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Original Article

Pre-existing diabetes and risks of morbidity and mortality after liver transplantation: A nationwide database study in an Asian population

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ABSTRACT

Background: Whether diabetes mellitus (DM) is associated with a higher risk of perioperative mortality and mortality after liver transplantation (LTx) remains unclear.
Methods: We compared the risk of postoperative mortality and morbidity in DM and non-DM patients undergoing LTx. We enrolled 558 DM patients who underwent LTx from 2000 to 2010.
Results: DM was associated with elevated 90-day risk of post-LTx stroke. Otherwise, the DM cohort did not exhibit significantly higher risks of postoperative morbidities, such as septicemia, pneumonia, and wound infection, than the non-DM cohort. Cox proportional hazards regression model showed that patients with DM with coexisting renal manifestations were at a significantly high risk of 30-day and 90-day postoperative mortality. Further comorbidity stratification analysis showed that DM cohort exhibited higher risk of mortality than the non-DM cohort if the patients had liver cancer, or did not have hypertension, ischemic heart disease, and chronic obstructive pulmonary disease.
Conclusion: DM is associated with elevated risk of 90-day post-LTx. Moreover, DM patients with coexisting renal manifestations exhibited an increased postoperative risk of mortality after LTx.

1. Introduction

Diabetes mellitus (DM) is commonly observed in patients with various pathological conditions of the liver, including hepatocellular carcinoma, chronic liver disease, and cirrhosis [1–4], which may require a liver transplantation (LTx) in the end stage. Researchers have proposed DM to be prognostic of an increased risk of perioperative complications and mortality in cardiovascular [5,6] and non-cardiac [7] operations. DM is associated with an increased risk of morbidity and mortality after a liver resection for colorectal liver metastasis [8] and hepatocellular carcinoma [9]. However, the effects of preexisting DM on the risk of perioperative morbidity and mortality after LTx are still not adequately defined.

Several previous studies have addressed the surgical risk of LTx in DM patients [10–12]. One earlier study showed that preexisting DM is associated with significant post-LTx morbidity and mortality [10], and in another study, researchers observed a higher risk of allograft rejection in patients with a poor postoperative control of blood glucose [12]. By contrast, another study concluded that the incidences of post-transplant complications and patient survival did not differ significantly between the DM and control groups [11]. However, these studies had been limited by a relatively small sample and a single institution.

To date, some studies have evaluated the risk of perioperative mortality and complications after LTx in DM patients in a population-based setting [13–16]. However, there has been no similar study in an Asian population. For our study, we conducted a retrospective case-matched study by enrolling more than 1000 patients to investigate the effects of DM on the risk of surgical mortality and morbidity after LTx, using data from the Taiwan National Health Insurance Research Database (NHIRD). We also examined the effects of coexisting medical conditions and diabetes-associated comorbidities on postoperative 30-day and 90-day mortality in patients with DM.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; NHIRD, National Health Insurance Research Database; LTx, liver transplantation.

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2. Materials and methods

2.1. Data sources

This study was a population-based retrospective cohort study analysis of the data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute (NHRI) in Taiwan. The National Health Insurance (NHI) program which is a mandatory single-payer social health insurance system which provides medical insurance for nearly 99% of 23 million people in Taiwan was launched in 1995. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) program. All beneficiaries' medical services, including inpatient and outpatient demographics, primary and secondary diagnoses, procedures, prescriptions, and medical expenditures were available in the dataset. We identified diseases using codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Two NHIRD datasets were used in this study including the catastrophic illness dataset and the diabetes dataset. The patients with the surgery of liver transplant (ICD-9-CM: 50.59) are registered in the catastrophic illness card to obtain care benefits. The diabetes dataset is diabetes patient original claim data extracted from the NHIRD file. Patients with diabetes-related ICD-9-CM-CM codes (ICD-9-CM: 250) were selected to construct this dataset.

2.2. Ethical approval

The electronic database with patient identifications was scrambled for further research access to protect personal privacy. This study was approved from full ethical review by the institutional review board of China Medical University (CMU-REC-101-012).

2.3. Definition of study population

From the catastrophic illness dataset, we enrolled the liver transplant patients with hospital claim code of ICD-9-CM: 50.59 between 2000 and 2010. We then identified liver transplant patients with preexisting diabetes (diabetes cohort), designated by the first-time diabetes (ICD-9-CM: 250) diagnosis before the year of liver transplant (index year) from the diabetes dataset. To ensure the diagnosis of diabetes, we only included patients with two outpatient and/or one inpatient claims for diabetes in the diabetes cohort.

Further, we also designed a control cohort consisting of non-diabetes liver transplant patients and randomly selected and matched them with diabetes cohort. To control for the confounding effects of age, sex, and index year, we constructed a matched variable containing the age at liver transplant, sex, and index year.

2.4. Definition of variables

The comorbidity history was identified at the baseline, including hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272), ischemic heart disease (ICD-9-CM: 410–414), mental disorders (ICD-9-CM: 290–319), chronic obstructive pulmonary disease (COPD; ICD-9-CM: 490–496), chronic renal disease (ICD-9-CM: 585), liver cirrhosis (ICD-9-CM: 571), hepatitis B (ICD-9-CM: V02.61, 070.20–070.33), hepatitis C (ICD-9: V02.62, 070.41, 070.44, 070.51, and 070.54), stroke (ICD-9-CM: 430–438), and liver cancer (ICD-9-CM: 155). We identified diabetes-associated comorbidities as potential contributors to 30-day and 90-day postoperative mortality were type 1 (ICD-9-CM: 250.x1 and 250.x3) or type 2 (ICD-9-CM: 250.x0 and 250.x2) diabetes by defining patients with ketoacidosis (ICD-9-CM: 250.1), coma (ICD-9-CM: 250.2 and 250.3), renal manifestations (ICD-9-CM: 250.4), eye involvement (ICD-9-CM: 250.5) or peripheral circulatory disorder (PCD; ICD-9-CM: 250.7) during the diagnosis date of diabetes to index date.

We aimed to compare the post-LTx 30-day and 90-day rates of mortality and 6 major surgical complications, including septicemia (ICD-9-CM: 038), pneumonia (ICD-9-CM: 480–488), acute renal failure (ICD-9-CM: 584), deep wound infection (ICD-9-CM: 958.3), acute myocardial infarction (ICD-9-CM: 410) and stroke (ICD-9-CM: 430–438), between patients with and without preoperative DM.

2.5. Statistical analysis

We performed using the SAS 9.3 package (SAS Institute Inc., NC, USA) to analyze the dataset. p-Value < 0.05 in 2-tailed tests was considered significant.

The Chi-square test was used to analyze the differences in categorical variables between diabetes cohort and comparison cohort. The continuous variables, such as age, were examined in both cohorts by Student's t test.

We used multivariable Cox proportional hazards model to calculate the adjusted mortality hazard ratio (HR) of 30-day or 90-day postoperative complications and mortality presented with 95% CIs between DM and non-DM cohorts, after controlling for age, gender, monthly income, occupation, comorbidity, and duration of diabetes. We categorized the diabetes severity, including ketoacidosis, coma, renal manifestations, eye involvement, peripheral circulatory disorders, and type 1 and type 2 diabetes, to estimate the impact of difference in diabetes severity on 30-day and 90-day postoperative mortality by multivariable Cox proportional hazards model.

For stratification analysis, we calculated the adjusted HR mortality between the two cohorts using the multivariable Cox proportional hazards model, stratified by the presence of comorbidities.

3. Results

3.1. Patient characteristics

Using data from the NHIRD, we enrolled 2167 patients undergoing LTx during the study period. Of the 2167 LTx patients, 26.5% (n = 575) had preexisting DM, and were designated as the DM cohort. The non-DM cohort consisted of 567 LTx patients, frequency-matched by gender, age, and index year (Fig. 1). The baseline clinical, demographic, and medical characteristics of the 2 cohorts are shown in Table 1. As expected, the 2 cohorts were comparable in age and gender. There were also no significant differences in monthly income and occupation between the 2 cohorts.

The DM patients were more likely to have several coexisting medical diseases, including hypertension, hyperlipidemia, ischemic heart disease, mental disorders, COPD, cirrhosis, chronic renal disease, and hepatitis C virus (HCV) infection (Table 1). However, the prevalence of stroke, hepatitis B virus (HBV) infection, and liver malignancy were not significantly different in the 2 cohorts.

3.2. Analysis of 30-day and 90-day post-LTx morbidity and mortality rate

Analysis using multiple Cox proportional hazards model showed that DM patients did not exhibit significantly higher risks of 30-day and 90-day post-LTx morbidities, including septicemia, pneumonia, acute renal failure, acute myocardial infarction, and wound infection (Table 2). However, DM was associated with significantly higher 90-day, but not 30-day, post-LTx risk of stroke (adjusted HR = 5.82; 95% CI = 1.76–19.3; Table 2).

The 30-day post-LTx mortality rate was 5.91% in the DM cohort, and 3.88% in the control cohort (adjusted HR = 1.26; 95% CI = 0.59–2.69; Table 2), whereas the 90-day mortality rates in DM and non-DM cohorts were 10.3% and 7.76% respectively (adjusted HR = 1.61; 95% CI = 0.94–2.74; Table 2). Despite poorer early survival probabilities for DM patients, the differences were not significant between the DM and non-DM cohorts.