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# Outcome of Living-Donor Liver Transplantation Using Grafts from Donors Treated for Fatty Liver

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**Background:** The aim of this study was to determine the efficacy of treating donors' fatty liver (FL) and to assess early graft function in recipients who received treated FL grafts in living-donor liver transplantation (LDLT).


**Material/Methods:** Data were collected for adult-to-adult LDLTs. Donors diagnosed with FL (FL group) received diet-exercise and pharmacological treatment. The perioperative findings and early transplanted graft function were compared with those of donors without FL (non-FL group) during the same period.

**Results:** Of 30 donors, 8 were determined to have FL. The median duration of treatment for FL was 58 days. The liver-to-spleen attenuation ratios on CT scan in the FL group were significantly improved after treatment: 0.95 (0.62–1.06) to 1.2 (1.12–1.46) ( $P=0.003$ ). Liver biopsy prior to donor surgery showed  $\leq 10\%$  fatty infiltration. Postoperative laboratory findings of the donors in the FL group were comparable to those in the non-FL group: maximum alanine transaminase ( $189.6 \pm 94.7$  IU/L vs.  $196.8 \pm 57.4$ ) and maximum total bilirubin ( $2.2 \pm 1.1$  mg/dL vs.  $1.7 \pm 0.5$  mg/dL). No major complications were observed after donor hepatectomy in either group. There were no significant differences between the 2 groups in early graft function, as evaluated by laboratory data, ascites volume, and bile production 2 weeks postoperatively. Graft and patient survival were 100% in both groups at 3 months.

**Conclusions:** Preoperative intentional treatment for FL was effective. Early graft function and donor postoperative course were comparable in the 2 groups. These results suggest that well-treated steatotic grafts can be used without jeopardizing donor safety.

**MeSH Keywords:** Diet Therapy • Fatty Liver • Liver Transplantation • Living Donors

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## Background

Liver transplantation is the only definitive treatment for end-stage liver disease. Graft selection is an important factor in achieving a good result after transplantation. In the field of cadaveric donor liver transplantation, a liver graft with moderate to severe steatosis (>30–60%) has been reported to be associated with an increased risk of primary nonfunction (PNF), impaired early graft function, and graft loss [1,2]. Furthermore, such macrosteatosis (MaS) is associated with a significantly lower 3-year overall survival among recipients of MaS (>6%) grafts compared to recipients with nonsteatotic grafts (57% vs. 95%;  $P=0.026$ ) [3]. Because of the shortage of cadaveric donors, however, the use of grafts with more than mild hepatosteatosis depends on the surgeon's decision and/or recipient's status [1,2].

In the setting of living-donor liver transplantation (LDLT), fatty infiltration in donor candidates is also encountered during their evaluation. Experiences in using living donor grafts with mild to moderate MaS have been reported in a few studies. Hayashi et al. reviewed 41 LDLTs using liver grafts with various degrees of fatty infiltration and concluded that mild (0–30% steatosis) to moderate (30–60% steatosis) fatty liver (FL) grafts provided comparable graft survival compared with non-FL grafts, although early graft function was slightly disturbed when an FL graft was implanted [4]. Another retrospective study reported that FL grafts with moderate (20–50% steatosis) showed comparable 1-year patient and graft survival compared with less steatotic grafts [5]. However, peak alanine transaminase (ALT) was significantly higher in the moderate FL graft group compared with less steatotic groups, possibly as a result of accelerated ischemia-reperfusion injury [5]. These findings suggested that up to a certain degree of FL would be acceptable for LDLT, paying attention to postoperative ischemia-reperfusion injury.

In this context, fatty infiltration in living donors is considered to be treatable, and a less steatotic graft might result in better posttransplant graft function [6]. Hwang et al. attempted to treat FL donors and reported the efficacy of short-term weight reduction for living donors with moderate to severe FL to alleviate excessive hepatic steatosis [6]. However, the graft function after LDLTs from these donors was not evaluated in the study.

The aim of the present study was to assess the efficacy of treatment for FL in living-donor candidates who were otherwise considered eligible, and to explore its effect on the safety of donor hepatectomy, as well as on early graft function, in recipients implanted with treated grafts.

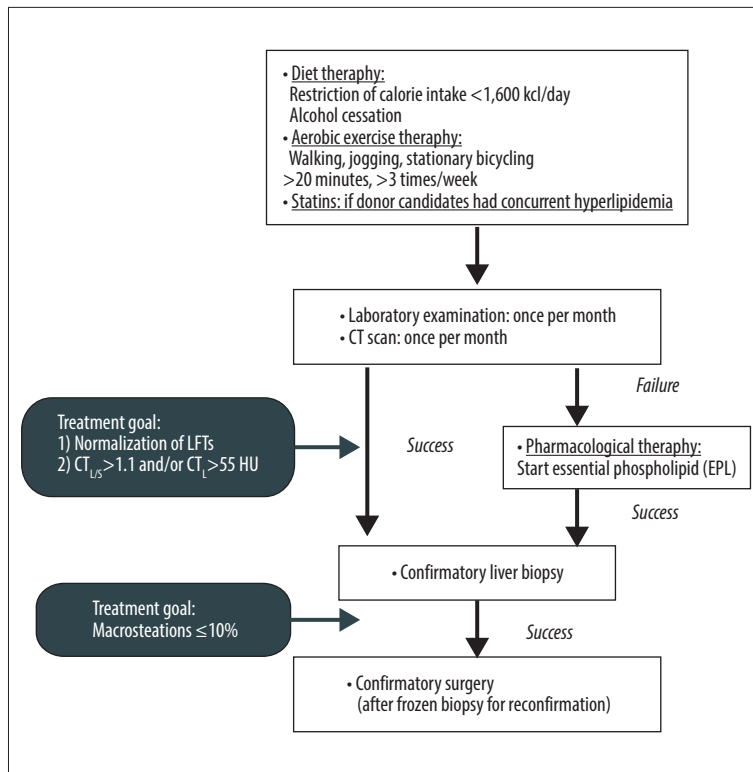
## Material and Methods

Data for this retrospective cohort study were collected from electronic medical chart review. Subjects were donor–recipient pairs who underwent adult-to-adult LDLT from October 2009 through August 2015 at Hokkaido University Hospital, Japan. This study was performed in accordance with the Declaration of Helsinki and was approved by the Review Board at our institution (#018-0088). Informed consent was obtained in the form of opt-out by the document. Those who rejected were excluded.

The eligibility criteria for living donors at our institute included the following: age 18–65 years, body mass index (BMI) less than 25 kg/m<sup>2</sup>, normal liver function tests (LFTs), and no other significant coexisting diseases such as diabetes mellitus, alcohol abuse, or psychiatric disorders. A donor candidate was diagnosed with FL (FL group) when the liver-to-spleen attenuation ratio on CT scan ( $CT_{L/S}$ ) was <1.1 and/or a hepatic attenuation value ( $CT_L$ ) of <55 HU was observed [7–9]. Hepatic and splenic attenuation values were measured on non-contrast CT scan by using the average of 4 circular region-of-interest (ROI) cursors in the liver and 3 in the spleen [7]. The locations of the liver for ROI cursors included right anterior, right posterior, left medial, and left lateral segments [7]. As a control group, donors without fatty infiltration during the same period were selected (non-FL group). For assessment of graft function, data from the corresponding recipient were collected and analyzed.

### Treatment protocol for donors with fatty liver

The treatment protocol for FL primarily comprised diet–exercise therapy and pharmacological intervention (Figure 1) [10,11]. Diet therapy included restriction of calorie intake to fewer than 1600 kcal/day regardless of body weight, and cessation of alcohol consumption. Donors were instructed to perform aerobic exercise (such as walking, jogging, and/or riding a stationary bicycle) for more than 20 min at least 3 times a week. Statins were prescribed when FL candidates had concurrent hyperlipidemia. When a poor response to diet–exercise therapy was recognized, essential phospholipid (1500 mg/day) was added. Treatment efficacy was evaluated by CT study and laboratory examination once per month. When  $CT_{L/S}$  was greater than or equal to 1.1, and  $CT_L$  was more than or equal to 55 HU, a liver biopsy was performed. Finally, when MaS  $\leq 10\%$  was histopathologically confirmed, the donor was considered to be eligible and the operation was planned. Frozen biopsy of a wedge-cut specimen just after laparotomy was also performed in all donors for reconfirmation.



**Figure 1.** Treatment protocol for FL donor candidates at our institution. When a poor response to diet–exercise therapy was recognized, EPL was added. Treatment efficacy was evaluated by a CT scan and laboratory examination once per month. When  $CT_{L/S}$  was greater than or equal to 1.1 and  $CT_L$  was more than or equal to 55 HU, a confirmation liver biopsy was performed. Candidates with  $MaS \leq 10\%$  on biopsy were considered eligible to be a living donor. All donors underwent intraoperative frozen wedge biopsies for reconfirmation.  $CT_L$  – hepatic attenuation value on CT scan;  $CT_{L/S}$  – liver-to-spleen attenuation ratio on CT scan; EPL – essential phospholipid; FL – fatty liver; LFT – liver function test; MaS – macrosteatosis.

### Protocol for immunosuppression

The immunosuppression protocol in our institute is basiliximab induction with a triple regimen of tacrolimus, mycophenolate mofetil, and steroids. Tacrolimus was started on day 4 after transplant, with a target trough level of 10–12 ng/ml during the first postoperative month. Mycophenolate mofetil 500 mg per day was started on day 1 after transplant and gradually increased to 1500 mg per day in 2–3 weeks. The steroid component was completely withdrawn by 4 weeks after transplant.

### Treatment assessment in donors with FL

To determine the effectiveness of treatment in the donors with FL, laboratory findings,  $CT_L$ ,  $CT_{L/S}$ , and BMI were assessed before and after treatment. The influence of the treatment on surgical parameters (surgical time and estimated blood loss) was determined. Short-term outcome after donor hepatectomy was evaluated using peak ALT, peak total bilirubin (T-Bil), and the incidence of morbidity greater than or equal to Clavien-Dindo grade IIIa.

### Assessment of graft function

To evaluate graft function, the following laboratory data were collected: ALT, T-Bil, platelet count (Plt), and prothrombin time-international ratio (PT-INR). The following clinical parameters were also assessed: ascites volume, bile production in recipients

determined through a biliary drainage tube, duration of hospitalization, incidence of PNF and acute cellular rejection (ACR), and 3-month graft and patient survival. Laboratory data, ascites volume, and bile production were noted on postoperative days (PODs) 1, 3, 7, 10, and 14.

### Statistical analysis

Continuous variables are expressed as mean±standard deviation (SD) or median with range. The significance level for all statistical testing was set at  $P < 0.05$  for a two-tailed test. Continuous variables were compared using the  $t$  test or the Mann-Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method. All statistical analyses were performed using JMP Pro®, version 12 (SAS Institute, Inc., Cary, NC, USA).

## Results

### Treatment efficacy in donors with FL

Baseline characteristics of donors in the FL and non-FL groups, as well as recipient demographic characteristics for each group, are shown in Table 1. Of 30 candidates, 8 donors were diagnosed with FL by CT evaluation during the study period and received diet–exercise therapy (FL group). All were successfully

**Table 1.** Baseline characteristics of donors and recipients.

	Non-FL group (n=22)	FL group (n=8) (Before treatment)	P value
<b>Donor</b>			
Age (years)	30 (18–54)	35.5 (21–50)	0.24
Sex, male: female	17: 5	8: 0	0.29
Body weight (kg)	63.7±14.1	71.8±6.6	0.15
BMI (kg/m <sup>2</sup> )	22.2±4.1	25.2±2.0	0.07
Graft type, right lobe: left lobe	0: 22	1: 7	0.27
Remnant liver volume to whole liver volume (%)	65.1±4.3	60.9±8.8	0.26
CT <sub>L</sub> (HU)	61.7 (59.7–71.3)	46.6 (32.7–63)	0.002
CT <sub>L/S</sub>	1.2 (1.1–1.39)	0.95 (0.62–1.06)	0.0007
<b>Recipient</b>			
Age (years)	56 (39–64)	56 (48–69)	0.72
Sex, male: female	11: 11	3: 5	0.69
<b>Diagnosis<sup>6</sup></b>			
HCC	6	2	1.0
HCV	4	0	0.55
PBC	3	1	1.0
Alcoholic	3	1	1.0
NASH	1	1	0.47
HBV	1	0	1.0
Others	4	3	0.34
MELD score	15.6±5.2	15.1±4.2	0.81
Graft volume (mL)	361.5±58.9	400.6±83.0	0.28
GV/SV ratio (%)	31.2±5.0	34.8±6.8	0.14

Age and CT values are presented as the median (range). The other data are presented as the mean±SD. BMI – body mass index; CT<sub>L/S</sub> – liver-to-spleen attenuation ratio on CT scan; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; PBC – primary biliary cirrhosis; NASH – non-alcoholic steatohepatitis; HBV – hepatitis B virus; MELD – model for end-stage liver disease; GV/SV – graft volume to standard volume; FL – fatty liver.

treated and eventually proceeded to donor surgery. Of those, 3 were treated with diet and exercise therapy only, while the other 5 needed additional pharmacological treatment. While heavy alcohol consumption was not observed in any of the donors in the FL group, donors were instructed to completely abstain during the treatment period. The median treatment duration in the FL group was 58 days (range 35–109 days). After the treatment, significant body weight and BMI reduction and CT<sub>L</sub> and CT<sub>L/S</sub> improvements were observed. Confirmatory liver biopsies revealed MaS ≤10% in all donors in the FL group (Table 2). There was no evidence of fibrosis, ballooning, or

lobular inflammation on histopathological examination of the biopsy samples.

Changes in physical status, CT value of the liver, LFTs, and the other laboratory findings in the FL group before and after treatment are shown in Table 3. These parameters, other than total cholesterol (T-Cho) and albumin (Alb) after treatment in the FL group, were comparable to those in the non-FL group. However, T-Cho and Alb were significantly lower in the FL group after treatment compared with those in the non-FL group.

**Table 2.** Summary of the physical, laboratory, and imaging changes after treatment for fatty liver.

Case No.	Sex/age	Coexisting diseases	Alcohol intake	Pharmacological treatment	Treatment duration (days)	Body weight (kg)		BMI (kg/m <sup>2</sup> )		CT <sub>L</sub> (HU)		CT <sub>L/S</sub>		MaS in confirmation Bx
						Before	After	Before	After	Before	After	Before	After	
1	M/47	None	Social	Lipitor, EPL	40	78.6	72.4	24.8	22.9	32.7	61.3	0.85	1.18	5%
2	M/50	None	None	none	36	71.0	68.0	25.2	24.1	52.3	65.3	1.03	1.38	<10%
3	M/47	None	Social	none	106	85.0	81.0	27.4	26.1	50.5	60	0.99	1.18	5–10%
4	M/21	None	None	EPL	46	68.4	62.3	24.1	22	44.7	67.7	0.91	1.46	5%
5	M/28	None	Social	EPL	75	72.9	62.9	28.5	24.6	38.3	60.3	0.75	1.2	10%
6	M/37	Hyper-lipidemia	Social	Lipitor, EPL	109	69.0	65.6	26.1	24.8	63	60.7	1.06	1.21	<5%
7	M/34	Migraine headache	Social	EPL	35	64.8	61.6	21.9	20.8	48.5	61.3	1.05	1.21	<5%
8	M/34	None	None	none	70	64.4	56.5	23.5	20.6	34.7	61.9	0.62	1.12	10%

EPL – essential phospholipid; CT<sub>L/S</sub> – liver-to-spleen attenuation ratio on CT scan; CT<sub>L</sub> – hepatic attenuation value on CT scan; MaS – macrosteatosis; N.S. – not stated.

**Table 3.** Therapeutic effects on donors after the treatment for fatty liver.

	Non-FL group (n=21)	FL group (n=9)		P value*	P value**
		Before treatment	After treatment		
Body weight (kg)	63.7±14.1	71.8±6.6	66.3±7.1	0.0004	0.64
BMI (kg/m <sup>2</sup> )	22.2±4.1	25.2±2.0	23.2±1.9	0.0009	0.53
CT <sub>L</sub> (HU)	61.7 (59.7–71.3)	46.6 (32.7–63)	61.3 (60–67.7)	0.003	0.79
CT <sub>L/S</sub>	1.2 (1.1–1.39)	0.95 (0.62–1.06)	1.2 (1.12–1.46)	0.0006	0.45
AST (IU/L)	19.5±5.6	26.4±4.9	22.6±4.9	0.11	0.19
ALT (IU/L)	18.6±9.2	39.0±20.2	23.8±10.3	0.03	0.21
γ-GTP (IU/L)	19.1±6.3	43.8±26.5	21.0±11.0	0.02	0.68
TG (mg/dL)	88.6±43.2	182.3±186.6	90.4±28.8	0.22	0.92
ALP (IU/L)	223.9±53.5	211.9±60.0	220.4±92.0	0.54	0.93
T-Cho (mg/dL)	199.3±25.4	205.6±48.5	166.4±16.3	0.06	0.004
Alb (mg/dL)	4.8±0.34	4.8±0.29	4.6±0.18	0.05	0.03
ChE (IU/L)	344.6±44.1	404.8±66.5	313.3±43.8	0.0001	0.11

CT values are presented as the median (range). The other data are presented as the mean±SD. \* FL group before treatment vs. after treatment; \*\* FL group after treatment vs. non-FL group. FL – fatty liver; CT<sub>L/S</sub> – liver-to-spleen attenuation ratio on CT scan; ALT – alanine transaminase; AST – aspartate transaminase; γ-GTP – gamma-glutamyl transferase; TG – triglyceride, ALP – alkaline phosphatase; T-Cho – total cholesterol; Alb – albumin; ChE – cholinesterase.

### Influence of treatment on donor surgery and postoperative course

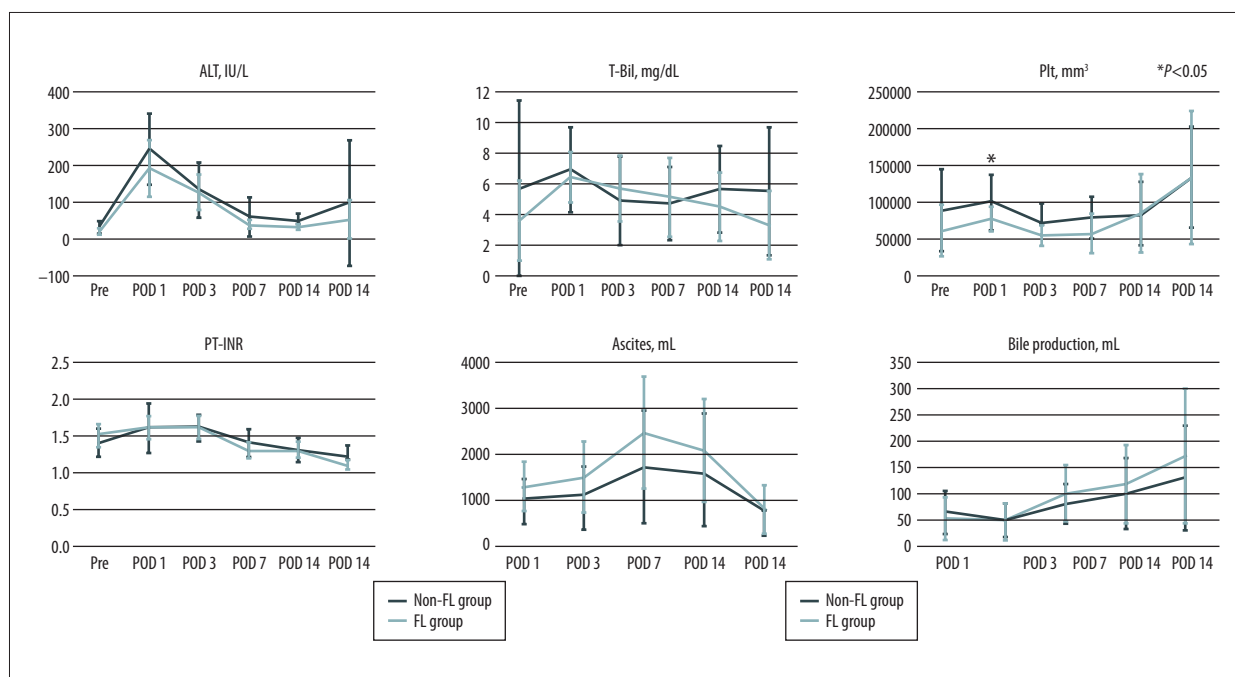
Surgical parameters and short-term outcome of donor hepatectomy are shown in Table 4. Surgical time and

estimated blood loss in the FL and non-FL groups were comparable: 404.8±53.1 min vs. 371.5±56.4 min ( $P=0.17$ ) and 180.6±134.7 mL vs. 200.2±193.7 mL ( $P=0.8$ ), respectively. The postoperative evaluation of maximum ALT and T-Bil in the FL and non-FL groups showed no significant differences:

**Table 4.** Surgical parameters and short-term outcomes in FL and non-FL donors.

	Non-FL group (n=21)	FL group (n=9)	P value
Surgical time (min)	371.5±56.4	404.8±53.1	0.17
Estimated blood loss (mL)	200.2±193.7	180.6±134.7	0.8
Maximum ALT (IU/L)	196.8±57.4	189.6±94.7	0.81
Maximum T-Bil (mg/dl)	1.7±0.5	2.2±1.1	0.26
Major morbidity	None	None	
Mortality	None	None	

All data are presented as the mean±SD. FL – fatty liver; ALT – alanine transaminase; T-Bil – total bilirubin.



**Figure 2.** Graft function 2 weeks after surgery in the FL and non-FL groups. Except for the platelet count on POD 1, there were no significant differences in postoperative laboratory findings, ascites volume, or bile production on PODs 1, 3, 7, 10, and 14. FL – fatty liver; POD – postoperative day.

189.6±94.7 IU/L vs. 196.8±57.4 IU/L ( $P=0.81$ ) and 2.2±1.1 mg/dL vs. 1.7±0.5 mg/dL ( $P=0.26$ ), respectively. Morbidity greater than or equal to the Clavien-Dindo classification of grade IIIa was not experienced in either group.

### Early graft function in recipients

Early graft function results in recipients is presented in Figure 2. There were no significant differences in postoperative laboratory findings during the first 2 weeks between the FL and non-FL groups, as shown on POD 7: ALT (38.6±9.8 IU/L vs. 58.6±52 IU/L;  $P=0.11$ ), T-Bil (5.1±2.5 mg/dL vs. 4.7±2.3 mg/dL;  $P=0.71$ ), Plt (56625±26934.8/mm<sup>3</sup> vs. 79636.4±27453.3/mm<sup>3</sup>;  $P=0.059$ ), PT-INR (1.3±0.11 vs. 1.4±0.19;  $P=0.68$ ), ascites volume (2479.6±1208.8 mL/day vs. 1764.2±1211 mL/day;

$P=0.18$ ), and bile production (100.9±51.4 mL/day vs. 81.3±36.8 mL/day;  $P=0.28$ ), respectively. Although Plt on POD 1 was significantly lower in the FL group than in the non-FL group (77375±15834.6/mm<sup>3</sup> vs. 100272.7±37665/mm<sup>3</sup>;  $P=0.033$ ), the count reached comparable levels soon thereafter. There was no significant difference in the length of the hospital stay: 79.1±39.1 days in the FL group vs. 83.4±37.9 days in the non-FL group,  $P=0.79$ . PNF was not observed in either group. ACR within 1 month was not observed in the FL group, while it was observed in 18.2% of the non-FL group ( $P=0.55$ ). Graft and patient survival at 3 months were 100% in both groups.

## Discussion

Our results show that treatment for donors with FL was effective, and they accomplished the goal in a median period of 58 days. The duration of treatment was almost the same as previously reported, in which the combination therapy of diet and exercise with or without medication was applied for treatment [6,12–14]. For pharmacological treatment, only lipid-lowering drugs such as statins and bezafibrate were used in some reports [12,14]. Because there is evidence showing the efficacy of in reducing LFTs in patients with FL and in improving liver morphology on imaging studies, we applied it in our treatment protocol [15,16].

Donor safety is one of the most important considerations in LDLT. Donor hepatectomy in those with fatty infiltration should be performed carefully because some investigators have reported that hepatosteatosis has a detrimental effect on the postoperative course after major hepatectomy [17–19]. A retrospective study including 386 patients who underwent hepatectomy for colorectal metastases found that increased morbidity, a higher incidence of infective complications, and significantly elevated postoperative LFT results were associated with the degree of underlying liver steatosis [17]. A meta-analysis of the major hepatectomies including living donation concluded that fatty infiltration of the liver directly influenced postoperative complications and mortality [18]. In our study, the donors in the FL group showed a comparable perioperative outcome to those in the non-FL group for operative time, estimated blood loss, postoperative T-Bil and ALT, and incidence rates of mortality and severe morbidity. Thus, the treatment for donor FL might contribute to donor safety.

We also evaluated early graft function using postoperative LFTs, ascites volume, and bile production. These parameters and the duration of hospitalization, incidence of PNF, and 3-month graft and patient survival were also similar between the FL and non-FL groups. These results suggest that the treatment for FL donors is a practical option for non-urgent recipients who can wait several months for LDLT. In terms of the impact of MaS on ACR, a 2.5-fold increased risk of ACR in donors with MaS >30% has been reported [20]. In our study, however, no ACR was experienced in the FL group, suggesting that amelioration of fatty infiltration in the graft might be attributable, at least in part, to inhibiting ACR.

In previous studies, the efficacy of treatment for FL was assessed by body weight, BMI, and preoperative liver biopsy [6,12–14]. Radiological evaluations including  $CT_L$  and  $CT_{L/S}$  were rarely used. Although the confirmation of histological improvement after the treatment is mandatory, inevitable complications should be considered when liver biopsy is performed, especially in the case of steatotic liver. Indeed, the most recent study by Novruzov et al. demonstrated that CT scans can provide

detailed evaluation of liver parenchyma to avoid unnecessary liver biopsy [21]. Thus, we selected imaging ( $CT_L$  and  $CT_{L/S}$ ) for screening rather than liver biopsy, to avoid the risk of biopsy-related complications. Several studies have revealed the correlation between  $CT_L$  or  $CT_{L/S}$  and histological severity of fatty infiltration [8,22,23]; they reported that a cut-off value of  $CT_L$  of 35–58 HU and  $CT_{L/S}$  of 0.9–0.98 provided a sensitivity of 79%–100% and 79%–91% and a specificity of 61.1–97% and 55.6–97% for detecting moderate MaS (>20–30%), respectively. These discrepancies in the sensitivity and specificity, likely due to the differences of cohort number, patients' characteristics, and performance of modality, can cause difficulty in determining an optimal cut-off value. However, in a large retrospective cohort study in Japan that evaluated the relationship between degree of fatty infiltration and  $CT_{L/S}$ , the authors argued that the optimal value of  $CT_{L/S}$  to predict >30% hepatosteatosis was 1.1 [7]. In addition, Park et al. reported that the cut-off value of 58 HU for  $CT_L$  provided an excellent sensitivity of 100% and a specificity of 95% for the diagnosis of MaS  $\geq$ 30% [8]. Furthermore, a very high reproducibility of CT attenuation value was demonstrated in the largest cohort study, including 6814 participants [9]. The authors of the study concluded that CT scans can be a reliable diagnostic tool for FL. Therefore, we selected  $CT_L$  55 and  $CT_{L/S}$  1.1 as a cut-off value by which donor candidates were considered to have equal to or more than moderate MaS. Actually, only less than 10% steatosis was observed by confirmatory liver biopsy, once candidates achieved  $CT_L$  >55 HU and  $CT_{L/S}$  >1.1. Therefore, these CT values might be useful as a noninvasive preoperative evaluation and could be a surrogate modality to liver biopsy.

Fatty infiltration of the liver is frequently encountered in the setting of LDLT. It is a common reason for ineligibility in living donation, which is reported in up to 38.4% of donors [24]. Non-alcoholic fatty liver disease (NAFLD) is a liver disorder with an increasing worldwide incidence rate, and the prevalence of this disease is increasing in parallel with obesity and metabolic syndrome. A cohort study in Japan showed that the rate of NAFLD identified by ultrasonography increased from 13% to 30% during the last decade [25]. As the population who have FL increases, management of donor candidates with FL becomes a more important issue.

## Conclusions

In conclusion, our study showed the efficacy of short-term treatment for FL for both donors and recipients. Because metabolic syndrome will become more prevalent in the future, management of donors with a FL is an important issue to consider. Diet and exercise with or without pharmacological therapy as well as noninvasive evaluation by  $CT_L$  and  $CT_{L/S}$  would be an option to resolve this issue.

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## Conflicts of interest

None.