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Incidence, Clinical Features, and Risk Factors of Early Neurological Complications After Orthotopic Liver Transplantation: A Single-Center Experience

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Background: Despite improvements in technical and pharmacological expertise, orthotopic liver transplantation (OLT) still leads to potentially serious neurological complications (NCs) with very strong implications for graft survival, functional outcomes, and mortality.

Material/Methods: We conducted a retrospective study with the aim of defining the incidence, etiology, and clinical features of early post-OLT NCs, and we searched for preoperative, intraoperative and postoperative risk factors associated with their occurrence.

Results: Among 376 patients who underwent OLT, 97 (25.8%) had at least 1 neurological manifestation and 24 (6.38%) had more than 1 neurological manifestation. Delirium/metabolic encephalopathy was the most frequent (14.1%), followed by seizures (3.7%) and clinical manifestations of neurotoxicity (3.7%), and then by osmotic demyelination syndrome and peripheral nervous system injury (2.9%). NCs were the cause of death in 9/97 patients, and 11 patients had severe sequelae. Having NCs was correlated with more severe liver disease, a history of chronic renal impairment, higher plasma sodium concentrations at postoperative day 2, higher perioperative delta sodium, and a higher probability of having postoperative acute renal impairment, postoperative infections, graft rejection, and more than 3 systemic complications. No preoperative neurological comorbidities were found to be risk factors for developing acute NCs early after OLT. Patients with NCs had worse outcomes: longer in-hospital length of stay, longer intensive care unit (ICU) stay, higher probability of ICU re-admission, higher probability of in-hospital death, and higher probability of needing rehabilitation after hospital discharge.

Conclusions: Understanding the pathophysiology of NCs after OLT may lead to the development of prevention strategies for often untreatable neurological diseases.

Keywords: Neurologic Manifestations • Neurotoxicity Syndromes • Transplants

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Introduction

Orthotopic liver transplantation (OLT) is the best therapeutic strategy for severe acute and chronic hepatic diseases from many etiologies – infectious, autoimmune, metabolic, toxic, and even neoplastic [1-3] – allowing better survival and quality of life in patients with end-stage liver disease [4]. Despite advancements in surgical technology and medical expertise over time, OLT can still lead to serious neurological complications (NCs) immediately after surgery or after many months or even years.

NCs occur in roughly 15% to 30% of patients undergoing OLT [5-9], much more frequently than in any other solid organ transplant with comparable technical difficulty (eg, heart, lung) [10,11], and are associated with higher mortality, higher risk of re-transplantation, and increased rates of rejection and infective complications [12-14]. Neurological disorders also result in disability and impairment of quality of life, as well as huge economic costs for healthcare systems [15,16].

NCs occurring in the transplantation setting can involve both central and peripheral nervous systems and can appear at any time after surgery. Many authors have proposed a temporal classification of NC after OLT according to the time of onset from transplant: acute (within 1 month), subacute (from 1 to 6 months), and chronic (after 6 months) [17,18].

Many studies have explored risk factors for OLT-related NCs with the aim of preoperatively identifying all patients with a higher risk profile. To date, known pre-transplant risk factors are older age [19], portosystemic encephalopathy (PSE) [20], higher model for end-stage liver disease (MELD) scores [19], previous alcohol abuse [21], malnutrition, kidney failure [22], and severe ascites [23]. Moreover, intra-transplant risk factors are sodium shift [24], coagulopathy, hypercholesterolemia [25], hypomagnesemia [26], and co-administration of tacrolimus (FK) with drugs that modify the immunosuppressant drug metabolism [27,28]. All this information can be used preoperatively to approximately assess the risk profile of an OLT candidate without an already standardized operative risk calculator. Better patient stratification before surgery may allow the undertaking of preventive measures to make an early diagnosis soon after the appearance of neurological impairment and to start an adequate therapeutic strategy as soon as possible to reduce long-term sequelae.

Since NCs after OLT have a strong impact on postoperative adverse outcomes, we assessed the incidence of NCs in our cohort of liver transplant patients to characterize the etiology of neurological symptoms/signs/syndromes, and to identify independently associated risk factors for their perioperative occurrence. Then, we analyzed all data and interpreted them from a neurological perspective to determine if the standard perioperative management could be improved.

Material and Methods

We performed a single-center retrospective study to determine the incidence of early postoperative NCs in our cohort of advanced liver failure patients undergoing liver transplant (primary outcome). Additionally, we clinically characterized the range of NCs according to etiology and assessed the preoperative, intraoperative, and postoperative risk factors for their occurrence (secondary outcomes). The study was approved by the local ethics committee (IRRB/27/21) and all enrolled patients signed an informed consent form for retrospective research data collection. To achieve all the above-mentioned aims, we reviewed the electronic medical charts from all adult patients who underwent OLT from June 2014 to October 2021. Inclusion criteria were: adult (≥18 years old) end-stage acute or chronic liver disease patients who underwent cadaveric OLT in the period between June 2014 to October 2021, and whose informed consent forms were available. Exclusion criteria were the absence of informed consent, age <18 years old and the absence of cadaveric OLT. No other exclusion criteria were applied. Patients were consecutively enrolled.

The process of data collection consisted of manual review of all medical documents in the electronic chart. We collected: a. **Demographic data:** height, weight, body mass index, sex, and age at OLT; b. **Clinically relevant pre-transplant information:** smoking habits; comorbidities, including pre-existing neurological comorbidities; use of central nervous system (CNS)-active drugs; liver disease etiology; severity and complications of liver disease including portosystemic encephalopathy (PSE) with at least 1 episode of PSE grade II according to the West Haven Criteria [29]; transjugular intrahepatic portosystemic shunt (TIPS) implantation; and already hospitalized at the time of OLT (eg, for acute liver failure or acute-on-chronic liver failure). We considered blood cholesterol level as a surrogate for nutritional status. As for liver disease etiology, if alcoholic, we considered the alcohol withdrawal time (more or less than 5 years before transplant), whereas if viral, we specified whether the infection had been eradicated; c. **Intraoperative relevant information**: split versus whole-organ transplant; plasma laboratory tests a few hours before OLT and immediately after surgery: sodium, magnesium, potassium, creatinine, lymphocyte count, and albumin; transplant technical details: time of cold and warm ischemia, type of graft preservation liquid, use of extracorporeal bypass, percentage of histologically documented graft macro- and micro-steatosis; d. **Postoperative relevant clinical information:** blood levels of sodium and magnesium on postoperative day (POD) 2 and sodium level shifts from POD 2 to the values assessed before and soon after surgery;

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occurrence of renal impairment including the need for continuous renal replacement therapy (CRRT) (defined according to KDIGO guidelines) [30]; infections; type of immunosuppressive induction drug, if administered; type of immunosuppressive maintenance regimen; graft rejection (diagnosed by biopsy and histological examination); pluri-complicated clinical course (more than 3 major systemic complications); administration of fluconazole; length of hospital stay; length of intensive care unit (ICU) stay; ICU re-admission; need for rehabilitation after hospital discharge; in-hospital death; and occurrence of neurological complications. By major systemic complications, we intend all relevant conditions leading to therapy changes or surgical procedures.

The follow-up period for each patient was from the time of transplantation to discharge or death. Information related to the post-discharge period was not collected, so we only focused on acute NCs occurring during surgical hospitalization. NCs were classified qualitatively, approximately following the Wu S-Y et al [9] and Dhar et al [12] models as follows: (1) encephalopathy (delirium, psychosis and/or consciousness impairment without neurological focal deficit and/or without structural changes on neuroimaging); (2) seizures/status epilepticus; (3) drug-related neurotoxicity: neurological symptoms/syndromes potentially related to calcineurin inhibitors (CNI) with improvement after drug reduction/suspension; (4) ischemic and hemorrhagic acute stroke; (5) central nervous system (CNS) infection; (6) osmotic demyelination syndrome (ODS); (7) cerebral edema; (8) other minor neurological manifestations; (9) peripheral nervous system disorders.

NCs were also classified according to a severity grading of fatal, major (if they caused a severe cognitive or motor disability), or minor (if they caused just a mild and/or transitory neurological deficit). All NC diagnoses were confirmed by a neurologist with extensive expertise in SOT-related NCs, neurotoxicity by immunosuppressive drugs, and end-stage organ diseases. Neurologists were consulted upon request by anesthesiologists during the ICU stay or by the transplant surgical team in step-down units. The neurology consultant, if clinically indicated, managed the neurological diagnostic work-up, including neuroimaging investigations.

Data were collected retrospectively. Continuous and categorical variables are expressed as median with interquartile range and as frequency with percentage, respectively. To compare continuous variables, the Wilcoxon test or *t* test was used when appropriate. Fisher's exact test was used to compare categorical variables among groups. To explore the differences between patients with neurological complications (NCs) and patients without neurological complications (nNCs), logistic regression models were used. Levels of significance were set with $P<0.05$. Statistical analyses were performed using SAS software version 9.4.

Results

From June 2014 to October 2021, a total of 376 end-stage liver disease patients underwent orthotopic liver transplantation in our institution, with 26.9% being female. The median age at time of transplantation was 58 years old (range, 50-62.5 years). Demographic and clinical features of the whole cohort are reported in **Tables 1 and 2**, which also show data for the patients divided into 2 groups according to the occurrence (NCs) or not (nNCs) of nervous system impairment signs soon after transplantation and during the hospital stay.

Patients With NCs

Ninety-seven out of 376 (25.8%) patients had at least 1 neurological manifestation and 24 (6.38%) had more than 1 neurological manifestation (eg, neurotoxicity and seizures, or neurotoxicity and critical illness polyneuropathy). Among all NCs, the most frequent was delirium/metabolic encephalopathy, affecting 14.1% (53/97) of patients, followed by seizures (3.7%) and clinical manifestations of neurotoxicity (3.7%), then ODS (2.9%) and peripheral nervous system injury (2.9%). Less frequently, we registered hemorrhagic stroke (1.3%), ischemic stroke (1.1%), cerebral edema (1.1%), CNS infections (0.3%) and other minor neurological manifestations (2.1%), such as headache, torticollis, or reactive depression. Most patients with NCs (73%) underwent instrumental diagnostic investigations: 32% had neuroimaging (brain computed tomography or magnetic resonance imaging) assessment, 14.4% had electroencephalography (EEG), and 26.8% received both exams. A structural brain abnormality was confirmed in 7.2% of patients in the whole population (27.8% in the NC group). Most patients (26 out of 40) who underwent EEG only had mild abnormalities, such as slow theta waves without epileptic significance; only 4 patients presented with major neurophysiological abnormalities such as epileptic discharges or status epilepticus. In 39 out of 97 (40%) patients, therapeutical changes were made, such as the introduction of antiseizures medication or the modifying of the immunosuppression regimen. In 20 (20.6%) patients, tacrolimus was stopped and in 4 (4.12%) patients the dosage was just reduced. This suggests that the administration of tacrolimus was withheld even when neurotoxicity was only suspected. In fact, neurotoxicity syndromes often do not have a very specific clinical picture (eg, tremors and consciousness impairment) but can lead to a severe neurological impairment if not immediately stopped. All patients with NC had an average blood concentration (measured at the time of the NC) of tacrolimus within the normal range. Most of the patients with NC (77/97) had minor sequelae or none,

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Table 1. Preoperative features in patients with neurological complications and without neurological complications.

Pre-operative features	nNC	NC	Total	*p*	OR
Height (cm), median	167	167	167	0.8536	–
Females, no. (%)	73 (19.4)	28 (28.8)	101 (26.9)	0.6053	–
Weight (kg), median	75.2	72.9	74	0.7153	–
BMI, median	27	26	26	0.7343	–
Age at OLT (years), median	58	57	58	0.2742	–
MELD, median	22	25	22	0.0003	1.07
Split, no. (%)	14 (3.7)	5 (1.3)	19 (5.1)	0.9575	–
Time from TIPS to OLT (days), median	390.5*	221#	299§	0.8069	–
Pre-op Na (mmol/L), median	139	138	139	0.1046	–
Pre-op K (mmol/L), median	3.8	3.9	3.8	0.1007	–
Pre-op Mg (mg/dl), median	2**	2°°	2§§	0.3356	–
Pre-op creatinine (mg/dl), median	0.8	0.9	0.8	0.3144	–
Pre-op lymphocyte count (/mcl), median	960	890	950	0.3344	–
Pre-op cholesterolemia (mg/dl), median	115***	50###	109§§§	0.302	–
Pre-op albuminemia (gr/dl), median	3.4	3.2	3.4	0.0205	0.52
Hypertension, no. (%)	71 (18.9)	25 (6.7)	96 (25.5)	0.9495	–
Diabetes mellitus, no. (%)	84 (22.3)	21 (5.6)	105 (27.9)	0.1116	–
Cardioembolic arrhythmia, no (%)	7 (1.9)	1 (0.3)	8 (2.1)	0.4004	–
Cerebrovascular disease history, no (%)	33 (8.8)	7 (1.9)	40 (10.6)	0.2091	–
COPD, no. (%)	22 (5.9)	5 (1.3)	27 (7.2)	0.3737	–
Endocrinopathies, no (%)	15 (4)	5 (1.3)	20 (5.3)	0.9338	–
Renal impairment history, no (%)	41 (10.9)	25 (6.7)	66 (17.6)	**0.0147**	**2.02**
Smoking, no. (%)	125 (33.3)	43 (11.4)	168 (45.5)	0.9611	–
Neurological comorbidities, no. (%)	41 (10.9)	20 (5.3)	61 (16.2)	0.1747	–
CNS drugs, no. (%)	108 (28.7)	40 (10.6)	148 (41.6)	0.4565	–
Beta-blockers, no. (%)	102 (27.1)	32 (8.5)	134 (35.6)	0.5274	–
PSE >2, no. (%)	61 (16.2)	49 (13)	110 (29.4)	**<0.0001**	**3.81**
Alcohol consumption history, no. (%)	95 (25.3)	36 (9.6)	131 (34.8)	0.5856	–
<5 years alcohol consumption, no. (%)	61 (16.2)	25 (6.7)	86 (22.9)	0.5843	–
TIPS, no. (%)	41 (10.9)	17 (4.5)	58 (15.4)	0.5067	–
Portal thrombosis, no. (%)	29 (7.7)	13 (3.5)	42 (11.2)	0.419	–
>3 comorbidities, no. (%)	50 (13.3)	19 (5.1)	69 (18.4)	0.715	–
Hyposodiemia, no. (%)	35 (9.3)	15 (4)	50 (13.3)	0.4665	–
Severe ascites, no. (%)	81 (21.5)	38 (10.1)	119 (31.7)	0.0564	–

Higher MELD scores, lower preoperative albuminemia, preoperative history of renal impairment, and at least 1 episode of PSE grade 2 were risk factors for postoperative NCs in OLT. * Calculated on 40 patients; ** calculated on 70 patients; *** calculated on 26 patients; # calculated on 15 patients; ## calculated on 18 patients; ### calculated on 6 patients; § calculated on 55 patients; §§ calculated on 2 patients; §§§ calculated on 32 patients. BMI – body mass index; K – potassium; MELD – Mayo End-Stage Liver Disease; Mg – magnesium; Na – sodium; OLT – orthotopic liver transplantation; Pre-op – preoperative; TIPS – transjugular intrahepatic portosystemic shunt; CNS – central nervous system; COPD – chronic obstructive pulmonary disease; NCs – neurological complications; nNCs – non-neurological complications; OR – odds ratio; PSE – portosystemic encephalopathy; TIPS – transjugular intrahepatic portosystemic shunt.

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Table 2. Hepatic disease etiology in patients with and without neurological complications.

Hepatic disease etiology	NC# (%)	nNC# (%)	total	p	OR
Viral etiology					
Yes	39 (10.4)	146 (38.8)	185 (49.2)	0.0405	0.61
No	58 (15.4)	133 (35.4)	191 (50.8)		
HCV eradication					
Yes	7 (1.9)	45 (12)	52 (13.9)	0.0885	–
No	33 (8.8)	98 (26.1)	131 (34.9)		
HCC					
Yes	44 (11.7)	149 (39.6)	193 (51.3)	0.1729	–
No	53 (14.1)	130 (34.6)	183 (48.7)		
Alcohol etiology					
Yes	31 (8.2)	80 (21.3)	111 (29.5)	0.5414	–
No	66 (17.6)	199 (52.9)	265 (70.5)		
NASH etiology					
Yes	15 (4)	15 (4)	30 (8)	0.6532	–
No	82 (21.8)	241 (64.1)	323 (85.9)		
Autoimmune etiology					
Yes	7 (1.9)	25 (6.7)	32 (8.5)	0.5967	–
No	90 (23.9)	254 (67.5)	344 (91.5)		
HCV etiology					
Yes	28 (7.5)	113 (30.1)	141 (37.5)	**0.0427**	**0.6**
No	69 (18.4)	166 (44.2)	235 (62.5)		
HBV etiology					
Yes	11 (2.9)	38 (10.1)	49 (13)	0.5662	–
No	86 (22.9)	241 (64.1)	327 (87)		
Wilson disease					
Yes	2 (0.5)	2 (0.5)	4 (1.1)	0.2879	–
No	95 (25.3)	277 (73.7)	372 (98.9)		
Hepatorenal polycystosis					
Yes	2 (0.5)	7 (1.9)	9 (2.4)	0.8043	–
No	95 (25.3)	272 (72.3)	367 (97.6)		
Other					
Yes	10 (2.7)	27 (7.2)	37 (9.8)	0.8572	–
No	87 (23.1)	252 (67)	339 (90.2)		

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Table 2 continued. Hepatic disease etiology in patients with and without neurological complications.

Hepatic disease etiology	NC# (%)	nNC# (%)	total	p	OR
Acute liver failure					
Yes	10 (2.7)	16 (4.2)	26 (6.9)	0.1309	–
No	87 (23.1)	263 (70)	350 (93.1)		
Critical condition before OLT					
Yes	17 (4.5)	24 (6.4)	41 (10.9)	**0.0172**	**2.26**
No	80 (21.3)	255 (67.8)	335 (89.1)		

A generic viral etiology of cirrhosis and HCV etiology appeared to be protective against NC onset after liver transplant. Being in a critical condition before surgery was significantly associated with developing NCs after OLT. HBV – hepatitis B virus; HCC – hepatocarcinoma; HCV – hepatitis C virus; NASH – non-alcoholic steatohepatitis; NCs – neurological complications; nNCs – non-neurological complications; OR – odds ratio.

Table 3. Clinical, instrumental, and prognostic details of NCs.

NC	n (%)
Total of patients with NC	97
Total of NC	125
Delirium/encephalopathy	53 (14.1)
Seizures	14 (3.7)
Neurotoxicity	14 (3.7)
ODS	11 (2.9)
PNS disease	11 (2.9)
Hemorrhagic stroke	5 (1.3)
Ischemic stroke	4 (1.1)
Cerebral edema	4 (1.1)
CNS infections	1 (0.3)
Others	8 (2.1)

Patients with NC	n
Total	97
EEG performed	40
Normal	9
Minor EEG abnormalities	26
Major EEG abnormalities	4
Neuroimaging performed	57
CT/MRI abnormalities	27
FK administration changes	24
FK dose reduction	4
FK withheld	20
Sequelae	
None or minor	77
Severe	11
Death because of NC	9

The most frequent was delirium/metabolic encephalopathy followed by seizures and clinical manifestations of neurotoxicity. Percentages were calculated on the total of 376 enrolled patients. N – number; NCs – neurological complications; ODS – osmotic demyelinating syndrome; PNS – peripheral nervous system; CNS – central nervous system; EEG – electroencephalogram; CT – computed tomography; MRI – magnetic resonance imaging; FK – tacrolimus.

whereas 9 of them died because of neurological disease and 6 died because of non-neurological causes; finally, 11 patients had severe sequelae (**Table 3**).

Preoperative Variables

We compared the group of patients with neurological complications (NC) and the group of patients without neurological complications (nNC), looking for any demographic or clinically associated risk factors. Among preoperative variables, we found that the group of patients with NC had higher MELD scores and lower plasma concentrations of albumin (**Table 1**) as well as a higher probability of having a history of chronic renal impairment (OR 2.02), at least 1 episode of PSE (OR 3.81), and a higher probability of being in critical condition before transplant (ie, having acute liver failure or already being hospitalized) (**Table 1**). Interestingly, hepatitis C virus (HCV) cirrhosis etiology was correlated with a lower probability of developing NCs (**Table 2**). No preoperative neurological comorbidities (any type), including chronic cerebrovascular disease, considered separately, were found to be risk factors for developing acute NC early after OLT.

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Table 4. Perioperative variables in patients with and without neurological complications.

Perioperative variables	nNC	NC	p	OR
Na POD 0 (mmol/l), median	146	146	0.9694	–
Na POD 2 (mmol/l), median	143	144	**0.0291**	**1.06**
Delta pre-op Na-Na POD 0, median	7	8	0.1069	–
Delta pre-op Na-Na POD 2, median	4	6	**0.0024**	**1.01**
Mg POD 0 (mg/dl), median	2.1	2	0.4402	–
Mg POD 2 (mg/dl), median	2.3	2.3	0.6734	–
CIT (minutes), median	390	405	0.1621	–
WIT (minutes), median	45	45	0.3801	–
Macrosteatosis (%), median	5*	5*	0.2371	–
Microsteatosis (%), median	5**	5**	0.3096	–
Na shift >7, no. (%)	103 (27.4)	41 (10.9)	0.091	–
Acute renal impairment, no. (%)	56 (14.9)	47 (12.5)	**<0.0001**	**3.74**
CRRT, no. (%)	13 (3.5)	25 (6.7)	**<0.0001**	**7.1**
PO infections, no. (%)	129 (34.3)	77 (20.5)	**<0.0001**	**4.48**
Rejection, no. (%)	21 (5.6)	20 (5.3)	**0.0006**	**3.19**
>3 complications, no. (%)	107 (28.5)	71 (18.9)	**<0.0001**	**4.39**
Fluconazole, no. (%)	10 (2.7)	4 (1.1)	0.8091	–
IS induction, no. (%)	19 (5)	18 (4.8)	0.943	–
Graft reconditioning, no. (%)	26 (6.9)	5 (1.3)	0.2028	–
Extracorporeal bypass, no. (%)	76 (20.2)	21 (5.6)	0.1925	–
FK administration, no. (%)	2 (72.9)	96 (25.5)	0.7642	–

Postoperative acute renal disease, need for CRRT, postoperative infections, rejection, having more than 3 postoperative complications, higher plasma concentration of Na at POD 2 and higher delta Na (preoperative to POD 2) were correlated with higher risk of developing early NCs after OLT. * Calculated on 105 patients; ** calculated on 103 patients. CRRT – continuous renal replacement therapy; IS – immunosuppression; FK – tacrolimus; Na – sodium; NCs – neurological complications; nNCs – non-neurological complications; OR – odds ratio; PO – postoperative; CIT – cold ischemia time; Mg – magnesium; pre-op – preoperative; POD – postoperative day; WIT – warm ischemia time.

Table 5. Outcome variables.

Outcome variables	nNC	NC	p	OR
In-hospital length of stay (days), median	14	36	**<0.0001**	**1.04**
ICU length of stay (days), median	3	10	**<0.0001**	**1.05**
ICU readmission, no. (%)	20 (5.3)	33 (8.8)	**<0.0001**	**6.65**
Intrahospital death, no. (%)	6 (1.6)	14 (3.7)	**<0.0001**	**7.67**
Rehab, no. (%)	11 (3)	19 (5.1)	**<0.0001**	**8.7**

Patients who experienced an NC during hospitalization after liver transplant have longer entire hospital stays and ICU stays, have higher risks of ICU re-admission and in-hospital death, and are more likely to be discharged to rehabilitation facilities (used as a surrogate measure of disability). ICU – intensive care unit; NCs – neurological complications; nNCs – non-neurological complications; OR – odds ratio.

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Perioperative Variables

Patients with NC had higher plasma sodium concentrations at POD 2 (P=0.0291) and higher delta sodium between POD 2 and preoperative concentrations (P=0.0024) (**Table 4**). Moreover, patients with NCs had a higher probability of having postoperative acute renal impairment (P<0.00001, OR 3.74), the need for CRRT (P<0.0001, OR 7.1), postoperative infections (P<0.0001, OR 4.48), graft rejection (P=0.0006, OR 3.19) and more than 3 systemic complications (P<0.0001, OR 4.39) (**Table 4**).

Outcomes

Compared to nNC patients, patients with NCs had longer in-hospital length of stay (P<0.0001), longer ICU stay (P<0.0001), higher probability of ICU re-admission (P<0.0001, OR 6.65), higher probability of in-hospital death (P<0.0001, OR 7.67), and higher probability of needing rehabilitation after hospital discharge (P<0.0001, OR 8.7) (**Table 5**).

Discussion

In our cohort of OLT recipients, we registered acute NCs soon after transplantation in almost 26%, a frequency exactly reproducing the findings reported in the literature [6-9,33]. The considerable number of studied phenomena in our cohort may even be underestimated due to the narrow observation time window, or it is possible that not all neurological findings were documented in the patient charts. The higher frequency of NCs seen in the liver transplantation setting, more than any other technically difficult solid organ transplant (eg, heart or lungs), has been commented on in the literature as being hypothetically due to brain damage caused by liver dysfunction. Brain injury related to liver function impairment could act as a predisposing factor for acute perioperative neurological diseases [16,31]. Consistently, our data strongly confirm that the main risk factor for post-transplantation NCs is the severity of the baseline liver disease with its complications, such as PSE, but renal impairment can also induce neurological dysfunction. Extra-cranial peripheral organ dysfunctions with a well-documented associated neurological impairment [32] can act as a predisposing factor for further perioperative NCs, but primary neurological diseases, including common cerebrovascular diseases, as comorbidities are not risk factors for postoperative NCs. We believe this result is important for neurologists consulted for their opinion on liver transplantation eligibility for end-stage liver disease patients with neurological comorbidities. Whether neurological comorbidities do not influence the neurological outcomes after liver transplantation needs to be confirmed in larger multicenter prospective studies, and a more detailed clarification of the type of neurological comorbidities (eg, neurodegenerative vs non-neurodegenerative disorders) is required. Although not standardized among centers, neurological consultation during the work-up for OLT eligibility is mostly considered for liver disease patients with a known neurological comorbidity or older cirrhotic patients; however, we believe that future efforts should focus on establishing a transplantation risk score calculator, including all statistically confirmed risk factors. Our study, consistent with the literature, acknowledges the severity of liver disease and other extra-cranial/peripheral organ dysfunctions potentially affecting the brain, such as renal impairment, as risk factors for early NCs after OLT. This strategy would allow for better preoperative stratification of liver transplant candidates, considering their risk of negative neurological outcomes, and for close observation of high-risk profile patients for postoperative neurological impairment to allow early recognition with fewer high-impact sequelae. In extreme cases, a cirrhotic patient's risk profile could argue against transplantation if the probability of highly disabling NCs is prohibitive. We are aware that this objective requires a prospective study in a larger population to carefully establish the role of neurological comorbidities, including the more frequent cerebral small-vessel disease or neurodegenerative diseases.

Finally, when NCs occur after a liver transplant, there are many adverse postoperative-associated outcomes: renal impairment, infections, rejection, and pluri-complicated courses. NCs also impact the length of hospital and ICU stays, ICU re-admission, in-hospital death, and patient discharge to rehabilitation facilities. All these adverse postoperative outcomes indicate the enormous size of the problem in terms of healthcare costs and patients' and families' quality of life.

A strength of our study is that all neurological diagnoses were confirmed by a neurology consultant well-integrated in the multidisciplinary transplantation team, and the main limitation of this investigation is its retrospective and single-center design.

Conclusions

NCs after OLT are common and are often severe, with a strong impact on survival, performance status, and long-term quality of life. NCs can nullify the health gain derived from the organ transplantation and, unfortunately, lead to a loss of functional autonomy. Our study, despite the limitation connected to its retrospective nature, shows the importance of identifying risk factors to focus on prevention of NCs, as treatment of brain injuries is often ineffective. Our results suggest the importance of extra-cranial conditions, such as the severity of pre-transplant liver disease or renal impairment, instead of neurological comorbidities, as potential risk factors for developing NCs after OLT.

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Abbreviations

OLT – orthotopic liver transplantation; **NCs** – neurological complications; **PRES** – posterior reversible encephalopathy syndrome; **ODS** – osmotic demyelination syndrome; **PSE** – portosystemic encephalopathy; **MELD** – model for end-stage liver disease; **FK** – tacrolimus; **CNS** – central nervous system; **TIPS** – transjugular intrahepatic portosystemic shunt; **POD** – postoperative day; CRRT – continuous renal replacement therapy; **ICU** – intensive care unit; **CNI** – calcineurin inhibitors; **EEG** – electroencephalography; **HCV** – hepatitis C virus.

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