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Using small size grafts in live donor liver transplantation: is size important?

Canlı vericili karaciğer naklinde küçük boyutlu greft kullanımı: boyut önemli mi?

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Abstract

Purpose: In living donor liver transplantation, it is preferred that the ratio of the weight of the graft to the weight of the recipient (GRWR) be higher than 0.8%. We aimed to compare recipients with a GRWR greater than 0.8% and those with a small GRWR regarding post-transplant complications and outcomes.

Materials and methods: Data of the patients who had undergone living donor liver transplant surgery in İstinye University Hospital Liver Transplant Unit between January 2017 and July 2022 were reviewed. The study group patients were classified as GRWR<0.8% (Group 1), GRWR 0.8-1% (Group 2), and GRWR>1% (Group 3) and compared regarding clinical data, complications, and mortality rates.

Results: Liver transplant recipients from 220 living donors were included. The mean recipient age was 53.6 (18-79). The comparative analysis between Group 1 (n=29), Group 2 (n=70), and Group 3 (n=121) revealed significant differences concerning the rates of bile leak and the length of hospital stay (p=0.033, p<0.05). Bile leak rates were 7.4% in Group 1, 6% in Group 2, and 0.8% in Group 3. The bile leakage rate was significantly lower in Group 3 than in Groups 1 and 2 (p=0.041, p<0.05).

The medians of hospitalization periods were 18 (7-40) days, 15 (5-46) days, and 16 (1-130) days in groups 1, 2, and 3. In addition, the median length of stay was higher in Group 1 than in groups 2 and 3 (p=0.033). In terms of other parameters, the three groups gave similar results.

Conclusion: Although a GRWR value of lower than 0.8 seems as a factor causing prolonged hospital stay, and a GRWR value of higher than 1 seems to lower the risk of biliary complications after a live donor liver transplantation, these changes are not associated with the changes in total complication and acute rejection rates and patient survival.

Key words: Graft recipient weight ratio, liver transplantation, live donor.

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Öz

Amaç: Canlı vericili karaciğer naklinde greft ağırlığının alıcı ağırlığına (GRWR) oranının %0,8'den yüksek olması tercih edilir. GRWR'si %0,8'in üzerinde olan alıcılar ile küçük GRWR'si olan alıcıları nakil sonrası komplikasyonlar ve sonuçlar açısından karşılaştırmayı amaçladık.

Gereç ve yöntem: Ocak 2017-Temmuz 2022 tarihleri arasında İstinye Üniversitesi Hastanesi Karaciğer Nakli Ünitesi'nde canlı vericili karaciğer nakli yapılan hastaların verileri incelendi. Çalışma grubu hastaları GRWR<0,8% (Grup 1), GRWR %0,8-1 (Grup 2) ve GRWR>%1 (Grup 3) olarak sınıflandırıldı ve klinik veriler, komplikasyonlar ve mortalite oranları açısından karşılaştırıldı.

Bulgular: 220 canlı donörden alınan karaciğer nakli alıcıları dahil edildi. Ortalama alıcı yaşı 53,6 (18-79) idi. Grup 1 (n=29), Grup 2 (n=70) ve Grup 3 (n=121) arasındaki karşılaştırmalı analiz, safra kaçağı oranları ve hastanede kalış süresi (p=0,033, p<0,05) açısından anlamlı farklılıklar ortaya koydu. Safra kaçağı oranları Grup 1'de %7,4, Grup 2'de %6, Grup 3'te %0,8 idi. Safra kaçağı oranı Grup 3'te Grup 1 ve Grup 2'ye göre anlamlı derecede düşüktü (p=0,041, p<0,05). Hastanede kalış sürelerinin ortancaları grup 1, 2 ve 3'te 18 (7-40) gün, 15 (5-46) gün ve 16 (1-130) gündü (p=0,033). Diğer parametreler açısından, üç grup benzer sonuçlar verdi.

Sonuç: Canlı vericili karaciğer nakli sonrası GRWR değerinin 0,8'den düşük olması hastanede kalış süresini uzatan bir faktör, GRWR değerinin 1'den büyük olması ise biliyer komplikasyon riskini azaltan bir faktör gibi görünse de, bu farklılıklar toplam komplikasyon, akut rejeksiyon ve hasta sağkalımı oranlarını etkilememektedir.

Anahtar kelimeler: Greft alıcı ağırlık oranı, karaciğer nakli, canlı vericili.

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Introduction

In living donor liver transplantation, it is traditionally preferred that the ratio of the weight of the graft to the weight of the recipient (GRWR) be higher than 0.8% [1]. The most important reason for this preference is the belief that in case of lower rates, parenchymal damage will occur in the recipient due to portal hypertension, and therefore the metabolic and synthetic capacities of the graft will decrease [2, 3]. This liver dysfunction picture, which can present itself with cholestasis, coagulopathy, ascites, and/or encephalopathy in the absence of immunological, technical, or infectious causes, is called “small size syndrome” (SSS) [4, 5]. However, as a result of advances in surgical techniques, such as modulation techniques and a better understanding of the pathophysiology compared to the past, the validity of this threshold value has been questioned in recent years [6]. Therefore, it is crucial to determine the most appropriate lower limit of GRWR for donors and living donor liver transplant recipients because if lower threshold values are accepted, donors will have a more limited chance of performing hepatectomy [1]. In addition, in this case, potential liver donors will be more encouraged to donate [7, 8].

Based on these considerations, we aimed to compare recipients with a GRWR greater than 0.8% and those with a small GRWR in our living donor liver transplant series regarding post-transplant complications and outcomes.

Materials and methods

The target population of this study was the patients who had undergone living donor liver transplant surgery in İstinye University Hospital Liver Transplant Unit between January 2017 and July 2022. After the study was approved by the clinical studies ethics committee of the same hospital, patient data were reviewed retrospectively through the electronic file system of our hospital. However, patients who had liver transplantation due to acute liver failure, patients with blood group incompatibility with their donor, patients who had left lobe graft transplantation, and patients with missing data were excluded.

After applying the inclusion and exclusion criteria, the remaining study group patients were classified as GRWR<0.8% (Group 1), GRWR 0.8-1% (Group 2), and GRWR>1% (Group 3), based on the graft-recipient weight ratio. Data, including age, gender, body mass index (BMI), duration of follow-up, MELD (Model for End-stage Liver Disease) score, the etiological factor causing liver failure, donor age, gender, and graft weight, were obtained from electronic files. These data were saved in a database. In addition to these parameters, information related to surgical complications, length of stay, length of stay in the intensive care unit, early rejection, and mortality were also transferred to the same database.

Three patient groups were compared regarding demographic and clinical data, complications, and mortality rates.

Living donor liver transplantation protocol

In the liver transplantation unit of our hospital, donor and recipient evaluations are made according to the AASLD (American Association for the Study of Liver Diseases) guidelines [9]. The transplant surgery was performed in patients with alcoholic liver cirrhosis after an abstinence period of at least six months. In addition, the University of California San Francisco (UCSF) criteria were considered in patients who underwent liver transplantation for hepatocellular carcinoma [10].

A threshold of 0.6% was accepted as the minimum acceptable GRWR. All grafts were right lobe grafts with or without the middle hepatic vein. This approach aimed to leave a liver remnant with good segment IV venous drainage. The removed liver was immediately washed with histidine-tryptophan-ketoglutarate solution (Custodiol; Köhler Chemie, Alsbach-Hähnlein, Germany) at 4°C. After the solution was completely drained from the liver, the graft weight was measured in grams with an automatic weighing machine. When calculating the graft-recipient weight ratio, the recipient weight was taken as the basis for the recipient’s dry weight. Therefore, 5%, 10%, or 15% were subtracted from the recipient’s measured weight, respectively, according to the presence of mild, moderate, or severe ascites. In addition, the weight was reduced by 5% in the presence of pedal edema. In cases where the graft did not include the middle hepatic vein, middle hepatic vein reconstruction was performed using a polytetrafluoroethylene (PTFE) graft in cases where the recipient’s portal vein or portal vein

was not suitable due to hepatocellular carcinoma or poor wall quality. Portal vein pressures were not measured routinely, and portal venous flow modulation was not performed in any patient.

Statistical analysis

SPSS (Statistical Package for Social Sciences, IBM SPSS Statistics v24, Armonk, New York, US) program was used for statistical analysis. First, the conformity of continuous quantitative data to normal distribution was evaluated with the Shapiro-Wilk test. Then, since continuous quantitative data did not follow a normal distribution, variances between groups were evaluated with the Kruskal-Wallis test. The relevant data were given as medians, minimum and maximum values. Finally, in the evaluation of nominal data, differences between groups were evaluated with Chi-square or Fisher's exact test and given with percentages. The difference between the groups was considered significant if the *p* value was less than 0.05.

Results

After applying the inclusion and exclusion criteria, liver transplant recipients from 220 living donors were included in the study. The mean age of the entire group was calculated as 53.6 (18-79). Approximately 70% (69.1%, n=152) of the patients were male, and 30.1% (n=68) were female. Follow-up periods ranged from 3 months to 51 months. The GRWR values of the patients ranged from 0.67% to 3%. When the whole group was divided into three according to GRWR values, there were 29 patients in Group 1, 70 in Group 2, and 121 in Group 3 (Table 1).

Comparison of three gorups concerning recipient and donor demographic data, recipient BMI, MELD scores revealed significant differences in terms of BMI (χ^2 (2)=51.201, p=0.000, p<0.05) and graft weight (χ^2 (2)=34.218, p=0.000, p<0.05). The BMI median of Group 1 (32.792 [22.9-44.4] kg/m^2) was higher than the median BMI values of both Group 2 (29.207 [19.1-45] kg/m^2) and Group 3 (24.913 [17-46.8) kg/m^2] (p=0.032, p=0.000).

In addition, Group 2 BMI median was calculated to be higher than Group 3 BMI median (p=0.000). The median graft weights were determined as 750 (525-1020), 800 (370-1260), and 922 (540-1500) grams in Group 1, Group 2, and Group 3, respectively. While no statistically significant difference was detected between Groups 1 and 2 (p=1.000), the median graft weight of Group 3 was higher than both Group 2 (p=0.000) and Group 1 (p=0.000). However, the three groups were similar regarding the other parameters examined.

The comparative analysis of three groups regarding the rates of bile leak, stricture, all complications, surgical (i.e., early) mortality, late mortality, length of hospital stay, and acute rejection revealed significant differences concerning the rates of bile leak and the length of hospital stay between the three groups (χ^2 (2)=6.843, p=0.033, p<0.05) (Table 2).

Table 1. Comparative analysis of the groups regarding demographic and clinical data

	Group 1 n:29	Group 2 n:70	Group 3 n:121	*p* value
Recipient age (year)	52 (22-68)	53.5 (18-75)	54 (19-79)	0.975
Recipient gender	Male: 25 (86.2%) Female: 4 (13.8%)	Male: 47 (67.1%) Female: 23 (32.9%)	Male: 80 (66.1%) Female: 41 (33.9%)	0.108*
Recipient BMI (kg/m^2)	32.792 (22.9-44.4)	29.207 (19.1-45)	24.913 (17-46.8)	**0.000**
Duration of follow-up (month)	27 (3-49)	16 (3-51)	19 (3-50)	0.94
MELD score	17 (6-37)	17 (7-34)	17 (6-36)	0.541
Donor age (year)	31 (18-46)	30 (12-48)	32 (18-55)	0.221
Donor gender	Male: 21 (72.4%) Female: 8 (27.6)	Male: 43 (61.4%) Female: 27 (38.6%)	Male: 78 (65%) Female: 42 (35%)	0.596*
Graft weight (gr)	750 (525-1020)	800 (370-1260)	922 (540-1500)	**0.000**

Kruskal Wallis test was performed, *Chi-square test, BMI: Body-mass index, MELD: Model for end-stage liver disease

Table 2. Comparison regarding complications and outcomes

	Group 1 n:29	Group 2 n:70	Group 3 n:121	*p* value
Bile leak	Present: 2 (7.4%) Absent: 25 (92.6%)	Present: 4 (6%) Absent: 63 (94%)	Present: 1 (0.8%) Absent: 117 (99.2%)	**0.041****
Stricture	Present: 5 (18.5%) Absent: 22 (81.5%)	Present: 6 (9%) Absent: 61 (91%)	Present: 10 (8.5%) Absent: 107 (91.5%)	0.309*
Other complications	Present: 9 (32.1%) Absent: 19 (67.9)	Present: 21 (30.9%) Absent: 47 (69.1%)	Present: 36 (30.8%) Absent: 81 (69.2%)	1.0*
Surgical mortality	Present: 2 (6.9%) Absent: 27 (93.1%)	Present: 3 (4.3%) Absent: 67 (95.7%)	Present: 12 (9.9%) Absent: 109 (90.1%)	0.376*
Late mortality	Present: 0 (0%) Absent: 29 (100%)	Present: 6 (8.6%) Absent: 64 (91.4%)	Present: 9 (7.4%) Absent: 112 (92.4%)	0.329**
Length of hospital stay (days)	18 (7-40)	15 (5-46)	16 (1-130)	**0.033**
Length of icu stay (days)	2 (1-11)	1 (1-12)	1 (1-26)	0.328
Acute rejection	Present: 12 (41.4%) Absent: 17 (58.6%)	Present: 18 (25.7%) Absent: 52 (74.3%)	Present: 37 (30.6%) Absent: 84 (61.4%)	0.299*
Rejection Time (days)	8 (4-21)	7.5 (3-13)	6.5 (3-16)	0.406

Kruskal Wallis test was performed. *Chi-square testi **Fisher's exact test

Bile leak rates in recipients were calculated as 7.4% in Group 1, 6% in Group 2, and 0.8% in Group 3. Bile leakage was observed at a lower rate in Group 3 than in Groups 1 and 2, and the difference was statistically significant (p=0.041, p<0.05).

The medians of hospitalization periods were determined as 18 (7-40) days, 15 (5-46) days, and 16 (1-130) days in Group 1, Group 2, and Group 3, respectively. The median length of stay in Group 1 was higher than in both groups (p=0.033). In terms of other parameters examined, the three groups gave similar results.

The causes of early and late mortality of the recipients and the etiological factors causing liver failure are given in Table 3, Table 4, and Table 5, respectively.

Seventeen (7.7%) of 220 patients died in the first month after surgery. The most common cause of these deaths is sepsis (n=10).

After excluding the patients who died in the early period, 15 of the remaining 203 patients died in the late period, and the most common causes were sepsis (n=5), hepatocellular carcinoma recurrence (n=4), and COVID-19 (Coronavirus disease-2019) (n=3).

Etiological factors were cryptogenic liver cirrhosis in 50, Hepatitis B in 46, and NASH (non-alcoholic steatohepatitis) in 42 patients. These patients constituted more than half (62.7%) of all patients. Twenty-three (10.5%) patients died, and stricture developed in 18 (8.2%) patients (Table 6). Stricture was the most common complication.

Table 3. Reasons for early mortality

	Number	Percentage among deaths	Percentage in the entire cohort
Acute rejection	1	5.9	0.5
Aspiration pneumoıa	2	11.8	0.9
Mesenteric ischemia	1	5.9	0.5
Pneumonia	1	5.9	0.5
Portal vein thrombosis	1	5.9	0.5
Sepsis	10	58.8	4.5
Variceal bleeding	1	5.9	0.5
TOTAL	17	100.0	7.7

Table 4. Reasons for late mortality

	Number	Percentage among deaths	Percentage in the entire cohort
Aspiration pneumonia	1	6.7	0.5
Covid	3	20.0	1.5
HCC recurrence	4	26.7	1.8
Cardiac arrest	1	6.7	0.5
Portal vein thrombosis	1	6.7	0.5
Sepsis	5	33.3	2.5
TOTAL	15	100.0	7.4

COVID: Coronavirus disease, HCC: Hepatocellular carcinoma

Table 5. Reasons for liver failure in the recipients

	Number	Percentage
Alcoholic hepatitis	16	7.3
Budd-Chiari syndrome	7	3.2
Fulminant hepatitis	1	0.5
HBV	46	20.9
Fulminant HBV	2	0.9
HBV+HCC	1	0.5
HBV+HDV	8	3.6
HBV+Autoimmune	1	0.5
HCC	1	0.5
HCV	11	5.0
Congenital hepatic fibrosis	1	0.5
Cryptogenic cirrhosis	52	23.6
NASH	42	19.1
Autoimmune	11	5.0
PBC	6	2.7
Primary hyperoxaluria	1	0.5
PSC	4	1.8
PSC+Autoimmune hepatitis	1	0.5
PVT	1	0.5
Thalassemia	1	0.5
Wilson disease	6	2.7
TOTAL	220	100.0

HBV: Hepatitis B, HDV: Hepatitis D, HCC: Hepatocellular carcinoma, PSC: Primary sclerosing cholangitis
PVT: Portal vein thrombosis, PBC: Primary biliary cirrhosis, NASH: Non-alcoholic steatohepatitis

Table 6. Complications

	Number	Percentage among deaths	Percentage in the entire cohort
Splenic bleeding	1	1.5	0.5
Dementia	1	1.5	0.5
Exitus	23	35.4	10.5
Hepatic vein thrombosis	1	1.5	0.5
Cardiopulmonary arrest	1	1.5	0.5
Myocardial infarction	1	1.5	0.5
RE-operation	5	7.7	2.3
RE-Transplantation	1	1.5	0.5
Right hepatic artery dissection	2	3.0	0.9
Bile leak	4	6.2	1.8
Sepsis	1	1.5	0.5
Stricture	18	27.7	8.2
STRICTURE+Bile leak	3	4.6	1.4
Deep vein thrombosis	3	4.6	1.4
TOTAL	65	100.0	30.0

Discussion

In our study, living donor liver transplant recipients were divided into three groups according to their GRWR values, and recipients with GRWR values lower than 0.8, between 0.8-1, and higher than 1 were compared in terms of complications and clinical outcomes. The fact that the demographic data of the three groups did not differ statistically is a finding that increases the reliability of comparisons made in terms of postoperative complications and results.

In our study, bile leakage complication was observed less frequently in the group with the highest GRWR value than in the other groups. At the same time, the duration of hospitalization was calculated to be longer in the group with the lowest GRWR value. These findings support the preference for high GRWR values in living donor liver transplantation. However, it is a fact that there was no difference in the rates of many surgical complications, including hepatic artery thrombosis, rejection, and mortality, in our study between recipient groups with different GRWR values.

Wong et al. [11] compared patients with a GRWR value less than 0.6 and patients with a GRWR value between 0.6 and 0.8 and greater than 0.8 regarding complications and postoperative clinical outcomes after living donor liver transplantation. These researchers reported no significant difference between the groups regarding postoperative vascular and biliary complications. They also noted that SSS was observed at a very low rate, even in recipients with a GRWR value below 0.6. In our study, the lowest GRWR value was 0.67, and unlike the study of Wong et al. [11], the hospitalization period was longer. Also, the rate of bile leakage was higher in the group with a low GRWR value.

Sethi et al. [1] compared recipients with a GRWR value of less than 0.8 and recipients with a high GRWR value in terms of postoperative complication rates and outcomes in 200 living donor liver transplantations they performed over a 2-year period. This study found that the two groups were similar in terms of mortality in the first three months, length of stay in the intensive care unit, and hospital stay. In addition, the rates of complications such as SSS, hepatic artery thrombosis, portal vein thrombosis, sepsis, and liver dysfunction were similar in the two groups.

Levesque et al. [12] also found that respiratory failure was observed more frequently in the group with a high GRWR value in their comparative analysis of 162 living donor liver transplant recipients. On the other hand, the frequency of other complications was similar in the two groups [12]. These investigators also found that 1-year graft and patient survival rates were not different between the two groups.

Feng et al. [13] noted in their meta-analysis, which included 4001 patients and 18 studies,

that a GRWR value lower than 0.8 was associated with a lower rate of 1- and 3-year survival after living donor liver transplantation. In addition, these investigators demonstrated that SSS was more common in the low GRWR group. However, there was no difference between the two groups regarding perioperative mortality, biliary complications, postoperative bleeding, and acute rejection rates. In our study, bile leakage was observed at a lower rate in the recipient group with a high GRWR value compared to the other groups.

Yan et al. [14] compared living donor liver transplant recipients with a GRWR value less than or greater than 0.8 in a meta-analysis of 16 studies and 3272 patients concerning operative time, blood loss, cold ischemia time, biliary complications, acute rejection, postoperative bleeding, hospital stay, perioperative mortality. They reported no significant difference between the two groups concerning 1-, 3-, and 5-year survival [14]. Ma et al. [15] conducted a meta-analysis including 7 retrospective studies and 1821 patients who underwent live donor liver transplantation. They stated that although SSS was associated with low graft survival in the medium term, it did not affect graft survival in the long term. In our study, no difference was found in terms of early and late mortality between recipients with high and low GRWR values. However, it should be noted that the mean follow-up period in our study varied between 3-51 months.

Miyagi et al. [16] compared recipients with a GRWR value of less than 0.8 and greater than 3.5 in terms of catastrophic complications such as portal vein thrombosis, hepatic artery thrombosis, and hepatic vein thrombosis in 188 living donor liver transplantations they performed over 18 years. As a result of their analysis, these authors found that the 5-year survival in the group with a low GRWR value was significantly lower than in the other groups [16]. These authors also stated that concomitant splenectomy with liver transplantation would increase survival rates in the group with low GRWR values. Bell et al. [17] compared living donor liver transplant recipients with a GRWR value of less than 0.8 and greater than 0.8 in a meta-analysis including 1833 patients and 8 studies concerning short-term and long-term outcomes. These investigators concluded that although the rate of CBS in the first group was twice that of the second group (10% and 5%), the two groups were similar in terms of 5-year survival, biliary complications, vascular complications, perioperative bleeding, postoperative mortality, and rejection. These findings are similar to our results.

Although a GRWR value of lower than 0.8 seems as a factor causing prolonged hospital stay, and a GRWR value of higher than 1 seems to lower the risk of biliary complications after a live donor liver transplantation, these changes are not associated with the changes in total complication and acute rejection rates and patient survival.

Conflict of interest: No conflict of interest was declared by the authors

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Contributions of the authors to the article

E.E. conceived the idea, collected the data, performed the data analysis, interpreted the data and wrote the manuscript. A.D. provided critical feedback and revised the manuscript.