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Article

Preoperative Levosimendan Administration in Heart Transplant Patients with Severe Hepatic and Renal Impairment: A Retrospective Study

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Abstract

Background: The cardio-renal syndrome and hepatic impairment play a critical role in end-stage heart failure (HF). Levosimendan is an effective inotropic agent used to maintain cardiac output similar to classic cardiotonic like dobutamine/dopamine. This current research aims to investigate the clinical outcomes of levosimendan and dobutamine/dopamine in Chinese heart transplant awaiting patients with severe hepatic or renal impairment. **Methods**: We performed a retrospective analysis of 568 heart transplant awaiting individuals with severe hepatic or renal impairment who treated with levosimendan or dobutamine/dopamine in our institution between January 2015 and December 2020. Univariate Cox proportional hazard models and Kaplan-Meier survival curves were applied. The primary endpoint was defined as death included inhospital mortality and the mortality at 30 days, 90 days, 180 days and 1 year after heart transplantation. **Results**: There were no significant differences in mortality rate at 30, 90, 180 days and 1 years after heart transplantation between the levosimendan and non-levosimendan groups, or between subgroups of patients with severe hepatic impairment or renal impairment. The results were consistent before and after propensity score matching. **Conclusions**: In the population with advanced heart failure awaiting heart transplantation, levosimendan did not increase short- or long-term mortality rates after surgery compared to dobutamine/dopamine, regardless of their hepatic or renal function. Severe hepatic or renal impairment were not necessarily considered a contraindication for levosimendan in these patients.

Keywords

levosimendan; hepatic impairment; renal impairment; heart transplantation

Introduction

Heart transplantation (HTx) is the gold standard for the treatment of end-stage heart disease and has achieved good results [1]. Although heart transplantation has significantly increased over the past two decades, the waiting list continues to increase as well [2]. The deterioration of the disease and the lack of donors have caused a large number of patients to die while waiting for HTx. The impairment of hepatic or renal function is highly prevalent in heart failure (HF) and is one of the most important independent risk factors for poor clinical prognosis in transplant patients. As a consequence, the treatment of patients with advanced HF awaiting HTx have attracted more and more attention in recent years.

Many inotropic agents, such as levosimendan, dobutamine, and dopamine are frequently used to maintain hemodynamic stability in patients with advanced HF. Levosimendan, an adenosine triphosphate (ATP)-sensitive potassium–channel opener and a calcium sensitizer, which perform positive inotropic effect through inhibiting phosphodiesterase and increasing cyclic phosphoadenylate concentrations [3]. By increasing the sensitivity of myocyte to calcium ion concentration, levosimendan does not impair diastolic relaxation. Furthermore, it does not affect calcium ion concentration, and can effectively prevent oxygen consumption from increasing as calcium ion concentration [4]. Notably, there are many studies that focus on hemodynamic and clinical effects of levosimendan and dobutamine but very limited data exist on the renal effects. Although levosimendan has been widely shown to be effective and safe for the treatment of HF, a systematic statistical study of its preoperative application, particularly for HTx awaiting patients with severe hepatic or renal impairment, has yet to be conducted.

Therefore, the purpose of this study was to analyze patients with advanced HF awaiting HTx with or without impaired renal or hepatic function to examine the effects of levosimendan.

Methods

Study Population and Data Collection

We collected retrospectively from electronic medical records the data of HTx recipients in Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, between January 2015 and December 2020. The inclusion criteria were: patients with any kind of levosimendan or dobutamine/dopamine inotropic support. There were 192 HTx recipients excluded due to lack of treatment with levosimendan or dobutamine/dopamine. Two HTx recipients were excluded due to incomplete data in electronic medical records. As a result of this study, data were collected on 374 individuals, of whom these findings are presented as a flowchart is shown in Fig. 1.

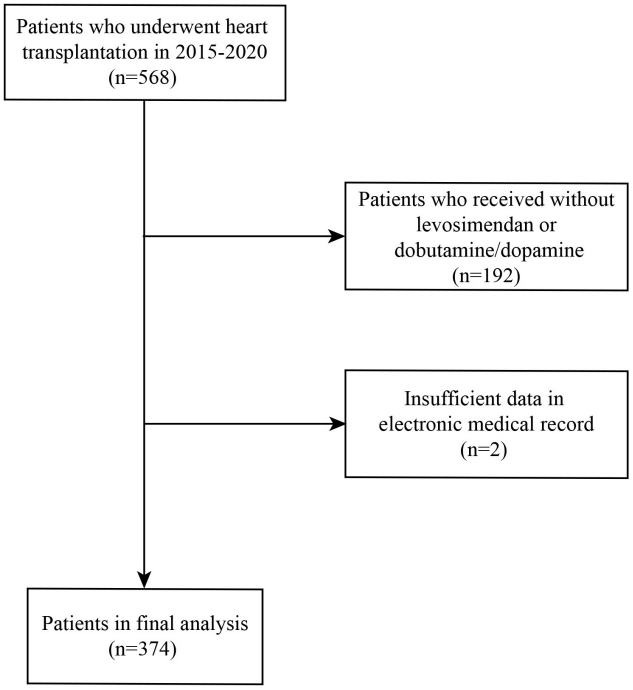

Fig. 1. Flow chart of patient recruitment.

Since January 1, 2015, organ donation from cardiac death donors has become the only legitimate source of organ transplantations in People's Republic of China. All donor grafts are allocated in accordance with Chinese law via the China Organ Transplant Response System. This study protocol has been approved by the Ethics Committee on Human Research at Union Hospital, Tongji Medical College of Huazhong University of Science and Technology. We obtained written informed consent from all participants.

In addition to demographic information, cardiovascular history and lifestyle, admission information, baseline medications and laboratory data, the clinical characteristics of participants were examined in the electronic medical records. Body mass index (BMI) is determined by dividing the weight in kilograms by the height in meters squared. Medical professionals assessed cardiac function according to the New York Heart Association (NYHA). According to the guidelines of the American Society of Echocardiography, the left ventricular ejection fraction (LVEF) was calculated. A computerized analyzer was used for quality control of all blood measurements and standard operating procedures were followed. Levosimendan group included the preoperative patients who received levosimendan during hospitalization, regardless of whether they received dobutamine/dopamine before receiving levosimendan. Non-levosimendan group included the preoperative patients who received dobutamine/dopamine without levosimendan during hospitalization. In order to eliminate time bias, admission days were measured as the period from the first day after surgery to the last day of hospitalization. Severe hepatic impairment was defined as total bilirubin (TBIL) >3 upper limit of normal, with any aspartate transaminase (AST) [5–7]. Severe renal impairment was defined as estimated glomerular filtration rate (eGFR) <30 or dialysis [8–10].

Outcomes

The primary endpoint of this analysis was all-cause mortality, included inhospital mortality and the mortality at 30 days, 90 days, 180 days and 1 year after surgery.

The secondary endpoints were postoperative complications, included respiratory complications, neurological complications, urological complications and liver injury, which diagnosed according to clinical presentation and related tests and examinations. All patients were followed until death occurred or until July 31, 2022.

Statistical Analysis

Variables with categorical characteristics are presented as frequencies and percentages, and are compared using the χ^2 test. A continuous variable is shown as the mean $\pm$ standard deviation (SD) for normally distributed values, and as the median (25th and 75th percentile) for non-normally distributed variables. The Shapiro-Wilk's test for normal distribution was used on continuous variables. We compared the differences between the groups using one-way ANOVA for normal distributed continuous variables and Kruskal-Wallis for non-normal distributed continuous variables.

In order to balance the two groups, we performed propensity score matching (PSM) based on the propensity score derived in multivariable logistic regression. The levosimendan group and non-levosimendan group were matched each patient for 1:1 based on PSM. Information included age, sex, BMI, smoking history, LVEF, treatment of angiotensin receptor blockers (ARBs) and β blocker,

Table 1. Clinical and biological characteristics according to levosimendan use.

Clinical characteristics	Levosimendan (n = 149)	Non-levosimendan (n = 225)	*p* value
Demographics			
Recipient age, years	47 (33, 56)	46 (29, 55)	0.270
Recipient sex (male), n (%)	117 (78.5)	158 (70.2)	0.075
Recipient BMI, kg/m^2	22.8 (19.4, 25.4)	21.5 (18.7, 24.3)	0.021
Donor heart cold ischemia time, min	353 (306, 393)	351 (300, 399)	0.710
Cardiovascular history and lifestyle			
Diabetes history, n (%)	9 (6.0)	18 (8.0)	0.473
Cardiac surgery history, n (%)	41 (27.5)	56 (24.9)	0.570
Hypertension history, n (%)	9 (6.0)	15 (6.7)	0.809
Smoking history, n (%)	63 (42.3)	72 (32.0)	0.043
Alcohol consumption, n (%)	36 (24.2)	47 (20.9)	0.456
Admission information			
NYHA class IV, n (%)	138 (92.6)	200 (88.9)	0.231
LVEF	23 (18, 30)	26 (20, 32)	0.003
ICM, n (%)	26 (17.4)	34 (15.1)	0.546
PAH, n (%)	81 (54.4)	100 (44.4)	0.060
Admission days	42 (31, 56)	35 (26, 51)	<0.001
Baseline medications			
Epinephrine/norepinephrine, n (%)	24 (16.1)	23 (10.2)	0.093
ACEI, n (%)	47 (31.5)	84 (37.3)	0.251
ARBs, n (%)	37 (24.8)	32 (14.2)	0.010
β blocker, n (%)	119 (79.9)	156 (69.3)	0.024
Diuretic, n (%)	144 (96.6)	222 (98.7)	0.186
IABP/ECMO, n (%)	8 (5.4)	8 (3.6)	0.396
Dialysis, n (%)	32 (21.5)	26 (11.6)	0.009
Laboratory data			
WBC, 1000/μL	6.6 (5.5, 8.4)	6.4 (4.7, 8.7)	0.215
Hemoglobin, g/dL	13.3 ± 2.2	13.2 ± 2.3	0.735
Platelet, 1000/μL	182.0 (139.5, 239.5)	183.0 (139.0, 229.5)	0.876
ALT, U/L	26.0 (17.0, 51.5)	29.0 (17.0, 49.5)	0.689
AST, U/L	30.0 (22.0, 42.5)	30.0 (22.0, 44.0)	0.746
Albumin, mg/dL	38.6 (36.1, 42.4)	39.5 (36.2, 42.5)	0.471
TG, mmol/L	1.00 (0.82, 1.27)	0.97 (0.74, 1.24)	0.283
TC, mmol/L	3.41 (2.93, 3.98)	3.41 (2.83, 4.20)	0.898
TBIL, μmol/L	28.6 (18.7, 41.3)	23.3 (15.4, 38.2)	0.041
LDL-C, mmol/L	2.12 (1.71, 2.60)	2.11 (1.69, 2.63)	0.966
SUA, μmol/L	533 (423, 647)	502 (378, 599)	0.057
Scr, μmoI/L	90 (74, 110)	85 (65, 106)	0.016
BUN, mg/dL	7.65 (5.80, 10.90)	7.20 (5.74, 9.31)	0.112
eGFR, mL/min/1.73 m^2	83 (65, 109)	90 (67, 126)	0.031
INR	1.25 (1.11, 1.47)	1.22 (1.10, 1.42)	0.270
NT-proBNP, pg/mL	4580 (2300, 8860)	3540 (1865, 8411)	0.208
cTnI, ng/mL	33.3 (3.8, 109.0)	54.3 (14.5, 155.1)	0.065

Data were expressed as means ± SDs, medians with interquartile range or n (%).

BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ICM, ischemic cardiomyopathy; PAH, pulmonary arterial hypertension; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; WBC, white blood count; ALT, alanine aminotransferase; AST, aspartate transaminase; TG, triglyceride; TC, total cholesterol; TBIL, total bilirubin; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; Scr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; SD, standard deviation.

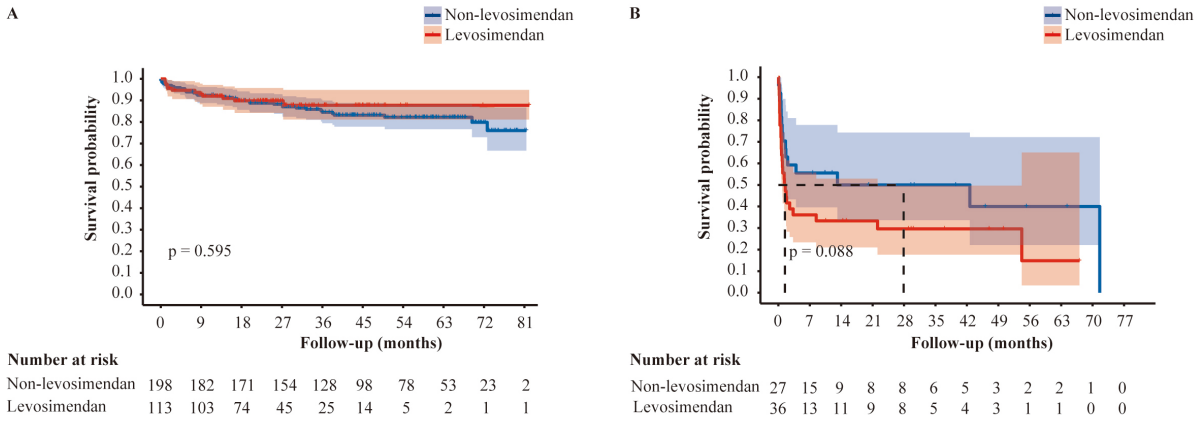

Fig. 2. Kaplan-Meier curve for post-transplant all-cause mortality in the patients according to eGFR. (A) eGFR≥30 mL/min/1.73 m^2. (B) eGFR <30 mL/min/1.73 m^2 or dialysis. eGFR, estimated glomerular filtration rate.

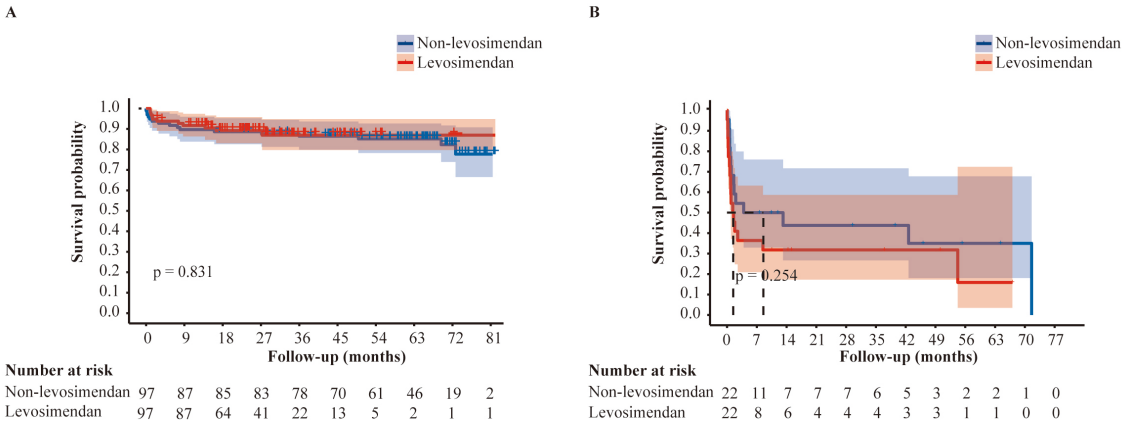

Fig. 3. Kaplan-Meier curve for post-transplant all-cause mortality in the patients according to eGFR after PSM. (A) eGFR ≥30 mL/min/1.73 m^2. (B) eGFR <30 mL/min/1.73 m^2 or dialysis. eGFR, estimated glomerular filtration rate; PSM, propensity score matching.

dialysis, TBIL and eGFR was used to calculate propensity scores. We used univariate Cox proportional hazard model to evaluate the mortality between groups. Statistics were analyzed using two-tailed significance tests, and statistical significance was defined as a p value < 0.05. All statistical analyses were performed using SPSS version 26.0 (IBM Inc., Chicago, IL, USA) and R Studio software version 3.5.3 (SAS Studio Inc., Boston, MA, USA).

Results

Baseline Characteristics

A total of 149 patients were included in levosimendan group, and 225 patients were included in non-levosimendan group (Table 1). Significant differences were identified for variables (recipient BMI, smoking history, LVEF, ARBs, β blocker, dialysis, TBIL, serum creatinine (Scr) and eGFR) across levosimendan group and non-levosimendan group. The baseline laboratory data, such as age, gender, treatment with epinephrine and norepinephrine, and other variables (except for TBIL, Scr and eGFR), did not show any linear trends between the two groups.

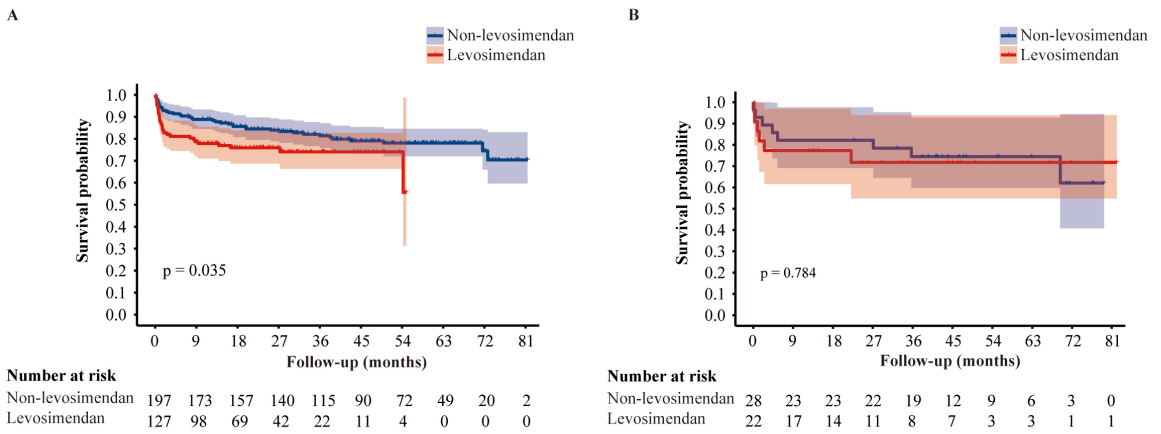

Fig. 4. Kaplan-Meier curve for post-transplant all-cause mortality in the patients according to TBIL. (A) TBIL ≤3.0 mg/Dl. (B) TBIL >3.0 mg/dL. TBIL, total bilirubin.

Associations between Levosimendan Use and Mortality According to eGFR

For the patients with an eGFR ≥30 mL/min/1.73 m^2, total mortality rates were 10.6% in levosimendan group and 17.2% in non-levosimendan group, respectively (HR 0.83, 95% CI 0.43–1.63, p = 0.596). Levosimendan group in-hospital mortality rates were 1.8%, while non-levosimendan group mortality rates were 4.0% (HR 0.44, 95% CI 0.09–2.08, p = 0.300) (Table 2; Fig. 2). After PSM, total mortality rates were 11.3% in levosimendan group and 16.5% in non-levosimendan group, respectively (HR 0.92, 95% CI 0.41–2.04, p = 0.831). Levosimendan group in-hospital mortality rates were 2.1%, while non-levosimendan group mortality rates were 5.2% (HR 0.39, 95% CI 0.08–2.03, p = 0.265).

In addition, there were no significant differences between groups in the 30-day mortality rates, 90-day mortality rates, 180-day mortality rates and 1-year mortality rates (Table 3; Fig. 3).

For the patients with an eGFR <30 mL/min/1.73 m^2, total mortality rates were 72.2% in levosimendan group and 55.6% in non-levosimendan group, respectively (HR 1.75, 95% CI 0.91–3.35, p = 0.093).

Levosimendan group in-hospital mortality rates were 19.4%, while non-levosimendan group mortality rates were 25.9% (HR 0.94, 95% CI 0.33–2.69, p = 0.910). After PSM, total mortality rates were 72.7% in levosimendan group and 63.6% in non-levosimendan group, respectively (HR 1.53, 95% CI 0.74–3.19, p = 0.255). Levosimendan group in-hospital mortality rates were 22.7%, while non-levosimendan group mortality rates were 31.8% (HR 0.88, 95% CI 0.28–2.79, p = 0.832). In addition, there were no significant differences between groups in the 30-day mortality rates, 90-day mortality rates, 180-day mortality rates and 1-year mortality rates.

Associations between Levosimendan Use and Mortality According to TBIL

For the patients with an TBIL ≤3.0 mg/dL, total mortality rates were 25.2% in levosimendan group and 20.8% in non-levosimendan group, respectively (HR 1.66, 95% CI 1.03–2.68, p = 0.037). Levosimendan group in-hospital mortality rates were 5.5%, while non-levosimendan group mortality rates were 6.6% (HR 0.90, 95% CI 0.36–2.25, p = 0.817) (Table 4; Fig. 4). In addition, significant differences were showed between groups in the 90-day mortality rates (p = 0.009), 180-day mortality rates (p = 0.017) and 1-year mortality rates (p = 0.009). After PSM, total mortality rates were 25.5% in levosimendan group and 24.5% in non-levosimendan group, respectively (HR 1.35, 95% CI 0.77–2.35, p = 0.294). Among the in-hospital mortality rates, 6.6% were in levosimendan group and 11.3% were in non-levosimendan group, and no intergroup difference was observed (HR 0.62, 95% CI 0.25–1.59, p = 0.321). There were no significant differences between groups in the 30-day mortality rates, 90-day mortality rates, 180-day mortality rates and 1-year mortality rates after PSM (Table 5; Fig. 5).

For the patients with an TBIL >3.0 mg/dL, total mortality rates were 27.3% in levosimendan group and 28.6% in non-levosimendan group, respectively (HR 1.16, 95% CI 0.40–3.37, p = 0.785). Levosimendan group in-hospital mortality rates were 9.1%, while non-levosimendan group mortality rates were 7.1% (HR 1.32, 95% CI 0.19–9.34, p = 0.785). After PSM, total mortality rates were 27.3% in levosimendan group and 18.2% in non-levosimendan group, respectively (HR 1.71, 95% CI 0.48–6.11, p = 0.409). Levosimendan group in-hospital mortality rates were 9.1%, while non-levosimendan group mortality rates were 4.5% (HR 1.97, 95% CI 0.18–21.72, p = 0.580). In addition, there were no significant differences between groups in the 30-

Table 2. Associations between levosimendan use and mortality according to eGFR.

eGFR	Outcomes	Event (%)		Levosimendan *vs.* non-levosimenda	
		Levosimendan	Non-levosimenda	HR (95% CI)	*p* value
≥30	Patients number	113	198		
	Respiratory complications	74 (65.5)	119 (60.1)	1.26 (0.78, 2.04)	0.347
	Neurological complications	6 (1.9)	12 (3.9)	0.87 (0.32, 2.38)	0.785
	Urological complications	16 (14.2)	11 (5.6)	2.80 (1.25, 6.28)	0.012
	Liver injury	13 (11.5)	7 (3.5)	3.55 (1.37, 9.17)	0.009
	In-hospital mortality	2 (1.8)	8 (4.0)	0.44 (0.09, 2.08)	0.300
	30-day mortality	2 (1.8)	5 (2.5)	0.69 (0.13, 3.57)	0.659
	90-day mortality	6 (5.3)	8 (4.0)	1.31 (0.46, 3.78)	0.616
	180-day mortality	6 (5.3)	12 (6.1)	0.88 (0.33, 2.34)	0.797
	1-year mortality	9 (8.0)	15 (7.6)	0.90 (0.46, 2.41)	0.897
	Total mortality	12 (10.6)	34 (17.2)	0.83 (0.43, 1.63)	0.596
<30 or dialysis	Patients number	36	27		
	Respiratory complications	29 (80.6)	24 (88.9)	0.52 (0.12, 2.22)	0.518
	Neurological complications	6 (16.7)	5 (18.5)	0.88 (0.24, 3.26)	0.848
	Urological complications	19 (52.8)	18 (66.7)	0.56 (0.20, 1.57)	0.270
	Liver injury	7 (19.4)	10 (37.0)	0.41 (0.13, 1.28)	0.124
	In-hospital mortality	7 (19.4)	7 (25.9)	0.94 (0.33, 2.69)	0.910
	30-day mortality	16 (44.4)	8 (29.6)	1.71 (0.73, 3.99)	0.217
	90-day mortality	22 (61.1)	11 (40.7)	1.81 (0.88, 3.73)	0.109
	180-day mortality	24 (66.7)	12 (44.4)	1.76 (0.88, 3.54)	0.113
	1-year mortality	24 (66.7)	12 (44.4)	1.85 (0.92, 3.70)	0.083
	Total mortality	26 (72.2)	15 (55.6)	1.75 (0.91, 3.35)	0.093

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

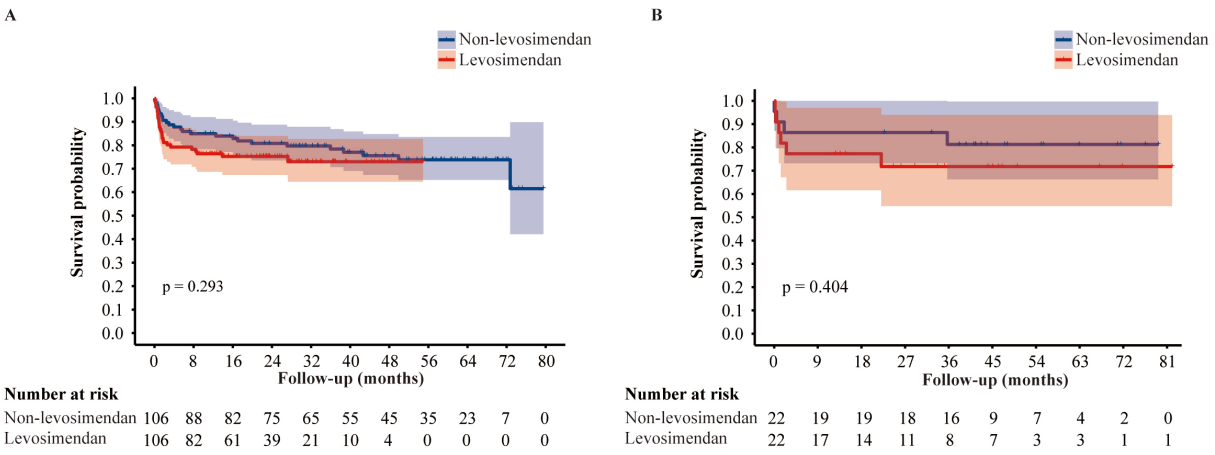

Fig. 5. Kaplan-Meier curve for post-transplant all-cause mortality in the patients according to TBIL after PSM. (A) TBIL ≤3.0 mg/dL. (B) TBIL >3.0 mg/dL. TBIL, total bilirubin; PSM, propensity score matching.

day mortality rates, 90-day mortality rates, 180-day mortality rates and 1-year mortality rates.

Discussion

As far as we know, this is the first study to explore the risk of perioperative complications and mortality in HF patients awaiting HTx who received levosimendan. Peri-

Table 3. Associations between levosimendan use and mortality according to eGFR after PSM.

eGFR	Outcomes	Event (%)		Levosimendan *vs.* non-levosimenda	
		Levosimendan	Non-levosimenda	HR (95% CI)	*p* value
≥30	Patients number	97	97		
	Respiratory complications	65 (54.6)	54 (45.4)	1.62 (0.90, 2.90)	0.106
	Neurological complications	6 (6.2)	6 (6.2)	1.00 (0.31, 3.22)	1.000
	Urological complications	13 (13.4)	3 (3.1)	4.85 (1.34, 17.61)	0.016
	Liver injury	11 (11.3)	2 (2.1)	6.08 (1.31, 28.19)	0.021
	In-hospital mortality	2 (2.1)	5 (5.2)	0.39 (0.08, 2.03)	0.265
	30-day mortality	2 (2.1)	5 (5.2)	0.39 (0.08, 2.00)	0.259
	90-day mortality	6 (6.2)	7 (7.2)	0.84 (0.28, 2.49)	0.750
	180-day mortality	6 (6.2)	8 (8.2)	0.74 (0.26, 2.12)	0.568
	1-year mortality	8 (8.2)	10 (10.3)	0.79 (0.31, 1.99)	0.612
	Total mortality	11 (11.3)	16 (16.5)	0.92 (0.41, 2.04)	0.831
<30 or dialysis	Patients number	22	22		
	Respiratory complications	15 (68.2)	20 (90.9)	0.21 (0.04, 1.18)	0.077
	Neurological complications	2 (9.1)	5 (22.7)	0.34 (0.06, 1.98)	0.230
	Urological complications	10 (45.5)	16 (72.7)	0.31 (0.09, 1.10)	0.070
	Liver injury	3 (13.6)	9 (40.9)	0.23 (0.05, 1.01)	0.051
	In-hospital mortality	5 (22.7)	7 (31.8)	0.88 (0.28, 2.79)	0.832
	30-day mortality	10 (45.5)	7 (31.8)	1.63 (0.62, 4.30)	0.319
	90-day mortality	14 (63.6)	10 (45.5)	1.69 (0.75, 3.81)	0.207
	180-day mortality	14 (63.6)	11 (50.0)	1.55 (0.70, 3.41)	0.279
	1-year mortality	15 (68.2)	11 (50.0)	1.66 (0.76, 3.62)	0.202
	Total mortality	16 (72.7)	14 (63.6)	1.53 (0.74, 3.19)	0.255

PSM: age, sex, BMI, smoking history, LVEF, ARBs, β blocker, dialysis, TBIL, eGFR.

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; PSM, propensity score matching; BMI, body mass index; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blockers; TBIL, total bilirubin.

operative complications and mortality rates in the patients who received levosimendan had a similar risk to those patients who received dobutamine/dopamine. Moreover, no difference in terms of mortality was observed between the two groups even in the patients with severe hepatic or renal impairment. These results suggest that levosimendan may be useful for the treatment of patients with severe hepatic or renal problems awaiting HTx.

Hepatic or renal impairment were highly prevalent in patients with HF due to the decline of cardiac output [11–14]. Consequently, protecting other organs may be equally or even more important than maintaining cardiac function in treatment of patients who waiting for HTx. The advantages of levosimendan have been widely reported in a number of studies [15–18]. In contrast to catecholamines, levosimendan has a different mechanism of action [19]. Levosimendan increases the sensitivity of cardiomyocytes to intracellular calcium level, resulting in an increase in myocardial contractility at minimal myocardial oxygen demand [20,21]. Due to its calcium-sensing properties, levosimendan may be more beneficial in relaxing the myocardium compared to catecholamines during diastole [22]. Levosimendan can effectively protect liver and kidney functions while preserving heart function, regardless of the presence of hepatic or renal impairment before it is used [23–28]. Partly of these protective effects due to their anti-inflammatory and anti-apoptotic properties [29,30].

Nevertheless, it is interesting to note that severe impairment of hepatic or renal function will lead to slower drug metabolism, and prolonged clearance time of active metabolites will easily lead to drug overdose, and then induce adverse reactions such as headache, hypotension, hypokalemia and malignant arrhythmia [31–35]. Even though there are individual case reports describing the application of levosimendan, severe hepatic or renal impairment are currently still considered as contraindications for levosimendan [36,37]. Regrettably, levosimendan has rarely been studied in patients with severe hepatic or renal impairment, and it has not been proved to be safe and effective for such patients to date. Therefore, for patients with HF and severe hepatic or renal impairment, if there is sufficient evidence to support that the therapeutic effect of levosimendan is not inferior to that of levosimendan applied to patients with HF and severe hepatic or renal impairment, it will be of great significance for broadening the therapeutic scope of levosimendan and for patients waiting for HTx.

Our findings are in line with the results have shown in previous studies [38,39]. In a multicenter retrospective study, HF patients were divided into levosimendan group and dobutamine group according to the drug treatment re-

Table 4. Associations between levosimendan use and mortality according to TBIL.

TBIL	Outcomes	Event (%)		Levosimendan *vs.* non-levosimenda	
		Levosimendan	Non-levosimenda	HR (95% CI)	*p* value
≤3.0 mg/dL	Patients number	127	197		
	Respiratory complications	86 (67.7)	124 (62.9)	1.24 (0.77, 1.98)	0.380
	Neurological complications	11 (8.7)	13 (6.6)	1.34 (0.58, 3.10)	0.490
	Urological complications	32 (25.2)	27 (13.7)	2.12 (1.20, 3.75)	0.010
	Liver injury	16 (12.6)	14 (7.1)	1.88 (0.89, 4.01)	0.100
	In-hospital mortality	7 (5.5)	13 (6.6)	0.90 (0.36, 2.25)	0.817
	30-day mortality	15 (11.8)	11 (5.6)	2.18 (1.00, 4.74)	0.050
	90-day mortality	23 (18.1)	16 (8.1)	2.35 (1.24, 4.45)	0.009
	180-day mortality	24 (18.9)	19 (9.6)	2.08 (1.14, 3.80)	0.017
	1-year mortality	28 (22.0)	22 (11.2)	2.12 (1.21, 3.70)	0.009
	Total mortality	32 (25.2)	41 (20.8)	1.66 (1.03, 2.68)	0.037
>3.0 mg/dL	Patients number	22	28		
	Respiratory complications	17 (77.3)	19 (67.9)	1.61 (0.45, 5.76)	0.463
	Neurological complications	1 (4.5)	4 (14.3)	0.29 (0.03, 2.76)	0.279
	Urological Complications	3 (13.6)	2 (7.1)	2.05 (0.31, 13.51)	0.454
	Liver injury	4 (18.2)	3 (10.7)	1.85 (0.37, 9.31)	0.455
	In-hospital mortality	2 (9.1)	2 (7.1)	1.32 (0.19, 9.34)	0.785
	30-day mortality	3 (13.6)	2 (7.1)	1.93 (0.32, 11.55)	0.471
	90-day mortality	5 (22.7)	3 (10.7)	2.21 (0.53, 9.27)	0.277
	180-day mortality	5 (18.5)	5 (17.9)	1.35 (0.39, 4.67)	0.635
	1-year mortality	5 (18.5)	5 (17.9)	1.35 (0.39, 4.67)	0.635
	Total mortality	6 (27.3)	8 (28.6)	1.16 (0.40, 3.37)	0.785

HR, hazard ratio; CI, confidence interval; TBIL, total bilirubin.

ceived [38]. The results showed that there were no significant differences in mortality rate at 30, 90, and 180 days after the cohort entry date between the levosimendan and dobutamine groups, or between subgroups of patients with an eGFR $\geq$30 mL/min/1.73 m^2 and eGFR <30 mL/min/1.73 m^2 or on dialysis. The results were consistent before and after PSM. Different from that, our research object is the patients waiting for HTx and their outcomes after HTx. The HF of these patients has developed to a late stage, and their general conditions, including cardiac function, hepatic or renal function, are often worse than those of ordinary HF patients. In addition, our follow-up time was relatively long, far more than 180 days. Longer follow-up time can better evaluate the impact of levosimendan on long-term survival. Moreover, the outcomes we focused on included not only short-term and long-term survival, but also perioperative complications, which were also closely related to the evaluation of the protection of levosimendan against systemic organs. Our results further confirm the efficacy and safety of levosimendan in patients with severe hepatic or renal impairment.

In clinical work, dobutamine/dopamine is one of the commonly used cardiotonic drugs. Therefore, patients in the levosimendan group often received dobutamine/dopamine treatment before receiving levosimendan treatment. This suggests that the patients were poor responders to dobutamine/dopamine. Patients in the levosimendan group had higher BMI and higher rate of smoking history in the index admission. Dialysis and therapeutic drugs included angiotensin-converting enzyme inhibitors (ACEI) and ARBs were more frequently used in the levosimendan group. In addition, there were higher level of TBIL and Scr, and lower level of LVEF and eGFR in the levosimendan group. To minimize bias, we calculated propensity scores according to the above important variables. The results showed that patients in the levosimendan group with an eGFR $\geq$30 mL/min/1.73 m^2 were suffered from higher rate of perioperative complications included urological complications and liver injury, statistical differences remained after PSM. For the patients with TBIL $\leq$3.0 mg/dL, a higher mortality rate was showed in the levosimendan group compare with that in the non-levosimendan group, while no significant difference was found between the two groups after PSM. There is a possibility that patients in the levosimendan group are sicker than those in the non-levosimendan group. Another possible reason is the differences in associated variables between groups. Certainly, for the patients with an eGFR <30 mL/min/1.73 m^2 or TBIL >3.0 mg/dL, there was no significantly statistic difference between the two groups in terms of perioperative complications and mortality rate, before and after PSM. Our results suggest that levosimendan did not increase mortality even in these patients awaiting HTx with severe hepatic or renal impairment.

Table 5. Associations between levosimendan use and mortality according to TBIL after PSM.

TBIL	Outcomes	Event (%)		Levosimendan *vs.* non-levosimenda	
		Levosimendan	Non-levosimenda	HR (95% CI)	*p* value
≤3.0 mg/dL	Patients number	106	106		
	Respiratory complications	75 (70.8)	68 (64.2)	1.35 (0.76, 2.41)	0.305
	Neurological complications	9 (8.5)	7 (6.6)	1.31 (0.47, 3.66)	0.604
	Urological complications	29 (27.4)	19 (17.9)	1.73 (0.90, 3.32)	0.103
	Liver injury	12 (11.3)	10 (9.4)	1.23 (0.51, 2.97)	0.653
	In-hospital mortality	7 (6.6)	12 (11.3)	0.62 (0.25, 1.59)	0.321
	30-day mortality	13 (12.3)	7 (6.6)	1.91 (0.76, 4.78)	0.169
	90-day mortality	21 (19.8)	12 (11.3)	1.84 (0.91, 3.75)	0.091
	180-day mortality	22 (20.8)	15 (14.2)	1.56 (0.81, 3.00)	0.187
	1-year mortality	25 (23.6)	16 (15.1)	1.66 (0.89, 3.11)	0.114
	Total mortality	27 (25.5)	26 (24.5)	1.35 (0.77, 2.35)	0.294
>3.0 mg/dL	Patients number	22	22		
	Respiratory complications	17 (77.3)	16 (72.7)	1.28 (0.32, 5.01)	0.728
	Neurological complications	1 (4.5)	3 (13.6)	0.30 (0.03, 3.15)	0.317
	Urological complications	3 (13.6)	2 (9.1)	1.58 (0.24, 10.52)	0.637
	Liver injury	4 (18.2)	2 (9.1)	2.22 (0.36, 13.62)	0.388
	In-hospital mortality	2 (9.1)	1 (4.5)	1.97 (0.18, 21.72)	0.580
	30-day mortality	3 (13.6)	2 (9.1)	1.50 (0.25, 8.98)	0.657
	90-day mortality	5 (22.7)	3 (13.6)	1.71 (0.41, 7.17)	0.462
	180-day mortality	5 (22.7)	3 (13.6)	1.71 (0.41, 7.17)	0.462
	1-year mortality	5 (22.7)	3 (13.6)	1.71 (0.41, 7.17)	0.462
	Total mortality	6 (27.3)	4 (18.2)	1.71 (0.48, 6.12)	0.409

PSM: age, sex, BMI, smoking history, LVEF, ARBs, β blocker, dialysis, TBIL, eGFR.

HR, hazard ratio; CI, confidence interval; TBIL, total bilirubin; PSM, propensity score matching; BMI, body mass index; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate.

Our retrospective study included a considerable number of HTx patients, focusing on the patients waiting for HTx with severe hepatic or renal impairment, and focusing on the perioperative complications and short-term and long-term mortality of patients after transplantation. The current study has important implications for public health and clinical practice. With the progress of drug application research, patients with severe hepatic or renal impairment waiting for HTx are not contraindications for levosimendan. We may be able to open a new door with levosimendan when dopamine isn't working. For patients waiting for HTx, more experienced treatment can better maintain cardiac function and systemic organ function, reduce the mortality of patients during the waiting period, and improve the outcome of HTx. Our research results can provide direction and focus for future prospective clinical research.

There may be some limitations in this study. Firstly, the retrospective nature of the study may cause selection bias in the study. Patients in the levosimendan group often have a history of medication with poor effects of dopamine. Compared with the non-levosimendan group, the situation of patients is much more complicated, which may be related to adverse outcomes. In addition, the application of levosimendan is more based on the judgment of clinicians. Therefore, the results of the study might not fully reflect the outcome of levosimendan in patients with severe liver or kidney impairment waiting for HTx. Secondly, since retrospective studies cannot control the integrity of medical records like prospective studies, in order to minimize the impact of confounding factors on the results, we used PSM to screen the test group and the control group, so that the selected research objects are comparable in clinical characteristics (potential confounding factors). However, despite this, the number of matched cases is still small, which may have some impact on the research results. Thirdly, the data of the study are from a single center, which may limit the universality of the study results. Fourth, although we included the data of heart transplant patients in our center from 2015 to 2020, the sample size is still small, especially after PSM, and the impact on the research results is still unknown.

Conclusions

In summary, this study demonstrated similar perioperative complications and mortality rates between the awaiting HTx patients with severe hepatic or renal impairment

who received levosimendan and the patients who received dobutamine/dopamine. Severe hepatic or renal impairment are not necessarily contraindicated for levosimendan in these patients.

Abbreviations

ATP, adenosine triphosphate; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TBIL, total bilirubin; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; SD, standard deviation; PSM, propensity score matching; ARBs, angiotensin receptor blockers; Scr, serum creatinine; HR, hazard ratio; CI, confidence cardiomyopathy; PAH, pulmonary arterial hypertension; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; WBC, white blood count; ALT, alanine aminotransferase; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; BUN, blood urea nitrogen; INR, international normalized ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I.

Availability of Data and Materials

The data that support the findings of this study are available from the Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Author Contributions

QZ performed for the study design, drafted and revised the manuscript. HL wrote the manuscript and interpreted data. QG contributed to the data collection and database organization. CL and TX participated in the statistical analysis of the data. JZ, GW, JS and ND interpreted the results. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The only source of graft for heart transplantation in China since January 1st, 2015, is donation after brain death. All donor grafts are allocated in accordance with Chinese law via the China Organ Transplant Response System. This study protocol has been approved by the Ethics Committee on Human Research at Union Hospital, Tongji Medical College of Huazhong University of Science and Technology (IORG No: IORG0003571).

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Conflict of Interest

The authors declare no conflict of interest.

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