factors that have been associated with increased disability or functional decline following critical illness include older age (Chelluri et al. 2004; Jackson et al. 2014), coexisting medical conditions (Needham et al. 2014; Pfoh et al. 2016), and sensory impairment including hearing and vision impairment (Ferrante et al. 2016).

Many hospital- and ICU-specific factors are also associated with long-term disability in older ICU survivors. Older adults who received mechanical ventilation were found to have 30% greater disability in activities

of daily living and 14% greater mobility difficulty at one year compared to those who were hospitalised but never received mechanical ventilation (Barnato et al. 2011). In a prospective cohort of patients age  $\geq 80$  in Canadian ICUs, younger age, lower severity of illness, lower Charlson comorbidity index, less frailty, and an admission diagnosis of CABG/valve replacement were associated with a greater likelihood of physical function recovery using the Short-Form 36 (SF-36) physical function score (Heyland et al. 2015). A diagnosis of severe sepsis was associated with worse functional limitations compared to non-sepsis hospitalisations in a US based cohort of older adults (Iwashyna et al. 2010). The 7-day post-ICU Functional Independence Measure (FIM), a patient-centred measure of disability that captures both motor and cognitive function, was associated with functional disability over the year after discharge in a cohort of adult ICU survivors that had been mechanically ventilated (Herridge et al. 2016).

### Long-Term Cognitive Impairment

Survivors of critical illness are at risk of developing cognitive impairment comparable to that conferred by moderate traumatic brain injury or mild Alzheimer's disease (Pandharipande et al. 2013). Older adults are no exception to this and in fact, because of an increased prevalence of prior cognitive impairment compared to the general population, may be at increased risk for cognitive decline after critical illness hospitalisation and consequences thereof (Gale et al. 2008). There are currently no prediction modelling studies to forecast cognitive impairment in older adults after critical illness (Haines et al. 2020). Most studies on cognitive impairment in critically ill patients have included diverse middle-aged populations with few studies specifically in older adults (Honarmand et al. 2020).

Several studies have evaluated determinants of cognitive decline after ICU

admission in the broader ICU population. The presence and duration of delirium have consistently been identified as risk factors for post-ICU cognitive impairment in systematic reviews (Sakusic et al. 2018; Salluh et al. 2015). Moreover, in a retrospective study of patients age 50-91 who had undergone cognitive testing over time, ICU admission was associated with greater long-term cognitive decline compared to patients without ICU admission; these findings were most pronounced for patients who had delirium while in the ICU (Schulte et al. 2019). Pre-ICU cognitive status, ICU length of stay, and hypoxia are also important factors that have been identified in a prior systematic review in all adult ICU patients (Sakusic et al. 2018) and should be considered as potential predictors of long-term cognitive impairment in future work. Additionally, sepsis should be evaluated as a potential predictor in future prediction modelling studies; in a cohort of older Medicare beneficiaries, of which slightly less than half were in the ICU, severe sepsis was significantly associated with greater odds of cognitive impairment among survivors (Iwashyna et al. 2010).

### Long-Term Mental Health Impairment

The consequences of depression and mental health disorders for older adults cannot be understated; in the general older adult population, depression and other mental health disorders have been associated with poor quality of life, worse cognition, reduced physical function, and increased mortality (Callahan et al. 2005; Han 2001; Mehta et al. 2003). Unfortunately, psychiatric morbidity is common after critical illness with increased rates of depression, anxiety, and post-traumatic stress disorders (Davydow et al. 2008), and no prediction models exist to predict onset of psychological impairment after critical illness in older ICU survivors. In middle-aged adults, age, lack of social support, traumatic

memories and depressive symptoms at ICU discharge predicted depression, anxiety, and post-traumatic stress disorder at 3 months of follow-up (AUC 0.76 derivation, 0.73 internal validation) (Milton et al. 2018). Multiple systematic reviews have synthesised evidence on psychiatric morbidity, depression, and post-traumatic stress disorder in survivors of critical illness; however, none have characterised the older adult population (Davydow et al. 2009; Davydow et al. 2008).

## Conclusions

With the ageing of our population, the number of older ICU survivors will only increase. Many of these older ICU survivors are at increased risk of poor long-term outcomes, including long-term mortality and impairments in physical function, cognitive function, and mental health. However, more than half of older ICU survivors will achieve functional recovery within 6 months of a critical illness (Ferrante et al. 2016), and few prediction models exist to distinguish between older adults those

who are at risk of persistent impairments and those who are likely to recover.

To appropriately guide decision-making for geriatric patients and their families, it is helpful for the clinician to be aware of factors associated with long-term outcomes in each of the aforementioned domains. Knowledge of these factors may inform treatment planning discussions using shared decision-making with patients and families. Prediction models that have been developed and externally validated specifically among older adults should be employed by clinicians when faced with the question of long-term mortality and physical performance. However, these studies are limited and do not exist for all domains of impairments, warranting future prediction modelling research for the breadth of adverse outcomes faced by older adults who survive a critical illness.

## Conflict of Interest

Dr. Ferrante is supported by a Paul B. Beeson Emerging Leaders in Aging Research Career Development Award from the National

Institute on Aging (K76AG057023) and the Yale Claude D. Pepper Older Americans Independence Center (P30AG021342). Dr. Jain is supported by the Yale Program in Geriatric Clinical Epidemiology and Aging-Related Research, which is funded by the National Institute on Aging (T32 AG019134). ■

## Key Points

- Older adults who survive a critical illness hospitalisation are at risk of higher long-term mortality compared to their younger counterparts and older adults who are hospitalised for non-critical acute care illnesses.
- For those who become chronically critically ill (CCI), the risk is even greater.
- Few prediction models exist to distinguish between older adults those who are at risk of persistent impairments and those who are likely to recover.
- These prediction models should be employed by clinicians when faced with the question of long-term mortality and physical performance.
- There is a need for more future prediction modelling research for the breadth of adverse outcomes faced by older adults who survive a critical illness.

## References

- Bagshaw SM, Stelfox HT, McDermid RC et al. (2014) Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *Canadian Medical Association Journal*, 186(2):E95-E102. doi:10.1503/cmaj.130639
- Baldwin MR (2015) Measuring and predicting long-term outcomes in older survivors of critical illness. *Minerva Anestesiologica*, 81(6):650-661.
- Baldwin MR, Narain WR, Wunsch H et al. (2013) A Prognostic Model for 6-Month Mortality in Elderly Survivors of Critical Illness. *Chest*, 143(4): 910-919. doi:10.1378/chest.12-1668
- Baldwin MR, Reid MC, Westlake AA et al. (2014) The feasibility of measuring frailty to predict disability and mortality in older medical intensive care unit survivors. *Journal of Critical Care*, 29(3): 401-408. doi:10.1016/j.jcrc.2013.12.019
- Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB (2011) Disability among Elderly Survivors of Mechanical Ventilation. *American Journal of Respiratory and Critical Care Medicine*, 183(8): 1037-1042. doi:10.1164/rccm.201002-0301OC
- Callahan CM, Kroenke K, Counsell SR et al. (2005) Treatment of depression improves physical functioning in older adults. *J Am Geriatr Soc*, 53(3) 367-373. doi:10.1111/j.1532-5415.2005.53151.x
- Chelluri L, Im KA, Belle SH et al. (2004) Long-term mortality and quality of life after prolonged mechanical ventilation. *Critical Care Medicine*, 32(1): 61-69. doi:10.1097/01.ccm.0000098029.65347.f9
- Chelluri L, Pinsky MR, Donahoe MP, Grenvik A (1993) Long-Term Outcome of Critically Ill Elderly Patients Requiring Intensive-Care. *JAMA*, 269(24): 3119-3123. doi:10.1001/jama.269.24.3119
- Covinsky KE, Pierluissi E, Johnston CB (2011) Hospitalization-Associated Disability "She Was Probably Able to Ambulate but I'm Not Sure." *JAMA*, 306(16): 1782-1793. doi:10.1001/jama.2011.1556
- Davydow DS, Desai SV, Needham DM, Bienvenu OJ (2008) Psychiatric morbidity in survivors of the acute respiratory distress syndrome: A systematic review. *Psychosomatic Medicine*, 70(4): 512-519. doi:10.1097/PSY.0b013e31816aa0dd
- Davydow DS, Gifford JM, Desai SV et al. (2009). Depression in general intensive care unit survivors: a systematic review. *Intensive Care Medicine*, 35(5): 796-809. doi:10.1007/s00134-009-1396-5
- Davydow DS, Gifford JM, Desai SV et al. (2008) Post-traumatic stress disorder in general intensive care unit survivors: a systematic review. *General Hospital Psychiatry*, 30(5): 421-434. doi:10.1016/j.genhosp-psych.2008.05.006
- de Lange DW, Brinkman S, Flaatten H et al. (2019) Cumulative Prognostic Score Predicting Mortality in Patients Older Than 80 Years Admitted to the ICU. *Journal of the American Geriatrics Society*, 67(6): 1263-1267. doi:10.1111/jgs.15888
- de Rooij SE, Abu-Hanna A, Levi M, de Jonge E (2005) Factors that predict outcome of intensive care treatment in very elderly patients: a review. *Critical Care*, 9(4): R307-R314. doi:10.1186/cc3536
- Detsky ME, Harhay MO, Bayard DF et al. (2017a) Discriminative Accuracy of Physician and Nurse Predictions for Survival and Functional Outcomes 6 Months After an ICU Admission. *JAMA*, 317(21): 2187-2195. doi:10.1001/jama.2017.4078
- Detsky ME, Harhay MO, Bayard DF et al. (2017b) Six-Month Morbidity and Mortality among Intensive Care Unit Patients Receiving Life-Sustaining Therapy A Prospective Cohort Study. *Annals of the American Thoracic Society*, 14(10): 1562-1570. doi:10.1513/AnnalsATS.201611-8750C
- Djaiani G, Ridley S (1997) Outcome of intensive care in the elderly. *Anaesthesia*, 52(12): 1130-1136. doi:10.1111/j.1365-2044.1997.237-az0369.x
- Ferrante LE, Murphy TE, Leo-Summers LS et al. (2019) The Combined Effects of Frailty and Cognitive Impairment on Post-ICU Disability among Older ICU Survivors. *American Journal of Respiratory and Critical Care Medicine*, 200(1): 107-110. doi:10.1164/rccm.201806-1144LE
- Ferrante LE, Murphy TE, Vander Wyk B et al. (2019) Predictors of Functional Decline Among Older Intensive Care Unit (ICU) Survivors. *American Journal of Respiratory and Critical Care Medicine*, 199 2.
- Ferrante LE, Pisani MA, Murphy TE et al. (2015) Functional Trajectories Among Older Persons Before and After Critical Illness. *JAMA internal medicine* 175(4): 523-529. doi:10.1001/jamainternmed.2014.7889

For full references, please email [editorial@icu-management.org](mailto:editorial@icu-management.org) or visit <https://iii.hm/14ph>