**Risk Factors for the Development of Long-Term PTSD, Depression and Anxiety Symptoms in Surrogate Decision-Makers of Critically Ill Patients**

**Project Outline and Statistical Analysis Plan**

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1. **Background**

Approximately one-fourth of all admissions to the hospital will include a stay in the Intensive Care Unit [1], an experience that is often life-altering to both patients and their family members. Due to ongoing cognitive impairment caused by critical illness [2], many patients rely on family members or surrogates to make medical decisions on their behalf, an role that has been associated both negative psychological sequalae and poor health-related quality of life for these surrogates [3-5]. In one study, 35% of patient surrogates experienced symptoms of post-traumatic stress 6 months after an ICU admission, while 15% experienced symptoms of anxiety and 6% experienced symptoms of depression [6], rates that are up to ten times higher than in the general population [7]. Identifying potential risk factors for adverse psychological outcomes in surrogates of critically ill patients could enable members of the health care team to more effectively target services and interventions towards those at highest risk.

Although prior studies have identified several possible risk factors for adverse psychological outcomes in patient surrogates, including younger surrogate age, female gender, and lower socioeconomic status [4], most studies have been limited in number of patients due to difficulty maintaining long-term follow up with surrogates [5, 6, 8-11]. To address these concerns, we sought to utilize a large database of 770 ICU surrogate-decision makers who had psychological outcomes measured at 6-months to identify potential risk factors for increased symptoms of anxiety, depression, and post-traumatic stress. We hypothesized that both patient-specific and surrogate-specific risk factors, as well as measures of communication quality within the ICU environment, would increase the prevalence of adverse psychological outcomes in surrogate decision-makers of critically ill patients.

1. **Objectives**

In this study, we sought to identify patient-, surrogate, and hospital-level risk factors for long-term depression, anxiety, and post-traumatic stress symptoms in surrogate decision makers of critically ill patients.

1. **Data and Patients**

This study is a retrospective secondary analysis of a database from a multicenter randomized trial of a communication intervention for adult surrogate decision-makers of critically ill patients. Primary outcomes were measured at 6 months and included surrogate PTSD symptoms as measured by the Impact of Events Score-Revises (IES-R) and surrogate depression and anxiety symptoms as measured by the Hospital Depression and Anxiety Scale.

We defined two primary outcomes: high post-traumatic stress symptom burden, defined as an IES-R score >=33 [13], and high depression and anxiety symptom burden, defined as a HADS score >= 22 [12, 14]. We pre-selected 36 potential risk factors based on characteristics of the surrogate, patient, use of professional support, and quality of communication (**Table 1**).

1. **Statistical Analysis**

We will provide descriptive statistics of the cohort, including characteristics of the surrogate and patient, and of provisions of care, including use of professional support and quality of communication. These statistics will be presented overall and stratified by each of the primary outcomes.

We will assess quality and completeness of the data for modeling. We have conducted exploratory analyses and found that rates of missingness are low (<1%) in the data. For our primary analysis, we will use complete case data. We will conduct sensitivity analyses to include data from subjects with missing data using appropriate imputation approaches.

We will conduct univariate logistic regression models for the 36 potential risk factors identified (**Table 1**) and will report coefficients, confidence intervals, and p-values for each. We will use a least absolute shrinkage and selection operator (LASSO) approach to identify the most significant predictors of each outcome, with the optimal model selected by minimization of the Bayesian information criterion (BIC). Priority variables of surrogate age, race, gender and patient age, sex, and illness severity as defined by enrollment Apache II score, will be retained in the model. We will construct multivariate logistic regression models of factors identified by LASSO, clustering variance estimates by hospital site.

We will report model coefficients, odds ratios, confidence intervals, and p-values for each factor in the adjusted model. We will visualize data using forest plots and plots of marginal estimates of covariates over ranges observed for covariates in the data. For example, we may plot the estimates association between patient age and risk of each outcome, adjusted for model covariates and presuming that patient age is a significant factor identified by LASSO.

We will conduct sensitivity analyses varying approach to missing data, lasso penalty parameter, use of correlated features in the model, and variations to the feature set used in the model, with coefficients, confidence intervals, and p-values reported for these analyses. All tests will be two sided, with a significance level of 0.05. Analysis will be performed using StateSE 17.0 (StataCorp LLC).

**5. Project Team**

* Kathryn Vessel: Pitt MS-4; lead author
* Rachel Butler: EDM Program manager; co-author; assist with data analysis
* Jason Kennedy: Associate Director, CCM Research Analytics; co-author; statistician
* Douglas White: PI, senior author

**6. References**

1. Barrett, M.L., et al., *Utilization of Intensive Care Services, 2011*, in *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. 2006: Rockville (MD).

2. Nelson, J.E., et al., *Brain dysfunction: another burden for the chronically critically ill.* Arch Intern Med, 2006. **166**(18): p. 1993-9.

3. Douglas, S.L. and B.J. Daly, *Caregivers of long-term ventilator patients: physical and psychological outcomes.* Chest, 2003. **123**(4): p. 1073-81.

4. Johnson, C.C., et al., *Psychological Sequelae in Family Caregivers of Critically III Intensive Care Unit Patients. A Systematic Review.* Ann Am Thorac Soc, 2019. **16**(7): p. 894-909.

5. Azoulay, E., et al., *Risk of post-traumatic stress symptoms in family members of intensive care unit patients.* Am J Respir Crit Care Med, 2005. **171**(9): p. 987-94.

6. Anderson, W.G., et al., *Posttraumatic stress and complicated grief in family members of patients in the intensive care unit.* J Gen Intern Med, 2008. **23**(11): p. 1871-6.

7. Haines, K.J., et al., *Psychosocial outcomes in informal caregivers of the critically ill: a systematic review.* Crit Care Med, 2015. **43**(5): p. 1112-20.

8. Van Pelt, D.C., et al., *Patient-specific, time-varying predictors of post-ICU informal caregiver burden: the caregiver outcomes after ICU discharge project.* Chest, 2010. **137**(1): p. 88-94.

9. Wintermann, G.B., et al., *Predictors of posttraumatic stress and quality of life in family members of chronically critically ill patients after intensive care.* Ann Intensive Care, 2016. **6**(1): p. 69.

10. de Ridder, C., et al., *Psychological Symptoms in Relatives of Critically Ill Patients: A Longitudinal Cohort Study.* Crit Care Explor, 2021. **3**(7): p. e0470.

11. Choi, J., et al., *Patterns of depressive symptoms in caregivers of mechanically ventilated critically ill adults from intensive care unit admission to 2 months postintensive care unit discharge: a pilot study.* Crit Care Med, 2012. **40**(5): p. 1546-53.

12. Cameron, I.M., et al., *Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care.* Br J Gen Pract, 2008. **58**(546): p. 32-6.

13. Creamer, M., R. Bell, and S. Failla, *Psychometric properties of the Impact of Event Scale - Revised.* Behav Res Ther, 2003. **41**(12): p. 1489-96.

14. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.

# **Table 1:** Pre-selected variables

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Risk Factor** | **Type of Variable** | **Variable name in dataset** |
| **Surrogate Information** | Surrogate Age | Continuous | surr\_age |
| Surrogate Gender | Categorical | surr\_female |
| Surrogate Race | Categorical | surr\_race\_recode |
| Surrogate Ethnicity | Categorical | surr\_hispanic |
| Surrogate Education | Categorical | surr\_edurecode |
| Surrogate Religious | Dichotomous (Y/N) | surr\_religious |
| Surrogate relationship to patient | Categorical | surr\_relationship |
| Surrogate past experience as a decision-maker | Dichotomous (Y/N) | surr\_mademeddecision |
| Surrogate distance from treating hospital | Continuous | surr\_dist |
| ADI of surrogate neighborhood of residence- total | Continuous | ADInat |
| ADI of surrogate neighborhood of residence- national quartile | Categorical | ADInatcat |
| **Patient Information** | Patient Age | Continuous | pt\_age |
| Patient Sex | Categorical | pt\_female |
| Patient Race | Categorical | pt\_race |
| Patient ethnicity | Categorical | pt\_hispanic |
| Length of mechanical ventilation | Continuous | ventdays\_total |
| Length of ICU stay, days | Continuous | iculos\_total |
| Length of hospital stay, days | Continuous | hosp\_los |
| Readmitted to ICU during hospital stay? | Dichotomous (Y/N) | icureadmit |
| Change in code status | Dichotomous (Y/N) | codechange |
| Presence of Advanced Directive in chart (per surrogate) | Dichotomous (Y/N) | surr\_ptadvdirective |
| Code status at time of enrollment | Categorical | codestatus\_enroll |
| Illness severity- APACHE upon enrollment | Continuous | enrollapache |
| PEG placed during hospital admission | Dichotomous (Y/N) | peg |
| Trach placed during hospital admission | Dichotomous (Y/N) | trach |
| Discharge disposition | Categorical | dispogroup |
| Functional Status, as defined by total KATZ-ADL score, at 6 months | Continuous | adltotal |
| Treating hospital | Categorical | site |
| Intervention group | Categorical | intervention |
| **Utilization of professional support during hospital stay** | Palliative care and/ or ethics consultation anytime during hospitalization | Dichotomous (Y/N) | palliaorder |
| Time from hospital admission to palliative care consult order | Continuous | palliadays |
| **Communication** | Overall quality of communication score @ 6-month f/u | Continuous | qoc\_total |
| Overall patient-centeredness of care score @ 6-month f/u | Continuous | pcc\_total |
| Total number of family meetings conducted while patient enrolled in study | Continuous | meettotal |
| Decisional regret scale | Continuous | drstotal |
| Reported burden of follow-up interview at 6-months | Ordinal (1-4) | burdeninterview |