

RESEARCH ARTICLE

Associations of Emergency Department Sedation and Analgesia and Hospital Outcomes in Mechanically Ventilated Patients

Lily Johnsky B.S.^{1,2}, Sonia M. Joshi M.D.^{1,3}, Zachary Gandee M.D.^{1,4}, Frank Wu M.D.^{1,5}, Jasmine Y. Gale M.D.^{1,6}, Lauren P. Eriquez MSN, AGACNP-BC^{1,7}, Arman Israelyan, D.O.^{1,8}, Jennifer Liu M.D.^{1,9}, Sarah E. Pajka M.D.^{1,10}, Liga Yusvirazi M.D.^{1,11}, Calvin A. Brown, III M.D.^{1,12}, Peter C. Hou M.D.^{1,13}

¹Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA

²Rush Medical College, Rush University, Chicago, Illinois, USA

³Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁴Department of Anesthesiology, The Warren Alpert Medical School of Brown University, Providence, RI, USA

⁵Department of Emergency Medicine, Lowell General Hospital, Lowell, MA, USA

⁶Department of Emergency Medicine, Concord Hospital, Concord, NH, USA

⁷Department of Internal Medicine, Atrius Health, Cambridge, MA, USA

⁸Department of Emergency Medicine, St. Alphonsus Regional Medical Center, Boise, ID, USA

⁹Department of Emergency Medicine, UTHealth McGovern Medical School, Houston, TX, USA

¹⁰Department of Emergency Medicine, University of Washington, Seattle, WA, USA

¹¹Department of Emergency Medicine, Kaiser Permanente Central Valley, Modesto, CA, USA

¹²Department of Emergency Medicine, UMass Chan - Lahey School of Medicine and The Lahey Clinic, Burlington, MA, USA

¹³Division of Emergency Critical Care, Department of Emergency Medicine, Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, Boston, MA, USA

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Corresponding Author: Peter C. Hou, Division of Emergency Critical Care, Department of Emergency Medicine, Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, Boston, MA, USA.

Abstract

Objective: Deep sedation has been hypothesized to be harmful in mechanically ventilated patients in the Emergency Department (ED). This study investigated the relationship between the level of sedation, immediately following ED intubation and within 24 hours of ICU admission, and hospital mortality.

Design: Retrospective cohort

Setting: Single center in Northeastern United States between January 1, 2016, and December 31, 2017

Patients: From the National Emergency Airway Registry of adult patients presenting to the ED, 294 patients underwent intubation and received mechanical ventilation. Patients who were intubated at a referring hospital, died in the ED, or required chronic mechanical ventilation prior to presentation were excluded.

Measurements and Main Results: Patients were classified as receiving deep or light sedation based upon the Richmond Agitation-Sedation Scale. A backward stepwise multivariable logistic regression was used to evaluate the primary outcome as a function of ED sedation depth. The primary outcome was hospital mortality, and secondary outcome was hospital length of stay. Of 294 mechanically ventilated ED patients, 79.9% received propofol and 63.6% were deeply sedated. There was a significant difference in median ED Richmond Agitation Sedation Scale (RASS) between survivors and non-survivors ($p < 0.001$). After multivariable logistic regression that adjusted for severity of illness and confounding variables between survivors and non-survivors, ED RASS remained a non-significant variable for hospital mortality, and ICU RASS and APACHE II score were associated with hospital mortality.

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Conclusion: Majority of mechanically ventilated patients receive deep sedation in the ED. ED RASS was not associated with hospital mortality.

Keywords: Emergency Department, Mechanical Ventilation, Sedation, Analgesia, ICU.

1. Introduction

Sedation and analgesia are crucial components of clinical care provided to critically ill patients in both the emergency department (ED) and intensive care unit (ICU) settings. Annually, at least 250,000 individuals are placed on mechanical ventilation in emergency departments across the United States¹. Analgosedation improves the patient-ventilator interaction and facilitates decreased work of breathing and efficient gas exchange². Analgosedation also alleviates pain and anxiety in the intubated patient, while minimizing the risk of awareness and its psychological ramifications, such as post-traumatic stress disorder (PTSD)³. Thus, the depth of sedation and choice of analgesic and sedative agents have various medical and psychological implications for both patient and provider⁴.

There are conflicting data in ED setting as to whether sedation impacts the duration of mechanical ventilation, hospital length of stay, and mortality. Most recently, a multicenter prospective cohort study showed that no significant difference in mortality exists between light versus deep sedation in the ED⁵. In contrast, others have reported worse clinical outcomes with deep sedation in the critically ill, including increased mortality, increased length of stay, and decreased ventilator-free days⁶⁻¹⁰. Hence, further work is needed to elucidate the relationship between sedation and mortality.

Our study sought to evaluate the association between depth of sedation and mortality in the immediate post-intubation period in the ED and within 24 hours of ICU admission. We also sought to characterize sedation strategies employed in the ED at our hospital.

2. Materials and Methods

2.1 Study Design, Setting, and Selection of Participants

This was a retrospective cohort study of patients requiring intubation and mechanical ventilation upon presentation to the hospital ED from January 1, 2016, through December 31, 2017. Patients were identified and intubation data were obtained from an existing database, the National Emergency Airway Registry (NEAR), a multi-center observational registry of de novo intubations in the ED (Supplemental Document

1). All mechanically ventilated patients were screened using the following inclusion criteria: (1) age ≥ 18 , (2) admission to the study ED requiring intubation with an endotracheal tube. Exclusion criteria included (1) intubation at an outside facility prior to ED arrival, (2) death in the ED, and (3) chronic mechanical ventilation prior to presentation. Inpatient data were abstracted from the electronic health record and stored in web-secure REDCap. Approval was obtained from the Human Research Committee prior to the start of data collection (IRB Protocol #2018P001311/PHS).

2.2 Measured Outcomes

Patient demographics, comorbidities, vital signs, laboratory values, the reason for intubation, length of hospital stay, and discharge disposition were collected. Specifically, history of severe organ failure or immunocompromise was recorded as one variable, as it is one of the factors used to calculate the Acute Physiology and Chronic Health Evaluation (APACHE II) score. Baseline severity of illness indices were collected by calculating the Sequential Organ Failure Assessment (SOFA) and APACHE II scores. Data surrounding ED intubation (induction agent, use of neuromuscular blockade) and additional analgesic/sedative agents administered both in the ED and within the first 24 hours of ICU admission were collected. Vasopressor use in the ED and ICU were also collected. Sedation depth was classified by the Richmond Agitation- Sedation Scale (RASS) score: light sedation was defined by a score greater than -3 and deep sedation was defined by a score from -3 to -5. The first RASS score in the ED post-intubation was collected along with the RASS score in the ICU 24 hours later. If no RASS score was recorded in the ED, the first RASS score documented in the ICU was used as a surrogate, as done in prior studies⁵⁻⁶. The primary outcome was in-hospital mortality and secondary outcome was hospital length of stay.

2.3 Statistical Analysis

Descriptive statistics were used to report patient characteristics. Continuous variables are presented with an average and standard deviation (SD), while data with non-normal distributions are presented with a median and interquartile range (IQR). Categorical variables are presented as percentages. We used conditional specification methods in the R package

multivariate imputation by chained equations (“mice”) to handle missing values¹¹. There were 89 missing values for the SOFA score and 55 for the APACHE II score. In this approach, each incomplete variable was regressed in turn on all other covariates, and the process was iterated until the regression estimate stabilized. The imputed value was chosen using predicted mean matching, which selects a value at random from among the observed data in which predicted values are closest to those of the one with a missing value.

The relationship between ED sedation depth and survival was tested with logistic regression by adjusting for potential confounding covariates. Patient’s baseline characteristics, such as age, immunocompromised status, mean arterial pressure, serum creatinine, and Glasgow coma scale score were not included in the model because these were already factored into the ED SOFA and ICU APACHE II scores. Statistically significant variables in univariate analysis with $p < 0.05$ were included in the model. A backward stepwise approach was used to obtain the best model and determine the independent predictors of mortality based on the Akaike information criterion and likelihood ratio test. Normality, statistical interactions, and collinearity (i.e., variance inflation factors) were assessed and the model used variables that were statistically independent. Model goodness of fit was assessed with the Hosmer-Lemeshow

test. Adjusted ORs (aORs) and corresponding 95% CIs were reported for variables in the multivariable model, adjusted for all variables in the model. All tests were two-tailed, and a p -value < 0.05 was considered statistically significant. Time (in days) to the primary outcome was assessed using the Kaplan-Meier Survival estimate and log-rank test, comparing deep and light sedation groups.

3. Results

3.1 Characteristics of Study Subjects

A total of 294 patients were included in the study analysis. Baseline patient characteristics are displayed in Table 1. Mortality was significantly higher in older individuals ($p < 0.001$) and those with a history of malignancy ($p = 0.002$). There were no significant associations between other comorbidities and mortality. Non-survivors had significantly lower mean arterial pressure ($p = 0.003$), higher serum creatinine ($p < 0.001$), and lower Glasgow coma score (GCS) ($p < 0.001$). Non-survivors were significantly more likely to have received vasopressors in the ED prior to intubation ($p = 0.018$) and received continued vasopressors in the ICU ($p = 0.02$). Furthermore, mean APACHE II and SOFA scores were significantly higher in non-survivors compared to survivors ($p < 0.001$). Median hospital length of stay was significantly shorter in non-survivors compared to survivors ($p < 0.001$) (Table 1).

Table 1. Baseline patient characteristics/demographics

Baseline Characteristics	All Subjects (n = 294)	Mortality Status		p-value
		Survivor (n = 227)	Non-survivor (n = 67)	
Age (median [IQR])	65 [54, 78]	63 [51, 74]	78 [60, 84]	<0.001
Female (%)	116 (39.5)	87 (38.3)	29 (43.3)	0.557
Race (%)				0.435
White	185 (62.9)	138 (60.8)	47 (70.1)	
Black	49 (16.7)	40 (17.6)	9 (13.4)	
Asian	15 (5.1)	11 (4.8)	4 (6)	
Other	45 (15.3)	38 (16.7)	7 (10.4)	
BMI (median [IQR])	26.5 [22.1, 30.7]	26.6 [23.4, 30.9]	25.1 [21.7, 30.1]	0.098
Comorbidities (%)				
Diabetes	81 (27.6)	59 (26)	22 (32.8)	0.344
Liver Disease	28 (9.5)	23 (10.1)	5 (7.5)	0.676
Malignancy	81 (27.6)	51 (22.5)	30 (44.8)	0.001
Moderate to Severe CKD	46 (15.6)	31 (13.7)	15 (22.4)	0.124
CHF	48 (16.3)	36 (15.9)	12 (17.9)	0.833
COPD	32 (10.9)	24 (10.6)	8 (11.9)	0.926
PVD	23 (7.8)	17 (7.5)	6 (9)	0.894
CVA or TIA	57 (19.4)	45 (19.8)	12 (17.9)	0.863
Dementia	20 (6.8)	13 (5.7)	7 (10.4)	0.284
Hemiplegia	4 (1.4)	3 (1.3)	1 (1.5)	1
Connective Tissue Disease	3 (1)	1 (0.4)	2 (3)	0.259

Peptic Ulcer Disease	6 (2)	3 (1.3)	3 (4.5)	0.265
History of Severe Organ Failure or Immunocompromise (%)	83 (28.2)	59 (26)	24 (35.8)	0.157
Mean Arterial Pressure (median [IQR])	65 [59, 79]	66 [60, 82]	61 [57, 68]	0.001
Arterial pH (median [IQR])	7.38 [7.30, 7.46]	7.38 [7.31, 7.46]	7.38 [7.21, 7.47]	0.397
Serum Creatinine (median [IQR])	1.04 [0.80, 1.51]	0.96 [0.76, 1.40]	1.33 [1.02, 2.17]	<0.001
Acute Renal Failure (%)	40 (13.6)	27 (11.9)	13 (19.4)	0.170
GCS (mean (SD))	6 (3.5)	7 (3.7)	4 (2.5)	<0.001
Vasopressors Received in ED Before Intubation (%)	49 (16.7)	31 (13.7)	18 (26.9)	0.018
Vasopressors Received in ED After Intubation (%)	88 (29.9)	65 (28.6)	23 (24.3)	0.458
Vasopressors Continued in ICU (%)	130 (44.2)	89 (39.2)	41 (61.2)	0.002
APACHE II Score (mean (SD))	22.7 (8.6)	20.9 (7.9)	28.9 (8)	<0.001
Hospital Length of Stay in Days (median [IQR])	9 [4, 15.8]	10 [5.5, 17]	4 [2, 11.4]	<0.001

Abbreviations: IQR = interquartile range; BMI = body mass index; CKD = chronic kidney disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; GCS = Glasgow Coma Score; SD = standard deviation; ED = emergency department; PVD = peripheral vascular disease; APACHE II = Acute Physiology and Chronic Health Evaluation II

3.1 Sedative/Analgesic Agents

Data related to analgo-sedation are outlined in Table 2. The most common sedative

and analgesic agents used in the ED were propofol (79.9%) and fentanyl (52.4%), respectively. In the ED, 63.9% received etomidate, 98.6% received neuromuscular blockade during ED intubation, 3.1% of patients received no sedation, and 4.1% of patients received no analgesia. In the ICU, the most common agents used were propofol (82%), fentanyl (65.6%), and midazolam (22.4%). In the ICU, 3.1% of patients received no sedation and 3.4% received no analgesia. Morphine use was more significantly associated with mortality in both ED and ICU settings ($p < 0.001$).

3.2 Sedation Level and Hospital Outcomes

Overall, 63.6% of mechanically ventilated patients received deep sedation while 36.4% received light sedation (Table 2). Median RASS score in the ED was -3.00 [-4.00 to -1.00] among survivors versus -4.00 [-5.00 to -2.00] among non-survivors ($p = 0.001$). Median RASS score in the first 24 hours of ICU stay was -2.00 [-4.00 to 0.00] among survivors versus -4.00 [-5.00 to -3.00] in non-survivors ($p < 0.001$). There was no significant difference in mortality between those who received deep sedation versus light sedation ($p = 0.089$, Table 2, Figure 1). A total of 60.8% of patients under deep sedation survived versus 73.1% in the light sedation group (inter-group difference, 12.3%).

Table 2. Analgo-sedation data

Sedation/Analgesia Status	All Subjects (n = 294)	Mortality Status		p-value
		Survivor (n = 227)	Non-Survivor (n = 67)	
Sedative Received in ED (%)				
Diazepam	1 (0.3)	1 (0.4)	0 (0.0)	1
Midazolam	81 (27.6)	69 (30.4)	12 (17.9)	0.064
Propofol	235 (79.9)	185 (81.5)	50 (74.6)	0.289
Ketamine	19 (6.5)	18 (7.9)	1 (1.5)	0.110
Lorazepam	44 (15)	36 (15.9)	8 (11.9)	0.552
Analgesic Received in ED (%)				
Morphine	7 (2.4)	1 (0.4)	6 (9)	<0.001
Hydromorphone	5 (1.7)	4 (1.8)	1 (1.5)	1
Fentanyl	154 (52.4)	125 (55.1)	29 (43.3)	0.119
Neuromuscular Blockade in ED (%)	290 (98.6)	225 (99.1)	65 (97.0)	0.183
Etomidate	188 (63.9)	144 (63.4)	44 (65.7)	0.849
No Analgesia in ED (%)	12 (4.1)	6 (2.6)	6 (9)	0.052
No Sedation in ED (%)	9 (3.1)	5 (2.2)	4 (6)	0.242

Sedative Received in ICU (%)				
Midazolam	66 (22.4)	55 (24.2)	11 (16.4)	0.238
Propofol	241 (82)	190 (83.7)	51 (76.1)	0.216
Ketamine	3 (1)	3 (1.3)	0 (0.0)	0.799
Lorazepam	20 (6.8)	15 (6.6)	5 (7.5)	1
Analgesic Received in ICU (%)				
Morphine	10 (3.4)	2 (0.9)	8 (11.9)	<0.001
Hydromorphone	23 (7.8)	15 (6.6)	8 (11.9)	0.242
Fentanyl	193 (65.6)	151 (66.5)	42 (62.7)	0.664
Neuromuscular Blockade in ICU (%)	25 (8.5)	18 (7.9)	7 (10.4)	0.689
Etomidate	5 (1.7)	5 (2.2)	0 (0.0)	0.492
No Analgesia in ICU (%)	10 (3.4)	7 (3.1)	3 (4.5)	0.865
No Sedation in ICU (%)	9 (3.1)	6 (2.6)	3 (4.5)	0.717
RASS Score in ED (median [IQR])	-3 [-4, -1]	-3 [-4, -1]	-4 [-5, -2]	0.001
RASS Score in the ICU (median [IQR])	-3 [-4, -1]	-2 [-4, 0]	-4 [-5, -3]	<0.001
Deep sedation/Light sedation (%)	187/107 (63.6/36.4)	138/89 (60.8/39.2)	49/18 (73.1/26.9)	0.089

Abbreviations: ED = emergency department; ICU = intensive care unit; RASS = Richmond Agitation-Sedation Scale; IQR = interquartile range; SD = standard deviation

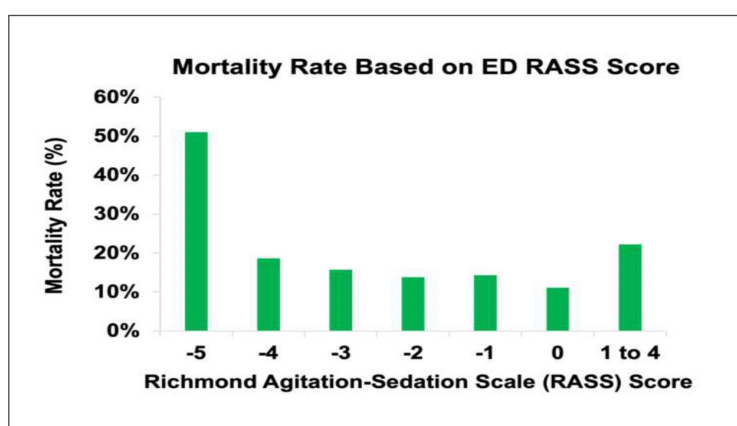


Figure 1. Mortality rate as a function of ED RASS score

Table 3 shows the multivariable logistic regression model with hospital mortality as the dependent variable to find independent factors that were associated with mortality. Identifiable confounding variables included in the model were: malignancy; vasopressor use in the ED and continued vasopressor use in the ICU; morphine use in the ED and in the ICU; RASS in the ED; RASS in the ICU; APACHE II scores, and ED SOFA scores. ED RASS level was not associated with mortality (aOR 1.13; 95% CI, 0.96-

1.33); in contrast, ICU RASS level was associated with mortality (aOR 0.58; 95% CI, 0.45-0.73). There was a significant association between the depth of sedation (light vs. deep) and hospital length of stay; subjects in the light sedation group had a significantly shorter duration of hospital stay compared to those in the deep sedation group ($p=0.034$, Table 4; Figure 2). On Kaplan-Meier analysis, survival did not diverge significantly between deep and light sedation groups (log-rank $p=0.3$, Figure 3).

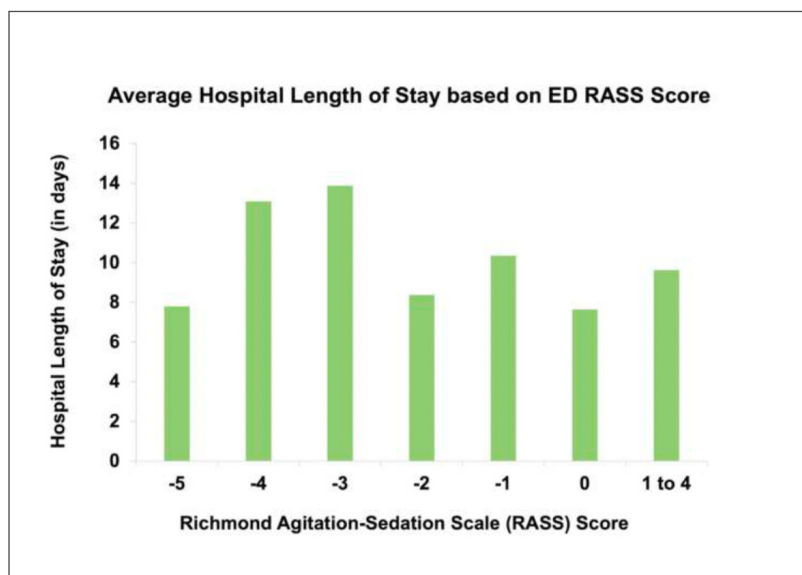
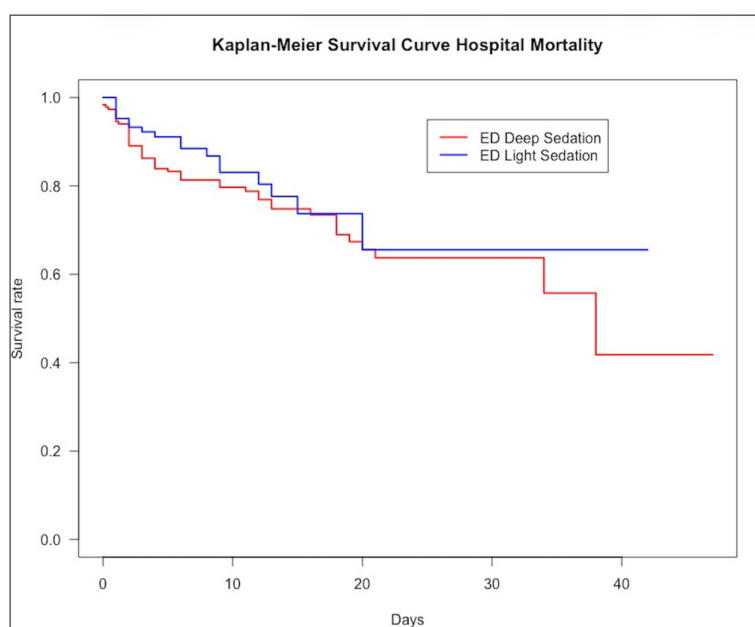
Table 3. Multivariable Logistic Regression Analysis with Hospital Mortality as the Dependent Variable

Variable	aOR	95% CI
Malignancy	1.72	0.84 to 3.51
Vasopressor before intubation in ED	0.99	0.39 to 2.45
Vasopressor continued in the ED	1.11	0.49 to 2.45
Morphine in the ED	10.56	0.99 to 287.79
Morphine in the ICU	14.66	2.63 to 126.14
ED RASS score	1.13	0.96 to 1.33
ED SOFA score	0.99	0.88 to 1.11
ICU RASS score	0.58	0.45 to 0.73
ICU APACHE score	1.09	1.04 to 1.16

Table 4. Association between sedation level in the ED and hospital length of stay

Secondary outcomes (days)	Deep Sedation (n = 187)	Light Sedation (n = 107)	Standard Error	p-value
Hospital Length of Stay (median [IQR])	10 [4.5, 18]	7 [4, 13]	1.4	0.034

The p-value for the secondary outcome was obtained from simple linear regression, comparing the deep and light sedation groups.

**Figure 2.** Average hospital length of stay as a function of ED RASS score**Figure 3.** Kaplan-Meier curve Log-rank $p = 0.3$

4. Discussion

Recent studies have begun to highlight the effects of sedation in the immediate postintubation period in the ED, as well as sequelae that carry over into the ICU. Deep sedation in the ICU is known to be associated with increased mortality as well as increased duration of mechanical ventilation^{7-8,10}. However, data regarding the relationship between level of ED sedation and mortality have been equivocal, necessitating further study in this area. Here, some of the findings demonstrated in a 2019 multicenter,

prospective cohort study conducted by Fuller *et al* were recapitulated. We followed similar methodology as Fuller *et al* with the goal of validating their team's results. In our study, more than half of mechanically ventilated patients received deep sedation in the ED, and those who received deep sedation in the ED experienced longer hospital length of stay compared to those who received light sedation. However, no significant difference in mortality between light and deep sedation in the ED was found. These results were consistent with those from Fuller's 2019 study.

Moreover, in survivors, the median RASS score was -3.00 in the ED and increased to -2.00 in the first 24 hours of ICU care. On the contrary, in non-survivors, median RASS score was -4.00 in both the ED and early ICU period, suggesting that deep sedation may persist across the transition to ICU care.

Subsequent work by Fuller et al. translated these observational findings into a multicenter before-and-after pilot trial. The study protocol prespecified implementation and feasibility outcomes¹³, and the completed trial reduced the proportion of deeply sedated patients from 60.2% to 38.8% without concerning trends in adverse events. The intervention group also had more ventilator-free and ICU-free days¹⁴. More recently, a retrospective cohort comparing patients intubated in the ED with those intubated in the ICU found that ED-intubated patients were less likely to achieve light sedation within 24 hours and had a longer median time to light sedation¹⁵. Together, these studies suggest that early ED sedation practices may affect subsequent ICU care and support further adequately powered trials of interventions targeting lighter sedation.

In our cohort, survivors had a significantly increased hospital length of stay compared to non-survivors. This may be explained by inter-relating factors. First, survivors may have experienced critical illness or devastating injury and required increased time to recover in the hospital. Second, non-survivors likely had poor prognosis, which may have led to earlier goals of care discussions in the ICU and may have led to withdrawal of ICU support.

Neuromuscular blockade was administered during ED intubation in 63.9% of patients in our cohort. The use of neuromuscular blockade is an important consideration in the immediate post-intubation period, as pharmacologic paralysis may affect clinical assessment of sedation and patient-ventilator interaction. The choice and duration of neuromuscular blockade may therefore influence the relationship between early post-intubation sedation and subsequent outcomes. However, our study did not characterize the specific neuromuscular blocking agents used or their duration of action, and we were therefore unable to assess whether differences in neuromuscular blockade selection contributed to differences in observed RASS scores or clinical outcomes.

The most common sedative and analgesic agents used in mechanically ventilated patients in the ED included propofol and fentanyl. This is consistent with prior studies, which showed that propofol, midazolam,

and fentanyl were the most frequently used agents in mechanically ventilated patients in the ED⁵⁻⁶. Furthermore, only 3.1% of mechanically ventilated patients received no sedation in the ED, while a prior multi-center study showed that roughly 20% received no sedation in the ED⁵. The small number of patients who received no sedation likely sustained intracranial injury and may have been intentionally not sedated in the ED (e.g., to perform a full neurologic exam), though specific cases were not analyzed in our study.

Although current guidelines from the Society of Critical Care Medicine recommend light sedation over deep sedation in the critically ill, this is a conditional recommendation, as there is low quality of supporting evidence¹². Prior studies did not demonstrate decreased mortality, delirium prevalence, or PTSD incidence with light sedation¹². Moreover, the guidelines suggest that a protocol-based, stepwise approach to analgo-sedation should be used in managing critically ill patients, though there is only moderate supporting evidence. Studies show that both daily sedation interruption and protocolized methods for sedation can achieve light sedation in mechanically ventilated patients in the ICU.

Because this was a single-center, retrospective study, the results may not be generalizable; the findings from this study reflect the sedation practices specific to our institution. Moreover, the sample size was 294, yielding relatively low power. Although some potentially eligible intubations may not have been captured in the registry, systematic reporting bias is unlikely given the NEAR established compliance procedures. Each participating site was required to submit a compliance plan outlining procedures for identifying and recording ED intubations, with a minimum capture requirement of 90%. Additionally, the first RASS value in the ED may not have been fully representative of sedation depth by the time the sedative agent was titrated to the desired level. The timing of RASS assessment relative to ED intubation and subsequent ICU admission may also have influenced our findings, particularly because sedation practices may change during the transition from the ED to the ICU. Although sedative and analgesic agents administered in the ED were captured, the dose, timing, and method of administration (e.g., intermittent intravenous bolus versus continuous infusion) were not evaluated. These factors may have influenced the observed RASS scores and could not be accounted for in our analysis. The specific neuromuscular blocking agent and duration of neuromuscular blockade were also not characterized.

These factors may have influenced observed RASS scores and could not be accounted for in our analysis. Further, RASS could have been confounded by underlying clinical conditions such as traumatic brain injury.

To control for misclassification bias, a systematic approach during the chart abstraction process was followed, and a standardized form on REDCap for data collection with precise definitions for each of the variables collected was used (Supplemental Document 2). Furthermore, if the missing data (SOFA and APACHE II scores) values markedly differ, this might alter the findings; however, the imputation process accounted for several key variables. Finally, the associations found in our study do not imply causal relationships but may be used for hypothesis generation.

5. Conclusion

In summary, analgosedation is a fundamental part of the care provided to mechanically ventilated patients in the ED, though its impacts on clinical outcomes, including mortality, have been mixed. Additional work is warranted to further clarify the relationship between sedation depth in the ED and morbidity and mortality.

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None

Conflict of Interest Disclosure

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Multiple Conflicts: CAB receives honoraria for speaking and provides expert testimony.

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