

Early mechanical ventilation for grade IV hepatic encephalopathy is associated with increased mortality among patients with cirrhosis: an exploratory study

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Background: Unresponsive patients with toxic-metabolic encephalopathies often undergo endotracheal intubation for the primary purpose of preventing aspiration events. However, among patients with pre-existing systemic comorbidities, mechanical ventilation itself may be associated with numerous risks such as hypotension, aspiration, delirium, and infection. Our primary aim was to determine whether early mechanical ventilation for airway protection was associated with increased mortality in patients with cirrhosis and grade IV hepatic encephalopathy.

Methods: The National Inpatient Sample was queried for hospital stays due to grade IV hepatic encephalopathy among patients with cirrhosis between 2016 and 2019. After applying our exclusion criteria, including cardiopulmonary failure, data from 1,975 inpatient stays were analyzed. Patients who received mechanical ventilation within 2 days of admission were compared to those who did not. Univariable and multivariable logistic regression analyses were performed to identify clinical factors associated with in-hospital mortality.

Results: Of 162 patients who received endotracheal intubation during the first 2 hospital days, 64 (40%) died during their hospitalization, in comparison to 336 (19%) of 1,813 patients in the comparator group. In multivariable logistic regression analysis, mechanical ventilation was the strongest predictor of in-hospital mortality in our primary analysis (adjusted odds ratio, 3.00; 95% confidence interval, 2.14–4.20; $P < 0.001$) and in all sensitivity analyses.

Conclusions: Mechanical ventilation for the sole purpose of airway protection among patients with cirrhosis and grade IV hepatic encephalopathy may be associated with increased in-hospital mortality. Future studies are necessary to confirm and further characterize our findings.

Key Words: hepatic encephalopathy; liver cirrhosis; mechanical ventilation

INTRODUCTION

Unresponsive patients commonly receive endotracheal intubation and mechanical ventilation in the absence of cardiopulmonary failure [1]. This is typically done to prevent the sequelae of aspiration, namely pneumonia, which could occur in those without a sufficient gag reflex. Trauma societies generally support recommendations in favor of endotracheal intuba-

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tion for patients with severe head trauma defined by a Glasgow Coma Scale score of 8 or less, but providers often also elect to perform this procedure in patients with medical delirium or other non-trauma-related indications [1,2]. However, endotracheal intubation and mechanical ventilation are associated with numerous risks such as aspiration, hypotension, ongoing delirium, and nosocomial pneumonia [3,4]. Patients who are intubated will ultimately remain hospitalized and in the intensive care unit for longer periods of time and may experience increased mortality [5]. Although these outcomes are mostly a consequence of acute illness and underlying comorbidities, endotracheal intubation and mechanical ventilation may independently impact outcomes due to direct or indirect effects on virtually every organ system [6]. Their use for strong indications such as cardiopulmonary failure is often unavoidable, but no randomized controlled trials have demonstrated that elective intubation for the sole purpose of airway protection is beneficial. A number of prospective and retrospective observational studies have attempted to address this issue among patients with trauma, medical delirium, or gastrointestinal bleeding with mixed results [7,8]. Consequently, it remains unclear whether this practice is clinically justified on a routine basis.

Among those with toxic-metabolic encephalopathies, patients with decompensated cirrhosis are especially vulnerable to the risks of mechanical ventilation with in-hospital mortality among this subset of patients exceeding 50% [9,10]. This is a consequence of factors such as impaired immunity, altered drug metabolism, circulatory dysfunction, and sarcopenia [11]. However, patients with grade IV hepatic encephalopathy often undergo this procedure early in their clinical course, prior to the implementation of diagnostic and therapeutic interventions and in the absence of other indications [12]. Previous observational studies have not assessed its relative impact on mortality in patients with cirrhosis, and society guidelines have not specifically addressed the issue [13]. The aim of this exploratory study is to determine whether early endotracheal intubation and mechanical ventilation for airway protection can affect clinical outcomes among patients with cirrhosis and grade IV encephalopathy. Our hypothesis is that this practice may be associated with increased in-hospital mortality.

MATERIALS AND METHODS

Patient Selection and Study Design

The National Inpatient Sample (NIS) is the largest public-

KEY MESSAGES

- Patients with cirrhosis and grade IV hepatic encephalopathy often undergo endotracheal intubation and mechanical ventilation early in their hospital course to prevent aspiration events.
- However, these individuals often have underlying multi-system dysfunction which makes them uniquely susceptible to the many risks of mechanical ventilation.
- Our study demonstrates that the use of endotracheal intubation and mechanical ventilation for airway protection among patients with cirrhosis and grade IV hepatic encephalopathy is associated with increased in-hospital mortality after adjusting for possible confounding variables.

ly-available inpatient dataset in the United States. It is sponsored by the Agency for Healthcare Research and Quality (AHRQ) for the Healthcare Cost and Utilization Project, which receives data from discharge abstracts from participating state partners. The unweighted dataset includes deidentified demographic, diagnosis, procedure, utilization, cost, and outcome data from a representative sample of over 7 million admissions annually from 48 states, covering more than 97% of the population nationwide. Because the NIS is publicly available and consists of deidentified retrospective data from numerous institutions with protocols to maintain patient anonymity, Institutional Review Board approval and patient consent are not required.

This study met the requirements set forth by the AHRQ. The NIS was screened from 2016–2019 for inpatient stays that included individuals who were 18 years or older with International Classification of Diseases, 10th revision (ICD-10) diagnosis codes for both grade IV hepatic encephalopathy (K72.91, K72.11, K70.41, K72.01, K71.11) and cirrhosis (K70.3, K70.30, K70.31, K74.4, K74.5, K74.6, K74.60, K74.69) [14–16]. Inpatient diagnoses listed in the NIS are prioritized in order of importance such that the diagnosis that most directly led to the inpatient admission is listed first. Therefore, we limited our search to admissions in which grade IV hepatic encephalopathy was listed as either the primary, secondary, or tertiary diagnosis. A separate cirrhosis diagnosis listed in the record was required largely to exclude patients who did not have cirrhosis such as those with acute liver failure.

Patients who had primary, secondary, or tertiary diagnoses of respiratory failure, shock, or cardiac arrest were then ex-

cluded, as were those who received upper endoscopy or arterial line placement within the first 2 days of admission, since there was a high likelihood that these individuals received endotracheal intubation for alternative indications aside from grade IV hepatic encephalopathy. Although not all patients who have cardiopulmonary failure or who undergo urgent endoscopy receive endotracheal intubation, we intentionally excluded this entire subset as a means of limiting our analysis to those who had grade IV hepatic encephalopathy but were otherwise clinically stable. Finally, patients who underwent liver transplantation anytime during the admission or those with missing outcome data were also excluded. The remaining cohort was then divided into an index group (those who had early mechanical ventilation within 2 days of admission) and a control group (those who did not). The following ICD-10 procedure codes were used to identify patients who underwent endotracheal intubation: 0BH17EZ, 0BH18EZ, 1GZ31CAEP, and 1GZ31CAND.

Data Collection

Demographics data was collected, including age, sex, race, and teaching status of the hospital (academic vs. private/rural). ICD-10 codes were then used to identify cirrhosis-specific diagnostic and prognostic factors such as disease etiology and the presence of ascites and hepatocellular carcinoma, in addition to the following comorbidities: chronic obstructive pulmonary disease, congestive heart failure, chronic kidney disease, and obesity. These covariates were chosen because (1) they are readily identifiable using specific diagnostic codes and (2) they are most likely to potentially impact outcomes in our cohort. The ICD-10 codes we selected were not exhaustive for the abovementioned diagnoses but represented the primary codes used by clinicians and often encompassed other less frequently used diagnostic codes. We did not incorporate diagnosis codes for jaundice or coagulopathy because these codes have been historically underutilized or misclassified [17]. Finally, we also identified the most common adjunctive diagnosis on admission aside from cirrhosis, hepatic encephalopathy, or any of the comorbidities previously listed. Missing data for race and sex was imputed using the Hmisc package in R (R Foundation, Vienna, Austria) [18]. In accordance with the NIS data user agreement, individual table cell counts of ≤ 10 were suppressed to maintain patient confidentiality.

Outcomes and Statistical Analysis

Our primary outcome was in-hospital mortality. We assessed

the impact of mechanical ventilation, in addition to all relevant demographics, cirrhosis-related factors, chronic comorbidities, and the most common adjunctive diagnosis on admission using logistic regression models. For these analyses, the data was stratified based on a combination of hospital characteristics and weighted using discharge weights provided by the AHRQ. All covariates with P-values < 0.10 in univariable analyses were included in multivariable analyses. Pre-specified sensitivity analyses were done to assess the impact of (1) defining early endotracheal intubation using a cutoff of one day rather than 2 days, (2) limiting the analysis only to patients with grade IV hepatic encephalopathy as a primary or secondary diagnosis (rather than including tertiary as well), and (3) limiting the analysis only to patients with grade IV hepatic encephalopathy as the primary diagnosis. A post-hoc sensitivity analysis was also done to assess the impact of hemodialysis since this modality can mitigate hepatic encephalopathy. Length of stay was also measured, and differences were assessed using Welch's t-test. All analyses were performed in R statistical software (version 4.0.2; R Core Team 2020) using the survey package [19].

RESULTS

Baseline Characteristics and Outcomes

A total of 1,975 patient stays were included in the study, of which 162 received endotracheal intubation within the first 2 days and 1,813 did not (Figure 1, Table 1). Based on the ICD-10 code scheme that we utilized (Table 2), the majority of patients had alcohol-related cirrhosis (57%) and ascites (54%). The most common comorbidity was chronic kidney disease (29%), and the most common adjunctive diagnosis on admission was acute kidney injury (26%). Among the patients who did not receive endotracheal intubation within the first 2 days, 51 (3%) were intubated later in their hospitalization.

Of those who received endotracheal intubation within the first 2 days, 64 (40%) died during their hospitalization, in comparison to 336 (19%) in the comparator group. Of the deaths that occurred in the comparator group, 36 were among the subset of 51 patients who received mechanical ventilation after the first 2 days. Length of stay in the early mechanical ventilation group (median, 7 days; interquartile range, 3–12 days) was significantly longer than the comparator group (median, 5 days; interquartile range, 3–9 days; $P=0.006$).

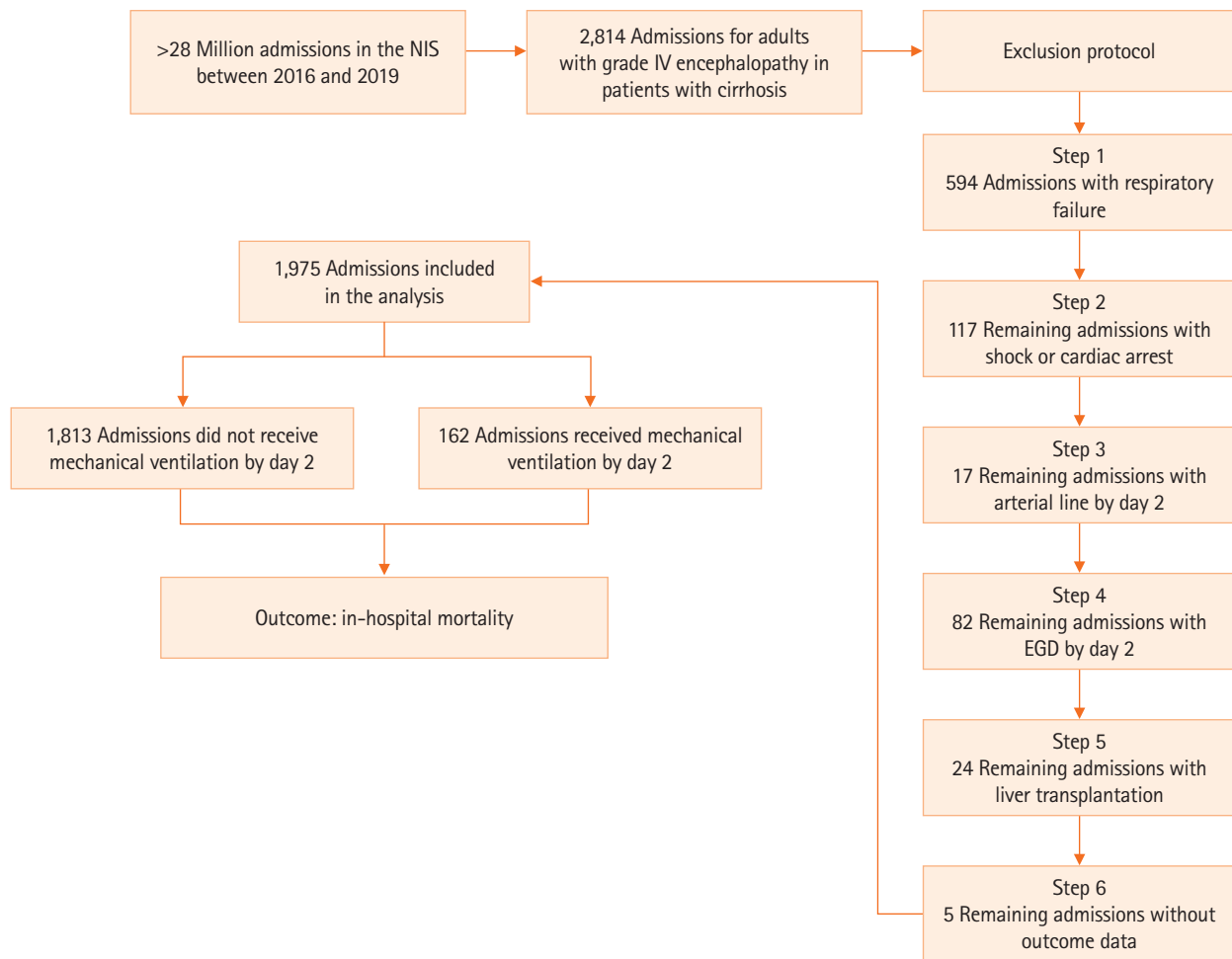


Figure 1. Flowchart of patients included in the study based on our screening and exclusion criteria. NIS: National Inpatient Sample; EGD: esophagogastroduodenoscopy.

Logistic Regression Analysis

In univariable logistic regression analysis, mechanical ventilation during the first 2 days was associated with increased odds for death (odds ratio [OR], 2.87; 95% confidence interval [CI], 2.07–4.00; $P < 0.001$). Additionally, cirrhosis due to alcohol use, ascites, hepatocellular carcinoma, and acute kidney injury were also associated with increased odds for death whereas female sex, chronic kidney disease and obesity were associated with reduced odds for death. In the multivariable model, mechanical ventilation (adjusted odds ratio [aOR], 3.00; 95% CI, 2.14–4.20; $P < 0.001$), ascites, hepatocellular carcinoma, and acute kidney injury were associated with increased odds for death whereas chronic kidney disease was associated with reduced odds for death (Table 3).

Pre-specified sensitivity analyses revealed that limiting our cohort to patients who received mechanical ventilation on

the first day only or among patients who had grade IV hepatic encephalopathy as either a primary or secondary diagnosis did not significantly impact our findings (Table 4). However, when we limited our cohort to those who had grade IV hepatic encephalopathy as a primary diagnosis only, mechanical ventilation, ascites, and acute kidney injury were the only factors associated with mortality in the multivariable model.

A post-hoc sensitivity analysis was done to determine whether the use of hemodialysis represented a confounding variable that accounted for the mortality benefit noted among patients with chronic kidney disease. We identified 52 patients who received hemodialysis by the second hospital day, of which 45 had chronic kidney disease. The exclusion of all patients who received hemodialysis diminished the association between chronic kidney disease and mortality in univariable analysis (OR, 0.82; 95% CI, 0.63–1.06; $P = 0.12$).

Table 1. Baseline characteristics of the study cohort

| Variable | No mechanical ventilation | Mechanical ventilation |
|---|---------------------------|------------------------|
| Demographics | | |
| Number | 1,813 | 162 |
| Age (yr) | 60 (52-67) | 58 (52-64) |
| Sex (female) | 769 (42) | 62 (38) |
| Race (white) | 1,182 (65) | 98 (60) |
| Hospital status (academic) | 1,137 (63) | 114 (70) |
| Cirrhosis-related factor | | |
| Cirrhosis etiology (alcohol-related) | 1,031 (57) | 101 (62) |
| Ascites | 982 (54) | 94 (58) |
| Hepatocellular carcinoma | 120 (7) | NA |
| Medical comorbidity | | |
| Chronic obstructive pulmonary disease | 190 (10) | 20 (12) |
| Congestive heart failure | 158 (9) | 17 (10) |
| Chronic kidney disease | 530 (29) | 39 (24) |
| Obesity | 205 (11) | 16 (10) |
| Most common adjunctive diagnosis | | |
| Acute kidney injury | 474 (26) | 35 (22) |

Values are presented as median (interquartile range) or number (%). Based on the requirements of data user agreement for the National Inpatient Sample, cells with patients counts less than or equal to 10 cannot be displayed and are denoted as not available (NA).

DISCUSSION

Our findings suggest that early endotracheal intubation for airway protection among patients with cirrhosis and grade IV hepatic encephalopathy may be associated with increased in-hospital mortality. Our analysis excluded patients who may have had strong indications for mechanical ventilation, namely cardiopulmonary failure, and assessed the impact of other covariates such as demographics, cirrhosis etiology and severity, and relevant acute and chronic comorbidities. The application of mechanical ventilation was the strongest predictor of mortality in all of our regression models. The aOR for mechanical ventilation was approximately 3, an effect size that is clinically meaningful for a study that excluded patients who have the highest risk for in-hospital death (i.e., those with shock and respiratory failure). The mortality rate for ventilated patients with hepatic encephalopathy in our study was comparable with rates cited in other recent studies and additional predictors of mortality in our multivariable models, including ascites and acute kidney injury, are well-established prognostic factors among patients with cirrhosis, suggesting that our cohort is similar to external cohorts [9,20,21]. Although the as-

Table 2. ICD-10 codes for the diagnoses incorporated in the study

| Diagnosis/procedure | ICD-10 code |
|---|---|
| Inclusion criteria | |
| Cirrhosis | K70.3, K70.30, K70.31, K74.4, K74.5, K74.6, K74.60, K74.69 |
| Grade IV hepatic encephalopathy (coma) | K72.91, K72.11, K70.41, K72.01, K71.11 |
| Exclusion criteria | |
| Respiratory failure | J95.821, J95.822, J96.00, J96.01, J96.02, J96.20, J96.90, J96.92 |
| Shock/cardiac arrest | I46, I46.2, I46.8, I46.9, R09.2, R57.0, R57.1, R57.8, R65.21, T78.2, T81.10, T81.12, T81.19 |
| Arterial line (procedure) | 03HC3DZ, 03HB3DZ, 04HL3DZ, 04HK3DZ |
| Upper endoscopy (procedure) | 0DJ08ZZ |
| Liver transplantation (procedure) | 0FY00Z0 |
| Cirrhosis-related factor | |
| Cirrhosis etiology (alcohol-related) | K70.3, K70.30, K70.31, K70.4, K70.40, K70.41 |
| Ascites | R18, R18.8, K70.31 |
| Hepatocellular carcinoma | C22.0 |
| Comorbidity | |
| Chronic obstructive pulmonary disease | J44.9, J44.1 |
| Congestive heart failure | I50, I50.1, I50.2, I50.20, I50.22, I50.3, I50.30, I50.32, I50.4, I50.40, I50.42, I50.8, I50.82, I50.83, I50.84, I50.89, I50.9 |
| Chronic kidney disease | N18, N18.1, N18.2, N18.3, N18.30, N18.31, N18.32, N18.4, N18.5, N18.6, N18.9 |
| Obesity | E66.01, E66.9 |
| Most common adjunctive diagnosis | |
| Acute kidney injury | N17.0, N17.1, N17.2, N17.8, N17.9, K76.7 |
| Endotracheal intubation (procedure) | 0BH17EZ, 0BH18EZ, 1GZ31CAEP, 1GZ31CAND |

ICD-10: International Classification of Diseases, 10th revision.

Table 3. Logistic regression analyses for factors associated with mortality

| Variable | OR/aOR (95% CI) | P-value |
|---------------------------------------|------------------|---------|
| Univariable model | | |
| OR (95% CI) | | |
| Mechanical ventilation | 2.87 (2.06–4.00) | <0.001 |
| Age | 0.99 (0.98–1.00) | 0.28 |
| Sex (female) | 0.76 (0.60–0.95) | 0.02 |
| Race (white) | 1.10 (0.87–1.39) | 0.43 |
| Hospital status (academic) | 1.02 (0.81–1.29) | 0.85 |
| Cirrhosis etiology (alcohol-related) | 1.42 (1.13–1.78) | 0.002 |
| Ascites | 1.85 (1.47–2.33) | <0.001 |
| Hepatocellular carcinoma | 2.09 (1.43–3.04) | <0.001 |
| Chronic obstructive pulmonary disease | 1.02 (0.72–1.44) | 0.93 |
| Congestive heart failure | 0.98 (0.67–1.44) | 0.93 |
| Chronic kidney disease | 0.75 (0.58–0.96) | 0.02 |
| Obesity | 0.64 (0.43–0.94) | 0.02 |
| Acute kidney injury | 1.84 (1.45–2.32) | <0.001 |
| Multivariable model | | |
| aOR (95% CI) | | |
| Mechanical ventilation | 3.00 (2.14–4.20) | <0.001 |
| Sex (female) | 0.89 (0.70–1.13) | 0.34 |
| Cirrhosis etiology (alcohol-related) | 1.24 (0.97–1.58) | 0.09 |
| Ascites | 1.62 (1.28–2.06) | <0.001 |
| Hepatocellular carcinoma | 2.12 (1.44–3.13) | <0.001 |
| Chronic kidney disease | 0.65 (0.50–0.85) | 0.002 |
| Obesity | 0.68 (0.46–1.02) | 0.06 |
| Acute kidney injury | 2.04 (1.59–2.62) | <0.001 |

Variables with $P < 0.10$ in univariable models were included in the multivariable model.

OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

sociation between chronic kidney disease and decreased mortality was unexpected, a post-hoc sensitivity analysis suggested that this finding may be partially explained by the fact that a number of these patients received hemodialysis, an intervention that can be used to treat hepatic encephalopathy and may have thus facilitated clinical improvement.

In addition to being consistent with previous reports in the literature, we believe that our findings have a strong physiologic basis. Patients with cirrhosis and hepatic encephalopathy are particularly susceptible to the complications of mechanical ventilation because of possible underlying circulatory, neurologic, and immunologic dysfunction [11]. Because mechanical ventilation itself may be associated with further impairment in cardiovascular and cognitive function and immune defense, patients with cirrhosis may be at a greater risk for developing shock, progressive delirium, and infection, among other complications [22–24].

Table 4. Multivariable logistic regression models for pre-specified sensitivity analyses

| Variable | aOR (95% CI) | P-value |
|--------------------------------------|------------------|---------|
| Sensitivity analysis 1 | | |
| Mechanical ventilation | 3.01 (2.12–4.28) | <0.001 |
| Sex (female) | 0.89 (0.70–1.14) | 0.35 |
| Cirrhosis etiology (alcohol-related) | 1.24 (0.97–1.58) | 0.09 |
| Ascites | 1.64 (1.29–2.08) | <0.001 |
| Hepatocellular carcinoma | 2.11 (1.43–3.12) | <0.001 |
| Chronic kidney disease | 0.65 (0.50–0.85) | 0.002 |
| Obesity | 0.69 (0.46–1.04) | 0.07 |
| Acute kidney injury | 2.02 (1.57–2.59) | <0.001 |
| Sensitivity analysis 2 | | |
| Mechanical ventilation | 2.64 (1.79–3.87) | <0.001 |
| Sex (female) | 0.82 (0.63–1.06) | 0.12 |
| Cirrhosis etiology (alcohol-related) | 1.15 (0.88–1.51) | 0.31 |
| Ascites | 1.58 (1.22–2.05) | <0.001 |
| Hepatocellular carcinoma | 1.98 (1.29–3.02) | 0.002 |
| Chronic kidney disease | 0.65 (0.48–0.87) | 0.004 |
| Obesity | 0.74 (0.49–1.14) | 0.18 |
| Acute kidney injury | 2.08 (1.59–2.72) | <0.001 |
| Sensitivity analysis 3 | | |
| Mechanical ventilation | 2.50 (1.56–4.02) | <0.001 |
| Sex (female) | 0.81 (0.59–1.12) | 0.20 |
| Race (white) | 1.31 (0.94–1.82) | 0.11 |
| Cirrhosis etiology (alcohol-related) | 1.25 (0.90–1.74) | 0.18 |
| Ascites | 1.60 (1.17–2.20) | 0.004 |
| Acute kidney injury | 1.78 (1.28–2.47) | <0.001 |

Variables with $P < 0.10$ in univariable models (not shown) were included in the multivariable models. Comparison were made between patients who received endotracheal intubation on day 1 only versus those who did not (sensitivity analysis 1) and between patients who had grade IV encephalopathy as the primary or secondary diagnoses only (sensitivity analysis 2) or primary diagnosis only (sensitivity analysis 3).

aOR: adjusted odds ratio; CI: confidence interval.

Although our findings are physiologically plausible and largely representative of the larger body of work involving mechanical ventilation in cirrhosis, our study is impacted by important limitations, largely due to the retrospective observational nature of the design. It may be influenced by multiple types of bias, including the effects of unmeasured confounding variables. Because we utilized a publicly-available deidentified dataset, our analysis was limited to covariates that were already present, and thus other key factors such as vital signs and laboratory parameters could not be included in our analyses. We attempted to exclude all patients with cardiopulmonary failure by using appropriate ICD-10 diagnosis and procedure codes, but we suspect that some individuals who received

endotracheal intubation and mechanical ventilation may have been more critically ill than those who did not receive these interventions in ways that we were unable to capture. Additional liver-specific prognostic factors such as model for end-stage liver disease (MELD) scores and Child-Turcotte-Pugh (CTP) classification were also unavailable, but by including only those with grade IV encephalopathy, our study effectively consisted of patients with CTP scores of 7 or higher (i.e., CTP B or C status). Furthermore, studies utilizing administrative datasets are commonly impacted by inaccurate or incomplete coding. Therefore, our study design focused on applying a fairly restrictive coding scheme that required separate diagnostic codes for grade IV hepatic encephalopathy (i.e., hepatic failure with coma) and cirrhosis for screening to increase the specificity of our cohort. However, it is possible that patients in the non-intubated group who were coded as having hepatic failure with coma may have actually had grade II or III hepatic encephalopathy whereas those who were intubated had true grade IV hepatic encephalopathy. Finally, we were unable to assess for differences in the medical management patients received (i.e., use of lactulose and/or rifaximin), which could have impacted outcomes as well.

In conclusion, this study is the first to our knowledge to demonstrate that mechanical ventilation for patients with cirrhosis and grade IV hepatic encephalopathy may be associated with increased in-hospital mortality in a comparative fashion. Our findings suggest that, in the absence of other strong indications for mechanical ventilation, it may be reasonable to consider deferring early endotracheal intubation for airway protection in select patients who are otherwise clinically stable and may respond to prompt medical management for hepatic encephalopathy. However, it is crucial to note that these preliminary findings should be interpreted cautiously in the context of our study limitations. Future retrospective studies that incorporate more granular patient data or prospective trials are necessary before specific clinical recommendations can be provided.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: SS. Formal analysis: SS. Funding acquisition: all authors. Methodology: all authors. Project administration: all authors. Visualization: SS. Writing—original draft: SS. Writing—review & editing: all authors.

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