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Impact of donor age on liver regeneration and function following adult living donor liver transplantation

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Abstract. The aim of the present study was to evaluate the impact of donor age on liver function and regeneration following living donor liver transplantation. Donors were divided into an elderly donor group (age >50 years old; n=8) and a young donor group (age <30 years old; n=35). The recipients were also divided into an elderly group (age >50 years old; n=5) and a young group (age <30 years old; n=25). Alanine aminotransferase, aspartate aminotransferase, total bilirubin (TB) and prothrombin time were recorded 1-5 days postoperatively. The liver regeneration ratio (LRR) was recorded 7 and 15 days postoperatively in donors and at 0.5, 1, 3 and 6 months postoperatively in recipients by contrast-enhanced multi-slice spiral computed tomography. Notably, the LRR in the young donor group was significantly increased compared with that in the elderly donor group at 7 days postoperatively (P<0.05). Among recipients, TB in the elderly group was significantly increased compared with that in the young group at 1-5 days postoperatively (P<0.05). The residual liver regeneration rate was decreased and the time of jaundice was prolonged in recipients in the elderly group 7 days postoperatively, but donor age had little impact on the short-term outcome of the residual liver and graft.

Introduction

Liver transplantation is a widely accepted therapy for end-stage liver disease. A large number of patients are awaiting liver transplantation (1). Furthermore, advancement in modern techniques of hepatectomy promoting the development of living donor liver transplantation (LDLT), using left lateral segment, left lobe and finally right lobe hepatectomy, has been a primary research focus in order to solve the shortage of donor livers (2).

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Hepatic regeneration following resections or injury involving <70% of total liver mass proceeds uneventfully until restitution of the original liver mass is complete, typically within 3-6 months in an otherwise healthy human liver (3). Liver regeneration post-transplantation is an important theoretical basis and a prerequisite for successful LDLT, but its clinical understanding remains incomplete. Liver regeneration is a complex process closely controlled at the molecular level. Notably, a number of clinical factors affect the process of liver regeneration, including the size of the liver remnant or graft postoperative c-reactive protein levels (4) and postoperative biliary leakage (5).

Aging changes biological processes in various organs and tissues, leading to the development of age-associated diseases and to aberrant body homeostasis (6). At present, the effect of age on the outcome of liver transplantation remains controversial (7). Tanemura *et al* (7) reported that donor age may affect liver regeneration during the early period in the graft liver and the late period in the remnant liver. Timchenko (6) reported that the loss of regenerative capacity may be the most significant age-associated alteration in the liver. However, other articles reported contrasting results (2,8,9).

The purpose of the present study was to clarify the effect of age on normal liver regeneration of donors and recipients following living donor liver transplantation. In the present study, 43 donors and 30 recipients undergoing adult living donor right lobe liver transplantation were evaluated to determine the impact of donor age on liver function and regeneration of donors and recipients following LDLT. Notably, complications following LDLT significantly affect liver regeneration (10). In the present study, patients with vascular and biliary complications, rejection and infection were excluded from data collection, contributing to a more objective and reliable evaluation of liver regeneration.

Patients and methods

Subjects. The study protocol was approved by the Medical Ethics Committee of Tianjin First Center Hospital (Tianjin, China) and all patients signed an informed consent form. A retrospective study was performed and samples were collected from a total of 240 donors and recipients undergoing adult LDLT at the Transplantation Center of Tianjin First Center Hospital between January 2015 and November 2017. The

selection criteria were as follows: i) Voluntary donors meeting physical condition requirements and approved by the Medical Ethics Committee, normal preoperative liver function, no liver fibrosis and no or mild steatosis; ii) donors aged >50 years and <30 years; iii) donors and recipients with complete records of alanine aminotransferase (ALT), aspartate aminotransferase (AST) total bilirubin (TB) and prothrombin time (PT) measurements at the early postoperative stage; iv) donors undergoing contrast-enhanced multi-slice spiral computed tomography (MSCT) at 7 and 15 days postoperatively, and recipients undergoing contrast-enhanced MSCT at 0.5, 1, 3 and 6 months postoperatively, with stable and quality imaging and no obvious artifacts; and v) donors and recipients without vascular or biliary complications, rejection or infection following LDLT. A total of 73 participants satisfied the above conditions.

General data of donors and recipients. The clinicopathological data of liver donors and recipients are summarized in Tables I and II. Whether the donor liver includes middle hepatic veins (MHVs) depends on the actual conditions of the donors and recipients, including the size of the donor liver, the estimated standard liver volume of (ESLV) and where the hepatic S4, S5 and S8 vein branches return flow to. If the liver from donors is small, or the S5 and S8 hepatic vein branch primarily flows into MHVs and the S4 hepatic vein branch predominantly flows into the left hepatic vein, the liver from donors may include MHVs.

Clinical biochemical examinations for donor and recipient plasma concentrations of ALT, AST, TB and PT on postoperative days 1-5 were performed with an Axon Auto Analyzer (Bayer AG, Leverkusen, Germany). The following levels were used as a reference: ALT (9-50 U/l), AST (15-40 U/l), TB (0-21 umol/l) and PT (10-18 sec).

MSCT and calculation of liver regeneration ratio (LRR). Contrast-enhanced CT scanning was performed using a dual-source CT scanner (Definition Flash; Siemens Healthineers, Erlangen, Germany). The enhanced images were transferred to the IQQA-Liver workstation (EDDA Technology, Inc., New Jersey, USA) for quantitative analysis of liver volume (Fig. 1). The volume of major vessels, including liver arteries, liver veins and portal veins in the liver, were excluded.

Donor total liver volume (TLV_1) was measured by MSCT prior to LDLT. Donor liver accurate volume (V_{1A}) was measured using the drainage method during LDLT, and remnant liver volume (RLV_1) was measured by MSCT during the early postoperative stage (7 and 15 days). (TLV_1-V_{1A}) was considered as the donor postoperative initial liver volume (ILV_1). Donor LRR (LRR_1) at the early postoperative stage was calculated by the following formula: LRR_1 (%)=(RLV_1-ILV_1)/ILV_1 x100%.

Recipient initial liver volume (ILV_2) was measured by using the drainage method during LDLT, and graft volume (GV_2) was measured by MSCT postoperatively (0.5, 1, 3 and 6 months). The following formula was used to calculate the LRR_2 of recipients at different time points following surgery: LRR_2 (%)=(GV_2-ILV_2)/ILV_2 x100%.

Statistical analysis. SPSS software, version 11.5 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data conforming to the normal distribution were expressed as the mean ± standard deviation. Age, height, body weight, ESLV, intraoperative measured liver volume (IMLV), LRR, Model for End-Stage Liver Disease (MELD) Score (11), graft-recipient weight ratio (GRWR) and index of liver function were compared between two groups (young and elderly) using an independent samples t-test. Sex constituent ratios and graft with or without MHVs were compared between two groups using the χ^2 test. $P<0.05$ was considered to indicate statistically significant differences.

Results

Comparison of general data. Age, height, body weight, ESLV, IMLV, graft with or without MHVs and sex exhibited no statistically significant differences between the donor and recipient groups. Notably, the MELD Score and GRWR exhibited no statistically significant differences between the elderly and young recipient groups (Tables I and II).

Comparison of postoperative liver function. Comparison of donor liver function recovery during the early postoperative stage revealed no statistically significant differences in ALT, AST, TB or PT 1-5 days following surgery between the elderly donor and the young donor groups (Fig. 2).

Comparison of recipient liver graft function at 1-5 days following surgery revealed that TB in the recipients receiving a liver graft from elderly donors was increased compared with those receiving a graft from young donors. The remaining indices of liver function exhibited no statistically significant differences (Fig. 3).

Comparison of postoperative liver regeneration. Comparison of donor LRR during the early postoperative stage revealed that the LRR at 7 days following surgery in young donors was significantly increased compared with that in elderly donors ($P<0.05$); however, no statistically significant differences were observed between the two groups at 15 days following surgery (Table III).

The recipient postoperative LRR exhibited no statistical significance between the two groups (Table IV).

Discussion

Normal liver has a high regeneration potential, as indicated by hepatocyte mitosis at 6-8 h following hepatectomy, and reaches its peak at 48 h (12). In certain cases, when reserved hepatocytes fail to replicate, hepatic progenitor cells are activated and differentiate into hepatocytes (13). A number of factors affect postoperative liver regeneration, including obesity, epithelial cell damage, adenosine triphosphate shortage and reduced ADAM metallopeptidase with thrombospondin type 1 motif 13 activity in hepatocytes caused by cold preservation during liver graft transport (6). The impact of age on liver regeneration is important in clinical practice (14). The evaluation of residual liver regeneration following LDLT is the most accurate method for identifying normal liver regeneration (15).

In the present study, it was demonstrated that the LRR in the young donor group was significantly increased (2-fold)

Table I. General data of donors.

Variable	Age (years)	Male	Female	Height (cm)	Weight (kg)	ESLV (l)	IMLV (l)	With MHV	Without MHVs
Group									
Elderly	56±4	5	3	164.88±7.26	68.44±14.01	11.24±0.14	0.77±0.20	3	5
Young	25±2	30	5	172.34±6.95	67.64±10.63	1.27±0.10	0.65±0.17	16	19
t/χ^2 value	-1.589	1.038		-2.720	0.180	-0.783	1.711	0.001	
P-value	0.265	0.308		0.493	0.219	0.181	0.218	0.978	

ESLV, estimated standard liver volume; IMLV, intraoperative measured liver volume; MHVs, middle hepatic veins.

Table II. General data of recipients.

Variable	Age (years)	Male	Female	Height (cm)	Weight (kg)	ESLV (l)	IMLV (l)	GRWR	MELD score	MHVs with/without
Group										
Elderly	40±10	5	0	171.40±3.36	69.64±8.58	1.28±0.08	0.66±0.15	1.03±0.25	19.00±5.79	2/3
Young	47±6	19	6	166.46±9.36	67.12±10.86	1.24±0.13	0.65±0.20	0.98±0.30	13.24±7.30	11/14
t/χ^2 value	-1.445	1.500		2.058	0.572	1.061	0.001	0.037	1.938	0.027
P-value	0.214	0.553		0.054	0.586	0.319	0.998	0.588	0.095	0.869

ESLV, estimated standard liver volume; IMLV, intraoperative measured liver volume; GRWR, graft to recipient weight ratio; MHVs, middle hepatic veins; MELD, Model for End-Stage Liver Disease.

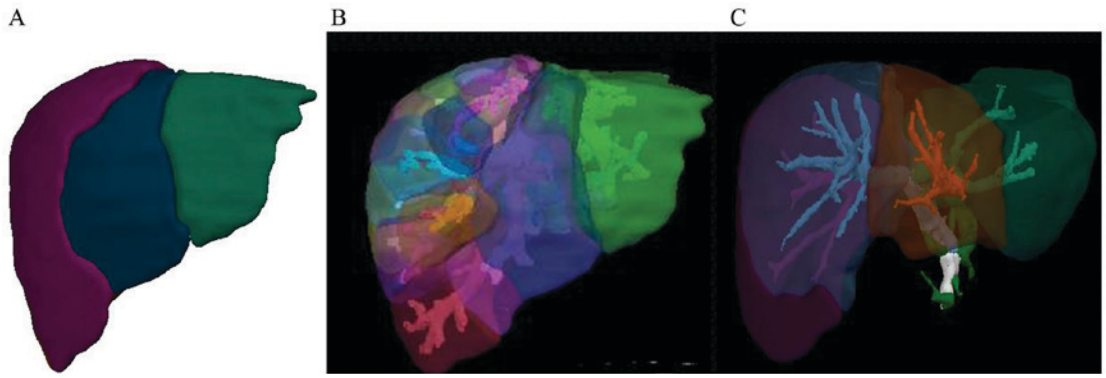

Figure 1. Liver volume and vascular distribution measured by IQQA in healthy donors. (A) From left to right, different colors represent liver right lobe, left inner lobe and left lateral lobe, respectively. (B) Distribution of liver vein in liver. (C) Distribution of portal vein in liver.

compared with that in the elderly donor group at 7 days following LDLT, suggesting impairment of residual liver regeneration in elderly donors 1 week following LDLT. However, there was no statistically significant difference in LRR between the young and elderly groups at 15 days following surgery, although long-term liver regeneration requires further follow-up. Zhang *et al* (9) observed the same tendency regarding the effect of transplantation age on liver regeneration. They observed that the LRR of the <30-year-old group was increased compared with that of the >50-year-old group during the early postoperative stage, but the LRR did not differ significantly between the two groups 1 month following surgery (9). There were no statistically significant differences in ALT, AST, TB or PT between the elderly and young donor groups at 5 days post-surgery, and the levels gradually returned to their normal ranges, suggesting that donor age does not affect early recovery of residual liver function following LDLT in the present study. The inconsistency of liver function and liver regeneration was caused by the strict preoperative assessment of included donors in this study. The volume of the residual liver was ~50% of ESLV, and all donors recovered well following surgery, which indicated that the decrease in liver regeneration is a subclinical process; additionally, the residual liver function was able to meet the metabolic requirements. According to the literature, the recovery of donor liver volume was still incomplete at 1 year post-donation, accounting for

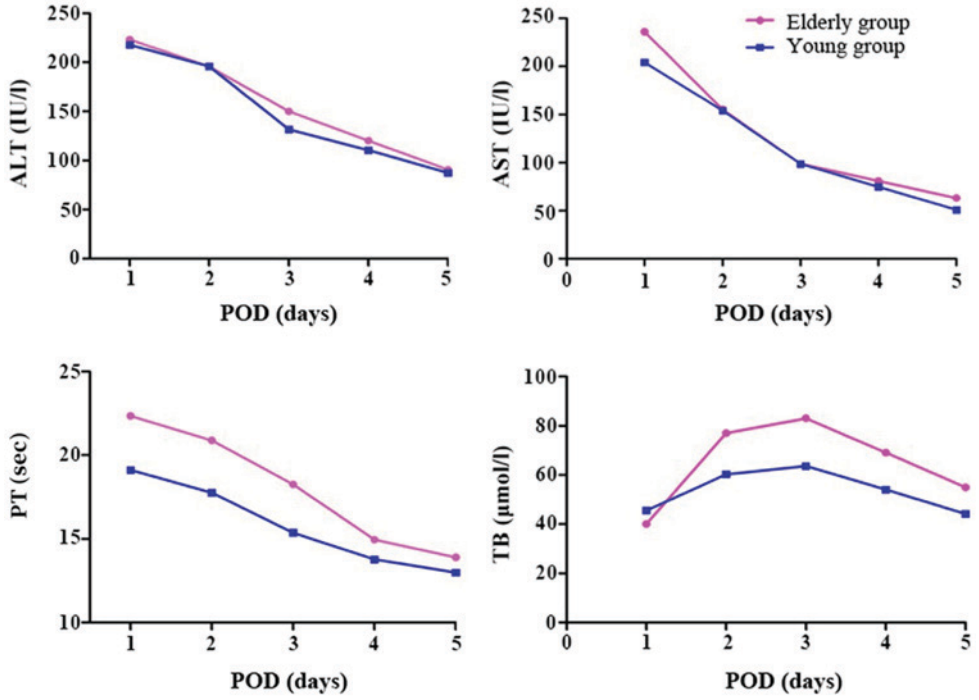

Figure 2. Postoperative liver function indices of donors. POD, postoperative day; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PT, prothrombin time.

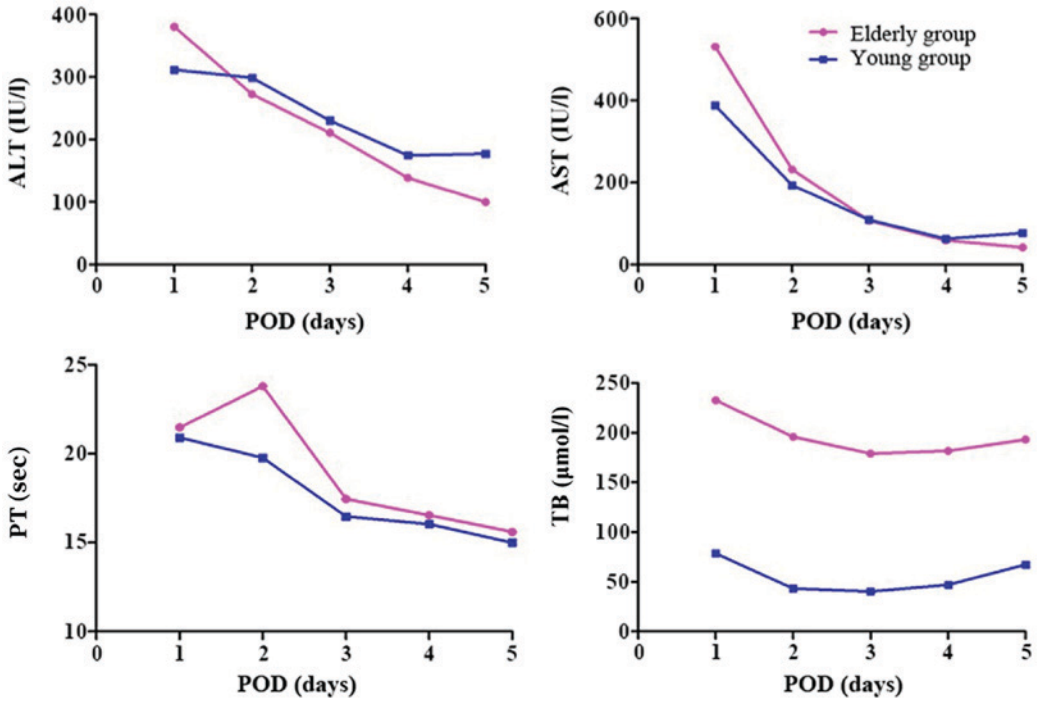

Figure 3. Postoperative liver function indices of recipients. POD, postoperative day; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PT, prothrombin time.

85% of the total preoperative volume; however, liver function had almost returned to normal (16).

The study by Tung *et al* (17) indicated that age did not affect the index of liver function in recipients at 7 and 30 days following liver transplantation. The present study demonstrated that TB on days 1-5 postoperatively in recipients of a liver graft from the elderly donor group was significantly increased compared with patients receiving a graft from the young donor group, indicating that the early duration of postoperative functional jaundice in recipients of a donor liver from the elderly group was prolonged, which is a supplement to the findings of the study by Tung *et al*. The increase in postoperative TB levels may be caused by impaired liver function and failure to meet the

Table III. Liver regeneration ratio of donors.

	Liver regeneration ratio at different time points (%)	
Variable	7 days	15 days
Group		
Elderly	20.4±5.3	38.1±3.3
Young	40.1±2.2	30.6±2.2
t value	-0.965	0.585
P-value	0.042	0.385

Table IV. Liver regeneration ratio of recipients.

	Liver regeneration ratio at different time points (%)			
Variable	0.5 months	1 month	3 months	6 months
Group				
Elderly	1.10±0.53	1.1.7±0.07	0.84±0.10	0.68±0.25
Young	1.05±0.39	1.00±0.33	0.90±0.38	0.97±0.33
t value	0.152	0.898	-0.284	-1.455
P-value	0.891	0.382	0.779	0.201

early requirements of energy metabolism following LDLT, but has no direct association with biliary complications. Iwamoto *et al* (18) reported no differences in the incidence of postoperative biliary complications or tissue biopsy between elderly and young liver donors. In the groups (recipients of elderly and young donor livers), the ALT, AST and PT at 1-5 days following surgery and the LRR of grafts at 0.5, 1, 3 and 6 months following surgery exhibited no statistically significant differences, which suggested that donor age has little impact on graft function and short-term regeneration following LDLT. This is consistent with the results reported by Ishigami *et al* (19).

According to the registration of the European Liver Transplant Registry, the 1-year survival rate of all patients undergoing liver transplantation between 1998 and 2001 was not directly associated with age (20). Other similar studies support this conclusion (21-23). Kim *et al* (24) considered that age was not an independent factor affecting liver regeneration and the patient's preoperative liver function should be taken into account, as the postoperative liver regeneration of patients with normal liver function was not much different. A single-center study reported that 129 patients who received a liver graft from donors aged >70 years exhibited no difference in postoperative survival, but the incidence of ascites and primary liver dysfunction was higher, which may be associated with delayed start of the graft function (25).

Regarding the impact of age on donor prognosis, it has been reported that the length of hospitalization of liver donors aged >50 years was longer compared with that of young donors; furthermore, the ability of postoperative protein synthesis is decreased, the duration of cholestasis is prolonged, TB levels increase significantly, and the incidence rate of postoperative complications is higher among older patients (26,27). For recipients receiving an elderly donor liver, there is a significant increase in the risk of postoperative microvascular thrombosis (14).

The maximum age limit for LDLT donors in various transplantation centers varies between 50 and 70 years. In Tianjin First Center Hospital, the age limit is 60 years. However, for donors aged >50 years, strict preoperative assessment is required. Diabetes, hypertension, fatty liver, prolonged intraoperative hepatic ischemia and hemodynamic instability are all factors associated with a poor prognosis in elderly donors (18,28,29). In the selection of transplant donors, the abovementioned factors are also associated with the prognosis of young liver donors (30). Selecting patients with adequate donor liver volume (ranging from 39.5 to 43.1% of ESLV) is crucial for their postoperative liver regeneration, and preserving a large residual liver is also beneficial for the donors in terms of early recovery of liver function and volume following surgery. This requires advanced preoperative imaging methods and software to accurately estimate liver volume, as the selection of donors with suitable liver volume is safer for donors and recipients (31).

Whether MHVs are included in the donor's liver theoretically will not affect the conclusions of the present study, because the basic postoperative conditions of recipients receiving livers with MHVs and without MHVs are similar, and they recovery well. Notably, there were certain limitations to the present study. First, the sample size was relatively small. Second, due to the inability to know the exact volume of the donors' residual liver, TLV_1-V_{1A} was considered as the donor ILV_1. The MSCT measurement may lead to overestimation of the liver volume (32), with the donor ILV_1 being higher compared with the actual volume. Thus, the actual LRR of donors may be higher compared with that calculated in the present study. Third, for more objective conclusions, all donors and recipients with complications were excluded, so it was not possible to evaluate the impact of complications on liver regeneration. Additional information will be collected in the future to further improve the study by increasing sample size, and patients with postoperative complications will be included for study to evaluate the effect of different complications on liver regeneration in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ML participated in research design, writing of the paper and data analysis. ZC, ZT, YJ and MX participated in data collection and data analysis. QJ participated in the research design. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of Tianjin First Center Hospital (Tianjin, China) and all patients signed an informed consent form.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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