ORIGINAL RESEARCH

Post liver transplantation delirium assessment using the CAM-ICU-7 scale: A cohort analysis

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ABSTRACT

BACKGROUND: We applied the Confusion Assessment Method (CAM)-Intensive Care Unit (ICU)-7 delirium scale to patients who underwent liver transplant (LT). **METHODS:** Retrospective cohort including patients who underwent LT for cirrhosis admitted to the ICU from June 2013 to June 2016 at the University of Alberta Hospital, Canada. Delirium was assessed using the CAM-ICU-7 scale (0–7 points) twice daily on days one and 3 post LT, with the highest score being considered. Primary endpoint was hospital mortality. **RESULTS:** Among all patients, 101/150 (67.3%) were men and mean age was 52.4 (SD 11.8) years. On days 1 and 3 post LT, mean CAM-ICU-7 scores were 1.8 (SD 1.3) and 1.6 (SD 1.8), respectively. Therefore, on days 1 and 3 post LT, 38/150 (25.3%) and 26/95 (27.4%) patients had delirium. While delirium on day 3 post LT was associated with higher hospital mortality (11.5% versus 0%; $p = 0.019$), it was not associated with length-of-hospital stay (29.2 versus 34.4 days; $p = 0.36$). Following adjustment for APACHEII score, delirium on day 3 post LT was associated with higher odds of hospital mortality (adjusted odds ratio [aOR] 1.89 [95% CI 1.02–3.50]). Following adjustment for Glasgow Coma Scale and mechanical ventilation, serum creatinine was associated with higher odds of delirium on day 3 post LT (aOR 2.02 [95% CI 1.08–3.77]). **CONCLUSIONS:** Using the CAM-ICU-7 scale, delirium was diagnosed in a fourth of patients who underwent LT. Delirium on day 3 post LT was associated with higher odds of hospital mortality.

KEYWORDS: confusion; delirium; liver failure; transplantation

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INTRODUCTION

Delirium is characterized by altered consciousness with a reduced ability to focus, sustain, or shift attention that develops quickly and fluctuates over the course of the day (1). Delirium is frequent among patients admitted to the intensive care unit (ICU) and it has been associated with greater ICU and hospital length-of-stay (LOS), mortality, and cost of care (2–7) Furthermore, delirium severity has also been associated with morbidity and mortality (8,9).

Validated tools to daily assess the presence of delirium are important but may be difficult to implement in the ICU. The Confusion Assessment Method for the ICU (CAM-ICU) has been the most used tool to detect delirium among critically-ill patients (10). It is simple and fast to execute by trained professionals at the bedside. However, much like other tools developed to diagnose delirium, it does not grade the severity of delirium (10,11) Therefore, a new score to detect and grade the severity of delirium in critically-ill patients was developed recently, the CAM-ICU-7 (11). This is an adaptation of the original CAM-ICU score in which a higher score is associated with a higher likelihood of in-hospital mortality or a lower likelihood of discharge to home. Furthermore, there is the potential for the grading of delirium severity to improve the quality of research and help clinicians to understand better the impact of proposed delirium management strategies.

Taking into account the advantages of using CAM-ICU-7, we hypothesized that this scale would also be associated with clinical outcomes among LT recipients. Therefore, the objectives of this study were the following: to quantify the presence and grading of delirium among LT recipients based on the CAM-ICU-7 scale, to study the association of delirium with hospital mortality and hospital LOS in these patients.

METHODS

This study was approved by the University of Alberta Hospital Ethics Committee and informed consent was waived. Informed consent was waived in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The study protocol and conduct abided by the principles of the Declaration of Helsinki (14). The study reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (15).

Design, setting, and patients

This was a single-center retrospective cohort study including consecutive patients who underwent elective or semi-elective LT for cirrhosis and were admitted to the ICU within 24 hours of the operation from June 2013 to June 2016 at the University of Alberta Hospital, Edmonton, Canada.

Only transplanted patients eligible for CAM-ICU assessment were considered. Patients in a coma (Glasgow Coma Scale score <8) or with a Richmond Agitation Sedation Scale (RASS) score of −4 (no response to voice, but movement or eye opening to physical stimulation) or −5 (no response to voice or physical stimulation) were ineligible for CAM-ICU assessments; therefore, they were excluded from the final cohort under analysis (10,13). Furthermore, patients lacking data on the primary endpoint were also excluded (Supplemental Figure 1).

Operational definitions

Delirium was assessed at the bedside by trained ICU nurses using the CAM-ICU tool twice daily on days 1 and 3 post ICU admission, with the highest scores being considered. Based on the RASS and CAM-ICU scores registered, the CAM-ICU-7 was computed for all eligible patients as per the original publication (Supplemental Figure 2). This included the evaluation of following domains (scoring): acute onset or fluctuation of mental status (0–1); inattention (0–2); altered level of consciousness (0–2); and disorganized thinking (0–2) (12). The final CAM-ICU-7 score ranged from 0 to 7 with 7 being most severe. Furthermore, the CAM-ICU-7 scores were categorized as 0–2: no delirium, 3–5: mild to moderate delirium, and 6–7: severe delirium (12).

The following characteristic of patients was retrieved from the prospective ICU electronic database by two researchers (FSC and CJK): age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHEII) score; Sequential Organ Failure Assessment (SOFA) score; Glasgow Coma Scale (CGS) score; hepatic encephalopathy (HE) grade based on West Haven criteria; invasive mechanical ventilation (IMV) status; oxygen pressure/oxygen inspired fraction (PF) ratio; vasopressors status; mean arterial pressure (MAP); continuous renal replacement therapy (CRRT) status; urine output; serum laboratory including hemoglobin, white blood cells' count, platelets' count, international normalized

ratio (INR), albumin, bilirubin (1 mg/dL = 17.1 µmol/L), alanine transferase (ALT), aspartate transferase (AST), creatinine (1 mg/dL = 88.4 µmol/L), sodium, pH, and lactate; ICU and hospital LOS and vital status.

The primary endpoint was hospital mortality and the secondary endpoint was hospital LOS.

Statistical analysis

Continuous variables were described as mean (SD), following normality analysis (Kolmogorov-Smirnov test), and categorical variables were described as frequency (number) (proportion [%]). Missing data across all values were 3.4% and no multiple imputations was performed.

Univariate comparisons were done using student *t*-test for continuous variables or Chi-square or Fisher exact test for categorical variables. Multivariable analysis was performed using logistic regression. Clinically and statistically ($p < 0.10$ on univariate analysis) covariates were included and the final models were obtained following a stepwise backward selection of covariates. Models' performance was assessed by C statistic (95% CI). The significance level considered was $\alpha = 0.05$ (two-tailed).

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (Armonk, NY: IBM Corp).

RESULTS

Baseline characteristics

Among the 150 patients who underwent elective or semi-elective LT for cirrhosis under analysis, mean age was 52.4 (SD 11.8) years and 101 (67.3%) were males. On day 1 post LT in the ICU, mean GCS score was 14 (SD 1) and only 3 (2.0%) patients had grade 3 HE (patients in a coma or with grade 4 HE were excluded as explained in the Methods section). At this time-point, 122 (81.3%) required IMV, 79 (52.7%) were on vasopressors, and only 4 (2.7%) underwent CRRT. At the same time-point, mean serum INR, bilirubin, creatinine, and sodium were 1.72 (SD 0.60), 6.7 (SD 5.2) mg/dL, 1.38 (SD 0.89) mg/dL, and 135 (SD 4) mmol/L, respectively (Supplemental Table 1).

Baseline characteristics between the initial cohort of patients (pre-exclusion criteria) and the cohort of patients under analysis (following exclusion criteria) were not substantially different. All these baseline characteristics are depicted in Supplemental Table 1.

Outcomes

Among the 150 patients under analysis, mean ICU and hospital LOS were 5.1 (SD 8.4) and 29.3 (SD 27.6) days, respectively. Furthermore, two (1.3%) patients died in the ICU; therefore, a total of three (2.1%) patients died during the index hospital stay (Supplemental Table 1).

Delirium on days 1 and 3 post liver transplant

Using the CAM-ICU-7, delirium was diagnosed in 38 (25.3%) patients on day 1 and in 26 (27.4%) patients on day 3 post LT. Delirium severity on day 1 post LT was as follows: 35 (92.1%) patients had mild to moderate delirium and three (7.9%) patients had severe delirium. Delirium severity on day 3 post LT was as follows: 22 (84.6%) patients had mild to moderate delirium and 4 (15.4%) patients had severe delirium (Table 1).

Between patients with and without delirium, the severity of delirium, based on the mean CAM-ICU-7 score, was only significantly higher in the former than in the latter on day 3 post LT (4 versus 1; $p = 0.025$) (Table 1).

Risk factors for delirium on day 1 or 3 post liver transplant

Patients with and without delirium on day 1 post LT had similar baseline characteristics. Patients with delirium on day 3 post LT had significantly lower mean GCS (14 versus 15; $p = 0.042$), higher proportion of grade 1–2 HE (46.2% versus 18.8%; $p = 0.024$), and higher mean creatinine (1.16 versus 0.70 mg/dL; $p = 0.013$) on that same day in comparison to others (Table 1). Additionally, median CAM-ICU7 scores on days 1 (2 versus 1; $p = 0.09$) and 3 (0 versus 1; $p = 0.61$) were similar between patients with and without alcohol-associated liver disease.

Noticeably, patients with delirium on day 1 (84.2% versus 80.4%; $p = 0.60$) or 3 (46.2% versus 31.9%; $p = 0.20$) post LT had similar proportions of IMV. Furthermore, they also had similar overall severity of disease, as per mean APACHEII score, on day 1 (21.3 versus 22.3; $p = 0.54$) or 3 (21.4 versus 22.4; $p = 0.40$) post LT (Table 1).

To minimize overfitting, we chose to adjust this analysis to two important clinical factors that may influence the CAM-ICU-7 assessments, GCS score and IMV status (16). Therefore, on adjusted analysis (GCS, IMV, and creatinine) using logistic regression, only higher serum creatinine on day 3 post LT was independently associated with higher

Table 1: Baseline characteristics stratified by delirium status on days 1 and 3 post liver transplant

	No. (%) or mean (SD)					
	Day 1 (*n* = 150)			Day 3 (*n* = 95)		
Characteristics	With delirium (*n* = 38)	Without delirium (*n* = 112)	*p*	With delirium (*n* = 26)	Without delirium (*n* = 69)	*p*
Demographics						
Age (years)	51.9 (10.9)	52.5 (12.1)	0.82	51.9 (9.0)	51.2 (12.9)	0.80
Sex (male)	22 (57.9%)	79 (70.5%)	0.15	15 (57.7%)	49 (71.0%)	0.22
BMI (kg/m^2)	25.0 (5.3)	26.0 (6.5)	0.99	28.1 (6.0)	25.8 (6.1)	0.16
Organ support						
APACHE II	21.3 (5.2)	22.3 (4.8)	0.54	21.4 (6)	22.4 (5)	0.40
Daily SOFA	9.1 (3.2)	9.7 (3.1)	0.37	7.6 (3.7)	5.8 (4.2)	0.06
GCS	14 (1)	14 (2)	0.33	14 (1)	15 (1)	0.042
HE			0.38			0.024
No	26 (68.4%)	63 (56.3%)		14 (53.8%)	56 (81.2%)	
Grade 1–2	12 (31.6%)	46 (41.1%)		12 (46.2%)	13 (18.8%)	
Grade 3	0 (0%)	3 (2.7%)		0	0	
IMV	32 (84.2%)	90 (80.4%)	0.60	12 (46.2%)	22 (31.9%)	0.20
PF ratio (mmHg)	224 (74)	220 (74)	0.87	234 (65)	236 (87)	0.92
Vasopressors	18 (47.4%)	61 (54.5%)	0.45	4 (15.4%)	12 (17.4%)	1.00
MAP (mmHg)	65 (13)	65 (11)	0.08	77 (14)	78 (14)	0.57
Noradrenaline (μg/min/kg)	0.04 (0.06)	0.06 (0.08)	0.36	0.01 (0.02)	0.02 (0.04)	0.11
CRRT	1 (2.6%)	3 (2.7%)	1.00	1 (1.1%)	1 (1.1%)	0.48
Urine output (mL/24 h)	1725 (852)	1969 (939)	0.95	2006 (1619)	1603 (1321)	0.22
Laboratory (serum)						
Hemoglobin (g/L)	98 (16)	101 (18)	0.32	NA	NA	
Whyte blood cells (×10^9/L)	10.7 (6.6)	10.0 (6.9)	0.64	NA	NA	
Platelets (×10^6/L)	119 (92)	111 (120)	0.74	54 (55)	61 (94)	0.72
INR	1.72 (0.50)	1.72 (0.63)	0.98	NA	NA	
Albumin (g/L)	25.3 (4.4)	25.5 (5.6)	0.83	NA	NA	
Bilirubin (mg/dL)	6.9 (4.4)	6.6 (5.5)	0.73	4.4 (4.9)	3.7 (5.2)	0.55
ALT (U/L)	571 (534)	784 (1005)	0.22	NA	NA	
AST (U/L)	836 (619)	1000 (787)	0.25	NA	NA	
Creatinine (mg/dL)	1.28 (0.70)	1.42 (0.95)	0.20	1.16 (0.72)	0.70 (0.81)	0.013
Sodium (mmol/L)	136 (4)	135 (4)	0.25	NA	NA	
pH	7.34 (0.07)	7.34 (0.07)	0.98	NA	NA	
Lactate (mmol/L)	2.7 (1.9)	3.2 (2.1)	0.26	NA	NA	
Delirium						
CAM-ICU-7 score	3 (3-4)	1 (1-2)	0.48	4 (3-5)	1 (0-1)	0.025
No (0–2)		112 (100%)			69 (100%)	

(*Continued*)

Characteristics	No. (%) or mean (SD)					
	Day 1 (*n* = 150)			Day 3 (*n* = 95)		
	With delirium (*n* = 38)	Without delirium (*n* = 112)	*p*	With delirium (*n* = 26)	Without delirium (*n* = 69)	*p*
Mild–moderate (3–5)	35 (92.1%)			22 (84.6%)		
Severe (6–7)	3 (7.9%)			4 (15.4%)		
Outcomes						
ICU LOS	3.7 (3.0)	5.6 (9.6)	0.45	4.7 (3.2)	7.8 (11.4)	0.08
Hospital LOS	34.7 (34.5)	27.6 (24.8)	0.71	29.2 (16.6)	34.4 (35.8)	0.36
ICU mortality	1 (2.6%)	1 (0.9%)	0.44	2 (7.7%)	0 (0%)	0.07
Hospital mortality	1 (2.7%)	2 (1.8%)	1.00	3 (11.5%)	0 (0%)	0.019

α = 0.05
APACHEII = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; GCS = Glasgow Coma Scale; HE = Hepatic encephalopathy; IMV = Invasive mechanical ventilation; PF = Oxygen pressure/oxygen inspired fraction; MAP = Mean arterial pressure; CRRT = Continuous renal replacement therapy; INR = International normalized ratio; ALT = Alanine transferase; AST = Aspartate transferase; CAM-ICU-7 = Confusion Assessment Method in Intensive Care Unit 7; ICU = Intensive care unit; LOS = Length-of-stay; NA = Non-available

Table 2: Independent risk factors for delirium on day 3 post liver transplant (*n* = 95)

	OR	*p*	aOR	*p*
GCS on day 3 (8–15)	0.80 (0.54–1.18)	0.26	0.80 (0.51–1.25)	0.33
IMV on day 3	1.71 (0.68–4.30)	0.25	0.83 (0.26–2.66)	0.76
Creatinine on day 3 (mg/dL)	1.01 (1.00–1.01)	0.019	2.02 (1.08–3.77)	0.027

C = 0.70 (95% CI 0.58–0.82). α = 0.05
aOR = Adjusted odds ratio; GCS = Glasgow Coma Scale; IMV = Invasive mechanical ventilation

odds of delirium on that same day (adjusted odds ratio [aOR] 2.02 [95% CI 1.08–3.77]; $p = 0.027$). The discriminative ability of this model was reasonable (C = 0.70 [95% CI 0.58–0.82]) (Table 2).

The association between delirium on day 1 or 3 and outcomes

While patients with delirium on day 1 post LT had similar hospital mortality than others (2.7% versus 1.8%), patients with delirium on day 3 post LT had significantly higher hospital mortality than others (11.5% versus 0%) (Table 1).

To minimize overfitting, we chose to adjust this analysis only to APACHEII score, a surrogate of severity of disease and a clinical factor known to be associated with the outcomes of critically-ill patients (17). Therefore, following adjustment for APACHEII score, with logistic regression, the presence of delirium on day 3 post LT (continuous variable) was independently associated with higher odds of hospital mortality (aOR = 1.89 [1.02–3.50]; $p = 0.042$). The discriminative ability of this model was very good (C = 0.90 [95% CI 0.81–0.99]) (Table 3).

The presence of delirium whether on day 1 or 3 post LT was not associated with hospital LOS (Table 1: $p > 0.30$ for both comparisons).

DISCUSSION

Key findings and comparisons with previous literature

In our cohort of patients who underwent elective or semi-elective LT at the University of Alberta Hospital, Edmonton, Canada, from 2013 to 2016, following exclusion of those in a coma post LT,

Table 3: Adjusted association of delirium on day 3 post liver transplant with hospital mortality (*n* = 95)

	OR	*p*	aOR	*p*
Delirium on day 3 (0–7)	1.88 (1.01–3.50)	0.046	1.89 (1.02–3.50)	0.042
APACHEII	1.14 (0.96–1.35)	0.15	1.15 (0.96–1.38)	0.14

C = 0.90 (95% CI 0.81–0.99). α = 0.05
aOR = Adjusted odds ratio; APACHEII = Acute Physiology and Chronic Health Evaluation II

25.3% and 27.4% had delirium on day 1 or 3 post LT, respectively, based on serial CAM-ICU-7 assessments. Furthermore, among those delirious patients, severe delirium (CAM-ICU-7 score of 6–7) was found in 7.9% and 15.4% of them on day 1 or 3 post LT, respectively.

In a previous study about delirium in the post LT context from Canada (*n* = 281), the prevalence of delirium was 10.0% during the ICU stay, at a median of 2 days following surgery, a figure lower than the one found in our study (18). In another study from the United States (*n* = 181), 21.0% of patients were diagnosed with delirium, at a mean of 7 days post LT, a proportion similar to the one we found (4) However, while we clearly defined delirium diagnosis as per CAM-ICU-7 evaluation, both of these studies used different definitions of delirium, without using any specific pre-existent delirium diagnostic tool systematically. Therefore, direct comparisons may be difficult to interpret.

To the best of our knowledge, there are no previous studies focusing not only on the diagnosis of delirium post LT, but specifically on the severity of delirium in this context. In our cohort, delirium severity increased from days 1 to 3 post LT, whether CAM-ICU-7 score was considered as a categorical (7.9% versus 15.4%) or a continuous (mean of 3 versus 4) variable. Furthermore, following adjustment for disease severity (APACHEII score), the odds of hospital mortality increased 89% per each increment in the CAM-ICU-7 score (0–7). This finding is in line with what was described in the original study validating the CAM-ICU-7 (12). As stated by its authors, because CAM-ICU-7 is based on the widely used CAM-ICU scale, it is likely an easy and rapid tool to execute and calculate at the bedside by already trained professionals with added diagnostic and prognostic values.

In our cohort, the presence of delirium was not associated with hospital LOS. Several studies have documented the opposite (18,19). However, while hospital LOS has been frequently used in studies about delirium as a probable surrogate of morbidity related to it, this may be difficult to generalize. Among transplant centers, there is wide known variability on the trajectory of patients inside the hospital during their index peri LT stay. Therefore, it is expected to observe differences in hospital LOS among them and it may be difficult to perform direct comparisons.

In our study, following adjustment for GCS score and IMV status, per each 1 mg/dL increment in serum creatinine on day 3 post LT, there was a two-fold increase in the odds of delirium at this same time point. In a previous study from the United Kingdom (*n* = 793), among other characteristics, patients with kidney dysfunction, therefore on a kidney-sparing immunosuppression regimen, were actually more likely to develop delirium post LT (19). These findings may suggest that preventive and therapeutic strategies for delirium management may be especially important in patients prone to or that effectively develop kidney dysfunction following transplant.

Taking into account all of our findings, we should make the following remarks. Firstly, delirium may be present in about a fourth of patients who underwent LT during the first few days of their ICU stay. Secondly, the use of a tool such as CAM-ICU-7 may help to better characterize delirium in this context. Thirdly, kidney dysfunction following LT may help to flag patients at increased risk of developing delirium, therefore warrants specific attention by clinicians.

Limitations

The results of our study need to be interpreted while considering the following limitations. Firstly, this was a single-center retrospective cohort; therefore, it may have been prone to selection bias. However, the reasonably sized sample, the defined inclusion and exclusion criteria, and the updated peri-LT management performed at our institution

may help to minimize such bias. Secondly, we were not able to retrieve data on medications used that knowingly impact the risk of delirium in the ICU, for example, sedatives or immunosuppressive drugs. Nevertheless, the fact that we excluded patients in a coma or with a RASS below –3 may have helped to minimize it, as these patients were more likely the ones on higher doses of sedatives. Also, immunosuppression was being provided as per institutional protocol based on international guidelines (Supplemental Table 2). Thirdly, we were also not able to retrieve data on the preventive and therapeutic strategies ongoing in the ICU to manage delirium. However, we should emphasize that our ICU has been continuously implementing the most updated management strategies for delirium, especially the non-pharmacological interventions, as recognized by evolving literature on the topic (20).

Despite these limitations, we think our study adds to the literature by validating the application of the CAM-ICU-7 tool to the patients who underwent LT and are then admitted to the ICU. This may help to better identify, quantify, avoid, or treat delirium in these patients and potentially improve their short-term outcomes. Future studies are needed to evaluate the impact of systematic approaches to the delirium management in transplanted patients. In this regard, the scoring of the delirium severity that the CAM-ICU-7 tool allows, may even help to titrate the efficacy of such management strategies (12).

CONCLUSIONS

Using the CAM-ICU-7 scale, delirium was diagnosed in about a fourth of patients who underwent LT. Delirium on day 3 post LT was associated with higher hospital mortality.

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