

Analysis of Risk Factors for Postoperative Delirium After Liver Transplantation

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Purpose: The study aimed to analyze the incidence of postoperative delirium (POD) and associated risk factors after liver transplantation (LT).

Patients and Methods: We identified and enrolled patients undergoing LT at the Second Xiangya Hospital, Central South University between August 2018 and May 2019. We abstracted their relevant clinical information and assigned the patients into a POD group and non-POD group to compare differences in clinical information. Risk factors of POD were analyzed using logistic regression.

Results: A total of 159 LT patients were enrolled. Forty-two patients exhibited delirium (26.4%). Of the 42 with delirium, 33 (78.6%) had delirium within 3 days postoperatively and a median duration of 5 days (quartile 3–7 days). The results of binary logistic regression are as follows: preoperative ammonia (≥ 46 vs < 46 $\mu\text{mol/L}$; OR 3.51, 95% CI [1.31–9.46], $P < 0.05$), Model for End-Stage Liver Disease (MELD) score (≥ 15 vs < 15 ; OR 3.33, 95% CI [1.27–8.79], $P < 0.05$), presence of hepatic encephalopathy (OR 3.30, 95% CI [1.20–9.07], $P < 0.05$), aspartate aminotransferase (AST) on day 1 postoperatively (OR 1.33, 95% CI [1.06–1.68], $P < 0.05$), anhepatic period (OR 1.04, 95% CI [1.02–1.06], $P < 0.01$). The POD group had a longer intubation time (2925.0 vs 1410.0 min, $P < 0.01$), ICU length of stay (6 vs 4 d, $P < 0.01$) and increased medical costs (43.96 vs 33.74 ten thousand yuan, $P < 0.01$).

Conclusion: The incidence of POD in LT patients is a significant clinical feature. Ammonia ≥ 46 $\mu\text{mol/L}$, MELD score ≥ 15 , hepatic encephalopathy, anhepatic period, and AST at 1 day postoperatively were independent risk factors for POD.

Keywords: liver transplantation, postoperative delirium, ammonia, hepatic encephalopathy, risk factors

Introduction

Delirium is an acute reversible neurocognitive disorder status, manifesting as disturbance of consciousness, attention deficit, change in cognitive ability, and disturbed sleep cycle.¹ The incidence of delirium in society is about 1–2%.^{2,3} Postoperative delirium (POD) is a delirium state arising after surgery. The incidence of POD differs due to surgical type and risk, with fluctuation between 12%–51%.⁴ The reports on the incidence of LT POD are substantially different in the literature. The incidence of LT POD has been reported to be 10.0%–26.7%,^{5,7} but Wang et al reported an incidence of up to 47.4%.⁸

There are few studies on the risk factors of LT POD. Previous studies have shown that a history of alcohol abuse, hepatic encephalopathy, acute physiology and chronic health evaluation II (APACHE) score ≥ 16 , Child-Pugh level C, Model for End-Stage Liver Disease (MELD) score ≥ 15 , preoperative hemodialysis, and

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liver donor type are related with the occurrence of LT POD.^{6,8} LT POD increases medical cost, prolongs the duration of mechanical ventilation, ICU length of stay, hospital length of stay, increases the incidence of other complications, and short-term and long-term mortality.^{5,7}

This retrospective study analyzed the clinical information of 159 LT patients from August 2018 to May 2019 in the Second Xiangya Hospital, Central South University, to confirm the incidence and identify relevant risk factors of LT POD.

Patients and Methods

Patients

LT patients in the Second Xiangya Hospital, Central South University from Aug. 2018 to May 2019 were enrolled. Inclusion criteria included: (1) age ≥ 18 years old, (2) liver donor after brain death, (3) whole orthotopic liver transplantation. Exclusion criteria included: (1) multi-organ transplantation, (2) postoperative diagnosis of organic brain lesions, (3) primary liver graft malfunction, (4) congenital or genetic diseases, (5) a Richmond agitation sedation scale (RASS) ≤ -4 .

We guarantee that there were not organs of prisoners, coerced, or paid individuals used in this study. We confirm all organs were from voluntary donation with written informed consent. This study was reviewed and approved by the Ethics Committee of the Second Xiang-ya Hospital. They were conducted in accordance with the Declaration of Istanbul (in addition to the Declaration of Helsinki).

Study Methods

We collected the following variables from the clinical records: sex, age, weight, previous medical history (ie, diabetes, hypertension, history of abdominal surgery, history of neuropsychosis), smoking history, alcohol abuse history, emergency surgery (preoperative hospitalization ≤ 3 d), preoperative diagnosis (eg, liver cancer, acute liver failure, pre-transplant hepatic encephalopathy), liver function staging (Child-Pugh staging, MELD score), laboratory results for 3 days preoperatively (hepatic and renal function, electrolytes, coagulation function, blood ammonia and lactic acid). We also collected intraoperative information: time of operation, anhepatic period, intraoperative blood transfusion (eg, red blood cell, plasma, cryoprecipitate), intraoperative lactic acid, hypotension measured as systolic pressure $<30\%$ of baseline value, surgical procedure (eg, classic, piggyback). Postoperative information

included: laboratory results on day one postoperatively (hepatic and renal function, electrolytes, coagulation function, blood ammonia and lactic acid), intubation duration, ICU length of stay, delirium duration, and postoperative hospital length of stay. We also collected information on the donor: age, liver weight, cold ischemia time, liver function on either the day before or day of harvest, electrolyte, donor liver pathological before infusion.

Two doctors independently diagnosed POD using the CAM-ICU scale. In there was no agreement, a third doctor made the diagnosis. Patients were assigned to either the POD or non-POD group (control group) to analyze the clinical information.

In our center, we used livers that were donated after brain death and obtained by in situ cold perfusions with liver and kidney together. The surgical procedure was either classic liver transplantation or modified piggyback liver transplantation with or without ligation of the splenic artery. After surgery, the patients were transferred into ICU with tracheal intubation. Basiliximab 20 mg was administered at 2 hours preoperatively and 4 days postoperatively. Methylprednisolone 500 mg was administered during the anhepatic period. Tacrolimus and mycophenolate mofetil were used for anti-rejection at 3 days postoperatively to maintain the concentration of tacrolimus at 8–12 ng/mL.

Statistical Analysis

SPSS 24.0 software was used to analyze the data. $P < 0.05$ was defined as statistical significance. Normally distributed data were expressed as mean \pm SD and analyzed by two-sample *t*-test. Non-normal measurement data were expressed as medians (Q25, Q75), and analyzed with the Mann–Whitney *U*-test. Dichotomous data were analyzed with a chi-square test. The univariate factors with a $P < 0.1$ were included in the binary logistic regression analysis.

Results

General Information

A total of 159 patients were enrolled (Figure 1). Forty-two were diagnosed with a POD (26.4%) with an average age of 47.38 ± 9.29 years. Our sample included 33 men and nine women (Table 1). A total of 117 patients were classified as non-POD (a control group), including 101 men and 16 women. The average age of the control group was 49.19 ± 8.98 years (Table 1).

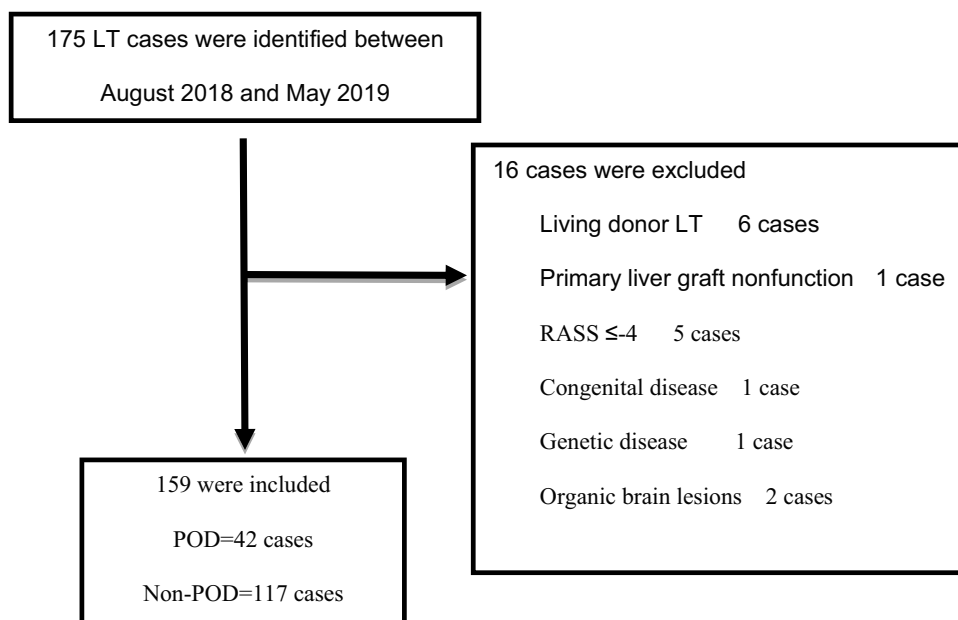


Figure 1 Flow chart of patients with LT.

Comparison of Clinical Information Between POD and Non-POD Groups

There was no statistical difference found with patient characteristics, such as age and sex ($P>0.05$) (Table 1). We analyzed the preoperative information and found the

following variables were statistically elevated in the POD group: acute hepatic failure, hepatic encephalopathy, Child-Pugh level C, MELD score ≥ 15 , white blood cells (WBC), percentage of neutrophils (N%), total bilirubin (TBIL), direct bilirubin (DBIL), international normalized ratio (INR), plasma fibrinogen (FIB), and ammonia. Liver cancer in the POD group was significantly lower than in controls (Table 2). Among the intraoperative variables, the following, time of operation, anhepatic period, intraoperative red blood cells and cryoprecipitate, lactic acid, and hypotension, were significant. These variables were significantly higher in the POD group compared to the non-POD group ($P<0.05$) (Table 3). Postoperative measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBIL, DBIL, INR, and FIB in the POD group were all significantly higher than those in the non-POD group ($P<0.05$) (Table 3). Donor characteristics (eg, age, sex) were not significantly different between POD and controls (Table 4).

Table 1 Patients' Characteristics

Variable	POD Group (n=42)	Non-POD Group (n=117)	P
Age (Y)	47.38±9.29	49.19±8.98	0.279
Male	33 (78.6%)	101 (86.3%)	0.236
Preoperative diabetes	6 (14.3%)	17 (14.5%)	0.969
Preoperative pulmonary infection	14 (33.3%)	23 (19.7%)	0.072
Preoperative hypertension	1 (2.4%)	8 (6.8%)	0.495
Smoking history	18 (42.9%)	43 (36.8%)	0.485
Drinking history	17 (40.5%)	38 (32.5%)	0.360
Abdominal surgery history	11 (26.2%)	19 (16.2%)	0.157
Neuropsychosis history	2 (4.8%)	3 (2.6%)	0.853
Emergency operation	19 (45.2%)	52 (44.4%)	0.925

Note: Data are shown as mean \pm SD or number (%).

Risk Factor of POD in LT Patients

We defined POD occurrence as the dependent variable of interest. Independent variables were selected from the univariate tests when the criteria of $P<0.1$ were met. Findings from the logistic regression were: preoperative ammonia (≥ 46 vs. <46 $\mu\text{mol/L}$; OR 3.51, 95% CI [1.31–9.46], $P<0.05$), MELD score (≥ 15 vs. <15 ; OR 3.33, 95% CI [1.27–8.79], $P<0.05$), presence of hepatic encephalopathy (OR 3.30, 95% CI [1.20–9.07], $P<0.05$), AST on day one

Table 2 Preoperative Information of LT Patients

Variable	POD Group (n=42)	Non-POD Group (n=117)	P
Liver cancer	4 (9.5%)	41 (35.0%)	0.002
Acute hepatic failure	19 (45.2%)	22 (18.8%)	0.001
Liver cirrhosis	36 (85.7%)	96 (82.1%)	0.588
Hepatitis B	28 (66.7%)	84 (71.8%)	0.532
Hepatitis C	3 (7.1%)	4 (3.4)	0.568
Alcoholic	7 (16.7%)	14 (11.0%)	0.337
Biliary	3 (7.1%)	8 (6.8%)	1.000
Autoimmunity	3 (7.1%)	2 (1.7%)	0.224
Other	2 (4.8%)	5 (2.6%)	0.868
Hepatic encephalopathy	21 (50.0%)	13 (11.1%)	<0.001
Child-pugh	12 (10,13)	9 (8,11)	<0.001
≥9	38 (90.5%)	75 (64.1%)	0.001
<9	4 (9.5%)	59 (35.9%)	
MELD	25 (15,33)	12 (6,22)	<0.001
≥25	21(50.0%)	21(17.9%)	<0.001
15–24	11(26.2%)	27(23.1%)	
<15	10(23.8%)	69(59.0%)	
WBC (10 ⁹ /L)	6.94 (4.09,12.00)	4.64 (3.08,6.39)	0.002
N%	78.15 (67.15,86.18)	70.30 (63.85,78.25)	0.003
HGB (g/L)	96.50 (75.75,114.00)	102.00 (85.00,124.00)	0.129
Na (mmol/L)	138.10 (132.70,141.45)	137.70 (135.20,139.80)	0.635
Mg (mmol/L)	0.83 (0.76,0.93)	0.81 (0.75,0.87)	0.264
CREA (μmol/l)	69.10 (52.20,111.70)	66.7 (54.6,89.6)	0.411
Creatinine clearance rate	101.49 (73.49,139.59)	103.24 (80.34,133.89)	0.708
PAB (mg/L)	79.45 (47.18,94.00)	85.4 (50.05,107.90)	0.170
ALB (g/L)	34.45 (29.85,37.50)	33.3 (29.65–36.3)	0.250
TBIL (μmol/L)	291.95 (217.85,429.75)	51.2 (23.9,300.1)	<0.001
DBIL (μmol/L)	165.35 (97.85,293.70)	32.5 (12.3,199.3)	<0.001
INR	2.55 (1.69,3.42)	1.54 (1.25,2.08)	<0.001
FIB (g/L)	1.43 (1.06,1.80)	1.60 (1.10,2.41)	0.043
Ammonia (μmol/L)	46.65 (32.33,69.63)	33.3 (27.85,41.5)	<0.001
≥46	22 (52.4%)	17 (14.5%)	<0.001
<46	20 (47.6%)	100 (85.5%)	

Note: Data are expressed as median [Q25, Q75] or number (%).

Abbreviations: WBC, white blood cells; N%, percentage of neutrophils; HGB, hemoglobin; Na, sodium ion; Mg, magnesium ion; CREA, serum creatinine; PAB, prealbumin; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; INR, international normalized ratio; FIB, plasma fibrinogen.

postoperatively (OR 1.33, 95% CI [1.06 –1.68], $P<0.05$), anhepatic period (OR 1.04, 95% CI [1.02 –1.06], $P<0.01$). There was no collinearity among those five factors, and the test of goodness for fit for the equation was 84.3% (Table 5).

Influence of Delirium

Of the patients diagnosed with POD, 78.6% (33/42) showed delirium 3 days postoperatively. The median duration was 5 (3–7) days. Intubation time, ICU length of stay,

Table 3 Intraoperative and Postoperative Information of LT Patients

Variable	POD Group (n=42)	Non-POD Group (n=117)	P
Time of operation (min)	510.00 (423.75,569.50)	429.00 (390.00,487.50)	<0.001
Anhepatic period (min)	75.00 (62.00,84.00)	65.00 (56.00,72.50)	0.001
Red blood cell (u)	8.75 (4.38,15.50)	6.00 (3.00,10.25)	0.01
Frozen plasma (mL)	1450 (1150,1825)	1250 (925,1650)	0.19
Cryoprecipitate (u)	30.00 (20.00,39.50)	20.00 (10.75,36.75)	0.006
Lactic acid (mmol/l)	4.50 (3.38,7.15)	3.80 (2.55,5.10)	0.008
Classic LT	35 (83.3%)	93 (79.5%)	0.589
Ligation of the splenic artery	7 (16.7%)	25 (21.4%)	0.515
ALT (u/l)	744.35 (399.68,1029.20)	473.10 (262.15,779.40)	0.012
AST (u/l)	1237.40 (720.98,2573.50)	867.50 (408.65,1415.80)	0.003
TBIL ($\mu\text{mol/l}$)	148.15 (101.83,223.33)	96.00 (55.05,157.80)	<0.001
DBIL ($\mu\text{mol/l}$)	108.45 (71.33,155.10)	65.70 (35.45,124.55)	0.001
ALB (g/l)	36.45 (32.60,40.86)	37.50 (35.40,40.90)	0.318
PAB (mg/l)	110.90 (94.30,127.68)	106.50 (92.20,127.50)	0.777
CREA ($\mu\text{mol/l}$)	90.75 (75.63,166.10)	83.50 (109.90,67.05)	0.067
Creatinine clearance rate	86.86 (48.43,99.52)	82.25 (64.39,102.80)	0.321
INR	1.67 (1.44,2.01)	1.53 (1.35,1.77)	0.024
FIB (g/l)	2.00 (1.45,2.50)	2.24 (1.80,2.68)	0.021
Ammonia ($\mu\text{mol/l}$)	34.60 (28.83,42.60)	37.30 (31.05,43.65)	0.247
Lactic acid (mmol/l)	2.17 (1.46,2.96)	2.34 (1.57,3.06)	0.387

Note: Data are expressed as median [Q25, Q75] or number (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, serum creatinine; PAB, prealbumin; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; INR, international standardized ratio; FIB, plasma fibrinogen.

and medical cost in the POD group were more than those in the non-POD group, but no statistical difference was found in postoperative hospital length of stay (Table 6).

Discussion

POD is a prevalent clinical feature in LT patients postoperatively with a reported incidence of 10.0%-26.7%.^{5,7} The incidence of LT POD in this study was 26.4%, which was consistent with other studies. Previous studies have shown that alcohol abuse history, hepatic encephalopathy, APACHE II score ≥ 16 , Child-pugh level C, MELD score ≥ 15 , preoperative hemodialysis, and deceased liver donor are potentially related with the occurrence of LT POD.^{6,8} In this study, we found that hepatic encephalopathy, preoperative ammonia,

MELD score, postoperative AST, and anhepatic period were the risk factors for POD via multivariate regression.

Currently, the pathogenesis of POD remains unclear as has been reported to be the result of multiple factors.⁹ The main physiopathologic mechanisms include blood-brain barrier injury, vascular endothelial cell injury, reduced cholinergic inhibitory receptor, neuroinflammation response, and disordered neurotransmitter.¹⁰ A systematic review on neuroimaging reported that white matter atrophy, edema, ischemic lesions, and inflammation in the frontal lobe, limbic system, parietal lobe and, temporal lobe were highly associated with POD.¹¹ The cause for POD in LT patients postoperatively is complicated, which often suggests multiple factors.

Table 4 Information of Donated Liver

Variable	POD Group (n=42)	Non-POD Group (n=117)	P
Age of donor (Y)	46 (37,56)	48 (39,55)	0.547
Liver weight (g)	1310 (1165,1475)	1340 (1155,1560)	0.879
Cold ischemia time (min)	506.00 (433.75,550.00)	470.00 (415.00,523.00)	0.105
ALT (u/l)	32.50 (22.20,51.70)	31.50 (20.27,58.05)	0.780
AST (u/l)	42 (24.95,73.15)	48.55 (29.00,90.12)	0.426
TBIL (μ mol/l)	13.65 (8.86,24.65)	13.00 (9.50,19.86)	0.588
ALB (g/l)	36.30 (30.96,42.53)	35.58 (31.16,40.52)	0.547
Na (mmol/l)	150.70 (140.00,162.45)	146.00 (139.00,155.00)	0.150
PT (sec)	12.50 (11.40,14.55)	12.40 (10.90,14.00)	0.584
INR	1.01 (0.96,1.24)	1.04 (0.92,1.20)	0.996
FIB (g/l)	3.15 (2.55,4.11)	3.20 (2.20,4.86)	0.949
Fatty liver	7 (16.7%)	27 (23.1%)	0.385

Note: Data are expressed as median [Q25, Q75] or number (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; Na, sodium; PT, plasma prothrombin time; INR, international standardized ratio; FIB, plasma fibrinogen.

Table 5 Multivariate Logistic Regression Analysis of Risk of Postoperative Delirium After Liver Transplantation

Variable	OR After Correction	95% CI	P
Hepatic encephalopathy	3.298	1.200–9.065	0.021
Preoperative blood ammonia (≥ 46)	3.513	1.306–9.455	0.013
MELD (≥ 15)	3.334	1.265–8.786	0.015
Postoperative AST	1.330	1.055–1.677	0.016
Anhepatic period	1.039	1.015–1.064	0.001

Hepatic encephalopathy is reported to be one of the independent risk factors for LT POD.^{7,8} The pathophysiologic mechanism of hepatic encephalopathy is complex and involves hyperammonemia, neuroinflammation reactions, neurotransmitter disorders, brain energy

metabolism, and other factors.¹² A neuroimaging study has demonstrated that during the development and progression of hepatic encephalopathy, patients will show interstitial edema,¹³ brain microstructural destruction,¹⁴ and white matter atrophy,¹⁵ all of which are related to attention deficit and cognitive dysfunction.¹⁶ The sites affected are located in the frontal lobe and basal ganglia¹⁷ and have similarities with the pathophysiologic mechanism of POD, suggesting a role in high POD postoperative incidence in patients with hepatic encephalopathy.

Accumulation of ammonia is one of the main factors for the development and progression of hepatic encephalopathy. When hepatic encephalopathy happens, ammonia is not always increased, and patients with ammonia do not necessarily have hepatic encephalopathy.¹⁸ A recent study reported

Table 6 Influence of LT POD

Variable	POD Group (n=42)	Non-POD Group (n=117)	P
POD Onset (day)	2(1,3)	-	-
POD Duration (day)	5(3,7)	-	-
Intubation time (min)	2925.0 (1857.5,5257.5)	1410.0 (1053.0–1727.0)	<0.001
ICU length of stay (d)	6 (4,8)	4 (3,4)	<0.001
Postoperative hospital length of stay (d)	28.0 (22.5,40.0)	26.0 (22.0,34.5)	0.378
Medical cost (ten thousand yuan)	43.96(35.25,55.76)	33.74(29.04,44.76)	0.001

Note: Data are expressed as median [Q25, Q75].

that ammonia had influences on the signaling pathway, gene expression and post-transcription protein modification,^{19,22} leading to damaged astrocytes, and manifesting as abnormal proliferation,^{23,24} the release of neurotransmitter²² or even apoptosis.²³ As a part of the blood-brain barrier, astrocytes protect neuron from the toxicity of ammonia.²⁵ Damage on this barrier will lead to brain edema.²⁶ The sites of brain edema include the frontal lobe, temporal lobe, parietal lobe, and insular lobe,^{17,25} which may be related to the occurrence of delirium occurring in patients with hyperammonemia. In this study, we found that there was no correlation between ammonia and hepatic encephalopathy, and that ammonia was an independent risk factor for POD.

In anhepatic period, the whole liver of the recipient is resected. The portal vein, hepatic artery, and inferior vena cava above and below the liver are cut off, leading to hemodynamic changes, such as a decrease in venous return, cardiac output, and systemic circulation arterial pressure. These changes have an influence on cerebral blood perfusion and result in insufficient blood supply in the brain tissue. Meanwhile, metabolites are accumulated in the anhepatic period, resulting in metabolic disorders, such as acidosis, causing ischemia hypoxia injury and delirium.

ALT and AST are often used to assess the extent of damage in hepatocytes.²⁷ In this study, AST was an independent risk factor for POD and AST increasing 1000u/l from the base level, the risk for the patient to suffer delirium increases by 1.33 times. Elevated postoperative AST and ALT possibly are related to the surgical operation and ischemia-reperfusion injury, suggesting the occurrence of delirium is closely related to donated liver injury and postoperative liver function recovery.

The MELD score is used to evaluate the severity of liver disease and acts as a general index for the distribution of liver and predicting mortality of patients waiting for transplant.²⁸ In this study, a MELD score of ≥ 15 suggested an elevated risk of delirium.

According to related reports, drinking history is considered as one of the risk factors causing POD.⁸ However, in this study, alcoholic cirrhosis was not a risk factor for LT POD, possibly because there were few patients with alcoholic cirrhosis. The donor data in our center indicated that age of the donor, weight of donated liver, liver function, Na^+ concentration, and coagulation function were not statistically different between the POD group and non-POD group.

In this study, the period of 3 days postoperatively has a higher incidence for delirium, during which period 78.6% of patients had developed POD. However, Lee et al,⁶ reported

that 88% of LT POD had the onset on the first day, which differs from our report. The reason was that there were more hepatic encephalopathy patients among LT POD patients (50%, 21/42), and the anesthesia resuscitation time was relatively long, influencing initial delirium evaluation. Wang et al⁸ reported that the median duration of delirium onset was 5.5 days, which was consistent with our study. In this study, intubation time, ICU length of stay, and medical cost in the group were more than those in the non-POD group.

There is a little study in LT POD of prevention and treatment. Prevention with multicomponent nonpharmacological approaches remains important, such as The Hospital Elder Life Program (HELP).²⁹ There is little evidence on the effects of nonpharmacological prevention. The pharmacological treatment of delirium in the ICU is still mostly based on clinical experience, as there is little high-quality evidence for its efficacy.³⁰

There are some limitations to our study. First, the study is retrospective, and the data are not comprehensive. Some potential information were not collected such as anaesthesia drug. Secondly, CAM-ICU has been widely applied in the clinic, and the experience from doctors and nurses influences the diagnosis of delirium, leading to bias.

Conclusion

Hepatic encephalopathy, high preoperative ammonia, high MELD score, high postoperative AST, and long anhepatic period are the independent risk factors for LT POD occurrence. Enhancing the screening on LT POD patients, carefully monitoring patients with high MELD score or hepatic encephalopathy, and taking effective intervention in a timely manner will be helpful to reduce the occurrence of LT POD.

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Disclosure

All authors declare no conflicts of interest related to this article.

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