CHEST Online Supplement

Acute Brain Dysfunction

Development and Validation of a Daily Prediction Model

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e-Appendix 1.

A. Methods

1. Inclusion and exclusion criteria

a) Inclusion Criteria

We enrolled adult patients in a medical or surgical intensive care unit (ICU) receiving treatment for respiratory failure or shock (cardiogenic or septic). We considered a patient to be in respiratory failure if, at the time of enrollment, they were receiving any of the following treatments: invasive mechanical ventilation, noninvasive positive pressure ventilation, continuous positive airway pressure, supplemental oxygen via a nonrebreather mask, or nasal cannula delivering heated high-flow oxygen. Patients were considered to be in cardiogenic shock if they were being treated at the time of enrollment with an intra-aortic balloon pump or any of the following medications administered for acute cardiac dysfunction: dopamine ≥ 7.5mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min, epinephrine at any dose, milrinone at any dose (if used with another vasopressor), or vasopressin ≥ 0.03 units/min (if used with another vasopressor). We considered a patient in septic shock when suspected or proven infection was documented in the setting of hypotension being treated with any of the previously listed medications. Patients who were on long-term ventilatory support prior to the acute illness that resulted in the hospitalization, qualified for enrollment in this study if they met criteria for shock (as defined above) or they had a new onset of respiratory failure, defined as either an increase of pressure support of 5 cmH_2O or positive end-expiratory pressure of 2 cmH_2O from baseline ventilatory settings.

b) Exclusion Criteria

Patients who meet the inclusion criteria will be excluded if they meet any of the following criteria:

(1) Cumulative ICU time > 5 days in the past 30 days, not including the current ICU stay, as this might create a state of flux regarding patients' cognitive baseline.

(2) Severe cognitive impairment (identified by a Clinical Dementia Rating Scale score of 3)[1,2] or neurodegenerative diseases that prevent a patient from living independently at baseline, including mental illness requiring institutionalization, acquired or congenital mental retardation, known brain lesions, traumatic brain injury, cerebrovascular accidents with resultant moderate to severe cognitive deficits or ADL disability, Parkinson's disease, Huntington's disease, severe Alzheimer's disease or dementia of any etiology.

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(3) ICU admission post cardiopulmonary resuscitation with suspected anoxic injury.
(4) An active substance abuse or psychotic disorder, or a recent (within the past 6 months) serious suicidal gesture necessitating hospitalization. This exclusion will enrich follow-up rates by avoiding patients with whom it is particularly challenging to maintain long-term contact.
(5) Blind, deaf, or unable to speak English, as these conditions would preclude our ability to perform the follow-up evaluation interviews.
(6) Overly moribund and not expected to survive for an additional 24 hours and/or withdrawing life support to focus on comfort measures only.
(7) Prisoners.
(8) Patients who live further than 200 miles from Nashville and who do not regularly visit the Nashville area.

(9) Patients who are homeless and have no secondary contact person available. This exclusion will enrich follow-up rates by avoiding patients with whom it is particularly challenging to maintain long-term contact.

(10) The onset of the current episode of respiratory failure, cardiogenic shock, or septic shock was > 72 hours ago.

(11) Patients who have had cardiac bypass surgery within the past 3 months (including the current hospitalization).

2. Summary of the BRAIN-ICU study protocol

The (BRAIN-ICU) study was conducted at Vanderbilt University Medical Center and Saint Thomas Hospital (both Nashville, TN, USA). Each day, study personnel screened
the census of the medical and surgical ICUs at each enrolling site. At enrollment, study personnel collected baseline information including sociodemographic, comorbid medical conditions, disability in basic and instrumental activities of daily living, baseline cognitive function, and baseline. Enrolled patients were followed daily in the hospital until they were discharged (or for up to 30 days). Each day, study personnel collected detailed physiologic and pharmacologic data used to calculate the covariates described below, including daily severity of illness scores, duration of delirium, duration of coma, duration of severe sepsis, duration of mechanical ventilation and mean daily doses of sedatives and opiates. Patients then underwent in-person follow-up assessments 3 and 12 months after discharge.

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Since we assessed mental status twice daily, if the two assessments didn't match we considered the worst outcome on that day (Coma / normal = coma; Coma / delirium = coma; Delirium / normal = delirium; Death / any state = death; Discharged / any state = discharged).

3. Definitions of Candidate Predictors and Rationale

Candidate predictors for the ABD-pm development were a priori selected according to: 1) strength of evidence from literature review, 2) expert input, 3) data availability, and 4) availability of similar coded variables in the electronic medical record at ICU admission. Although some factors may be predictive (e.g., alcohol abuse) they may not be present or accessible in coded formats and potentially exportable to external ICUs, or they may be coded, but not available at the time of admission (e.g., discharge ICD-9/10 codes).

Candidate variables at ICU admission included:

a. Age at enrollment

b. Medical versus Surgical ICU type

c. Modified Acute Physiology and Chronic Health Evaluation II score:[3] A scoring system that was originally created to measure the severity of illness of medical and surgical patients admitted to the intensive care unit (ICU). The score is calculated from 12 routine measurements including age, temperature, mean arterial pressure, arterial pH, heart rate, respiratory rate, serum sodium, serum potassium, creatinine, hematocrit, and white blood cell count, , all within the first 24 hours of admission to the ICU. Scores can range from 0 to 71, with increasing score reflecting greater severity of illness.

d. Modified Sequential Organ Function Assessment (SOFA):[4] An organ dysfunction scoring system and is a validated marker of severity of illness over time.[5] The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological system. For each system, points can range from 0 for no dysfunction to 4 for organ system failure. Total SOFA scores may range from 0 to 24, with higher scores indicating increased levels of organ dysfunction. The score used for this model did not include the neurological component since one of the key outcomes of interest was neurological in nature.

e. Use of medications to treat Alzheimer's at hospital admission, as a marker of history of dementia.

f. Use of mechanical ventilation: Defined as the use of invasive mechanical ventilation or noninvasive positive pressure ventilation.
g. Sepsis: is defined as the presence of infection plus at least 2 systemic inflammatory response syndrome features, recorded prospectively. Sepsis diagnosis was adjudicated by 3 Intensivists [PPP, TDG, EWE].

Candidate variables available on a daily basis included

a. Current day's brain function status. See e-Table 1 for definition of day's brain function states.

b. Daily mechanical ventilation status. Defined as above at the time of admission, however, on a daily basis.

c. Daily sepsis: Defined as above at the time of admission, however, on a daily basis.

d. Modified Sequential Organ Function Assessment (SOFA)[4]: to evaluate daily severity of illness. In the calculation of the SOFA score, the worst values for each parameter in the 24 hour period were used. The score did not include the neurologic component SOFA score since daily brain function (normal, delirium, or coma) was included as a unique daily predictor.

e. Use of Sedation in the last 24 hours (benzodiazepine, opioids, propofol, and antipsychotics).

f. Daily updated length of stay: given that time in the ICU may independently affect risk of developing delirium.

4. Definition of Outcomes: See **e-Table 1**.

e-Table 1. Definition of Five Outcomes States for Daily Acute Brain Dysfunction Prediction Model

Acute Brain Dysfunction Transition States	Remains in ICU	CAM-ICU	RASS
Normal State	Yes	Negative	RASS ≥ - 3
Delirious State	Yes	Positive	RASS ≥ - 3
Comatose State	Yes	Unable to Assess	RASS < -3
Final Transition States			
ICU discharge	No	Not measured	Not measured
ICU death	No	Not measured	Not measured

ICU, Intensive Care Unit; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; RASS, Richmond Agitation Sedation Scale.

5. Approach to Missing Data

   When a delirium assessment was missing, for reasons other than death or coma, which occurred 1% of ICU days, we used single imputation to assign mental status for that day; the imputation relied on the mental status on the day before and after the missing assessment as well as whether discharge or death occurred the day after the missing assessment. Missing laboratory data used for admission APACHE II[3] score and SOFA[4] score and daily medications were assumed to be normal. Last observation carried forward was used for the SOFA score and daily medications.

6. R Code for Model Predictions and Example Data

   The enclosed R code file with filename "trx_probs.R" defines an R function, "trx_probs", that takes as input a data frame of predictor inputs (i.e., current cognitive status, age at enrollment, etc.) and outputs the probability of transitioning to each of the outcome states (i.e., "Normal", "Delirious", "Comatose", "ICU Discharged", "ICU Death") using the multinomial logit model. Also available upon request is an R data file with filename "model-data.RData". This file stores data needed to compute transition probabilities, including the model formula and estimated coefficients, and also includes an example data frame that can be used as

input to the "trx_probs" function. Finally, the enclosed CSV file with filename "variable-descriptions.csv" includes a list of predictor variable names, descriptions, types, and R formats. The "trx_probs" function assumes that the input variables are formatted as described in the "variable-descriptions.csv" file.

trx_probs

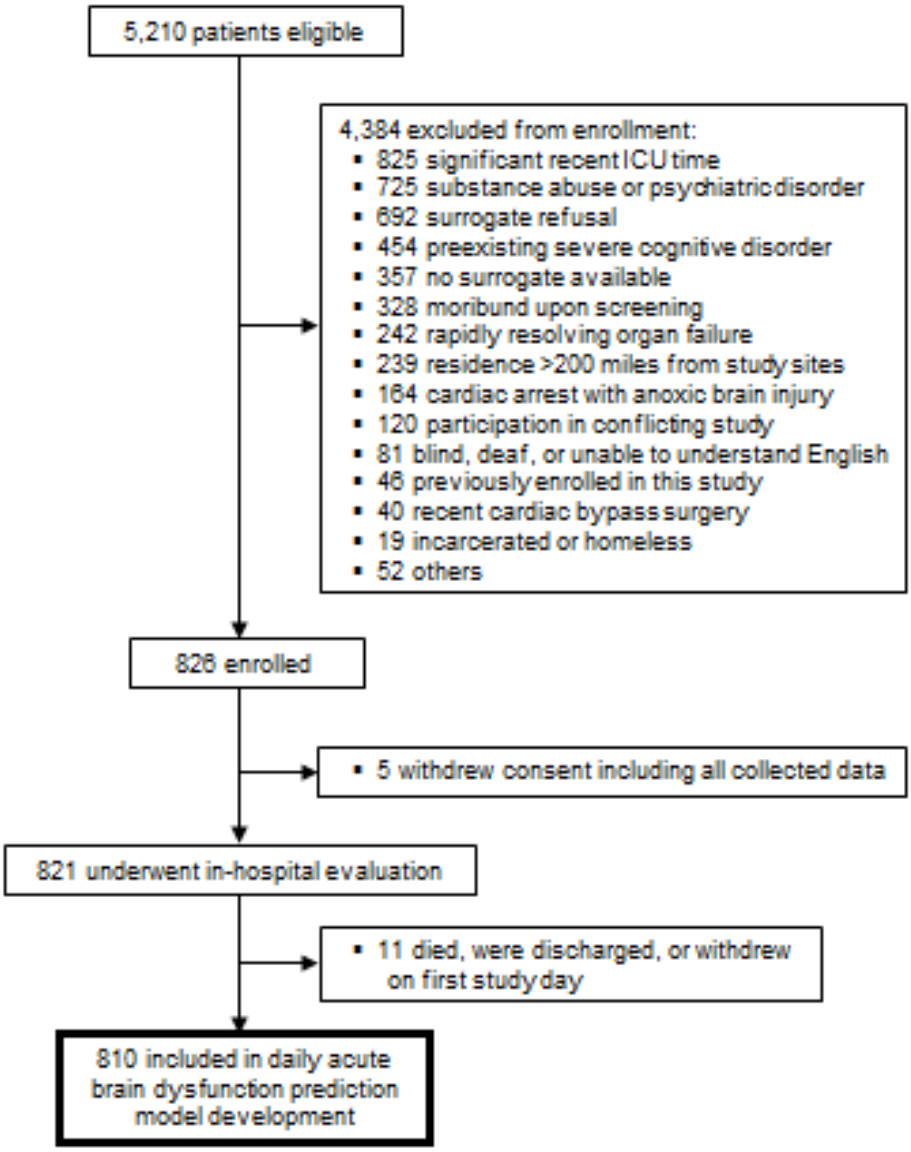
```
## load model data (coefficients and formula)
load("model-data.RData")

## function to calculate transition probabilities
## dat - data frame with input variables as described
##       in the 'variable-descriptions.csv' file; factor
##       variables must be formatted using the factor
##       levels provided in the description, and in the
##       order specified (this function does not check);
##       the range of quantitative variables observed in
##       the model training data is also provided
## form - model formula
trx_probs <- function(dat, form=mod.form, beta=mod.beta) {

  ## compute study.day.1 variable
  dat$study.day.1 <- dat$study.day == 1

  ## compute model matrix
  mmx <- model.matrix(form, dat)

  ## compute linear predictors
  lin <- mmx %*% beta

  ## compute next day status probabilities (for all but 'Normal')
  prb <- exp(lin) / (1+rowSums(exp(lin)))

  ## compute next day normal probability
  nprb <- matrix(1-rowSums(prb), nrow=nrow(prb))
  colnames(nprb) <- 'Normal'

  ## return all probabilities
  return(cbind(nprb, prb))
}

## example
# trx_probs(example.data)
```

variable descriptions

Name	Type/ Frequency	Levels/Values	Description
icu.status.today	factor; daily	Normal; Delirious; Comatose	Current cognitive status
sepsis.locf	factor; daily	Not septic today; Septic today	Septic in the current 24h (LOCF)?
home.antialz	factor; baseline	No; Yes	Receiving anti-Alzheimer's agents prior to hospitalization?
icu.type	factor; baseline	Medical; Surgical	ICU type
age.enroll	numeric; baseline	[18-99]	Age in years at enrollment
mod.apache	integer; daily	[2-44]	Modified APACHE (omits GCS) at enrollment
daily.sofa.mod.locf	integer; daily	[1-18]	Daily SOFA, modified (no CNS component, LOCF)
study.day	integer; daily	[1-29]	Study day (count from 1)
on.vent.l24	logical; daily	TRUE; FALSE	On ventilator in last 24h?
rcvd.benz	logical; daily	TRUE; FALSE	Received benzodiazepines in last 24h?
rcvd.op	logical; daily	TRUE; FALSE	Received opioids in last 24h?
rcvd.apsy	logical; daily	TRUE; FALSE	Received antipsychotics in last 24h?
rcvd.prop	logical; daily	TRUE; FALSE	Received propofol in last 24h?
on.vent.enr	logical; baseline	TRUE; FALSE	On ventilator at enrollment

B. Results

1. e-Figure 1: Enrollment



Patients meeting inclusions and exclusions criteria. The exclusions criteria were all part of the parental study (BRAIN-ICU cohort).

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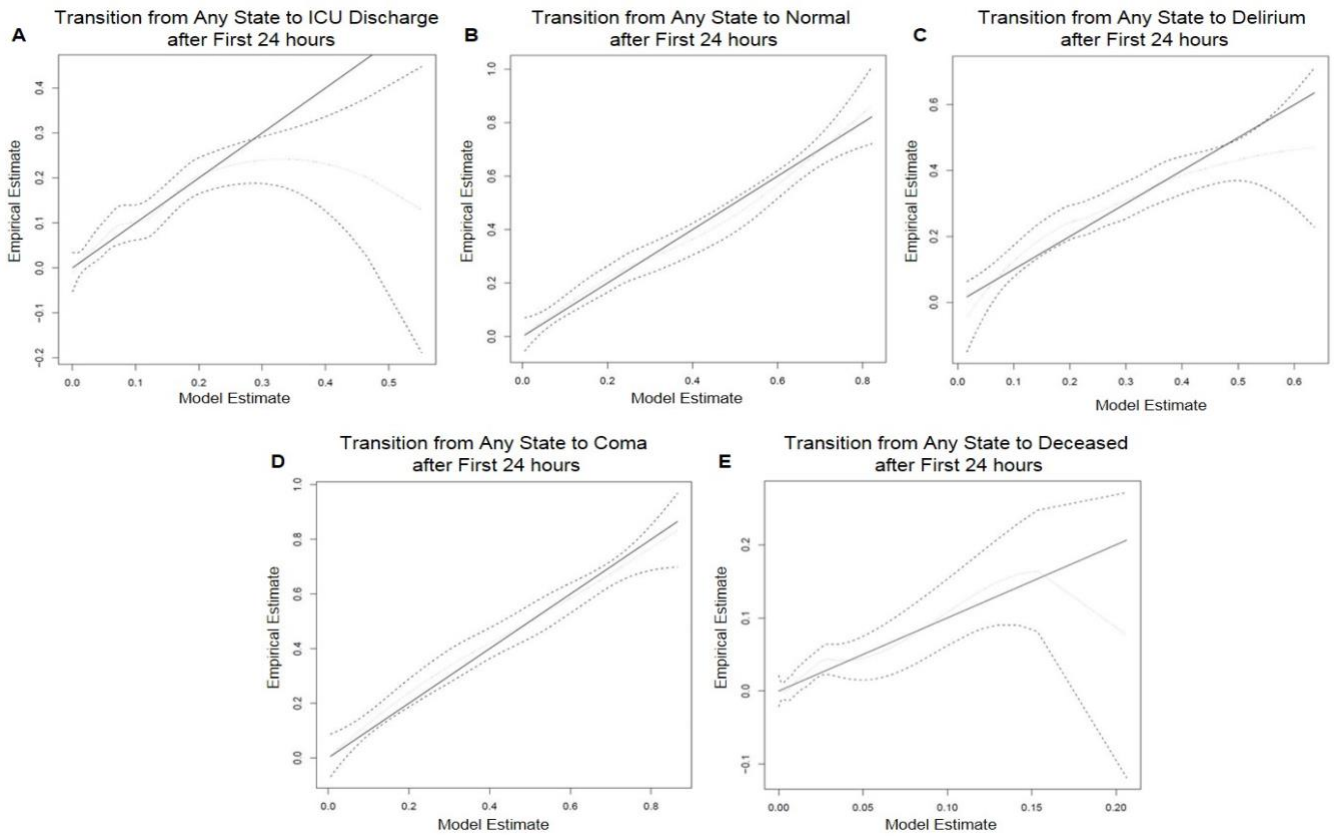
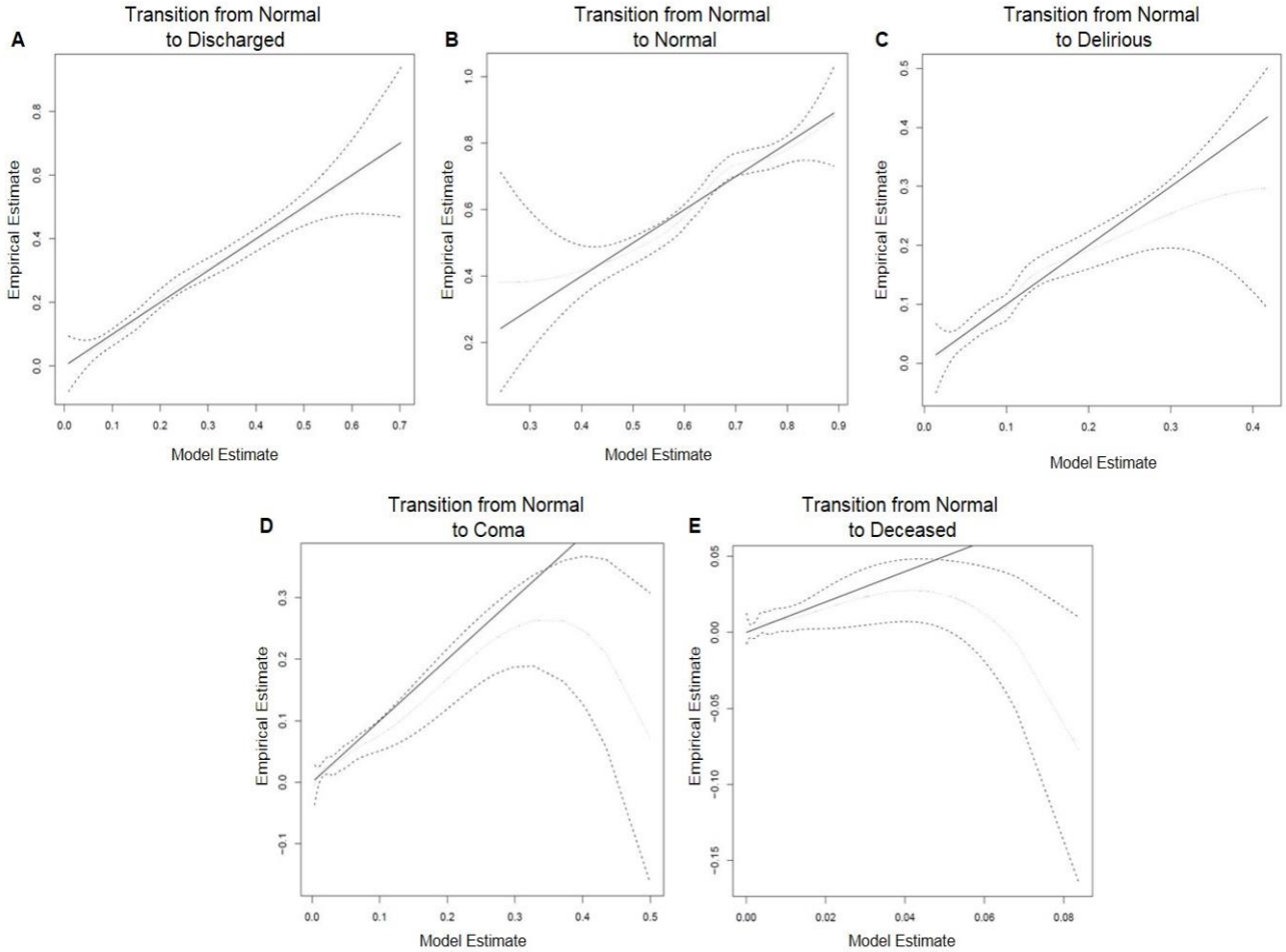
2. Group Level Calibration for Transitions from Any Brain Function State to Each Outcome State after First 24 hours

e-Figure 2 Legend: Model Calibration for each Transition. Each of the graphs illustrates the empirically estimated proportion of transitions on the Y-axis, and the transition model-estimated proportion of transitions on the X-axis. Perfect calibration is represented by the straight line with slope of 1 and intercept of 0. The empirical estimate and 95% upper and lower confidence bounds are represented by dotted and dashed lines, respectively. Each of the transition states are shown below. Panel A: Transition from Any State to ICU Discharge after First 24 hours; Panel B: Transition from Any State to Normal after First 24 hours; Panel C Transition from Any State to Delirium after First 24 hours; Panel D: Transition from Any State to Coma after First 24 hours; Panel E: Transition from Any State to Deceased after First 24 hours.



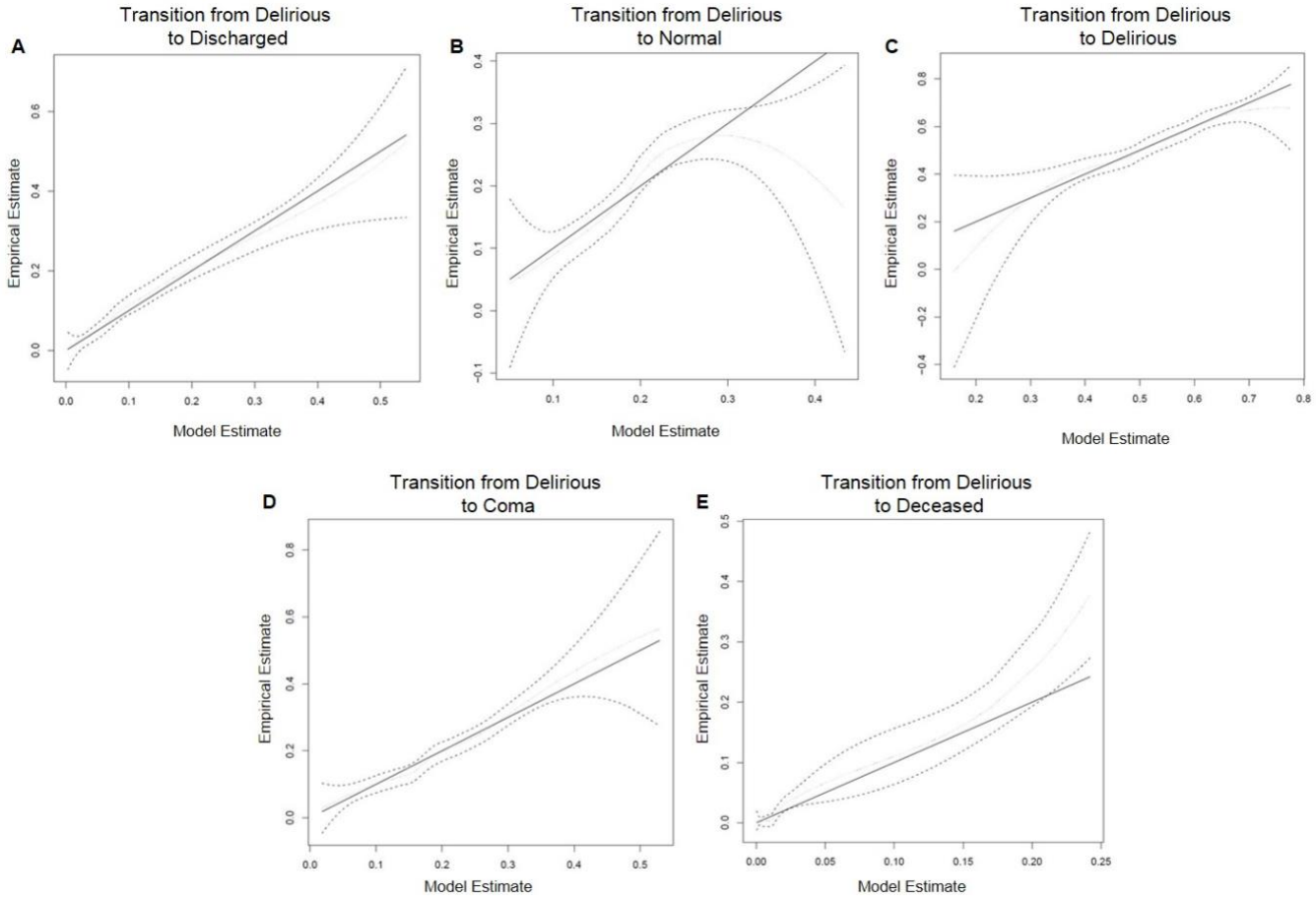
3. Patient Level Calibration for Each Transition Probability That Began with a Normal State

e-Figure 3 Legend: Model Calibration for each Transition. Each of the graphs illustrates the empirically estimated proportion of transitions on the Y-axis, and the transition model-estimated proportion of transitions on the X-axis. Perfect calibration is represented by the straight line with slope of 1 and intercept of 0. The empirical estimate and 95% upper and lower confidence bounds are represented by dotted and dashed lines, respectively. Each of the transition states are shown below. Panel A: Transition from Transition from Normal to Discharged; Panel B: Transition from Normal to Normal; Panel C: Transition from Normal to Delirious; Panel D: Transition from Normal to Coma; Panel E: Transition from Normal to Deceased.



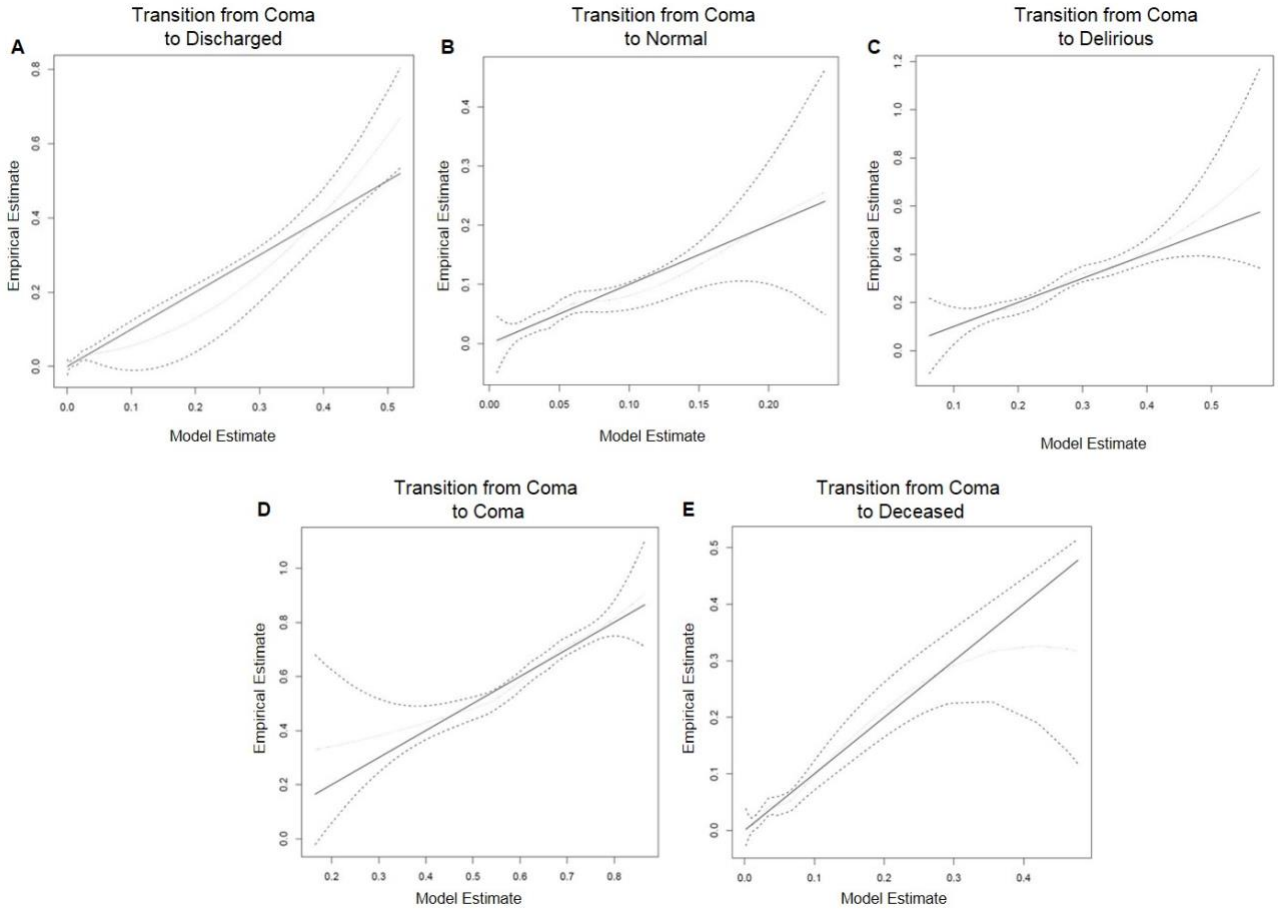
4. Patient Level Calibration for Each Transition Probability That Began with a Delirious State

e-Figure 4 Legend: Model Calibration for each Transition. Each of the graphs illustrates the empirically estimated proportion of transitions on the Y-axis, and the transition model-estimated proportion of transitions on the X-axis. Perfect calibration is represented by the straight line with slope of 1 and intercept of 0. The empirical estimate and 95% upper and lower confidence bounds are represented by dotted and dashed lines, respectively. Each of the transition states are shown below. Panel A: Transition from Delirious to Discharged; Panel B: Transition from Delirious to Normal; Panel C: Transition from Delirious to Delirious; Panel D: Transition from Delirious to Coma; Panel E: Transition from Delirious to Deceased.



5. Patient Level Calibration for Each Transition Probability That Began with a Coma State

e-Figure 5 Legend: Model Calibration for each Transition. Each of the graphs illustrates the empirically estimated proportion of transitions on the Y-axis, and the transition model-estimated proportion of transitions on the X-axis. Perfect calibration is represented by the straight line with slope of 1 and intercept of 0. The empirical estimate and 95% upper and lower confidence bounds are represented by dotted and dashed lines, respectively. Each of the transition states are shown below. Panel A: Transition from Coma to Discharged; Panel B: Transition from Coma to Normal; Panel C: Transition from Coma to Delirious; Panel D: Transition from Coma to Coma; Panel E: Transition from Coma to Deceased.



e-Table 2. Daily Transition Probabilities Based on the Brain Function Status on the Current Day

Brain Function Status Current Day	Transition State Probability for the Following Day*				
		Brain Function Status			
	ICU discharge	Normal	Delirium	Coma	ICU death
Normal	0.209	0.650	0.096	0.039	
Delirium	0.086	0.188	0.545	0.169	0.005
Coma	0.019	0.050	0.251	0.642	0.012

*Each value represents the probability of transitions from any one of the current brain function states (the first column) into any one of the 5 outcomes states. For example, the probability of transitioning from a current normal state to a delirious state on the following day would be 0.096.

C. References

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