Retrospective Cohort Study

Warm ischemia time and elevated serum uric acid are associated with metabolic syndrome after liver transplantation with donation after cardiac death

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Abstract

AIM
To describe the prevalence of posttransplant metabolic...
syndrome (PTMS) after donation after cardiac death (DCD) liver transplantation (LT) and the pre- and postoperative risk factors.

METHODS

One hundred and forty-seven subjects who underwent DCD LT from January 2012 to February 2016 were enrolled in this study. The demographics and the clinical characteristics of pre- and post-transplantation were collected for both recipients and donors. PTMS was defined according to the 2004 Adult Treatment Panel-III criteria. All subjects were followed monthly for the initial 6 mo after discharge, and then, every 3 mo for 2 years. The subjects were followed every 6 mo or as required after 2 years post-LT.

RESULTS

The prevalence of PTMS after DCD donor orthotopic LT was 20/147 (13.6%). Recipient’s body mass index ($P = 0.024$), warm ischemia time (WIT) ($P = 0.045$), and posttransplant hyperuricemia ($P = 0.001$) were significantly associated with PTMS. The change in serum uric acid levels in PTMS patients was significantly higher than that in non-PTMS patients ($P < 0.001$). After the 1st mo, the level of serum uric acid of PTMS patients rose continually over a period, while it was unaltered in non-PTMS patients. After transplantation, the level of serum uric acid in PTMS patients was not associated with renal function.

CONCLUSION

PTMS could occur at early stage after DCD LT with growing morbidity with the passage of time. WIT and post-LT hyperuricemia are associated with the prevalence of PTMS. An increased serum uric acid level is highly associated with PTMS and could act as a serum marker in this disease.

Key words: Posttransplant metabolic syndrome; Liver transplantation; Donation after cardiac death; Uric acid; Warm ischemia time

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Core tip: The objective of the current retrospective analysis was to describe the pre- and postoperative risk factors for prevalence of posttransplant metabolic syndrome (PTMS) after liver transplantation (LT) with donation after cardiac death (DCD). PTMS could occur at early stage after DCD LT with growing morbidity as time goes on. The warm ischemia time and posttransplant hyperuricemia were associated with the prevalence of PTMS. An increased serum uric acid level was highly relevant to PTMS and could act as a serum marker in this disease.

INTRODUCTION

Liver transplantation (LT) is still the standard treatment for patients with end-stage liver disease. The increasing disparity between patients and supply of donor livers prompts the surgeons to expand the donor pool. Thus, the usage of livers from donation after cardiac death (DCD) donors has increased rapidly. In the last two decades, about 5.0% of the adult LTs were performed using grafts from DCD donors in the United States[1]. Despite the high risk of a series of acute complications correlated with the warm ischemia time (WIT)[2], several parallel studies showed that the clinical outcomes of LT using more restrictive DCD donor criteria including body mass index (BMI) < 29 kg/m$^2$ and functional WIT < 20 min were comparable to those with standard brain-dead donors[3]. Thus, the long-term prognosis of DCD LT has gained increasing attention.

After LT, patients often develop a series of metabolic alterations such as hyperglycemia, hypertension, dyslipidemia, and obesity[4]. These metabolic derangements were defined as posttransplant metabolic syndrome (PTMS), which is correlated with cardiovascular disease, and hence, under intensive focus. Reportedly, the prevalence of PTMS is 39%-58% over a period of 1-6 years after LT in Western countries and 35.6% in Asia[5,6]. However, data on specific assessment of the morbidity of PTMS after DCD LT are still lacking.

The present retrospective analysis described the prevalence of PTMS after DCD LT and the pre- and postoperative risk factors.

MATERIALS AND METHODS

Ethics

This is a retrospective cohort study. One hundred and forty-seven subjects with DCD liver transplantation at the First Affiliated Hospital of Xi’an Jiao Tong University from January 2012 to February 2016 were enrolled in this study that was approved by the Ethics Committee of the Institute (No. XJTU1AF2018LSK-084).

Donation and transplantation

Since the Chinese organ donation system has been developed, DCD donor is the primary legal source of the organ for transplantation. All the organ donations are confirmed by the Maastricht categories of DCD type III: Awaiting cardiac arrest controlled[7]. Mechanical support is withdrawn in the operating room in a majority of the cases. Five minutes after the declaration of death by an independent physician, donor grafts are recovered via double in situ perfusion with combined liver and...
kidney rapid resection technique. Organ allocation is conducted according to the waiting list from the organ transplantation division of Chinese Medical Association. All the transplants are performed using the primary orthotopic LT (OLT) as the standard technique. For immunosuppressive protocol, we used the standard three-drug regimen including steroid, tacrolimus/cyclosporine, and mycophenolate mofetil (MMF). For recipients with hepatocellular carcinoma (HCC), steroid-free protocol was applied as described by Shen et al[8].

Demographics and clinical characteristics
The pre- and post-transplantation demographics and clinical characteristics were collected for both recipients and donors. PTMS was defined according to the 2004 Adult Treatment Panel-III criteria[10]. A patient would be diagnosed as PTMS if ≥ 3 of the following five conditions were fulfilled: (1) Obesity; (2) high fasting glucose level (≥ 100 mg/dL); (3) hypertriglyceridemia (≥ 150 mg/dL); (4) low high-density lipoprotein (HDL) level (< 40 mg/dL (male) or < 50 mg/dL (female)); and (5) high blood pressure (≥ 130/85 mmHg); or pharmacological treatment for each of these conditions. The diagnosis of obesity was adjusted according to the characteristics of the Asian population and defined as a BMI ≥ 27.5 kg/m² in accordance with the 2004 World Health Organization (WHO) guidelines[10]. Hyperuricemia was defined as a serum uric acid level > 420 μmol/L within 1 mo post-transplantation, and the complications included acute kidney injury (AKI), renal insufficiency, acute rejection, and biliary complications.

Follow-up
All subjects were followed monthly for the initial 6 mo after discharge, and then, every 3 mo for 2 years. The subjects were followed every 6 mo or as required after 2 years post-LT. Data of the donors and recipients were uploaded to the China Liver Transplant Registry, a database and official website for national data gathering.

Statistical analysis
Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc., Chicago, IL, United States). Continuous data are presented as mean ± standard deviation and were compared using t-tests. Categorical data are presented as frequencies (percentages) and were compared using chi-squared tests or Fisher’s exact test as appropriate. Univariate and multivariate logistic regressions were conducted to explore the factors associated with PTMS. Odds ratios (OR) were presented with 95% confidence intervals (CIs). Variables with P < 0.1 in the univariate analysis were included in the multivariate logistic regression. The stepwise procedure was used to identify the variables independently associated with PTMS in the final multivariate model. Kaplan-Meier method was employed to determine the survival of patients after LT, and log-rank test was used to determine the difference in survival between PTMS and non-PTMS patients. P < 0.05 was considered statistically significant.

RESULTS

Demographics and clinical characteristics of the recipients
The mean age of the recipients was 45.6 ± 10.8 year old, and 121/147 (82.3%) recipients were male. Furthermore, 98 (66.7%) patients in the cohort underwent transplantation because of hepatitis B virus (HBV)-related liver disease, while other original diseases of the recipients included hepatitis C virus (HCV) infection (15, 10.2%), alcoholic liver disease (6, 4.1%), autoimmune hepatitis (9, 6.1%), and drug-induced liver dysfunction. Thirty-four percent of patients of the cohort received LT because of HCC.

The BMI of PTMS patients was significantly greater than that of non-PTMS patients (23.5 ± 4.3 vs 21.8 ± 2.8, P = 0.021). The proportions of obesity (20% vs 3.1%, P = 0.002) and metabolic syndrome (10% vs 3.1%, P = 0.02) at transplantation, AKI (35% vs 10.2%, P = 0.002), and hyperuricemia (55.0% vs 15.0%, P < 0.001) within one month after transplantation were significantly higher in PTMS patients as compared to non-PTMS patients. The other characteristics pre- and post-transplantation did not differ significantly between the two groups (Table 1). None of the patients presented a clinical history of gout.

Demographics and clinical characteristics of the donors
The mean age of the donors was 41.1 ± 14.2 years, and 121/147 (82.3%) donors were male. The BMI and WIT of donors for PTMS patients were significantly greater than those of donors for non-PTMS patients (BMI: 24.0 ± 4.7 vs 22.2 ± 3.2, P = 0.029; WIT: 10.8 ± 2.7 vs 9.2 ± 2.5, P = 0.034) (Table 2).

The medical reasons for donors were predominantly brain trauma (61.9%) as well as cerebrovascular accident, anoxia, encephalopathy, and brain tumor.

Risk factors of PTMS for DCD recipients
The median follow-up period was 32.1 (range: 14-81) mo. Twenty (13.6%) among one hundred and forty-seven subjects were diagnosed with PTMS; among these, seven (4.8%) were diagnosed by the 6th mo after DCD LT. The morbidities of postoperative obesity, diabetes, hypertension, and dyslipidemia were 12.2%, 31.3%, 10.9%, and 22.4%, respectively.

The BMI of the recipients, WIT, AKI, and hyperuricemia were found to be significantly associated with PTMS according to the univariate logistic regression (Table 3). Moreover, BMI (OR = 10.9, 95%CI: 1.38-86.3, P = 0.024), WIT (OR = 1.23, 95%CI: 1.01-1.50, P = 0.045), and hyperuricemia (OR = 11.8, 95%CI: 2.85-48.8, P = 0.001) remained significant parameters according to the final multivariate logistic regression analysis (Table 4).

Change in serum uric acid level in patients with and without PTMS
The pre-LT level of serum uric acid was compared between PTMS and non-PTMS, and no significant difference was found (255 ± 96 vs 273 ± 84, P =
The change in the serum uric acid level post-LT over a period was verified with PTMS and non-PTMS, respectively. The level of serum uric acid rose from 273 ± 96 to 400 ± 118 μmol/L in PTMS patients (P < 0.001) and from 273 ± 84 to 350 ± 103 μmol/L in non-PTMS patients (P < 0.001) during the first month after the surgery. After the 1st mo, the level of serum uric acid in PTMS patients continued to increase over time (P<0.001), while it remained unchanged in non-PTMS patients (P=0.847) (Table 5 and Figure 1).

**Correlation between serum uric acid level and estimated glomerular filtration rate in patients with and without PTMS**

Serum uric acid was significantly correlated with estimated glomerular filtration rate (eGFR) pre-transplantation in all patients. Subsequently, the changes in the serum uric acid were significantly associated with the corresponding changes in eGFR among non-PTMS patients, while serum uric acid in PTMS patients did not appear to be correlated with eGFR over a period (Table 6).

**Survival and freedom from complications**

One-year patient and graft estimated survival rates of DCD LT were 94.8% and 88.2%, respectively. The graft loss might be related to infection (2/16, 12.5%), biliary complications (3/16, 18.8%), vascular complications (2/16, 12.5%), primary graft failure (1/16, 6.3%), intra-abdominal hemorrhage (2/16, 12.5%), rejection (2/16, 12.5%), and tumor recurrence (4/16, 25%). No events were recorded in the recipients with PTMS.

**DISCUSSION**

Controlled DCD donors constitute the most potential donors in China since 2010. This is the first study assessing the prevalence of MS for DCD LT. In the current study, the prevalence of PTMS is 13.6% for the whole cohort. PTMS could occur at the early stage after DCD LT with growing morbidity with the passage of time.

The prevalence of PTMS was found to be remarkably lower than that reported in the previous studies[5,6,11,12]. Several potential reasons might be able to explain the relatively low prevalence. First, the morbidities of pre-transplant MS and its components in the current study were significantly lower than those reported previously. The prevalence of PTMS was almost triple with respect to that reported in the previous studies.
to pre-transplant MS within 2 years post-surgery. The prevalence might further rise in prolonged follow-up periods. Second, different etiologies might also cause the lower morbidity of PTMS. Unlike Europe or United States, HBV, not non-alcoholic steatohepatitis (NASH) or HCV, was the most common indication for LT observed at our center. HCV is reported to be related to diabetes mellitus and NAFLD in liver disease reports. Some investigators also found a higher rate of PTMS in HCV recipients in multiple studies. Conversely, only a few studies showed the relationship between HBV and post-LT metabolic issues. Finally, the mean age (46 years old) of this cohort was relatively young. Although we did not find age as an independent risk factor for PTMS in the current study, it has been widely accepted that older recipients have a higher prevalence of metabolic disorders.

In the current study for DCD patients, BMI, WIT, and hyperuricemia were found to be associated with PTMS. Ischemia-reperfusion injury resulting from prolonged WIT could lead to a series of post-OLT complications. However, whether WIT exerted any influence on PTMS has not yet been elucidated. Also, hepatic ischemia-reperfusion injury induced insulin resistance. A clinical study found an early occurrence of new-onset diabetes after transplantation, which is related to the type of liver graft and warm ischemic injury. Perera et al. reported the differences in the metabolites in the microdialysate samples of liver grafts from DCD and brain deaths. These studies indicated that WIT might contribute to hepatic metabolomic changes post-transplantation. In this study, the ineluctable WIT, rather than cold ischemia time, for DCD LT was found to be an independent risk factor of the post-transplantation metabolic syndrome; nonetheless, further experiments are essential for exploring the underlying mechanism.

Another intriguing finding of this research was derived from the analysis of serum uric acid after LT. To date, only a few studies are available on the predictors of PTMS. Hyperuricemia is one of the potential metabolic complications of LT. The elevated level of serum uric acid has frequently been observed post-transplantation and reportedly, associated with ischemia-reperfusion injury, renal dysfunction, and immunosuppressive therapy. In addition, some studies demonstrated the correlation of hyperuricemia with the development of metabolic syndrome; however, its role on PTMS has not yet been deduced. Herein, we found hyperuricemia to be associated with PTMS.

Subsequently, we explored whether the elevated serum uric acid level was associated with PTMS and found rapidly increased levels of the acid in patients with PTMS in the first month post-surgery. Compared with the non-PTMS cohort, patients with metabolic syndrome exhibited a higher preoperative BMI and donor BMI. Although obesity is one of the risk factors of hyperuricemia, the mean uric acid level before surgery of the two groups was normal. Furthermore, BMI may not be the reason for the sudden increase in the level of uric acid level immediately after LT. Other differences between the two cohorts were that patients in the PTMS group suffered shorter WIT and more AKI in the perioperative period than the non-PTMS group; the prolonged WIT of DCD LT led to worse ischemia-reperfusion injury and caused
Table 5  Serum uric acid level change of patients who did and did not develop posttransplant metabolic syndrome

| Time point            | PTMS          | Overall P value | Non-PTMS        | Overall P value |
|-----------------------|---------------|-----------------|-----------------|-----------------|
| Pre-LT (Baseline)     | 255 ± 96      | < 0.001         | 273 ± 84        | < 0.001         |
| Post 3 mo             | 400 ± 118     |                 | 350 ± 103       |                 |
| Post 6 mo             | 432 ± 80      |                 | 355 ± 81        |                 |
| Post 12 mo            | 446 ± 72      |                 | 360 ± 78        |                 |
| Post 24 mo            | 460 ± 96      |                 | 360 ± 83        |                 |
| Post 36 mo            | 512 ± 76      |                 | 348 ± 90        |                 |

PTMS: Pre-LT < 0.001, *P* 3 mo vs. Baseline = 0.017, *P* 6 mo vs. Baseline = 0.002; Non-PTMS: *P* 3 mo vs. Baseline = 0.002, *P* 6 mo vs. Baseline = 0.034, *P* 12 mo vs. Baseline = 0.847. PTMS: Posttransplant metabolic syndrome.

Table 6  Correlation coefficient between serum uric acid level and estimated glomerular filtration rate in patients who did and did not develop posttransplant metabolic syndrome

|     | PTMS       | Overall P value | Non-PTMS      | Overall P value |
|-----|------------|-----------------|---------------|-----------------|
| Pre-LT | -0.74     | < 0.001         | -0.28         | 0.002           |
| P3 mo  | -0.44     | 0.052           | -0.43         | < 0.001         |
| P6 mo  | 0.076     | 0.750           | -0.22         | 0.014           |

PTMS: Posttransplant metabolic syndrome; LT: Liver transplantation.

Figure 1  Posttransplant levels of serum uric acid in patients with and without posttransplant metabolic syndrome. The red folding line reflects the serum uric acid level change of patients who did develop posttransplant metabolic syndrome (PTMS) [data are presented as mean ± standard error of mean (SEM), and n = 20], and the azure folding line reflects the situation of patients without PTMS (data are presented as mean ± SEM, and n = 127). The abscissa in the figure indicates the period from pre-LT transplantation to post-liver transplantation 24th mo. PTMS: Posttransplant metabolic syndrome; Post-LT: Post-liver transplantation.

AKI[26]. Warm ischemia could also induce breakdown of hepatocellular ATP to purine catabolites that are oxidized, and in turn, become uric acid after reperfusion[27]. This phenomenon renders uric acid as one of the markers to predict the hepatic injury due to ischemia[28]. Renal dysfunction caused by AKI is also associated with the elevated level of uric acid[22,20]. Although not found in the current study, prolonged WIT remains a potential cause for the tendency of a rapid rise in the level of serum uric acid in the perioperative period of LT.

After a sharp increase in the first month, the level of uric acid stabilized in the non-PTMS cohort. Moreover, it continued to increase in PTMS patients and overstepped the upper limit of normal blood uric acid concentration. Intriguingly, after adjusting for renal function, the disparity in the values persisted. This indicated that the increased serum uric acid level was highly associated with PTMS. Recently, accumulating evidence suggested that uric acid, the final product of the purine degradation in human, was an independent predictor of metabolic syndrome. Choi et al[29] found a significantly high prevalence of MS in the hyperuricemia population. Li et al[31] reported that the increase in the serum uric acid level within the normal range could predict the risk of metabolic syndrome. A meta-analysis reported a linear disposition from a uric acid increase on the prevalence of MS[32]. However, any evidence supporting the relationship between hyperuricemia and PTMS was absent. Based on the current data, we hypothesized that uric acid could serve as a serum marker for the prevalence of PTMS.

Nevertheless, the present study had several limitations. First, our results were based on a single center retrospective study. Second, the follow-up period of the current study was relatively short than the previous long-term retrospective studies, thereby limiting the results of patients' survival and complications. Third, the donor source did not allow comparison of the data from DCD with DBD LT.

In conclusion, the current study showed that PTMS could occur at the early stage after DCD LT with growing morbidity with the passage of time. For the first time, we found that prolonged warm ischemia and post-LT hyperuricemia were associated with prevalent PTMS. Also, increased serum uric acid level was highly associated with PTMS and could serve as a serum marker for monitoring such a disease.

ARTICLE HIGHLIGHTS

Research background
Liver transplantation (LT) is still the standard treatment for patients with end-stage liver disease. The usage of livers from donation after cardiac death (DCD) donors has increased rapidly. Current research shows that some risks of a series of acute and chronic complications are correlated with the warm ischemia time (WIT). Thus, the long-term prognosis of DCD LT has gained increasing attention.

Research motivation
After LT, patients may develop a series of metabolic disorders which is called...
posttransplant metabolic syndrome (PTMS). However, data on specific assessment of the morbidity of PTMS after DCD LT are still lacking. Therefore, this study aimed to further explore the prevalence of PTMS after DCD LT and the pre- and postoperative risk factors, to provide evidence for clinical decision rules.

Research objectives

The present retrospective analysis describes the prevalence of PTMS after DCD LT and the pre- and postoperative risk factors that are relevant to the occurrence of PTMS, and provides evidence for clinical judgment.

Research methods

This is a retrospective cohort study. One hundred and forty-seven subjects who underwent DCD liver transplantation from January 2012 to February 2016 were enrolled in this study. The pre- and post-transplantation demographics and clinical characteristics were collected for both recipients and donors. All subjects were followed monthly for the initial 6 mo after discharge, and then, every 3 mo for 2 years. The subjects were followed every 6 mo or as required after 2 years post-LT. All data were used to perform statistical analyses and identify the variables independently associated with PTMS in the final multivariate model.

Research results

In this retrospective cohort study, the prevalence of PTMS after DCD donor orthotopic LT was 13.6%. Recipient’s body mass index, WIT, and posttransplant hyperuricemia were significantly associated with PTMS. The change in serum uric acid level in PTMS patients was significantly higher than that in non-PTMS patients. After the 1st month, the level of serum uric acid of PTMS patients rose continually over a period, while it was unaltered in non-PTMS patients. After transplantation, the level of serum uric acid in PTMS patients was not associated with renal function.

Research conclusions

PTMS could occur at early stage after LT DCD with growing morbidity as time goes on. For the first time, we found that prolonged WIT and the posttransplant hyperuricemia were associated with the prevalence of PTMS, and an increased serum uric acid level was highly associated with PTMS and could serve as a serum marker for monitoring such a disease.

Research perspectives

In this study, the ineluctable WIT rather than cold ischemia time for DCD LT was found initially as an independent risk factor of PTMS. Nonetheless, further experiments are essential for exploring the underlying mechanism. Our data also indicated that the increased serum uric acid level was highly associated with PTMS. Although prolonged WIT remains a potential cause for the tendency of a rapid rise in the level of serum uric acid in the perioperative period of LT, after a sharp increase in the first month, the level of uric acid stabilized in the non-PTMS cohort. However, it continued to increase in PTMS patients and overstepped the upper limit of normal blood uric acid concentration. Intriguingly, after adjusting for renal function, the disparity in the values persisted. Recently, accumulating evidence also suggests the standpoint that uric acid is an independent predictor of metabolic syndrome. In consideration of our research results, more prospective studies are urgently required to provide evidence for clinical verification. Future research should include larger cohorts of patients from multiple centers to expand the sample size and establish a more comprehensive long-term follow-up to improve the statistical database containing more factors, including PTMS and survival rate.

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