Int J Clin Exp Med 2018;11(12):13581-13588
www.ijcem.com /ISSN:1940-5901/IJCEM0070698

Original Article

Impact of recipients with hypertension on the survival after liver transplantation: an analysis of the US national database

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Received December 10, 2017; Accepted September 5, 2018; Epub December 15, 2018; Published December 30, 2018

Abstract: Background: Live transplantation (LT) has been the treatment of choice for chronic and acute liver failure. And patients after liver transplantation are prone to have hypertensive disease. However, the effect of recipient with hypertension on the post-transplantation survival is unclear. Method: This research used the Scientific Registry of Transplant Recipients database (2008-2012), 22701 patients were assessed, and 4882 hypertension recipients have been included. We evaluated differences in patient characteristics between recipient from HTN and non-HTN. Patient survival was assessed using Kaplan-Meier methodology and Cox regression analyses. Result: Recipients without hypertension obtain higher post transplanted survival compared with recipients with hypertension (one-year survival: 87% versus 86%, and five-year survival: 69% versus 64%, P<0.001, respectively). And the graft survival also experienced the same result (one-year survival: 85% versus 84%, and five-year survival: 65% versus 61%, P<0.001). Cox regression analyses manifest that recipients with hypertension were independently risk factor of post transplanted survival (hazard ratio, 1.17; 95% confidence interval, 1.01-1.26). Conclusion: These data mean that recipients with hypertension and graft with hypertension experienced significantly worse survival after liver transplantation.

Keywords: Liver transplantation, hypertension, recipient, survival, outcome

Introduction

Liver transplantation (LT) has been the most effective therapy for patients with end-stage liver disease. Because of its positive results, an increase number of patients received LT, resulting in a relative shortage of liver grafts. Therefore, to better match the donors and recipients, analyses that define the effect of specific donor and recipient characteristics on the risk of post-transplant survival must been performed.

Hypertension has been a serious global public health problem. The total number of people suffering from hypertension in the world in 2010 is about 1.33 billion, and the number of future is still growing [1, 2]. The estimated prevalence of hypertension in the US general population is ranged from 32% to 40.6% [1, 2]. Hypertension has been shown to be an important risk factor to influence patient survival post LT by cardiovascular disease and chronic nephrosis, since we found the prevalence of hypertension post LT is very high, ringing from 40% to more than 80% [3-7]. Especially in first month after LT, prevalence of hypertension among recipients was higher than 80% measured by ambulatory blood pressure monitoring (ABPM) [3]. It has been proved that hypertension after LT develops in the first 6 months after transplantation because of systemic vasoconstriction, high concentration of endothelin 1, arteriosclerosis [8], and increase of peripheral

Table 1. Comparison of the baseline characteristics of recipients and donors

Recipient characteristic	HTN recipients (n=4882)	Non-HTN recipients (n=17819)	P
Age (years)	54.1±9.5	52.6±9.2	<0.001
Male	3383 (69.3)	12034 (67.5)	0.018
Race			
White	3348 (68.6)	13080 (72.1)	<0.001
Black	622 (12.7)	1431 (9.0)	<0.001
Asian	227 (4.6)	837 (4.9)	0.902
Hispanic	637 (13.0)	2297 (12.9)	0.923
Other	48 (1.1)	174 (1.1)	0.899
DM	1934 (39.6)	3239 (18.2)	<0.001
HCC	1293 (26.5)	4110 (23.1)	<0.001
Cause of liver disease			
HCV	2196 (45.0)	8172 (45.9)	0.277
HBV	188 (3.9)	955 (5.4)	<0.001
NASH	403 (8.3)	815 (4.6)	<0.001
Alcohol	786 (16.1)	2489 (14.0)	<0.001
Autoimmune disease	330 (6.8)	2133 (12.0)	<0.001
Other	979 (20.1)	3255 (18.3)	0.005
Dialysis within 1 week	533 (10.9)	1283 (7.2)	<0.001
MELD score	20±9	21±9	<0.001
Donor characteristic	HTN donors (n=4882)	Non-HTN donors (n=17819)	P
Age (years)	53.8±12.4	36.5±15.8	<0.001
Male	2960 (60.6)	10552 (59.2)	0.076
Race			
White	3288 (67.3)	12229 (72.1)	<0.001
Black	826 (16.9)	2678 (9.0)	<0.001
Asian	111 (2.3)	399 (4.9)	0.874
Hispanic	610 (12.5)	2357 (12.9)	0.188
Other	47 (1.0)	156 (1.1)	0.553
BMI (kg/m^2)	29±6	26±6	<0.001
DM	515 (10.5)	1689 (9.5)	0.027
Cause of death			
Anoxia	709 (14.5)	2714 (15.2)	0.223
Cerebrovascular accident	2187 (44.8)	7686 (43.1)	0.038
Trauma	1830 (37.5)	6984 (39.2)	0.030
Other	156 (3.2)	434 (2.4)	0.003
WIT (min)	42.3±18.7	41.2±18.5	0.233
CIT (h)	7.5±3.3	7.4±3.7	0.354
DCD	244 (5.0)	981 (5.8)	0.175
DRI	1.82±0.43	1.81±0.42	0.457

HTN: hypertension; DM: diabetes mellitus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: non-alcoholic steatohepatitis; BMI: body mass index; DRI: donor risk index; WIT: warm ischemia time; CIT: cold ischemia time; MELD: Model for End-Stage Liver Disease.

vascular resistance [9]. Long term status of high blood pressure (BP) would affect the lifetime service of vessel, which result in cardiovascular disease and chronic nephrosis. And many factors have contribution to hypertension post LT, such as immunosuppressive medication, BMI, hyperglycemia post PT, age, leading to poor outcomes among recipients with hypertension [7, 10].

In our previous study, we have indicated that LT patients receiving hypertension grafts had a lower survival rate than that of non-hypertension grafts [11]. But whether recipients with hypertension have a negative influence on the survival of recipients post LT is still unclear. There's few research discussing about the relationship about patients with hypertension and the outcomes after LT. Thus, this study will confirm if recipients with hypertension affected the survival post LT.

We compared the survival of patients and grafts which have hypertension before LT with those which non-hypertension recipients, using the national registry database in the USA. We want to know whether preventing hypertension has beneficial to the survival of the patient post LT.

Materials and methods

Data sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and it has been described elsewhere. The Health Resources

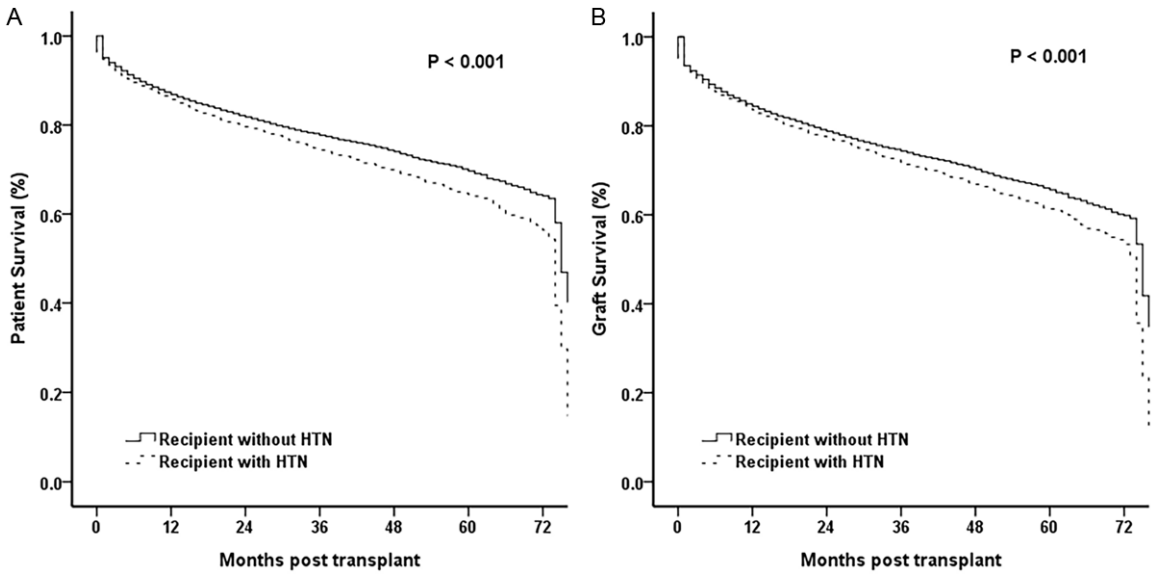

Figure 1. Kaplan-Meier survival curves comparing overall patient (A) and graft survival (B) of recipients with HTN and without HTN. Recipients with HTN had significantly lower patient survival and graft survival than those without HTN.

and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors [12]. The study protocol was approved by the Ethics Committee of Zhejiang University (Hangzhou, China).

Study cohort

All LT patients with a first isolated LT carried out between 1 January 2008 and 30 September 2012 were eligible for inclusion into the study. Recipients were considered to have hypertension if there's records of "recipient's history of hypertension". Finally, 22,701 patients were assessed, and 4882 hypertension recipients have been included.

We made an analysis of the potentially confounding factors for recipients, namely the characteristics contain age, male, race, history of diabetes mellitus (DM), history of hepatocellular carcinoma (HCC), whether the patients had liver diseases categorized by the causes (hepatitis B virus (HBV); hepatitis C virus (HCV); alcohol; non-alcoholic steatohepatitis (NASH); autoimmune disease (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis); and other causes), model for end-stage liver disease (MELD) score. And donor variables include age, male, race, body mass index (BMI), history of diabetes mellitus (DM), warm ischemia time (WIT); cold ischemia time (CIT); donation after cardiac death (DCD); donor risk index (DRI) [13]; and cause of death.

Outcome measures

The major outcomes were depended on patient survival and graft survival. And time-to-outcome was considered as the outcome measure. Patient follow-up was defined as the time from transplantation until the date of death or last known follow-up. The occurrence and date of death were obtained from data reported by the transplantation centers, and were completed using data from the US Social Security Administration and OPTN.

Statistical analyses

The baseline characteristics were compared between the study cohort which were classified if the recipients had hypertension. Statistical difference was made using the Student's t-test for continuous variables, and the chi-square test for categorical variables. Survival was assessed using Kaplan-Meier curves and compared with log-rank tests. Cox proportional hazard models were created for the time-to-survival and time-to-graft loss to evaluate the potential predictors of the outcome measures. Variables that were significantly different in the baseline comparison as well as those clinically relevant even if similar at baseline were included in the models. Results were expressed as

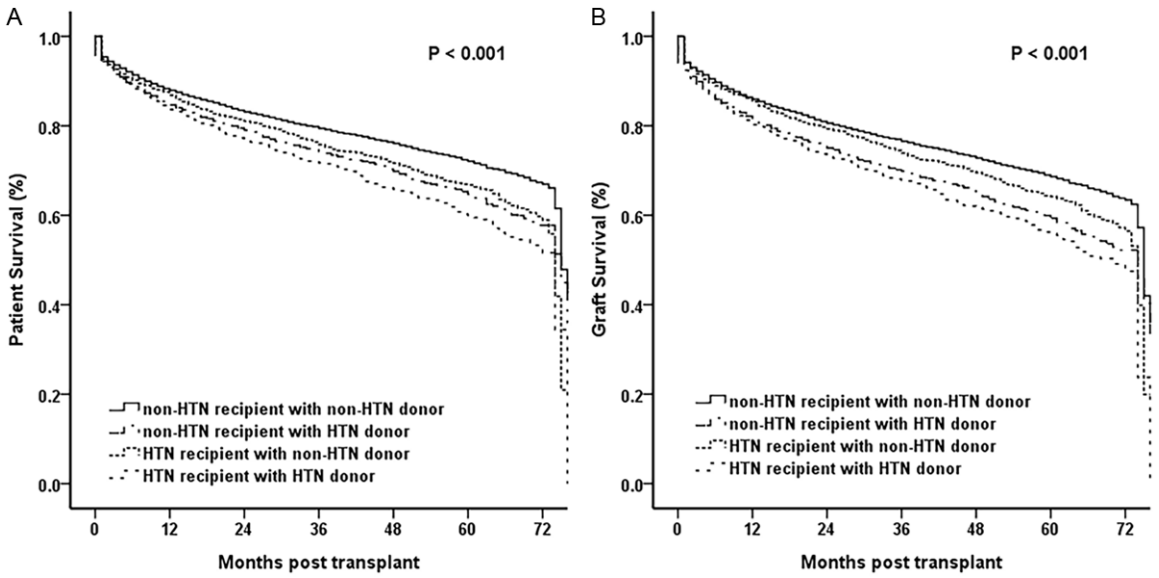

Figure 2. Kaplan-Meier survival curves comparing overall patient (A) and graft survival (B) of donor-recipient paring with HTN or with not. Non HTN recipients with non HTN donors had the highest patient survival and graft survival than other cohorts. Lowest curve stand for the survival of that is NTH recipients with HTN donors.

hazard ratios (HRs) with 95% confidence intervals (CIs). A standard alpha level of 0.05 (two-sided) was taken to indicate statistical significance. Analyses were conducted using SPSS ver22.0 (SPSS, Chicago, IL, USA).

Results

In all, 22701 patients who undertaken a first isolated LT between 1 January 2008 and 30 September 2012 were assessed. And 4882 (21.5%) recipients had hypertension (HTN) and 17819 (78.5%) recipients didn't.

Baseline characteristics

The baseline characteristics of recipients with hypertension (n=4882) and those without hypertension (n=17819) are listed in **Table 1**. HTN recipients were older (HTN recipients 54.1±9.5 years vs. non-HTN recipients 52.6±9.2 years; P<0.001), and the percentage of male is higher in HTN recipients (HTN recipients 69.3% vs. non-HTN recipients 67.5%; P=0.018). There was, however, a greater proportion of HCC recipients in the HTN recipients' cohort (HTN recipients 26.5% vs. non-HTN recipients 23.1%; P<0.001), same as proportion of DM recipients (HTN recipients 39.6% vs. non-HTN recipients 18.2%; P<0.001). They had lower MELD scores (HTN recipients 20±9 vs. non-HTN recipients 21±9; P<0.001), whereas were opposite likely to be on dialysis 1 week before LT (HTN recipients 10.9% vs. non-HTN recipients 7.2%; P<0.001). In addition, the prevalent of major causes of liver disease was significantly higher in HTN recipients, include NASH (HTN recipients 8.3% vs. non-HTN recipients 4.6%; P<0.001), alcohol (HTN recipients 16.1% vs. non-HTN recipients 14%; P<0.001), oppositely, HBV (HTN recipients 3.9% vs. non-HTN recipients 5.4%; P<0.001) and autoimmune disease (HTN recipients 6.8% vs. non-HTN recipients 12.0%; P<0.001) were less causes. Besides, HTN recipients were associated with more adverse factors of graft quality, such as donor age (HTN donors 53.8±12.4 years vs. non-HTN donors 36.5±15.8 years; P<0.001), BMI (HTN donors 29±6 kg/m^2 vs. non-HTN donors 26±6 kg/m^2; P<0.001), history of DM (HTN donors 10.5% vs. non-HTN donors 9.5%; P=0.027). And WIT, CIT, DCD and DRI didn't express significant difference in donor characteristic.

Patient and graft survival

The graft survival rates were 84%, 72%, and 61% at 1, 3, 5 years respectively for recipients with hypertension. And 85%, 74%, and 65%, respectively, for recipients without hypertension (log rank <0.001, **Figure 1A**). Similarly, the patient survival rates were 86%, 74% and 64% for recipients with hypertension and 87%, 78%

Table 2. Cox proportional hazard regression analyses

Variable	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Hypertension	1.25	1.07-1.49	1.17	1.01-1.26
DRI	1.68	1.58-1.75	1.41	1.34-1.55

DRI: donor risk index.

and 69% for those without hypertension at 1, 3 and 5 years (log rank <0.001, **Figure 1B**).

In addition, the HTN recipients after LT with the donors without hypertension leaded to a significantly higher survival contrasted with those with HTN donors (log rank P<0.001, **Figure 2A**), and the non-HTN recipients showed the same tendency (log rank P<0.001, **Figure 2A**). Graft survival is considered as the exactly alike measure with patient survival (**Figure 2B**).

Predictors of graft loss at multivariate analyses

A Cox regression hazard model is measured if the factor is considered as significant predictor of graft loss. HTN recipients were associated with an increased risk of mortality for patients after LT (HR=1.17; 95% CI=1.01-1.26, **Table 2**). It determined that the recipient with hypertension was an independent risk predictor of graft loss.

Discussion

Using comprehensive clinical data from the SRTR database, the result of present study showed the recipient with hypertension was an independent risk predictor of graft loss, based on the data from 2008-2012. Compared between the study cohorts' baseline characteristics, we found many risks showed statistical differences which we already knew had impact of recipient survival after LT, such as the history of Diabetes Mellitus, history of hepatocellular carcinoma, age. Under the adjustment of factors including those that might represent a selection bias, the increased risk of death of patients post LT remained significant if the recipients had hypertension or not, even using donor with hypertension also can influence the patient survival after LT. Since this is the first study to compare the outcome of LT recipients with HTN and those without HTN, the choice if the patients are suitable for LT should assess the history of hypertension will be significant, and the donors without hypertension can be more appropriate for the patients waiting LT, this notion shows recipients and donors should be employed with caution.

On analyzing the characteristics of recipients with HTN, history of DM was the main indication in study cohorts (HTN 39.6% vs. non-HTN 18.2%), and history of HCC was the leading indication (26.5% vs. 23.1%), and liver disease caused by alcoholic (24%) followed by NASH (22%), the second and third indications in the recipients, although liver disease caused by HCV did not expressed the significant difference. Diabetes Mellitus before LT had been proved many times that it influences the prognosis of LT, and There are many theories about the mechanism, Shintani Y thought that it because virus has directly effect on insulin signal [14], whilst Petit suggested it just is phenotypic manifestation of classic risk factors of DM [15]. So the difference between the groups about characteristics baseline may lead to the worse survival after LT. There're many accompanying diseases of hypertension, like coronary disease, DM, obesity [16]. From the research of Malaysia, the morbidity of hypertension of DM patients is up to 92.4% [17], thus, we should not ignore the relationship of DM and hypertension. They all can affect the survival of patients after LT. And the older age of recipients with HTN suggested lesser patient survival compared with recipients without HTN. These factors had been shown to be associated with worse survival after LT in previous studies [18-20]. With the older age, body constitution, the condition of blood vessel, underlying diseases and immunocompetence continue the downward trend, it will obviously increase the difficulty of LT.

Following, we found that the donors in HTN group were older than that in non-HTN group (HTN donors 53.8±12.4 years vs. non-HTN donors 36.5±15.8 years; P<0.001). Recent years, liver grafts from elder donors were widely used in LT. And Lai's study has showed that there was no significant difference in the 5-year survival rate between the elderly donors (50-60) and the younger donors (30-49) for patients after LT [21]. In addition, the BMI (HTN donors 29±6 kg/m^2 vs. non-HTN donors 26±6 kg/m^2; P<0.001) and history of DM (HTN donors 10.5% vs. non-HTN donors 9.5%; P=0.027) showed

significant differences in HTN group and non-HTN group of donors, but the mean values were similar. Furthermore, In the HTN group, the number of donor death caused by cerebrovascular accidents was larger, while, head trauma was smaller. This may be associated with age, since older people are more likely to develop cerebrovascular accident.

Besides, there are some other authors suggested that these factors were associated with leading to HTN [7, 10], especially post transplantation. But few study consider if the recipients with HTN have worse survival after transplantation. The present study suggested the recipient with hypertension was associated with graft loss using Cox regression analyses and comparing mortality between the study cohorts. In addition, liver transplantation is becoming more widespread, but demand of donors exceeds supply. To increase the donors, we have to expand selected range, DCD donors and elder donors already are been used duo to improvements in surgical methods and immunosuppression [22]. In the current study, both recipient with HTN and those without HTN used the HTN donors suggested worse patient survival after LT. Thus, it should be considered cautiously whether the donors with HTN.

With the widely application of liver transplantation, the impact on the postoperative liver transplant recipients has much more factors, and there are varied of evaluation methods. Now donor risk index (DRI) on is accepted as an independent predictor of the prognosis after liver transplantation survival risk. The original concept of DRI was been raised by Feng S in 2006 [13]. It was not simply categorizing possible influential factors for prognosis of liver transplantation survival on donor. After years of research, different areas, such as Europe, the United States, all have their own DRI improved calculation method, it already has been widely used and it's very reliable. In this study, we used the Cox proportional hazards regression analysis, DRI is an independent risk factors for the prognosis of liver transplantation survival. This conclusion consistent with the internationally recognized, and explained the reliability of our study.

Further study, we found that donor preoperative with a history of hypertension might impact on the prognosis of liver transplantation survival. In this study, the group of the preoperative hypertension receptors, according the donor has a history of hypertension or not, divided into two groups. From the survival curve, we found the survival of the donor without preoperative hypertension was obviously higher than the other; and the result of the group of receptors without preoperative hypertension was same as above. This suggested us to touch the further study about the effect of preoperative hypertension on prognosis of liver transplantation. Our previous study has confirmed the effect of donor hypertension on post-LT [11], moreover this study is consistent with our previous study and further demonstrates previous studies.

There are several limitations in this study. First, it has a few limitations mainly related to the data, because of the registry-based nature of this study. We couldn't know the exactly time about the duration of HTN before LT, and the absence of HTN level prevented us from discussing the further relationship between recipients with HTN and patient survival. Second, any large database is subject to reporting bias, data entry errors, and inaccuracies. Although the SRTR database can't avoid this problem, it may be less of a concern in the SRTR database due to the mandatory participation of all transplant centers in the US and the electronic data system [23].

In summary, using the largest study cohort available for analysis and the longest follow-up periods available to date, the current study suggests that recipients with HTN display inferior graft and patient survival than those without HTN when other predictors of post-transplantation survival were taken into considered. It has contribution to screen appropriate recipients for transplantation. For recipients with HTN, matching the donors without HTN to them can be safer than the donors with HTN. Our result may have implications for the indications of liver transplantation. Further studies are warranted to investigate the impact of hypertension deeply.

Acknowledgements

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The

interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. This work was supported by the Public Welfare Technology Application Research Plan of Zhejiang Province, China (No. 2017C33025), Key Research and Development Project of Science and Technology Department of Zhejiang, China (No. 2015C03053), and Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents.

Disclosure of conflict of interest

None.

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