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ORIGINAL ARTICLE

Neurological events after liver transplantation: a single-center experience

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Summary

The aim of this study was to identify potential risk factors linked to neurologic events (NE) occurring after liver transplantation (LT) and use them to construct a model to predict such events. From odds ratios (OR) of risk factors, a scoring system was assessed using multivariate regression analysis. Forty-one of 307 LT patients presented NE (13.3%), with prolonged hospital stay and decreased post-LT survival. On multivariate analysis, factors associated with NE included: severe pre-LT ascites OR 3.9 (1.80–8.41; $P = 0.001$), delta sodium ≥12 mEq/l OR 3.5 (1.36–8.67; $P = 0.01$), and post-LT hypomagnesemia OR 2.9 (1.37–5.98; $P = 0.005$). Points were assigned depending on ORs as follows: ascites 4 points, and hypomagnesemia and delta sodium ≥12 mEq/l, 3 points each (score range = 0–10 points). ROC curve analysis suggested good discriminative power for the model, with a *c*-statistic of 0.72 (CI 0.62–0.81; $P < 0.0001$), best performance for a cutoff value >3 points (71% sensitivity, 60% specificity). NE risk increased progressively from 6.4%, to 10.3%, 12.8%, 31.5% and 71.0% as scores rose from 0 to 3, 4, 6–7 and 10 cumulative points, respectively. The score described helps to identify patients potentially at risk for neurologic events, and its prevention would decrease morbidity and mortality after LT.

Introduction

Risk of neurological events (NE) occurring after liver transplantation (LT) is relatively high [1]. These events may present as seizures, delirium, impaired consciousness, or focal neurologic signs, at rates reported between 9 and 42% [1,2], higher than for other solid organ transplants. The reason for this increase remains unexplained; possible causes include surgical procedure complexity, structural central nervous system (CNS) changes resulting from hepatic encephalopathy (HE) [3,4], metabolic disturbances [3,5,6] and drugs used following LT [1]. Neurotoxicity secondary to calcineurin inhibitors (CNI) has been studied in the past [7]. However, controversy persists over which patients are at greater risk for developing NEs following transplantation.

Increased mortality and morbidity, in the form of greater incidence of acute cellular rejection (ACR) [3–6], prolonged hospital stay [1–3], higher rates of in-hospital infections [3–5] and poorer quality of life [1,3] have all been associated with NEs. Ultimately, LT costs are probably higher in these patients, making early identification of those potentially at risk for developing NE important, in order to implement measures attempting to reduce NEs incidence.

We recently reviewed our clinical care algorithms used at our institution following LT. We aimed to identify risk factors associated with NEs, develop a predictive-prognostic

risk score and applied it to establish its impact on LT outcomes in a cohort of adult liver transplant recipients.

Methods

Study patients

A retrospective, single-center analysis was performed on 307 consecutive adult (≥18 years), deceased (n = 285) or living donor (n = 22) LT recipients, operated between October 2001 and December 2013 at the Austral University Hospital. The Institutional Review Board approved the study protocol and written informed consent was obtained from all patients (or from a family member), which was conducted in conformance with the 1975 Helsinki Declaration. The primary outcome of the study was NEs occurring after LT, while secondary outcomes were patient survival, length of hospital stay (LOS), biopsy-proven ACR rate [8], and short-term re-hospitalization (<30 days post-LT).

Pre- and post-transplant recipient variables and laboratory values included for the analysis were those that we hypothesized or that had been previously reported by other authors as linked to NEs, namely [1–3,5,6,9]: recipient age, gender, alcohol-related liver disease, presence or history of hepatic encephalopathy (HE) West Haven criteria grade >II [10] and presence of clinically severe ascites. The latter was defined as requirement of at least 1 therapeutic paracentesis. Pre-LT serum sodium level <126 mEq/l was defined as severe hyponatremia. Donor age, as well as cold and warm ischemia duration was registered. Post-LT variables included renal replacement therapy (RRT), serum sodium and magnesium levels, concomitant drugs, and units of blood product consumption (BPC) during transplant surgery. Differences between serum sodium levels immediately before LT and up to 72 h after LT (defined as delta sodium) of ≥12 mEq/l were considered indicative of increased risk for developing osmotic demyelinization syndrome (ODS) [11–13]. Institutional protocol precluded transplant in patients with serum sodium <115 mEq/l until serum sodium levels reached 120 mEq/l, and strict sodium control was conducted during and after LT to avoid any significant shifts. Hypomagnesemia (<1.6 mEq/l) was assessed immediately prior to, or during NEs, as well throughout post-LT period until hospital discharge. Drugs on record as administered prior to NE development included fluconazole, fentanyl, and immunosuppressive drugs. Fluconazole was prescribed as antifungal prophylaxis following recommended clinical guidelines [14]. Immunosuppression with Tacrolimus (Tac) or cyclosporine A (CsA), with or without mycophenolate mophetil (MMF) was registered. Tac and CsA trough levels during immediate post-transplant period were measured daily prior to morning dose (C0). In patients presenting NEs, blood levels were registered prior to or on the same day of the event. In those patients with impaired renal function before LT, induction therapy with basiliximab was indicated and CNIs delayed.

Neurological events: definition, assessment and follow-up

Patients presenting NEs were examined by a neurologist. Positive findings included: impaired consciousness (stupor or coma), delirium, seizures (partial or generalized) or focal neurologic deficit (excluding tumors), visual impairment or slurred speech. Stupor was defined as impaired consciousness clinically evidenced by low external responsiveness, or lack of arousal from a sleep-like state or a Glasgow Coma Scale score <9 points [12]; while coma was defined as unconsciousness with unresponsiveness to external stimuli or a Glasgow Coma Scale score <4. Delirium was assessed following American Psychiatric and Critical Care Associations guidelines [15]. Focal neurological signs were considered present if motor and/or sensory deficit was evidenced on physical examination (hemiparesis/hemiplegia, hemianopsia, dysarthria, aphasia/dysphasia). Generalized or partial tremor was considered a minor event and not included for the analysis.

Central nervous system imaging, either computed axial tomography (CAT) or magnetic resonance image (MRI) was obtained in all patients presenting NEs to look for or rule out presence of leucoencephalopathy, hemorrhage, ischemic signs or ODS [11,13]. Additionally, electroencephalogram and/or lumbar puncture were performed when necessary. Neurological signs and symptoms were monitored during follow-up. LT patients with persistent deficits were considered to have permanent neurological impairment (PNI).

Statistical analysis

Univariate and multivariate analysis, using logistic regression were performed to identify significant variables related to NE. Those variables with a P value <0.1 in the univariate analysis were included in the multivariate regression model, which was further generated by stepwise backward elimination (Wald test), $P < 0.05$. NE risk was estimated applying Odds Ratios (OR) and 95% Confidence Intervals (CI). OR's derived for each risk factor in the multivariate analysis were subsequently used as weights (rounded OR values) to construct a simple clinical prediction rule (e.g: OR 3.4, was allotted with 3 or 0 points for presence or absence of the risk variable related to NEs, respectively). Final scores corresponded to sum of points for each individual patient. Calibration and validation of the model was performed by Hosmer-Lemeshow test and bootstrapping technique (1000 samples), respectively. Model goodness of fit and discrimination power was assessed by receiver-operating

characteristic curve (ROC) and concordance statistic calculated. Correlation between ordinal data was measured using Goodman & Kruskall Gamma. Finally, Kaplan–Meier survival curves were performed and compared using log-rank test. Collected data was analyzed with SPSS software (version 20.0 IBM for Mac).

Results

Table 1 describes baseline characteristics of patients presenting at least one NE. Overall, 41 of 307 patients presented a NE (13.3%) within a median of 8.0 days after LT. Chronic Hepatitis C virus infection and alcoholic-related cirrhosis were the most frequent indications for LT. No patient had Wilson disease. Fifty-one NEs were identified, namely: seizures 33.3% (n = 17), altered mental status 23.5% (stupor n = 8 and coma n = 4), focal neurologic signs 21.6% (n = 11), visual disturbance or slurred speech 17.6% (n = 9), and delirium 9.8% (n = 5). CNS imaging (CAT/MRI) revealed no visible CNS pathology in 13 patients (31.7%), ODS in 8 (19.5%), leukoencephalopathy and ischemic signs in seven patients each (17.1%), and cerebral hemorrhage in 1 (2.4%). Incidence of ODS in the cohort was 2.6%. EEG was performed in three patients and cerebrospinal fluid analysis in two patients. No CNS infections or tumors were found. In any patients presenting a NE, CNIs were discontinued and replaced by steroids or MMF or mammalian target of rapamycin inhibitors (mTOR: Sirolimus or Everolimus) until event resolution, and then either restarted at lower dose or replaced by mTORs.

Permanent neurological impairment was present in 16 of 41 patients presenting NE (39%). Compared to patients with full neurological recovery (n = 25, 61%), those with PNI presented delta serum sodium levels ≥12 mEq/l more often (38.5% vs. 5.9%; P = 0.027), lower cholesterol levels (P = 0.10), and were more frequently on fluconazole (80% vs. 28%; P = 0.002) and fentanyl (80% vs. 48%; P = 0.04) before the event developed. Higher Tac trough levels, though not statistically significant, were also observed in patients with PNI (Table 2). Radiological findings among patients with PNI included ODS five patients, leukoencephalopathy syndrome five patients, normal CAT or MRI scans four patients, and signs of ischemia two patients.

Table 1. Clinical characteristics of patients presenting neurological events.

Variable	Value
Age (years)	53 ± 12
Gender: Male [*n* (%)]	19 (46.3)
Alcohol-related Cirrhosis [*n* (%)]	8 (21.2)
ALF [*n* (%)]	3 (9.1)
Retransplantation [*n* (%)]	1 (2.5)
SLK transplantation [*n* (%)]	3 (9.1)
LDLT [*n* (%)]	0 (0.0)
MELD	18 ± 9
Cholesterol (mg/dl)*	94 ± 44
Creatinine (mg/dl)*	1.32 ± 1.29
Serum Sodium (mEq/l)*	132 ± 6
Serum Albumin (g/dl)*	2.7 ± 0.6
HE* [*n* (%)]*	12 (30.0)
Severe Ascites* [*n* (%)]*	25 (62.5)
CIT (minutes)	480 ± 118
Blood product consumption (units)†	30 ± 23
LOS (days)	42 ± 36
ACR [*n* (%)]	21 (60.0)

Normal values: serum sodium 135–145 mEq/l, serum total cholesterol <200 mg/dl, serum creatinine 0.7–1.3 mg/dl, and serum magnesemia 1.6–2.2 mEq/l.
*Pre-LT variables.
†Post-LT variables.

Neurological events: higher transplant morbidity and mortality

Kaplan–Meier curves showed survival rates at 5 years following LT among patients with NE to be numerically lower

Table 2. Comparative analysis between patients with and without permanent neurological impairment (PNI).

Variable	NE without PNI n = 25 (61%)	NE with PNI n = 16 (39%)	P value
Age (years)	54 ± 13	48 ± 12	0.74
MELD*	19 ± 10	24 ± 11	0.36
Cholesterol (mg/dl)*	108 ± 49	78 ± 24	0.10
Creatinine (mg/dl)*	1.15 ± 1.00	2.05 ± 1.52	0.76
Albumin (g/dl)*	2.9 ± 0.5	2.3 ± 0.8	0.18
Serum sodium (mEq/l)*	132 ± 4	129 ± 5	0.59
HE [*n* (%)]*	8 (32)	6 (40)	0.43
Severe Ascites [*n* (%)]*	17 (68)	10 (68)	0.59
Donor age (years)	42 ± 18	39 ± 14	0.06
Delta Sodium (mEq/l)†	7 ± 4	12 ± 6	0.09
Hypomagnesemia [*n* (%)]†	13 (54)	6 (37)	0.24
CIT (minutes)	496 ± 108	490 ± 119	0.38
Blood product consumption (units)†	25 ± 16	49 ± 38	0.02
Basiliximab [*n* (%)]†	12 (48)	9 (56)	0.42
Fluconazole [*n* (%)]†	7 (28)	12 (80)	0.002
Fentanyl [*n* (%)]†	12 (48)	12 (80)	0.04
Tac levels (ng/ml)†	7.6 ± 6.4	11.6 ± 3.6	0.14
CsA levels (ng/ml)†	234 ± 133	183 ± 69	0.44
RRT after LT [*n* (%)]†	3 [12]	4 (25)	0.25

Normal values: serum sodium 135–145 mEq/l, serum albumin 3.5–4.5 g/dl, serum total cholesterol <200 mg/dl, serum total bilirubin 0.2–1.0 mg/dl, serum creatinine 0.7–1.3 mg/dl, serum magnesemia 1.6–2.2 mEq/l.
*Pre-LT variables.
†Post-LT variables.

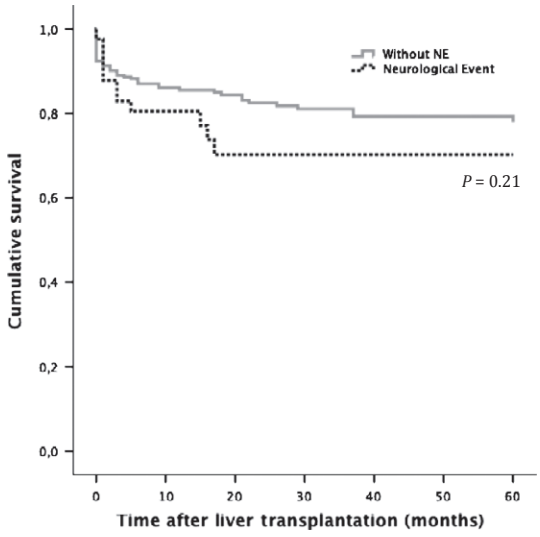
compared with patients not presenting NEs (73.1% vs. 82.1%; $P = 0.21$) (Fig. 1). Patients with PNI presented lower 5-year survival rates compared with patients recovering fully (43.7% vs. 75.0%, $P = 0.027$) (Fig. 2). Main causes of death among patients with NE were sepsis ($n = 5$) and cardiovascular events ($n = 4$). LOS was longer for patients presenting NE (43 ± 36 days vs. 17 ± 15; $P = 0.001$), and ACR event rate was higher among patients presenting NEs compared with those patients without NE (55% vs. 29%; $P = 0.001$). However, no significant difference in short-term re-hospitalization rate was observed (19% vs. 22%; $P = 0.52$).

Risk factors of NE: toward a predictive-prognostic model

Patients with NE had higher mean pre-LT serum creatinine levels (1.44 ± 1.39 vs. 1.07 ± 0.82 mg/dl; $P = 0.04$), lower serum cholesterol (93 ± 43 mg/dl vs. 117 ± 91 mg/dl, $P = 0.02$), and higher incidence of pre-LT severe ascites (67.5% vs. 36.1%; $P < 0.0001$), compared with patients not developing CNS complications. Additionally, no significant differences were observed in MELD score at transplantation (21 ± 9 vs. 18 ± 10; $P = 0.44$), serum albumin (2.7 ± 0.6 g/dl vs. 2.8 ± 0.7 g/dl; $P = 0.43$), or serum sodium (133 ± 6 vs. 133 ± 10; $P = 0.53$). When patients with or without severe pre-LT ascites were compared, lower cholesterol levels (92 ± 53 mg/dl vs. 125 ± 95 mg/dl; $P < 0.0001$) were observed in the former, although pre-LT serum sodium levels were similar.

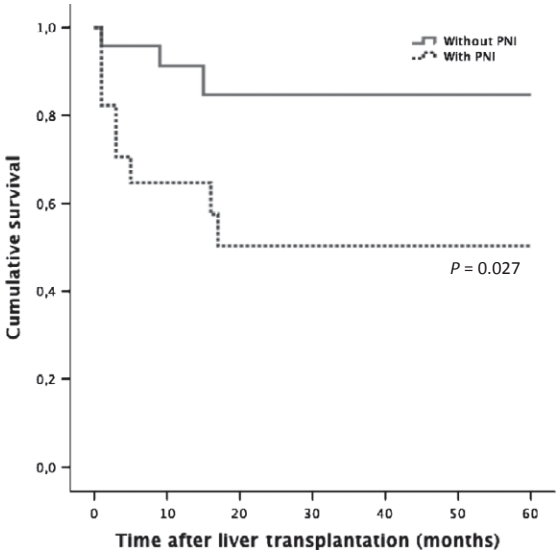
Regarding post-LT variables, patients with NEs had higher delta sodium after LT (7.3 ± 4.5 vs. 5.4 ± 3.7 mEq/l; $P = 0.008$), more prolonged cold ischemia time (CIT) (475 ± 108 vs. 445 ± 147 min; $P = 0.02$) and presented hypomagnesemia after LT more frequently (47% vs. 25%; $P = 0.004$). There was a significant difference in BPC during LT surgery between patients with or without NE (30 ± 23 units vs. 20 ± 21 units; $P = 0.01$).

Considering immunosuppression, basiliximab induction was more common among patients presenting NEs (51% vs. 26%; $P = 0.001$). At time of NE, 22 patients were receiving Tac (54%), 11 patients CsA (27%) and six patients no CNI. Mean blood trough levels of Tac and CsA at time of NE were 8.6 ± 6.4 ng/ml (median of 5.1 ng/ml) and 219 ± 116 ng/ml (median of 153 ng/ml), respectively.



Event/Time (months)	12	36	60
No NE (n = 264)	228	218	217
NE (n = 41)	33	30	30

Figure 1 Kaplan Meier Survival curves of patients with and without neurological events after liver transplantation. Kaplan Meier patient survival analysis comparing patient subgroups with and without neurologic events (NE). Overall survival rate at 5 years following LT of patients with NE was numerically lower than in patients without NE (73.1% vs. 82.1%; $P = 0.21$).



Event/Time (months)	12	36	60
MNE without PNI (n = 24)	22	21	21
MNE with PNI (n = 17)	11	9	9

Figure 2 Kaplan Meier Survival curves comparing patients with neurological events with or without permanent neurologic impairment. Kaplan Meier patient survival curves at 5 years following liver transplantation among patients with neurologic events (NE) with and without permanent neurological impairment (PNI). Overall survival rate at 5 years after transplantation of patients with PNI was lower than in patients without PNI (43.7% vs. 75.0%; $P = 0.027$).

Only five of 22 patients receiving Tac and two of 11 with CsA, had blood levels >10 ng/ml and >300 ng/ml, respectively, when NE occurred.

Univariate logistic regression analysis indicated the only significant pretransplant variable associated with NE was severe ascites OR 3.6 (1.81–7.45; $P < 0.0001$). Post-LT variables associated with NE included: hypomagnesemia OR 2.7 (1.37–5.36; $P = 0.004$), delta sodium ≥12 mEq/l OR 3.6 (1.51–8.79; $P = 0.004$), use of Fluconazole OR 2.1 (1.04–4.01; $P = 0.03$) and immunosuppression with Tac OR 2.1 (1.05–4.07; $P = 0.03$). Variables that remained associated with NE after multivariate logistic regression analysis were severe pre-LT ascites OR 3.9 (1.80–8.41; $P = 0.001$), delta sodium ≥12 mEq/l OR 3.5 (1.36–8.67; $P = 0.01$), and hypomagnesemia OR 2.9 (1.37–5.98; $P = 0.005$; Table 3). Model calibration with Hosmer-Lemeshow test showed no significant differences between observed and expected events ($P = 0.99$). Bootstrap validation showed overfitting was negligible and therefore no adjustment of logistic regression model estimates was required (Table 4).

Points in the predictive scoring system for NE were allocated as follows: severe pre-LT ascites (absence = 0 points, presence = 4 points), post-LT hypomagnesemia (absence = 0 points, presence = 3 points), and delta sodium ≥12 mEq/l (absence = 0 points, presence = 3 points) (Table 5). Final scores ranged from 0 to 10 points, and ROC curve revealed good discriminatory power for the model with a *c*-statistic of 0.72 (CI 0.62–0.81; $P < 0.0001$), and best performance for a cutoff >3 points (71% sensitivity, 60% specificity) (Fig. 3). Positive and negative predictive values were 0.21 and 0.92, respectively. The model was more accurate than the MELD scoring system to

Table 4. Multivariate logistic regression analysis of risk factors associated with neurological events and Bootstrapped bias corrected – confidence intervals.

VARIABLE	β	OR (CI 95%)	Bootstrapping CI 95%	*P*
Ascites*	1.36	3.9 (1.80–8.41)	1.91–10.91	0.001
Delta Sodium ≥12 mEq/l†	1.29	3.5 (1.36–8.67)	1.23–9.87	0.005
Hypomagnesemia†	1.05	2.9 (1.37–5.98)	1.23–6.82	0.005

β coefficient.
*Pre-LT variables.
†Post-LT variables.

Table 5. Predictive model for neurological events: points assigned to each variable.

Variable	Comments	Points
Ascites*	Presence	4
	Absence	0
Delta Sodium ≥12 mEq/l†	Presence	3
	Absence	0
Hypomagnesemia†	Presence	3
	Absence	0

*Pre-LT variables.
†Post-LT variables.

Table 3. Logistic regression analysis of predictive factors related to neurologic events after liver transplant.

Variable	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Age (years)	1.2 (0.99–1.05)	0.08	–	
Alcohol-related Cirrhosis	1.9 (0.83–4.31)	0.13		
ALF	0.6 (0.19–2.28)	0.51		
LDLT	0.9 (0.87–0.94)	0.06	–	
MELD*	1.1 (0.98–1.05)	0.47		
Cholesterol*	0.9 (0.98–1.01)	0.12		
Creatinine*	1.3 (0.93–1.69)	0.12		
Albumin*	0.8 (0.49–1.36)	0.44		
Sodium (mEq/l)*	0.9 (0.96–1.02)	0.65		
HE*	1.8 (0.89–3.56)	0.10		
Ascites*	3.6 (1.81–7.45)	<0.0001	3.9 (1.80–8.41)	0.001
Donor age (years)	0.9 (0.97–1.02)	0.41		
Delta Sodium ≥12 mEq/l†	3.6 (1.51–8.79)	0.004	3.5 (1.36–8.67)	0.01
Hypomagnesemia†	2.7 (1.37–5.36)	0.004	2.9 (1.37–5.98)	0.005
CIT <8 hs†	0.6 (0.28–1.10)	0.09	–	
Tac†	2.1 (1.05–4.07)	0.03	–	
CsA†	1.3 (0.59–2.68)	0.54		
Use of Fluconazole†	2.1 (1.04–4.01)	0.03	–	

*Pre-LT variables.
†Post-LT variables.

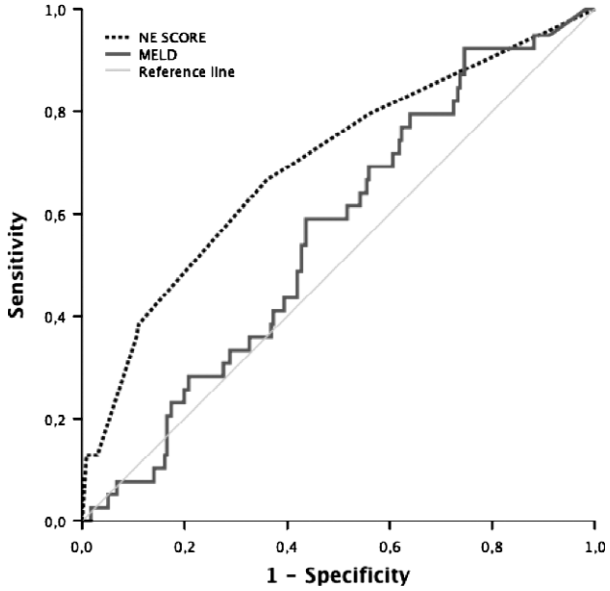


Figure 3 Predictive model for neurologic events after liver transplantation. A predictive prognostic score for NE was constructed (0–10 points), with two categories for presence or absence of each of the following variables: severe pre-LT ascites (0 or 4 points), post-LT hypomagnesemia (0 or 3 points), and delta sodium ≥12 mEq/l (0–3 points). Comparative analysis regarding ROC curves between NE predictive model and MELD score revealed better discriminative power for NE model, c-statistic of 0.72 (CI 0.62–0.81; $P < 0.0001$) and 0.55 (CI 0.46–0.64; $P = 0.24$), respectively.

predict NE events (Fig. 3). Risk of NE increased progressively as scores went from 0 to 3, 4, 6–7 to 10 points in the following percentages: 6.4% ($n = 8/124$), 10.3% ($n = 6/58$), 12.8% ($n = 10/78$), 31.5% ($n = 12/38$), and 71% ($n = 5/7$), respectively (Fig. 4). A clinical nomogram and different clinical scenarios are shown in Table 6 and Fig. 5.

Table 6. Possible clinical scenarios and application.

Clinical example	Outcome and future strategy
A. 54-year-old male patient with severe pre-LT ascites is subjected to LT and develops a delta sodium >12 mEq/l during surgery	Patient score = 7 points, probability of developing a NE during follow-up is 31.5%. Management: avoid hypomagnesemia and delay or replace CNIs
B. 65-year-old female patient with severe pre-LT ascites who undergoes LT, no hyponatremia prior to LT	Patient score = 4 points. Probability of developing NE post-LT is 12.8%. Significant sodium shifts should be avoided and hypomagnesemia mandatory in this example

We further evaluated whether individual NE risk factors were specifically related to any single NE. Presence of pre-LT ascites ($n = 122$, 40.3%) was linked to development of seizures OR 7.1 (CI 1.97–25.40; $P = 0.001$), as well as to visual symptoms or slurred speech OR 5.4 (CI 1.12–26.68; $P = 0.02$). Delta sodium ≥12 mEq/l ($n = 28$, 9.7%) significantly increased risk for developing ODS OR 28.1 (CI 5.72–153.23; $P \leq 0.0001$), visual disturbance or slurred speech OR 5.1 (CI 1.21–21.64; $P = 0.04$), and focal neurological signs OR 6.1 (CI 1.65–22.14; $P = 0.01$). Presence of hypomagnesemia after LT ($n = 83$, 28%) was related to development of visual dysfunction or slurred speech OR 9.7 (CI 1.97–47.80; $P = 0.002$). None of these risk variables were significantly related to delirium.

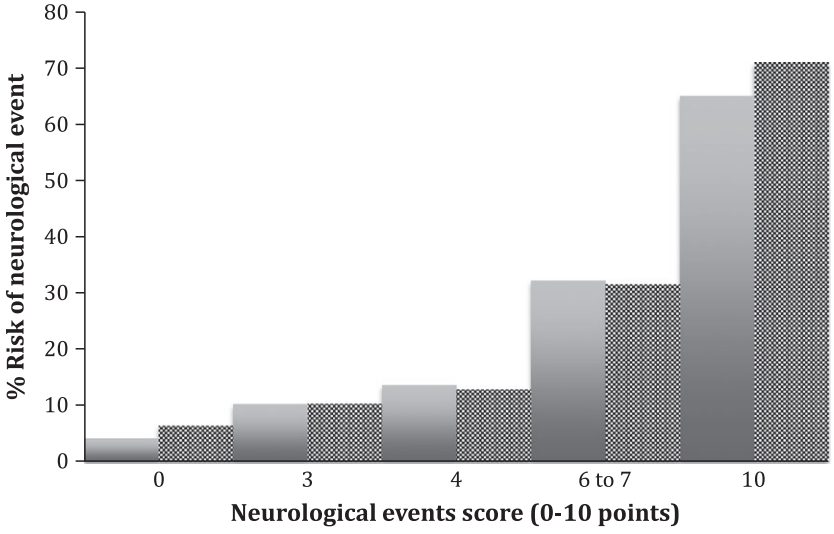


Figure 4 Correlation between points allotted in the predictive model and risk for development of neurological events. Progressive increase of NE risk was observed as score rose from 0 to 3, 4, 6–7 and 10 points: 6.4% ($n = 8/124$), 10.3% ($n = 6/58$), 12.8% ($n = 10/78$), 31.5% ($n = 12/38$), and 71% ($n = 5/7$), respectively (Goodman & Kruskall Gamma, $P = 0.0001$). Expected events = gray bars, Observed events = stippled gray bars.

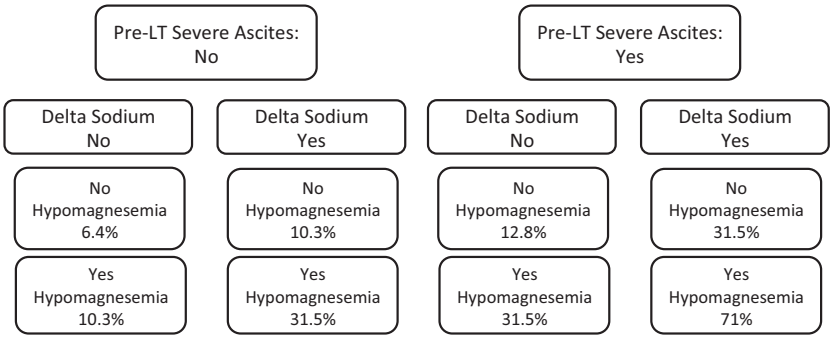


Figure 5 Nomogram for neurological event risk calculation. Clinical nomogram was constructed based on presence or absence of each risk variable to simplify scoring. Neurological event risk percentages shown.

Discussion

These results provide relevant information for the field of NEs after LT. We have evaluated pre- and post-LT risk factors associated with NE development and constructed a predictive clinical model. The score helps to identify patients at high risk for NEs during the immediate post-LT period. Cumulative NE incidence was similar in our cohort (13.3%) to other published series [1–5]. Most common events in the series were seizures (33%) and impaired state of consciousness (23%)[1]. As observed by other authors [1,3][9], no CNS tumors or infections were observed in the 41 patients with NEs.

Previous studies have suggested that pretransplant factors such as age, chronic alcohol consumption, serum bilirubin, low serum cholesterol levels, MELD score [6], and history of HE might be associated with NE following LT [3,4]. Great disparity exists in terms of HE definition, grade and classification [2–4,16]. There is also disagreement regarding alcohol consumption as a risk factor [6]. In our series, severe pretransplant ascites turned out to be a risk factor, probably because it is a surrogate marker for malnutrition and renal dysfunction, potentially altering drug pharmacokinetics. Pharmacokinetic changes are additionally explained by cell membranes phospholipid–cholesterol ratio changes in patients with liver disease, ultimately affecting the blood–brain barrier [17]. Although, no significant differences were observed between patients with or without pre-LT ascites in pre-LT serum sodium, lower cholesterol levels were observed.

Among post-LT factors, while pre- and post-LT hyponatremia has been proposed as a risk factor for adverse events following LT [3], delta sodium ≥12 mEq/l remains an important variable for ODS [13]. ODS did not exceed 2.6% in our cohort, an incidence similar to previously published series [2,4,11,13]. Additionally, delta sodium ≥12 mEq/l was related to development of focal neurological signs. Interestingly, no differences in pre-LT serum sodium levels were observed between patients with or without NE. Lower NE incidence among patients with LDLT [18–20] and shorter CIT [18] has been described; however, protective mechanisms of shorter ischemia duration are not clearly understood. Association of post-LT hypomagnesemia and development of NE remains controversial. Some studies identified it as a risk factor for NE, especially seizures [3,21], whereas other series found no association [5]. In this cohort, low magnesium levels were an independent variable for NE development and were more specifically related to visual disturbances or slurred speech.

Consequently, the sum of multiple variables and not isolated risk factors probably increase risk for developing some NEs. Prompt identification of risk variables would help avoid exposing these patients to known neurotoxic drugs. CNIs play a key role in the development of NE, although the exact mechanism is not fully understood. Proposed mechanisms include induction of cytotoxic edema, mitochondrial damage, and CNS neurotransmitter imbalance [1,22]. CNI-induced neurotoxicity is probably triggered by increased blood–brain barrier permeability [17], genetic predisposition [23] and pharmacokinetic changes triggered by low cholesterol and albumin levels, or impaired renal function, commonly seen in patients with end-stage liver disease, causing some patients to be at higher risk for neurotoxicity under CNI immunosuppression. Tac use was more prevalent among patients with neurologic events in this series, and the drug reached higher concentrations in patients presenting permanent neurological deficit. Nevertheless, six patients not receiving a CNI still manifested NE. Although certain authors have described NEs as associated with CNI levels [7], we now believe exposure to a CNI is just another of many variables associated with these events. Another potentially neurotoxic drug combination, fluconazole and Tac was more frequently administered to patients developing NE. This could be due to higher BPC observed in these patients.

Higher Tac trough levels, although not statistically significant, probably induced by Fluconazole enzymatic inhibition were observed in patients with PNI. Finally, induction with basiliximab was more frequent among patients developing NE, given that these patients had higher pre-LT serum creatinine. Whether basiliximab induction may lower the rate of NE in high-risk patients is still a matter of debate, and randomized clinical trials are needed to answer this question.

Increased mortality rate [3,5,6], longer intensive care unit and general LOS [3,16,18,19], higher incidence of ACR and in-hospital infection events [3,9] have all been reported in patients presenting NEs. In this study, a trend toward higher mortality, higher ACR rate, and longer LOS was observed. Higher ACR rates were probably due to CNI discontinuation in these patients. Ultimately, patients with PNI showed the highest mortality rate, and sepsis was the most common cause of death.

Consequently, we have recently modified our clinical management algorithms, and striving to avoid significant sodium shifts, hypomagnesemia and potentially neurotoxic drug combinations, particularly in patients with severe pre-LT ascites. Anidalofungin has replaced Fluconazole for Candida prophylaxis, and Tac starting dose has been delayed or reduced and combined with MMF in patients with high risk for NE (unreported data).

Limitations to this study include the following: the fact that data are retrospective even though results were statistically significant; that the scoring system proposed, although clinically relevant, needs to be further assessed in a prospective external cohort; and finally, that analysis of molecular inflammatory pathways involved in triggering NE is lacking.

In summary, prevention of NEs should become an integral part of liver transplant patient management. The predictive model we describe, based on the presence of severe pre-LT ascites, delta sodium shift ≥12 mEq/l, and hypomagnesemia showed sufficient accuracy (AUROC > 0.7) to support its use as an additional clinical tool to identify high-risk patients and decrease post-LT morbidity and mortality.

Authorship

FP: collection and analysis of data. Performed research and wrote manuscript. MM, MF, DA, AGC, MB, MPR, SC, OA and LGP: contributed with important reagents. VM: collected data. RQ: statistical analysis. MS: performed research/study design.

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