Int J Clin Exp Med 2015;8(7):10315-10320
www.ijcem.com /ISSN:1940-5901/IJCEM0009208

Review Article

Application of elderly donor for liver transplantation

Jiang Li, Kai Wang

Department of Transplant Surgery, Tianjin First Central Hospital, Tianjin 300192, China

Received April 16, 2015; Accepted June 20, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: Recently, much more attention has been paid on application of elderly donor due to the shortage of organs. Although liver quality of elderly donors may be sub-optimal comparing with that from younger donors, primary non-function of a liver graft is a rare event. On the other hand, long-term graft and recipient survival for usage of elderly grafts has become a major concern and focus of research. Many transplant centers have changed the upper limit of donor age from previous 50 to 70 or even 75-year-old and achieved good graft function. Although some scholars believed that liver transplant using elderly grafts was associated with high probability of delayed liver function recovery, graft loss and hepatitis C recurrence, reports from several transplant centers document that long-term survival of grafts and recipients may be significantly improved through certain screening of donors and recipients before transplant. In conclusion, it is very important and relatively safe to use grafts from elderly donors to expand the donor pool. However, elderly donors and corresponding recipients must be carefully selected before transplant. The long-term effect of advanced age on grafts and recipients need to be evaluated through a comprehensive and long-term in-depth observation.

Keywords: Liver transplantation, graft, age, survival, complications

Introduction

The growing discrepancy between the number of patients listed for liver transplantation (LT) and the inadequate organ supply is a common problem in the medical community. Expansion of the donor pool is currently achieved with living donor transplantation, split LT, and the so-called extended criteria donors (ECDs) [1, 2]. Previously, usage of older donors has been recognized as one of the most important prognostic factors for patient and graft survival [3]. However, more attention has been paid to application of elderly donor for liver transplantation which may be an effective way to reduce the waiting time and solve the problem of organs shortage.

Trend for application of elderly donor grafts

The analysis of proposed grafts showed that donors 50 years old had a significantly much higher rate of usage, whereas other groups had a discarding rate of around 40% [1]. In foreign countries, many transplant centers have changed the upper limit of donor age from 50 to 65 years old. In recent years, some centers tried to use livers from 70-year-old or even 75-year-old donor and achieved good graft function [4, 5].

Data from UNOS shows that in the past ten years, the proportion of elderly donors in cadaveric donation has increased than before. Proportion of grafts from donors older than 50 years was 20% (753 cases) in 1993, 30.2% (1599 cases) in 2002 and 33.8% (2242 cases) in 2012, respectively. The proportion of donors older than 65 years in all donors has increased from 4.1% in 1993 to 7.8% in 2012 [6]. From 1999 to 2009 in Spain, the number of donors over 70 years old increased from 3.8/million to 8.8/million (increased by 132%) which represented 25.4% of all organ donation number in Spain [6].

Pathophysiology for elderly donor grafts

Graft livers from the elderly donors were thought to be sub-optimal comparing with that from young donors because elderly grafts were much smaller than younger grafts and more prone to

become fibrosis. However, this change caused by age was not due to morphological smaller of liver cells, but decreased numbers of liver cells [7]. Additionally, ultra-microscopic change of grafts from older donors would limit the use of oxygen and other nutrients [8]. One important function of liver is the antioxidant capacity which supported by glutathione reductase in the liver tissue. However, with increasing age, glutathione reductase is decreased ($P = 0.008$) and glutathione transferase-S-microsome in the microsomes is increased (GST) ($P < 0.001$) [9]. Moreover, the content of cytochrome P450 in liver cells is declined by 16% from 40 years old to 69 years old and 32% after 70 years old [10]. Tanemura et al [11] found that in living donor liver transplantation, the right graft livers in elderly donor group had higher proportion of fatty liver than the younger donor group (47.1% vs. 19.6%, $P = 0.03$), there are also differences of moderate fatty liver occurring between two groups (41.2% vs. 13.0%, $P = 0.014$). But there were also studies suggest that synthetic function of the liver will not be affected by the age because of good reserve function, dual blood supply and regeneration capacities of liver which are far beyond metabolic needs [12].

Promising results on application of elderly donors

Much more attention has been paid on the graft and the recipient long-term survival for usage of elderly grafts. For the whole liver transplantation using cadaveric grafts, survival rates of grafts and recipients in elderly donor group were good and comparable with that in young donor group. In Anderson et al study, there were 741 patients including 91 patients received livers from donors 60 years old or older and 650 patients had donors younger than 60 years old. Overall patient survival rates in the group using donors 60 or older were 86.8%, 72.6%, and 67.6% at 1, 3, and 5 years, respectively, and did not differ significantly from survival in the group receiving transplants from donors less than 60 (87.1%, 81.8%, and 75.5%; $P = 0.39$). The 1-, 3-, and 5-year graft survivals for patients receiving transplants from donors 60 or older were 82.4%, 65%, and 62.5%, respectively, and were not significantly different from those in the group using donors younger than 60 (84%, 78.6%, and 72.3%, respectively ($P = 0.39$) [4]. Jiménez-Romero et al reported that long-term survival of patients underwent liver transplantation using graft from donors aged over 70 years were analyzed. All patients were divided into three groups (donor age < 60 years, donor age 60-70 years, donor age > 70 years), There was no difference among three groups in 1, 3, 5-year survival rate of recipients (P = 0.5416), or 1, 3, 5-year graft survival ($P = 0.6956$) [13].

Controversies on the application of older donor grafts

Borchert et al found that there were no differences in frequency of re-transplant and rejection between elderly donor (older than 70 years) group and younger donor group [14]. Clinical indicators within three months after transplant were normal and without significantly affecting capabilities of fat and protein synthesis.

However, some scholars believed that liver transplant using elderly grafts had relatively higher probability in primary liver non-function, delayed graft function recovery, graft loss and patients death [15-17]. In one prospective study, 149 cases of first liver transplantations performed between 2000 and 2005 were divided into two groups according to donor age: group A, < 60 yr old (n = 102); and group B, ≥ 60 yr old (n = 47). There were no statistically differences between two groups in chronic and acute rejection, vascular complications, infections and anastomotic biliary strictures. But non-anastomotic biliary strictures (NABS) were clearly more frequent in the older donor group (17% vs. 4.9%; OR 3.9; $P = 0.025$). NABS without arterial complication was diagnosed in 10.6% of cases in group B versus 1% in group A (OR = 12; P = 0.012). Graft survival in the first year was 86.67% in the younger donor group and 71.43% in the older group ($P < 0.05$), but there was no difference between two groups in patient survival.

In a multivariate regression analysis, donor age equal to or greater than 60 years is the only relevant factor for intrahepatic biliary nonischemic stricture (OR = 15.4, $P = 0.024$). In addition, there are other adverse impacts for liver transplantation using elderly donors. Stewart et al [18] reported that the donor age greater than 50 years was a significant predictor of graft loss causing by hepatic artery thrombosis (RR = 1.45, $P < 0.001$), and the risk will gradually increase each additional 10 years; when

the donor when aged 70 and over, the risk increased 61% compared with the previous group (RR = 1.61, $P < 0.001$). Another study [19] found that transplants using grafts from donors greater than 50 years old are close to three times more likely to use more than one box (10 units) of RBCs when compared to transplants using younger donors.

Application of elderly donor and HCV recurrence

It worth emphasizing that for elderly donors must be carefully selected for hepatitis C virus (HCV) infected recipients. Generally, grafts from elderly donors were thought to promote donor HCV recurrence after liver transplantation. In a retrospective study including 201 cases of HCV-related liver transplant patients (46 cases of LDLT, 155 cases of cadaveric liver transplantation) [20], there was significant correlation between the donor age and liver fibrosis progression after liver transplantation. Relative risk for donors older than 45-year-old was 8.17 ($P = 0.001$), and researchers believed that the donor age determined HCV recurrence after liver transplantation. It's beneficial for HCV-positive living donor liver transplant recipients to choose younger donors. Selzner et al [20] conducted a long-term study, they also believed that HCV infection was one of the two independent risk factors affecting liver transplant recipients and graft survival ($P < 0.02$, HR = 3). Grafts and recipients survival in 1, 3, 5 year for HCV (+) recipients in elderly donor group (donor age ≥ 60 years) were lower than that in younger donor group (donor age < 60 years) ($P < 0.009$).

Application of elderly donor and recipient selection

Although there may be some adverse effects to prognosis of patients, transplantation using grafts from elderly donors can help reduce the mortality of patients on waiting list. Therefore, many studies support the application of suboptimal graft livers from elderly donors through certain screening on both of donor and recipient in order to improve the graft and recipient long-term survival. Segev et al divided all transplant recipients into screened group and unscreened group according to whether going through recipient screening or not. Graft and recipient survival was observed after transplantation using grafts from donors older than 70 years. The results showed that: after the selection, 3-year graft survival rate of elderly donor group could reach 74.9% which was similar with that in average age group (< 70 years, 75.0%, $P = 0.6$) and ideal age group (< 40 years, 77.3%, $P = 0.2$); There was no difference among three groups on 3-year survival rate for transplant recipients (81.2% VS 80.2%, $P = 0.9$; 81.2% VS 81.2%, $P = 0.8$). However, without recipient selection, graft and recipient survival rates in elderly donor group was significantly lower than that in young donor group. Graft 3-year survival rates in old age group, average age group and the ideal age group were 50.4%, 70.7% ($P < 0.001$) and 74.7% ($P < 0.001$), respectively; Transplant recipients 3 year survival rates were 64.4%, 77.4% ($P < 0.001$) and 80.0% ($P < 0.001$), respectively [21].

Application of elderly donor and grafts condition

In addition to recipient selection, grafts condition should also be screened in order to benefit patient prognosis. Cascales et al [5] reported their study on the application of elderly DBD donors and showed that average age of donors was 77.3 ± 2 years old and average cold ischemia time was 270.45 ± 76.27 minutes. The liver function was good without tumor recurrence after a follow-up of 23.2 ± 8.2 months which suggested that cold ischemia time (5 hours) was very important for recovery of elderly liver. One retrospective study was conducted in Germany that 230 liver transplantations have been performed in which 54 donor organs (23.5%) were from individuals > 65 years of age. The overall 1-year mortality was 22.2% (12/54) among recipients of organs from older donors versus 19.5% among recipients whose donors were < 65 years (P = NS), there was no statistical difference between two groups. The author believed that short cold ischemic time was the fundamental factor for better prognosis of grafts from elderly donors. In this study, the average cold ischemia time of elderly graft was less than 9 hours.

Kim et al [22] evaluated all risk factors for grafts survival after transplantation applying the DCD (donation after cardiac death) donors older than 65 years. All recipients were followed up for average 62.1 months after trans-

plantation, multivariate analysis showed that four factors such as HCV infection (P = 0.021), MELD score > 20 (P = 0.014), blood glucose levels > 200 mg/dL when the grafts were obtained and the time from skin incision to abdominal aorta clamping > 40 minutes (P = 0.040) were correlated with grafts dysfunction. Grafts 5-year survival rates without any risk factor or with one, two, three or four factors were 100%, 82.0%, 81.7%, 39.3% and 25.0%, respectively (P < 0.05). Good results can be achieved by using elderly donor as long as proper recipient selection, appropriate donor blood sugar control and efficient grafts harvesting were guaranteed.

Application of elderly donor for LDLT

Living donor liver transplantation (LDLT) has gained more and more attention as an alternative remedy for the shortage of organs and LDLT significantly shorten the waiting time and reduce mortality of recipients. Compared with cadaveric grafts applying for whole liver transplantation, grafts from living donors need regeneration in the body of recipients. So graft function and survival may be affected by donor age. Previous studies suggest that donor age should be limited to less than 50 years for living donor liver transplantation in adult [23, 24], which this will promote graft function and ensure donor safety. Compared with whole liver transplantation, LDLT grafts have to be involved in recovery of liver regeneration and liver synthetic function after transplantation which will directly affect the early and long-term prognosis of grafts. Studies have shown that liver endothelial cells of elderly grafts are more prone to be damaged by cold ischemia, which can explain why grafts from elderly donors are more prone to become fatty liver; Additionally, ATP synthesis capacity of liver decreased after reperfusion which will harm capacities of regeneration and synthesis, delay functional recovery of grafts and cause significant hyperbilirubinemia after transplantation [25]. In an experimental study using rodent model showed that the ability of the elderly liver cells proliferating by cell-cycle was significantly reduced [26, 27]. Tanemura et al [12] conducted a study on right lobe LDLT and found that donor age (≥ 50 years) was an independent risk factor to affect regeneration of the remnant liver 6 months after transplant (P = 0.04). And whether left or right lobe LDLT, donor age (≥ 50 years) was an independent risk factor to impact liver regeneration one week after transplant (P < 0.05). There was no difference between younger group (0.53 ± 0.10) and older group (0.50 ± 0.09) in initial graft liver volume/standard liver volume (GLV/SLV). But GLV/SLV gradually changed to be obviously different (younger group vs. older group was 1.02 ± 0.21 vs. 0.87 ± 0.28, P = 0.014) one week after transplantation. And this effect of donor age on regeneration of the liver may be associated with stem cells or progenitor cells in liver. In Ono et al [28] study, $Thy1^+$ cells which were considered to be human liver progenitor cells were counted in recipients after LDLT. All LDLT donors were divided into older group (6 cases, donor age ≥ 50 years) and younger group (9 cases, donor age ≤ 30 years). Residues liver regeneration was evaluated by CT scan on 7th and 30th day after transplantation. Liver regeneration speed was significantly higher in young donor group than older donor group (P = 0.042). $Thy1^+$ cells count kept decreasing with age increasing. Therefore, researchers believed that the decreasing number of liver progenitor cells may be one reason for decline of liver regeneration in elderly donors.

In summary, under the current environment of donor shortage, it is very important and relatively safe to use grafts from elderly donors to expand the donor pool. However, elderly donors must be carefully selected before transplant [29]. The long-term effect of old age on grafts and recipients need to be evaluated through a comprehensive and long-term in-depth observation.

Acknowledgements

The work was supported by grants from National Natural Science Foundation of China (Grant No. 81400680) and National High Technology Research and Development Program of China (Grant No. 2012 AA021001).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kai Wang, Department of Transplant Surgery, Tianjin First Central Hospital, Tianjin 300192, China. E-mail: wangkai1978@hotmail.com

References

[1] Cescon M, Grazi GL, Cucchetti A, Ravaioli M, Ercolani G, Vivarelli M, D'Errico A, Del Gaudio M and Pinna AD. Improving the outcome of liver transplantation with very old donors with updated selection and management criteria. Liver Transpl 2008; 14: 672-679.

[2] Rauchfuss F, Voigt R, Dittmar Y, Heise M and Settmacher U. Liver transplantation utilizing old donor organs: a German single-center experience. Transplant Proc 2010; 42: 175-177.

[3] Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, O'Grady JG, Castaing D, Klempnauer J, Jamieson N, Neuhaus P, Lerut J, de Ville de Goyet J, Pollard S, Salizzoni M, Rogiers X, Muhlbacher F, Garcia Valdecasas JC, Broelsch C, Jaeck D, Berenguer J, Gonzalez EM, Adam R; European Liver Transplant Association. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet 2006; 367: 225-232.

[4] Anderson CD, Vachharajani N, Doyle M, Lowell JA, Wellen JR, Shenoy S, Lisker-Melman M, Korenblat K, Crippin J and Chapman WC. Advanced donor age alone does not affect patient or graft survival after liver transplantation. J Am Coll Surg 2008; 207: 847-852.

[5] Cascales Campos PA, Romero PR, Gonzalez R, Zambudio AR, Martinez Frutos IM, de la Pena J, Bueno FS, Robles Campos R, Miras M, Pons Minano JA, Sanmartin Monzo A, Domingo J, Bixquert Montagud V and Parrilla Paricio P. Improving the waiting list by using 75-year-old donors for recipients with hepatocellular carcinoma. Transplant Proc 2010; 42: 627-630.

[6] Frontera JA. How I manage the adult potential organ donor: donation after cardiac death (part 2). Neurocrit Care 2010; 12: 111-116.

[7] Wakabayashi H, Nishiyama Y, Ushiyama T, Maeba T and Maeta H. Evaluation of the effect of age on functioning hepatocyte mass and liver blood flow using liver scintigraphy in preoperative estimations for surgical patients: comparison with CT volumetry. J Surg Res 2002; 106: 246-253.

[8] Briceno J, Marchal T, Padillo J, Solorzano G and Pera C. Influence of marginal donors on liver preservation injury. Transplantation 2002; 74: 522-526.

[9] Miyagi SJ, Brown IW, Chock JM and Collier AC. Developmental changes in hepatic antioxidant capacity are age-and sex-dependent. J Pharmacol Sci 2009; 111: 440-445.

[10] Zeeh J and Platt D. The aging liver: structural and functional changes and their consequences for drug treatment in old age. Gerontology 2002; 48: 121-127.

[11] Tanemura A, Mizuno S, Wada H, Yamada T, Nobori T and Isaji S. Donor age affects liver regeneration during early period in the graft liver and late period in the remnant liver after living donor liver transplantation. World J Surg 2012; 36: 1102-1111.

[12] Serste T and Bourgeois N. Ageing and the liver. Acta Gastroenterol Belg 2006; 69: 296-298.

[13] Jimenez-Romero C, Clemares-Lama M, Manrique-Municio A, Garcia-Sesma A, Calvo-Pulido J and Moreno-Gonzalez E. Long-term results using old liver grafts for transplantation: sexagenerian versus liver donors older than 70 years. World J Surg 2013; 37: 2211-2221.

[14] Borchert DH, Glanemann M, Mogl M, Langrehr J and Neuhaus P. Adult liver transplantation using liver grafts from donors over 70 years of age. Transplant Proc 2005; 37: 1186-1187.

[15] Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM and Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006; 6: 783-790.

[16] Selzner M, Kashfi A, Selzner N, McCluskey S, Greig PD, Cattral MS, Levy GA, Lilly L, Renner EL, Therapondos G, Adcock LE, Grant DR and McGilvray ID. Recipient age affects long-term outcome and hepatitis C recurrence in old donor livers following transplantation. Liver Transpl 2009; 15: 1288-1295.

[17] Valadao RM and Terrault NA. Older donors: mounting risks for the hepatitis C-infected liver transplant recipient? Liver Transpl 2009; 15: 677-681.

[18] Stewart ZA, Locke JE, Segev DL, Dagher NN, Singer AL, Montgomery RA and Cameron AM. Increased risk of graft loss from hepatic artery thrombosis after liver transplantation with older donors. Liver Transpl 2009; 15: 1688-1695.

[19] Modanlou KA, Oliver DA and Grossman BJ. Liver donor's age and recipient's serum creatinine predict blood component use during liver transplantation. Transfusion 2009; 49: 2645-2651.

[20] Selzner N, Girgrah N, Lilly L, Guindi M, Selzner M, Therapondos G, Adeyi O, McGilvray I, Cattral M, Greig PD, Grant D, Levy G and Renner EL. The difference in the fibrosis progression of recurrent hepatitis C after live donor liver transplantation versus deceased donor liver transplantation is attributable to the difference in donor age. Liver Transpl 2008; 14: 1778-1786.

[21] Segev DL, Maley WR, Simpkins CE, Locke JE, Nguyen GC, Montgomery RA and Thuluvath PJ. Minimizing risk associated with elderly liver donors by matching to preferred recipients. Hepatology 2007; 46: 1907-1918.

[22] Kim DY, Moon J, Island ER, Tekin A, Ganz S, Levi D, Selvaggi G, Nishida S and Tzakis AG. Liver transplantation using elderly donors: a risk factor analysis. Clin Transplant 2011; 25: 270-276.
[23] Kiuchi T, Tanaka K, Ito T, Oike F, Ogura Y, Fujimoto Y and Ogawa K. Small-for-size graft in living donor liver transplantation: how far should we go? Liver Transpl 2003; 9: S29-35.
[24] Lee DS, Gil WH, Lee HH, Lee KW, Lee SK, Kim SJ, Choi SH, Heo JS, Hyon WS, Kim GS, Paik SW, Koh KC and Joh JW. Factors affecting graft survival after living donor liver transplantation. Transplant Proc 2004; 36: 2255-2256.
[25] Nardo B, Masetti M, Urbani L, Caraceni P, Montalti R, Filipponi F, Mosca F, Martinelli G, Bernardi M, Daniele Pinna A and Cavallari A. Liver transplantation from donors aged 80 years and over: pushing the limit. Am J Transplant 2004; 4: 1139-1147.
[26] Chen WD, Wang YD, Zhang L, Shiah S, Wang M, Yang F, Yu D, Forman BM and Huang W. Farnesoid X receptor alleviates age-related proliferation defects in regenerating mouse livers by activating forkhead box m1b transcription. Hepatology 2010; 51: 953-962.
[27] Suzuki A, Sakaguchi T, Inaba K, Suzuki S and Konno H. Impact of cell cycle disruption on impaired hepatic regeneration in aged livers with ischemic insult. J Surg Res 2012; 173: 267-277.
[28] Ono Y, Kawachi S, Hayashida T, Wakui M, Tanabe M, Itano O, Obara H, Shinoda M, Hibi T, Oshima G, Tani N, Mihara K and Kitagawa Y. The influence of donor age on liver regeneration and hepatic progenitor cell populations. Surgery 2011; 150: 154-161.
[29] Alamo JM, Barrera L, Marin LM, Bernal C, Suarez G, Serrano J, Gomez MA and Padillo FJ. Results of liver transplantation with donors older than 70 years: a case-control study. Transplant Proc 2011; 43: 2227-2229.