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Brain CT Scan Diagnostic and Prognostic Value in Patients With Acute Liver Failure and Cerebral Edema: A Multicenter Cohort Study

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OBJECTIVE: Patients with acute liver failure (ALF) may develop cerebral edema. We aimed to study the CT scan diagnostic and prognostic value among patients with ALF and cerebral edema.

DESIGN: International multicenter retrospective cohort.

SETTING: U.S. Acute Liver Failure Study Group prospective registry.

PATIENTS: Consecutive patients with ALF within the registry from January 1998 to August 2016.

INTERVENTIONS: The primary exposure was cerebral edema on CT scan. The primary endpoint was 21-day post-inclusion transplant-free survival (TFS).

MEASUREMENTS AND MAIN RESULTS: Among 2108 patients with ALF, 243 (11.5%) had a brain CT scan. Among those 243 patients, 105 (43.2%) had cerebral edema and 11 (4.5%) later developed tonsillar herniation. Patients with cerebral edema on CT scan were younger (36 vs. 46 yr; $p < 0.001$) and more often females (81.0% vs. 63.8%; $p = 0.003$), had more acetaminophen-related ALF (61.0% vs. 39.4%; $p < 0.001$), required more frequently invasive mechanical ventilation on day 1 (73.3% vs. 55.8%; $p = 0.005$), and had higher maximum days 1–7 model for end-stage liver disease (MELD) score (39 vs. 35; $p = 0.002$) than others. Following adjustment for confounders (age, acetaminophen toxicity, and severity of disease by MELD), cerebral edema was associated with lower odds of 21-day TFS (adjusted odds ratio = 0.36 [95% CI, 0.18–0.72]; *C*-statistic = 0.81 [95% CI, 0.75–0.86]; $p = 0.003$). However, cerebral edema was not associated with selection for liver transplant (22.9% vs. 16.1%; $p = 0.18$).

CONCLUSIONS: In our cohort of patients with ALF, brain CT scan use increased overtime. Among those with a brain CT scan, about two in five had cerebral edema. Cerebral edema on CT scan was independently associated with worse 21-day TFS but did not preclude transplant. Brain CT scan may provide additional diagnostic and prognostic information in selected patients with ALF.

KEYWORDS: cerebral edema; death; intracranial hypertension; liver failure; transplant

Acute liver failure (ALF) is a rare disease that often leads to multiple organ failure (1). Albeit regional and etiology-related variations, without emergent liver transplant (LT), spontaneous survival has improved over the decades but remains around 30–50% (2).

In ALF, after massive liver cell death, multiple inflammatory mediators spill into the systemic circulation and may impair the function of the brain and other organs (3). Cerebral edema may develop early in the disease course in up to 20% of patients (4). If not timely diagnosed and treated, intracranial hypertension and death from tonsillar herniation may occur (1, 5).

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KEY POINTS

Question: How important brain CT scan may be in patients with acute liver failure (ALF) and cerebral edema?

Findings: In a multicenter cohort of patients with ALF, brain CT scan was available in 11.5%. Cerebral edema was present in 43.2% of patients who underwent a brain CT scan. Cerebral edema was associated with lower odds of transplant-free survival but not with transplant access.

Meaning: Brain CT scan may have diagnostic and prognostic value in patients with ALF and cerebral edema. Brain CT scan may be an additional tool to assess cerebral edema in ALF.

In patients with ALF, early diagnosis of cerebral edema remains a challenge. In its early stages, cerebral edema may be undetectable on standard physical examination (6). Hyperammonemia of greater than or equal to 100–150 µmol/L has been associated with increased risk of cerebral edema and thus has been used as a surrogate for neurologic complications (7). Ultrasound with optic nerve sheath diameter measurement or transcranial Doppler studies have been used at the bedside to detect signs of cerebral edema but with limitations regarding sensitivity, specificity, and operator variability (8, 9). Invasive intracranial pressure (ICP) monitoring with a bolt seemed not to improve these patients' neurologic outcomes and it may be associated with a low risk of intracranial bleeding (10).

For critically ill patients such as those with ALF, standard brain CT may be helpful with the differential diagnosis of acute encephalopathy (11). Yet, its role on cerebral edema diagnosis remains scarcely studied (12). Therefore, brain MRI has been increasingly used to characterize hepatic encephalopathy (HE) features, including cerebral edema, in patients with liver cirrhosis (13). However, CT scan continues to be more widely available and much easier to perform than MRI for critically ill patients (14).

Accordingly, we hypothesized that CT scan could help to diagnose cerebral edema in patients with ALF and could have prognostic value. Therefore, the objectives of this study were the following: 1) determine how frequently patients with ALF underwent a brain CT scan, 2) assess the prevalence of cerebral edema on CT scan, 3) and study the prognostic value of cerebral edema on CT scan.

MATERIALS AND METHODS

Design, Setting, Participants, and Ethics

This was a retrospective analysis of the ALF prospective registry from the U.S. Acute Liver Failure Study Group (USALFSG). Consecutive patients with ALF (see Operational definitions) were included in the registry at up to 32 North-American tertiary-care hospitals (see Acknowledgments) from January 1998 to August 2016. Patients were excluded if they had: acute liver injury without ALF criteria, liver cirrhosis, or lack of data on the primary endpoint (**Fig. S1**, http://links.lww.com/CCX/B501). The institutional review board at all enrolling sites within the USALFSG (University of Alberta Health Research Ethics Board, Pro00041365, A multicenter group to study acute liver failure [ALF], approval November 27, 2013 renewed until January 6, 2026) has approved this study's protocol. Informed consent was obtained from the next of kin as patients were unable to provide it themselves due to HE. All research procedures abided by the principles of the Declaration of Helsinki (15). This study's reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline (16).

Operational Definitions, Data Collection, Exposures, and Endpoints

ALF was defined after fulfillment of all the following criteria: 1) any degree of HE, 2) international normalized ratio (INR) of greater than or equal to 1.5, 3) acute illness onset of less than 26 weeks, and 4) no evidence of liver cirrhosis (17).

The USALFSG Registry data repository included demographic, clinical, and outcomes' data. The following data on day 1 post-inclusion was retrieved: age, sex, ALF etiology, HE grade (West Haven criteria), organ support requirements (invasive mechanical ventilation [IMV], vasopressors, and renal replacement therapy [RRT]), laboratory serum profile (INR, bilirubin, ammonia, creatinine, lactate, and pH), and further cerebral edema targeted therapies (hypertonic fluid therapy, active hypothermia, and ICP monitor device) (5, 7, 10, 18). To evaluate disease severity, the maximum days 1–7 post-inclusion model for end-stage liver disease (MELD) score was used. This score is calculated based on serum INR, bilirubin, and creatinine (19). It was developed for assessing the risk of mortality among patients with cirrhosis in the LT wait-list, but has also been validated for mortality prediction in patients with ALF (19).

The ALF management at different recruiting centers along the years was based on up-to-date specific guidelines but remained at local clinicians' discretion (17). In general, cerebral edema treatment relied on the following interventions: quiet environment and avoidance of patient overstimulation, sedation, treatment of fever and seizures, hypertonic fluids such as saline or mannitol (to promote brain osmotic shifts), vasopressors (to optimize cerebral perfusion pressure), RRT (to clear serum ammonia), and hypothermia (in selected cases) (3, 4, 6, 17). The placement of an intracranial bolt to monitor ICP was also at local clinicians' discretion.

The primary exposure was cerebral edema diagnosed on standard brain CT scan performed within 21 days post-inclusion at local clinicians' discretion. Although the timing and reason for brain CT request was not properly captured in the registry data, we believe clinicians tended to select patients for brain CT if there was any suspicion of intracranial damage. In this context, cerebral edema was more likely to develop in patients with high-grade HE. Brain CT data were obtained from neuroradiology reports from each enrolling site. Radiology features of cerebral edema in the context of severe ALF, and not explained by other concomitant condition, included most frequently at least one of the following: sulcal effacement, ventricular or cistern narrowing, gray-white matter abnormal contrast, midline shift, or tonsillar herniation (20, 21).

The primary endpoint from studies using the USALFSG Registry has been defined as 21-day post-inclusion transplant-free survival (TFS) (1, 2, 7). The 21-day post-inclusion LT rate was also studied.

Sample Size Calculation

Based on previous literature, to detect a difference of at least 20% in 21-day TFS, with a power (beta) of 0.80 and a statistical significance (alfa) of 0.05, we would require an overall sample size of at least 200 individuals (22, 23).

Statistical Analysis

Categorical variables were presented as frequency (%) and continuous variables as median (interquartile range [IQR]). Univariable comparisons of baseline characteristics and outcomes were performed with Chi-square or Mann-Whitney tests where appropriate. For the initial cohort (n = 2108), missing data across all variables was 7.6% and no multiple imputation was performed.

Multivariable analysis was performed with logistic regression to study the adjusted association between cerebral edema on CT scan and 21-day TFS. Variables initially included in the model were those clinically important and with a p value of less than 0.10 on univariable comparisons. A stepwise backward elimination approach was used while avoiding overfitting (one covariable per at least 10 events). Collinearity was avoided by using the variance inflation factor. Adjusted odds ratios (aORs) were presented with 95% CIs. The final model's discriminative ability for 21-day TFS was studied with receiver operating curves and C-statistic (95% CI). Statistical significance was defined as p value below alfa of 0.05 (two-tailed).

Statistical analysis was performed using IBM SPSS Statistics, version 29.0 (IBM Corp, North Castle, NY).

RESULTS

Baseline Characteristics and Outcomes

From 1998 to 2016, 2304 patients with ALF were enrolled in the USALFSG prospective registry. Among these patients, 2108 had complete data on the primary endpoint and were thus analyzed (Fig. S1, http://links.lww.com/CCX/B501).

Among 2108 patients with ALF enrolled, median (IQR) age was 40 (29–52) years and 1461 (69.3%) patients were females (**Table 1**). The most common ALF etiology was acetaminophen toxicity in 963 (45.7%) patients (**Table S1**, http://links.lww.com/CCX/B501).

On day 1 post-inclusion, 988 (48.4%) patients had grade 3/4 HE, 1023 (48.6%) required IMV, 440 (20.9%) were on vasopressors, and 480 (22.8%) required any modality of RRT (176 on continuous RRT and 304 on intermittent RRT). On this same day, median (IQR) serum INR, bilirubin, ammonia, and lactate were 2.7 (2.0–4.2), 6.9 (3.6–19.1) mg/dL, 95 (61–157) µmol/L, and 4.3 (2.4–8.8) mmol/L, respectively.

TABLE 1.
Baseline Characteristics and Outcomes of Patients With Acute Liver Failure Stratified by Brain CT Scan Status

Characteristic (Median [Interquartile Range] or *n* [%])	Total (*n* = 2108)	With CT Scan (*n* = 243)	Without CT Scan (*n* = 1865)	*p*
Age (yr) (*n* = 2108)	40 (29–52)	41 (29–53)	40 (29–52)	0.53
Sex (female) (*n* = 2108)	1461 (69.3%)	173 (71.2%)	1288 (69.1%)	0.50
Acetaminophen toxicity (*n* = 2107)	963 (45.7%)	118 (48.8%)	845 (45.3%)	0.31
Grade 3/4 hepatic encephalopathy (West Haven criteria), day 1 (*n* = 2043)	988 (48.4%)	152 (66.4%)	836 (46.1%)	< 0.001
Invasive mechanical ventilation, day 1 (*n* = 2105)	1023 (48.6%)	154 (63.4%)	869 (46.7%)	< 0.001
Vasopressors, day 1 (*n* = 2105)	440 (20.9%)	63 (25.9%)	377 (20.2%)	0.041
Renal replacement therapy, day 1 (*n* = 2105)	480 (22.8%)	84 (34.6%)	396 (21.3%)	< 0.001
International normalized ratio, day 1 (*n* = 2071)	2.7 (2.0–4.2)	2.9 (2.0–4.2)	2.7 (2.0–4.2)	0.78
Bilirubin (mg/dL), day 1 (*n* = 2076)	6.9 (3.6–19.1)	5.5 (2.9–14.2)	7.3 (3.8–20.0)	< 0.001
Ammonia (µmol/L), day 1 (*n* = 1221)	95 (61–157)	108 (71–173)	93 (60–153)	0.008
Creatinine (mg/dL), day 1 (*n* = 2095)	1.65 (0.90–3.10)	1.74 (0.97–3.21)	1.61 (0.90–3.05)	0.24
Lactate (mmol/L), day 1 (*n* = 1147)	4.3 (2.4–8.8)	3.8 (2.1–7.0)	4.4 (2.5–9.1)	0.031
pH, day 1 (*n* = 1587)	7.42 (7.36–7.48)	7.42 (7.36–7.48)	7.41 (7.35–7.47)	0.26
Maximum model for end-stage liver disease, days 1–7 (*n* = 2082)	36 (29–43)	36 (30–42)	36 (29–43)	0.56
21-d liver transplant (*n* = 2098)	479 (22.8%)	46 (19.0%)	433 (23.3%)	0.13
21-d transplant-free survival (*n* = 2108)	1003 (47.6%)	121 (49.8%)	882 (47.3%)	0.46
21-d overall survival (*n* = 2041)	1376 (67.4%)	160 (67.2%)	1216 (67.4%)	0.95
Year of enrollment (*n* = 2108)				< 0.001
1998–2007	1175 (55.7%)	35 (14.4%)	1140 (61.1%)	
2008–2016	933 (44.3%)	208 (85.6%)	725 (38.9%)	

On days 1–7 post-inclusion, median (IQR) maximum MELD score was 36 (29–43). Overall, 479 (22.8%) patients were transplanted within 21 days post-inclusion. Furthermore, 1003 (47.6%) patients survived without transplant within 21 days post-inclusion. The three most frequent causes of death were the following: multiple organ failure (33.6.0%), liver failure (23.8%), and cerebral event (18.9%) (**Table S2**, http://links.lww.com/CCX/B501). All baseline characteristics and outcomes are depicted in Table 1.

Brain CT Scan Availability

Among 2108 patients with ALF enrolled, 243 (11.5%) had a brain CT scan with available details (Table 1). Patients who had a brain CT scan had more often grade 3/4 HE (66.4% vs. 46.1%; $p < 0.001$) or the need for IMV (63.4% vs. 46.7%; $p < 0.001$), vasopressors (25.9% vs. 20.2%; $p = 0.041$), or RRT (34.6% vs. 21.3%; $p < 0.001$) on day 1 post-inclusion than others. Patients with a brain CT scan were more often on continuous RRT (17.3% vs. 7.2%; $p < 0.001$), but had similar use of intermittent RRT (17.3% vs. 14.0%; $p = 0.40$) than those without any RRT. Furthermore, patients with a brain CT scan had also higher median serum ammonia (108 vs. 93 µmol/L; $p = 0.008$) on day 1 post-inclusion than those without a CT scan. However, median serum INR on day 1 post-inclusion (2.9 vs. 2.7; $p = 0.78$) and maximum MELD score on days 1–7 post-inclusion (36 vs. 36; $p = 0.56$), as well as LT (19.0% vs. 23.3%; $p = 0.13$) and TFS (49.8% vs. 47.3%; $p = 0.46$) within 21 days of study inclusion rates, were similar between those who got a brain CT scan and those who did not. In addition, brain CT scan was more frequently performed in the 2008–2016 period than in the 1998–2007 period (22.3% vs. 3.0%; $p < 0.001$). All baseline characteristics and outcomes stratified by brain CT scan status are detailed in Table 1.

Cerebral Edema on CT Scan

Among 243 patients with ALF who underwent a brain CT scan, 105 (43.2%) had features of cerebral edema (**Tables 2**; and **Table S3**, http://links.lww.com/CCX/B501). Among these 243 patients, 17 (7.0%) patients experienced any intracranial bleeding event (4 patients had an intracranial bolt) and 5 developed cerebral edema. Intracranial bleeding events were categorized as follows: punctate bleeding foci in five, parenchymal hematoma in four, subarachnoid bleed in five, and subdural hematoma in three patients. Overall, 21 (8.6%) patients had findings consistent with recent brain ischemia and 3 developed cerebral edema. Overall, 11 (4.5%) patients ended up developing tonsillar herniation.

Patients with cerebral edema were younger (36 vs. 46 yr; $p < 0.001$) and more often females (81.0% vs. 63.8%; $p = 0.003$), had more acetaminophen-related ALF (61.0% vs. 39.4%; $p < 0.001$), and required more frequently IMV on day 1 post-inclusion (73.3% vs. 55.8%; $p = 0.005$) than those without cerebral edema. Furthermore, patients with cerebral edema had higher median serum INR (3.3 vs. 2.5; $p = 0.001$), ammonia (132 vs. 94 µmol/L; $p = 0.001$), and lactate (4.5 vs. 3.3 mmol/L; $p = 0.025$) on day 1 post-inclusion, as well as maximum MELD score on days 1–7 post-inclusion (39 vs. 35; $p = 0.002$), than those without cerebral edema.

Among patients with cerebral edema on CT scan, 24 (22.9%) required a LT and 38 (36.9%) died up to 21 days post-inclusion. Among these 38 dead patients, 16 (42.1%) experienced a fatal intracranial event. Among patients with intracranial bleeding events, Three (17.6%) required a LT and 7 (41.2%) were alive up to 21 days post-inclusion. Among patients with tonsillar herniation, 1 (9.1%) was transplanted and 3 (27.2) were alive up to 21 days post-inclusion.

Patients with cerebral edema were as likely to be transplanted (22.9% vs. 16.1%; $p = 0.18$) but less likely to survive without LT within 21 days post-inclusion (41.9% vs. 55.8%; $p = 0.032$) than those without cerebral edema. In fact, among only patients with cerebral edema ($n = 105$), 21-day overall survival was higher for those transplanted in comparison to those who did not get a LT (95.5% vs. 54.3%; $p < 0.001$). In addition, cerebral edema on CT scan prevalence was similar between the 2008–2016 and 1998–2007 periods (41.3% vs. 54.3%; $p = 0.15$).

All baseline characteristics and outcomes stratified by cerebral edema status are depicted in Table 2.

Interventions Targeting Cerebral Edema

The USALFSG Registry captured some interventions to monitor, prevent, or treat potential cerebral edema (**Table S4**, http://links.lww.com/CCX/B501). Among 243 patients with ALF who underwent a brain CT scan, those with cerebral edema were more often under sedation (73.3% vs. 55.8%; $p = 0.005$) or subjected to active hypothermia (15.2% vs. 3.6%; $p = 0.001$) on day 1 post-inclusion than those without cerebral edema. Among patients with cerebral edema on brain CT scan, none of these interventions was associated with 21-day TFS (**Table S5**, http://links.lww.com/CCX/B501).

Association of Cerebral Edema With 21-day Transplant-Free Survival

Spontaneous survivors were younger (36 vs. 44; $p = 0.013$), had more acetaminophen-related ALF (61.2% vs. 36.4%; $p < 0.001$), and had lower median serum INR (2.5 vs. 3.2; $p < 0.001$), bilirubin (3.9 vs. 9.5 mg/dL; $p < 0.001$), ammonia (92 vs. 135 µmol/L; $p = 0.001$), and lactate (2.5 vs. 6.2 mmol/L; $p < 0.001$) on day 1 post-inclusion, as well as maximum MELD score on days 1–7 post-inclusion (33 vs. 39; $p < 0.001$), than those that were transplanted or died up to 21 days post-inclusion (**Table 3**). Furthermore, spontaneous survivors had less cerebral edema than others (36.4% vs. 50.0%; $p = 0.032$). All baseline characteristics and outcomes stratified by survival status are detailed in Table 3.

Following adjustment for non-collinear significant confounders, namely age, etiology (acetaminophen toxicity vs. other), and disease severity (maximum MELD score on days 1–7 post-inclusion), cerebral edema was associated with lower odds of 21-day TFS (**Table 4**: aOR [95% CI] = 0.36 [0.18–0.72]; $p = 0.003$). The discriminative ability of this model for 21-day TFS was reasonably good (*C*-statistic [95% CI] = 0.81 [0.75–0.86]).

TABLE 2.
Baseline Characteristics and Outcomes of Patients With Acute Liver Failure Stratified by Cerebral Edema Status on Brain CT

Characteristic (Median [Interquartile Range] or *n* [%])	Total (*n* = 243)	Cerebral Edema on CT Scan (*n* = 105)	No Cerebral Edema on CT Scan (*n* = 138)	*p*
Age (yr) (*n* = 243)	41 (29–53)	36 (27–45)	46 (32–59)	< 0.001
Sex (female) (*n* = 243)	173 (71.2%)	85 (81.0%)	88 (63.8%)	0.003
Acetaminophen toxicity (*n* = 242)	118 (48.8%)	64 (61.0%)	54 (39.4%)	< 0.001
Grade 3/4 hepatic encephalopathy (West Haven criteria), day 1 (*n* = 229)	152 (66.4%)	69 (71.9%)	83 (62.4%)	0.13
Invasive mechanical ventilation, day 1 (*n* = 243)	154 (63.4%)	77 (73.3%)	77 (55.8%)	0.005
Vasopressors, day 1 (*n* = 243)	63 (25.9%)	27 (25.7%)	36 (26.1%)	0.95
Renal replacement therapy, day 1 (*n* = 243)	84 (34.6%)	42 (40.0%)	42 (30.4%)	0.12
International normalized ratio, day 1 (*n* = 237)	2.9 (2.0–4.2)	3.3 (2.2–4.9)	2.5 (1.9–3.7)	0.001
Bilirubin (mg/dL), day 1 (*n* = 238)	5.5 (2.9–14.2)	6.4 (3.2–11.8)	5.1 (2.5–15.7)	0.34
Ammonia (μmol/L), day 1 (*n* = 178)	108 (71–173)	132 (81–209)	94 (59–146)	0.001
Creatinine (mg/dL), day 1 (*n* = 239)	1.74 (0.97–3.21)	1.50 (0.91–3.10)	1.84 (0.98–3.55)	0.40
Lactate (mmol/L), day 1 (*n* = 168)	3.8 (2.1–7.0)	4.5 (2.8–7.6)	3.3 (1.9–6.7)	0.025
pH, day 1 (*n* = 203)	7.41 (7.36––7.48)	7.42 (7.36–7.48)	7.41 (7.35–7.47)	0.31
Maximum model for end-stage liver disease, days 1–7 (*n* = 239)	36 (30–42)	39 (31–45)	35 (28–40)	0.002
21-d liver transplant (*n* = 242)	46 (19.0%)	24 (22.9%)	22 (16.1%)	0.18
21-d transplant-free survival (*n* = 243)	121 (49.8%)	44 (41.9%)	77 (55.8%)	0.032
21-d overall survival (*n* = 238)	160 (67.2%)	65 (63.1%)	95 (70.4%)	0.24
Year of enrollment (*n* = 243)				0.15
1998–2007	35 (14.4%)	19 (18.1%)	16 (11.6%)	
2008–2016	208 (85.6%)	86 (81.9%)	122 (88.4%)	

DISCUSSION

Main Results and Comparisons With Previous Literature

In our large multicenter North-American cohort of patients with ALF, brain CT scan was performed in 11.5% of patients, with its prevalence increasing overtime. Patients who had a brain CT scan had more often organ failures, including grade 3/4 HE or hyperammonemia. Furthermore, among those who underwent a CT scan, cerebral edema was diagnosed in 43.2% of patients. Finally, the presence of cerebral edema on CT scan was independently associated with worse 21-day TFS, but did not definitively preclude LT.

In a single-center North-American cohort study with 15 patients with ALF and grade 3/4 HE, 4 patients had cerebral edema on CT scan and 12 patients had intracranial hypertension diagnosed with an epidural monitoring device (24). Based on their results, the authors stated that brain CT scan may not be useful to diagnose cerebral edema in patients with ALF. In another single-center North-American cohort study including 12 patients with ALF, cerebral edema was present on CT scan in 7 of 8 patients with grade 3/4 HE but in none of the 4 patients with grade 1/2 HE (25). Considering their findings, the authors concluded that CT scan may be useful to detect cerebral edema in patients with ALF and grade 3/4 HE. In another single-center North-American cohort study with 25 patients with ALF, 12 had cerebral

TABLE 3.
Baseline Characteristics and Outcomes of Patients With Acute Liver Failure Stratified by 21-day Survival Status

Characteristic (Median [Interquartile Range] or *n* [%])	21-Day Transplant-Free Survival (*n* = 121)	21-Day Liver Transplant or Death (*n* = 122)	*p*
Age (yr) (*n* = 243)	36 (28–51)	44 (33–56)	0.013
Sex (female) (*n* = 243)	85 (70.2%)	88 (72.1%)	0.75
Acetaminophen toxicity (*n* = 242)	74 (61.2%)	44 (36.4%)	< 0.001
Grade 3/4 hepatic encephalopathy, day 1 (*n* = 229)	75 (64.1%)	77 (68.8%)	0.46
Invasive mechanical ventilation, day 1 (*n* = 243)	74 (61.2%)	80 (65.6%)	0.48
Vasopressors, day 1 (*n* = 243)	25 (20.7%)	38 (31.1%)	0.06
Renal replacement therapy, day 1 (*n* = 243)	43 (35.5%)	41 (33.6%)	0.75
International normalized ratio, day 1 (*n* = 237)	2.5 (1.7–3.7)	3.2 (2.3–4.7)	< 0.001
Bilirubin (mg/dL), day 1 (*n* = 238)	3.9 (2.2–6.8)	9.5 (4.2–19.8)	< 0.001
Ammonia (μmol/L), day 1 (*n* = 178)	92 (59–138)	135 (81–188)	0.001
Creatinine (mg/dL), day 1 (*n* = 239)	1.64 (0.93–3.30)	1.79 (1.09–3.13)	0.78
Lactate (mmol/L), day 1 (*n* = 168)	2.5 (1.8–4.5)	6.2 (3.8–11.0)	< 0.001
pH, day 1 (*n* = 203)	7.40 (7.35–7.47)	7.41 (7.36–7.48)	0.47
Maximum model for end-stage liver disease, days 1–7 (*n* = 239)	33 (27–39)	39 (34–46)	< 0.001
Cerebral edema (*n* = 243)	44 (36.4%)	61 (50.0%)	0.032
Year of enrollment (*n* = 243)			0.19
1998–2007	21 (17.4%)	14 (11.5%)	
2008–2016	100 (82.6%)	108 (88.5%)	

TABLE 4.
Adjusted Association of Cerebral Edema on Head CT With 21-day Transplant-Free Survival in Patients With Acute Liver Failure

Variable	Adjusted OR	95% CI	*p*
Age (yr)	0.97	0.95–0.99	0.002
Acetaminophen toxicity (vs. other)	3.70	1.94–7.01	< 0.001
Maximum model for end-stage liver disease score, days 1–7	0.90	0.86–0.93	< 0.001
Cerebral edema on CT scan	0.36	0.18–0.70	0.003

OR = odds ratio.

Model: *n* total = 238; *n* events = 121; chi-square (*df*) = 73 (4); *C*-statistic (95% CI) = 0.81 (0.75–0.86); $p < 0.001$. Variance inflation factor for collinearity < 1.20.

edema on CT scan and all died (26). The authors concluded that cerebral edema increased the risk of death. Finally, in another single-center North-American cohort study with 22 patients with ALF, acute changes in serum osmolality were associated with changes in the intracranial cerebrospinal fluid (CSF) volume measured by serial brain CT scans (12). Based on their results, the authors suggested that brain CT scan may be a useful tool to quantify CSF volume and use it as a surrogate for the risk of cerebral edema.

The four cohort studies described included single-center and small samples of patients with ALF (12, 24–26). Furthermore, only three of them highlighted the potential usefulness of CT scan to detect directly or through a surrogate (CSF volume) cerebral edema (12, 25, 26). In addition, only one report studied the association of cerebral edema on CT scan with more robust patients' outcomes, such as survival (26).

Overall, our study contributes valuable real-world robust data on the use of brain CT scan in patients with ALF. According to our findings, sicker patients, especially those with grade 3/4 HE or hyperammonemia, were more likely to get a brain CT scan. Furthermore, brain CT scan was more frequently ordered in the latter inclusion period. This may suggest that clinicians were increasingly more aware of the relevance of detecting as early as possible intracranial complications in patients with ALF. Also in our cohort, about two in five patients who got a brain CT scan had features of cerebral edema. This result points toward the potential utility of CT scan for a timely diagnosis of cerebral edema in patients with severe ALF. Finally, in our cohort, patients with cerebral edema diagnosed by CT scan had worse TFS. This finding highlights how cerebral edema may become a feature of severe ALF that may increase the risk of mortality among these patients. Taken altogether, our findings suggest that brain CT scan may be an important tool to use in the approach to patients with severe ALF.

In the ICU, clinical assessment, often based on pupils' examination and serial serum ammonia determinations, compounded by ultrasound measurement of the optic nerve sheath diameter or transcranial Doppler studies, may help to identify patients at higher risk of cerebral edema, but with caveats. Brain CT scan, which is widely available and easier to perform than MRI, may add to this approach. In fact, it seems to be important, not only for acute encephalopathy differential diagnosis, but also for detecting cerebral edema and help stratify the risk of short-term mortality. In addition, once cerebral edema is diagnosed, therapeutic strategies may be timely optimized to protect the brain and prevent intracranial hypertension progression and coning. This way, patients may stabilize and either wait for the liver to spontaneously recover or undergo emergent LT (27).

Limitations, Strengths, and Future Directions

The results of our study need to interpret in the context of the following limitations. First, this was a retrospective analysis from a North-American registry database, which may have led to selection bias. However, the large sample size, the multicenter nature, and the prospective enrollment of patients meeting specific entry criteria in the USALFSG Registry may have helped to minimize such bias.

Second, cerebral edema was diagnosed based on recognized features on standard CT scan (20, 21). In fact, the gold standard for cerebral edema diagnosis in patients with ALF remains difficult to set. Earlier stages of cerebral edema may be hard to detect even on CT scan (14). Furthermore, age-related anatomy may pose additional challenges to cerebral edema diagnosis. Therefore, cerebral edema prevalence may be hard to correctly estimate. Despite these difficulties, our aim was to study how CT scan may help to diagnose cerebral edema and what clinical impact this may have.

Third, ICP quantification requires invasive measurement (5). In our cohort, only 5.3% of patients who underwent brain CT scan had an ICP monitor device in place on day 1. The following reasons may help to explain such low proportion of intracranial bolt use: 1) intracranial bolt placement requires advanced technical expertise, which may have been unavailable at some sites, 2) the associated risk of intracranial bleeding is not negligible, thus some clinicians may have refrained from using it, and 3) and more recent reports suggested it has had a dubious impact on these patients' outcomes (10, 28).

Fourth, data regarding when and why the brain CT scans were performed were unavailable. This may have added to selection bias and limited our ability to capture all cases of cerebral edema or other intracranial pathologies, as well as how these radiology features evolved overtime. However, the fact that sicker patients had more often a brain CT scan may suggest that clinicians were at least aiming to perform a differential diagnosis, which may include ALF-related cerebral edema.

Fifth, the study inclusion period was long, stretching from 1998 to 2016. Although this was necessary to include so many patients at multiple sites, this may have introduced bias related to improvement of clinical care overtime. However, we tried to compare patients' characteristics and endpoints between two different time periods (1998–2007 vs. 2008–2016) to try to mitigate such bias.

Despite these limitations, we believe that our study provides data on the use of brain CT scan to diagnose cerebral edema in patients with ALF that could upgrade the clinical approach to these patients. Future studies could build on our report, perhaps by further investigating how CT scan may integrate with noninvasive bedside tools for cerebral edema assessment, such as automated pupillometry (8, 9, 21, 29). In addition, the potential role of brain CT scan as a tool to measure cerebral edema treatment response requires further validation (12).

CONCLUSIONS

In our cohort of patients with ALF, brain CT scan use increased overtime. Among those with a brain CT scan, about two in five had cerebral edema. Cerebral edema on CT scan was independently associated with worse 21-day TFS but did not preclude transplant. Brain CT scan may provide additional diagnostic and prognostic information in selected patients with ALF.

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