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Delirium Predicts Three-Month Mortality in Critically Ill Patients: A New Model

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DISSERTATION

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Dedication

I would like to dedicate this paper to my Poppop, Fred LaPilusia. He passed away in October 2017 after he underwent cardiac surgery and developed delirium in the intensive care unit. His experience of delirium in the ICU and poor outcome made this project even more meaningful to me, and emphasized the importance of the implications of this study. I am deeply saddened that he will not be there for the completion of my doctorate degree, as he was always amazed at the academic achievement of his children and grandchildren. At family gatherings, he often stated, “There are more degrees around this table than in a thermometer.” I am hopeful the results of this study will lead to the development of delirium prevention and treatment interventions so fewer grandfathers become a statistic in future papers about the relationship between delirium and mortality.

Acknowledgments

I would like to express my deepest gratitude to everyone who helped me with the completion of this study and supported me throughout my journey in graduate school.

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Abstract

Delirium is a neurocognitive disorder defined as an acute disturbance in attention, awareness, and cognition with a fluctuating course not better explained by a preexisting condition (American Psychiatric Association, 2013). It is prevalent in up to 70% of hospital patients and 82% of patients in the intensive care unit (ICU; Ely, Speroff, Gordon, & Bernard, 2004; Kavanagh & Gottfried, 2007; Mcnicoll, Pisani, Ely, Gifford, & Inouye, 2005). The impact of delirium on mortality is inconsistent in the literature. Many studies have concluded that delirium prevalence is associated with increased risk of mortality (Cole, 2004; Kavanagh & Gottfried, 2007; Moskowitz et al., 2017; Pandharipande et al., 2013; Pauley et al., 2015), while others suggest delirium does not increase risk of patients dying (Levkoff et al., 1992; Wolters et al., 2014). The objective of this retrospective observational study was to determine if delirium is an independent predictor of mortality and develop a new model predicting three-month mortality of critically ill patients. Of the 165 patients followed in this study, 42 (25.5%) were deceased at three months and 123 (74.5%) survived. The most accurate model of predicting three-month mortality had an area under the curve of 0.89 (CI: 0.81 to 0.94), which included delirium burden defined as the fraction of the number of days patients were positive for individual features of delirium during their hospital stay. The main finding of the present study is the development of a new model that accurately predicts three-month mortality of critically ill patients. This study provides further evidence that delirium is an independent predictor of mortality and new evidence that delirium fraction improves the accuracy of a predictive models of mortality. We also identified individual features of delirium that are more predictive of mortality than others. Future research is needed to develop prevention measures and treatment interventions for delirium in the ICU and on hospital floors to reduce risk of patient mortality.

Keywords: delirium, mortality, ICU, critically ill patients and delirium

Delirium Predicts Three-Month Mortality in Critically Ill Patients: A New Model

Delirium is a neurocognitive disorder defined by the *Diagnostic and Statistical Manual for Mental Disorders, 5th Edition* (DSM-5) as an acute disturbance in attention, awareness, and cognition with a fluctuating course that is not better explained by a preexisting condition (American Psychiatric Association, 2013). It is prevalent in up to 70% of hospital patients and 82% of patients in the intensive care unit (ICU; Ely et al., 2004; Kavanagh & Gottfried, 2007; Mcnicoll et al., 2005; Pisani et al., 2010). The assessment tool primarily used to determine if a critically ill patient is experiencing delirium is the Confusion Assessment Method – Intensive Care Unit (CAM- ICU; McNicoll, Pisani, Ely, Gifford, & Inouye, 2005). The CAM-ICU is well-validated with high specificity and sensitivity in both ventilated and nonventilated patients in the ICU, and accurately diagnoses delirium based on the DSM-5 criteria (American Psychiatric Association, 2013; Brooks, Spillane, Dick, & Stuart-Shor, 2014; Guenther, Popp, Koecher, & Muders, 2010). The CAM-ICU contains four features: (a) acute onset or fluctuating course, (b) inattention, (c) altered level of consciousness, and (d) disorganized thinking. Standard scoring of the CAM-ICU identifies patients as positive for delirium if both features one and two are present, and either feature three or four (Ely et al., 2001). The disorder can be described as acute or persistent, can fluctuate in severity, and must not be better explained by a preexisting condition. Other symptoms include disorientation and memory impairment (Marcantonio, 2012).

Delirium often occurs in patients after undergoing a surgical procedure and typically develops between 24 and 72 hours after surgery (Deiner & Silverstein, 2009). Patients positive for delirium experience an increased ICU and hospital-stay duration, as well as longer duration of mechanical ventilation, medical complications, and worse long-term cognitive functioning (Kavanagh & Gottfried, 2007; Maldonado, Wysong, & Starre, 2009; Pandharipande et al., 2013;

Zhang, Pan, & Ni, 2013). They also require increased care needs, which result in greater health care costs and a national burden of up to $152 billion each year (Leslie & Marcantonio, 2008; Milbrandt et al., 2004). Although delirium can develop in patients of all ages, delirium is especially prevalent and severe in patients over the age of 60.

Increased age has been determined as the most significant risk factor for delirium (Elie & Cole, 1998; Pisani, Murphy, Araujo, & Van Ness, 2010; Plaschke, Fichtenkamm, & Schramm, 2010; Silbert, Evered, Lewis, & Hons, 2007; Vaurio, Sands, & Wang, 2006). Other risk factors for the development of delirium include dementia, severity of medical illness, and administered anesthetics (Campbell, Cook, Adey, & Cuthbertson, 2008; Kavanagh & Gottfried, 2007). Although the pathophysiology of delirium remains poorly understood (Hshieh, Fong, Marcantonio, & Inouye, 2008; Hughes, Patel, & Pandharipande, 2012; Inouye, 2006), hypotheses suggest that neuroinflammation, acetylcholine deficiencies, and neurotransmitter impairments are related to patients' acute brain dysfunction (Hshieh et al., 2008; Hughes et al., 2012; Inouye, 2006; McGrane et al., 2011; van den Boogaard et al., 2010; van Gool, van de Beek, & Eikelenboom, 2010).

Previous research demonstrates that anticholinergic activity is significantly associated with delirium development (Caeiro et al., 2004; Flacker, Cummings, & Jr, 1999; Francis, Palmer, Snape, & Wilcock, 1999; Golinger, Peet, & Tune, 1987; Han et al., 2001; Mussi, Ferrari, Ascari, & Salvioli, 1999; Salahudeen, Duffull, & Nishtala, 2014; Tune & Bylsma, 1991). One hypothesis suggests the impact of anesthetics on anticholinergic activity in the brain causes neuroinflammation, which leads to neurodegeneration and the development of delirium (van Gool et al., 2010). The use of anesthetics during surgery has been determined to have a dose-response increase the risk for developing delirium (Kavanagh & Gottfried, 2007;

Maldonado et al., 2009; Pandharipande et al., 2013; Rohan et al., 2005), such that the more anesthetic administered and the deeper the sedation, the greater chance a patient will develop delirium (Farag, Chelune, Schubert, & Mascha, 2006; Sieber et al., 2010). The mechanisms of propofol decrease acetylcholine release and therefore affect the anticholinergic activity in patients' brains (Kikuchi, Wang, Sato, & Okumura, 1998; Xie et al., 2011; Xing et al., 1998). Interleukin-6 and C-reactive protein are inflammatory biomarkers that regulate anti-inflammatory responses in the brain (Wong & Arsequell, 2003; Xing et al., 1998) that are also associated with an increased risk for delirium in surgical patients (Bryson & Wyand, 2006; Burkhart et al., 2010; Cerejeira, Nogueira, Luís, Vaz-Serra, & Mukaetova-Ladinska, 2012; Girard & Jackson, 2010; Plaschke, Hill, & Engelhardt, 2007; Plaschke et al., 2010; Pol, 2012; Siepe et al., 2011). Other potential etiologies of delirium include chronic oxidative stress and excess cortisol (Ali et al., 2011; Maldonado & Kapinos, 2008). Although there are a number of common pathophysiological factors that have been shown to lead to delirium development, no one mechanisms has been proven to cause delirium (Ali et al., 2011; Hughes et al., 2012) and it is unlikely that there is a single pathway to delirium (Maldonado & Kapinos, 2008; Watt, Budding, & Koziol, 2009). Given the wide range of cognitive impairments associated with delirium, it is likely that multiple etiologies impact the functioning of a wide range of neural networks and result in neuropathology (Maldonado, 2013; Maldonado & Kapinos, 2008; Watt et al., 2009).

The impact of delirium on mortality is inconsistent in the literature. Many studies have concluded that delirium prevalence is associated with increased ICU mortality and long-term mortality (Cole, 2004; Kavanagh & Gottfried, 2007; Moskowitz et al., 2017; Pandharipande et al., 2013; Pauley et al., 2015), while others suggest delirium does not increase risk of patient

mortality (Levkoff et al., 1992; Wolters et al., 2014). Some studies have found a dose-dependent effect of delirium duration on mortality, suggesting increased delirium burden is associated with higher risk of mortality (Pisani et al., 2009; Shehabi et al., 2010). Most previous studies have defined delirium burden in one of two ways: (a) total number of days the patient is positive for delirium and (b) delirium as a binomial ("never delirium" and "ever delirium"; Milbrandt et al., 2004; Pisani et al., 2009; Shehabi et al., 2010). Total number of days with delirium has been accepted as valid measure of delirium burden, however, it is limited because it is dependent on the survival status of a subject. In addition, most delirium studies only focus on the prevalence of delirium in the ICU and not throughout the entire hospital stay (i.e., from ICU admission to hospital discharge, including floor stay when appropriate). Defining delirium burden as days with delirium and only assessing for delirium in the ICU may be limiting our understanding of the true relationship between delirium and mortality of hospital patients.

I conducted a retrospective, observational, cohort study to determine if delirium is an independent predictor of six-month mortality and develop a new way to define delirium burden that is not impacted by patient survival. The present study proposed a new measure of delirium burden, delirium fraction, and evaluated if it improves the accuracy of predictive models of patient morality. The present study also investigated the individual features of delirium and their relationship with risk of three-month mortality. An improved ability to predict patients' risk of mortality will allow for the development of strategies to reduce mortality in critically ill patients.

Material and Methods

Study Design and Participants

I conducted a retrospective observational study of adult patients admitted to a medical or surgical ICU at a medical center in Boston, MA between October 2013 and May 2016. The ICU

census was reviewed daily for admitted patients who met the following criteria: (a) they were mechanically ventilated, (b) the anticipated time to extubation was less than 48 hours, (c) the patients were receiving IV fentanyl or hydromorphone or propofol, and (d) dexmedetomidine was anticipated to be used by the attending physician for at least eight hours prior to extubation. Exclusion criteria included any baseline focal neurological disorder and allergies to latex, dexmedetomidine, propofol, fentanyl, hydromorphone, or remifentanil. Given the minimal risk and time-sensitive nature of this study, the eligible patients were enrolled with a waiver of informed consent. The protocol was approved by the Partners Human Research Committee, the Institutional Review Board of Partners HealthCare, as well as by the Institutional Review Board at Antioch University New England.

Data Collection

Baseline demographics and medical diagnoses were obtained upon admission. Daily laboratory data and information regarding exposure to anesthesia was collected throughout the duration of the patients' stay in the ICU. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) and chronic disease burden was determined by the Charlson Comorbidity Index (CCI).

Delirium Assessment

Enrolled patients' neurological status was assessed daily by study staff throughout the patients' stay in the ICU and on the hospital floor. The assessments were performed by trained study staff specifically for the purpose of this study. Evaluations were performed using the Richmond Agitation – Sedation Scale (RASS) and the Confusion Assessment Method for the ICU (CAM-ICU) at least once daily. Level of arousal was evaluated by RASS. Patients with a RASS level of -4 (no response to voice, but movement or eye opening to physical stimulation) or

-5 (no response to voice or stimulation) were defined as comatose. Patients were assessed for delirium if they responded to verbal information with eye opening (RASS scores of -3 to +4). Delirium was measured using the CAM-ICU in the ICU and on the hospital floors based on the four features: (a) acute onset or fluctuating course, (b) inattention, (c) altered level of consciousness, and (d) disorganized thinking. All ICU patients who were discharged to the hospital floor continued to be assessed for delirium and coma status until hospital discharge.

Delirium Status

Delirium status was defined two ways in this study: (a) the standard definition of delirium based on the CAM-ICU and (b) using the individual features of the CAM-ICU.

Standard CAM-ICU. Standard scoring of the CAM-ICU identifies patients as positive for delirium if both features one and two are present, plus either feature three or four (Ely et al., 2001). A positive CAM-ICU and a RASS score between -3 and +4 were required for a classification of delirium. Patients were defined as normal if they were not delirious or comatose.

CAM-ICU features. In this study, the four individual features of the CAM-ICU were assessed and used to define patients' delirium status. The features were separated into four distinct variables to further elucidate the relationship of the specific components of delirium and mortality.

Delirium Burden

Delirium burden was also defined two different ways in this study: (a) delirium days, and (b) delirium fraction.

Delirium days. The sum of the total number of days the patients were positive for delirium based on the standard CAM-ICU assessment was calculated as a measure of delirium

burden. In addition, the total number of days the patients were positive for each of the four individual features were summed to represent delirium burden.

Delirium fraction. One shortcoming of using the total number of days to quantify delirium burden is that it is impacted by survival status. Patients who die in the ICU or hospital will tend to have fewer total days of delirium, even if they might have been delirious throughout their hospital stay prior to death. To remove the impact of survival status on the definition of delirium burden, we used the fraction of days the patients met criteria for delirium as a measure of delirium burden. Delirium fraction is defined as the total number of days the patients were positive for delirium based on the CAM-ICU divided by the total number of days the patients were assessed for delirium. The formula to calculate the fraction of delirium days is:

$$\text{Delirium fraction} = \frac{\text{Number of days positive for delirium}}{\text{Number of days assessed for delirium}}$$

The fractions of days patients were positive for the individual features of delirium were also used as measures of delirium burden. Each of the four CAM-ICU features were calculated as a measure of delirium burden and represented as a distinct variable. For example, the formula to calculate the delirium fraction of the first delirium feature is:

$$\text{Delirium fraction (Feature 1)} = \frac{\text{Number of days positive for acute onset or fluctuating course}}{\text{Number of days assessed for delirium}}$$

Therefore, delirium burden was represented as the fraction of the number of days patients were positive for delirium, as well as four separate fractions based on the number of days patients met criteria for each of the individual features of delirium.

Outcomes and Covariates

Hospital patient mortality (survival or death) was measured at discharge, and patient medical records were used to determine morality at three months following discharge. Covariates

were collected at admission and during the patients' hospital stay and were selected *a priori* based on previous research studies and clinical suspicion. These included age, sex, APACHE II, CCI, total doses of benzodiazepines, opiates, propofol, and dexmedetomidine, and total length of hospital stay.

Statistical Analyses

We used logistic regression with lasso regularization to predict mortality at three months. The objective of the model is to find the optimal weight β and bias b that achieve

$$\underset{\beta,b}{\text{minimize}} \frac{1}{N}\sum_{i=1}^{N} CE(y_i, \text{sigmoid}(\beta^T x_i + b)) + \lambda\|\beta\|_1 ,$$

where N is the number of patients; $CE(y, y') = -y \log y' - (1-y)\log(1-y')$ is the cross-entropy between the actual binary delirious state y and the predicted probability of being delirious y'; $\|\beta\|_1$ is the L1-norm of the weight β; and λ is the regularization strength. The predicted probability of being delirious y' for a variable vector x is:

$$y' = \text{sigmoid}(\beta^T x + b) = P(y = \text{delirious}|x) = \frac{1}{1+\exp(-\beta^T x - b)} .$$

Due to the sparse-inducing property of lasso regulation, the selected variables are indicated by non-zero weights in β.

Nested 5-fold cross-validation was applied for model training. For the outer loop, the patients were randomly split into five folds, where one fold was used as an independent held-out testing set and the other four folds were used as the training set. An inner loop was performed on the training set to decide the optimal regularization strength λ. To do this, the training set was further randomly split into five folds. For a specific value of λ, a logistic regression model was trained on the four folds and the loss was evaluated on the rest one validation fold. The five validation losses were then averaged to obtain the validation loss for the specific λ. Bayesian optimization was applied to find the λ that minimizes the validation loss. A logistic regression

model with the optimal λ was then trained on all training sets where the five folds in the inner loop were combined. This model was applied to the rest testing fold in the outer loop to obtain the testing performance. The average performance of the five testing folds in the outer loop was used as the reported performance. Finally, the reported selected variables were obtained from the model trained on all data including the training and testing sets in the outer loop.

Receiver operator characteristic (ROC) curves were generated with predicted probabilities from the logistic regression models. The area under the ROC curve (AUC) was used as a metric to assess the performance of the models for binary classification. The 95% confidence intervals are obtained using bootstrap implemented in MatLab 2017a.

Results

Patients' Characteristics

A total of 165 mechanically ventilated ICU adult patients were included in the outcome analysis. Their characteristics are reported in Table 1. The cohort was divided into two groups according to whether they were alive at three months or deceased. Out of 165 patients, 42 (25.5%) were deceased at three months and 123 (74.5%) were alive at three months, as shown in Figure 1. Patients in the deceased group were older, had higher Charlson Comorbidity Index scores (baseline comorbidities), and were more likely to have an admission diagnosis of sepsis, myocardial ischemia, or liver failure compared to patients in the alive group. The mean length of total hospital stay was similar for both groups, but the deceased at three months group was positive for coma more days than the alive at three months group.

Prediction Models of Three-Month Mortality

The models predicting three-month mortality included either data only from the patients' stay in the ICU or their entire hospital length of stay (ICU and hospital floor). Different

definitions of delirium status (standard CAM-ICU or CAM-ICU features) and delirium burden (delirium days or delirium fraction) were included in the models to identify which is most predictive of three-month mortality. The models are summarized in Figures 5 and 6.

Standard CAM-ICU with delirium days. The AUC of the model with the total number of days delirious in the ICU based on the standard administration of the CAM-ICU was 0.63 (CI: 0.53 to 0.73). The AUC of the model based on patients' delirium status throughout their entire hospital stay (ICU and hospital floor) was 0.68 (CI: 0.57 to 0.77).

Standard CAM-ICU with delirium fraction. The AUC of the model with delirium burden defined as the fraction of days the patients were positive for delirium in the ICU was 0.78 (CI: 0.66 to 0.87). The model with data from the ICU and the hospital floor has an AUC of 0.82 (CI: 0.71 to 0.89).

CAM-ICU features with delirium days. The model predicting three-month mortality based on the number of days patients were positive for each of the CAM-ICU features in the ICU was 0.65 (CI: 0.54 to 0.74), and the AUC was 0.74 (CI: 0.64 to 0.82) for the patients' entire length of stay.

CAM-ICU features with delirium fraction. The AUC of the model with delirium burden defined as the fraction of days the patients were found positive for each of the individual CAM-ICU features in the ICU was 0.80 (CI: 0.69 to 0.87). The model based on patient delirium burden in the ICU and the hospital floor was 0.89 (CI: 0.82 to 0.94).

Model comparisons. The models with the standard methods of defining delirium status and delirium burden were compared to the models with delirium burden defined as delirium fraction and delirium status defined as the individual features of delirium. The models with delirium burden defined as the fraction of days the patients were positive for the individual

features of the CAM-ICU had significantly higher AUCs compared to models with delirium burden defined as the total number of days the patients were positive for delirium based on the standard CAM-ICU. This was true for both the models that were based on the data in just the ICU ($p = 0.0001$) and the data from the ICU and hospital floor ($p = 0.0001$).

Discussion

The main finding of the present study was the development of a new model that accurately predicts three-month mortality of critically ill patients. This study provided further evidence that delirium is an independent predictor of mortality (Ely et al., 2004; McCusker et al., 2002; Shehabi et al., 2010) and new evidence that the addition of delirium burden improves the accuracy of a predictive model of mortality. The eight models included in this study contain many overlapping covariates, but the selected variables in each of the models are different. The variability in the models suggests that different definitions of delirium burden and delirium status, and the difference in the length of time the patients were assessed impacted the selection of the variables and the accuracy of the prediction models.

Our study confirmed previous research that APACHE II, Charlson Comorbidity Index age, length of hospital stay, and coma are associated with increased risk of mortality in critically ill patients (Ely, 2004, Pisani, 2009). The inclusion of total drug doses in the models is also consistent with previous findings that sedatives are related to delirium development and patient mortality (Ely et al., 2004; Pisani et al., 2009; Rasmussen & Johnson, 2003; Reade & Finfer, 2014). Specifically, dexmedetomidine and propofol were selected in more prediction models than opiates and benzodiazepines, suggesting that lower doses of dexmedetomidine and greater doses of propofol are greater predictors of mortality. This confirms that management and choice

of anesthetics can have important effects on the outcome of patients treated in the ICU (Reade & Finfer, 2014).

The results of this study suggested that models employing data collected from patients' entire length of hospital stay (ICU and hospital floor) provide more accurate predictive models than those using data only collected in the ICU. This is consistent with the general tendency that greater amounts of data allow for better predictability and suggests that it is important to continue to monitor patients' delirium status and neurological health even after they are discharged from the ICU. Further research is needed to develop possible floor interventions that could improve patients' outcomes and decrease risk of mortality after discharge.

This study provided important evidence that delirium fraction, a novel measurement of delirium burden, is more predictive than total number of delirium days, and that certain features of delirium are more predictive of mortality than others. Previous studies have found that the total number of days with delirium is an independent predictor of mortality (Kiely et al., 2010; Pisani et al., 2009; Shehabi et al., 2010), however, as stated earlier, total number of days is affected by patients' survival status. Patients who are delirious in the hospital throughout their length of stay and then die in the ICU will have a higher delirium fraction than patients who are delirious for the same number of days, but then improve on the hospital floor. I believe delirium fraction is more representative of the severity of patients' brain dysfunction and would therefore be a better predictor of three-month mortality. In addition, the predictive models that defined delirium burden as the four distinct features of delirium selected only a subset of the delirium features. This suggests that certain symptoms of delirium may be more predictive than others, and more closely associated with brain dysfunction. Specifically, the third feature of delirium, altered level of consciousness, was the only delirium feature to be included in all the predictive

models and was one of only four variables included in the most accurate model (CAM-ICU features with delirium fraction). Altered level of consciousness alone is not sufficient to meet the criteria for delirium based on the CAM-ICU. However, according to the results, it is a consistent predictor of three-month mortality. Disorganized thinking, on the other hand, was not included in any of the models, which suggests it is not predictive of survival outcome. Identifying individual features that are more predictive of mortality could suggest specific types of brain dysfunction that could be analyzed in greater depth and targeted as a means to reduce risk of death.

Previous research suggests that the addition of risk factors to predictive mortality models based on the APACHE II score alone does not improve accuracy (Campbell et al., 2008; van den Boogaard et al., 2010). Specifically, van den Boogaard et al. (2010) added delirium to a model based on just the APACHE-II score predicting in-hospital mortality and found that there was no significant difference between the model with delirium and the model without delirium. Similarly, in the model based on data collected in the ICU with delirium burden represented as the total number of days, delirium was not included in the model. Our model based on data collected in the ICU and on the hospital floors included delirium days, but the number of days patients were delirious was negatively associated with mortality. However, in the other models that defined delirium burden as delirium fraction, delirium was selected and did improve the accuracy of the models significantly. This confirms that the addition of delirium burden represented as the total number of days divided by total number of days assessed is more predictive than standard definition of delirium burden, and that the addition of delirium burden to a model can improve the accuracy of mortality prediction. By increasing the accuracy of the ability to predict three-month morality of critically ill patients, more effective preventative interventions can be developed and implemented to improve their chance of survival.

Our study has several important limitations. The first limitation is related to the assessment of delirium using the CAM-ICU. In this study, delirium status was assessed once a day, but due to the fluctuating course of delirium, the prevalence of delirium in this study may have been underestimated. Second, in the multivariable analysis, I adjusted for a number of covariates (age, preexisting comorbidities, illness severity, etc.), but did not investigate the specific admission diagnoses and their association with delirium prevalence or mortality risk. Therefore, I do not know if delirium burden is more accurate at predicting the mortality of patients with certain diagnoses compared to others. Third, the sample size was small compared to other research studies investigating the relationship of delirium and mortality. This prevented me from being able to develop a more complicated model. Although the sample was respectively small, the patients in this study had a broad range of admission diagnoses and level of illness severity.

Another limitation of the study is the fact that many of the variables in this study were based on behavioral assessment. Previous research suggests there are other richer data sources associated with delirium that are more direct measures of neurological illness, such as electroencephalogram (EEG) and biomarkers. An increase in slow activity and decrease in occipital alpha rhythm on the EEG characterize delirium, which can be assessed continuously for extensive periods of time (Dellen, 2014; Jacobson, Leuchter, & Walter, 1993; Koponen & Partanen, 1989; Reischies et al., 2005). Delirium is also associated with an unbalanced neuroinflammatory response with higher levels of cortisol, interleukin-6, and c-reactive protein that can be assessed daily through blood draws (Cerejeira et al., 2012; Plaschke, Hill, & Engelhardt, 2007; Plaschke et al., 2010; van Gool et al., 2010). In future work, inclusion of EEG

data or inflammatory biomarkers could make it possible to further improve predictions of patient morality.

Further research is also needed to investigate whether there might be a cause-and-effect relationship between delirium and mortality. Although delirium burden is an independent predictor of mortality, it remains unknown if delirium directly causes increased mortality or if delirium burden is an indicator of overall systemic or neurological injury during critical illness, which then results in increased mortality.

In summary, in this retrospective, observational, cohort study, I found that delirium among ICU patients is associated with higher three-month mortality even after adjusting for important covariates. In addition, I developed a new predictive model of patient mortality that is improved by the addition of delirium burden. Specifically, we demonstrated that delirium fraction (number of days with delirium divided by number of days assessed) is more predictive of mortality than total number of days hospital patients are positive for delirium. I also identified certain features of delirium that are more predictive of mortality than others. Further research will be needed to understand the role of underlying brain states, inflammation, as well as cause-and-effect relationships between delirium and mortality.

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Table 1
Patient Demographics and Clinical Characteristics

Characteristics	Alive at 3 Months (Total n = 123)	Deceased at 3 Months (Total n = 42)	*
Age, mean (SD)	57 (14)	64 (13)	*
Male (%)	79 (64)	26 (62)	
Race			
White (%)	106 (86)	35 (83)	
Black (%)	10 (8)	2 (5)	
Hispanic (%)	4 (3)	1 (2)	
Admission Diagnoses			
Sepsis (%)	14 (11)	10 (24)	*
Acute Respiratory Failure (%)	73 (59)	25 (60)	
Cardiac Shock (%)	1 (1)	1 (2)	
Myocardial Ischemia (%)	0 (0)	1 (2)	*
Cardiac Arrhythmia (%)	9 (7)	0 (0)	*
Upper Airway Obstruction (%)	1 (1)	1 (2)	
GI Surgery (%)	8 (6)	1 (2)	
Surgery (%)	29 (23)	6 (14)	
Pancreatitis (%)	3 (3)	2 (4)	
Liver Failure (%)	7 (6)	6 (14)	*
Renal Failure (%)	20 (16)	8 (19)	
Obstructive Sleep Apnea (%)	2 (2)	0 (0)	
Charleson Comorbidity Index (SD)	3(2)	4(3)	*
APACHE II Score, mean (SD)	22 (8)	24 (10)	
Total Days in Hospital, mean (SD)	29 (41)	21 (11)	
Daily Dose of Propofol, mean (SD)	456 (657)	467 (285)	
Daily Dose of Opiates, mean (SD)	1353 (2690)	513 (992)	
Daily Dose of Benzodiazepines, mean (SD)	27 (218)	7 (24)	
Daily Dose of Dexmedetomidine, mean (SD)	665 (6734)	13 (55)	
Delirium days during hospital stay, mean (SD)	4 (6)	4 (4)	
Coma days during hospital stay, mean (SD)	4 (5)	6 (5)	*

Note. APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SD = standard deviation; y = years; * = statistically significant. Patients were sometimes given more than one admission diagnosis by the medical team, resulting in totals > 100%.

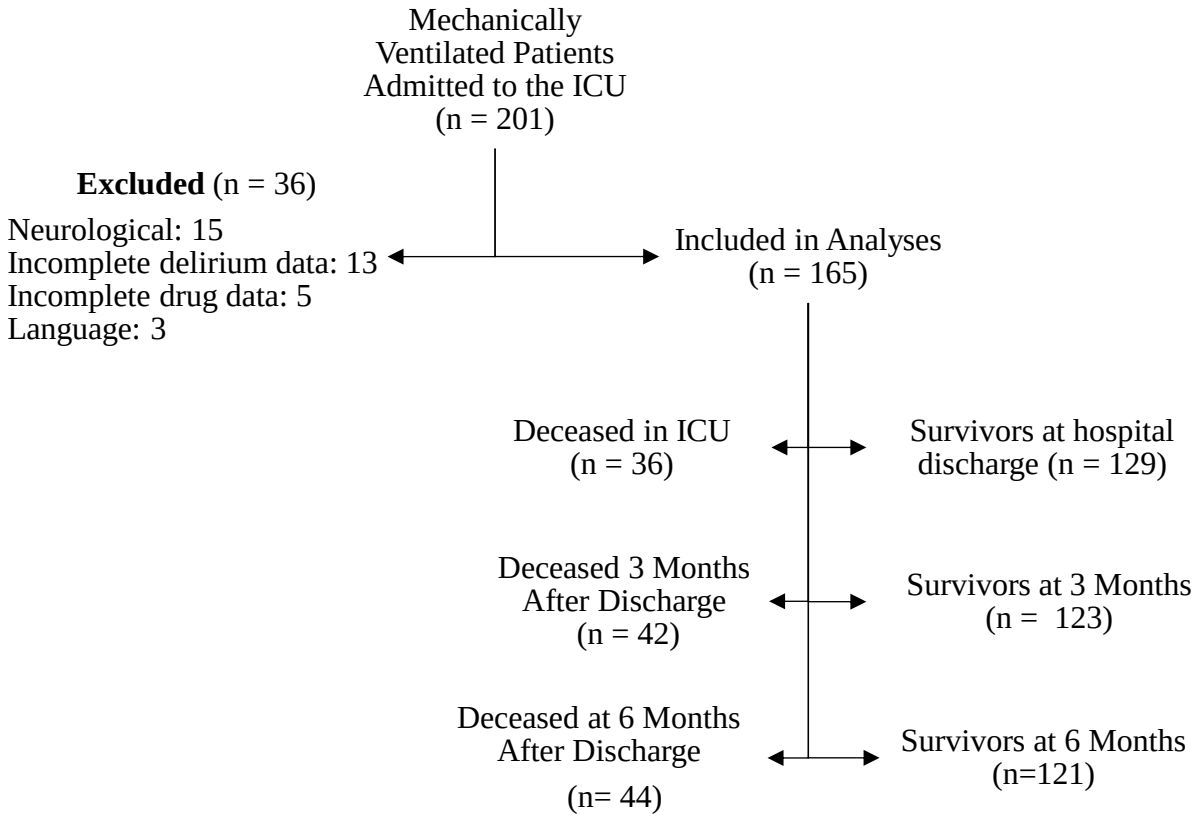

Figure 1. Participant flow chart and survival status from enrollment through six-months after hospital discharge.

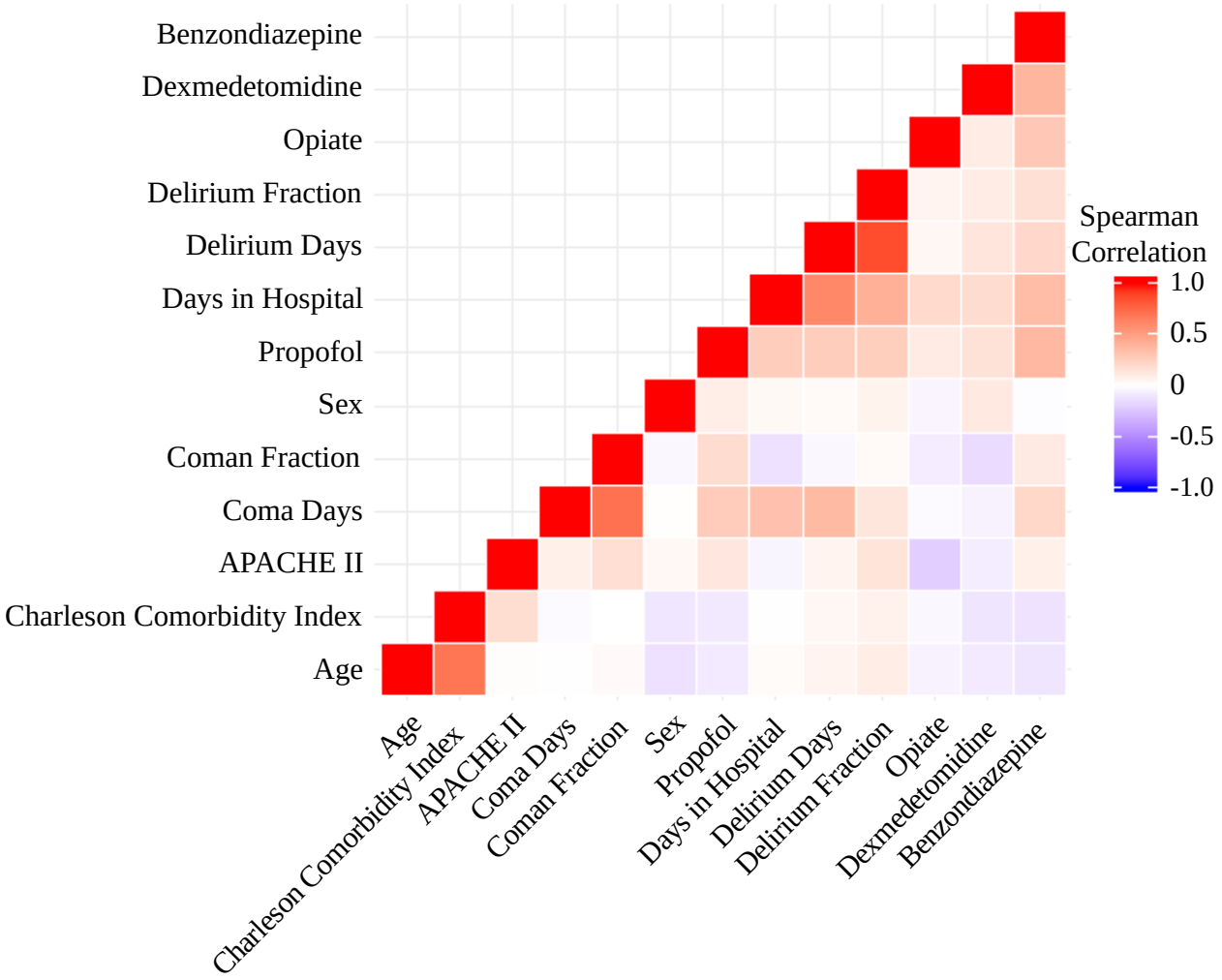

Figure 2. Spearman's rank correlation coefficient statistic was used to estimate a rank-based measure of association between the variables. Missing values were handled by casewise deletion. Non-normality of data was confirmed using the Shapiro–Wilk test. APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; CCI = Charleson Comorbidity Index.

Variables	ICU			
	Standard with Days	Standard with Fractions	Features with Days	Features with Fractions
Age	0.25	0.21	0.20	0.07
Sex				
Charlson Comorbidity Index	0.42	0.47	0.42	0.48
Length of Stay	-0.46		-0.43	
APACHE II				
Coma	0.69	1.19	0.63	1.05
Delirium (Standard)		0.22		
Fluctuating Course (Feature 1)			-0.15	
Inattention (Feature 2)				0.05
Altered Consciousness (Feature 3)			0.20	0.36
Disorganized Thinking (Feature 4)				
Dexmedetomidine Total	-0.24	-0.05	-0.23	-0.05
Propofol Total	0.35	0.10	0.31	0.03
Opiate Total				
Benzodiazepine Total	0.02			

Figure 3. The variables include in the models predicting three-month mortality of mechanically ventilated critically ill patients based on the data observed in the ICU. The values listed in the table are the beta values, with the higher values representing a greater impact of the variable on predicting mortality at three-months. The empty variables had a beta value of 0.00 and were not included in the models. The shaded variables are the selected variables in the individual models.

Variables	ICU and Hospital Floor			
	Standard with Days	Standard with Fractions	Features with Days	Features with Fractions
Age	0.26	0.17	0.25	
Sex				
Charlson Comorbidity Index	0.42	0.52	0.52	0.13
Length of Stay	-0.43	-0.19	-0.15	
APACHE II		-0.02	0.05	
Coma	0.71	1.39	0.79	0.38
Delirium (Standard)	-0.08	0.62		
Fluctuating Course (Feature 1)			-1.37	
Inattention (Feature 2)			0.45	
Altered Consciousness (Feature 3)			0.46	1.19
Disorganized Thinking (Feature 4)				
Dexmedetomidine Total	-0.25	-0.07	-0.23	-0.08
Propofol Total	0.35	0.07	0.43	
Opiate Total			0.09	
Benzodiazepine Total	0.02		0.02	

Figure 4. The variables include in the models predicting three-month mortality of mechanically ventilated critically ill patients based on the data observed in the ICU and on the hospital floor. The values listed in the table are the beta values, with higher values representing a greater impact of the variable on predicting mortality at three-months. The empty variables had a beta value of 0.00 and were not included in the models. The shaded variables are the selected variables in the individual models.

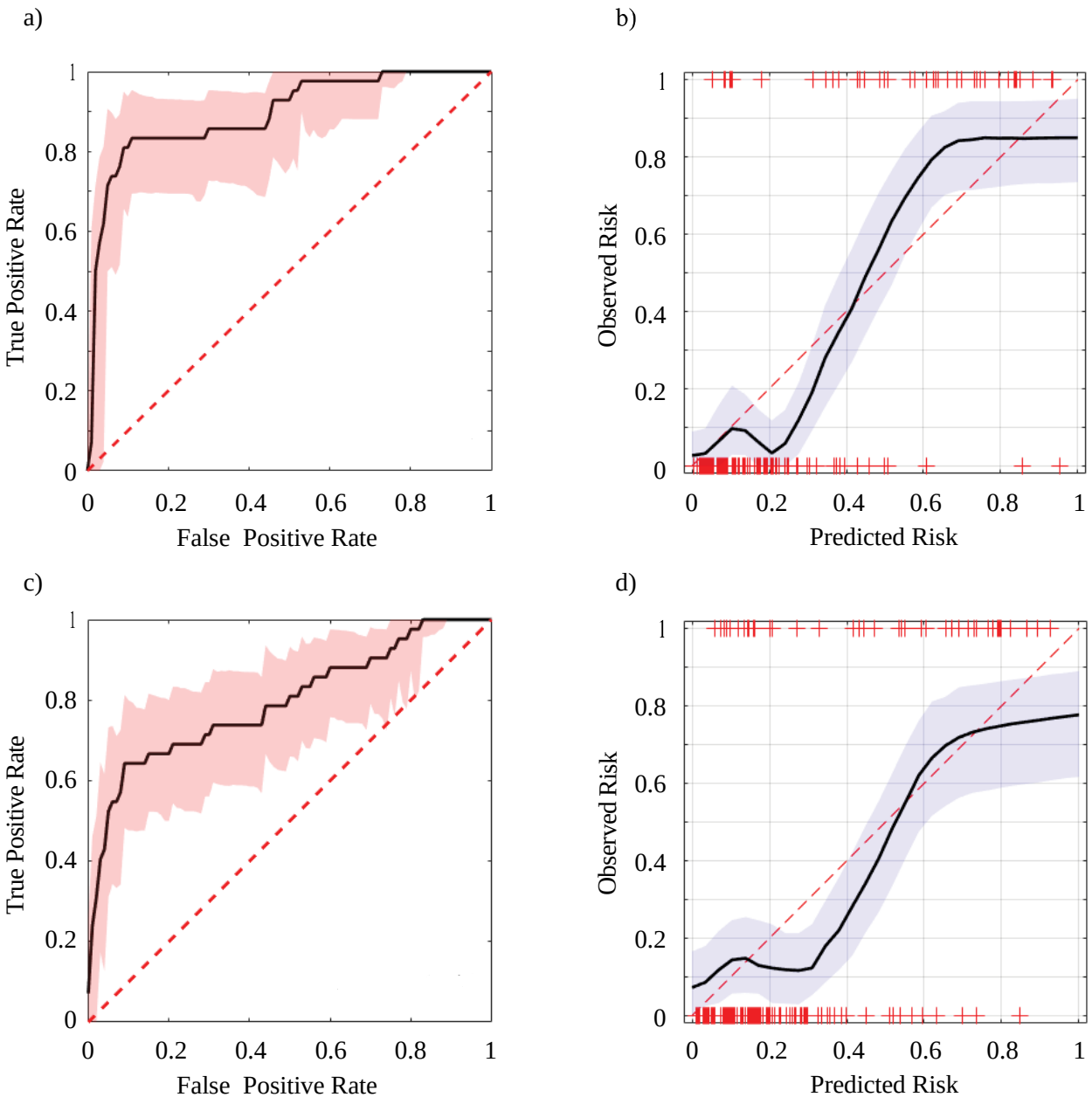

Figure 5. Receiver operative characteristic (ROC) curves and calculated area under the curves (AUC). The prediction model of three-month mortality with the fraction of CAM-ICU features (a) and the risk calibration plot (b) with data from the ICU and on the hospital floor (AUC: 0.89). The prediction model of three-month mortality (c) based on data collected in the ICU only (AUC: 0.80) and the risk calibration plot (d).