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The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient

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Abstract

Rationale: Intensive care unit (ICU) delirium is highly prevalent and a potentially avoidable hospital complication. The current cost of ICU delirium is unknown.

Objectives: To specify the association between the daily occurrence of delirium in the ICU with costs of ICU care accounting for time-varying illness severity and death.

Research Design: We performed a prospective cohort study within medical and surgical ICUs in a large academic medical center.

Subjects: We analyzed critically ill patients (N = 479) with respiratory failure and/or shock.

Measures: Covariates included baseline factors (age, insurance, cognitive impairment, comorbidities, APACHE-II score) and time-varying factors (SOFA score, mechanical ventilation, and severe sepsis). The primary analysis used a novel 3-stage regression method: first, estimation of the cumulative cost of delirium over 30 ICU days and then costs separated into those attributable to increased resource utilization among survivors and those that were avoided on the account of delirium's association with early mortality in the ICU.

Results: The patient-level 30-day cumulative cost of ICU delirium attributable to increased resource utilization was \$17,838 (95% CI, \$11,132 to \$23,497). A combination of professional, dialysis, and bed costs accounted for the largest percentage of the incremental costs associated with ICU delirium. The 30-day cumulative incremental costs of ICU delirium that were avoided due to delirium-associated early mortality was \$4,654 (95% CI, \$2,056 to 7,869).

Conclusions: Delirium is associated with substantial costs after accounting for time-varying illness severity and could be 20% higher if not for its association with early ICU mortality.

Keywords

cost analysis; delirium; critical care

INTRODUCTION

Delirium is a manifestation of acute brain dysfunction characterized by alterations in attention, consciousness, and cognition.^{1,2} Delirium is associated with a number of poor outcomes including long-term cognitive impairment^{3,4}, mortality^{5,6}, and increased healthcare costs.^{7,8} Over a decade ago, Milbrandt et al. examined the association between delirium prevalence and total ICU costs.⁹ Understanding this relationship is critical considering that critical care services account for almost 1% of the entire U.S. gross domestic product.¹⁰ Furthermore, as ICU survival increases¹¹, patients and the healthcare system may be increasingly exposed to costs previously avoided by early mortality.

Using a cross-sectional design, Milbrandt et al. estimated that developing delirium during an ICU stay was associated with a 39% increase in the cost of ICU care. Delirium-associated mortality, however, was unaccounted for and in truth may mask some of the costs of

delirium. In addition to accounting for mortality, a longitudinal cohort analysis would be more accurate at measuring the cost of delirium than previous work. Finally, there have been numerous management and organizational changes in ICU care over time.

The primary aim of this study was to provide an estimate of the effect of delirium on ICU cost that accounts for the competing mortality risk as well as the time-dependent nature of ICU exposures and delirium.¹² Additionally, we estimate the effect of delirium on costs categorized according to cost categories (e.g., pharmacy, laboratory, diagnostic radiology, therapy, central supply, and professional/bed expenses/dialysis) that make up the total cost.

METHODS

Setting & Participants

We performed an analysis among patients enrolled in the prospective cohort study “Bringing to Light the Risk Factors and Incidence of Neuropsychological dysfunction in ICU” survivors (BRAIN-ICU). BRAIN-ICU included 18 and older adults admitted to surgical or medical ICUs admitted for shock or respiratory failure. We excluded patients if they were unable to complete in-person follow-up (e.g., distance, language barriers, severe dementia, homelessness, severe psychiatric illness). We have previously published full details of the BRAIN-ICU cohort study.^{4,13} The Institutional Review Board at Vanderbilt University Medical Center approved the study.

For this specific analysis, we excluded patients without available cost data and with persistent coma. We additionally excluded patients receiving a solid-organ transplant, due to the extreme, outlier, transplantation costs that occur in a limited population (n=10). Additional study population characteristics are in the online supplement. We received approval for the study from the Vanderbilt University Medical Center Institutional Review Board.

Measures:

The primary exposure variable was daily delirium or coma. Specifically, we excluded patients with persistent coma from analyses, but we have categorized transiently comatose patients as being delirious to understand the overall cost associated with acute brain dysfunction while in the ICU. Trained research personnel ascertained delirium status twice daily using the Confusion Assessment Method for the ICU (CAM-ICU)^{14,15} and the Richmond Agitation Sedation Scale.^{16,17} The CAM-ICU is a four-part scale to assess the presence or absence of delirium, with a sensitivity and specificity of 80% and 96%, respectively.¹⁸ Each day patients with delirium or coma status are compared to patients with normal mental status.

We included time-constant and time-varying covariates, chosen *a priori*, which potentially confound in the relationship between delirium and cost or mortality. Covariates included insurance status (insured or uninsured), age (in years), Charlson comorbidity score,¹⁹ pre-existing cognitive dysfunction as measured by the Short Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE)²⁰ with a score of ≥ 3.3 indicating impaired cognition, Acute Physiology and Chronic Health Evaluation II Score (APACHE II) at

enrollment,²¹ daily modified sequential organ failure assessment (SOFA),²² daily severe sepsis status (yes or no),²³ daily mechanical ventilation status (yes or no), and the day of ICU stay. Detailed covariate information is available in the online supplement. Charlson comorbidity score is a validated measure of pre-existing comorbid illness, with a score ranging from 0 to 33. APACHE II is a measure of illness severity at admission, with scores ranging from 0 to 71. SOFA is a validated measure of daily illness severity in the ICU, with scores ranging from 0 to 24.

The primary dependent (outcome) variable for this investigation was total ICU cost. The financial information for each participant was obtained directly from the medical system's finance department. Vanderbilt University Medical Center utilizes a comprehensive cost accounting system developed within the Allscripts® (EPSi™) software. The system utilizes a combination of standard costing combined with absorption costing in the forms of studied RVUs and/or Cost to Charge ratios. The system is applied to all clinical activity for hospitals settings. Direct cost centers receive indirect allocations to determine total cost; then all costs are allocated to patient care activity. Costs are organized by General Ledger categories (e.g. Pharmacy, etc.). We include the total cost, or combination of the direct and indirect costs. As professional fees were not part of the cost accounting system at the time of study, we estimated the cost of professional (i.e. consultative) services separately using the Medicare Relative Value Payment for the hospital's geographic region as of 2013.²⁴ We itemized costs according to service categories that included: (1) Pharmacy, (2) Laboratory (3) Diagnostic Radiology, (4) Therapy Services (i.e., Respiratory, Physical, Occupational, and Speech Therapy), (5) Central Supply, and (6) Professional Services, Bed Expenses, and Dialysis. All costs were discounted to 2007 dollars using a 3% annual rate as recommended by the American Thoracic Society for such analyses.²⁵

Statistical Analysis

We summarized patient characteristics using frequencies (percentage), means, and medians (interquartile range). To estimate the total incremental cost of delirium accounting for mortality and time-varying nature of delirium as well as other ICU exposures, we used a model described by Basu and Manning.¹² The analytic models were able to incorporate the time-varying nature of delirium, and differing patterns of mental status in patients' ICU stays to estimate the total incremental ICU costs, independent of severity of illness variables and length of stay. Importantly, the method separates the total incremental cost of delirium into two parts: The first is the incremental cost of delirium among survivors, known as the intensity effect. The intensity effect reflects the difference in costs for a normal mental status day versus a day with delirium among survivors. Quantifying this effect is essential when delirium independently alters the amount of resources a patient consumes while in the ICU. The second is the incremental cost of delirium as a result of delirium-associated increases in ICU mortality.^{6,26} This is what we call the "mortality effect". Quantification of the mortality effect induced cost can provide an estimate of the costs that would potentially increase should delirium-associated mortality decrease. The intensity and mortality costs added together reflect the health care economics of the overall cost of ICU delirium.

The Basu and Manning estimator is implemented using a three-part model, where the estimate of mean cost is obtained as the sum of conditional predictions from each of the three models as described below. These estimates represent the population level costs for the cohort of patients with similar observed characteristics, as in our sample, and adjusts for costs associated with delirium-related risk of ICU mortality. Costs are estimated over standardized intervals, and for the purposes of this study, an interval of one day was used as a patient period. The three model-steps are as follows:

Step 1) For each patient period in the ICU, the first part of the multi-part model estimated the probability of survival (S) and the hazard rate for death in any interval (h) by fitting a Cox model as a function of daily mental status and time-constant covariates (e.g. age), and time-varying covariates (e.g. SOFA). Follow-up time was 30 ICU days. Any dates of death after 30 days were censored at 30 days.

Step 2) The second part modeled the expected cost for intervals where a patient died. To obtain the expected cost for those intervals of competing risk (μ_1), we modeled cost using a quasi-Poisson model with a log link as a function of their daily mental status, the proportion of time the subject spent alive in a given day (0 for days they were alive and a number between 0 and 1 for the proportion of time alive on the day of death), ICU study day and the time-constant and time-varying covariates.

Step 3) The third part of the model obtained the expected cost for those intervals where subjects were alive for the whole day (μ_2) where the cost was estimated using a quasi-poisson model with a log link as a function of their daily mental status, ICU day and the above specified covariates.

For each day in the ICU, we combined the estimates obtained from Steps 1–3 to compute the expected cost in an interval (ICU day) written as the product of the survivor function in that interval and cost accumulated in that interval. As denoted in Basu and Manning, the cost for any individual in interval j is specified as below:

$$\hat{\mu}_j(X) = \hat{S}_j(X) * \left[\hat{h}_j(X) * \hat{\mu}_{1j} + (1 - \hat{h}_j(X)) * \hat{\mu}_{2j}(X) \right]$$

Here $\hat{S}_j(X)$ is the survival function, $\hat{h}_j(X)$ represents the hazard of death during interval j given that the subject was observed to be alive till then, $\hat{\mu}_{1j}$ represents the expected costs of an individual if the subject dies in that interval and $\hat{\mu}_{2j}$ represents the expected costs of the same individual had he not died in that interval. This equation captures the fact that the rate of accumulation of costs during the interval where the subject dies may be different from those who do not die in this interval.

To then obtain the incremental effect of delirium on cost partitioned into mortality (first part of the equation below) and intensity effects (second part of the equation below), we used the equation below.

$$\frac{\Delta\mu}{\Delta t} = \sum_{j=1}^{30} \left[\left[\frac{\Delta S_j}{\Delta t} \left[(h_j * \mu_{1j}) + ((1 - h_j) * \mu_{2j}) \right] + S_j * \left[\frac{\Delta h_j}{\Delta t} * (\mu_{1j} - \mu_{2j}) \right] \right] + \left[S_j * \left[h_j * \frac{\Delta \mu_{1j}}{\Delta t} + (1 - h_j) * \frac{\Delta \mu_{2j}}{\Delta t} \right] \right] \right]$$

We report the results as the mean adjusted cumulative incremental cost of delirium and break it down into the incremental costs attributable to intensity of services and incremental costs attributable to mortality. The intensity effect estimates the cost-accumulation due to delirium being associated with healthcare utilization. The mortality effect estimates the cost associated with delirium being associated with ICU mortality. The incremental effects were computed using recycled prediction method (See Online Supplement for further detail) where the model constructed is used to predict the expected cost in each interval assuming a delirium/coma exposure every day and then subtracting it from the expected cost assuming a normal mental status for every day.²⁷ We obtained confidence intervals for the incremental cost associated with delirium using 250 bootstrap iterations. The bootstrap procedure was conducted by clustering by subject to account for the correlated responses within subjects.

In addition to the total cost analysis, we repeated the above analysis for the six specific itemized cost service categories that encompassed the total cost. Initially, we ran models with bed expenses and dialysis as separate categories; however, due to limited daily variability in daily cost and inability of models to converge, we combined these categories. These additional analyses provide a further understanding of the relationship between ICU delirium and incremental costs across the specific categories. Further details of the Basu and Manning methodology are available in the Online Supplement. All analyses were performed using R version 3.2.4 (www.r-project.org)

RESULTS

826 patients were originally enrolled in the BRAIN-ICU study. 521 patients from the BRAIN-ICU study were from Vanderbilt University Medical Center. Of these, 517 had available cost data, and we further excluded 28 patients that were persistently comatose, and ten solid organ transplant patients, leaving a total of 479 patients in the final analysis (See Online Data Supplement - Figure E1). Descriptive characteristics of patients, including acute diagnoses, are included in Table 1. The median (interquartile range) ICU length of stay was 11 days (7-18) and 14% of patients (n = 65) died within 30 days and before ICU discharge. Three hundred and seventy-six (78.5%) patients experienced at least one day of delirium throughout their ICU stay.

Over the course of a 30-day ICU stay, the mean incremental cumulative ICU cost related to persistent delirium in survivors was \$17,838 (95% CI \$11,132 to \$23,497). An additional cumulative cost of \$4,654 (95% CI \$2,056 to \$7,869) could be hypothetically realized if delirium's associated ICU mortality was eliminated. Figure 1 demonstrates the independent costs of delirium attributable to intensity of services, as well as the additional costs that would be expected in the absence of delirium-associated early mortality.

We additionally assessed the incremental costs of ICU delirium across service specific categories (Table 2). As with the overall cost analysis, we divided the costs into those that were attributable to intensity of service utilization and those attributable to mortality. The largest delirium associated cost attributable to increased service utilization was seen in the combined category of professional, bed-expenses, and dialysis costs with pharmacy costs accounting for the next largest cost. The largest delirium-associated costs that were avoided due to early mortality were seen for the same expense categories. The incremental costs of delirium among survivors over time for each cost category are displayed in Figure 2. One can additionally see the costs of delirium by cost categories that include those costs avoided on the account of delirium's association with early mortality in the ICU for each category.

DISCUSSION

We found substantial increased costs associated with delirium in the ICU, after adjusting for time-varying severity of illness and length of stay. Over a 30-day ICU time period, the incremental cost of persistent daily delirium or coma attributable to increased service intensity is about \$18,000. This is about \$600 per day, however, this cost is variable depending on the day in the ICU, with the highest costs occurring after the first week. Increased ICU mortality among delirious patients masks a substantial amount of the cost of delirium. If mortality among patients experiencing delirium were to be eliminated, the cost of delirium could be over 20% higher.

There has only been one other study to date that specifically examined the costs of delirium in the ICU. The increased cost for ICU delirium in that prior study appeared to be due to increased duration of stay.⁹ This previous study, although the first of its kind, left a number of uncertainties. First, the analysis did not account for delirium-related mortality and time-dependent changes in the exposures. Although the prior study showed the associated between occurrence of delirium and costs associated with increased length of stay, due to the cross-sectional nature it was uncertain if the delirium preceded or followed multiple days in the ICU. The current study, however, clearly links an ICU day of delirium with the increase in daily cost of ICU care beyond length of stay. In addition, the prior study was unable to adjust for time-dependent changes in severity of illness, whereas the current study adjusts for daily differences in risk. Finally, the earlier work did not consider the effect of the competing risk of mortality on cost. The present analysis addresses each of these concerns and continued to find an increased cost associated with ICU delirium.

This study not only confirms but strengthens the association of delirium with the costs of care. We found that over a cumulative 30-day period that the incremental cost of 30 days of persistent delirium attributable to intensity of utilization due to delirium is about \$18,000. Therefore, delirium accounts for a proportion of the ICU cost after adjusting for age, comorbidities and time-varying changes of severity of illness adjustments (i.e., APACHE, SOFA, and mechanical ventilation status). The cost differences attributable to delirium remain following adjustment and appear to accumulate throughout a one-month ICU course, especially after the first week in the ICU.

Overwhelmingly, the costs of delirium reflect increased intensity of services among ICU survivors. There are many possible explanations for the increases in resource intensity, such as, (1) prolonged ICU length of stay, (2) broader availability and depth of therapeutic interventions (3) more cultural awareness of delirium resulting in higher frequency of monitoring, and (4) attempting treatments to address the symptoms of delirium (e.g., pharmacologic interventions). Upon examining more specific cost categories, we found incremental cost differences attributable to delirium across many of these categories that support these hypotheses. Professional, bed expenses, and dialysis costs accounted for the greatest difference among patients experiencing delirium, especially after the first week. This likely reflects the need for prolonged mechanical ventilation associated with delirium^{6,28,29}, additional consultative services, and procedural care. Pharmacy costs accounted for the second largest cost throughout the entire ICU stay, likely in the form of additional sedatives which may lead to a feed-forward cascade of more delirium, more treatments, and increased costs. Antipsychotics have risen in the delirium treatment algorithm, despite limited supporting data³⁰, and may be linked to additional pharmacy costs. In addition, delirium is associated with a number of complications that may drive up the cost of care including aspiration,³¹ nosocomial infections,³² restraint use,³³ that may be reflected in the additional respiratory, diagnostic radiology, and laboratory costs.

Importantly, as ICU mortality continues to improve over time,¹¹ the cumulative costs of delirium may potentially increase, especially if delirium-associated mortality specifically was reduced. Although the theoretical increase in cost is upwards of \$4,654, more realistic increases would be lower, as to date, interventions have only partially reduced delirium incidence and mortality^{2,34}. The study allows us to see that delirium's relationship with early ICU mortality appears to hide some of the costs of delirium. Prior research has shown that delirium is a potentially preventable condition.^{2,34,35} As evidence-based methods on delirium prevention and treatment grows, these additional costs that would have accrued if patients had not expired, have the potential to be unmasked as delirium associated mortality is minimized.

Delirium's high cost and high prevalence should stimulate hospital and ICU leaders to invest resources in delirium reducing interventions. Multicomponent interventions such as the Hospital Elder Life Program, have already seen success outside the ICU in reducing delirium and cost.³⁶ Measures to reduce benzodiazepine exposure, a leading delirium risk factor, may hold promise.^{35,37–39} Measures to improve sleep quality⁴⁰, extended family visitation⁴¹ and early mobilization³⁴ are additional measures associated with decreased delirium and coma and may come at little cost. Multi-component bundles, such as the Awakening Breathing Coordination Delirium Monitoring and Early Mobility (ABCDE)⁴² bundles have combined many of these elements and reduced days of delirium and mechanical ventilation.² On average, if one does not include the "mortality costs", reducing a day of delirium would lead to a cost savings of about \$440 (Total incremental cost of delirium/30 days = 30-day incremental cost attributed to intensity – 30-day incremental cost attributed to mortality = \$13,184/30 days). In light of the high prevalence of ICU delirium that is upwards of 80%,⁴³ the cost savings would be substantial.

There are a number of limitations to the current analysis worth considering. First, hospitals' ability to recognize delirium and their response to delirium may vary, so generalization to other institutions may be limited.^{44,45} Second, healthcare utilization and costs are variable nationally and internationally, and therefore the costs may not be representative of other U.S. or international hospital system. For example, the costs of pharmaceuticals are higher in the United States compared to international healthcare systems, and therefore, costs attributable to delirium may be reduced in these systems⁴⁶. In addition, the majority of costs are from the hospital perspective, not Medicare allowable costs, and differences in payer mix may yield differences in absolute costs, however we would not expect a difference in the relative associations of delirium and coma with increased costs. Also, as the cost perspective is from the hospital, it does not account for additional direct and indirect costs to society attributable to delirium in the ICU. For example, episodes of delirium produce a long-term cognitive impairment.⁴ This may reduce future workplace productivity, increase subsequent health care utilization, and require additional long-term care at home and in nursing facilities following the index hospitalization.⁴⁷ This limitation is balanced by the quality of our ICU cost data that was directly measured on an itemized, daily basis for each enrolled patient and obtained directly from the hospital finance system. Finally, although our analysis is strengthened with the application of a novel, modern statistical method to adjust for daily changes in risk and length of stay, our study is still observational in nature and subject to residual confounding.

In conclusion, we found that delirium is associated with a significant increase in ICU costs, even after accounting for daily changes in illness severity and length of stay. The primary cost driver is increased "intensity" of care among survivors, especially pharmacy costs, adjusting for time-varying changes in illness severity. Reducing delirium may lead to substantial cost savings in the ICU that are underestimated due to delirium-associated mortality. These findings should focus attention on the significant health and financial burdens imposed by delirium to motivate investment in the resources required for the prevention and mitigation of delirium. Future trials and quality improvement efforts to prevent and treat delirium should measure and weigh the costs of interventions with potential savings outlined in this study together with improvements in other key cognitive, functional, and quality of life outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cumulative incremental costs attributable to delirium. The solid line represents the adjusted cumulative incremental cost that is attributable to intensity of utilization due to delirium. The dotted line represents the increased cost one would incur if not for delirium-associated early ICU mortality. Vertical bars represent 95% confidence intervals that were obtained using 250 bootstrap iterations.

Figure 2:

Cumulative incremental costs attributable to delirium for service-specific costs. The solid line represents the adjusted cumulative incremental cost that is attributable to intensity of utilization due to delirium. The dotted line represents the increased cost one would incur if not for delirium-associated early ICU mortality. Vertical bars represent 95% confidence intervals that were obtained using 250 bootstrap iterations.

Table 1:**Patient Characteristics of Cohort (N = 479)**

Covariate	(N = 479)
Age at enrollment, mean ($\pm$ SD)	57 ($\pm$ 15)
Male, % (N)	52% (248)
White Race, % (N)	88% (420)
Insured – Yes, % (N)	95% (454)
ICU Type - Medical, % (N)	59% (298)
Charlson comorbidity score, median (IQR)	2.0 (1.0 to 4.0)
Cognitively Impaired, % (N)	12% (57)
APACHE II score at ICU admission, mean ($\pm$ SD)	25.3 ($\pm$ 8.5)
SOFA at enrollment, median (IQR)	9.0 (7.0, 12.0)
Mechanical Ventilation – Ever, % (N)	90% (430)
ICU Admission Diagnosis, % (N)	
Sepsis, ARDS	27% (130)
CHF / Cardiogenic Shock	12% (56)
Airway protection	11% (54)
Hepatobiliary / pancreatic surgery	6% (29)
Gastric surgery	6% (27)

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute Respiratory Distress Syndrome; CHF: Congestive Heart Failure;
 SOFA: Sequential Organ Failure Assessment

Table 2:

Estimates of the 30-day cumulative incremental effects of ICU delirium divided into portions attributable to intensity and mortality.

Cost Type [*]	Incremental cost attributed to intensity of utilization (95% CI)	Incremental cost attributed to mortality (95% CI)
Total Cost	17838 (11132, 23497)	4654 (2056, 7869)
Pharmacy	4018 (2582, 5020)	843 (334, 1396)
Laboratory	1185 (539, 2047)	270 (14, 604)
Diagnostic Radiology	665 (373, 1028)	142 (45, 244)
Respiratory, Physical Therapy, and Occupational Therapy	904.3 (520, 1339)	324 (138, 536)
Central Supply	2434 (1592, 3229)	399 (−47, 766)
Professional, Bed Expenses, and Dialysis	13965 (8698, 19457)	4564 (1666, 7872)

The cumulative incremental cost of delirium is broken down into two unique costs. The first column represents the adjusted cumulative incremental cost that is attributable to the intensity of resource utilization due to delirium. The second column represents the increased cost that would be incurred if not for delirium-associated early ICU mortality reducing the costs (since death stops any further costs of care). Costs include the 95% confidence intervals that were obtained using 250 bootstrap iterations.

* Total costs of \$17,838 indicates the incremental cost attributed to intensity of resource utilization, and were it not for early mortality associated with delirium, the costs would be an additional \$4654, thus total costs would be \$22,492.