의학박사 학위논문

간이식 환자에서 수술 전 대동맥 확장도의 특징과 수술 후 사망률에 미치는 영향

Characteristics of aortic distensibility and its effect on all-cause mortality after liver transplantation

울산대학교 대학원

의 학 과

장 동 민

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지도교수 황 규 삼

이 논문을 의학박사 학위 논문으로 제출함

2018년 2월

울산대학교 대학원
의 학 과
장 동 민

장동민의 의학박사학위 논문을 인준함

심사위원 송 준 걸 인

심사위원 김 상 현 인

심사위원 신 원 정 인

심사위원 김 성 훈 인

심사위원 황 규 삼 인

울 산 대 학 교 대 학 원

2018 년 2 월

Abstract

Introduction: Aortic distensibility (AD) is one of the earliest detectable manifestations of structural alterations of the aorta in various conditions. Patients with impaired liver function had characteristic properties of blood vessels, such as systemic vasodilation and decrease of systemic vascular resistance. This study investigated characteristics of AD in liver transplantation (LT) candidates, and its effect on all-cause mortality after LT.

Patients and methods: In this study, a total of 646 consecutive LT candidates were included. AD was measured retrospectively by B-mode transthoracic echocardiography on parasternal long-axis view using "image-J" software. LT candidates were categorized according to low (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) and high ($\geq 3.13$ $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) AD groups. Survival analysis was performed using Kaplan-Meier method. All-cause mortality based on AD value was investigated using Cox proportional hazard regression model. To investigate the risk factors related to low AD in LT candidates, multivariate logistic regression was performed.

Results: Over 47-month median follow-up period, 94 patients (13.9%) expired after LT. LT recipients with low AD (n = 254) group had higher mortality rate than high AD (n = 422) group (29.5% *vs.* 4.5%, Log-rank p <0.001), and was independently associated with risk of mortality (hazard ratio, 6.55; 95% CI, 3.99−10.76; p <0.001). The risk factors related low AD were age, body mass index, mean arterial pressure, left ventricular ejection fraction, QTc interval, and C-reactive protein.

Conclusions: This study suggested that LT candidates with low AD (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) had significantly higher risk in all-cause mortality, and proposes that non-invasive and relatively simple measurement of AD by echocardiography may serve an additional prognostic index for survival after LT.

Key words: aortic distensibility, liver transplantation, mortality

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Abbreviations

LT: liver transplantation

CRP: C-reactive protein

BNP: B-type natriuretic peptide

CTP: Child-Turcotte-Pugh

MELD: model for end-stage liver disease

AS: aortic strain

AD: aortic distensibility

ASI: aortic stiffness index

LV: left ventricle

CRP: C-reactive protein

LVEF: left ventricle ejection fraction

ESV: end systolic volume

EDV: end diastolic volume

E: early mitral inflow velocity

A: late mitral inflow velocity

DT: deceleration time

s′: systolic mitral valve annular velocity

e′: early diastolic mitral valve annular velocity

a′: late diastolic mitral valve annular velocity

TDI : tissue Doppler imaging

ADD: aortic diastolic diameter

ASD: aortic systolic diameter

SBP: systolic blood pressure

DBP: diastolic blood pressure

SV: stroke volume

TPR: total peripheral resistance

CO: cardiac output

ROC curve: receiver operating curve

HR: hazard ratio

AUC: area under the curve

AGEs: advanced glycation end-products

IL-6: interleukin-6

TNF-α: tumor necrosis factor-α

Introduction

The aorta is the first gateway for the transmission of blood containing large quantity of oxygen and nutrients through the whole body. Because the aorta is thought to be a starting point for systemic circulation, it plays a crucial role in hemodynamic aspects. Decreased aortic distensibility impairs the ability of the aorta which regulate the blood ejected by left ventricle (LV), resulting in excessive pulsatile afterload which may promote LV remodeling and deteriorate cardiac function[1]. Aortic distensibility (AD) is one of the earliest detectable manifestations of adverse structural and functional alterations within the aorta[2]. Decreased AD reflects increased mechanical tension of the aortic wall, and it is known as an important parameter of increased LV load, a cardiovascular events and atherosclerotic disease[3-5]. In addition, decreased AD is known to prediction of cardiovascular events and all-cause mortality in general population and population with ESRD, hypertension, and diabetes[6].

Deterioration of liver function was also associated with the cardio-vascular system. As live function decreases, the cirrhotic patients will demonstrate cardiovascular abnormalities which are characterized by a hyperdynamic circulation such as increased cardiac output and heart rate accompanied by low systemic vascular resistance[7]. As a result, cardiac remodeling and deterioration of cardiac function also occur, which is known as *"cirrhotic cardiomyopathy"*[7, 8]. In addition, patients with impaired liver function had characteristic properties of blood vessels, such as systemic vasodilation and decrease of systemic vascular resistance, which results in reduction of central blood volume and the hyperdynamic circulation[9]. However, no study has conducted in LT candidates on the role of aorta which is crucial hemodynamic organ immediately following the heart.

Therefore, this study mainly focused in the aorta which is the beginning of the systemic circulation, and the aim of this study were to investigate characteristics of AD in LT candidates and its effect on all-cause mortality and graft failure after LT.

Patients and methods

Study population

Between September 2011 and December 2013, 916 consecutive patients who underwent LT at Asan Medical Center were included, and the data were retrospectively analyzed after receiving approval from the local institutional review board (protocol number 2017-0592).

Peri-operative evaluation and baseline characteristics

All LT candidates had performed routine preoperative evaluation. Medical history and physical examination included diabetes, hypertension, variceal bleeding, intractable ascites and smoking history. Current medications were investigated including beta-blockade and diuretics. Computed tomography was performed for evaluating coronary arteries. A baseline corrected QT (QTc) interval was measured on preoperative electrocardiography. Biochemical laboratory tests included measuring hemoglobin, platelet, prothrombin time, creatinine, glucose, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, C-

reactive protein (CRP), and B-type natriuretic peptide (BNP). Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD) score were evaluated to identify the severity of liver function. Donor- and operation-related variables included donor type (living or deceased donor), antibody (ABO) compatibility, the amount of blood transfused during surgery, ischemic time, graft-to-recipient body weight ratio, and total anesthetic time.

Echocardiographic data

Two-dimensional and Doppler transthoracic echocardiography were performed by an experienced sonographer, and attending staff cardiologists interpreted and confirmed them, and the entire process was recorded on the computer. Left ventricular internal dimension, the thickness of left ventricular posterior wall and interventricular septum, and the size of the left atrium and ascending aorta were measured. The left ventricle ejection fraction (LVEF), end-systolic volume (ESV) and end-diastolic volume (EDV) were obtained using the Teichholz M-mode method along the parasternal long-axis view[10]. LV mass was determined by the M-mode derived cubed method along the parasternal long-axis view, and the LV mass index

was calculated as LV mass divided by the body surface area. Early and late mitral inflow velocity (E and A), the deceleration time (DT) of the early mitral inflow velocity and E/A ratio were measured using pulsed-wave Doppler. Systolic mitral valve annular velocity (s´) and early and late diastolic mitral valve annular velocity (e´ and a´) were measured using tissue Doppler imaging (TDI), and E/e´ ratio was calculated.

Aorta related variables from echocardiographic measurements

To measure aortic strain (AS), aortic distensibility (AD) and aortic stiffness index (ASI), we captured the aorta from real-time B-mode echocardiography on parasternal long-axis view by commercially available program "oCam" (version 418; OhSoft, Inc., Seoul, Korea). From the captured image, the size of the aortic diameter was measured at a level of 3 cm above the aortic valve (Fig. 1) using the "Image J" software, which is an open tool for scientific image analysis, developed at the National Institutes of Health (https://imagej.nih.gov/ij). Aortic diastolic diameter (ADD) was measured at the peak of QRS complex (end-diastolic period) and systolic diameter (ASD) was measured at the time of full opening of the aortic valve[11,

[12]. ADD and ASD were measured twice by the same investigator; the mean value of coefficient of variation ([SD/mean] x 100) were 0.29% and 0.25%, respectively[13]. The frequently used formulas to calculate the parameters were as follows;

$$\text{Aortic strain (AS, \%)} = \frac{\text{ASD} - \text{ADD}}{\text{ADD}} \times 100$$

$$\text{Aortic distensibility } (\text{cm}^2 \cdot \text{dyn}^{-1} \cdot 10^{-6}) = 2 \times \frac{\text{AS}}{\text{SBP} - \text{DBP}}$$

$$\text{Aortic stiffness index (pure number)} = \frac{\ln(\text{SBP}/\text{DBP})}{\text{AS}}$$

The AS was relative change of diameter, and the AD was relative diameter change for a pressure increment during cardiac cycle. The ASI was ratio of logarithm of systolic/diastolic pressures to relative change of diameter[2, 4, 11, 14, 15]. Systolic (SBP) and diastolic blood pressure (DBP) were obtained at the brachial artery by a sphygmomanometry immediately before performing transthoracic echocardiography, and the difference of pressure between SBP and DBP was the pulse pressure.

To estimate total peripheral resistance (TPR), we calculated cardiac output (CO) as EDV−ESV (stroke volume, SV) and SV multiplied by heart rate. TPR was subsequently calculated as mean arterial pressure divided by CO. For these formulas, all parameters were obtained from transthoracic echocardiography noninvasively.

Outcome and follow-up

All LT candidates were followed for at least three years and up to 5.5 years from the day of LT until the last day of follow-up (December 31, 2016). Entire data was collected from electronic medical records and our database, which was updated periodically by the Asan Organ Transplantation Center. Outcomes included one-year and overall period all-cause mortality and graft failure throughout the entire follow-up period. The graft failure was defined as a recipient undergoing re-transplantation or death from any cause, whichever was first[16].

Statistical analysis

For descriptive analysis, the categorical variables are expressed as numbers and percentages and were compared using the X^2 test or Fisher's exact test. Continuous variables are shown as the mean ± standard deviation or median and interquartile range. This study estimated the statistical significance of the biochemical laboratory, intraoperative data, and preoperative echocardiographic parameters using the t-test or Mann-Whitney U test, as appropriate.

For time-to-event outcome (graft failure and mortality rate), LT candidates were categorized into tertile of AD. We analyzed other variables according to the tertile of AD by one-way ANOVA and Kruskal-wallis test with Tukey post hoc tests for continuous data, and by Fisher's exact test for categorical data. Three groups were analyzed for all-cause mortality and graft failure by the Kaplan-Meier method using the Log-rank test. Potential confounders such as clinical parameter (sex, age, BMI, MELD score, mean arterial pressure, QTc interval), medical history (hypertension, diabetes mellitus, coronary disease, and current use of beta-blocker and diuretics), surgical factor (deceased donor and ABO incompatible living

donor), and biochemical laboratory data (prothrombin time, creatinine, total bilirubin, CRP, BNP) and echocardiographic parameter (LVEF, tissue Doppler s′, E/A, E/e′, DT, and AD) were included in univariate analysis on all-cause mortality. We also categorized to two groups according to low (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) and high (≥3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) AD. Then, univariate and multivariate analysis were performed using Cox proportional hazard regression model to estimate adjusted hazard ratio (HR). To investigate the risk factors related to low AD in LT candidates, multivariate logistic regression was performed with the variables used in multivariate logistic regression.

Here, p <0.05 is considered statistically significant. We performed all statistical analysis and graphical representations using R 3.2.3 (http://www.r-project.org/), Prism (version 7; GraphPad Software, Inc., La Jolla, CA), and SAS (version 9.4: SAS Institute inc., Cary, NC).

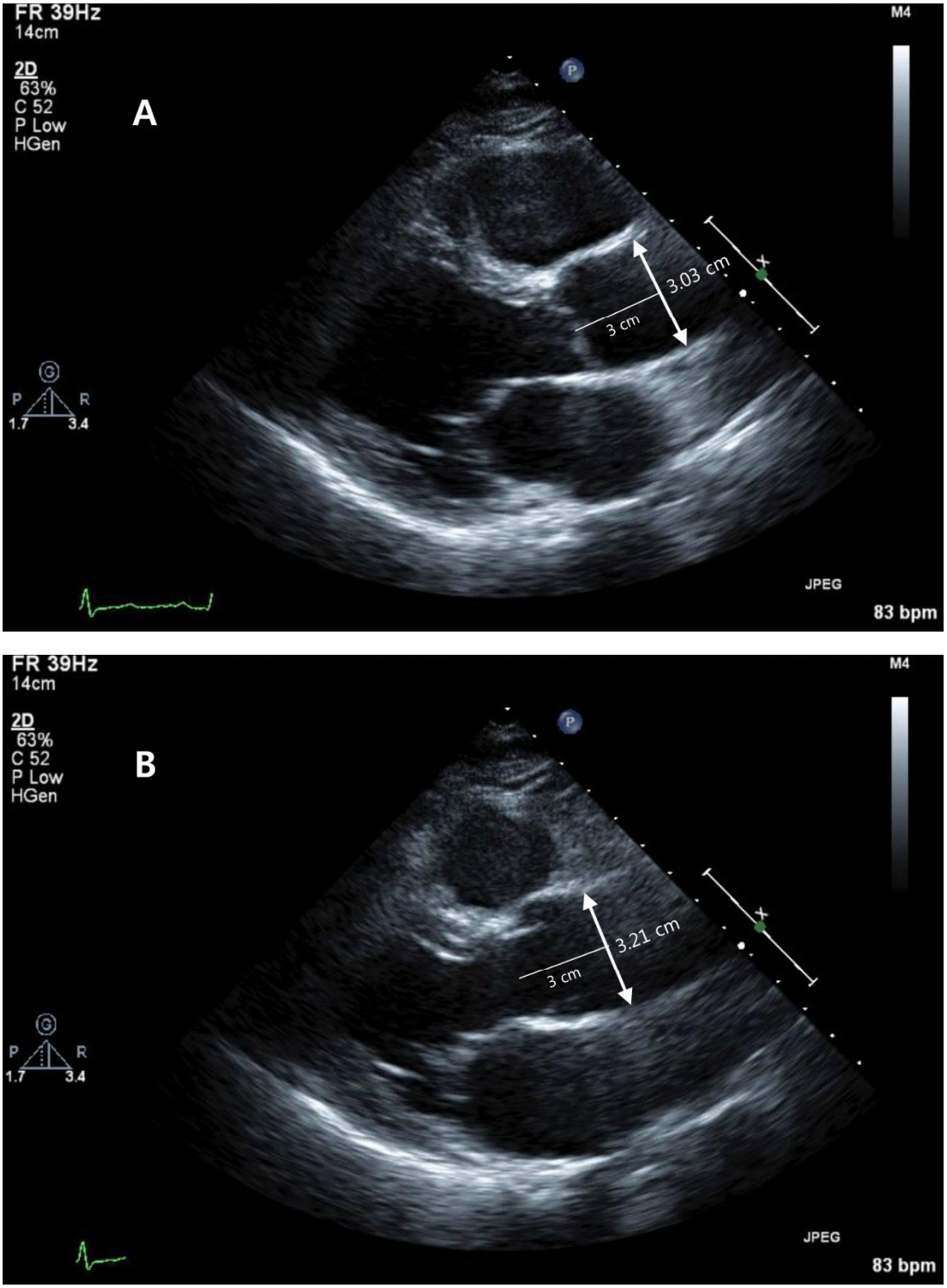

Fig. 1. B-mode transthoracic echocardiography on parasternal long-axis view. (A) is end-diastolic period (the peak of QRS complex), and (B) is the time of full opening of the aortic valve. The size of the aortic diameter was measured at a level of 3 cm above the aortic valve (white solid line). Two white arrows indicate internal edges of the aorta.

Results

A total of 240 patients were excluded for the following reasons: pediatric patients (age <18 years, n = 37), re-transplantation after initial graft failure (n = 37), valvular heart disease more than moderate grade regurgitation (n = 3), atrial fibrillation (n = 6), left ventricular ejection fraction <55% (n = 2), multi-organ transplantation (n = 3), transplantation combined with another operation (n = 3), or incomplete preoperative data (n = 149). A total of 676 patients were included in final analysis, and pre-transplant clinical and echocardiographic data were evaluated. Of these patients, 60 patients underwent deceased donor LT and 616 patients underwent living-donor LT. The median hospital stay and intensive care unit stay after surgery were 24 days and 3 days, respectively. Table 1 shows an overview of baseline characteristics of the 676 LT candidates.

Associations of aortic distensibility with graft failure or all-cause mortality after liver transplantation

During a 47-month median follow-up period (IQR, 40−54 months), 101 patients (14.9%) had graft failure (death, n = 94; re-transplantation, n = 9), and 94 patients (13.9%) expired after LT. 49 patients (7.2%) had graft failure, and 44 patients (6.5%) expired within one year after LT. The causes of mortality were recurrent cancer (n = 47, 50%), graft failure (n = 13, 13.9%), respiratory failure (n = 11, 11.7%), sepsis (n = 10, 10.6%), massive bleeding after LT (n = 3, 3.2%), cardiac complication (n = 2, 2.1%), neurologic complication (n = 2, 2.1%), and unknown (n = 6, 6.4%).

In survival analysis, LT candidates were categorized into three groups based on tertile of AD: lowest tertile (≤2.77 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$, n = 225), middle tertile (2.77−5.11 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$, n = 226), and highest tertile (≥5.11 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$, n = 225) (Table 2). Graft failure rates were 32.0% for lowest tertile, 10.6% for middle tertile, and 2.2% for highest tertile (Fig. 2, Log-rank p <0.001). All-cause mortality rates were 31.1% for lowest tertile, 8.8% for middle tertile, and 1.7 % for highest tertile (Fig. 2, Log-rank p <0.001). The cutoff values of the AD on graft failure and all-cause mortality were obtained by receiver operating curve (ROC

curve), and cutoff value was 3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ of AD in both graft failure (AUC, 0.761, sensitivity: 76.2%, specificity: 69.4) and all-cause mortality (AUC, 0.771, sensitivity: 79.8%, specificity: 69.4) (Fig.3). When LT candidates were categorized into high (≥3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$, n = 422) and low (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$, n = 254) AD groups (Table 3), all-cause mortality (n = 75, 29.5% vs. n = 19, 4.5%) and graft failure rate (n = 77, 31.3% vs. n = 24, 5.7%) were significantly higher in low AD group (Log rank test, p <0.001) (Fig. 4).

On univariate analysis, low AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ (hazard ratio (HR), 7.07; p <0.001), preoperative serum CRP ≥ 0.81 mg/dl (HR, 2.42; p = 0.001), and Tissue Doppler s´ (HR, 0.88; p = 0.048) were significantly associated with all-cause mortality (Table 4). Echocardiographic parameters (LVEF, E/A, E/e', DT) which were representing cardiac function, and clinical parameter (age, sex BMI, MBP, history of diabetes mellitus, hypertension, coronary disease, smoking, use of beta-blocker, and use of diuretics) which were correlated with AD were not significantly associated with all-cause mortality. On multivariate analysis adjusted by potential confounders, low AD (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) was

independently associated with all-cause mortality (HR, 6.55; p <0.001) in the entire population (Table 4). Other factors independently related to all-cause mortality were CRP ≥0.81 mg/dl (HR, 2.41; p <0.001), creatinine (HR, 1.24; p = 0.003), and Tissue Doppler s´ (HR, 0.87; p = 0.024) (Table 4). Within 1-year after LT, AD of <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ was also independently associated with all-cause mortality (HR, 5.08; p <0.001) (Table 5). CRP ≥0.81 mg/dl and MELD score ≥25 were other factors independently associated with all-cause mortality within one-year after LT (Table 5).

The risk factors related to low AD (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) in LT candidates were age (odds ratio (OR), 1.030; p = 0.003), body mass index (OR, 1.051; p = 0.043), mean arterial pressure (OR, 1.025; p = 0.001), LVEF (OR, 0.939; p = 0.001), QTc interval (OR, 1.006; p = 0.020), and CRP (OR, 1.200; p = 0.004) (Table 6).

Table 1. Baseline characteristics of patients underwent transplantation.

Total number of patients	n = 676
Preoperative characteristics of patients	
Age, years	53 (48−58)
Sex, male	523 (77.3)
Weight, kg	65 (58−73)
Height, cm	167 (161−172)
Body mass index, kg/m^2	23.7 (21.5−26.0)
MELD score	12 (9−19)
Child-Turcotte-Pugh classification (A/B/C)	214 (31.7)/263 (38.9)/199 (29.4)
Etiology of liver disease (may overlap with other diseases)	
Hepatocelluar carcinoma	352 (52.0)
Hepatitis B virus	436 (64.5)
Hepatitis C virus	52 (7.6)
Alcohol	117 (17.3)
Others	87 (12.8)
QTc interval, ms	449 (428−469)
Medical history	
Hypertension	91 (13.4)
Diabetes mellitus	147 (21.7)
Current use of beta-blocker	158 (23.3)
Current use of diuretics	212 (31.3)
History of variceal bleeding	189 (27.9)
Intractable ascites	153 (22.6)
Hepatic encephalopathy	132 (19.5)
Current smoker	69 (10.2)
Preoperative biochemical laboratory variables	
Hemoglobin, g/dl	10.8 (9.4−12.5)
Platelet, x 10^3/mm^3	62 (40−91)
Prothrombin time, INR	1.36 (1.16−1.67)
Total bilirubin, mg/dl	1.9 (1.1−5.0)
Albumin, g/dl	3.1 (2.7−3.5)
Aspartate aminotransferase, IU/L	38 (28−61)
Alanine aminotransferase, IU/L	24 (16−38)
Glucose, g/dl	110 (95−138)
Creatinine, mg/dl	0.76 (0.62−0.93)
C-reactive protein, mg/dl	0.29 (0.11−0.90)
B-type natriuretic peptide, pg/ml	66 (33−125)
Donor- and operation-related variables	
Donor type (deceased/living single/living dual)	60 (8.8)/570 (84.4)/46 (6.8)
ABO incompatible living donor	145 (21.4)
Cold ischemic time, min	87 (70−106)
Warm ischemic time, min	40 (34−50)
Graft-recipient weight ratio, %	1.13 (0.97−1.35)
Total anesthetic time, min	807 (724−889)

Data are expressed as n (%) or median (25th−75th percentiles). MELD, model for end-stage liver disease; INR, international normalized ratio.

Table 2. Clinical and echocardiographic parameters by tertiles of aortic distensibility.

Aortic distensibility, $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	***Lowest tertile (≤2.77) (n = 225)***	***Middle tertile (2.77−5.11) (n = 226)***	***Highest tertile (≥5.11) (n = 225)***	***p value***
Preoperative characteristics of patients				
Age, years	54 (50−59)	53 (47−58)	53 (47−57)	0.114
Sex, male	173 (76.8)	179 (79.2)	171 (76.0)	0.703
Body mass index, kg/m^2	24.0 (21.6−26.9)	23.9 (21.6−26.1)	23.2 (21.3−25.1)	0.088
MELD score	13 (9−19)	12 (9−19)	12 (9−19)	0.897
Systolic blood pressure, mmHg	111 (100−122)	109 (100−121)	104 (95−112) *†	<0.001
Diastolic blood pressure, mmHg	68 (62−78)	70 (63−76)	67 (60−74) *†	0.035
Heart rate, beats/min	69 (63−79)	70 (61−80)	66 (59−76) *†	0.009
Etiology of liver disease (may overlap with other diseases)				
Hepatocelluar carcinoma	123 (54.6)	121 (53.5)	108 (48.0)	0.317
Hepatitis B virus	144 (64.0)	154 (68.1)	138 (61.3)	0.314
Hepatitis C virus	14 (6.2)	15 (6.4)	23 (10.2)	0.216
Alcohol	39 (17.3)	35 (15.4)	43 (19.1)	0.596
Others	34 (15.1)	27 (11.9)	26 (11.5)	0.198
QTc interval, ms	452 (429−473)	447 (425−467)	446 (428−465)	0.172
Medical history				
Hypertension	38 (16.8)	34 (15.0)	19 (8.4) *	0.022
Diabetes mellitus	54 (24.0)	49 (21.6)	44 (19.5)	0.520
Current use of beta-blocker	48 (21.3)	51 (22.5)	59 (26.2)	0.444
Current use of diuretics	75 (33.3)	68 (30.0)	69 (30.6)	0.731
History of variceal bleeding	52 (23.1)	64 (28.3)	73 (32.4)	0.087
Intractable ascites	52 (23.1)	51 (22.5)	50 (22.2)	0.728
Hepatic encephalopathy	51 (22.6)	49 (21.6)	32 (14.2)	0.123
Current smoker	18 (8.0)	34 (15.0)	17 (7.5) †	0.013

Table 2, continued

Preoperative biochemical laboratory variables				
Hemoglobin, g/dl	10.7 (9.2−12.4)	10.8 (9.4−12.6)	10.8 (9.5−12.4)	0.507
Platelet, x 10^3/mm^3	61 (41−92)	67 (41−96)	59 (40−85)	0.260
Prothrombin time, INR	1.38 (1.14−1.68)	1.35 (1.15−1.67)	1.36 (1.19−1.63)	0.943
Total bilirubin, mg/dl	1.9 (1.1−5.0)	2.2 (1.0−6.3)	1.8 (1.1−4.9)	0.648
Albumin, g/dl	3.10 ± 0.57	3.18 ± 0.57	3.15 ± 0.55	0.324
Aspartate aminotransferase, IU/L	38 (28−55)	39 (29−63)	40 (28−62)	0.490
Alanine aminotransferase, IU/L	24 (17−37)	25 (17−39)	24 (16−38)	0.597
Glucose, g/dl	114 (96−141)	110 (95−138)	109 (95−132)	0.440
Creatinine, mg/dl	0.75 (0.61−0.93)	0.79 (0.64−0.92)	0.75 (0.61−0.93)	0.397
C-reactive protein, mg/dl	0.40 (0.12−1.07)	0.27 (0.11−0.84) *	0.24 (0.10−0.67) *	0.014
B-type natriuretic peptide, pg/ml	66 (32−121)	70 (34−140)	62 (34−118)	0.766
Donor- and operation-related variables				
Deceased donor	23 (10.2)	24 (10.6)	13 (5.7)	0.134
Total anesthetic time, min	813 (736−880)	790 (706−882)	820 (737−909)	0.099
Echocardiographic measurements				
LV dimension in systole, mm	30.0 (27.0−33.0)	29.5 (27.0−33.0)	30.0 (27.0−33.0)	0.955
LV dimension in diastole, mm	50.0 (46.0−54.0)	50.0 (47.0−54.0)	50.0 (47.0−54.0)	0.546
LV posterior wall thickness in systole, mm	14.0 (13.0−15.0)	14.0 (13.0−16.0)	14.0 (13.0−15.0)	0.240
LV posterior wall thickness in diastole, mm	9.0 (8.0−10.0)	9.0 (8.0−10.0)	9.0 (8.0−9.0) *†	<0.001
Interventricular septal thickness in systole, mm	14.0 (12.0−15.0)	13.0 (12.0−15.0)	13.0 (12.0−14.0) *†	0.037
Interventricular septal thickness in diastole, mm	9.0 (8.0−10.0)	9.0 (8.0−10.0)	9.0 (8.0−10.0) *†	0.002
Left atrium, mm	39.0 (36.0−43.0)	39.0 (36.0−43.0)	39. (36.0−43.0)	0.877
Aorta, mm	33.2 ± 3.6	33.3 ± 3.8	32.0 ± 3.4*†	0.001
LV mass index, g/m^2	91.5 (78.0−103.9)	88.6 (77.8−103.6)	86.9 (75.2−99.5)	0.125
End-systolic volume, ml	40 (33−48)	38 (30−48)	40 (33−48)	0.561
End-diastolic volume, ml	109 (90−132)	106 (90−133)	114 (95−131)	0.480
Stroke volume, ml	69 (57−85)	69 (57−85)	74 (59−86)	0.228
LV ejection fraction, %	63.5 ± 4.0	64.2 ± 3.9	64.9 ± 4.5*	0.001

Table 2, continued

Peak E velocity, cm/s	71 (58−85)	73 (58−84)	73 (63−87)	0.237
Peak A velocity, cm/s	66 (55−81)	63 (55−75)	63 (52−76)	0.191
Deceleration time, ms	214 (187−241)	209 (180−238)	211 (183−238)	0.430
Tissue Doppler s´, cm/s	8.4 (7.5−9.5)	8.6 (7.7−9.6)	8.3 (7.4−9.3)	0.293
Tissue Doppler e´, cm/s	7.2 (6.0−8.6)	7.6 (6.3−8.7)	7.7 (6.6−8.8)	0.039
Tissue Doppler a´, cm/s	9.4 (8.2−11.0)	9.4 (8.3−10.7)	9.1 (7.7−10.6)	0.139
E/A	1.02 (0.85−1.28)	1.12 (0.87−1.38)	1.19 (0.91−1.42) *	0.002
E/e´	10 (8−12)	9 (8−11)	9 (8−12)	0.253
Aortic stiffness-related echocardiographic measurements				
Diastolic diameter of the aorta, cm	2.70 ± 0.32	2.59 ± 0.32*	2.39 ± 0.32*†	<0.001
Systolic diameter of the aorta, cm	2.81 ± 0.32	2.79 ± 0.34	2.74 ± 0.34*	0.034
Aortic strain, %	3.85 (2.87−4.78)	7.47 (6.45−8.86) *	14.13 (11.44−17.73) *†	<0.001
Aortic distensibility, $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	1.97 (1.44−2.41)	3.81 (3.34−4.32) *	7.28 (6.07−9.41) *†	<0.001
Aortic stiffness index (β), pure number	11.62 (9.41−15.39)	5.92 (5.13−6.93) *	3.21 (2.47−3.88) *†	<0.001
Total peripheral resistance, $dyn \cdot s/cm^5$	1391 (1106−1722)	1383 (1108−1668)	1321 (1070−1686)	0.521

Data are expressed as n (%), mean ± SD, or median (25th−75th percentiles).

* $p < 0.05$ vs. the lowest tertile of aortic distensibility.

† $p < 0.05$ vs. middle tertile of aortic distensibility. MELD, model for end-stage liver disease; INR, international normalized ratio; LV, left ventricle.

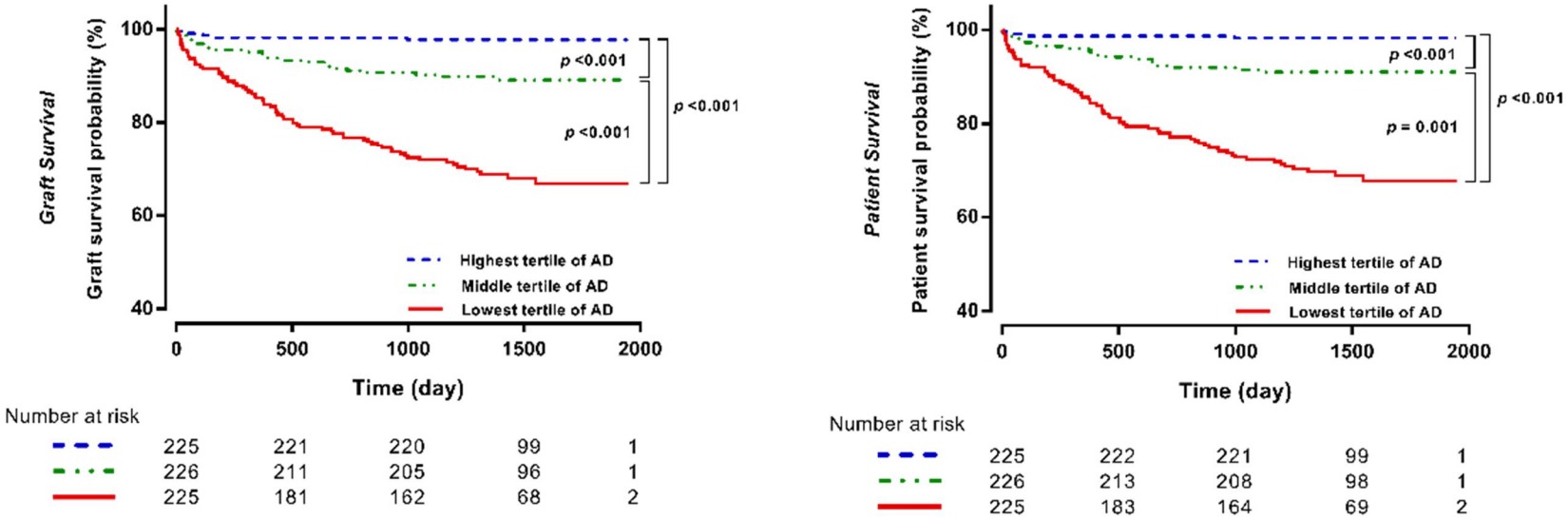

Fig. 2. Kaplan-Meire curve for overall period cumulative graft and patient survival according to tertiles of aortic distensibility. Lowest tertile, AD ≤2.77; middle, 2.77−5.11; highest tertile, ≥5.11. AD, aortic distensibility ($cm^2 \cdot dyn^{-1} \cdot 10^{-6}$).

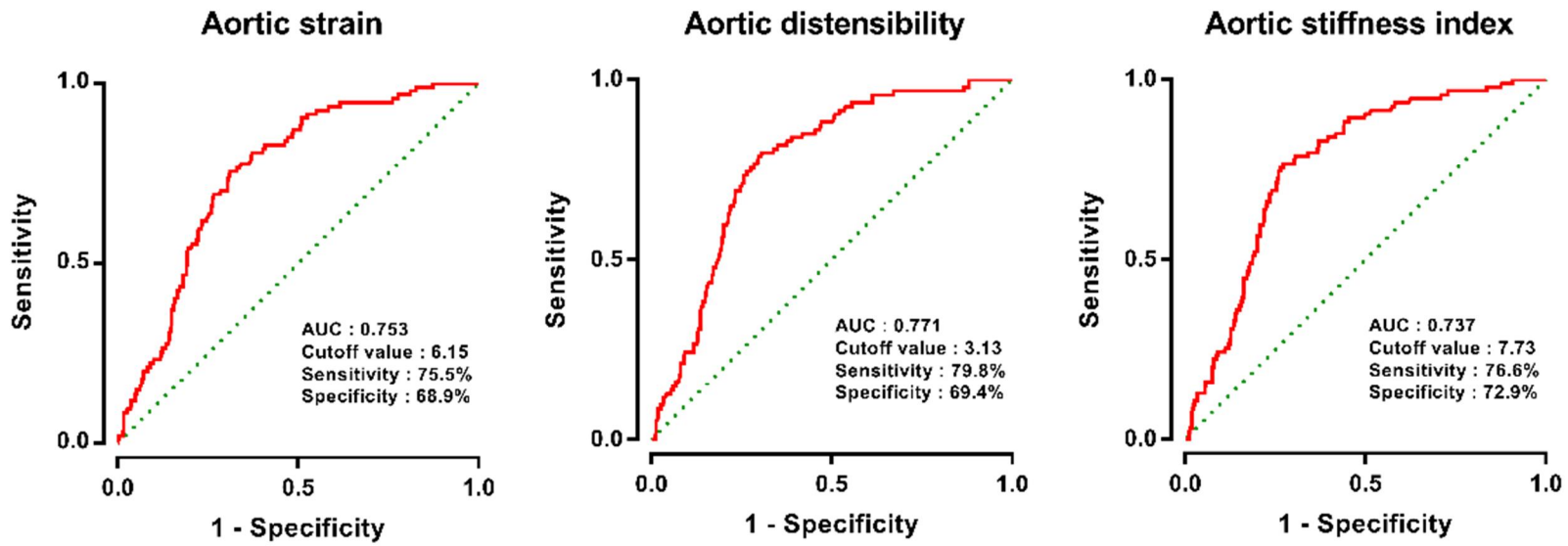

Fig. 3. Receiver operating curve on all-cause mortality. The unit of each parameter is percent (%) for aortic strain, $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ for aortic distensibility, and pure number for aortic stiffness index. AUC, area under the curve.

Table 3. Clinical and echocardiographic parameters by the cutoff value of aortic distensibility.

Aortic distensibility, $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	***Low AD <3.13 (n = 254)***	***High AD ≥3.13 (n = 422)***	***p value***
Preoperative characteristics of patients			
Age, years	54 (49−59)	53 (47−57)	0.042
Sex, male	196 (77.1)	327 (77.4)	0.998
Body mass index, kg/m^2	24.1 (21.5−26.8)	23.4 (21.5−25.7)	0.067
MELD score	13 (9−19)	12 (9−18)	0.240
Systolic blood pressure, mmHg	111 (100−122)	107 (97−116)	<0.001
Diastolic blood pressure, mmHg	68 (62−78)	69 (61−75)	0.226
Heart rate, beats/min	70 (63−80)	67 (60−77)	0.008
Etiology of liver disease (may overlap with other diseases)			
Hepatocelluar carcinoma	134 (52.7)	218 (51.6)	0.844
Hepatitis B virus	162 (63.7)	274 (64.9)	0.826
Hepatitis C virus	16 (6.3)	36 (8.5)	0.365
Alcohol	46 (18.1)	71 (16.8)	0.747
Others	38 (14.9)	49 (11.6)	0.254
QTc interval, ms	451 (430−473)	447 (427−466)	0.056
Medical history			
Hypertension	43 (16.9)	48 (11.3)	0.053
Diabetes mellitus	62 (24.4)	85 (20.1)	0.228
Current use of beta-blocker	54 (21.2)	104 (24.6)	0.361
Current use of diuretics	83 (32.6)	129 (30.5)	0.626
History of variceal bleeding	61 (24.0)	128 (30.3)	0.092
Intractable ascites	62 (24.4)	91 (21.5)	0.520
Hepatic encephalopathy	58 (22.8)	74 (17.5)	0.223
Current smoker	21 (8.2)	48 (11.3)	0.246
Preoperative biochemical laboratory variables			
Hemoglobin, g/dl	10.6 (9.2−12.4)	10.9 (9.5−12.5)	0.244
Platelet, x $10^3/mm^3$	63 (41−91)	62 (40−92)	0.606

Table 3, continued

Prothrombin time, INR	1.38 (1.15−1.70)	1.35 (1.17−1.63)	0.434
Total bilirubin, mg/dl	2.0 (1.1−5.5)	1.9 (1.0−5.0)	0.374
Albumin, g/dl	3.11 ± 0.56	3.16 ± 0.57	0.240
Aspartate aminotransferase, IU/L	38 (28−57)	39 (28−62)	0.380
Alanine aminotransferase, IU/L	24 (16−37)	25 (16−39)	0.641
Glucose, g/dl	113 (96−142)	109 (95−136)	0.238
Creatinine, mg/dl	0.76 (0.61−0.94)	0.76 (0.62−0.92)	0.917
C-reactive protein, mg/dl	0.40 (0.12−1.09)	0.24 (0.10−0.68)	0.001
B-type natriuretic peptide, pg/ml	65 (33−120)	66 (34−134)	0.471
Donor- and operation-related variables			
Deceased donor type	28 (11.0)	32 (7.5)	0.166
Total anesthetic time, min	812 (732−880)	803 (718−894)	0.821
Echocardiographic measurements			
LV dimension in systole, mm	30.0 (27.0−33.0)	30.0 (27.0−33.0)	0.352
LV dimension in diastole, mm	50.0 (46.0−54.0)	50.0 (47.0−54.0)	0.122
LV posterior wall thickness in systole, mm	14.0 (13.0−16.0)	14.0 (13.0−15.0)	0.419
LV posterior wall thickness in diastole, mm	9.0 (8.0−10.0)	9.0 (8.0−10.0)	<0.001
Interventricular septal thickness in systole, mm	14.0 (12.0−15.0)	13.0 (12.0−15.0)	0.024
Interventricular septal thickness in diastole, mm	9.0 (8.0−10.0)	9.0 (8.0−10.0)	0.006
Left atrium, mm	39 (36−43)	39 (36−43)	0.880
Aorta, mm	32.6 ± 3.6	33.2 ± 3.6	0.040
LV mass index, g/m^2	91 (78−103)	88.4 (76.3−102.5)	0.221
End-systolic volume, ml	40 (32−48)	39 (31−48)	0.316
End-diastolic volume, ml	108 (90−132)	111 (92−132)	0.649
Stroke volume, ml	69 (57−84)	72 (58−85)	0.228
LV ejection fraction, %	64 (60−67)	65 (62−67)	0.002
Peak E velocity, cm/s	71 (58−84)	73 (61−86)	0.197
Peak A velocity, cm/s	66 (55−81)	63 (53−75)	0.025
Deceleration time, ms	210 (185−238)	211 (183−240)	0.877

Table 3, continued

Tissue Doppler s′, cm/s	8.5 (7.5−9.8)	8.4 (7.5−9.4)	0.277
Tissue Doppler e′, cm/s	7.2 (6.0−8.6)	7.6 (6.4−8.8)	0.017
Tissue Doppler a′, cm/s	9.4 (8.2−11.1)	9.3 (8.0−10.6)	0.034
E/A	1.02 (0.84−1.28)	1.16 (0.89−1.41)	<0.001
E/e′	10 (8−12)	9 (8−12)	0.393
Aortic stiffness-related echocardiographic measurements			
Diastolic diameter of the aorta, cm	2.69 (2.48−2.88)	2.45 (2.21−2.71)	<0.001
Systolic diameter of the aorta, cm	2.81 ± 0.32	2.76 ± 0.35	0.090
Aortic strain, %	4.01 (2.99−5.29)	10.47 (7.81−14.55)	<0.001
Aortic distensibility, $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	2.10 (1.51−2.57)	5.34 (3.97−7.60)	<0.001
Aortic stiffness index (β), pure number	10.77 (8.98−14.9)	4.42 (3.11−5.70)	<0.001
Total peripheral resistance, $dyn \cdot s/cm^5$	1389 (1101−1713)	1364 (1078−1681)	0.673

Data are expressed as n (%), mean ± SD, or median (25th−75th percentiles). AD, aortic distensibility; MELD, model for end-stage liver disease; INR, international normalized ratio; LV, left ventricle.

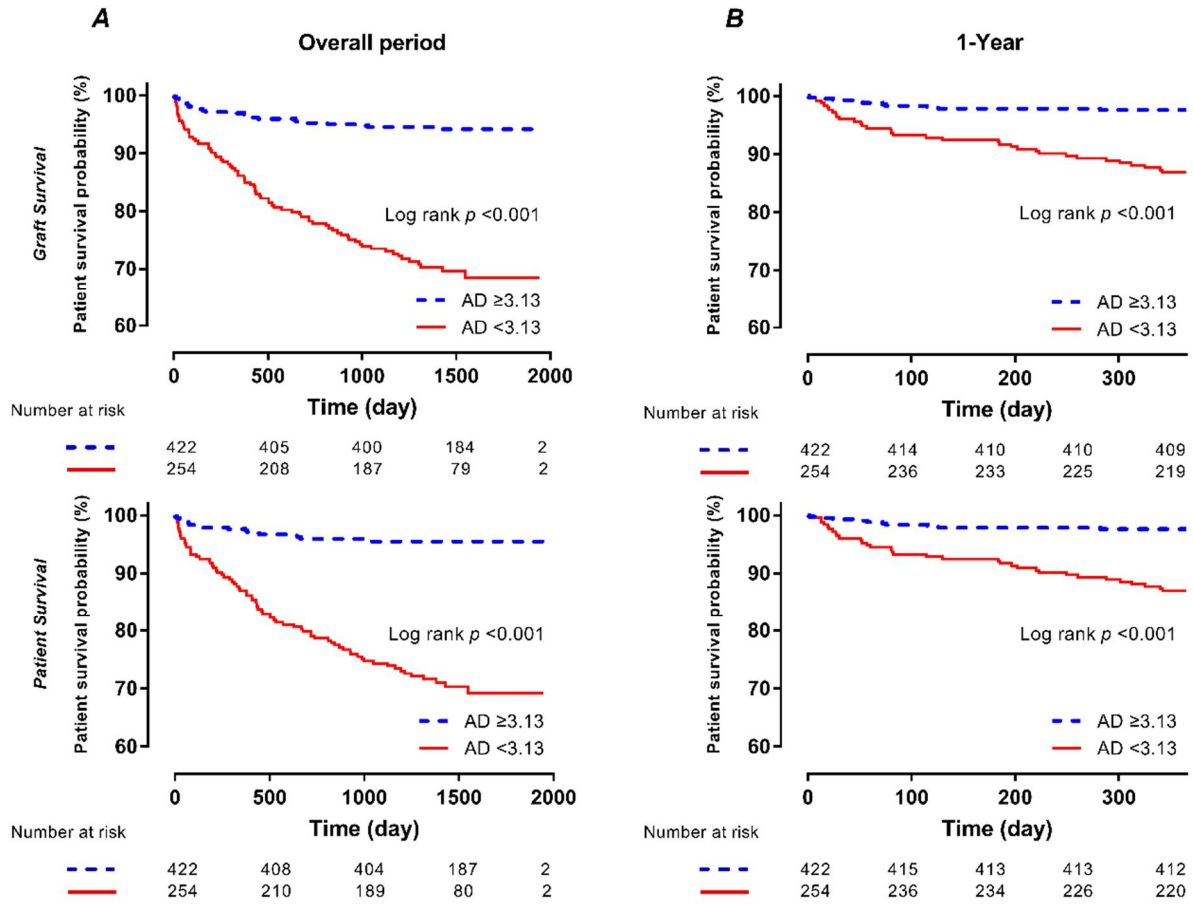

Fig. 4. Kaplan-Meire curve for overall period and 1-year cumulative graft and patient survival according to low and high aortic distensibility groups. (*A*) overall follow-up period; (*B*) 1-year follow-up period. AD, aortic distensibility ($cm^2 \cdot dyn^{-1} \cdot 10^{-6}$).

Table 4. Univariate and multivariate analyses of factors related to all-cause mortality.

	Univariate analysis		***Multivariate analysis***	
	Hazard ratio (95% CI)	***p value***	***Hazard ratio (95% CI)***	***p value***
Age, years	0.99 (0.96−1.02)	0.704		
Sex, male	1.49 (0.82−2.70)	0.184		
Body mass index, kg/m^2	0.96 (0.91−1.03)	0.318		
MELD score ≥25	1.36 (0.58−3.19)	0.474		
Mean arterial pressure, mmHg	0.98 (0.96−1.00)	0.161		
Hypertension	1.22 (0.67−2.20)	0.510		
Diabetes mellitus	0.88 (0.51−1.50)	0.641		
Coronary disease	1.09 (0.70−1.68)	0.689		
Current smoker	0.90 (0.41−1.97)	0.802		
Current use of beat-blocker	0.92 (0.53−1.58)	0.773		
Current use of diuretics	1.06 (0.66−1.71)	0.792		
Deceased donor	1.17 (0.60−2.26)	0.635		
ABO incompatible living donor	1.28 (0.73−2.24)	0.377		
LV ejection fraction, %	1.06 (0.89−1.25)	0.505		
Tissue Doppler s´, cm/s	0.88 (0.77−0.99)	0.048	0.87 (0.78−0.98)	0.024
E/A	0.74 (0.38−1.44)	0.384		
E/e´	1.07 (1.01−1.14)	0.023		
Deceleration time, ms	0.99 (0.99−1.00)	0.408		
Low AD, <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	7.07 (4.21−11.87)	<0.001	6.55 (3.99−10.76)	<0.001
QTc interval, ms	0.99 (0.98−1.00)	0.064		
Prothrombin time, INR	0.83 (0.47−1.47)	0.529		
Creatinine, mg/dl	1.14 (0.93−1.38)	0.189	1.24 (1.07−1.43)	0.003
Total bilirubin, mg/dl	1.01 (0.98−1.04)	0.449		
C-reactive protein, ≥0.81 mg/dl	2.42 (1.46−4.02)	0.001	2.41 (1.58−3.68)	<0.001
B-type natriuretic peptide, pg/ml	0.99 (0.99−1.00)	0.278		

CI, confidence interval; MELD, model for end-stage liver disease; AD; aortic distensibility; INR, international normalized ratio; LV, left ventricle.

Table 5. Cox proportional hazard regression on factors related all-cause mortality and graft failure

Mortality	*HR (95% CI)*	*p value*	*Graft failure*	*HR (95% CI)*	*p value*
Overall mortality (entire patients, n = 94)			***Overall graft failure (entire patients, n = 101)***		
AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	6.55 (3.99−10.76)	<0.001	AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	5.60 (3.53−8.88)	<0.001
CRP ≥0.81 mg/dl	2.41 (1.58−3.68)	<0.001	CRP ≥0.81 mg/dl	2.38 (1.56−3.65)	<0.001
Creatinine, mg/dl	1.24 (1.07−1.43)	0.003	Creatinine, mg/dl	1.20 (1.03−1.40)	0.017
Tissue Doppler s´, cm/s	0.87 (0.78−0.98)	0.024	E/e´	1.07 (1.02−1.13)	0.007
			QTc	0.99 (0.98−0.99)	0.022
One-year mortality (entire patients, n = 44)			***One-year graft failure (entire patients, n = 49)***		
AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	5.08 (2.50−10.33)	<0.001	AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$	5.26 (3.31−8.35)	<0.001
CRP ≥0.81 mg/dl	3.40 (1.71−6.73)	0.001	CRP ≥0.81 mg/dl	1.96 (1.32−2.92)	0.001
MELD ≥25	2.10 (1.08−4.07)	0.028	Creatinine, mg/dl	1.19 (1.03−1.38)	0.018

HR, hazard ratio; CI, confidence interval; AD, aortic distensibility; CRP, C-reactive protein; QTc, corrected QT interval; E, early mitral inflow velocity; e´, early diastolic mitral valve annular velocity; MELD, MELD, model for end-stage liver disease.

Table 6. Multivariate logistic regression analysis on the risk factors related to low aortic distensibility (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$).

Risk factor	***Odds ratio (95% CI)***	***p value***
Age, year	1.030 (1.010−1.052)	0.003
Body mass index, kg/m^2	1.051 (1.001−1.103)	0.043
Mean arterial pressure, mmHg	1.025 (1.009−1.040)	0.001
LV ejection fraction, %	0.939 (0.903−0.977)	0.001
QTc interval, ms	1.006 (1.001−1.011)	0.020
C-reactive protein, mg/dl	1.200 (1.059−1.360)	0.004

CI, confidence interval; LV, left ventricle.

Discussion

The main findings of this study provide the following. First, when comparing the three groups divided by tertile of AD, there were significant statistical differences in all-cause mortality and graft failure between the groups in LT candidates. Second, when classifying to low and high AD as the cut-off value (AD = 3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) obtained from the ROC curve, low AD group had 5.60-fold higher HR for graft failure, and 6.55-fold higher HR for all-cause mortality. Finally, the central cause of decreased AD in LT candidates was the loss of restoration of the aorta during diastolic period. To our knowledge, this is the first study to directly investigate characteristics of the aorta using transthoracic echocardiography in LT candidates.

From recent studies referring to nonalcoholic fatty liver disease, a few potential mechanisms of decreased AD in LT candidates could be elucidated. First, the progression of insulin resistance may promote decrease of AD. Carbohydrate intolerance in LT

candidates had been extensively reported[17-21], and basal serum insulin levels were significantly higher in LT candidates, therefore the term "*hepatogenous diabetes"* is widely used to describe the hyperglycemia in end-stage liver disease [17, 18]. As shown in table 1, fasting serum glucose was out of normal range, and these level of serum glucose correspond to one of the diagnostic criteria of the metabolic syndrome which was known as pre-diabetic condition[22]. Accumulation of advanced glycation end-products (AGEs) may occur in the aortic wall[23], and AGEs pathologically cross link largely with collagen[24], which may contribute to increase collagen component in the aortic tissue[25]. Eventually, the ratio of elastin to collagen fibers in the aorta is altered and AD is decreased, and such interaction between AGEs and collagen fibers occurs in patients regardless of the presence of diabetes mellitus[26]. Second, oxidative stress and inflammatory cytokines may play an important role in accelerating atherosclerosis. In healthy individuals, the level of reactive oxygen species balanced between formation and elimination. However, oxidative stress is remarkable characteristic in the pathogenesis of both acute and chronic liver disease[27-33]. The causes of oxidative stress origin from

exogenous materials (e.g. alcohol and drugs), endogenous materials (e.g. liver enzyme system) and cellular dysfunctions (mitochondrial metabolism)[27]. Once oxidative stress is triggered, various cellular elements such as DNA, proteins, fatty/lipid acids damage to hepatocytes, and the damaged cellular elements repeatedly continue a vicious cycle of increasing the reactive oxygen species[27]. In addition, increased oxidative stress affect processes of endothelial dysfunction and atherosclerosis, including expression of adhesion molecule, vascular smooth muscle proliferation, apoptosis in the endothelium, oxidation of lipids, and altered vasomotor activity[34, 35], as a result, the aorta may be calcified and AD may be decreased as well. Third, the systemic inflammation in cirrhosis may aggravate atherosclerotic reaction of the aorta. Whatever may be the precise cause, the cirrhosis is the final step of various progressive liver diseases[36-39]. The cirrhotic patients frequently demonstrate systemic inflammation in the same context of the cirrhosis-associated immune dysfunction syndrome[40]. The integration of both systemic inflammation and immunologic dysfunction is suggested to describe the pathophysiologic mechanism of the natural history of cirrhosis[40, 41]. The systemic inflammation could be initiated by intrinsic factors as a

result of hepatocyte injury or other organ damage, by antigens derived from the bacteria, or by the bacteria itself from the intestine by bacterial translocation[40-42]. As in the situation mentioned above, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are released, and serum level of CRP is increased[43-45]. Although there may be some controversy about the relationship between systemic inflammation and atherosclerotic reaction, a few studies suggest that systemic inflammation may increase AD[46, 47]. In our results, AD of <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ and patients in the lowest and middle AD tertile were significantly associated with 1-year and overall period all-cause mortality (Fig. 3). Although pathophysiological explanations about all-cause mortality could not be yet accurately explained, all-cause mortality might reflect the existence of similar pathophysiologic mechanisms, such as diabetic feature, oxidative stress, and especially systemic inflammation in a wide range of conditions[6].

According to recent studies, the 1-year survival rates after LT considerably exceeds 80% [48], and 5-year survival rates are 83% and 84% for living donor and deceased donor liver

transplantation, respectively[49]. The success rates of LT have prominently improved as a result of preservation solutions, immunosuppressants, and surgical and anesthetic techniques[50, 51]. Numerous studies for post-operative outcomes have been conducted [16, 52-59], and the efforts to reduce post-operative mortality rate and to evaluate better prognostic factors after LT are still ongoing progress. The most common cause of the mortality within the first year (early phase) after LT is infection, and the next is rejection[60]. After one year (late phase), infectious complications are decreasing[61], and the malignant disease is most common cause of death during late phase and all period after LT[60, 62-64]. According to our result, the infection accounted for 36% of the cause of mortality, and late phase mortality was mainly due to recurrence of malignancy (76%). Especially, recurrence of malignancy was the leading cause of overall period mortality (51%). Despite high survival rate as mentioned above, 8-12% of patients undergoing LT due to hepatocellular carcinoma (HCC) experience a post-transplant HCC recurrence or metastatic carcinoma, which leads to death in most studies[65-68]. Although tumor size, tumor burden, microinvasion, and alpha-fetoprotein (AFP) are considered as risk factor of malignancy recurrence, the central

reason may be the decrease of immunity due to the use of immunosuppressants[68, 69]. Although there is no clear relationship between the mortality and decreased AD in LT candidates, complex interactions might exist between immunity and inflammatory response, which are not fully understood up to the present time. And also, it is difficult to explore the relationship between recurrence of malignancy and decreased AD, because numerous factors are known to relate in recurrence. However, from the point of inflammation, decreased AD may be a series of inflammatory response, and the recurrence of malignancy is closely associated with inflammatory reaction[70]. Therefore, there seem to be a connecting link between the AD and recurrence of malignancy. Especially, it is well known that pro-inflammatory cytokines such as IL-6 and TNF-α, which may be associated with AD, play an important role in recurrence of malignancy[70, 71]. In addition, our result showed that decreased AD associated with malignancy-related mortality is similar to the risk of established predictors, such as pre-operative serum CRP level[72]. Furthermore, an important finding of our analysis is that decreased AD is a powerful predictor of all-cause

mortality, and it is notable that the AUC of AD related to the mortality is greater than the AUC of serum CRP alone (AUC, 0.771 vs. 0.643, $p = 0.001$, data not shown).

As we mentioned above, it is well-known fact that the aorta is mainly composed with elastin and collagen fibers, and the histological composition of the aorta varies according to location and function. The proximal aorta is predominant with the elastin which tolerate stressful systolic stimulation and mediate the stroke volume toward the distal aorta. Meanwhile, distal arteries tend to decrease AD according to increased collagen fibers[2, 73]. If the aorta is gradually injured by mechanical or chemical stress over a period time, repetitive inflammatory responses of the vessel wall continue, and the composition of the contents in the vessel wall progressively has been changed from elastin to collagen fiber. As a result, the aortic wall will be calcified and has decreased AD. Although the calcified aorta with reduced elastic component could maintain the ability of extension due to very high pressure during the systolic period, the extended aorta might seem to be difficult to return to its original shape in the diastolic period. Interestingly, the dilated aorta could also

be observed in this study. As shown in table 3, systolic diameter of the aorta was not different between low AD and high AD groups (2.81 cm *vs.* 2.76 cm; $p = 0.090$), however, the aorta was significantly dilated during diastolic period in low AD group compared with high AD group (2.69 cm *vs.* 2.45 cm; $p < 0.001$). In addition, the systemic circulation in cirrhosis is already vasodilated because of increased release of nitric oxide (NO) and several cytokines[7]. Like diastolic dysfunction of the heart, which seen in the patients with cirrhotic cardiomyopathy[74, 75], in this context, the dilated aorta during diastolic period might be named as *"cirrhotic diastolic dysfunction of the aorta"*. Therefore, the dilated aorta during diastolic period is central process of increased AD in cirrhotic patients, and such characteristic may be related to the systemic vasodilation affected by NO, which is common in cirrhotic patients[76]. In addition, decreased AD appears to aggravate organ damage through impaired transmission of pulsatile energy to target organs such as the brain and kidney[77], and there might also be an influence on the transplanted liver.

Limitations

There were some limitations in this study. First, this is a single-institution and retrospective study using preoperative echocardiography. Therefore, data acquired from the electrical medical record registry might have caused a selection bias. Second, surgical methods and causes of liver disease were heterogenous. Most of LT candidates in our institute underwent living donor LT electively. In general, the patients undergoing elective living donor LT had less severe disease and lower MELD score. On the other hand, the patients who underwent transplantation from a deceased donor (8.8%) were mainly performed emergency operation, and they were in more poor condition and had higher MELD score. In addition, a certain portion of patients (21.4%) received a liver which was incompatible for ABO blood type. For this reason, multivariate adjusted analysis was conducted including potential confounding variables such as MELD score, donor type, and compatibility to reduce potential bias. Third, it is well known that there are many influential factors that affect the AD. Therefore, we also conducted analysis by

multivariable adjustment including well-known variables, such as age, sex, body mass index, pre-operative serum creatinine and CRP, and history of diabetes mellitus, hypertension, coronary artery disease, current use of beta blocker and diuretics, and current smoking.

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Conclusions

This study suggested that LT recipients with low AD <3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$ had significantly high risk in all-cause mortality and graft failure in multivariable adjusted analysis. Although there are many parameters developed to evaluating prognosis for LT, pre-transplant measurement of the AD by the echocardiography may be thought to have a remarkably high prognostic value in LT. Therefore, this study proposes that non-invasive and relatively simple measurement of the AD by the echocardiography may serve an additional prognostic index for survival and graft outcome after LT.

References

1. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. Circ Res 1992;71(3):490-502.

2. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. J Am Coll Cardiol 2011;57(14):1511-22.

3. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27(21):2588-605.

4. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 2002;15(5):426-44.

5. Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA. "Inflammation and arterial stiffness in humans". Atherosclerosis 2014;237(2):381-90.

6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55(13):1318-27.

7. Moller S, Henriksen JH. Cirrhotic cardiomyopathy. J Hepatol 2010;53(1):179-90.

8. Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol 2014;11(3):177-86.

9. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology 2006;43(2 Suppl 1):S121-31.

10. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976;37(1):7-11.

11. Eren M, Gorgulu S, Uslu N, Celik S, Dagdeviren B, Tezel T. Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. Heart 2004;90(1):37-43.

12. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of

progression to hypertension in nonhypertensive subjects. Hypertension 2005;45(3):426-31.

13. Goodkin DE, Ross JS, Medendorp SV, Konecsni J, Rudick RA. Magnetic resonance imaging lesion enlargement in multiple sclerosis. Disease-related activity, chance occurrence, or measurement artifact? Arch Neurol 1992;49(3):261-3.

14. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11(11):990-6.

15. Kocarslan A, Kocarslan S, Aydin MS, Altiparmak IH, Demir D, Sezen H, et al. Relationship Between Echocardiographically Evaluated Aortic Stiffness and Prolidase Activity in Aortic Tissue of Patients with Critical Coronary Artery Disease. Arch Med Res 2016;47(3):200-6.

16. Shin WJ, Song JG, Jun IG, Moon YJ, Kwon HM, Jung K, et al. Effect of

ventriculo-arterial coupling on transplant outcomes in cirrhotics: Analysis of pressure-volume curve relations. J Hepatol 2017;66(2):328-37.

17. Cavallo-Perin P, Cassader M, Bozzo C, Bruno A, Nuccio P, Dall'Omo AM, et al. Mechanism of insulin resistance in human liver cirrhosis. Evidence of a combined receptor and postreceptor defect. J Clin Invest 1985;75(5):1659-65.

18. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. Hepatology 2005;42(5):987-1000.

19. Riggio O, Merli M, Cangiano C, Capocaccia R, Cascino A, Lala A, et al. Glucose intolerance in liver cirrhosis. Metabolism 1982;31(6):627-34.

20. Campbell JA, Tagnon HJ. The intravenous glucose-tolerance test in liver disease. N Engl J Med 1946;234:216-21.

21. Kawaguchi T, Taniguchi E, Itou M, Sakata M, Sumie S, Sata M. Insulin resistance and chronic liver disease. World J Hepatol 2011;3(5):99-107.

22. Alberti KG, Zimmet P, Shaw J, Group IDFETFC. The metabolic syndrome--a new worldwide definition. Lancet 2005;366(9491):1059-62.

23. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med 1988;318(20):1315-21.

24. Powell JT, Vine N, Crossman M. On the accumulation of D-aspartate in elastin and other proteins of the ageing aorta. Atherosclerosis 1992;97(2-3):201-8.

25. Schnider SL, Kohn RR. Effects of age and diabetes mellitus on the solubility and nonenzymatic glucosylation of human skin collagen. J Clin Invest 1981;67(6):1630-5.

26. Sims TJ, Rasmussen LM, Oxlund H, Bailey AJ. The role of glycation cross-links in diabetic vascular stiffening. Diabetologia 1996;39(8):946-51.

27. Vuppalanchi R, Juluri R, Bell LN, Ghabril M, Kamendulis L, Klaunig JE, et al. Oxidative stress in chronic liver disease: relationship between peripheral and hepatic measurements. Am J Med Sci 2011;342(4):314-7.

28. Bhatia V, Bhardwaj P, Elikkottil J, Batra J, Saraya A. A 7-day profile of oxidative stress and antioxidant status in patients with acute liver failure. Hepatol Int

2008;2(4):465-70.

29. Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2004;99(8):1497-502.

30. Comporti M, Arezzini B, Signorini C, Vecchio D, Gardi C. Oxidative stress, isoprostanes and hepatic fibrosis. Histol Histopathol 2009;24(7):893-900.

31. Lieber CS. Role of oxidative stress and antioxidant therapy in alcoholic and nonalcoholic liver diseases. Adv Pharmacol 1997;38:601-28.

32. Aboutwerat A, Pemberton PW, Smith A, Burrows PC, McMahon RF, Jain SK, et al. Oxidant stress is a significant feature of primary biliary cirrhosis. Biochim Biophys Acta 2003;1637(2):142-50.

33. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. J Hepatol 2001;35(2):297-306.

34. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87(10):840-4.

35. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. Am J Cardiol 2003;91(3A):7A-11A.

36. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44(1):217-31.

37. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. J Hepatol 2012;57(6):1336-48.

38. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346(16):1221-31.

39. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116(6):1413-9.

40. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61(6):1385-96.

41. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61(2):396-407.

42. Dirchwolf M, Ruf AE. Role of systemic inflammation in cirrhosis: From pathogenesis to prognosis. World J Hepatol 2015;7(16):1974-81.

43. Haukeland JW, Damas JK, Konopski Z, Loberg EM, Haaland T, Goverud I, et al. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. J Hepatol 2006;44(6):1167-74.

44. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016;64(4):1249-64.

45. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63(5):1272-84.

46. Li N, Zhang GW, Zhang JR, Jin D, Li Y, Liu T, et al. Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. Nutr Metab Cardiovasc Dis 2015;25(2):218-23.

47. Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR, Wilkinson IB. C-

reactive protein is associated with arterial stiffness in apparently healthy individuals. Arterioscler Thromb Vasc Biol 2004;24(5):969-74.

48. Neuberger J. Liver transplantation. J Hepatol 2000;32(1 Suppl):198-207.

49. Reichman TW, Katchman H, Tanaka T, Greig PD, McGilvray ID, Cattral MS, et al. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. Transpl Int 2013;26(8):780-7.

50. Qian YB, Cheng GH, Huang JF. Multivariate regression analysis on early mortality after orthotopic liver transplantation. World J Gastroenterol 2002;8(1):128-30.

51. Hofer I, Spivack J, Yaport M, Zerillo J, Reich DL, Wax D, et al. Association between anesthesiologist experience and mortality after orthotopic liver transplantation. Liver Transpl 2015;21(1):89-95.

52. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med 1999;341(27):2049-53.

53. Adam R, Cailliez V, Majno P, Karam V, McMaster P, Caine RY, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 2000;356(9230):621-7.

54. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(2):464-70.

55. Therapondos G, Flapan AD, Plevris JN, Hayes PC. Cardiac morbidity and mortality related to orthotopic liver transplantation. Liver Transpl 2004;10(12):1441-53.

56. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35(5):1179-85.

57. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology 2003;37(1):192-7.

58. John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. Hepatology 2001;34(5):889-95.

59. Chen HP, Tsai YF, Lin JR, Liu FC, Yu HP. Recipient Age and Mortality Risk after Liver Transplantation: A Population-Based Cohort Study. PLoS One 2016;11(3):e0152324.

60. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10(6):1420-7.

61. Iwatsuki S, Starzl TE, Gordon RD, Esquivel CO, Todo S, Tzakis AG, et al. Late mortality and morbidity after liver transplantation. Transplant Proc 1987;19(1 Pt 3):2373-7.

62. Lukes DJ, Herlenius G, Rizell M, Mjornstedt L, Bacman L, Olausson M, et al. Late mortality in 679 consecutive liver transplant recipients: the Gothenburg liver transplant experience. Transplant Proc 2006;38(8):2671-2.

63. Rabkin JM, de La Melena V, Orloff SL, Corless CL, Rosen HR, Olyaei AJ. Late

mortality after orthotopic liver transplantation. Am J Surg 2001;181(5):475-9.

64. Gelson W, Hoare M, Dawwas MF, Vowler S, Gibbs P, Alexander G. The pattern of late mortality in liver transplant recipients in the United Kingdom. Transplantation 2011;91(11):1240-4.

65. Toso C, Cader S, Mentha-Dugerdil A, Meeberg G, Majno P, Morard I, et al. Factors predicting survival after post-transplant hepatocellular carcinoma recurrence. J Hepatobiliary Pancreat Sci 2013;20(3):342-7.

66. Vivarelli M, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. Liver Transpl 2005;11(5):497-503.

67. Nissen NN, Menon V, Bresee C, Tran TT, Annamalai A, Poordad F, et al. Recurrent hepatocellular carcinoma after liver transplant: identifying the high-risk patient. HPB (Oxford) 2011;13(9):626-32.

68. Chan EY, Larson AM, Fix OK, Yeh MM, Levy AE, Bakthavatsalam R, et al.

Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. Liver Transpl 2008;14(7):956-65.

69. Xiol X, Guardiola J, Menendez S, Lama C, Figueras J, Marcoval J, et al. Risk factors for development of de novo neoplasia after liver transplantation. Liver Transpl 2001;7(11):971-5.

70. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. Eur J Cancer 2005;41(16):2502-12.

71. Nakazaki H. Preoperative and postoperative cytokines in patients with cancer. Cancer 1992;70(3):709-13.

72. An HJ, Jang JW, Bae SH, Choi JY, Yoon SK, Lee MA, et al. Serum C-reactive protein is a useful biomarker for predicting outcomes after liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2012;18(12):1406-14.

73. Lee RT, Kamm RD. Vascular mechanics for the cardiologist. J Am Coll Cardiol 1994;23(6):1289-95.

74. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut 2008;57(2):268-78.

75. Jang DM, Jun IG, Moon YJ, Shin WJ, Song JG, Hwang GS. Pretransplant Left Ventricular Dysfunction Adversely Affects Perioperative Outcomes in Pediatric Liver Transplantation: A Retrospective Observational Study. Transplant Proc 2016;48(10):3328-35.

76. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991;337(8744):776-8.

77. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 2005;46(1):200-4.

국문요약

서론

대동맥 확장도는 다양한 조건에서 대동맥의 구조 변화의 초기에 감지 가능한 징후 중 하나이다. 간기능이 손상된 환자들은 전신 혈관 확장과 전신 혈관 저항 감소와 같은 혈관의 특징을 나타내며, 간이식 수혜자들에게 혈관에 문제가 있을 수 있음을 추론해 볼 수 있을 것이다. 그러므로 이 연구는 간이식 수혜자들에게서 대동맥 확장도의 특징과, 간이식 후 사망률에 대한 영향에 대하여 조사해보고자 한다.

연구 대상 및 방법

본 후향적 관찰 연구는 간이식을 시행받은 총 646 명의 간이식 수혜자들을 대상으로 하였다. 대동맥 확장도는 B-mode 경흉부 초음파의 흉골좌연 장축 단면 영상에서 측정하였다. 간이식 수혜자들은 낮은 ($<3.13\ cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) 및 높은 ($\geq 3.13\ cm^2 \cdot dyn^{-1} \cdot 10^{-6}$) 대동맥 확장도 군으로 분류하였다. 생존분석은 Kaplan-Meier 방법을 사용하여 수행되었다. Cox 비례 위험 회귀 모델을 사용하여 대동맥 확장도 값에

따른 전반적인 사망률을 조사하였다. 낮은 대동맥 확장도와 관련된 위험인자를 알아보기 위해 다변량 로지스틱 회귀분석을 시행하였다.

결과

47 개월 중앙값의 추적관찰 기간 동안, 94 명(13.9%)의 환자들이 사망하였다. 낮은 대동맥 확장도를 갖는 간이식 수혜자 군 (n = 254)은 높은 대동맥 확장도를 같는 군 (n = 422)에 비해서 높은 사망률을 나타내었으며 (29.5% *vs.* 4.5%, Log-rank p <0.001), 사망률에 대한 위험과 독립적으로 연관되었다 (위험비, 6.55; 95% 신뢰구간, 3.99−10.76; p <0.001). 낮은 대동맥 확장도와 관련된 위험인자로는 연령, 체질량 지수, 평균 동맥압, 좌심실 구혈률, QTc 간격, 그리고 C-반응성 단백질이었다.

고찰 및 결론

본 연구는 낮은 대동맥 확장도 (<3.13 $cm^2 \cdot dyn^{-1} \cdot 10^{-6}$)를 갖는 간이식 수혜자들은 전체 사망률에서 유의하게 높은 위험비를 갖는다는 것을 확인하였다. 따라서 본 연구는 비 침습적이고 비교적 단순한 심초음파를 이용하여 측정한 대동맥 확장도는

간이식 후의 생존에 대한 추가적인 예후지표가 될 수 있다고 제안한다.

중심단어: 간이식, 대동맥 팽창도, 사망률