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ORIGINAL ARTICLE

Long-term risk of a fatty liver in liver donors

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Abstract

Aim: Approximately 30 years have passed since the first experience of living donor liver transplantation. The time to evaluate the long-term safety of living donors has been fulfilled. Meanwhile, nonalcoholic fatty liver disease is increasingly common and a critical problem. The aim of this study was to evaluate the safety of living donor, focusing on fatty liver postdonation hepatectomy.

Methods: Living donors ($n = 212$, 1997–2019) were evaluated by computed tomography (CT) at >1-year postdonation. A liver to spleen (L/S) ratio of <1.1 was defined as fatty liver.

Results: Among 212 living liver donors, 30 (14.2%) detected fatty liver at 5.3 ± 4.2 years postdonation. The cumulative incidence rates of fatty liver were 3.1%, 12.1%, 22.1%, and 27.7% at 2, 5, 10, and 15 years postdonation, respectively. Of 30 subjects who developed fatty liver, 18 (60%) displayed a severe steatosis (L/S ratio <0.9). Five (16.7%) had a prior history of excessive alcohol abuse. More than 30% developed metabolic syndrome including obesity, hyperlipidemia, and diabetes. Although six (20%) had a Fib-4 index of >1.3, which included a case with a Fib-4 index of >2.67, no significant increased Fib-4 index was observed in the subjects with fatty liver as compared to those without fatty liver ($p = 0.66$). The independent predictive risk factors for developing fatty liver were male sex, pediatric recipient, and higher body mass index (>25) at donation.

Conclusion: Living donors with risk factors for developing fatty liver should be carefully followed-up for the prevention and management of metabolic syndrome.

KEYWORDS
body mass index, liver transplantation, living donor, pediatrics

1 | INTRODUCTION

Approximately 30 years have passed since the first experience of living donor liver transplantation (LDLT) in Japan. Due to a severe shortage of deceased donors in Japan (i.e. <100 deceased donors per year), LDLT is the mainstay for LT. Of note, living donor safety is the fundamental principle of LDLT. Although the risk factors for postoperative complications in living donors have been investigated,[1,2]

there is limited evidence of the long-term outcomes of living donors. A recent nationwide survey in Korea showed that 89 of 12 371 donors died during 7.9 ± 4.6 years of follow-up after liver donation.[3] Importantly, the mortality rate of living donors was significantly higher than that of a matched healthy group.[3] A multicenter study in Japan ($n = 374$), however, demonstrated that long-term favorable quality of life in living donors was maintained in comparison to the standard population.[4]

Metabolic syndrome and obesity are regarded as a global epidemic. Consistently, nonalcoholic fatty liver disease (NAFLD) is a critical problem.[5] It is estimated that NAFLD affects one-third of the adult population.[6] Furthermore, approximately 10%–20% of patients with NAFLD seem to develop nonalcoholic steatohepatitis (NASH), which leads to liver cirrhosis. Additionally, NAFLD is a risk factor for the development of hepatocellular carcinoma (HCC).[7] Worldwide, 200 million people suffered from HCC associated with NAFLD.[6] Because of the increasing prevalence of NAFLD, there may be an unmet need for the evaluation of living donor safety. Furthermore, because liver graft steatosis is one of the risk factors for graft dysfunction, development of fatty liver of living donors postdonation may be associated with the recipient status. The genetic risk factors for NAFLD such as *PNPLA3* and *TM6SF2* have been detected.[6] Developing fatty liver may be a risk for both recipients and donors, in particular, who is a blood-related family member, as usually seen in LDLT.

Herein, we evaluated the incidence, risk factors, and clinical impact of fatty liver in living donors in a long-term after donation hepatectomy.

2 | METHODS

2.1 | Patients

We retrospectively evaluated 264 living donors for LT in our institutes between Sept 1997 and Feb 2019. The eligibility for a living donor was based on institutional requirements according to the Japanese transplant committee, as follows: (1) blood relative within the second degree or spouse of recipient; (2) absence of physical and mental illness; (3) ABO-identical or compatible; (4) age, 20–65 years; and (5) volunteered freely with an understanding of the risks and benefits. In particular, the eligibility criteria for living donor on liver steatosis at our institute required a nonenhanced computed tomography (CT) liver (L)-to-spleen (S) ratio (L/S ratio) of greater than 1.1 within 6 months before donation hepatectomy. This was confirmed by intraoperative pathological diagnosis, i.e. macrovesicular steatosis less than 5% of hepatocytes. Among these donors, 212 cases who underwent follow-up nonenhanced-CT examinations at >1 year after donation hepatectomy (mean: 1983 days), were enrolled in the study. The follow-up schedule for living donors in our institute consisted of laboratory examinations and CT evaluation at 1, 3, and 12 months after donation, and annually thereafter until at least 5 years postdonation. To identify the predictive risk factors for the development of a fatty liver postdonation hepatectomy, we evaluated the following clinical parameters: sex, age, height, weight, body mass index (BMI), history of diet-exercise, daily alcohol consumption, donation surgery, ratio of graft volume relative to standard liver volume (Gv/Sv), laboratory data (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], total cholesterol [T-cho], triglyceride [TG]), and relationship to the recipient. We also collected the recipients' information, i.e. pediatric or adult, and primary liver disease (Table 1). Daily alcohol consumption was categorized by quantity of daily ethanol intake, i.e. light: ≤20.0, moderate: 20.1–59.9, heavy: ≥60[8] (Table 1). In addition, to evaluate the status of living donors with or without developing fatty liver postdonation, we compared the clinical parameters, including the age, years until CT evaluation, laboratory data, AST-to-platelet ratio index (APRI), Fibrosis-4 (Fib-4) index, waist circumference (cm), and the subcutaneous and visceral fat area (cm^2) at the umbilical level (Table 3). The waist circumference and subcutaneous and visceral fat area were evaluated using the SYNAPSE VINCENT software program (Fujifilm).[9]

2.2 | Evaluation of hepatic steatosis

The ratio of attenuation values in nonenhanced-CT imaging between the liver and spleen was evaluated as the L/S ratio. Both the liver and spleen attenuation values were evaluated as the mean value measured by areas of circular regions-of-interest, as shown in Figure 1. The L/S ratio was calculated by the average attenuation value of the liver (3 points) divided by the attenuation value of the spleen. The cutoff value of the L/S ratio to predict steatosis was 1.1, according to previous reports.[10,11]

2.3 | Statistical analysis

Patient characteristics are reported as the median and range or the mean and standard deviation. Continuous variables were evaluated by the Mann–Whitney *U* test. The frequencies of categorical variables were evaluated by Fisher's exact test. A multivariate regression analysis was performed using logistic regression and Cox proportional hazards regression. The highly correlated variables were excluded from the regression models to avoid multicollinearity. All statistical analysis were performed using JMP Pro version 16 (SAS Institute). p values of <0.05 were considered statistically significant.

3 | RESULTS

3.1 | The incidence of fatty liver in living donors after donation hepatectomy

We evaluated 212 living donors in the long term after donation hepatectomy (i.e. average postoperative follow-up period: 5.6 ± 4.3 years). The cutoff value of the L/S ratio for fatty liver was <1.1.[10] Thirty

TABLE 1 Univariate analysis for predictive risk factors of a fatty liver in the long-term postdonation

	No fatty liver	Fatty liver	*p*
Demographics	*n* = 182	*n* = 30	
Male, *n* (%)	94 (51.7%)	22 (73.3%)	0.024*
Age at donation	34.0 (18.0–66.0)	33.5 (21.0–62.0)	0.90
Height at donation (cm)	163.9 ± 8.4	167.7 ± 7.5	0.027*
Weight at donation (kg)	59.2 ± 11.0	69.3 ± 12.9	<0.0001**
BMI at donation	22.0 ± 3.1	24.6 ± 3.8	0.0003**
LS ratio of first CT exam pre-surgery	1.202 ± 0.14	1.203 ± 0.13	0.82
Diet-exercise Tx at donation, *n* (%)	18 (10.1%)	9 (30.0%)	0.0066*
Recipient: pediatrics	50 (27.5%)	15 (50.0%)	0.017*
Relationship with recipient, *n* (%)			
Father	20 (11.0%)	11 (36.7%)	0.0009**
Mother	28 (15.4%)	5 (16.7%)	0.86
Husband	19 (10.4%)	3 (10.0%)	0.94
Wife	16 (8.8%)	1 (3.3%)	0.26
Son	38 (20.1%)	6 (20.0%)	0.98
Daughter	26 (14.3%)	2 (6.7%)	0.40
Siblings	19 (10.4%)	2 (6.7%)	0.50
Grandfather or grandmother	6 (3.3%)	0	0.17
Others	8 (4.4%)	0	0.11
Daily alcohol consumption (g) until donation, *n* (%)[8]			
None	44 (24.2%)	6 (20.0%)	0.69
Light (≤20.0)	80 (44.0%)	11 (36.7%)	
Moderate (20.1–59.9)	40 (22.0%)	8 (26.7%)	
Heavy (60≤)	17 (9.3%)	5 (16.7%)	
Recipient's primary disease, *n* (%)			
BA	41 (22.5%)	11 (36.7%)	0.11
HBV	27 (14.8%)	1 (3.3%)	0.048*
HCC	23 (12.6%)	1 (3.3%)	0.09
PBC	23 (12.6%)	2 (6.7%)	0.99
Fulminant	15 (8.24%)	3 (10.0%)	0.75
HCV	12 (6.6%)	2 (6.7%)	0.95
EtOH	7 (3.9%)	2 (6.7%)	0.45
NASH	6 (3.3%)	1 (3.3%)	0.99
PSC	4 (2.2%)	0	0.42
ADPKD	4 (2.2%)	1 (3.3%)	0.68
Congenital metabolic disease	4 (2.2%)	1 (3.3%)	0.68
Wilson	3 (1.7%)	0	0.49
Others	13 (7.1%)	5 (17.2%)	0.71
Donor surgery, *n* (%)			
Left lateral lobe	28 (15.4%)	13 (43.3%)	0.0010**
Left hepatic lobe	91 (50.0%)	12 (40.0%)	0.31
Right hepatic lobe	63 (34.6%)	5 (16.7%)	0.040*
Graft volume (Gv, g)	421.3 ± 153.8	375.7 ± 134.8	0.12
Gv/standard liver volume	43.3 (22.0–133.7)	68.8 (26.9–139.8)	0.0014*
Remnant volume	773.2 ± 245.7	925.0 ± 263.7	0.0060*

(Continues)

TABLE 1 (Continued)

	No fatty liver	Fatty liver	*p*
Laboratory data at donation			
AST (U/L)	19.8 ± 6.0	22.0 ± 7.3	0.10
ALT (U/L)	19.7 ± 11.9	24.9 ± 12.7	0.013*
GGT (U/L)	25.8 ± 23.6	31.3 ± 20.4	0.061
T-cho (mg/dL)	184.2 ± 33.7	195.1 ± 31.0	0.13
TG (mg/dL)	86.7 ± 51.5	100.2 ± 46.2	0.071

Note: Data are shown as mean ± standard deviation or median and interquartile range.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; BMI, body mass index; EtOH, alcoholic cirrhosis; Fib4, fibrosis 4; GGT, gamma-glutamyl transferase; Gv, graft volume; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; T-cho, total cholesterol; TG, triglyceride; Tx, treatment.

*$p < 0.05$, **$p < 0.005$; Mann–Whitney *U* test or Fisher's exact test.

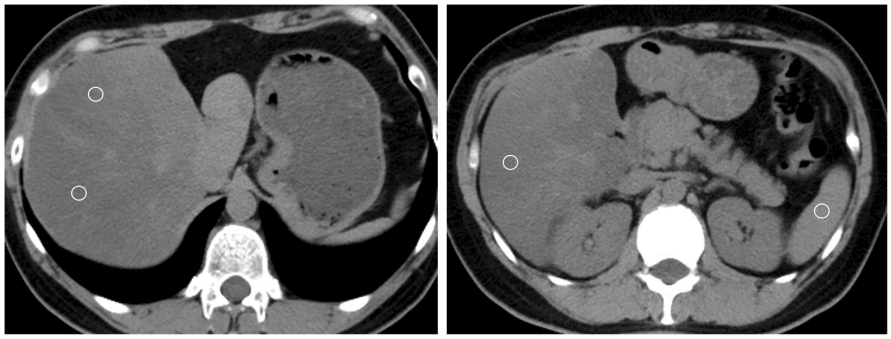

FIGURE 1 The ratio of attenuation values on nonenhanced-CT between the liver (L) and spleen (S) was evaluated as the L/S ratio. The mean liver and spleen attenuation values were measured in circular regions-of-interest. The L/S ratio was calculated as the average attenuation value of the liver (3 points) divided by the attenuation value of the spleen. The cutoff value of the L/S ratio for the prediction of steatosis was 1.1 according to a previous report.[10]

(14.2%) of 212 living donors developed fatty liver at 5.3 ± 4.2 years postdonation hepatectomy (Figure 2A). The 6, 19, 26, and 27 of living donors developed fatty liver until 2, 5, 10, and 15 years postdonation hepatectomy, respectively. The cumulative incidence rates of fatty liver in living donors displayed 3.1%, 12.1%, 22.1%, and 27.7% at 2, 5, 10, and 15 years postdonation, respectively (Figure 2B). Of the 30 living donors with fatty liver, 18 (60%) showed an L/S ratio of <0.9, indicating severe fatty liver (Figure 2A). The L/S ratio of subjects who developed a fatty liver gradually decreased postdonation hepatectomy (Table S1). In addition, six (20%) had a Fib-4 index of >1.3, which included a case with a Fib-4 index of >2.67 (2.839). Five (16.7%) subjects had a prior history of excessive alcohol abuse (daily 60 g or higher[8]) before hepatectomy (Table 1). Further, greater than 30% of subjects developed metabolic syndrome, i.e. 10 (33.3%) of obesity (BMI 25 or higher), 12 (40%) of hyperlipidemia, and 15 (50.0%) with an abnormal range of HbA1c (prediabetes: A1c 5.7%–6.4%, 11 subjects; diabetes: A1c 6.5% or higher, four subjects) were observed.

3.2 | The risk factors for fatty liver in living donors after donation hepatectomy

To evaluate predictive risk factors for the development of fatty liver in living donors after donation hepatectomy, we evaluated the clinical parameters at donation hepatectomy between the living donors with ($n = 30$) and without ($n = 182$) fatty liver postdonation hepatectomy (Table 1). Univariate analyses revealed significant differences in the following factors (Table 1): male sex (fatty liver vs. no fatty liver: 73.3% vs. 51.7%, *$p = 0.024$), height (167.7 ± 7.5 cm vs. 163.9 ± 8.4, *$p = 0.033$), weight (68.9 ± 12.9 kg vs. 59.2 ± 11.0, **$p < 0.0001$), BMI (24.6 ± 3.8 vs. 22.0 ± 3.1, **$p = 0.0003$), history of diet-exercise treatment for donation (30.0% vs. 10.1%, *$p = 0.0066$), pediatric recipient (50.0% vs. 27.5%, *$p = 0.017$), father of recipient (36.7% vs. 11.0%, **$p = 0.0009$), left lateral graft (43.3% vs. 15.4%, **$p = 0.0010$), Gv/Sv (68.8% [26.9–139.8] vs. 43.3 [22.0–133.7], *$p = 0.0014$), remnant liver volume (925.0 ± 263.7 mL vs. 773.2 ± 245.7, *$p = 0.006$), and ALT (24.9 ± 12.7 U/L vs. 19.7 ± 11.9, *$p = 0.013$). A multivariate logistic regression analysis showed that male sex (*$p = 0.011$), pediatric recipient (**$p = 0.0010$), and higher BMI at liver donation (>25, *$p = 0.0033$) were significant risk factors for fatty liver during long-term follow-up after donation (Table 2). Furthermore, the multivariate analysis using Cox proportional hazards model confirmed that male sex (hazard ratio [HR], 2.42, *$P = 0.040$), pediatric recipient (HR, 3.62, *$p = 0.0014$), and BMI > 25 at donation (HR, 2.94, *$p = 0.0083$) were significant risk factors for developing fatty liver of living donor after donation.

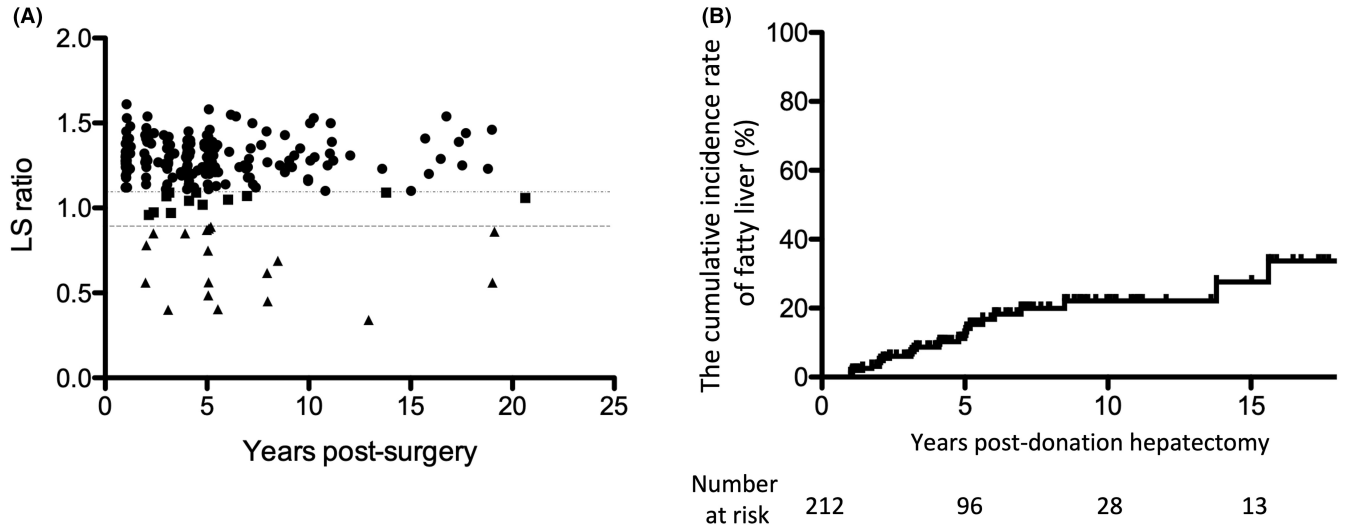

FIGURE 2 The occurrence of a fatty liver postdonation hepatectomy. (A) The relationship between the L/S ratio of living donors and the time posttransplantation. Each dot represents the lowest L/S ratio among subjects who developed a fatty liver during the postdonation course or the most recent data for the subjects who did not develop a fatty liver. In the dot plots, filled squares, triangles, and circles indicate an L/S ratio <1.1, <0.9 and otherwise, respectively. (B) The cumulative incidence rate of fatty liver postdonation hepatectomy is shown.

TABLE 2 Multivariate analysis of predictive risk factors for fatty liver after surgery

Risk factors	Odds ratio	95% CI		*p*-value
		Lower	Upper	
Male	3.162	1.24	8.03	0.011*
Pediatric recipient	4.340	1.78	10.56	0.0010**
BMI > 25	3.823	1.58	9.27	0.0033*

Abbreviation: BMI, body mass index.
*$p < 0.05$, **$p < 0.005$.

3.3 | Differences in clinical parameters in the long-term postdonation between subjects with and without a fatty liver

To evaluate the liver function and metabolic syndrome involving a fatty liver, we compared the data postdonation between subjects with and without a fatty liver. As expected, the AST (30.9 ± 14.9 vs. 21.1 ± 5.9, **$p < 0.0001$), ALT (48.4 ± 41.8 vs. 18.9 ± 12.8, **$p < 0.0001$), GGT (84.9 ± 166.6 vs. 30.7 ± 29.5, **$p < 0.0001$), TG (163.4 ± 132.5 vs. 103.0 ± 75.9, **$p = 0.0004$), APRI (0.49 ± 0.28 vs. 0.34 ± 0.13, **$p = 0.0009$), waist circumference (93.10 ± 10.89 vs. 80.36 ± 9.48, **$p < 0.0001$), subcutaneous fat area (199.47 ± 110.95 vs. 125.69 ± 74.10, **$p = 0.0002$), and visceral fat area (132.03 ± 67.94 vs. 63.15 ± 45.50, **$p < 0.0001$) were significantly higher in the donors who developed a fatty liver than in those who did not (Table 3). Of note, the visceral fat area in the subjects who developed a fatty liver was nearly twice that in the subjects who did not develop a fatty liver. However, no significant increase in the Fib4-index was observed in living donors who developed a fatty liver during long-term follow-up compared to those without a fatty liver.

3.4 | Relationship between recipients and living donors in the development of steatosis

To clarify whether fatty liver in living donors eventually influenced graft steatosis in LT recipients during long-term follow-up, we evaluated the correlation of the L/S ratio between recipients and living donors. An L/S ratio of <1.1 was found after LT in 40 recipients (18.9%, filled squares and empty circles, Figure 3A). Of the 40 LT recipients with fatty liver, seven cases had related living donors who developed fatty liver (empty circles, 17.5%, Figure 3A). In addition, on evaluating the L/S ratio of recipients at the same time of donor CT examination, 27 (12.7%) recipients displayed an L/S ratio of <1.1 (Figure 3B). Consistently, both fatty liver in recipient and donor (empty circles, Figure 3B) was observed in only five cases. Both data in Figure 3A,B revealed that fatty liver did not necessarily coincide in both the recipient and donor (*R* squares were 0.00358 and 0.014 in Figure 3A,B, respectively). Moreover, the graft survival rates after LT did not differ according to the development of fatty liver in the living donor (Figure 3C) as well as diet-exercise treatment predonation (Figure 3D).

4 | DISCUSSION

In this study, we demonstrated that 14.2% of living donors developed fatty liver after donation hepatectomy. Consistently, recent single-institution studies in Japan revealed that the incidence of fatty liver in the living donor after donation hepatectomy was 3.8%–14.5%.[12,13] In the general population, a cross-sectional study of Japanese adults ($n = 11\,714$) revealed NAFLD in 20.4% of subjects.[14] Another study of 8352 adult subjects who received a health checkup revealed that the prevalence of NAFLD was 29.7%.[15] Worldwide, the increasing incidence of NAFLD is affecting the suitability of potential living

TABLE 3 Differences in clinical parameters between living donors who did and did not develop a fatty liver in the long-term postdonation

	No fatty liver	Fatty liver	*p*
Demographics	*n* = 182	*n* = 30	
Age at CT evaluation	40.1 (22.1–80.8)	41.4 (25.5–74.6)	0.64
Years postdonation until CT	5.27 ± 3.97	7.48 ± 5.66	0.033*
Laboratory data at CT evaluation			
Platelet ($\times 10^4/\mu L$)	21.9 ± 5.6	22.7 ± 5.9	0.45
AST (U/L)	21.1 ± 5.9	30.9 ± 14.9	<0.0001**
ALT (U/L)	18.9 ± 12.8	48.4 ± 41.8	<0.0001**
GGT (U/L)	30.7 ± 29.5	84.9 ± 166.6	<0.0001**
T-cho (mg/dL)	185.5 ± 34.4	194.5 ± 27.2	0.12
TG (mg/dL)	103.0 ± 75.9	163.4 ± 132.5	0.0004**
APRI	0.34 ± 0.13	0.49 ± 0.28	0.0009**
Fib4-index	1.06 ± 0.56	1.01 ± 0.56	0.66
Waist circumference (cm)	80.36 ± 9.48	93.10 ± 10.89	<0.0001**
Subcutaneous fat area (cm^2)	125.69 ± 74.10	199.47 ± 110.95	0.0002**
Visceral fat area (cm^2)	63.15 ± 45.50	132.03 ± 67.94	<0.0001**

Note: Data are shown as mean ± standard deviation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; Fib4, fibrosis 4; GGT, gamma-glutamyl transferase; T-cho, total cholesterol; TG, triglyceride.

*$p < 0.05$, **$p < 0.005$; Mann–Whitney *U* test.

donor candidates. A recent study reported that 68.3% of potential LDLT donors were not suitable due to NAFLD.[16] Thus, fatty liver is a considerable problem in the LDLT setting. With diet-exercise or pharmacological treatment, the problems associated with fatty liver in living donor candidates can be substantially improved in order to eventually meet the selection criteria for donors (e.g. less than 5% steatosis).[11] In this study, we thought to examine the risk of developing fatty liver after donation hepatectomy in order to guarantee the safety of living donors. Our data demonstrated that more than half of patients who developed fatty liver progressed to severe fatty liver (L/S ratio < 0.9; Figure 2), and the visceral fat area in donors with a fatty liver was nearly twice that in donors without a fatty liver. Previous studies have demonstrated that obesity is negatively associated with the physical quality of life of living donors.[17,18] Of note, these patients may be at risk for the development of NASH, leading to cirrhotic liver failure as well as HCC. We demonstrated living donors who developed fatty liver during long-term follow-up seldom showed an increased Fib-4 index. One case in which the Fib-4 index increased to >2.67, did not demonstrate any macroscopically morphological change (e.g. liver cirrhosis). A previous study showed that steatotic liver progresses to NASH in ~40% of cases.[5,19] Further, NAFLD has been reported to be associated with ischemic heart disease and stroke.[20] Careful follow-up and treatment are required for living donors, in particular those who have severe fatty liver and an increased Fib-4 index.

We showed that male sex was a significant risk factor for the development of fatty liver after donation hepatectomy. Although an international study and meta-analysis showed no sex differences in the global prevalence of NAFLD,[5] a study in Japan revealed that the prevalence of NAFLD was 32.2% in men (*n* = 5811) and 8.7% in women (*n* = 5903).[14] Another study of Japanese adults who received a health checkup showed that the prevalence of NAFLD was 41.0% in men (*n* = 2627) and 17.7% in women (*n* = 2448).[15] These studies in Japan support our Japanese data showing that male sex was a significant risk factor for fatty liver after donation-hepatectomy.

However, the possibility was raised that male sex was the only risk factor for fatty liver, regardless of the involvement of a living donor; we therefore conducted a subanalysis of male living donors (*n* = 116, Figure S1). The occurrence of fatty liver and abnormal liver functional test results after donation hepatectomy was significantly associated with being a male living donor for a pediatric recipient (*n* = 26, Figure S1). In addition, all 10 male donors for pediatric recipients were the recipient's father. This result suggests that not only male sex but donation for a pediatric recipient (i.e. being the recipient's father) is a risk factor for the development of fatty liver postdonation hepatectomy.

We demonstrated that donation for a pediatric recipient was a risk factor for the development of fatty liver (Table 2). Reportedly, high levels of stress and the burden on most parents of pediatric organ transplant recipients continues after transplantation.[21] It assumed that this stressful situation may affect nutrition or alcoholic intake and suggests that, in addition to consideration of the liver function, we should consider family, social, and psychological aspects in follow-up care for living donors.[18] On the other hand, in living donors for adult recipients, future health risks may be a matter of concern, in particular, life-threatening disease similar to the

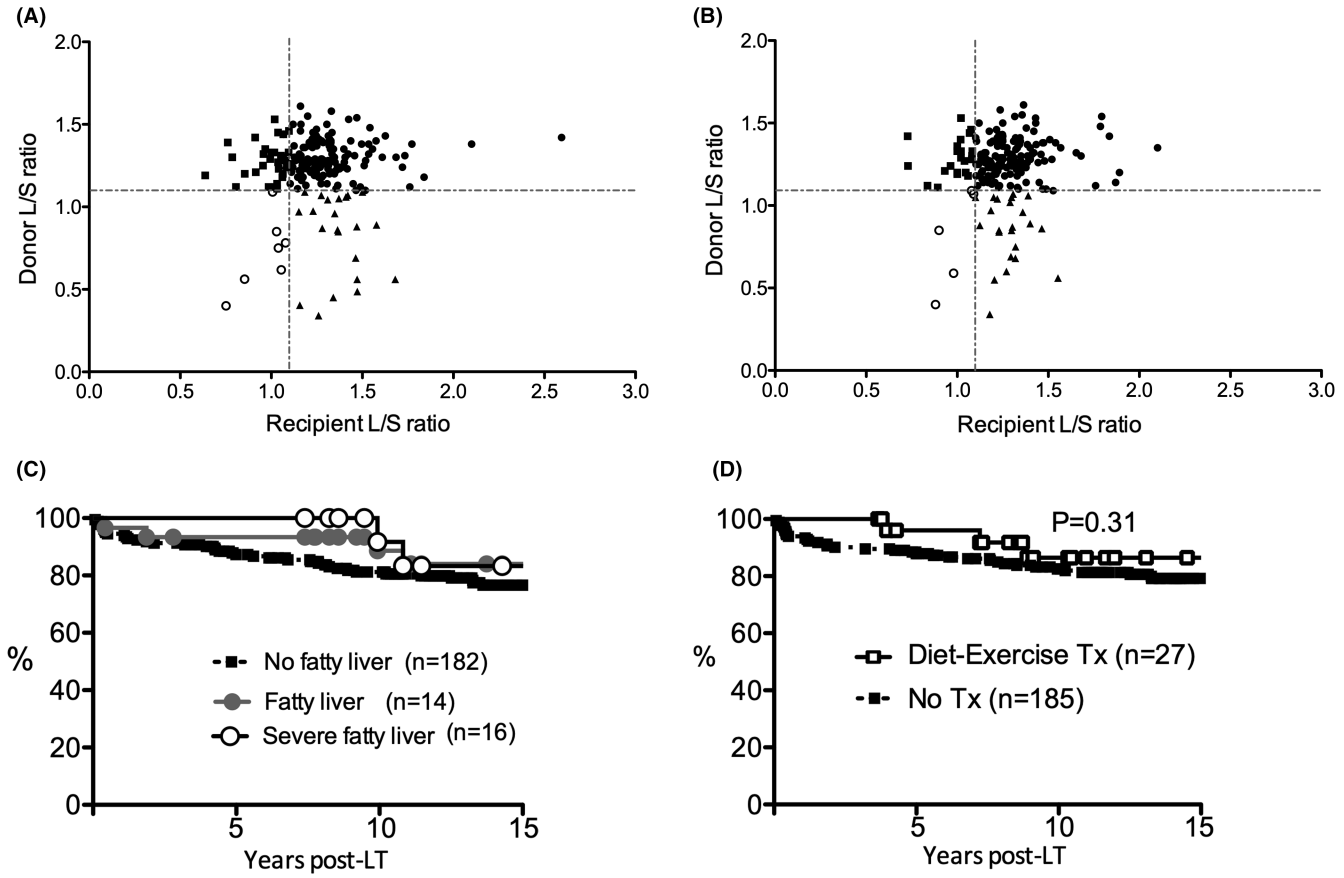

FIGURE 3 The relationship between the recipient's status and fatty liver of living donor during long-term follow-up after donation hepatectomy. (A) The correlation between the L/S ratio of the graft liver of recipients and those of living donors during long-term follow-up after transplantation. Each dot for donors represents the lowest L/S ratio among subjects who developed a fatty liver during the postdonation course or the most recent data for the subjects who did not develop a fatty liver. Each dot for recipients represents the most recent L/S ratio. CT examinations of recipients were conducted at 10.55 ± 5.91 years post-LDLT. Empty circles ($n = 7$) indicate cases in which the L/S ratio was <1.1 in both the recipient and living donor. Filled triangles ($n = 23$) and filled squares ($n = 33$) indicate donors and recipients, respectively, with an L/S ratio of <1.1. Filled circles indicate cases in which neither the living donor nor the recipient developed fatty liver. (B) The correlation between the L/S ratio of the recipient and donor by evaluating at the same time (i.e. the timing of CT examination in donors). Empty circles ($n = 5$) indicate cases in which the L/S ratio was <1.1 in both the recipient and living donor. Filled triangles ($n = 23$) and filled squares ($n = 22$) indicate donors and recipients, respectively, with an L/S ratio of <1.1. Filled circles indicate cases in which neither the living donor nor the recipient developed fatty liver. (C) The graft survival rates of LDLT recipients showed no differences between the groups discriminated by the fatty liver of living donor long-term after donation hepatectomy. (D) There was no significant difference in the graft survival rate between the recipients who received a liver graft from living donors who underwent diet-exercise treatments ($n = 27$, empty squares) and those who received a graft from untreated donors ($n = 185$, solid squares).

recipients. Further studies are required to elucidate the precise reasons for the differences of the relationship to LT recipients in the occurrence of fatty liver.

With respect to the development of fatty liver in a living donor, careful attention has been paid to the liver graft status of the recipient. The risks for the development of NAFLD were identified genomic variants (e.g. PNPLA3 and TM6SF2).[22] Because most living donors were blood-related, the development of fatty liver in the living donor may predict steatosis in the recipient. Our data fortunately showed no correlation between fatty liver in the living donor and the recipient's liver status (Figure 3). Because the liver of recipients was a strictly controlled function and they completely discontinued alcoholic consumption, the development of fatty liver in living donors may depend on environmental factors, including lifestyle factors such as diet and exercise behavior after donation hepatectomy.

The present study was associated with some limitations. First, the study population was relatively small, as it was conducted at a single institute. Second, data were not collected from all living donors over longer observation periods (e.g. 5 years after donation hepatectomy). In our institute, living donors have basically been followed for at least 5 years. We recently recommend for living donors to be followed for as long as possible. Most living donors, however, discontinued hospital visits beyond 5 years after donation hepatectomy. To guarantee the safety of LDLT, an analysis based on data collecting over a longer follow-up period

is required. Furthermore, as mentioned above, our comparison between donors and recipients was limited because the liver condition under a different circumstance, such as alcohol abuse. Finally, we collected the data from CT findings to define fatty liver according to the L/S ratio. The recent development of abdominal echography[23] may provide more accurate and meaningful data on the development of fatty liver and the evaluation of the risk of advanced fibrosis.

In conclusion, we demonstrated the prevalence of fatty liver in living donors during long-term follow-up after donation hepatectomy. The data revealed that living donors with fatty liver did not have a significant risk of developing advanced fibrosis. To provide a healthy, long life for living donors according to their relatively young age, transplant teams should maintain careful multidisciplinary follow-up.

AUTHOR CONTRIBUTIONS

Ryoichi Goto, Norio Kawamura, Masaaki Watanabe, Yoshikazu Ganchiku, Akihisa Nagatsu, Toshiya Kamiyama, Tsuyoshi Shimamura, and Akinobu Taketomi designed the research study and contributed to data collection. Ryoichi Goto, Kazufumi Okada, and Yoichi M. Ito analyzed the data. Ryoichi Goto and Yoichi M Ito wrote the article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

ETHICS STATEMENTS

Approval of the research protocol: The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board at Hokkaido University Hospital (#021–0177).

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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REFERENCES

1. Taketomi A, Kayashima H, Soejima Y, Yoshizumi T, Uchiyama H, Ikegami T, et al. Donor risk in adult-to-adult living donor liver transplantation: impact of left lobe graft. Transplantation. 2009;87(3):445–50.
2. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Operative morbidity of living liver donors in Japan. Lancet. 2003;362(9385):687–90.
3. Choi JY, Kim JH, Kim JM, Kim HJ, Ahn HS, Joh JW. Outcomes of living liver donors are worse than those of matched healthy controls. J Hepatol. 2022;76(3):628–38.
4. Morooka Y, Umeshita K, Taketomi A, Shirabe K, Yoshizumi T, Yamamoto M, et al. Long-term donor quality of life after living donor liver transplantation in Japan. Clin Transplant. 2019;33(6):e13584.
5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
6. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol. 2019;16(7):411–28.
7. Enomoto H, Ueno Y, Hiasa Y, Nishikawa H, Hige S, Takikawa Y, et al. Transition in the etiology of liver cirrhosis in Japan: a nationwide survey. J Gastroenterol. 2020;55(3):353–62.
8. Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S, et al. Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2009;32(11):2123–32.
9. Katahira M, Moriura S, Ono S. Estimation of visceral fat area using criteria for metabolic syndrome: a cross-sectional study. Diabetes Metab Syndr. 2022;16(8):102584.
10. Iwasaki M, Takada Y, Hayashi M, Minamiguchi S, Haga H, Maetani Y, et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. Transplantation. 2004;78(10):1501–5.
11. Fujii Y, Kawamura N, Zaitsu M, Watanabe M, Goto R, Kamiyama T, et al. Outcome of living-donor liver transplantation using grafts from donors treated for fatty liver. Ann Transplant. 2020;25:e920677.
12. Fang W, Noda M, Gotoh K, Morooka Y, Noda T, Kobayashi S, et al. Fatty liver disease in living liver donors: a single-institute experience of 220 donors. Transpl Int. 2021;34(11):2238–46.
13. Takagi K, Umeda Y, Yoshida R, Watanabe N, Kuise T, Yoshida K, et al. Short-term and long-term outcomes in living donors for liver transplantation: cohort study. Int J Surg. 2020;84:147–53.
14. Hamaguchi M, Takeda N, Kojima T, Ohbora A, Kato T, Sarui H, et al. Identification of individuals with nonalcoholic fatty liver disease by the diagnostic criteria for the metabolic syndrome. World J Gastroenterol. 2012;18(13):1508–16.
15. Eguchi Y, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. J Gastroenterol. 2012;47(5):586–95.
16. Rajaram RB, Jayaraman T, Yoong BK, Koh PS, Loh PS, Koong JK, et al. Non-alcoholic fatty liver disease and obesity among adult donors are major challenges to living-donor liver transplantation: a single-center experience. Asian J Surg. 2022;45(1):441–7.
17. Chandran B, Bharathan VK, Shaji Mathew J, Amma B, Gopalakrishnan U, Balakrishnan D, et al. Quality of life of liver donors following donor hepatectomy. Indian J Gastroenterol. 2017;36(2):92–8.
18. Dew MA, Butt Z, Liu Q, Simpson MA, Zee J, Ladner DP, et al. Prevalence and predictors of patient-reported long-term mental and physical health after donation in the adult-to-adult living-donor liver transplantation cohort study. Transplantation. 2018;102(1):105–18.
19. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015;62(5):1148–55.
20. Kim D, Choi SY, Park EH, Lee W, Kang JH, Kim W, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology. 2012;56(2):605–13.
21. Cousino MK, Rea KE, Schumacher KR, Magee JC, Fredericks EM. A systematic review of parent and family functioning in pediatric solid organ transplant populations. Pediatr Transplant. 2017;21(3):e12900.
22. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461–5.

23. Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2020. J Gastroenterol. 2021;56(7):593–619.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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