HHS Public Access

Author manuscript

Metab Brain Dis. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Metab Brain Dis. 2015 August ; 30(4): 1063–1071. doi:10.1007/s11011-015-9679-8.

The Confusion Assessment Method for the Intensive Care Unit in Patients with Cirrhosis

Eric S. Orman, MD, MSCR[1], **Anthony Perkins, MS**[2,3], **Marwan Ghabril, MD**[1], **Babar A. Khan, MD, MS**[1,2,3], **Naga Chalasani, MD**[1], and **Malaz A. Boustani, MD, MPH**[1,2,3]

[1]Department of Medicine, Indiana University School of Medicine

[2]Center for Aging Research, Indiana University School of Medicine

[3]Regenstrief Institute, Inc.

Abstract

Background—In the intensive care unit (ICU), delirium is routinely measured with the widely-used, validated Confusion Assessment Method for the ICU (CAM-ICU), but CAM-ICU has not been studied in patients with cirrhosis. We studied a group of patients with cirrhosis to determine the relationship between delirium measured by CAM-ICU and clinical outcomes.

Methods—Consecutive patients with cirrhosis admitted to the ICU from 2009 to 2012 were included in a retrospective cohort study. Patients were screened twice daily for coma and delirium during their ICU stay using the Richmond Agitation Sedation Scale (RASS) and CAM-ICU. The association between delirium/coma and mortality was determined using multiple logistic regression. RASS and CAM-ICU were also compared to a retrospective assessment of hepatic encephalopathy (HE).

Results—Of 91 patients with cirrhosis, 26 (28.6%) developed delirium/coma. RASS/CAM-ICU had fair agreement with the HE assessment (κ 0.38). Patients with delirium/coma had numerically greater mortality in-hospital (23.1% vs. 7.7%, $p = 0.07$) and at 90 days (30.8% vs. 18.5%, $p = 0.26$), and they also had longer hospital length of stay (median 19.5 vs. 6 days, $p < 0.001$). Delirium/coma was associated with increased inpatient mortality, independent of disease severity (unadjusted OR 3.6; 95% CI, 0.99–13.1; MELD-adjusted OR 5.4; 95% CI, 1.3–23.8; acute physiology score-adjusted OR 2.2; 95% CI, 0.53–8.9). Delirium/coma was also associated with longer length of stay after adjusting for disease severity.

Conclusion—In critically ill patients with cirrhosis, delirium/coma as measured by the RASS and CAM-ICU is associated with increased mortality and hospital length of stay. For these patients, these measures provide valuable information and may be useful tools for clinical care. RASS and CAM-ICU need to be compared to HE-specific measures in future studies.

Keywords

Liver cirrhosis; Delirium; Hepatic encephalopathy; Intensive care unit

Correspondence: Eric S. Orman, MD, MSCR 702 Rotary Circle Suite 225 Indianapolis, IN 46202 esorman@iu.edu Phone: (317) 278-1630 Fax: (317) 278-6870.

Conflict of Interest: The authors declare that they have no conflict of interest.

INTRODUCTION

Delirium is a neurologic disorder characterized by a fluctuating disturbance of attention and awareness with impaired cognition (Diagnostic and statistical manual of mental disorders 2013). Delirium is common in hospitalized patients, and its presence, severity, and duration are associated with increased length of stay, costs, and mortality (Ely et al. 2004; Klein Klouwenberg et al. 2014; McAvay et al. 2006; Milbrandt et al. 2004; Young et al. 2010). Delirium is easily diagnosed using the Confusion Assessment Method (CAM), a simple 4-item instrument with excellent test characteristics that a variety of healthcare providers can perform quickly and reproducibly (Inouye et al. 1990; Wong et al. 2010). CAM is recommended in more than 30 clinical practice guidelines, has been translated into over 20 languages, and has been adapted for use in emergency rooms, nursing homes, and intensive care units (CAM-ICU) (Ely et al. 2001; Wei et al. 2008). CAM-ICU has been validated in multiple studies, and is recommended for routine clinical use by the Society of Critical Care Medicine (Barr et al. 2013; Gusmao-Flores et al. 2012; Jacobi et al. 2002).

Delirium can be caused by medical conditions such as liver failure, which causes hepatic encephalopathy (HE), and overt HE is defined as a subtype of delirium (Ferenci et al. 2002; Rosenberg et al. 2013). Overt HE is a significant burden to the health care system, with substantial associated mortality and costs, and it is unique to patients with liver disease (Stepanova et al. 2012). In patients with suspected HE, some authors have advocated screening for delirium with CAM (Cordoba 2011). CAM and CAM-ICU may have particular value in patients with cirrhosis because of their existing widespread use in clinical practice and because HE commonly causes delirium. However, CAM-ICU's performance in patients with cirrhosis is not known. Because of the unique contribution of HE to delirium in cirrhosis, standard delirium measurement in this population may differ from other populations. We aimed to determine the association between delirium measured by CAM-ICU and clinical outcomes in critically ill patients with cirrhosis. We also examined CAM-ICU in relation to overt HE because of the significant potential impact of HE on delirium measurement.

METHODS

Study Sample

Consecutive adult patients admitted to the ICUs of Wishard Memorial Hospital (WMH) between May 2009 and October 2012 were included in this retrospective cohort study. The cohort was comprised of patients who were being screened for eligibility for a randomized trial of delirium management (NCT00842608), which requires the presence of delirium as assessed by CAM-ICU. Patient selection and inclusion and exclusion criteria have been described previously (Campbell et al. 2011). In particular, patients were excluded if they had severe mental illness or alcohol-related delirium. The study took place at WMH, an urban, tertiary-care, county hospital affiliated with the Indiana University School of Medicine. At this hospital, medical school faculty and housestaff provide medical care.

Screened patients' billing records were used to identify those with cirrhosis diagnostic codes (ICD-9-CM 456.0, 456.1, 456.2, 456.21, 567.23, 571.2, 571.5, 572.2, 572.3, 572.4, 789.59). This set of codes has been shown to be highly sensitive to the presence of cirrhosis (Nehra et al. 2013). For patients with these codes, we reviewed the electronic medical records to determine a definitive diagnosis of cirrhosis. This diagnosis was either proven histologically, or based on clinical, laboratory, endoscopic, and imaging characteristics. For patients screened during multiple hospital admissions, we only included the first admission. The study was approved by the Indiana University School of Medicine Institutional Review Board.

Delirium, Coma, and Hepatic Encephalopathy

Patients were screened twice daily in the ICU by trained research personnel using CAM-ICU (**Online Resource**). CAM-ICU can be used to diagnose delirium on the basis of (1) an acute change or fluctuating course of mental status, (2) inattention, and either (3) an altered level of consciousness or (4) disorganized thinking. CAM-ICU can detect delirium with a sensitivity of 80% and specificity of 96% (area under the receiver operating characteristic curve 0.97); it has high interrater reliability; and it can be performed in patients who are intubated (Ely et al. 2001; Gusmao-Flores et al. 2012). Patients cannot be diagnosed with delirium if they are comatose; comatose patients are those who are unable to respond to verbal stimuli (Khan et al. 2012). Coma was therefore excluded immediately prior to CAM-ICU using the Richmond Agitation Sedation Scale (RASS) (**Online Resource**). RASS has been shown to be a valid, appropriate instrument for this purpose and is commonly employed both in research settings and in practice (Ely et al. 2004; Ely et al. 2003; Khan et al. 2012). When the RASS score was ≤ −4, patients were considered comatose and not eligible for CAM-ICU assessment. Those with a positive CAM-ICU at any point during their ICU stay were considered to have delirium; those with a RASS ≤ −4 were considered to have coma.

Overt HE (West-Haven grade ≥ 2) was ascertained by independent review of the electronic medical record by two hepatologists. HE assessors were blinded to the results of RASS/CAM-ICU. HE assessment was performed (1) on the same date as the first positive CAM-ICU or RASS, or (2) for those without delirium or coma, on the date of first RASS/CAM-ICU assessment. Discordant HE assessments were resolved by consensus.

Outcomes

The primary outcome was in-hospital mortality. The secondary outcomes were 90-day mortality and hospital length of stay. To determine mortality accurately, follow-up data were obtained using the Regenstrief Medical Record System, a comprehensive database capturing all inpatient and outpatient data including death certificate information for patients who die both inside and outside of Indiana.

Variables

In addition to delirium, coma, and outcomes, we assessed additional potential confounding variables. These included age, sex, race/ethnicity, etiology of cirrhosis, principal discharge diagnosis, the presence of hepatocellular carcinoma, and measures of disease severity.

Measures of disease severity were both cirrhosis-specific (Child-Pugh and Model for End-Stage Liver Disease [MELD]) and general (acute physiology score [APS] derived from APACHE II (Knaus et al. 1985)).

Statistical Analysis

Continuous variables were reported as means (standard deviation) when normally distributed, or medians (interquartile range) otherwise, and categorical variables were reported as counts and proportions. Bivariate comparisons were made with the Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables. Concordance between RASS/CAM-ICU assessments and HE assessments were quantified using the κ statistic. The relationships between the composite exposure of delirium and/or coma (delirium/coma) and the outcomes were assessed using logistic regression for mortality and Poisson regression for length of stay. The composite of delirium/coma was chosen because coma is considered grade 4 overt HE according to the gold standard West-Haven criteria. Overt HE is a subtype of delirium, and delirium cannot be diagnosed in the presence of coma, so the composite appeared most appropriate. We reported unadjusted models, as well as models adjusted for relevant confounders. Multivariate models were restricted to one or two covariates due to sample size limitations. All analyses were performed using SAS version 9.3.

RESULTS

Patient Characteristics

Of 3,147 patients screened for delirium/coma during 3,748 admissions, 91 had cirrhosis and were included in this analysis (Figure 1). The mean age was 55.8 years (SD 8.8), and 63.7% were male. 87.9% of patients had alcoholic liver disease or viral hepatitis. 76.7% of patients had Child-Pugh B or C cirrhosis, and the mean MELD was 14.1 (SD 7.8). 18 patients were receiving mechanical ventilation on the day of HE assessment. The most common reasons for admission were altered mental status, gastrointestinal bleeding, and infection. These diagnoses were specified from the principal hospital discharge diagnosis. Delirium/coma (positive CAM-ICU and/or RASS ≤ -4) was present in 26 (28.6%), and 18 (19.8%) had delirium without coma (positive CAM-ICU and RASS > -4). Patients with delirium/coma appeared slightly older than those without delirium/coma, were more likely to be female, and were less likely to have alcoholic liver disease (Table 1). APS was greater in the group with delirium/coma, but Child-Pugh scores and MELD were similar. None of the 5 patients with hepatocellular carcinoma had delirium/coma.

Delirium/Coma and HE

Interrater reliability for assessment of HE was good (κ 0.57). Disagreements were most common in intubated patients receiving sedation. After excluding those with coma, interrater reliability was slightly improved (κ 0.65). Overt HE was present in 22 (24.2%). Concordance between RASS/CAM-ICU and HE assessment was fair (κ 0.38) and was also improved when comatose patients were excluded (κ 0.45). Of the 22 patients with HE, 13 screened positive for delirium/coma by RASS/CAM-ICU (sensitivity of RASS/CAM-ICU for HE = 59%; positive predictive value = 50%), whereas out of 69 patients without HE, 56

screened negative for delirium/coma by RASS/CAM-ICU (specificity of RASS/CAM-ICU = 81%; negative predictive value = 86%). RASS/CAM-ICU assessment was strongly dependent on whether patients were intubated (delirium/coma present in 78% of intubated patients vs. 16% of non-intubated patients, $p < 0.001$). In contrast, HE did not appear related to intubation status (HE in 28% of intubated vs. 23% of non-intubated, $p = 0.76$). In intubated patients, the sensitivity of RASS/CAM-ICU for HE was 100%, and specificity was 31%; in non-intubated patients, the sensitivity of RASS/CAM-ICU was 47%, and specificity was 93%. Ammonia levels were similar in those with and without delirium/coma (Table 1) and in those with and without HE (47 [38–67] vs. 42 [35–75] μmol/L, $p = 0.87$).

Outcomes

11 patients died in the hospital (6 with delirium/coma), and an additional 9 died within 90 days (2 with delirium/coma). Inpatient mortality was numerically greater for those with delirium/coma compared to those without (23.1% vs. 7.7%, $p = 0.07$), as was 90-day mortality (30.8% vs. 18.5%, $p = 0.26$). Excluding those with coma, mortality was also numerically greater for those with delirium both in-hospital (22.2% vs. 7.7%, $p = 0.10$) and at 90 days (33.3% vs. 18.5%, $p = 0.20$). Bivariate comparisons of demographic and clinical factors with mortality are presented in Table 2. Increasing APS, increasing MELD score, and increasing Child-Pugh score were associated with increased inpatient and 90-day mortality. In addition, HE was significantly associated with increased mortality at 90 days. Median length of hospital stay was longer in those with delirium/coma (19.5 vs. 6 days, $p < 0.001$).

In multivariate analysis, delirium/coma remained associated with increased odds of inpatient and 90-day mortality. Table 3 shows the relationships between delirium/coma and outcomes adjusting for relevant confounders. Several of these models result in a weakening of these associations, with loss of statistical significance (particularly for 90-day mortality). However, the effect estimates of the models had consistent direction toward increased mortality with delirium/coma. The increase in length of stay for coma/delirium patients remained strong and consistent after adjusting for all variables. This increase was also apparent when restricting the analysis to the time after delirium assessment or diagnosis and in those who survived to discharge (data not shown).

DISCUSSION

Delirium is a form of acute brain dysfunction caused by an underlying medical condition. It occurs in hospitalized patients frequently, and is a particular concern in those with high illness acuity and multiple comorbidities (Fick et al. 2002; McNicoll et al. 2003; Siddiqi et al. 2006). Patients with cirrhosis are at high risk of developing delirium, due to a high prevalence of infections, frequent electrolyte disturbances and kidney injury, and HE (Belcher et al. 2013; Jepsen et al. 2010; Merli et al. 2010). In this study of critically ill patients with cirrhosis, we found that nearly 30% developed delirium or coma during their ICU stay. Those with delirium/coma had greater short-term mortality and spent more days in the hospital.

Delirium assessment with CAM-ICU and RASS is a promising tool for the care of patients with cirrhosis. In this population, existing measures of acute brain dysfunction have been developed exclusively for the assessment of HE and have notable limitations. Limitations of the gold standard West Haven criteria include significant subjectivity and interrater variability (Bajaj et al. 2011). These limitations have been improved using the HE Scoring Algorithm, which incorporates neuropsychological assessments that are objective; however, this system requires significant time and expertise and is therefore not practical for routine HE assessment (Hassanein et al. 2009). HE assessment using other measures, such as the Clinical HE Staging Scale and the Modified-Orientation Log, are promising, but have not been widely validated (Ortiz et al. 2007; Salam et al. 2012). In contrast, CAM and CAM-ICU have been validated across healthcare settings and are already used widely (Gusmao-Flores et al. 2012; Wei et al. 2008). CAM-ICU can be administered in less than two minutes; it can be performed by various members of the healthcare team with minimal training; and it can be implemented in an ICU with high compliance and reliability (Ely et al. 2001; Pun et al. 2005; Soja et al. 2008). In comparison to general clinical judgement of HE severity, CAM-ICU is likely to be more reproducible and may offer more uniform recognition of delirium if used universally for screening. Indeed, the significant subjectivity and variability seen with the West Haven criteria is also likely to be seen in general clinical judgement. An additional strength of CAM-ICU is its accuracy in intubated patients and those receiving sedation (Ely et al. 2001). Indeed, in this study, sedated patients were the subject of most HE assessment interrater disagreements; in this group, RASS and CAM-ICU may provide a more uniform assessment of mental status.

Despite these strengths, CAM-ICU has several weaknesses that limit its impact. First, unlike the West Haven criteria and other measures, CAM-ICU is a purely binary diagnostic test and does not provide a quantification of delirium severity. Severity quantification is provided by other delirium measures, such as the Delirium Rating Scale, but these require significant expertise and are not practical for routine use (Trzepacz et al. 2001). A severity measure based on CAM has recently been developed and validated in an elderly population and may have value for patients with cirrhosis (Inouye et al. 2014). Another limitation of CAM-ICU is the potential for under-detection of delirium. Although CAM-ICU is highly sensitive for delirium in intubated patients, several studies have shown that its sensitivity may be diminished in healthier patients (McNicoll et al. 2005; Neufeld et al. 2011). Indeed, in this study, we also found a high sensitivity of CAM-ICU for HE in intubated patients and a high specificity in those who were not intubated.

A thorough discussion of the impact of delirium in cirrhosis is challenging because of the semantics inherent in describing *delirium* and *encephalopathy*. Delirium is a disturbance in attention, awareness, and cognition developing over a short period of time and fluctuating in severity (Diagnostic and statistical manual of mental disorders 2013). Delirium and encephalopathy are synonymous, but terminology for this condition varies widely, and other terms such as acute mental status change, confusion, and acute brain dysfunction are also used to describe this phenomenon (Morandi et al. 2008). Several authors have called for delirium terminology to be standardized to maintain clarity and have encouraged the use of “delirium” instead of other terms (Morandi et al. 2008). Whereas general delirium and

encephalopathy refer to the same phenomenon, HE is a wide-ranging spectrum of neurocognitive impairment occurring in the setting of liver disease specifically (Bajaj et al. 2011). Overt HE refers to a clinically apparent change in mental status, and is, by definition, a subtype of delirium (Diagnostic and statistical manual of mental disorders 2013; Ferenci et al. 2002). Like general delirium, overt HE is often precipitated by infections, electrolyte disturbances, and volume imbalances. These similarities can make it difficult to discern whether HE is causing a specific episode of delirium; thus, patients with cirrhosis and delirium are often treated empirically for overt HE. Despite overt HE's definition as a subtype of delirium, this is the first study to our knowledge to assess HE using a delirium-specific instrument.

The association between delirium and coma with poor clinical outcomes is not surprising, given similar findings in other populations (Ely et al. 2004; Klein Klouwenberg et al. 2014; McAvay et al. 2006; Milbrandt et al. 2004). In addition, the association between HE and increased mortality is well-established (Infante-Rivard et al. 1987; Jepsen et al. 2010). However, outcomes have not been previously described in critically ill patients with cirrhosis and delirium. Mortality in patients with cirrhosis in the ICU has been examined in several recently published studies. Increased mortality has been associated with several factors including liver-specific measures such as MELD (and its components) and Child-Pugh, and general ICU measures such as Sequential Organ Failure Assessment, APACHE II, and the need for mechanical ventilation (Bahirwani et al. 2013; Cavallazzi et al. 2012; Cholongitas et al. 2012; Filloux et al. 2010; Levesque et al. 2012; Tu et al. 2011). In addition to these liver-specific and general ICU measures of disease severity, this study demonstrates that formal delirium assessment may have additional prognostic value. Although 15 of the patients in this study participated in the randomized trial of delirium management, only those with delirium were eligible for the trial; thus any effect of the trial intervention would bias the results toward the null. Our findings are also consistent with other papers showing relatively low mortality for patients with gastrointestinal bleeding (Shawcross et al. 2012) and a close relationship between delirium and infections (Shawcross et al. 2011).

Despite the novelty of these findings, this study has several limitations. First, although the size of the overall screened cohort was substantial, there were relatively few patients with cirrhosis (<3%). This low prevalence is likely due in part to the fact that WMH is not a transplant center. The only liver transplant center in the state is Indiana University Hospital, and that hospital provides much of the care for patients in the catchment area with end stage liver disease. Such referral patterns likely result in a selection bias where Indiana University Hospital provides care for more of the sicker patients, leaving a comparatively “healthy” population of individuals with cirrhosis at WMH. Indeed, MELD and mortality in this study were substantially less than in other similar cohorts (Bahirwani et al. 2013). Therefore, this study's findings need to be generalized to sicker populations in future studies. The low prevalence of cirrhosis at WMH also led to a relatively small sample size, which resulted in many statistically non-significant results and which limited our ability to perform multivariate analyses. We therefore used only one or two covariates in the regression models. However, the models' large effect estimates and consistent direction support a harmful impact of delirium on clinical outcomes. In addition, MELD and Child-Pugh have

excellent prognostic validity in cirrhosis, so the models controlling for these variables strongly support the relationships between delirium and outcomes. Furthermore, these findings are also consistent with prior work demonstrating poor outcomes with delirium in non-cirrhotic populations (Ely et al. 2004; McAvay et al. 2006). Another limitation of this study is the retrospective assessment of HE based on chart review. This design probably explains the HE assessment reviewer disagreement and also some of the CAM-ICU and HE disagreement. Since delirium is characterized by acute fluctuations, such disagreements would be expected when CAM-ICU and the clinical HE assessments are performed at different times during the day. Notably, reviewer disagreement was greatest in those who were intubated and sedated, the group in whom CAM-ICU is most reliable. Although we report the test characteristics of CAM-ICU and RASS in relation to HE, these analyses should be interpreted with extreme caution, as this study is lacking a true HE gold standard. In addition, it should be noted that disagreements between RASS/CAM-ICU and the HE assessment do not invalidate the pre-defined relationship between the underlying concepts (overt HE as a subtype of delirium); rather, the disagreements reflect differences between the specific instruments. Prospective real-time evaluations of HE should be included for comparison in future studies of CAM-ICU.

In conclusion, we found that delirium and coma as assessed using CAM-ICU and RASS is common in critically ill patients with cirrhosis and is associated with increased mortality and longer hospital stays. CAM-ICU is already recommended in clinical practice guidelines for the ICU and has been widely implemented in multiple clinical and research settings, and therefore may be a valuable tool for the care of hospitalized patients with cirrhosis. Further work is needed to better clarify the relationship between delirium and HE assessments and to investigate how standard delirium management may impact outcomes in patients with cirrhosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Funding: This work was supported, in part, by the National Institutes of Health, KL2 TR001106, UL1 TR001108 and R01 AG034205.

REFERENCES

Bahirwani R, Ghabril M, Forde KA, et al. Factors that predict short-term intensive care unit mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2013; 11:1194–1200. e1192. doi:10.1016/j.cgh.2013.03.035. [PubMed: 23602820]

Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, Morgan MY. Review article: the design of clinical trials in hepatic encephalopathy--an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. Aliment Pharmacol Ther. 2011; 33:739–747. doi:10.1111/j.1365-2036.2011.04590.x. [PubMed: 21306407]

Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013; 41:263–306. doi:10.1097/CCM.0b013e3182783b72. [PubMed: 23269131]

Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology. 2013; 57:753–762. doi:10.1002/hep.25735. [PubMed: 22454364]

Campbell NL, Khan BA, Farber M, et al. Improving delirium care in the intensive care unit: the design of a pragmatic study. Trials. 2011; 12:139. doi:10.1186/1745-6215-12-139. [PubMed: 21645330]

Cavallazzi R, Awe OO, Vasu TS, et al. Model for End-Stage Liver Disease score for predicting outcome in critically ill medical patients with liver cirrhosis. J Crit Care. 2012; 27:424, e421–426. doi:10.1016/j.jcrc.2011.11.014. [PubMed: 22227088]

Cholongitas E, Agarwal B, Antoniadis N, Burroughs AK. Patients with cirrhosis admitted to an intensive care unit. J Hepatol. 2012; 57:230–231. author reply 231–232 doi:10.1016/j.jhep.2012.01.024. [PubMed: 22387666]

Cordoba J. New assessment of hepatic encephalopathy. J Hepatol. 2011; 54:1030–1040. doi:10.1016/j.jhep.2010.11.015. [PubMed: 21145874]

Diagnostic and statistical manual of mental disorders. 5th edn. American Psychiatric Association; Washington, D.C: 2013.

Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001; 286:2703–2710. [PubMed: 11730446]

Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004; 291:1753–1762. doi:10.1001/jama.291.14.1753. [PubMed: 15082703]

Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003; 289:2983–2991. doi:10.1001/jama.289.22.2983. [PubMed: 12799407]

Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002; 35:716–721. doi:10.1053/jhep.2002.31250. [PubMed: 11870389]

Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc. 2002; 50:1723–1732. [PubMed: 12366629]

Filloux B, Chagneau-Derrode C, Ragot S, Voultoury J, Beauchant M, Silvain C, Robert R. Short-term and long-term vital outcomes of cirrhotic patients admitted to an intensive care unit. Eur J Gastroenterol Hepatol. 2010; 22:1474–1480. doi:10.1097/MEG.0b013e32834059cd. [PubMed: 21389797]

Gusmao-Flores D, Salluh JI, Chalhub RA, Quarantini LC. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care. 2012; 16:R115. doi:10.1186/cc11407. [PubMed: 22759376]

Hassanein T, Blei AT, Perry W, et al. Performance of the hepatic encephalopathy scoring algorithm in a clinical trial of patients with cirrhosis and severe hepatic encephalopathy. Am J Gastroenterol. 2009; 104:1392–1400. doi:10.1038/ajg.2009.160. [PubMed: 19455117]

Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology. 1987; 7:660–664. [PubMed: 3610046]

Inouye SK, Kosar CM, Tommet D, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. Ann Intern Med. 2014; 160:526–533. doi:10.7326/m13-1927. [PubMed: 24733193]

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990; 113:941–948. [PubMed: 2240918]

Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002; 30:119–141. [PubMed: 11902253]

Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010; 51:1675–1682. doi:10.1002/hep.23500. [PubMed: 20186844]

Khan BA, Guzman O, Campbell NL, et al. Comparison and agreement between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in evaluating patients' eligibility for delirium assessment in the ICU. Chest. 2012; 142:48–54. doi:10.1378/chest.11-2100. [PubMed: 22539644]

Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ. 2014; 349 g6652 doi:10.1136/bmj.g6652.

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985; 13:818–829. [PubMed: 3928249]

Levesque E, Hoti E, Azoulay D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. J Hepatol. 2012; 56:95–102. doi:10.1016/j.jhep.2011.06.024. [PubMed: 21835136]

McAvay GJ, Van Ness PH, Bogardus ST Jr, Zhang Y, Leslie DL, Leo-Summers LS, Inouye SK. Older adults discharged from the hospital with delirium: 1-year outcomes. J Am Geriatr Soc. 2006; 54:1245–1250. doi:10.1111/j.1532-5415.2006.00815.x. [PubMed: 16913993]

McNicoll L, Pisani MA, Ely EW, Gifford D, Inouye SK. Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. J Am Geriatr Soc. 2005; 53:495–500. doi:10.1111/j.1532-5415.2005.53171.x. [PubMed: 15743296]

McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc. 2003; 51:591–598. [PubMed: 12752832]

Merli M, Lucidi C, Giannelli V, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol. 2010; 8:979–985. doi:10.1016/j.cgh.2010.06.024. [PubMed: 20621200]

Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med. 2004; 32:955–962. [PubMed: 15071384]

Morandi A, Pandharipande P, Trabucchi M, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. Intensive Care Med. 2008; 34:1907–1915. doi:10.1007/s00134-008-1177-6. [PubMed: 18563387]

Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singal AG. Use of administrative claims data for identifying patients with cirrhosis. J Clin Gastroenterol. 2013; 47:e50–54. doi:10.1097/MCG.0b013e3182688d2f. [PubMed: 23090041]

Neufeld KJ, Hayat MJ, Coughlin JM, Huberman AL, Leistikow NA, Krumm SK, Needham DM. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. Psychosomatics. 2011; 52:133–140. doi:10.1016/j.psym.2010.12.018. [PubMed: 21397105]

Ortiz M, Cordoba J, Doval E, Jacas C, Pujadas F, Esteban R, Guardia J. Development of a clinical hepatic encephalopathy staging scale. Aliment Pharmacol Ther. 2007; 26:859–867. doi:10.1111/j.1365-2036.2007.03394.x. [PubMed: 17767470]

Pun BT, Gordon SM, Peterson JF, et al. Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. Crit Care Med. 2005; 33:1199–1205. [PubMed: 15942331]

Rosenberg R, Renvillard SG, Hjerrild S. Organic delirious states and other psychiatric disorders: lessons for the hepatologists. Metab Brain Dis. 2013; 28:235–238. doi:10.1007/s11011-012-9340-8. [PubMed: 23129291]

Salam M, Matherly S, Farooq IS, et al. Modified-orientation log to assess hepatic encephalopathy. Aliment Pharmacol Ther. 2012; 35:913–920. doi:10.1111/j.1365-2036.2012.05038.x. [PubMed: 22348593]

Shawcross DL, Austin MJ, Abeles RD, et al. The impact of organ dysfunction in cirrhosis: survival at a cost? J Hepatol. 2012; 56:1054–1062. doi:10.1016/j.jhep.2011.12.014. [PubMed: 22245890]

Shawcross DL, Sharifi Y, Canavan JB, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol. 2011; 54:640–649. doi:10.1016/j.jhep.2010.07.045. [PubMed: 21163546]

Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006; 35:350–364. doi:10.1093/ageing/afl005. [PubMed: 16648149]

Soja SL, Pandharipande PP, Fleming SB, et al. Implementation, reliability testing, and compliance monitoring of the Confusion Assessment Method for the Intensive Care Unit in trauma patients. Intensive Care Med. 2008; 34:1263–1268. doi:10.1007/s00134-008-1031-x. [PubMed: 18297270]

Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol. 2012; 10:1034–1041. e1031. doi:10.1016/j.cgh.2012.05.016. [PubMed: 22642955]

Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci. 2001; 13:229–242. [PubMed: 11449030]

Tu KH, Jenq CC, Tsai MH, et al. Outcome scoring systems for short-term prognosis in critically ill cirrhotic patients. Shock. 2011; 36:445–450. doi:10.1097/SHK.0b013e31822fb7e2. [PubMed: 21841535]

Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc. 2008; 56:823–830. doi:10.1111/j.1532-5415.2008.01674.x. [PubMed: 18384586]

Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA. 2010; 304:779–786. doi:10.1001/jama.2010.1182. [PubMed: 20716741]

Young J, Murthy L, Westby M, Akunne A, O'Mahony R. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ. 2010; 341:c3704. doi:10.1136/bmj.c3704. [PubMed: 20667955]

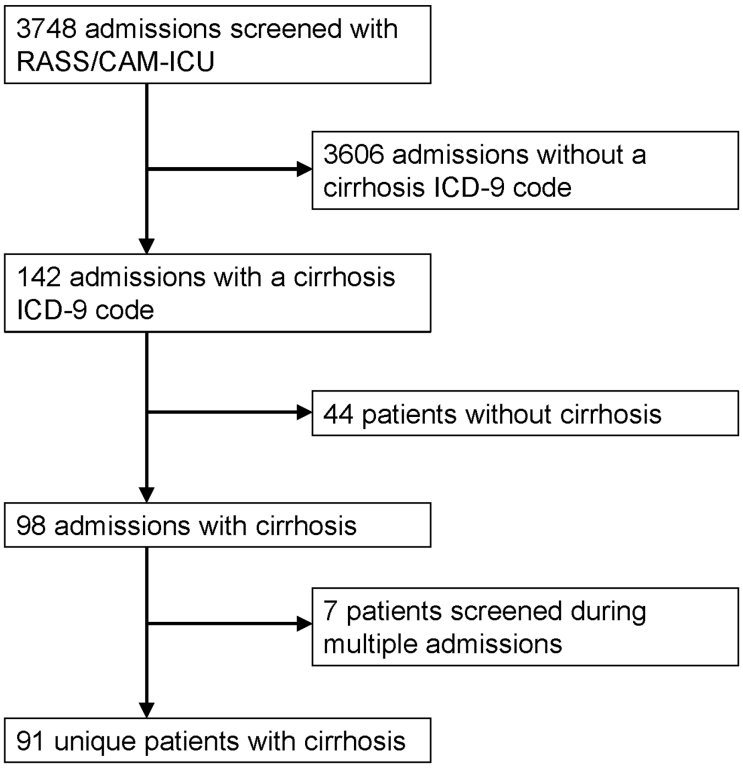

Figure 1.
Flowsheet of patients screened for delirium/coma who had cirrhosis.

Table 1

Characteristics of patients with and without delirium/coma.

	Delirium/coma − (N=65)	Delirium/coma + (N=26)	p-value
Age*	54.8 (8.6)	58.4 (9.2)	0.18
Sex, % male	67.7	53.9	0.24
Race/ethnicity, %			0.92
Non-Hispanic white	61.5	57.7	
Non-Hispanic black	35.4	38.5	
Hispanic	3.1	3.8	
Cirrhosis etiology, %			0.004
Viral hepatitis	21.5	30.8	
Alcohol	24.6	38.5	
Viral + alcohol	44.6	11.5	
NASH	7.7	3.8	
Other	1.5	15.4	
Principal discharge diagnosis, %			0.04
Altered mental status	10.8	30.8	
GI bleeding	23.1	15.4	
Infection	12.3	23.1	
Other	53.9	30.8	
Ascites, %	66.2	57.7	0.48
Hepatic encephalopathy, %	13.8	50.0	<0.001
Hepatocellular carcinoma, %	7.7	0.0	0.32
Acute physiology score*	6.5 (4.4)	10.4 (6.0)	0.003
Leukocyte count (10^9/L)*	7.9 (4.2)	8.1 (5.0)	>0.99
Platelets (10^9/L)*	97 (54–132)	95 (73–126)	0.77
Sodium (mmol/L)*	135 (5.8)	135 (5.6)	0.76
Creatinine (mg/dL)*	0.9 (0.7–1.8)	1.1 (0.7–1.5)	0.38
Albumin (g/dL)*	2.9 (0.7)	2.9 (0.7)	0.72
Bilirubin (mg/dL)*	1.8 (0.9–3.8)	1.3 (1.0–2.9)	0.75
INR*	1.5 (0.4)	1.4 (0.3)	0.12
Ammonia (μmol/L)*†	48 (35–68)	44 (37–88)	0.90
Child-Pugh*	8.8 (2.4)	8.8 (2.2)	0.86
Child-Pugh, % A/B/C	25.0/35.9/39.1	19.2/34.6/46.2	0.84
MELD*	14.3 (8.3)	13.4 (6.5)	0.96

*Continuous variables presented as mean (SD) or median (IQR).

†Ammonia only available in 39/65 subjects without delirium/coma, compared to 23/26 with delirium/coma.

Table 2

Mortality according to patient characteristics.

	Inpatient mortality, %	p-value	90-day mortality, %	p-value
Delirium/coma		0.07		0.26
Yes	23.1		30.8	
No	7.7		18.5	
Age, mean (alive/dead)	55.9/55.8	0.96	55.7/56.4	0.79
Sex		0.52		0.43
Male	10.3		19.0	
Female	15.2		27.3	
Race/ethnicity		0.38		0.91
Non-Hispanic white	16.4		21.8	
Non-Hispanic black	6.1		24.3	
Hispanic	0.0		0.0	
Cirrhosis etiology		0.92		0.86
Viral hepatitis	13.6		22.7	
Alcohol	11.5		23.1	
Viral + alcohol	12.5		25.0	
NASH	0.0		0.0	
Other	20.0		20.0	
Principal discharge diagnosis		0.28		0.26
Altered mental status	6.7		20.0	
GI bleeding	10.5		15.8	
Infection	28.6		42.9	
Other	9.3		18.6	
Hepatic encephalopathy		0.13		0.02
Yes	22.7		40.9	
No	8.7		15.9	
Hepatocellular carcinoma		0.48		0.008
Yes	20.0		80.0	
No	11.6		18.6	
Acute physiology score, mean (alive/dead)	7.1/11.7	0.02	6.9/10.0	0.053
Child-Pugh		0.04		<0.001
A	0.0		0.0	
B	9.4		12.5	
C	21.6		43.2	
MELD, mean (alive/dead)	13.2/20.4	0.01	12.6/19.1	0.001

Table 3

Association between delirium/coma and outcomes.

Model covariates	Inpatient mortality OR 95% CI	90-day mortality OR 95% CI	Length of stay IRR 95% CI
Unadjusted	3.6 (0.99–13.1)	2.0 (0.69–5.6)	2.5 (1.9–3.4)
Age and sex	3.7 (0.96–13.9)	1.8 (0.63–5.4)	2.7 (2.0–3.6)
MELD	5.4 (1.3–23.8)	2.4 (0.79–7.5)	2.5 (1.9–3.4)
Child-Pugh	4.2 (1.1–16.9)	2.4 (0.73–8.5)	2.5 (1.9–3.4)
Acute physiology score	2.2 (0.53–8.9)	1.3 (0.43–4.2)	2.2 (1.7–2.8)
Hepatic encephalopathy	2.8 (0.68–11.2)	1.2 (0.39–4.0)	2.7 (2.0–3.7)
HE and MELD	4.8 (1.01–23.1)	1.7 (0.48–5.8)	2.7 (2.0–3.7)
HE and APS	1.6 (0.36–7.1)	0.8 (0.24–2.9)	2.3 (1.8–3.0)