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Prevalence, predictive factors, and survival outcome of new-onset diabetes after liver transplantation

A population-based cohort study

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Abstract

The aim of the present nationwide population-based cohort study was to explore the prevalence, risk factors, and survival outcome of new-onset diabetes (NOD) in recipients after liver transplantation.

The National Health Insurance Research Database of Taiwan was searched for ICD-9-codes, 2248 patients who had received liver transplant without pretransplant diabetes from July 1, 1998 to December 31, 2012 were included in the study. The preoperative risks factors were considered and analyzed using logistic regression analysis, following adjustments for age and sex. All patients were followed up until the end of the study or death.

The final dataset included 189 patients with NOD and 2059 without diabetes after liver transplantation. The prevalence of NOD was 8.4% and in 64% NOD appeared in the first year after liver transplantation. Preoperative clinical events, alcoholic liver cirrhosis, and hepatic encephalopathy were the most important risk factors for NOD after liver transplantation. The mortality rate was lower in NOD recipients than in non-NOD recipients within 5 years.

In this study, we provide evidence that NOD recipients had better 5-year survival outcomes in this clinical population. The most important identifiable predictive factors for NOD after liver transplantation were alcoholic hepatitis, ascites, hepatic coma, and esophageal varices.

Abbreviations: DM = diabetes mellitus, HE = hepatic encephalopathy, ICD-9-CM = International Classification of Disease, Revision 9, IPD = inpatient department, LT = liver transplant, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, Clinical Modification, NOD = new-onset diabetes, NODALT= new-onset diabetes after liver transplantation, OPD = outpatient department.

Keywords: liver transplantation, new-onset diabetes, population-based study

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1. Introduction

Diabetes is a common clinical problem associated with liver transplantation (LT) surgery.[1–2] The incidence of new-onset diabetes (NOD) after liver transplantation (NODALT) has been reported to range between 7.2% and 38% in different studies.[1–11] Previous evidence has shown that NOD contributes to an increased risk of cardiovascular disease, infections, and rejection, all of which are leading causes of mortality among LT recipients.[12–14] However, the mechanisms underlying NODALT are not completely understood.

Various factors have been associated with the development of NOD following transplantation surgery, including recipient age, sex, obesity, viral infections, hypomagnesemia, and immunosuppression therapy.[8,9,15–21] A complete pretransplantation evaluation of the risk factors associated with NODALT would assist in the care of post-LT patients and decrease the comorbidities of LT recipients. However, the risk factors for NOD following LT have not been well elucidated.

Previous reports have indicated that NOD is a serious complication of liver transplantation that negatively affects both patient and graft survival[12,13]; however, this relationship has been questioned. A recent study showed that NOD was associated with an improved 5-year survival after LT.[22]

In order to identify independent risk factors and to elucidate the long-term effects of NOD in patients undergoing LT, we conducted a retrospective population-based cohort study of liver transplant recipients between 1998 and 2012 and investigated

the prevalence, predictive factors, and survival outcomes of patients with NODALT.

2. Materials and methods

2.1. Data collection

We conducted a retrospective, population-based, cohort study using Taiwan's National Health Insurance (NHI) database. De-identified and computerized data were provided by the Bureau of National Health Insurance. This agency organizes claim data for the entire NHI system and established the National Health Insurance Research Database (NHIRD). The NHIRD contains basic patient information, medical data from raw hospital medical claims, including clinical diagnostic codes based on the International Classification of Disease, Revision 9, Clinical Modification (ICD-9-CM). According to the NHI program, the diagnosis for LT must be supplied by a qualified gastroenterologist or transplant surgeon.

This study was evaluated and approved by the NHIRD research committee (NHIRD-103-103) and the institutional review board of Chang Gung Memorial Hospital.

2.2. Patient selection and identification

The flow chart indicates the patient selection and identification procedure applied in this study (Fig. 1). LT recipients were identified from the NHIRD database using the ICD-9-CM codes V427 (LT status) and 996.82 (complications of transplanted liver), from July 1998, when LT was first covered by health insurance in Taiwan, to December 2012. Over this period, 4086 post-LT patients were registered in the NHIRD. This prospective group of patients was reviewed and any LT recipient who did not undergo transplantation in Taiwan was excluded. Applying these criteria, 1148 patients were excluded due to absence of an LT surgery code (identified as codes 505, 75020A, or 75020B). A total of 614 patients, who had been diagnosed as having diabetes mellitus (DM, ICD-9-CM 250, A181) before LT surgery and another 76 patients, in which the diagnosis of DM could not be confirmed before LT surgery, were also excluded. The final study cohort consisted of 2248 LT recipients (Fig. 1).

Child-Pugh classification is a modern classification and useful to assess the liver cirrhosis severity in cirrhotic patients, before transplant.[23,24] The laboratory assessment is a limitation in our study. Preoperative medical comorbidities and diabetes (include pre-LT diabetes and post-LT NOD) were identified from diagnoses in medical notes recorded either in the outpatient department (OPD) >3 times or the inpatient department (IPD). All diagnoses were verified using the ICD-9-CM codes. The following comorbidities were identified among patients in our study cohort: chronic hepatitis (ICD-9-CM 070, 571, 573.3, A347), alcoholic hepatitis (ICD-9-CM571.2, 571.3), hepatitis B (ICD-9-CM 070.2,070.3, V0261,V0269), hepatitis C (ICD-9-CM070.41,070.44,070.51,070.54,070.7, V0262), liver cirrhosis (ICD-9-CM, 571.5,571.2,571.6), hepatocellular carcinoma (ICD-9-CM155 plus treatment code), hypertension (ICD-9-CM 401–405), coronary heart disease (ICD-9-CM 410–414, A279), peptic ulcer (ICD-9-CM 531, 532, 533), portal hypertension (ICD-9-CM 572.3), obesity (ICD-9-CM 278), ascites (ICD-9-CM 789.5), hepatic coma (ICD-9-CM 070.0, 070.20, 070.21, 070.31, 070.41, 070.51, 572.2, 348.3), esophageal varices (ICD-9-CM 456), chronic kidney disease (ICD-9-CM 585), pulmonary diseases (ICD-9-CM 490–496, A323, A325), hyperlipidemia (ICD-9-CM 272), gout (ICD-9-CM 274), bacteremia (ICD-9-CM 038, 998.5), pneumonia (ICD-9-CM 480–486), and urinary tract infection (ICD-9-CM 559.0).

NODALT was identified from the relevant IDC-9-CM codes (ICD-9-CM 250, A181) for patients who had medical details recorded either in the IPD or registered >3 times in the OPD. Death was defined as detection of insurance death codes or the termination of national health insurance.

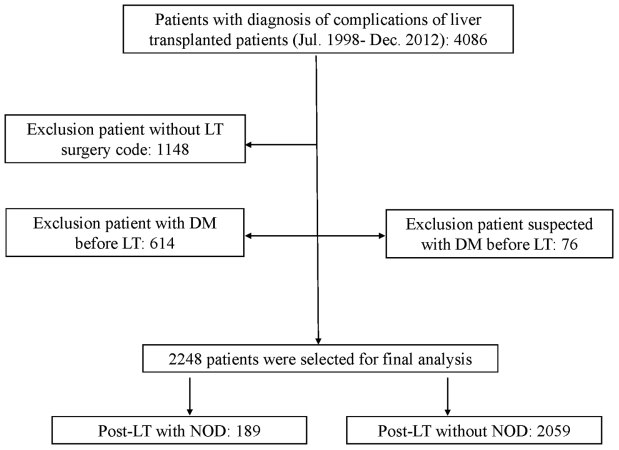

Figure 1. Study design and flow chart of patient selection.

2.3. Measurements

The primary outcome parameter was prevalence of NOD and the independent risk factors for NOD following LT, included demographic and clinical factors. The secondary outcome was survival and adverse effects of NODALT, including frequency of NOD in the intensive care unit (ICU), length of hospital stay, bacteremia (ICD-9-CM 038), pneumonia (ICD-9-CM 486), and urinary tract infection (ICD-9-CM 599.0). Primary and secondary outcomes were compared between patients with or without NOD following LT. The prevalence of NODALT was evaluated at different time periods including hospital stay, 6 months, 1 year, 5 years, 10 years, and overall, defined from the 14.5 years covered by the study data. Post-LT mortality rates were also calculated at 6 months, 1 year, 3 year, 5 year, 7 year, 9 year, 11 year, and overall (14.5 years). The survival time was calculated from the date of LT surgery to the date of death. The post-LT immunosuppressant used was investigated.

2.4. Statistical analysis

Between-group differences in the distribution of demographic data and, coexisting medical conditions were evaluated using *t* test, chi-squared, or Fisher exact tests, as appropriate for the type and distribution of the data. Kaplan-Meier estimates with log-rank tests were used to compare between-group prevalence and survival during the follow-up period. For analyses of mortality, patients were followed up until an event (death) or censoring (loss to follow-up or end of the follow-up period), whichever occurred first. Risk factors for NODALT were evaluated using multivariate logistic regression analysis adjusted for age, sex, and individually adjusted for preexisting alcoholic hepatitis and hepatic coma. Odds ratios (ORs), with 95% confidence intervals (CIs), were calculated for identified predictive factors. All analyses were performed using SAS software

(version 9.3, SAS Institute Inc, Cary, NC), with a two-sided $P < 0.05$ considered to be statistically significant.

3. Results

3.1. Study population and baseline characteristics

The data were collected from 189 LT patients "with" NOD and 2059 LT patients "without" NOD; relevant demographic information of the study group is reported in Table 1. LT patients with NOD were likely to be older and of male sex than LT patients without NOD, and with a higher risk of preoperative chronic hepatitis (97.88% vs 92.03, $P = 0.0034$), including alcoholic hepatitis (25.40% vs 16.61%, $P = 0.0023$) and hepatitis C (26.98% vs 18.99%, $P = 0.0081$), ascites (56.08% vs 45.02%, $P = 0.0035$), hepatic coma (43.39% vs 31.03%, $P = 0.0005$), and esophageal varices (60.32% vs 47.94%, $P = 0.0011$).

3.2. Prevalence of new-onset diabetes after liver transplantation

A total of 189 NOD patients were diagnosed from LT recipients during the study period. Prevalence of NOD in recipients after LT at hospital stay, or after follow-up of 6 months, 1 year, 5 years, 10 years, and over the entire interval of data collection for this study (14.5 years) are reported in Table 2. The 6-month post-LT NOD prevalent rate was 50.79%, comprising nearly half of all NOD patients. The 1-year post-LT NOD prevalent rate was 64.02%. Cumulative prevalence of post-LT NOD within the first year and overall are shown in Figure 2.

3.3. Predictive factors of new-onset diabetes in liver transplantation

Univariate analysis was used to determine the independent factors that could discriminate patients with and without NODALT. The significant factors identified, included age, sex, chronic hepatitis, ascites, hepatic coma, and esophageal varices and were then further analyzed by logistic regression, with multivariable models adjusted for age and sex (Table 3). Alcoholic hepatitis (Hazard ratio [HR], 1.517; 95% confidence interval [95% CI], 1.062–2.168; $P = 0.0220$), ascites (HR, 1.453; 95% CI, 1.074–1.965; $P = 0.0153$), esophageal varices (HR, 1.568; 95% CI, 1.064–2.311; $P = 0.0230$), and hepatic coma (HR, 1.537; 95% CI, 1.133–2.084; $P = 0.0057$) were retained important preoperative risk factors for post-LT NOD.

3.4. Post-LT adverse effects

The clinical variables identified by univariate analysis as being associated with post-LT NOD are reported in supporting information Table S1, http://links.lww.com/MD/B31. The length of ICU stay was shorter in LT patients with NOD, compared to those without NOD ($P < 0.015$). The incidence rates of bacteremia, pneumonia, and urinary tract infection were not significantly different between NOD and non-NOD patients.

3.5. Post-LT immunosuppressant used

Five common immunosuppressants were listed and analyzed in Table 4. The results showed that the treatment with tacrolimus ($P = 0.0001$) and mycophenolate mofetil ($P = 0.0128$) drugs have a higher ratio in recipients with NODALT than without NODALT.

3.6. Post-liver transplantation mortality rates and survival outcomes

A total of 24 patients with NOD and 300 patients without NOD died during the study period. Mortality rates at 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 11 years, and overall

Table 1

General demographics of the study subjects.

	Recipients without NODALT (n = 2059)	Recipients with NODALT (n = 189)	*P*
Age	43.40 (19.70)	49.89 (9.77)	<0.0001*
Sex			0.0372*
Female	652 (31.67)	46 (24.34)	
Male	1407 (68.33)	143 (75.66)	
Chronic hepatitis	1895 (92.03)	185 (97.88)	0.0034*
Alcoholic hepatitis	342 (16.61)	48 (25.40)	0.0023*
Hepatitis B	962 (46.72)	91 (48.15)	0.7068
Hepatitis C	391 (18.99)	51 (26.98)	0.0081*
Liver cirrhosis	1688 (81.98)	164 (86.77)	0.0980
Hepatic cell cancer	879 (42.69)	89 (47.09)	0.2424
Hypertension	318 (15.44)	19 (10.05)	0.0469
Coronary heart disease	100 (4.86)	14 (7.41)	0.1261
Peptic ulcer	905 (43.95)	95 (50.26)	0.0947
Portal hypertension	187 (9.08)	14 (7.41)	0.4400
Obesity	4 (0.19)	0 (0.00)	0.7036
Ascites	927 (45.02)	106 (56.08)	0.0035*
Hepatic coma	639 (31.03)	82 (43.39)	0.0005*
Esophageal varices	987 (47.94)	114 (60.32)	0.0011*
Renal failure	59 (2.87)	7 (3.70)	0.5136
Pulmonary diseases	263 (12.77)	22 (11.64)	0.6541
Hyperlipidemia	153 (7.43)	16 (8.47)	0.6056
Gout	126 (6.12)	10 (5.29)	0.6475

NODALT = new-onset diabetes after liver transplantation. Values are mean and standard deviation. *t* test, chi-square test, or Fisher exact test were used to examine the differences in the demographic characteristics of liver transplant recipients between with and without NODALT.

Table 2

Prevalence of NOD in recipients after liver transplantation.

Times	NOD patient number	Percentage, %	Acumination NOD patient number	Acumination percentage, %
Hospital stay	19	10.05	19	10.05
6 mo	77	40.74	96	50.79
1 y	25	13.23	121	64.02
5 y	49	25.93	170	89.95
10 y	18	9.52	188	99.47
>10 y	1	0.53	189	100.00

NOD = new-onset diabetes.

(14.5 years) are reported in Table 5. There was no significant difference at the overall (14.5 years) survival rate in patients with or without NOD ($P = 0.1203$) (Table 5). However, Kaplan-Meier survival curves showed survival rate have significant difference ($P = 0.0209$) among 3 patients groups (Fig. 3). There were a higher 5-year survival rate in patients with NOD than patients without NOD ($P = 0.0190$) and with diabetes before transplantation ($P = 0.0041$). However, there was no significant difference between patients without NOD and with diabetes before transplantation ($P = 0.2564$). For avoiding liver cancers bias, 114 patients with post-transplantation liver cancer in non-NOD recipients and 11 patients with post-transplantation liver cancer in NOD recipients were excluded. The Kaplan-Meier survival analysis also showed a higher 5-year survival rate in patients with NOD than without NOD ($P = 0.0063$) (Fig. S1, http://links.lww.com/MD/B31).

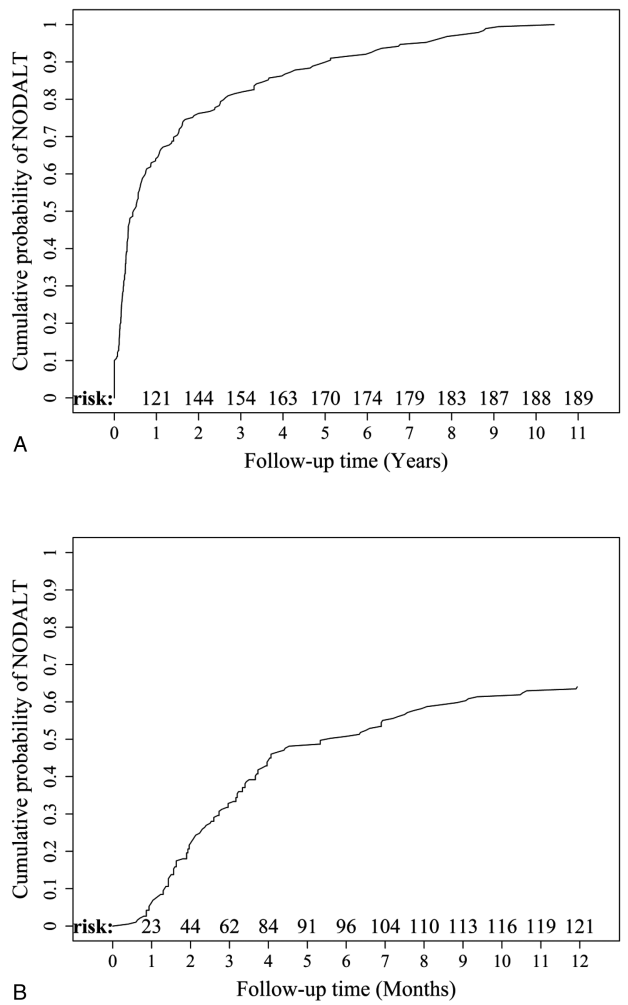

Figure 2. Unadjusted Kaplan-Meier prevalence curves of NODALT. A, Probability of NODALT over the 14.5 years covered by the study. B, Probability of NODALT within the first year. NODALT = new-onset diabetes after liver transplantation.

4. Discussion

We performed a retrospective, population-based, cohort study of patients who received an LT between 1998 and 2012, with the aim of investigating the prevalence, predictive factors, and survival outcome associated with NODALT.

4.1. Key findings

We found that 8.4% (189/2248) of patients receiving LT in Taiwan developed postoperative NOD, and the prevalence (8.4%) was higher in NODALT than the whole population (4.31%–6.38% from 2000–2009) in Taiwan. The first year incidence (121/2248 = 5.38%) was also higher in NODALT group than Taiwan general population (0.764%–0.932%).[25] The 4 important identifiable risk factors for NOD were alcoholic hepatitis, ascites, hepatic coma, and esophageal varices. Furthermore, the 5-year mortality rate was lower in patients who developed NOD post-LT.

4.2. Interpretation of current results and comparison with previous studies

In our 14-year cohort study, 8.4% of transplant recipients developed NODALT, with the majority of recipients diagnosed in the early post-LT period. The incidence rate of post-LT NOD is within the lower range of previously reported incidences rate of 7.2% and 38%.[1–11] The difference in incidence rate may be

Table 3

Pre-LT risk predictors of NOD after liver transplantation by multivariate analysis.

Parameter	Adjusted OR (95% CI)	*P*
Chronic hepatitis	2.411 (0.860, 6.759)	0.0942
Alcoholic hepatitis	1.517 (1.062, 2.168)	0.0220*
Hepatitis C	1.328 (0.925, 0.925)	0.1244
Ascites	1.453 (1.074, 1.965)	0.0153*
Hepatic coma	1.537 (1.133, 2.084)	0.0057*
Esophageal varices	1.568 (1.064, 2.311)	0.0230*

CI = confidence interval, LT = liver transplant, NOD = new-onset diabetes, NODALT = new-onset diabetes after liver transplantation, OR = odds ratio.Logistic regression were used to examine the OR adjusted by age and sex for chronic hepatitis, alcoholic hepatitis, hepatitis C, ascites, hepatic coma, and esophageal varices individually.

Table 4

Immunosuppressant use of liver transplant recipients with or without NOD.

	Recipients without NODALT (n = 2059)	Recipients with NODALT (n = 189)	*P*
Cyclosporin (Neoral)	413 (20.06)	43 (22.75)	0.3782
Tacrolimus (FK506)	1813 (88.05)	184 (97.35)	0.0001*
MMF	1531 (74.36)	156 (82.54)	0.0128*
Rapamune	379 (18.41)	40 (21.16)	0.3516
Everolimus	180 (8.74)	13 (6.88)	0.3814

MMF = mycophenolate mofetil, NOD = new-onset diabetes, NODALT = new-onset diabetes after liver transplantation. Chi-square test or Fisher exact test were used to examine the differences in the demographic characteristics of liver transplant recipients between with and without NODALT.

Table 5

Mortality rate of liver transplant recipients with or without NOD.

	Recipients without NODALT (n = 2059)		Recipients with NODALT (n = 189)		
	n (%)	Median	n (%)	Median	*P*
Mortality (6 mo)	107 (5.20)	66	1 (0.53)	122	0.0041*
Mortality (1 y)	168 (8.16)	119.5	4 (2.12)	222	0.0023*
Mortality (3 y)	246 (11.95)	216	15 (7.94)	508	0.0389*
Mortality (5 y)	280 (13.60)	251.5	17 (8.99)	567	0.0190*
Mortality (7 y)	294 (14.28)	270	21 (11.11)	739	0.0535
Mortality (9 y)	298 (14.47)	278.5	23 (12.17)	742	0.0942
Mortality (11 y)	300 (14.57)	281	23 (12.17)	742	0.0864
Mortality (overall)	300 (14.57)	281	24 (12.70)	824.	0.1203

NODALT = new-onset diabetes after liver transplantation. Log-rank test were used to examine the differences in the demographic characteristics of liver transplant recipients between with and without NODALT.

explained by differences in the criteria used to define NODALT among studies. As the NHIRD is a large secondary database, information on laboratory-based measures of DM, such as blood glucose, glycosylated hemoglobin (HbA1c), and insulin levels, were not available for inclusion in our retrospective analysis. We identified patients who developed NODALT uniquely from ICD-9-CM codes for NOD as recorded inpatient medical charts either in the IPD or if appearing >3 times in the OPD following LT. As this is a study-specific definition for NOD, it is possible that the true incidence rate for NODALT may have been underestimated.

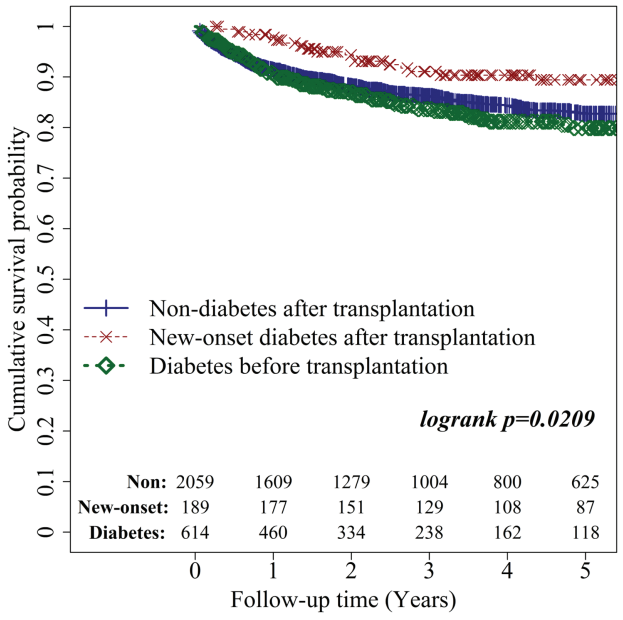

Figure 3. Five-year patient survival curves of NODALT by unadjusted Kaplan-Meier curves. NODALT = new-onset diabetes after liver transplantation.

Hepatitis C virus-related cirrhosis is an important indication for LT and has been identified as a major risk factor for the development of NOD in solid organ transplant recipients.[9,15,17,26] Obesity is also as an important risk factor for NOD.[2,5,21] In this population, the very low frequency of obesity recipients (4/2248) and fewer hepatitis C virus infection rates (442/2248, 19.7%) compared to those of Western countries (approximately 30%–40%)[9,18,20,27] might have contributed to the lower incidence rate observed.

The mechanism underlying the development of NODALT is complex. Previous studies have proposed that risk factors for NODALT are associated with specific underlying factors including age, sex, body mass index, viral infection, and pretransplant comorbidities.[21,28] In addition, administration of immunosuppressive agents, including tacrolimus and steroids, which cause insulin resistance and pancreatic β-cell dysfunction,[29,30] may increase the risk of developing NODALT. The following preoperative potential risk factors for NOD were available in the NHIRD records: age, sex, and pretransplantation comorbidities. Male sex and age have been identified as independent risk factors for the presence of post-transplant diabetes in many studies.[4,31,32] Our report also showed that older patients and males were more likely to have NOD, which is consistent with the results of the meta-analysis by Li et al.[5,20,32].

LT patients with NOD were likely to have a higher risk of preoperative hepatitis C, alcoholic hepatitis, ascites, hepatic coma, and esophageal varices. Viral or alcoholic cirrhosis are usually reasons patients with hepatic failure require an LT.[33–35] The relationship between hepatitis C virus infection and NODALT has been underlined in many studies.[15–17,20] However, hepatitis C is not consistently associated with NODALT following adjustments for age and sex in the current study. Alcohol hepatitis was found to be significantly associated with the risk of post-LT NOD in our study. Previous studies have also provided evidence for a relationship between NOD and alcohol-related cirrhosis.[7,20] Esophageal varices secondary to

portal hypertension are a serious complication of liver cirrhosis, which cause uncontrollable active bleeding. The presence of ascites is correlated with the severity progression and cardiac dysfunction among patients with hepatic cirrhosis.[36,37] Hepatic encephalopathy (HE) associated coma occurring before liver transplant can have a substantial negative impact on post-transplant outcomes.[38] However, the relationship between HE and NODALT has not been investigated. In this study, following adjustments for age and sex, of these pretransplantation risk factors, alcoholic hepatitis, esophageal varices, ascites, and hepatic coma were consistently identified as having a significant impact on postoperative NOD. It is implied that preoperative conditions of esophageal varices, ascites, and hepatic coma may be important predictors of NODALT.

NOD is a significant metabolic complication after LT that is associated with infection risk and decreased graft survival.[12,13] In our 14.5-year cohort study, the incidence rates of infection, including bacteremia, pneumonia, and urinary tract infection are evaluated, but no significant differences between NOD and non-NOD patients after LT were identified. However, the length of ICU stay was shorter in LT patients with NOD, compared with those without NOD. Previous reports indicated that a higher mortality was associated with NODALT over a long-term follow-up.[12–14] However, contrasting results indicating a better outcome in NOD recipients have also been reported.[22] Our data also confirm the latter finding and indicate that postoperative NOD has a positive influence on patient outcome and survival. The length of ICU stay was shorter in LT patients with NOD, compared with those without NOD. Previous reports showed that various factors could cause post-LT patient death, including age, infection, rejection, major organs dysfunction, primary disease recurrence, and technical complications.[39–41] In this study, the 5-year mortality rate post-LT was lower in patients with NOD than in those without NOD. Hence, a prospective study regarding diabetes onset should be set up to clarify these differences and to identify the survival outcome in NODALT.

4.3. Limitations

Our large retrospective population-based cohort study has several limitations that warrant consideration. Foremost, the NHIRD is a secondary database and, therefore, does not include actual medical examination data, such as physical examination findings, laboratory results, or specific etiological data relative to DM leading to LT, or intraoperative data, such as operative time, hemodynamics, or medications used during surgery that may be closely linked to the development of NOD after LT. Our cohort included patients over a 14.5-year period, dating back to 1998, and, therefore, the data include differences and variations in the selection criteria for LT, the type of liver donor (deceased or living donor), and family history. Previous studies have shown that the immunosuppressive regimen and high corticosteroids exposure play a critical role in NODALT development. As data regarding the immunosuppressive regimen and use of corticosteroid were not collected, it remains a limitation of this study.

In addition, diagnostic clarification was important because the use of different definitions before publication made it difficult to assess the incidence of NODAT or the importance of different risk factors. The actual incidence of NODALT is difficult to establish, because different classification systems and definitions have been used over the years.

5. Conclusions

The incidence of NODALT was higher in older LT recipients than in younger recipients. Alcoholic hepatitis, ascites, hepatic coma, and esophageal varices were the 4 most important, identifiable preoperative risk factors for NODALT in the present study. Furthermore, the development of NOD following LT was associated with better 5-year survival rates in this clinical population. We also recommend that further prospective studies be performed to clarify the role of NOD in survival outcomes for LT patients.

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