Impact of Severity of Illness on Health State Transitions During Intensive Care Unit Admission: Application of Markov Multi-State Transition Modeling

By

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ABSTRACT

There is insufficient understanding of the relationship between the severity of physiologic illness and the transitions in cognitive and functional health states of patients during the course of an intensive care unit (ICU) stay. To this end, the fundamental aim of this project was centered on developing a predictive model for state transitions during ICU admission in order to determine the relevance of indices of illness severity and other potentially modifiable risk factors that may inform clinical decision-making. The motivating data for this work was derived from the BRAIN-ICU (Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors) study. Five health transition states (normal, delirium, coma, death, and discharge) were considered in the parent study, as were clinical indices of illness severity such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology And Chronic Health Evaluation (APACHE) scores. The transition states constitute multiple end points laden with scientific information that can be elucidated by sophisticated modeling approaches now afforded by the advent of advanced statistical computing. Since the current state of a patient may be related to his/her previous states, the BRAIN-ICU data was analyzed with accommodation for multiple outcome categories (the transition states) by relating state-transition probabilities to patient covariates and past states via a polytomous regression with Markov structure. This analysis strategy addressed competing risk explicitly by assessing the effect of previous states while evaluating the motivating question of the impact of severity of illness.

ACKNOWLEDGEMENTS

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CHAPTER I

Introduction and Background

In clinical medicine, outcome improvement from existing treatments has led to increased difficulty in demonstrating additional mortality benefits with new interventions. Information on morbidity (e.g. quality of life) has become increasingly desirable, thus the interest in outcome measures that provide information on fatal and non-fatal events. However, main-stream approaches to the analysis of multi-level or multiple categorical outcomes in longitudinal clinical studies are suboptimal and reveal some of the challenges associated with the analysis of longitudinal data. For example, analysis of clinical studies frequently employs simple combined outcomes that make a binary distinction between event (fatal or non-fatal) and no event, which are then analyzed using traditional statistical two-sample methods. However, simple binary outcomes ignore critical information and do not distinguish between types or severity of events. Furthermore, in the setting of survival analysis such binary outcomes are analyzed by the traditional the time-to-first event method, which ignores cumulative events (or repeated measures), and represents remarkable loss of potentially relevant information. In addition, the time-to-first event analysis may inadvertently capture less severe early events at the expense of later more serious events, and hence different effects or patterns than might have been observed by incorporating all events. Similarly, outside of survival improvement evaluation, the analysis of categorical outcome longitudinal data by collapsing the categories of outcome to become amenable to the application of logistic regression is fraught with the same problem of information loss.

Longitudinal studies can provide abundant insight when analytical approaches preserve scientific information by incorporating the entire data available for each participant instead of discarding portions of it. Advances in statistical computing now affords us intuitive, flexible, explicit, and transparent approaches for longitudinal data analysis. In this context, we demonstrate the use of Markov multi-state models to analyze longitudinal data obtained from observations of cognitive and functional health states of patients during the course of an intensive care unit (ICU) stay. Herein, observations of health states are recognized as a continuous-time process in which patients move between various states albeit observed at arbitrarily chosen pre-specified intervals per study protocol. The description of how patients move between various health states is provided by a multi-state model that relies on the first-order Markov assumption that the current health state of a patient depends only on his/her previous health state; alternatively stated, the evolution of a future health state depends on the current health state. The motivating data for this work is a subset from the BRAIN-ICU (Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors) study: a prospective multicenter cohort study conducted to estimate the prevalence of

long-term cognitive impairment after critical illness in a heterogeneous population of critically ill patients. The description of the motivating data is preceded by a succinct review of the two general classes of models for longitudinal data analysis. Subsequently, we present the rationale for the use of multi-state transition model vis-a-vis the motivating data, and then specify the model with respect to its parameters and likelihood function. The crux of our analysis—model fitting, assessment, and interpretation—is addressed followed by a discussion of the results, subject matter relevance, model critique, and future directions.

Methods for Analysis of Longitudinal Data

The modeling approaches for longitudinal data analysis can be grouped into two broad categories of models known as marginal and conditional models.

Marginal Models

In the context of serial data, marginal models separates the time points.

$$\mathrm{E}[Y_{ij}|\boldsymbol{x}_{ij}] = \boldsymbol{x}_{ij}\boldsymbol{\beta} \tag{1}$$

$$\mathrm{Cov}[\boldsymbol{Y}_i] = \boldsymbol{\Sigma}_i(\boldsymbol{\alpha}) \tag{2}$$

As shown in equation 1, the marginal expectation of the outcome variable ($\boldsymbol{Y}$) is modeled as a function of covariates ($\boldsymbol{X}$), and a model is specified for longitudinal correlation (that is, within-person correlation across time points of the outcome variable) and the correlation parameters ($\boldsymbol{\alpha}$) estimated (equation 2). The implication of this approach as delineated in equations 1 and 2 is that the correlations may not necessarily be functions of the marginal expectation. A marginal model considers population-averaged rate rather than the conditional rate. Examples of models accommodated under this construct include:

1. Univariate generalized linear models (GLMs) which employ likelihood-based estimation approaches. Specific link functions allow modeling of different types of outcomes, thus we have GLMs for count outcomes and GLMs for binary outcomes.

2. Generalized estimating equations (GEE) represents another good example of a marginal modeling approach typically employed when subject-specific estimates are not of interest. GEE is a semi-parametric method that uses moment-based estimation strategy and therefore particularly applicable when parametric modeling assumptions such as the specification of a complete probability distribution is undesirable if not impossible. GEE is specified by a mean model and a correlation model:

   - A regression model for the mean outcome, e.g. linear model, logistic

- A model for longitudinal correlation, e.g., independence, exchangeable

If working independence is assumed, and intra-subject correlation corrected for post fitting, one would say that GEE is a marginal model considering only the mean.

3. An extended linear model constitutes another marginal modeling approach. This approach is exemplified by generalized least squares (GLS) models, which are fully correlation-specified multivariate fixed-effect models. GLS is like weighted least squares but employs a covariance matrix that is not diagonal; thus each subject being measured at a different set of times can have his/her own shape of variance-covariance matrix. The underlying estimation strategy could be ordinary maximum likelihood (ML), Newton-Raphson (or other iterative methods), or restricted maximum likelihood (REML). The use of REML is usually motivated by the desire for unbiased estimates when the sample size is small or when the number of parameters estimated is particularly large relative to the sample size.

If the primary analysis goal is to generate inference regarding the mean outcome as a function of covariates and time, then a marginal mean model may be sufficient.

Conditional Models

There are two general categories of conditional models: Mixed-effects models and transition models. Mixed-effects models use subject-specific random effects $\boldsymbol{\gamma}_i$ to explain a correlation structure as delineated in equation 3.

$$\mathrm{E}[Y_{ij}|\boldsymbol{x}_{ij}, \boldsymbol{\gamma}_i] = \boldsymbol{x}_{ij}\boldsymbol{\beta} + \gamma_i \tag{3}$$

A variety of models can be accommodated under the mixed-effects construct:

1. Linear and non-linear mixed-effects models, which assume that each subject has a regression model characterized by subject-specific parameters that are a combination of fixed effects parameters common to all subjects in the population and random subject-specific perturbations. Of note, the subject-specific random effects induce a correlation structure. The underlying estimation strategy is usually likelihood-based (REML or ordinary ML) and thus requires specification of complete parametric probability distribution, however random effects may be estimated using empirical Bayes estimators.

2. Generalized linear mixed-effects models (GLMM). Here as in the case of GLMs above, we also have GLMMs for count outcomes and binary outcomes, however the parameter estimates obtained from via GLMM estimate subject specific contrasts $\boldsymbol{\beta}$, as in other conditional models.

Essentially, a GLMM is defined by a random component describing outcomes given subject-specific effects and a systematic component describing conditional mean given subject-specific effects. Conditional and ordinary ML are two inference approaches used for GLMM. The conditional likelihood approach treats the random effects as if they are fixed parameters and eliminates the subject-specific effects by conditioning on their sufficient statistics; thus this likelihood-based approach does not require a specified distribution for the random effects. The ordinary ML method treats the random effects as unobserved nuisance variables and integrates over their assumed distribution to obtain the marginal likelihood for the outcome $\boldsymbol{Y}$.

Transition models specify the conditional expectation of current outcomes Y_{ij} as a function of covariates and previous outcomes $Y_{i(j-1)}$ as denoted in equation 4.

$$E[Y_{ij}|\boldsymbol{x}_{ij}, Y_{i(j-1)}] = \boldsymbol{x}_{ij}\boldsymbol{\beta} + Y_{i(j-1)}\boldsymbol{\alpha} \tag{4}$$

An equivalent statement is that the conditional expectation of future outcomes $Y_{i(j+1)}$ is a function of covariates and current outcomes Y_{ij} as delineated in equation 5.

$$E[Y_{i(j+1)}|\boldsymbol{x}_{ij}, Y_{ij}] = \boldsymbol{x}_{ij}\boldsymbol{\beta} + Y_{ij}\boldsymbol{\alpha} \tag{5}$$

In transition models response dependence is induced among the serial measurements for subject i $\boldsymbol{Y}_i = Y_{i1}, \ldots, Y_{im_i}$ because the past outcomes $\{Y_{i1}, \ldots, Y_{i(j-1)}\}$ explicitly influence the current outcome Y_{ij}, $j = 1, \ldots, m_i$. The Markov assumption is the basis for equations 4 and 5. Also, in the context of transition models there exist generalized linear transition models (GLTM) with link functions for specific types of outcomes, e.g. identity link for continuous outcomes and logit link for binary outcomes. A GLTM corresponds to the assumed exponential family model for the outcome $\boldsymbol{Y}$ given covariates and past outcomes. GLTM is defined by random and systematic components. The estimation strategy for transition models is the same as in standard GLM for independent data because outcomes are conditionally independent given their history (assuming the conditional mean model is correctly specified). If the Markov model is correctly specified, then the model-based standard errors are valid; otherwise a good practice is to use robust standard error estimates. Higher-order transition models are limited to the available data. Transition models can be extended to an outcome that has multiple categories, e.g. ordered outcome. In the context of the motivating data, herein below we demonstrate the application of transition models to an outcome that represents various health states, of which death is as an absorbing state. This concept is fully developed in the model specification

section on page .

Although it is beyond the scope of this work to provide a comprehensive review of all contemporary methods for longitudinal data analysis, for a measure of completeness it is important to recognize marginalized models, which are a relatively newer class of models for the analysis of longitudinal data. The principle is to embed a marginal mean structure within a complete multivariate probability model based on mixed-effects and/or transition models; and then in a regression setting decompose the mean model from the random variation (dependence) model. This is represented mathematically in equations 6 and 7, respectively.

$$Mean: \quad g_\mu(\mathrm{E}[Y_{ij}|\boldsymbol{X}_i]) \quad = \quad \boldsymbol{x}_{ij}\boldsymbol{\beta} \tag{6}$$

$$Dependence: \quad g_\rho(\mathrm{E}[Y_{ij}|\boldsymbol{X}_i, \boldsymbol{Z}_{ij}]) \quad = \quad \Delta_{ij}(\boldsymbol{X}_i) + \boldsymbol{Z}_{ij}\boldsymbol{\alpha}_{ij} \tag{7}$$

Of note, $g_\mu(\cdot)$ and $g_\rho(\cdot)$ are usually the same such that the mean and dependence parameters are on the same scale, however occasionally they might differ and therefore may not be on the same scale. The random variables are contained in the vector $\boldsymbol{Z}_{ij}$. Some extensions of marginalized models include:

- Marginalized latent variable models, which combine a marginal mean regression model with the flexibility of a GLMM in an effort to characterize subject-level heterogeneity.
- Marginalized transition models, which combine a marginal mean model with an associated GLM to characterize systematic variation in the expected outcome as a function of covariates and time. Dependence among repeated measurements on the same subject is induced by specifying the association between past outcomes and current outcome that are assumed to be conditionally independent.
- Marginalized transition and latent variable model are primarily intended for relatively long response series that contain two sources of response dependence (serial and long range).

A comprehensive treatment of the methods for longitudinal data analysis has been provided by Diggle, Heagerty, Liang, and Zeger (2002).

Motivating Data: BRAIN-ICU Study

The BRAIN-ICU study was conducted at two major medical centers in Nashville, TN: Vanderbilt University Medical Center and Saint Thomas Hospital. It was a prospective multicenter cohort study conducted to estimate the prevalence of long-term cognitive impairment after critical illness in a heterogeneous population of critically ill patients. The primary hypothesis tested in the study was that severe cognitive impairment up to 1 year post hospital discharge is associated with two in-hospital predictors: the duration of delirium

(defined as the number of hospital days with delirium) and dosage of analgesic and sedative medications administered during hospitalization. Details pertaining to this study, including endpoint and covariate definitions, inclusion and exclusion criteria, and findings have been published elsewhere (Pandharipande, Girard, Jackson, Morandi, Thompson, Pun, Brummel, Hughes, Vasilevskis, Shintani, et al., 2013). The study included adult patients admitted to medical or surgical ICU for the management of cardiogenic shock, septic shock, or respiratory failure. Patients were evaluated daily for delirium and level of consciousness until hospital discharge or study-day 30 (in-hospital phase), and then follow-up was at 3 and 12-months post-hospital discharge.

Five health states (normal, delirium, coma, death, and discharge) were present in the parent study, as were clinical indices of illness severity such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology And Chronic Health Evaluation (APACHE) scores. Data were collected on many other covariates considered relevant to the ICU clinical course of patients. Some of these covariates include: Age, sex, educational level, Charlson co-morbidity index, preexisting cognitive impairment, ApoE genotype, stroke risk, duration of severe sepsis, duration of hypoxemia, mean dose of sedatives, and mean dose of analgesics. The fundamental aim of the current work is to develop a predictive model for health state transitions during ICU admission with a focus on the potential relevance of indices of illness severity (SOFA and APACHE scores) and other potentially modifiable risk factors that may inform clinical decision-making. This aim stems from our incomplete understanding of the relationship between the severity of physiologic illness and the transitions in cognitive and functional health states of patients during the course of an intensive care unit (ICU) stay. The current work is entirely based on the analysis of ICU hospitalization data from the BRAIN-ICU study.

CHAPTER II

Model Specification

Rationale for State-transition Modeling

Various health states constitute multiple end points that contain relevant information regarding disease process/progression or patients clinical course. For instance, what health states occur with high frequency; how do subjects transition from state to state; what are the transition probabilities? These are all important questions that warrant answers in the context of different types of research studies or programmatic endeavors focused on risk factor interventions, disease management, diagnosis, screening, or treatment. The answers to such questions, which facilitate decision making, can be unmasked using approaches such as multi-state modeling now made feasible by advanced statistical computing. The dilemma of competing risk is another justification for applying multi-state modeling to the motivating data. For instance, how do we account for coma when considering delirium days in the BRAIN-ICU study? Herein, multi-state modeling provides an explicit, intuitive, flexible, transparent, and simplified method for analyzing the motivating data. Finally, in addition to the above advantages, multi-state models can still accommodate time-dependent covariates, time to an outcome, and repeated outcomes.

Multi-state modelling methods have been applied to a spectrum of medical and non-medical research studies Jackson and Sharples (2002); Jackson, Sharples, Thompson, Duffy, and Couto (2003); Sharples (1993); Kay (1986); Satten and Longini (1996); Gentleman, Lawless, Lindsey, and Yan (1994); Sharples, Jackson, Parameshwar, Wallwork, and Large (2003); Sweeting, De Angelis, Neal, Ramsay, Irving, Wright, Brant, Harris, Trent HCV Study Group, and HCV National Register Steering Group (2006); Sweeting, Farewell, and De Angelis (2010); Buter, van den Hout, Matthews, Larsen, Brayne, and Aarsland (2008); Aspinall, Carniel, Jaquet, Woo, and Hincks (2006).The current work focuses on fitting multi-state models to the motivating data, relying on the *Markov* assumption, that future health states depends on the current state. While this work relies on the exposition and statistical software developed by Jackson (2011), refer to Cox and Miller (1965) for a more comprehensive review of Markov chain theory.

Definitions

Health States

The health states used in this study include normal, delirium, coma, death, and discharge. While death, delirium, and coma are easy to conceptualize as distinct, it is important to clearly define or distinguish

between normal and discharge states. The discharged status indicates that the patient was enrolled, followed for however long in the hospital, and later discharged alive from the hospital. In most cases, a discharge would indicate a successful course of clinical treatment, however some patients were discharged to hospice care, so "successful" might be debatable in those cases; however, we will not pursue this further. The normal status indicates that a patient was in the hospital and had at least one assessment on that day, and was deemed to be in normal state on that particular day regardless of the patients status on the previous day.

It is important to recognize that some patients withdrew during the course of the parent study. Patients (or surrogates, if the patients were unable to consent/withdraw on their own) could withdraw at anytime during the course of the study. Most of them allowed the use of data already collected, but did not want further assessment. There were a few who requested that all collected research data be destroyed. A patient or surrogate must actively request to be withdrawn from the study in order to have a withdrawn status. The research team assessed all patients in the ICU daily for all health states. It is possible that a patient was not assessed on a given day for a few reasons: he/she may have been in a long clinical procedure when the research team was available, or the family may have requested that the patient not be assessed that day. But an assessment not being done does not indicate study withdrawal.

Model

The schematic of a multi-state model that captures the five health states in the BRAIN-ICU data is illustrated in Figure 1. The logic of the diagram is that at anytime t a patient is in a state $S(t)$ from which he/she can transition between adjacent health states (the curved arrows) or can transition directly to death from any state (the straight arrows), however death is an absorbing state from which no patient can transition (Jackson, 2011). Progression within a transition space $1, \ldots, R$ is dictated by *transition intensities* $q_{rs}(t, z(t))$ for a pair of states r and s, which may depend on time of the biological process t and/or covariates $z(t)$ that are time-varying or patient-specific (Jackson, 2011). According to Jackson (2011) the instantaneous risk of moving from state r to state s is captured by the intensity as delineated by equation 8, and the q_{rs} form a $R \times R$ matrix Q whose rows sum to zero, so that the diagonal entries are defined by $q_{rr} = -\sum_{s \neq r} q_{rs}$.

$$q_{rs}(t, z(t)) = \lim_{\delta t \to 0} (S(t + \delta t) = s | S(t) = r)/\delta t. \tag{8}$$

Of note, the context of our data warrants the notion of rates as opposed to probabilities. This is because although it is desirable to have information on exact event times, it is indeed not what happens in reality. Quite frequently longitudinal datasets have health state information at specified regular intervals, but not information on the actual time within the interval where the change in health state occurred. Thus in

actuality, longitudinal data like the BRAIN-ICU represent discrete time approximations of a continuous time process, and therefore the estimates of hazard rates more appropriate than the calculation of probabilities. However, since we usually do not have information on exact timing, a direct calculation of hazards rates is not possible, but its relationship with probability can be exploited for indirect calculation. That is, if we assume a constant hazard rate in a *time-homogeneous* Markov model, and transition intensities q_{rs} that are independent of time t, then the time spent in each state has an exponential probability distribution. This mathematical relationship forms the basis of various link functions employed in the calculation of hazard rates in the setting of discrete time approximation of continuous time.

$$Q = \begin{pmatrix} q_{11} & q_{12} & q_{13} & q_{14} & q_{15} \\ q_{21} & q_{22} & q_{23} & q_{24} & q_{25} \\ q_{31} & q_{32} & q_{33} & q_{34} & q_{35} \\ q_{41} & q_{42} & q_{43} & q_{44} & q_{45} \\ q_{51} & q_{52} & q_{53} & q_{54} & q_{55} \end{pmatrix}$$
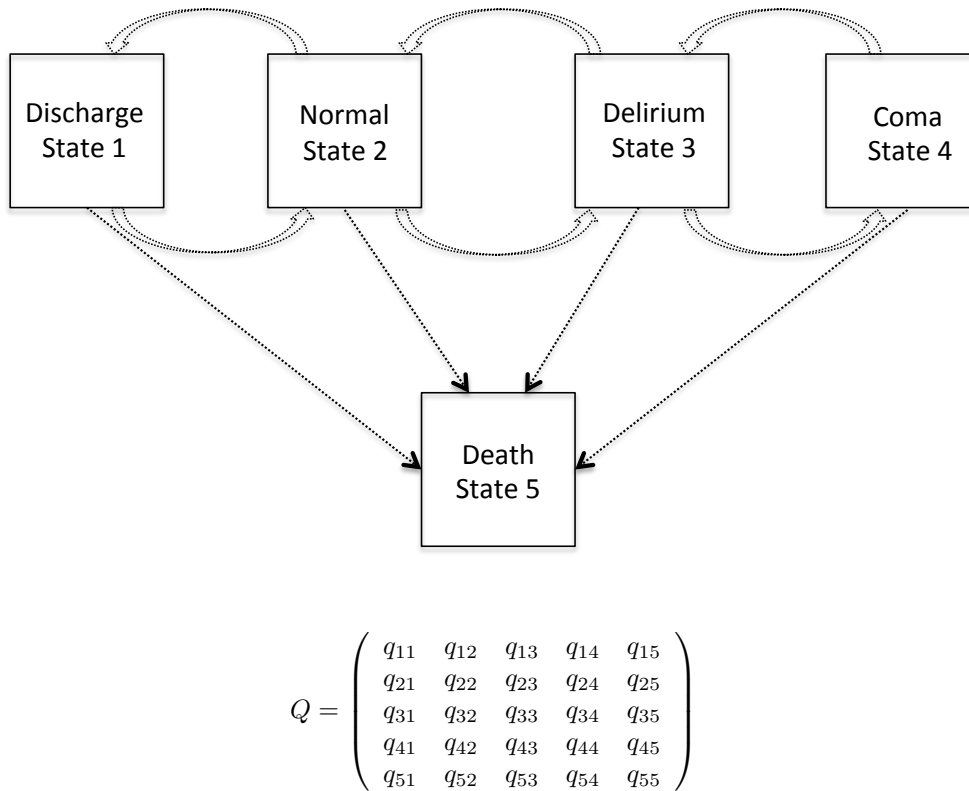
Figure 1: A generalized multi-state model for health states in the BRAIN-ICU data.

In the generic construct depicted by Figure 1 adapted from Jackson (2011) patients can transition back and forth between health states and can die from any state, however no one recovers from death because it is an absorbing state. Allowable transitions between states are specified in the transition matrix utilized for model fitting. Thus, this generic model is flexible enough to accommodate modeling assumptions about feasible health state transitions.

Model Structure

Likelihood Function

According to Jackson (2011), the likelihood function for a general multi-state model used in `msm package` is calculated from the *transition probability matrix* Q as a product of probabilities of transition between observed states, over all individuals i and observation times j, as delineated in equation 9. The components of $L_{i,j}$ are elements of the transition matrix at the $S(t_{ij})$th row and $S(t_{i,j+1})$th column, evaluated at $t = t_{i,j+1} - t_{ij}$. The likelihood $L(Q)$ can be maximized using optimization algorithms such as the `optim` function in R.

$$L(Q) = \prod_i L_i = \prod_{i,j} L_{i,j} = \prod_{i,j} p_{S(t_{ij})S(t_{i,j+1})}(t_{i,j+1} - t_{ij}). \tag{9}$$

Sampling times are assumed to be ignorable for all models in `msm package`, which implies that no relevant information regarding the value of a particular observation can be deduced implicitly from the actual time the observation was made.

Covariates

As stated earlier, the *transition intensities* may be dependent on the time t—capturing the temporal evolution of the biological process—or covariates that are time-dependent or patient-specific. The msm models the impact of covariates $\mathbf{z}_{ij}$ on the transition intensity for individual i at time j using proportional hazards model proposed by Cox (1992) and Marshall and Jones (1995). As demonstrated by Jackson (2011) using the construct of Marshall and Jones (1995) the elements q_{rs} of the transition intensity matrix is replaced by the covariate vector as shown in equation 10.

$$q_{rs}(z(t)) = q_{rs}^{(0)} \exp(\boldsymbol{\beta}_{rs}^{\top} \mathbf{z}(\mathbf{t})). \tag{10}$$

The new transition probability matrix Q then determines the likelihood, which is then maximized over the $q_{rs}^{(0)}$ and $\boldsymbol{\beta}_{rs}$.

CHAPTER III

Data Analysis

Software

All analysis was conducted using R (R Development Core et al., 2012), and for sake of reproducibility the R programming codes are shown in this document. The `msm package` version 1.4 developed by Jackson (2011) was central to the analysis. The rationale for using `msm` for fitting multi-state model to the motivating data is that it can model transition rates in terms of covariates, and accommodates data with a variety of observation schemes including censoring. The `msm package` for R is freely available from http://CRAN.R-project.org/package=msm. There are various extensions to the use of `msm` that have not been explored or show-cased in this work; please refer to Jackson (2011) for complete detail of the full range of capabilities of the `msm`. Other packages for R were indispensable for the entire exercise. These include `Hmisc` (Harrell, 2014a), `rms` (Harrell, 2014b), `knitr` (Yihui, 2014), and `xtable` (Dahl, 2014).

Data Description and Summaries

Description

```
latex(describe(oneobs, descript="Distribution of baseline variables in the BRAIN−ICU data"),
    file="", size="smaller")
```

Distribution of baseline variables in the BRAIN-ICU data
13 Variables   826 Observations

id : Patient ID

	n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
	826	0	826	11590	11042	11084	11207	11414	12099	12222	12264

```
lowest : 11001 11002 11003 11004 11005
highest: 12301 12302 12303 12304 12305
```

age.enroll : Age at enrollment

	n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
	821	5	809	60.18	32.57	39.73	50.87	61.24	70.74	78.24	81.81

```
lowest : 18.60 19.04 19.12 19.12 19.55
highest: 91.60 92.12 93.08 98.28 98.92
```

sex.pp : Sex

	n	missing	unique
	821	5	2

```
Male (420, 51%), Female (401, 49%)
```

edu : Years of education

	n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
	796	30	20	12.32	8	9	12	12	14	16	18

```
lowest :  0  1  3  4  5, highest: 15 16 17 18 20
```

charlson.score : Charlson score

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	14	2.636	0	0	1	2	4	6	7

	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Frequency	145	148	167	127	97	42	43	18	13	8	5	5	1	2
%	18	18	20	15	12	5	5	2	2	1	1	1	0	0

---

iqcode.score.e: IQCODE score at enrollment (missing -> 3)

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	36	3.122	3.000	3.000	3.000	3.000	3.125	3.438	3.812

```
lowest : 1.625 2.688 2.750 2.812 2.875
highest: 4.562 4.625 4.688 4.750 4.812
```

---

apoe : ApoE type

n	missing	unique
583	243	6

	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Frequency	3	59	14	356	132	19
%	1	10	2	61	23	3

---

e4.type : ApoE E4 type

n	missing	unique
583	243	2

E4- (418, 72%), E4+ (165, 28%)

---

stroke.risk : Framingham stroke risk score

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	31	10.32	1	3	6	9	14	19	22

```
lowest :  0  1  2  3  4, highest: 26 27 28 29 30
```

---

num.apache : APACHE II at ICU admission

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	45	25.4	12	14	19	25	31	36	40

```
lowest :  2  6  7  8  9, highest: 45 46 47 50 56
```

---

apache.aps : APACHE APS at enrollment

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	44	21.15	9	11	15	21	26	31	35

```
lowest :  0  1  2  3  4, highest: 39 40 42 45 48
```

---

sofa : SOFA at enrollment

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	22	9.501	4	5	7	9	12	14	15

```
lowest :  0  2  3  4  5, highest: 18 19 20 21 22
```

---

sofa.mod : Modified SOFA (omits GCS) at enrollment

n	missing	unique	Mean	.05	.10	.25	.50	.75	.90	.95
821	5	19	6.73	2	3	5	7	9	11	12

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Frequency	6	14	31	64	90	106	98	95	87	75	68	41	20	10	6	6	1	2	1
%	1	2	4	8	11	13	12	12	11	9	8	5	2	1	1	1	0	0	0

The distribution of the baseline variables in the analysis dataset is provided above. However, Table 1 provides additional summaries and is inclusive of variables measured more than once during the study.

Summaries

```
s1 ←summary(∼ iqcode.score.e + charlson.score + stroke.risk + sex.pp + age.enroll +
    mean.hal.icu + mean.prop.icu + cum.sevsepsis + mean.benz.icu + mean.op.new.icu +
    mean.dex.icu + cum.onstatin + cum.offstatin + cum.hypoxic.del + sofa + sofa.mod +
    num.apache + apache.aps
                , data=icuDat
                , method="reverse"
                )
latex(s1, file =""
        , where="!h"
        , exclude.missing=TRUE
        , digits=2
        , size="smaller"
        , landscape = FALSE
        , prmsd = TRUE
        , middle.bold=TRUE
        , booktabs=TRUE
        , caption = "Summary of variables in the \\textbf{BRAIN−ICU} analysis data"
        , label="MyTable1")
```

Table 1: Summary of variables in the **BRAIN-ICU** analysis data

IQCODE score at enrollment (missing -> 3)	3.00 **3.00** 3.12 (3.11±0.28)
Charlson score	1.0 **2.0** 4.0 (2.5±2.2)
Framingham stroke risk score	5.0 **9.0** 14.0 (10.1± 6.2)
sex.pp : Female	47% (5324)
Age at enrollment	51 **61** 71 (60±15)
Cumulative mean dose of haloperidol in ICU	0.00 **0.00** 0.18 (1.02±3.19)
Cumulative mean dose of propofol in ICU	0 **12** 851 (717±1337)
Cumulative days of severe sepsis	0.0 **3.0** 7.0 (4.5±5.2)
Cumulative mean dose of benzodiazepines in ICU (MDZ = 2.5*LZ = 0.5*DZM)	0.0 **1.1** 10.3 (13.9±33.1)
Cumulative mean dose of opiates in ICU (fentanyl = morphine*50 = hydromorphine*7.5)	24 **492** 1575 (1132±1615)
Cumulative mean dose of dexmedetomidine in ICU	0 **0** 0 (57±326)
Cumulative days on statins (in hospital)	0.0 **0.0** 0.0 (1.5±3.9)
Cumulative days off statins (in hospital)	2.0 **7.0** 13.0 (8.4± 7.4)
Cumulative days of hypoxic delirium	0.0 **1.0** 3.0 (2.0±2.9)
SOFA at enrollment	7.0 **10.0** 12.0 (9.7± 3.5)
Modified SOFA (omits GCS) at enrollment	5.0 **7.0** 9.0 (6.9±3.0)
APACHE II at ICU admission	20.0 **26.0** 31.0 (25.9± 8.6)
APACHE APS at enrollment	16 **21** 27 (22± 8)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. Numbers after percents are frequencies.

Data Reduction

Hierarchical Clustering

```
vc←varclus(∼ sex.pp + age.enroll + edu + charlson.score + iqcode.score.e + stroke.risk +
    sofa + sofa.mod + num.apache + apache.aps, sim = "hoeffding", data=oneobs)
plot(vc) # n = 826
```
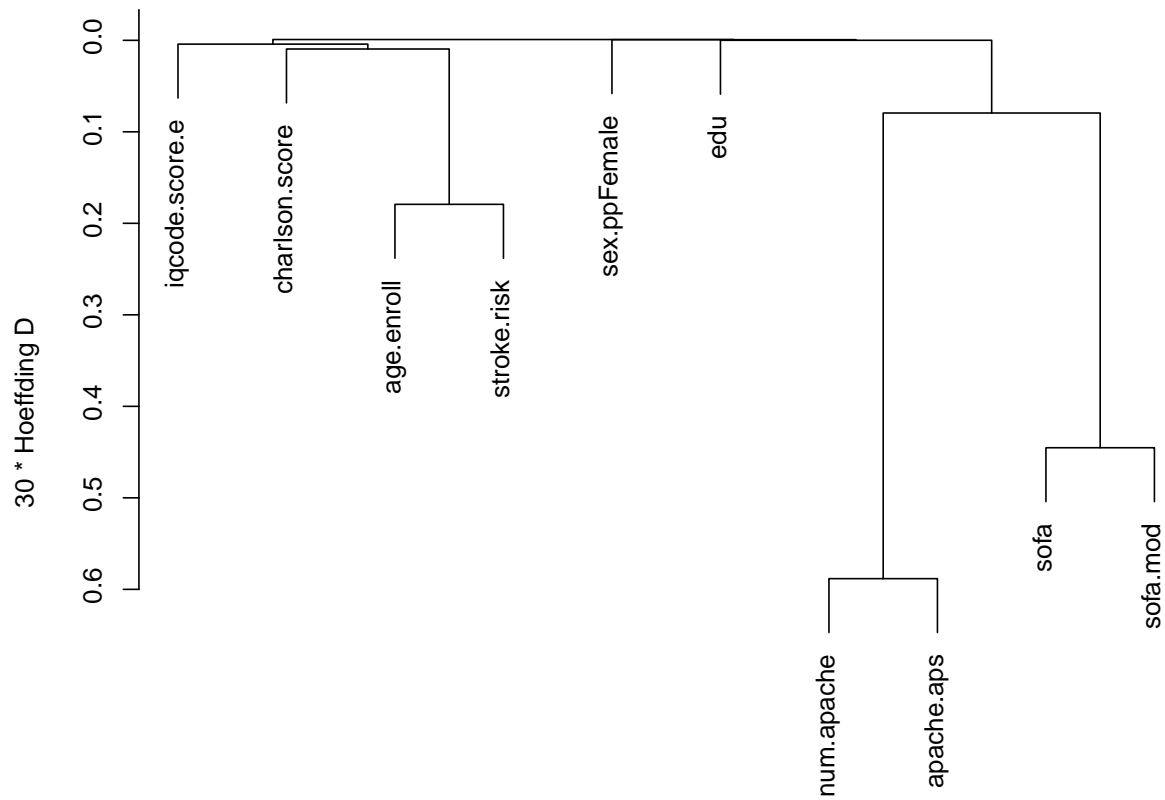

Figure 2: Hierarchical clustering of candidate predictors using Hoeffding's D as a similarity measure (n=826)

An examination of the inter-relationship among variables is demonstrated in Figure 2 using hierarchical variable clustering based on Hoeffding's D as a similarity measure. Evidently APACHE II at ICU admission (`num.apache`) and APACHE APS at enrollment (`apache.aps`) are strongly related, which is not surprising given the common components that comprise both scoring schemes. Similarly, there is an apparent strong

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similarity between SOFA (`sofa`) and the modified SOFA (`sofa.mod`) scores at enrollment. In general, in the absence of an overriding reason, variables that share strong similarities should not be the same model. Of note, the cluster analysis does not demonstrate any strong relationship among other variables. However, added objectivity regarding the choice of variables for model building can be achieved via redundancy analysis.

Redundancy Analysis

```
redun(~ sex.pp + age.enroll + edu + charlson.score + iqcode.score.e + stroke.risk +   sofa +
    sofa.mod + num.apache + apache.aps, data=oneobs, r2=0.8, nk=5)
```

```
Redundancy Analysis

redun(formula = ~sex.pp + age.enroll + edu + charlson.score +
    iqcode.score.e + stroke.risk + sofa + sofa.mod + num.apache +
    apache.aps, data = oneobs, r2 = 0.8, nk = 5)

n: 796   p: 10    nk: 5

Number of NAs:    30
Frequencies of Missing Values Due to Each Variable
        sex.pp      age.enroll              edu charlson.score iqcode.score.e     stroke.risk
             5               5               30              5              5               5
          sofa        sofa.mod      num.apache      apache.aps
             5               5               5              5


Transformation of target variables forced to be linear

R^2 cutoff: 0.8   Type: ordinary

R^2 with which each variable can be predicted from all other variables:

        sex.pp      age.enroll              edu charlson.score iqcode.score.e     stroke.risk
         0.092           0.736            0.077          0.237          0.089           0.542
          sofa        sofa.mod      num.apache      apache.aps
         0.936           0.906            0.977          0.976

Rendundant variables:

num.apache sofa

Predicted from variables:

sex.pp age.enroll edu charlson.score iqcode.score.e stroke.risk sofa.mod apache.aps

  Variable Deleted   R^2 R^2 after later deletions
1      num.apache 0.977                     0.977
2            sofa 0.936
```

The results of the redundancy analysis clearly demonstrates the presence of redundant variables: `sofa` and `num.apache` can be predicted with high coefficient of determination ($R^2 \geq 0.8$) from all other variables in the equation. This makes the case that we can eliminate them and employ all other variables as potential predictors during modeling building. The results of the redundancy analysis affirms the conclusions drawn

from the above hierarchical clustering analysis. In addition the large sample size relative to the candidate predictors provide adequate degrees of freedom to incorporate all these non-redundant candidate predictors, as deemed fit, during modeling.

Graphical Evaluation

The distribution of health states in relation to baseline modified SOFA scores, baseline APACHE APS scores, and age at enrollment are explored graphically using extended box plots. Regarding the extended boxes, the left and right margins represent the 0.05 and 0.95 quantiles, and the black dots within the boxes represents the mean. Three vertical lines completely bisect the extended boxes of which the central vertical line represents the median (0.5 quantile) while the lateral lines depict the 0.25 and 0.75 quantiles. The 0.375 and 0.625 quantiles are delineated by two indentations that reside midway between the median and the 0.25 and 0.75 quantiles respectively. Similarly, the 0.125 quantile is depicted by the indentation midway between the 0.5 and 0.25 quantiles while the 0.875 quantile is represented by the indentation between the 0.75 and 0.95 quantiles.

Modified SOFA at enrollment vs. transition states: Overall

```
p2a <- bpplotM(sofa.mod ~ status.today.imp, data=icuDat, nloc="left")
p2a
```
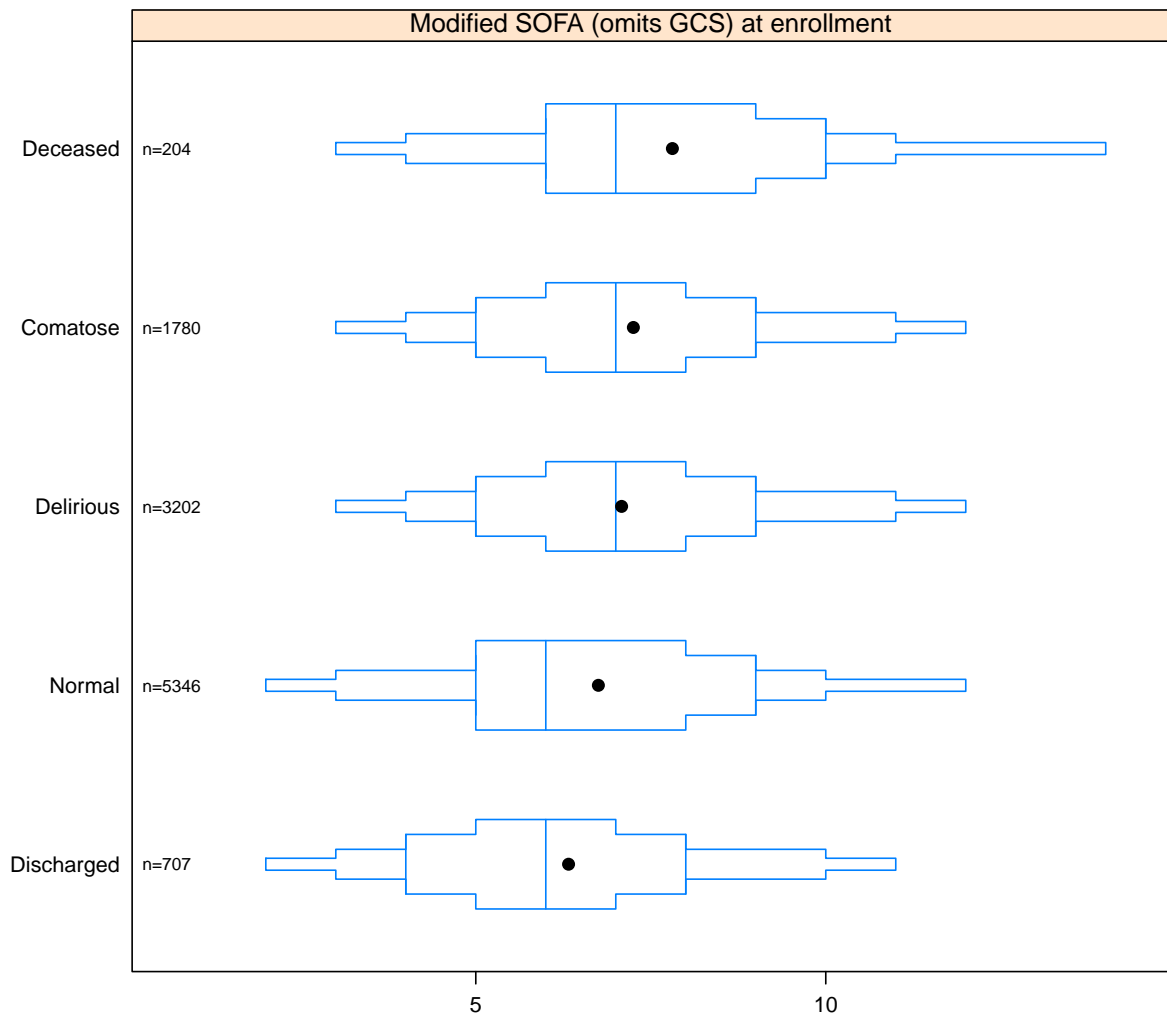
Figure 3: Modified SOFA at enrollment vs. health states: Overall

Modified SOFA at enrollment vs. transition states: By sex

```
p2b ← bpplotM(sofa.mod ∼ status.today.imp∗sex.pp, data=icuDat, nloc="left")
p2b
```


Figure 4: Modified SOFA at enrollment vs. health states: By sex

Conventional wisdom indicates that death, coma, and delirium, in decreasing order, are undesirable health states. In this context, the plots in Figures 3 and 4 indicate a trend towards higher mean and median SOFA scores with increasing severity of health state. This pattern remains apparent when stratified by sex with no remarkable distinction between the sexes.

APACHE APS at enrollment vs. transition states: Overall

```
p3a <- bpplotM(apache.aps ~ status.today.imp, data=icuDat, nloc="left")
p3a
```


Figure 5: APACHE APS at enrollment vs. health states: Overall

APACHE APS at enrollment vs. transition states: By sex

```
p3b ← bpplotM(apache.aps ∼ status.today.imp∗sex.pp, data=icuDat, nloc="left")
p3b
```


Figure 6: APACHE APS at enrollment vs. health states: By sex

Figures 5 and 6 illustrate health states versus APACHE distribution patterns similar to those observed for SOFA scores.

Age at enrollment vs. transition states: Overall

```
p4a <- bpplotM(age.enroll ~ status.today.imp, data=icuDat, nloc="left")
p4a
```


Figure 7: Age at enrollment vs. health states: Overall

Age at enrollment vs. transition states: By sex

```
p4b ← bpplotM(age.enroll ∼ status.today.imp∗sex.pp, data=icuDat, nloc="left")
p4b
```
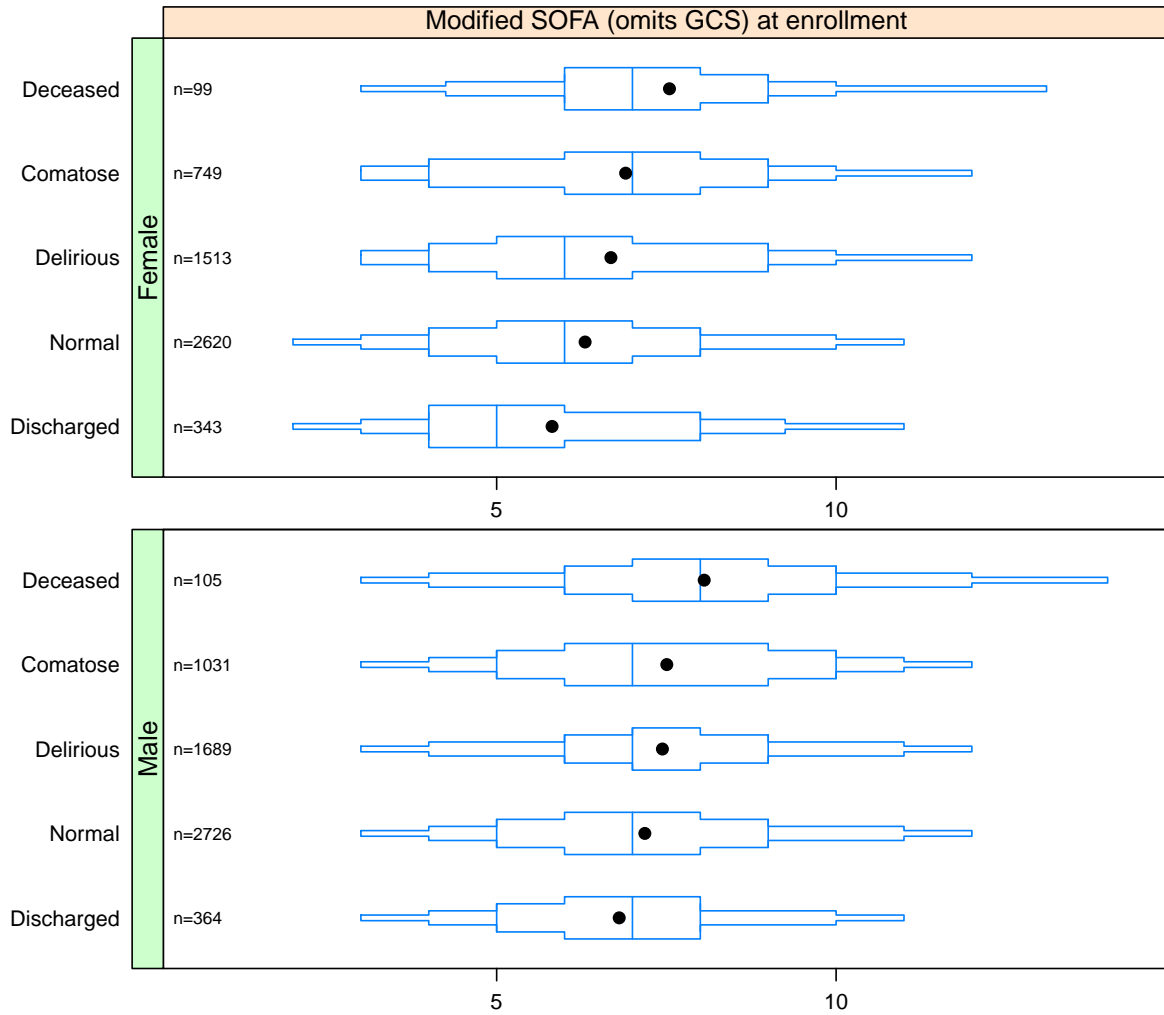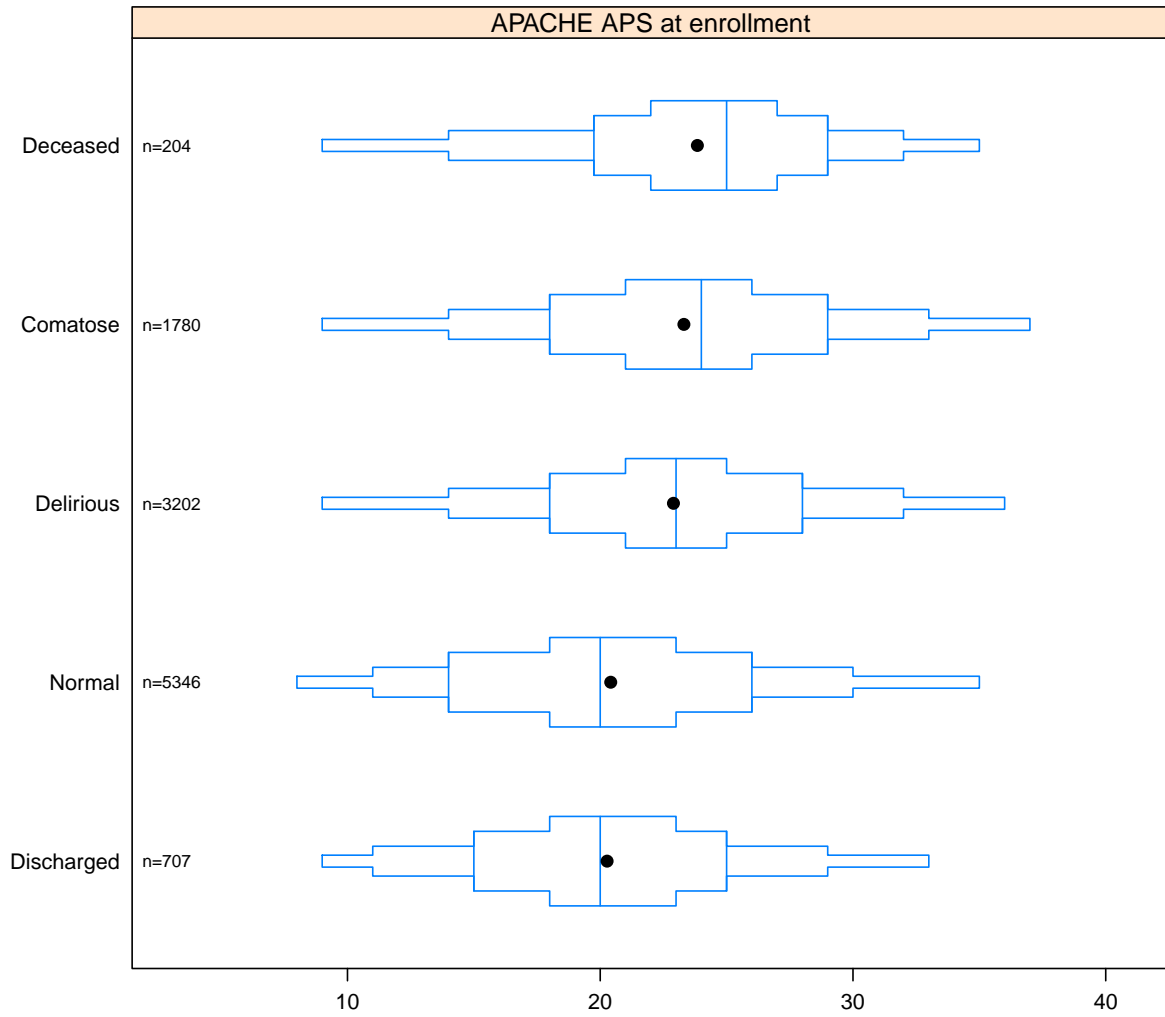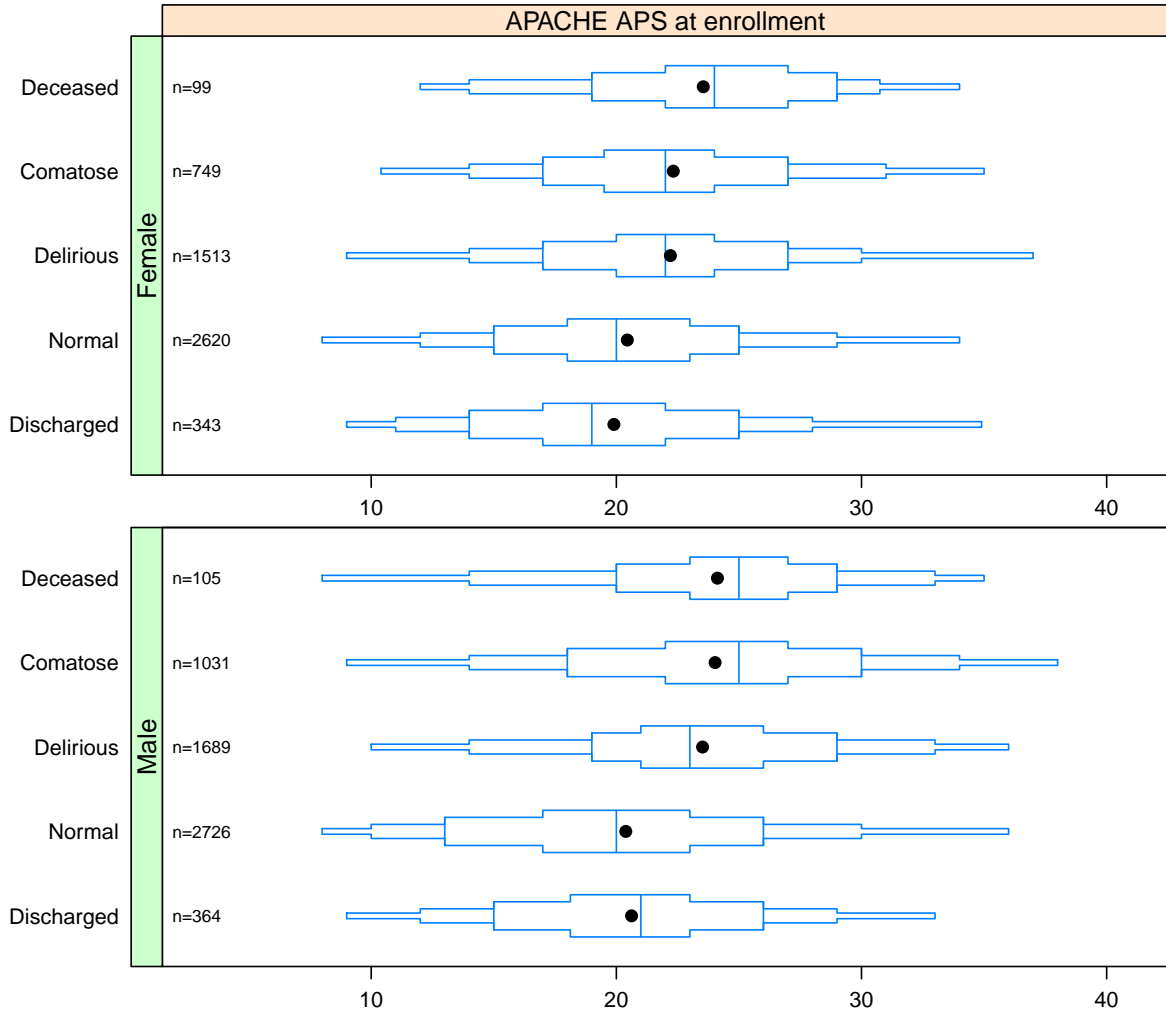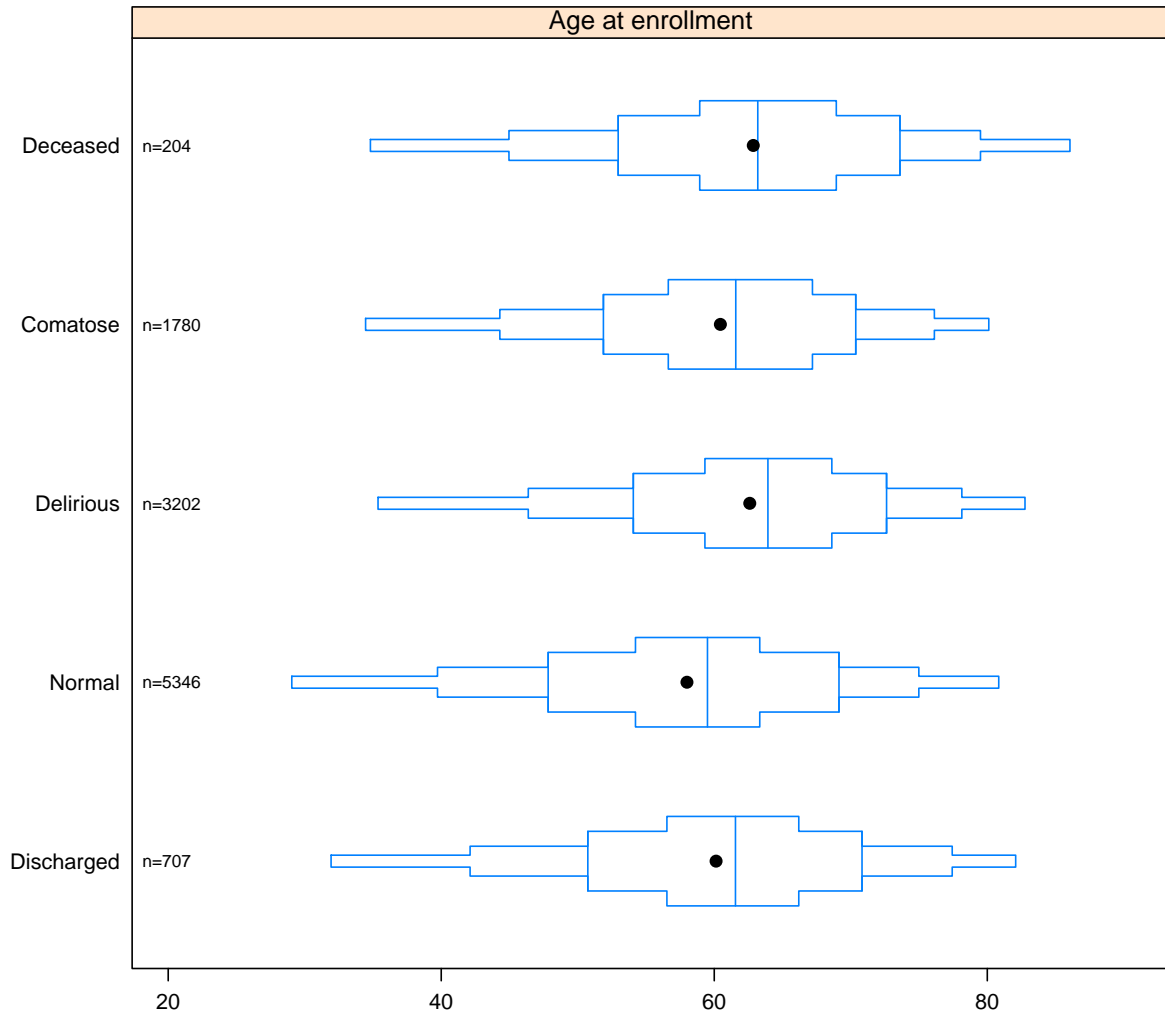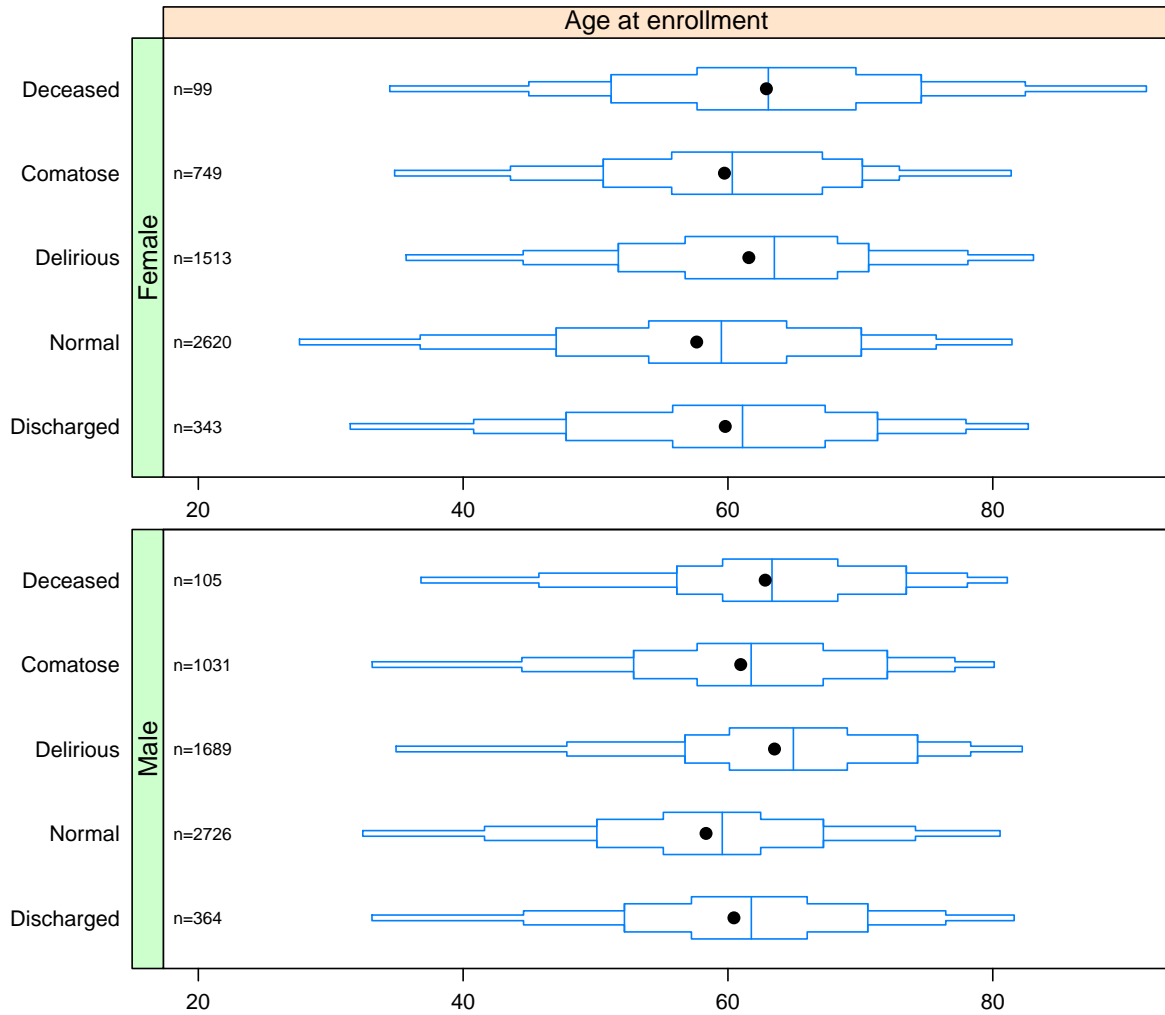

Figure 8: Age at enrollment vs. health states: By sex

Figures 7 and 8 suggest that the distribution of health states by age is devoid of any distinct pattern even when stratified by sex.

Modeling

Health State Transitions and Matrix Specification

State Transitions

```
t4 ← statetable.msm(states
                    , id
                    , data=icuDat
                    )
rownames(t4) ← colnames(t4) ← c("Discharged", "Normal", "Delirious", "Comatose", "Deceased
    ")
print(xtable(t4,
             caption = "Frequency table of health states in the \\textbf{BRAIN-ICU}
             Data.",
             label="MyTable4"),
             include.rownames=TRUE,
             format.args=list(big.mark=","))
```

	Discharged	Normal	Delirious	Comatose	Deceased
Discharged	136	0	0	0	0
Normal	499	4,340	351	94	11
Delirious	58	676	2,071	344	39
Comatose	14	100	543	1,023	93
Deceased	0	0	0	0	60

Table 2: Frequency table of health states in the **BRAIN-ICU** Data.

Table 2 summarizes the multi-state data as a frequency table of pairs of transition states. It captures the reality that death is an absorbing state from which no subject emerges. However, in addition it delineates that the discharged state in the study represents an exit from ICU stay, and thus the absence of any transition from the discharged state to any of the other states.

Transition Matrix

The transition matrix for the allowed state transitions in this analysis of continuous-time Markov chain is delineated in Table 3. Note that study design and/or assumptions specific to an analytical objective serve to determine the matrix specification of allowed transitions. Zero entries in the transition matrix denote were instantaneous transitions are not allowed from state r to state s. The non-zero entries, in this instance the conventional 1, indicate allowed transitions. The values in the matrix are by no means the actual transition values, rather they just specify the matrix structure.

```
Q ← rbind(c(0, 0, 0, 0, 0)
          , c(1, 0, 1, 1, 1)
          , c(1, 1, 0, 1, 1)
          , c(1, 1, 1, 0, 1)
          , c(0, 0, 0, 0, 0)
          )
rownames(Q) ← colnames(Q) ← c("Discharged", "Normal", "Delirious", "Comatose", "Deceased")
```

```
print(xtable(Q
            , caption = "Matrix specification of allowable transitions"
            , label="Q")
    , include.rownames=TRUE
    , format.args=list(big.mark=",")
    )
```

	Discharged	Normal	Delirious	Comatose	Deceased
Discharged	0.00	0.00	0.00	0.00	0.00
Normal	1.00	0.00	1.00	1.00	1.00
Delirious	1.00	1.00	0.00	1.00	1.00
Comatose	1.00	1.00	1.00	0.00	1.00
Deceased	0.00	0.00	0.00	0.00	0.00

Table 3: Matrix specification of allowable transitions

```
# generate crude intitial transition values
options(digits=6)
Q.crude <- crudeinits.msm(states ~ study.day
                         , id
                         , data=icuDat
                         , qmatrix=Q
                         )
print(xtable(Q.crude
      , caption = "Illustration of crude initial transition values"
      , label="Q.crude"))
```

	Discharged	Normal	Delirious	Comatose	Deceased
Discharged	-0.00	0.00	0.00	0.00	0.00
Normal	0.09	-0.18	0.07	0.02	0.00
Delirious	0.02	0.21	-0.35	0.11	0.01
Comatose	0.01	0.06	0.31	-0.42	0.05
Deceased	0.00	0.00	0.00	0.00	-0.00

Table 4: Illustration of crude initial transition values

Table 4 is for instructive purposes to demonstrate crude initial transition values generated using the above-specified transition matrix Q. These crude estimates still provide some insight. For example, the transition intensities indicate that a patient in a normal state will probably transition to a discharged state than to either a delirious, comatose, or deceased state (transition intensities: 0.09, 0.07, 0.02, and 0.00, respectively). Please see 25 for more details about the interpretation of transition intensities and the negative diagonal entries. In the context various models herein below, we will revisit the insight that transition intensities can provide. The main point of illustrating the transition matrix in Table 3 and crude initial values in Table 4 is that the model likelihood function is maximized by numerical optimization approaches using that matrix and such initial transition values. However, in the actual modeling process below we allow initial transition values to be generated automatically using the `msm` function with a call to `gen.inits=TRUE` argument. This approach is better because it tends to provide more sensible initial values, which become important for

achieving convergence during optimization of unstable models with a flat or multi-modal likelihood.

Model Fitting: Simple Model

```
#m1: simple bidirectional model
icuDat <- icuDat[order(icuDat$id, icuDat$study.day), ]
m1 <- msm(states ~ study.day
          , subject = id
          , data=icuDat
          , qmatrix = Q
          , death = TRUE
          , method = "BFGS"
          , gen.inits = TRUE
          )
# The computer time required for this invocation of the msm function was 1.60 secs. This was
    determineed using the system.time() function in R.
```

```
m1p <- print(m1, digits=5)
```

```
print(xtable(m1p), floating=FALSE)
```

	base.Estimate	base.L	base.U
Normal - Discharged	0.10	0.09	0.11
Normal - Normal	-0.21	-0.23	-0.20
Normal - Delirious	0.09	0.08	0.10
Normal - Comatose	0.02	0.01	0.03
Normal - Deceased	0.00	0.00	0.21
Delirious - Discharged	0.01	0.00	0.02
Delirious - Normal	0.29	0.27	0.32
Delirious - Delirious	-0.49	-0.52	-0.46
Delirious - Comatose	0.18	0.16	0.21
Delirious - Deceased	0.01	0.00	0.02
Comatose - Discharged	0.01	0.00	0.02
Comatose - Normal	0.01	0.00	0.06
Comatose - Delirious	0.50	0.46	0.55
Comatose - Comatose	-0.59	-0.63	-0.55
Comatose - Deceased	0.07	0.06	0.09

Table 5: Simple bidirectional model: Baseline transition intensities. L and U represent lower and upper 95% confidence limits, respectively

The simple model is a base model that tells us how likely a patient is to experience the transition to a state (i.e. an event) given his/her current state. The parameters of the simple bidirectional model are transition intensities (or rates, or hazards), they are not probabilities. In the model specification chapter on page 7 we indicated that according to Jackson (2011) the transition intensities represent the instantaneous risk of moving from state r to state s. We also pointed out that the diagonal entries q_{rr} of the resulting matrix of these intensities are defined by $q_{rr} = -\sum_{s \neq r} q_{rs}$ i.e. minus the sum of the rest of the row (page 8). In the context of the results delineated in Table 5, a person in the normal state has an instantaneous risk of 0.1 for transition to a discharged state. Note that -0.21 is a diagonal entry that is minus the sum

of $0.10, 0.09, 0.02, \& 0.00$, thus consistent with the above definition; these diagonal entries deal with the same-state situation and are not intensities. The results also suggest that a patient in a delirious state has a similar transition intensity (0.01) for either discharge or death. This finding is not inconsistent with the precarious nature of delirium as a medical condition. Similarly, the model demonstrates that once a patient is in a comatose state he/she is more likely to become deceased than to transition to a normal or discharged state. Additional insight can be derived from the transition intensities. For instance, a person in the normal state is about 5 (0.10/0.02) times more likely to transition to a discharged compared to comatose state. This inference is determined from the ratio of normal-discharged and normal-comatose transition intensities (Table 5). Similar conclusions or inferences can be deduced based on the interest or curiosity of an investigator. However, non-experts would be better served by knowing the mean time a patient spends in each transient state (sojourn time) and transition probabilities, both of which are available via the extractor functions in the `msm package` as demonstrated on pages 32 and 32.

Model Fitting: Covariate Models

We explored two covariate models with the intent to determine whether the combined presence of SOFA and APACHE scores improves model performance.

Reduced Covariate Model

```
m2 <- msm(states ~ study.day
         , subject = id
         , data=icuDat
         , qmatrix = Q
         , death = 5
         , gen.inits = TRUE
         , covariates = ~ sofa.mod
         , method = "BFGS"
         , control = list(fnscale = 17000
                        , maxit = 10000)
         )
# The computer time required for this invocation of the msm function was 71.4 secs. This was
    determineed using the system.time() function in R.

m2p <- print(hazard.msm(m2)
       , digits=5
       , zero.print = "."
       )
```

From the reduced covariate model in Table 6, a unit increase in SOFA score was significantly associated with a decrease in the risk of transitioning from either normal to discharged (5% decrease) or delirious to normal (6% decrease), and a marginally significant decrease in the risk of transition from a comatose to delirious state (3% decrease). Similarly, each unit increase in SOFA score was significantly associated with

```
print(xtable(m2p$sofa.mod), floating=FALSE)
```

	HR	L	U
Normal - Discharged	0.95	0.93	0.98
Normal - Delirious	0.99	0.96	1.03
Normal - Comatose	0.96	0.87	1.05
Normal - Deceased	0.98	0.59	1.61
Delirious - Discharged	0.99	0.77	1.28
Delirious - Normal	0.94	0.92	0.97
Delirious - Comatose	0.98	0.95	1.02
Delirious - Deceased	1.37	1.11	1.70
Comatose - Discharged	0.93	0.69	1.27
Comatose - Normal	0.72	0.40	1.28
Comatose - Delirious	0.97	0.94	1.00
Comatose - Deceased	1.02	0.96	1.10

Table 6: Reduced covariate model: Hazard ratios associated with SOFA score. Baseline transition intensities. L and U represent lower and upper 95% confidence limits, respectively

37% (line 8 in Table 6) increased hazard of transition to death from a delirious state.

Full Covariate Model

```
m3 ← msm(states ∼ study.day
          , subject = id
          , data=icuDat
          , qmatrix = Q
          , death = 5
          , gen.inits = TRUE
          , covariates = ∼ apache.aps + sofa.mod + age.enroll
          , method = "BFGS"
          , control = list(fnscale = 17000
                          , maxit = 10000)
          )
# The computer time required for this invocation of the msm function was 3466.8 secs. This
    was determineed using the system.time() function in R.
```

```
m3p ← print(hazard.msm(m3)
       , digits=5
       , zero.print = "."
       )
```

Table 7 delineates the hazard ratios associated with APACHE score in the full covariate model. A unit increase in APACHE score was significantly associated with 2% decrease in the risk of transition from delirious to normal state. Similarly there was 1% increase in the risk of transition from normal to delirious state for each unit increase in APACHE score, although this association was marginally significant.

Table 8 provides the hazard ratios associated with SOFA score in the full covariate model. The already noted impact of SOFA score in the reduced model (Table 6) was preserved although the effect on the hazard of transition from a comatose to delirious state was no longer significant. Likewise, each unit increase in

```
print(xtable(m3p$apache.aps), floating=FALSE)
```

	HR	L	U
Normal - Discharged	1.00	0.99	1.02
Normal - Delirious	1.01	1.00	1.03
Normal - Comatose	0.99	0.95	1.03
Normal - Deceased	1.14	0.96	1.37
Delirious - Discharged	0.98	0.89	1.08
Delirious - Normal	0.98	0.97	0.99
Delirious - Comatose	0.99	0.98	1.01
Delirious - Deceased	0.90	0.76	1.06
Comatose - Discharged	1.07	0.67	1.70
Comatose - Normal	1.03	0.87	1.23
Comatose - Delirious	0.99	0.98	1.01
Comatose - Deceased	0.99	0.96	1.02

Table 7: Full covariate model: Hazard ratios associated with APACHE score. Baseline transition intensities. L and U represent lower and upper 95% confidence limits, respectively

```
print(xtable(m3p$sofa.mod), floating=FALSE)
```

	HR	L	U
Normal - Discharged	0.95	0.92	0.98
Normal - Delirious	0.98	0.94	1.02
Normal - Comatose	0.96	0.87	1.06
Normal - Deceased	1.04	0.54	2.02
Delirious - Discharged	1.04	0.83	1.31
Delirious - Normal	0.96	0.93	0.99
Delirious - Comatose	1.00	0.95	1.04
Delirious - Deceased	1.88	0.99	3.58
Comatose - Discharged	0.91	0.56	1.47
Comatose - Normal	0.72	0.46	1.11
Comatose - Delirious	0.98	0.95	1.02
Comatose - Deceased	1.04	0.95	1.14

Table 8: Full covariate model: Hazard ratios associated with SOFA score. Baseline transition intensities. L and U represent lower and upper 95% confidence limits respectively

SOFA score was associated with 88% (HR 1.88, 95% CI 0.99 to 3.58; line 8 in Table 8) increased hazard of transition to death from a delirious state.

Table 9 demonstrates the hazard ratios associated with age in the full covariate model. In general, a unit increase in enrollment age was associated with a small $(1 - 2\%)$ but marginally significant increase in the hazard of transition from a normal to delirious or comatose states, comatose to delirious or deceased states, and a decrease in the risk of transition from a delirious to normal state.

```
print(xtable(m3p$age.enroll), floating=FALSE)
```

	HR	L	U
Normal - Discharged	1.00	1.00	1.01
Normal - Delirious	1.01	1.01	1.02
Normal - Comatose	1.02	1.00	1.04
Normal - Deceased	0.98	0.85	1.14
Delirious - Discharged	1.07	1.01	1.12
Delirious - Normal	0.99	0.98	0.99
Delirious - Comatose	1.01	1.00	1.01
Delirious - Deceased	0.98	0.89	1.07
Comatose - Discharged	0.99	0.88	1.12
Comatose - Normal	1.13	0.98	1.31
Comatose - Delirious	1.01	1.00	1.02
Comatose - Deceased	1.02	1.00	1.03

Table 9: Full covariate model: Hazard ratios associated with age. Baseline transition intensities. L and U represent lower and upper 95% confidence limits respectively

Model Comparisons

Baseline, Reduced, and Full Covariate Models

To assess the contribution of covariates and inform our decision on which model to employ in subsequent analysis, we compared the baseline, reduced, and full covariate multi-state models using the likelihood ratio test.

```
lrtest.msm(m1, m2); lrtest.msm(m2, m3)
```

```
   -2 log LR df           p
m2    52.07 12 0.0000006014
```

```
   -2 log LR df         p
m3    102.8 24 9.849e-12
```

The likelihood ratio tests indicate that the introduction of covariates significantly improved model performance. Furthermore, the full covariate model is demonstrably superior to the reduced covariate model as evidenced by the result from the comparison of their likelihood functions. In this context, we henceforth concentrate on the full model with a focus on the impact of the covariates on patient health state transitions. In addition, we will consider a number of extractor functions, which provide added information regarding the study participants. These extractor functions include transition intensity and probability matrices, mean sojourn times, and probability of the next state. Finally, we evaluate the survival plots for the full covariate model as well as its assessment using prevalence plots. However before proceeding with looking evaluating the extractor functions, it is instructive to compare our full covariate model to a traditional

modeling approach.

Full Covariate Model vs. Binary Logistic Model

```
at1 <- select(icuDat, id, status.today.imp, sofa.mod, apache.aps, age.enroll)
at2 <- at1[at1$status.today.imp %in% c("Deceased"), ] # only deceased 204
at3 <- at1[(at1$status.today.imp =="Normal" | at1$status.today.imp=="Discharged"), ]
at4 <- at3[which(!duplicated(at3$id)), ]
at5 <- rbind(at2, at4)
at5$binary <- ifelse(at5$status.today.imp=="Deceased", 1, 0) #binary outcome meassure: Death
    = 1, otherwise = 0
b <- lrm(binary~sofa.mod + apache.aps + age.enroll, data=at5)
b
```

```
Logistic Regression Model

lrm(formula = binary ~ sofa.mod + apache.aps + age.enroll, data = at5)

                         Model Likelihood      Discrimination     Rank Discrim.
                           Ratio Test              Indexes            Indexes
Obs                 890   LR chi2     43.69   R2        0.073    C       0.647
 0                  686   d.f.            3   g         0.613    Dxy     0.294
 1                  204   Pr(> chi2) <0.0001  gr        1.846    gamma   0.296
max |deriv| 0.000000007                       gp        0.104    tau-a   0.104
                                              Brier     0.168


          Coef     S.E.    Wald Z Pr(>|Z|)
Intercept  -3.6084 0.4520  -7.98  <0.0001
sofa.mod    0.0976 0.0314   3.11   0.0019
apache.aps  0.0334 0.0122   2.74   0.0062
age.enroll  0.0156 0.0056   2.78   0.0054
```

```
# -2*logLik(m1) # simple bidirectional multi-state model
# -2*logLik(m2) # reduced covariate multi-state model: sofa.mod only
# -2*logLik(m3) # full covariate multi-state model: sofa.mod + apache.aps + age.enroll
# -2*logLik(b)  # Binary (dead or alive) logistic model: sofa.mod + apache.aps + age.enroll
lrtest.msm(m1, m3) # comparing full covariate model vs base model to obtian lR Chisq for
    full model.
```

```
   -2 log LR df         p
m3    154.9 36 1.11e-16
```

The binary logistic model is a mainstream approach that can be used to characterize the impact of the chosen covariates on the binary outcome (dead or alive), but it falls short of all the additional information that the multi-state model provides. For instance, the logistic model demonstrates that the overall impact of APACHE score is significant and provides understanding regarding the relevance of APACHE to mortality. Furthermore, it provides knowledge of the impact of either SOFA score or age on the binary outcome measure. Thus the binary model is limited in that it sheds light only on mortality. However, we were privileged to a significant degree of added insight from the full covariate multi-state model. This reality might become more crucial when assessing therapeutic interventions for signals of efficacy and/or effectiveness not only with respect to mortality but to other endpoints that are relevant to the overall well-being of patients. In addition, it is also apparent from the likelihood ratio chi square statistics that the full multi-state model

$(\text{LR}\chi^2_{36} : 154.9)$ is superior to the binary logistic model $(\text{LR } \chi^2_3 : 43.69)$ indicating that there is real covariate information about states other than death.

Extractor Functions

Transition Intensity Matrix

```
# transition intensity matrix for specified values
options(digits=1)
qmatrix.msm (m3, covariates = list (age.enroll=mean(icuDat$age.enroll), sex.pp="Male",
    sofa.mod=mean(icuDat$sofa.mod)))
```

```
          Discharged
Discharged 0
Normal      0.09186486 ( 0.0701017638402,    0.12038)
Delirious   0.00948678 ( 0.0006720997355,    0.13391)
Comatose    0.00083535 ( 0.0000000005776,1208.18478)
Deceased    0
          Normal
Discharged 0
Normal     -0.18490788 (-0.2576355554146,   -0.13271)
Delirious   0.43452637 ( 0.3345097596169,    0.56445)
Comatose    0.00124529 ( 0.0000012174053,    1.27381)
Deceased    0
          Delirious
Discharged 0
Normal      0.06993300 ( 0.0487385689065,    0.10034)
Delirious  -0.66842913 (-0.9507728652918,   -0.46993)
Comatose    0.60667963 ( 0.4396422926142,    0.83718)
Deceased    0
          Comatose
Discharged 0
Normal      0.02308850 ( 0.0098277094807,    0.05424)
Delirious   0.21529665 ( 0.1420381969531,    0.32634)
Comatose   -0.69430563 (-1.0773964712205,   -0.44743)
Deceased    0
          Deceased
Discharged 0
Normal      0.00002152 ( 0.0000000176814,    0.02619)
Delirious   0.00911933 ( 0.0004893889552,    0.16993)
Comatose    0.08554536 ( 0.0407388416569,    0.17963)
Deceased    0
```

The transition intensity matrix and corresponding 95% confidence intervals capture the transition intensities for a male patient who has a mean age of 59.92 and a mean SOFA score of 6.92. In this example, a patient who is in the normal state and has the specified covariate values is more likely transition to a discharged state (transition intensity: 0.09) than to a delirious (transition intensity: 0.06) or comatose state (transition intensity: 0.02). This matrix serves to illustrate one of the unique features of multi-state models fitted using the `msm package`. The fact that specific covariate values can be specified allows for direct comparison of transition intensities of patient groups defined by specific covariate settings. In the context of an intervention study, this feature can provide remarkable insight into the efficacy or effectiveness of the intervention. Similarly, it is a good way to evaluate the impact of various covariate values on different groups of participants.

Transition Probability Matrix

```
options(digits=1)
# Fitted transition probability matrix P(t) over an interval t = 30 days
(pm3 <- pmatrix.msm(m3, t = 30, ci = "normal"))
```

```
           Discharged                     Normal
Discharged 1.00000 (1.000000,1.00000)  0
Normal     0.82096 (0.677766,0.88519)  0.06105 (0.026312,0.07047)
Delirious  0.73250 (0.565849,0.83758)  0.07778 (0.029082,0.08703)
Comatose   0.62828 (0.494019,0.79617)  0.07711 (0.023481,0.08731)
Deceased   0                           0
           Delirious                      Comatose
Discharged 0                           0
Normal     0.02785 (0.010257,0.03206)  0.01235 (0.003138,0.01445)
Delirious  0.03551 (0.011226,0.03981)  0.01574 (0.003961,0.01813)
Comatose   0.03522 (0.009181,0.03966)  0.01562 (0.003106,0.01810)
Deceased   0                           0
           Deceased
Discharged 0
Normal     0.07779 (0.049775,0.29009)
Delirious  0.13847 (0.088547,0.37118)
Comatose   0.24377 (0.141888,0.43436)
Deceased   1.00000 (1.000000,1.00000)
```

For this evaluation of transition probabilities we do not specify any specific covariate settings, thus the results represent transition probabilities with covariate values set to their means in the data. The estimated 30-day transition probability matrix depicts the probability of being in a particular state within the time period. For instance, a typical study patient who is in a normal state has a probability of ≈ 0.08 of being dead in 30 days. In contrast, a delirious study patient has a probability of ≈ 0.08 of being normal in 30 days, but a ≈ 0.14 probability of death within the time period. The confidence interval reported here required a computationally intensive process of drawing a random sample of size $n = 1000$ from the multivariate normal distribution of the maximum likelihood estimates and covariance matrix, and then transforming. Bootstrapped confidence intervals can also be obtained by specifying `ci = "boot"` in the `pmatrix.msm` argument.

Mean Sojourn Times

```
options(digits=3)
sojourn.msm(m3) # Mean soujourn times describes the average period in a single stay in a
    state.
```

```
          estimates    SE     L     U
Normal         4.74  0.160  4.44  5.07
Delirious      2.03  0.067  1.90  2.17
Comatose       1.72  0.069  1.59  1.86
```

Mean sojourn times (in days) represent the estimated times spent in each transient state r for a specified set of covariate values. In conjunction the probability of the next state (below), soujourn times intuitively

provide full definition of a continuous-time Markov model although without event sequencing information.

Probability of the Next State

```
pnext.msm(m3);options(digits=1) # The matrix of prob that the next state after r is state s,
    for each r and s.
```

```
          Discharged                     Normal
Discharged 0                             0
Normal     0.484147 (0.43022222,0.51559) 0
Delirious  0.011496 (0.00345275,0.03501) 0.610980 (0.55823017,0.64131)
Comatose   0.005829 (0.00008916,0.27541) 0.004211 (0.00007947,0.16939)
Deceased   0                             0
          Delirious                      Comatose
Discharged 0                             0
Normal     0.426035 (0.36582845,0.46223) 0.087936 (0.05980805,0.11871)
Delirious  0                             0.375699 (0.32979746,0.40697)
Comatose   0.864089 (0.55151511,0.88663) 0
Deceased   0                             0
          Deceased
Discharged 0
Normal     0.001881 (0.00002750,0.11006)
Delirious  0.001825 (0.00003126,0.08031)
Comatose   0.125871 (0.08026686,0.15075)
Deceased   0
```

As stated above, a knowledge of the probability of the next state in combination with an understanding of the sojourn times contribute to our intuitive understanding of the transition state model. Based on the full covariate model, the output from `pnext.msm function` indicates that in this study cohort a person in the normal state the highest probability for the next state is discharge. Similarly, when a patient is comatose the probability of the next state is highest for delirium (0.86) but also substantial for death (0.13).

Model Plots and Additional Assessment

Survival Plots

```
# plots of expected probability of survival against time from each transient state.
#plot(m1, main = "simple model: no covariates", legend.pos=c(4,0.2))
#plot(m2, main = "Reduced covariate model", legend.pos=c(4,0.2))
plot(m3, main ="Full covariate model", sub ="Legend: state 2 = normal, state 3 = delirious,
    state 4 = comatose", xlab= "Time in days", legend.pos=c(4,0.2))
```
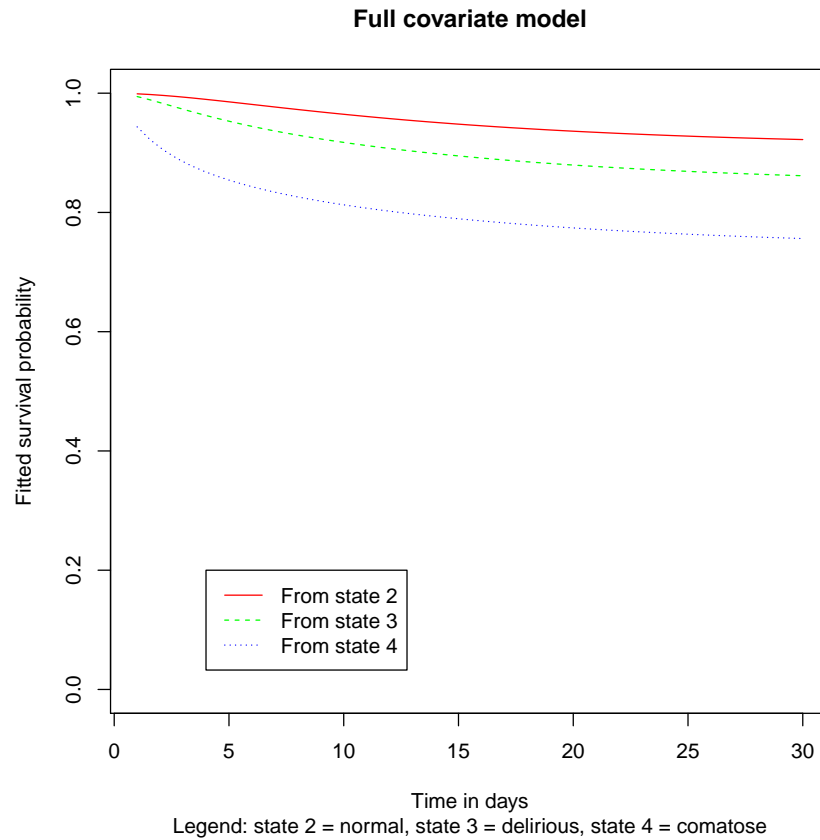
Full covariate model

Figure 9: Survival probability plot

The survival plots provide graphical evaluation of the probability of survival for patients by category of health states. While the same probabilities can be obtained directly from the transition probability matrix, a visual display helps depict differences in survival (defined as not entering the absorbing state) by category of health state. Figure 9 illustrates that the 30-day survival probabilities in BRAIN-ICU study population decreases with increasing health state severity.

Prevalence Plots

```
# prevalence plots: observed and expected prevalence
pr3 <- prevalence.msm(m3, times  = seq(0, 30, 2))
plot.prevalence.msm(m3, mintime=0, maxtime=30)
```
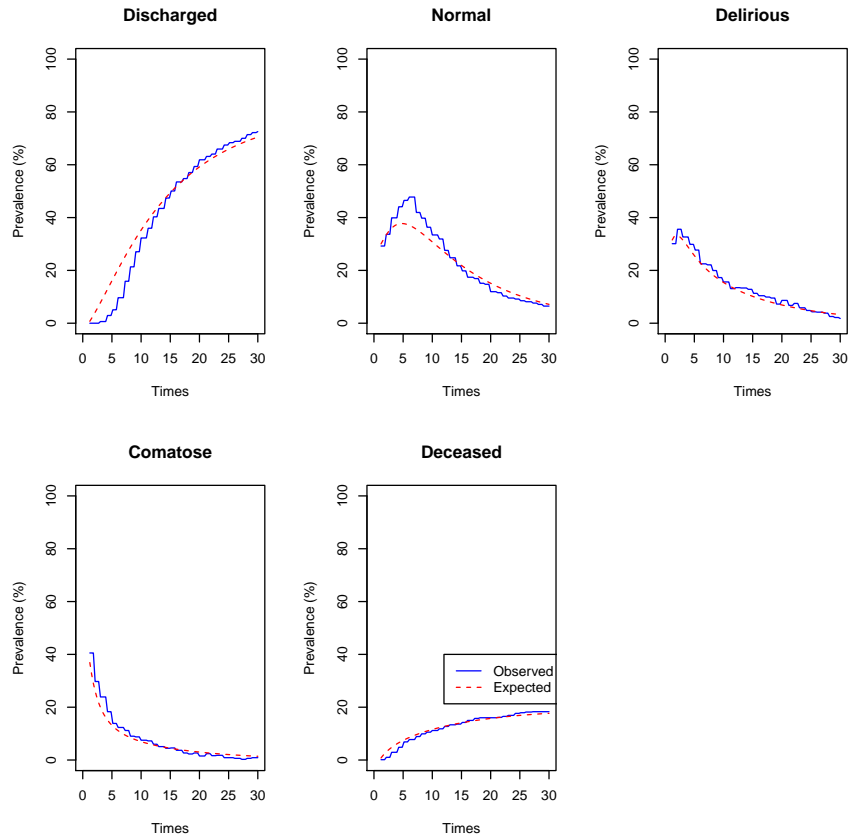
34

Figure 10: Prevalence plots from full covariate model

The prevalence plots provide an assessment of model performance by comparing expected and observed percentages for each health state. From the plots in Figure 10 it is apparent that the predicted number of patients who are discharged, normal, or comatose are overestimated until after the first 10 days of ICU stay. The expected and observed percentages for delirious and deceased patients are congruent throughout the time period. These prevalence plots indicate excellent model performance. In addition, from a practical perspective the model has reasonable clinical application because it is understandable that on average clinicians will be more informed about the possibility of a patient's discharge after some days of ICU care as opposed to very early in the course of admission.

Ratio of Transition Intensities

```
# Ratio of progression rate q23 from a normal to delirious state versus the corresponding
    recovery rate q32
options(digits=3)
qratio.msm(m3
          , ind1=c(3,2)
          , ind2=c(2,3)
          , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.1)
                            , sofa.mod=quantile(icuDat$sofa.mod, 0.1))
          #, ci="bootstrap"
          , cl = 0.95
          # , B=1000
          )
```

estimate	se	L	U
11.53	2.38	7.69	17.29

```
qratio.msm(m3
          , ind1=c(3,2)
          , ind2=c(2,3)
          , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.9)
                            , sofa.mod=quantile(icuDat$sofa.mod, 0.9))
          #, ci="bootstrap"
          , cl = 0.95
          # , B=1000
          )
```

estimate	se	L	U
3.550	0.993	2.052	6.141

```
# Ratio of progression rate q43 into a comatose state versus the corresponding recovery rate
    q34
options(digits=3)
qratio.msm(m3
          , ind1=c(4,3)
          , ind2=c(3,4)
          , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.1)
                            , sofa.mod=quantile(icuDat$sofa.mod, 0.1))
          # , ci="bootstrap"
          , cl = 0.95
          # , B=1000
          )
```

estimate	se	L	U
2.821	0.608	1.849	4.303

```
qratio.msm(m3
          , ind1=c(4,3)
          , ind2=c(3,4)
          , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.9)
                            , sofa.mod=quantile(icuDat$sofa.mod, 0.9))
          # , ci="bootstrap"
          , cl = 0.95
          # , B=1000
          )
```

estimate	se	L	U
2.790	0.852	1.534	5.076

In our assessment of the ratio of transition intensities, we jointly modeled age and SOFA score using specific

covariate settings. First, at 0.1 quantile for age and 0.1 quantile for SOFA score. Second, at 0.9 quantile for

age and 0.9 quantile for SOFA score. By estimating the ratio of two entries of the transition intensity matrix, we assessed the ratio of the progression rate q_{23} into a delirious state to the recovery rate q_{32} at 0.1 and 0.9 quantiles for age and SOFA. The use of extreme covariate values was designed to compare and contrast the impact of patient characteristics on health states. Similarly, we also assessed the ratio of progression rate q_{34} into a comatose state to the recovery rate q_{43} at the same specified covariate values.

The ratio of transition intensities for a patient within the 10% quantiles of age and SOFA score indicates that recovery from a delirious to normal state is 11.5 times as likely as progression from a normal to delirious state, in contrast with a patient in the 90% age and SOFA score quantiles who is only 3.6 times as likely. These findings are consistent with what an investigator will expect since any patient in the 90% quantile for age and SOFA score will by any account be considered sicker (higher SOFA score) and at greater risk of adverse events.

At the same specified extreme covariate values, that is 10% and 90% quantiles of age and SOFA scores, a comparison of the ratio of transition intensities for recovery from a comatose to delirious state versus progression from delirious to comatose state did not show any striking disparity (2.82 vs. 2.79 for 10% vs. 90% quantiles of age and SOFA score). This finding may suggest that in this cohort there is a certain threshold of illness that patients exceeds after which specific covariate characteristics have less impact on the potential for recovery.

Simulation Studies

Raw Transitions

```
# For specified covariate values we generate the transition intensity matrices for our
    simulations
mat1 <- qmatrix.msm(m3, , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.1)
                        , sofa.mod=quantile(icuDat$sofa.mod, 0.1))
            )
mat2 <- qmatrix.msm(m3, , covariates=list(age.enroll=quantile(icuDat$age.enroll, 0.9)
                        , sofa.mod=quantile(icuDat$sofa.mod, 0.9))
            )
# simulation1: patients in the 0.1 quantile of age and SOFA score group
set.seed(2000)
cat('Patient #\tStates for Days 1-30\n')
```

```
Patient #        States for Days 1-30
```

```
for(i in 1 : 10) {
  s <- sim.msm(mat1$estimates, mintime=1, maxtime=30, start=2)
  cat(i, '\t\t', approx(s$times, s$states, 1 : max(s$times), method='constant')$y, '\n', sep
      ='')
}
```

```
1                222222222223222
2                22233323342222
```

```
3               22222222233222
4               22
5               2222222222222222
6               22
7               2222
8               224333322222
9               222222222222233222222222
10              2222222
```

```
# simulation2: patients in the 0.9 quantile of age and SOFA score group
set.seed(2000)
cat('Patient #\tStates for Days 1-30\n')
```

```
Patient #        States for Days 1-30
```

```
for(i in 1 : 10) {
    s <- sim.msm(mat2$estimates, mintime=1, maxtime=30, start=2)
    cat(i, '\t\t', approx(s$times, s$states, 1 : max(s$times), method='constant')$y, '\n', sep
        ='')
}
```

```
1               22222222222
2               2222223222
3               222222222223
4               22222222222
5               222344
6               2222222222233333232433333
7               2
8               2222233443322222233343322434
9               222222222222
10              22223
```

We used simulation studies to assess our model by simulating the raw state transitions of 10 patients in each category of the above-specified covariate values (0.1 vs. 0.9 quantiles of age and SOFA scores). These single trajectory simulations were effected using the `sim.msm function`. The mean age in the 0.1 quantile age group is $\approx$ 40 years and the mean SOFA score (i.e. modified SOFA score) in the 0.1 quantile SOFA score group is 3. The corresponding numbers for the 0.9 quantile age and SOFA score groups are $\approx$ 78 years and 11 respectively. Thus patients in the 0.9 quantile groups are much older and sicker and therefore one would expect more transitions towards increasingly severe or undesirable health states. The results of the raw transitions are consistent with one would expect. The corresponding health states represented by the integers 2, 3, and 4 are normal, delirious, and comatose states, respectively. Of the 10 patients in the 0.1 quantile groups only 2 patients (patients 2 and 8) experienced a comatose health state, and interestingly, despite how ominous the state of coma is, these individuals ended up transitioning to normal states. In fact, every patient in that group ended up in normal states at the end of the simulation. On the contrary, in the sicker group patients 3, 6, 10 remained in the delirious state) in addition to patients 5 and 8 whom remained in comatose states at the simulation.

Aggregate Transitions

We explored aggregate evaluation of the above findings by simulating multiple trajectories of intermittently observed states. The `simmulti.msm function` in the `msm package` was used for this purpose. The `simmulti.msm function` calls on the `sim.msm function` repeatedly to produce a simulated trajectory for each individual; in this case with the specified covariate values as dictated by the covariate-specifications of the derived transition matrices. The results of the simulations are illustrated graphically using extended box plots.

The box plots in Figures 11 and 12 demonstrate a clear difference in the distribution of health states between the two disparate populations simulated, and further insight is gained in the context of the distribution of health states in the original dataset (Figure 13). Please refer to 16 for a reminder on the how to interpret the extended boxes in the plots. Strikingly, patients within the 0.1 quantile age and SOFA score group account only for 14 deceased states (Figures 11) in the population compared to 116 deceased states accounted for by the sicker patients in the 0.9 quantile group (Figures 12). The same pattern of remarkable disparity is evident for all other health states. Compared to the overall real study population (Figure 13) our artificial sicker group had more than half the number of deaths. In addition, this sicker group had a significant number of comatose and delirious states that far exceeds those associated with patients in the 0.1 quantile age and SOFA score group. These are all remarkable findings that have been made apparent by more efficient use of data via multi-state modeling. It does indicate the importance of such analysis strategies when evaluating the therapeutic efficacy and effectiveness of treatments.

```
icuDat$time ← icuDat$study.day
icuDat$subject ← icuDat$id
icuDat ← icuDat[order(icuDat$id, icuDat$time), ]
sim1 ← simmulti.msm(icuDat, start=2, qmatrix=mat1$estimates, death=TRUE, drop.absorb=TRUE)
sim2 ← simmulti.msm(icuDat, start=2, qmatrix=mat2$estimates, death=TRUE, drop.absorb=TRUE)
```

```
par(mfrow=c(2,1))
sim1$state ← factor(sim1$state, labels=c("Discharged", "Normal", "Delirious", "Comatose", "
    Deceased"))
bpplotM(sim1$time ~ sim1$state, nloc="left")
```
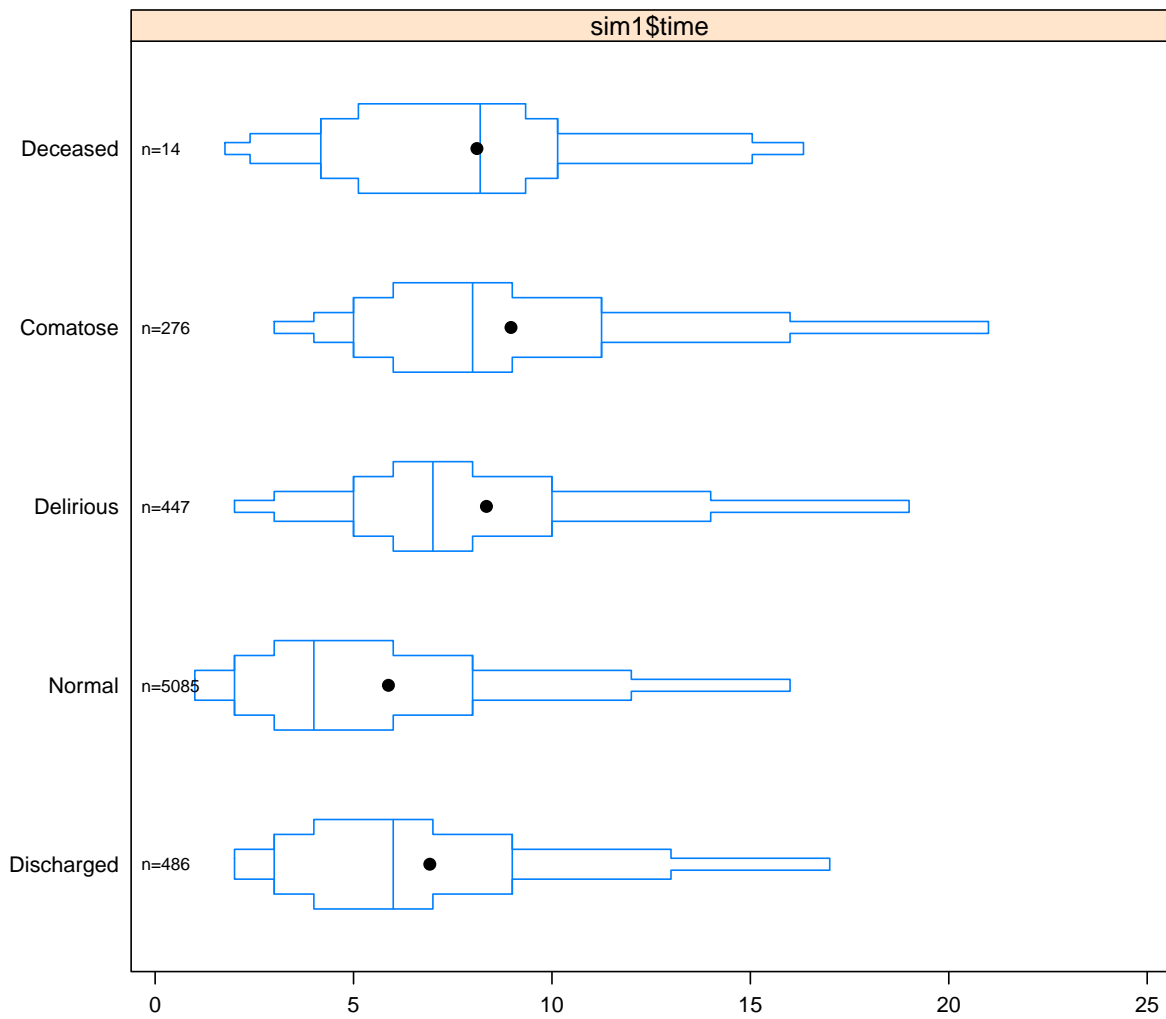
Figure 11: Plot of simulation results for patients in the 0.1 quantile age and SOFA score group

```
sim2$state ← factor(sim2$state, labels=c("Discharged", "Normal", "Delirious", "Comatose", "Deceased"))
bpplotM(sim2$time ~ sim2$state, nloc="left")
```
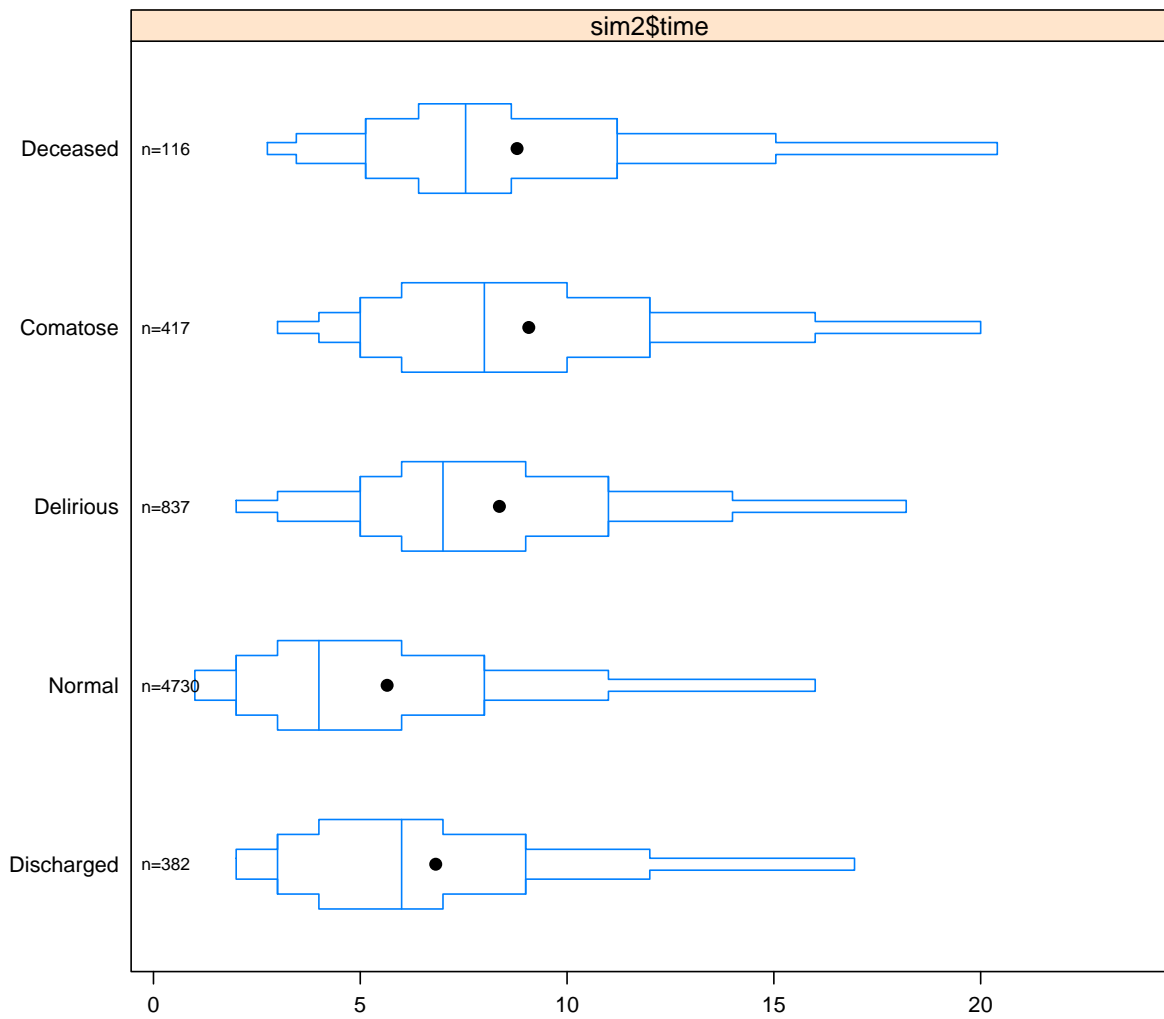
Figure 12: Plot of simulation results for patients in the 0.9 quantile age and SOFA score group

```
bpplotM(icuDat$study.day ~ icuDat$status.today.imp , nloc="left")
```
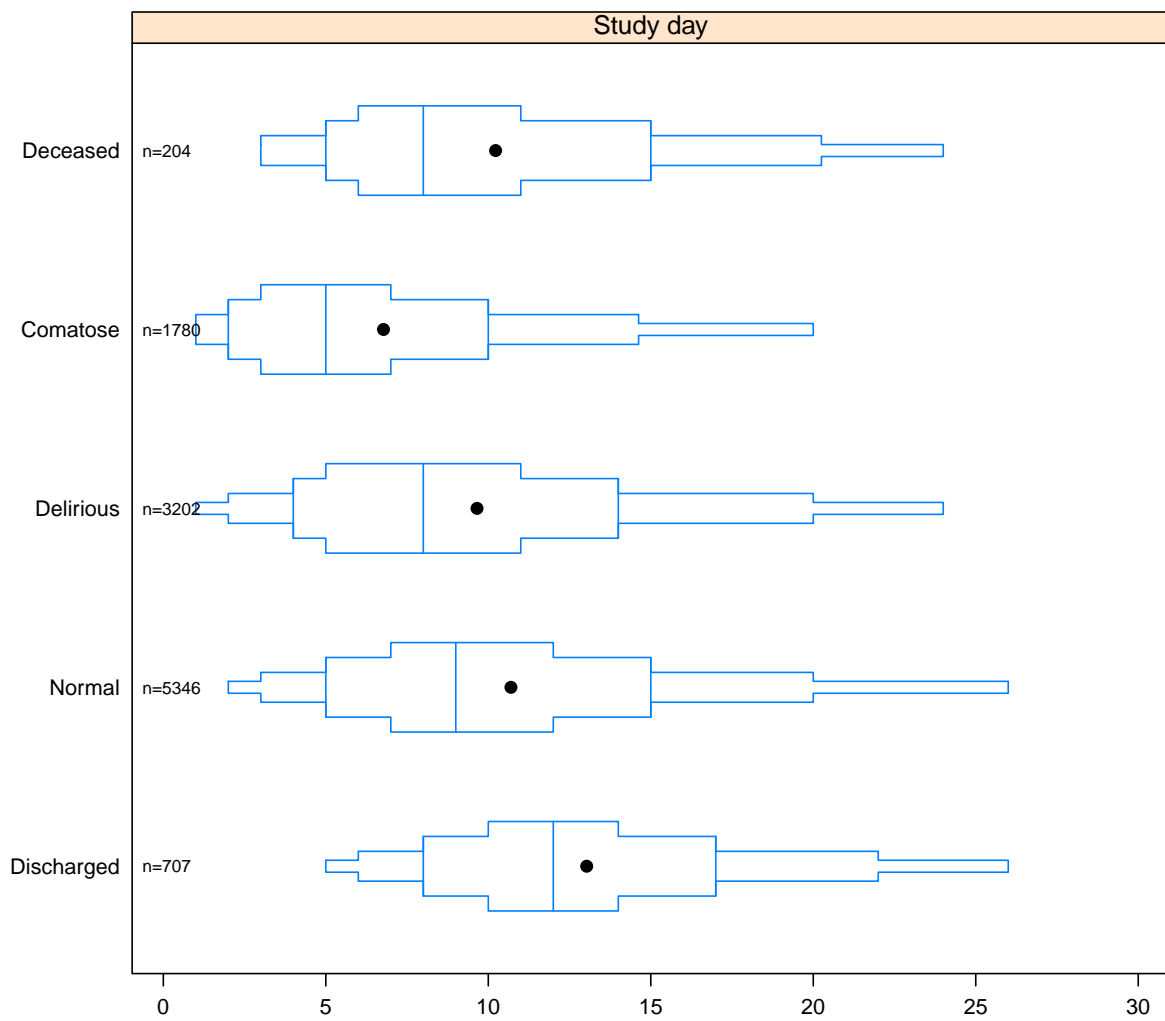
Figure 13: Plot of states versus time in BRAIN-ICU study population

CHAPTER IV

Discussion and Conclusions

Discussion

We have demonstrated an alternative approach for the analysis of multiple outcomes in a longitudinal data construct. This approach is contrary to mainstream modus operandi where multiple outcomes are collapsed into simple binary or composite outcome measures for the application of logistic regression methods or time-to-first event analysis as in the case of survival improvement evaluation. Such run-of-the mill methods are fraught with remarkable loss of information; not only do they negate the proper or full-understanding of a patient's clinical journey, and how various factors—e.g. treatment in the case of an intervention trial—might affect that journey, they inevitably lead to poor estimation of true treatment or covariate effects on the burden of morbidity.

In the work presented here, the Markov multi-state transition models provide a lot of insight that otherwise would have remained, at best, mere conjectures or hypothetical considerations. The simple bidirectional model tells us how likely a patient is to transition from one state to another, while the covariate models inform us of the impact of patient attributes on all pre-specified possible health state transitions. The extractor functions associated with the `msm package` employed in this analysis provides additional relevant and interesting scientific information some of which are: the probability of being in a particular state within a time period (transition probability), the estimated times spent in each transient state for specific covariate values (mean sojourn times), and the probability that each state is next. These additional information collectively allow investigators to have a more intuitive understanding of the study population via the multi-state models. Such greater depth of understanding cannot be accomplished if traditional methods were employed.

Perhaps due to the origin of the dataset used in this study, one is reminded of the current practice of using ventilator-free days (VFD) as an outcome measure in critical care studies. Under the current practice investigators count the days off the ventilator (until day 28) during ICU stay, but subjects who die are assigned a VFD of 0. The efficacy of an intervention is based on analysis of the differences in VFD between treatment groups using traditional two-sample comparisons. There are many problems with this construct, but we note only a few. The current approach ignores the VFD for the subjects that die. The difference in VFD may be due to lower mortality and/or more days free off ventilation. Furthermore, intermittent need and triggers for ventilator support is not fully taken into account. Death and VFD are two competing endpoints, so analyzing one without the other does not address competing risk explicitly. Since VFD is an outcome of interest, subjects who die are censored at the time of death, which violates a fundamental

assumption of survival analysis, ignores or fails to characterize the realities of critical care outcomes given the underlying complexities of disease mechanisms. Of note Schoenfeld and Bernard (2002) did not employ the time-to-event method in their analysis, which was therefore devoid of a censoring problem in the formal sense. However, multi-state modeling provides a solution to these issues associated with the use of VFD. Firstly, not only can competing risk be addressed explicitly, we can capture the intermittent need for assisted ventilation, which are indeed state transitions. In addition subjects who die can contribute to the analysis because their VFD will be counted. Essentially, what investigators need to analyze are the transitions in health stats between normal, ventilator supported state, other relevant states, and death. In this context, the real efficacy of interventions can be determined. Furthermore, it is very straightforward to conduct a formal statistical hypothesis test to determine covariate (treatment) effect on the transitions in and out of assisted ventilation or other states of interest. Here a likelihood ratio test between models with and without the covariate of interest will provide the answer to the question by comparing the LR $\chi^2_{\texttt{d.f.}}$ accounting for the degrees of freedom (d.f.) spent. For example, the effect of treatment on a particular transition (e.g. normal to ventilator assistance) will cost 2 d.f if the analysis is of 2 possible state transitions.

It is important to acknowledge that the number of parameters tackled during multi-state transition modeling can be challenging and thus a potential disadvantage in the sense that it requires adequate sample size and strong computing platform. However, the flexibility that multi-state modeling offers for depicting complex patterns should justify usage. In the context of an intervention trial, a complex pattern that can be depicted is to assess differences in therapeutic efficacy between two interventions in terms of the probabilities of improvement pare passu as assessment of the similarities in probabilities for events between the two interventions. Such a complex pattern would otherwise be difficult to delineate using current mainstream methods.

Conclusion

This study showcases some, but not all of the benefits of employing multi-state modeling strategies. We deem it important to conclude by listing some of those major advantages.

- Intuitiveness.
- Flexibility.
- Transparency.
- Excellent for informing medical decisions especially when such decision problems can be articulated in terms of states.
- Applicable for the assessment or comparison of various types of interventions: primary prevention, screening, diagnosis, and treatment.

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- Explicit approach for dealing with the problem of competing risk.

- Offers more interpretable predictions of more features of patient responses.

- Allows for quantitative hypotheses testing about covariate effect on various health states either collectively or singularly.

- Offers more efficient use of data and provides a better approach for looking at multiple endpoints. Provides clear insight about the experience of patients as opposed to the black box that classical approaches create by just looking at mortality or any other single outcome measure (e.g. ventilator free days, as discussed above) with accounting for intermittent changes that may very relevant regarding the assessment of true disease burden or therapeutic efficacy and effectiveness.

Future directions for employing the use of multi-state modeling can incorporate a random effects structure to accommodate unexplained variation in transition probabilities between individuals. In this context, a Bayesian statistical perspective can be employed using simulation techniques like MCMC. Furthermore, higher order Markov transition models can also be considered albeit with suitable constraints to make estimation feasible.

APPENDICES

Computing Environment

All analyses were conducted using the following versions of R (R Development Core et al., 2012), the operating system, and add-on packages `Hmisc` (Harrell, 2014a), `msm` (Jackson, 2011), `rms` (Harrell, 2014b), `xtable` (Dahl, 2014), and others:

- R version 3.1.1 (2014-07-10), `x86_64-apple-darwin10.8.0`
- Base packages: base, datasets, graphics, grDevices, grid, methods, splines, stats, utils
- Other packages: diagram 1.6.2, dplyr 0.2, Formula 1.1-2, gcookbook 1.0, ggplot2 1.0.0, Hmisc 3.14-4, knitr 1.6, lattice 0.20-29, msm 1.4, plyr 1.8.1, rattle 3.1.0, rms 4.2-0, shape 1.4.1, SparseM 1.05, survival 2.37-7, xtable 1.7-3
- Loaded via a namespace (and not attached): assertthat 0.1, cluster 1.15.2, codetools 0.2-8, colorspace 1.2-4, digest 0.6.4, evaluate 0.5.5, expm 0.99-1.1, formatR 0.10, gtable 0.1.2, latticeExtra 0.6-26, MASS 7.3-33, Matrix 1.1-4, munsell 0.4.2, mvtnorm 1.0-0, parallel 3.1.1, proto 0.3-10, RColorBrewer 1.0-5, Rcpp 0.11.2, reshape2 1.4, scales 0.2.4, stringr 0.6.2, tools 3.1.1

The reproducible research framework `knitr` (Yihui, 2014) was used.

R Codes: Packages and Global Formatting

```
# Packages and global formatting
require(knitr)     # Reproducible research platform
require(Hmisc)     # Has many support functions extremely useful when working with knitr and
    LaTeX e.g, escape special characters in R strings for LaTeX presentation.
require(rms)       # Faithful functions for regression modelling: data reduction,
    imputatation, modeling, etc
require(gcookbook)# Data visualisation.
require(ggplot2)   # Data visualisation
require(grid)
require(xtable)    # Format R data frames as LaTeX tables.
require(diagram)   # For flowchart production if the need arises
require(dplyr)     # Data munging: tbl_df() for printing dataframes
require(msm)       # The wonderful package for multi-state transition modeling


opts_chunk$set(dev="pdf"
```

```
                    , fig.path="graphics/plot"# puts all figures in a folder in the current
                        directory called "graphics." If you use this, you need to create the
                        graphics folder first. It also starts each figure's filename with "plot"
                    , fig.lp = ""
                    , out.width=".7\\textwidth"
                    , fig.keep="high"
                    , fig.show="hold"
                    , fig.align="center"
                    , comment=NA
                    , size="small"
                    , cache=TRUE
                    , autodep=TRUE
                    )

options(formatR.arrow=TRUE, formatR.blank=TRUE, formatR.brace.newline=FALSE)
render_listings()
# Suppresses "##" in R output. The "##" is useful if you want people to be able to copy and
    paste your code in the output file, though.
# this allows for code formatting inline.
knit_hooks$set(inline = function(x) {
    if (is.numeric(x)) return(knitr:::format_sci(x, 'latex'))
    x = as.character(x)
    h = knitr:::hilight_source(x, 'latex', list(prompt=FALSE, size='scriptsize'))
    h = gsub("([_#$%&])", "\\\\\\\\1", h)
    h = gsub('(["\'])', '\\1{}', h)
        gsub("```\n+```\n", "", x)
        gsub('^\\\\\\begin\\{alltt\\}\\s*|\\\\\\\\end\\{alltt\\}\\s*$', '', h)})
par(las = 1)
options(width = 90, tidy = TRUE, scipen = 6, digits = 4)
```

```
# For native bibliography of R packages
write_bib(sub("^.*/", "", grep("^/", searchpaths(), value=TRUE)),
file="mydoc.bib")
```

R Codes: Data Management

```
#Data input and preparation
rm(list=ls())
setwd("~/Dropbox/BiosGradPgm/ThesisInfo/PreparatoryWork")

load("uche_braindata.RData") #load main datasets brain.daily and uche.oneobs
data <- brain.daily #calls data into memory
```

```
oneobs ← uche.oneobs #calls data into memory


dat ← merge(data, oneobs, by=c("id")) # merge both datasets by id var
dat1 ← dat[with(dat, study.date ≤ death.date + 1), ] # the makes certain that we capture
    the health state before death in addition to discharge
dat2 ← dat[with(dat, study.date ≤ hospdis.date + 1), ] # this makes certain that we
    capture the health state before discharge in addition to discharge itself.
dat3 ← rbind(dat1, dat2)
dat3$states ← as.factor(dat3$status.today.imp)
dat4 ← dat3[!dat3$status.today.imp %in% c("Withdrawn"), ] # this eliminates the few
    subjects that withdrew from the study.
dat5 ← dat4[!is.na(dat4$states), ]   # a clean dataset
dat5$states ← as.integer(dat5$states)


v ← c("id", "iqcode.score.e",  "study.day", "states", "status.today.imp", "sofa.mod", "
    apache.aps", "sofa", "num.apache", "charlson.score", "sex.pp", "age.enroll",  "
    mean.hal.icu", "mean.prop.icu", "cum.sevsepsis", "mean.benz.icu", "mean.op.new.icu", "
    mean.dex.icu", "cum.onstatin", "cum.offstatin", "cum.hypoxic.del", "stroke.risk")


icuDat ← dat5 ← dat5[, v] # subsetting
save(icuDat, file = "icuDat.RData") # saving data for future direct use etc.
```

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