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CLINICAL RESEARCH

Impact of age on the incidence of complications after liver transplantation: A single-center retrospective study

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Abstract
Background and objective: Advances in surgical technique, postoperative management, and immunosuppressive therapy have led to a steady increase in the number of patients undergoing organ transplantation. This study aimed to compare the incidence of postoperative complications between young and elderly patients undergoing liver transplantation (LT) at a single university hospital.
Method: The medical records of 253 patients who underwent LT between January 2010 and July 2017 were retrospectively reviewed. The patients were divided into two groups: those younger than 65 years (group Y, n = 231) and those older than 65 years (group O, n = 22). Data on patient demographics, perioperative management, and postoperative complications were collected.
Results: The patients' baseline characteristics, including underlying diseases and the Model for End-Stage Liver Disease scores, were not different between groups. Preoperative laboratory findings were not significantly different between the two groups, except for hemoglobin level. The total amounts of infused fluid and packed red blood cells were higher in group O than in group Y. The postoperative plasma creatinine level was higher in group O than in group Y; however, the incidence of postoperative complications was not considerably different between the two groups. In addition, there was no difference in the survival rate after LT depending on age.

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Introduction

Liver transplantation (LT) has been recognized as the standard treatment for patients with end-stage liver disease based on accumulated experience and improvements in long-term outcome.[1] The prolongation of life span has increased the number of patients waiting for organ transplantation, and the median age of liver transplant recipients has also increased owing to advances in surgical technique, intensive care, postoperative surgical treatment, and immunosuppressive therapy.[2,3] However, the reported outcomes among elderly liver transplant recipients have varied widely. An early study from a single center reported a longer hospital stay and lower survival rate in patients aged >60 years.[4] The causes of high mortality were as follows: comorbidities before surgery, malignancy, cardiovascular and/or neurological disease after LT, increased risk of infection, increased resource utilization, and lower life expectancy.[5,6] Consequently, most of the recently published studies showed similar outcomes in elderly recipients compared with younger recipients, with elderly patients showing a significantly lower incidence of acute rejection but higher incidences of infection and cancer.[7–10] Advanced age alone is not a cause of transplant rejection; however, several studies have shown that the risk of complications is higher in elderly liver transplant recipients because of their high physiological age, functional status, and preoperative comorbidities.[11]

Although the number of candidates for LT has increased, organ availability does not fully meet the demand. Therefore, proper organ allocation and utilization are necessary, and it is important to determine whether there would be any difference in the risk of complications and outcomes after LT in elderly patients compared with younger patients. To clarify this issue, we aimed to evaluate the relationship between age and the risk of post-LT complications and to identify the important factors for safely performing LT in elderly patients.

Methods

This study was approved by the institutional review board (n. 2017–156). The medical records of patients who underwent LT from January 1, 2010 to July 31, 2017 were computer-searched, and data from 360 patients were collected (Figure 1).

A total of 253 patients were ultimately included in the study, after excluding 107 patients because of cerebral disease that could affect mental status, missing data about mental status after LT, retransplantation, or additional surgery.

The patient records were reviewed retrospectively, including hospitalization records, progress reports, consultation records, preoperative evaluation reports, anesthesia records, intensive care unit (ICU) records, nursing records, and discharge records. A preoperative examination was performed within 1 day before surgery, and postoperative tests were carried out within 1 day after transfer to the ICU.

Postoperative complications after surgery and before discharge were assessed by referring to the discharge records. Cardiac complications were defined as cardiac-related diseases such as angina and arrhythmia that needed treatment. Respiratory complications were defined as respiratory infections such as pneumonia that required management. Neurological complications included neurological problems such as cerebral hemorrhage that required treatment. The incidence of delirium was assessed in cases in which delirium was diagnosed in patients under psychiatric consultation and needed medical treatment with haloperidol or other drugs for delirium. In accordance with the Acute Kidney Injury Network (AKIN) criteria,[12] patients with postoperative acute kidney injury were diagnosed. The infection rate was reviewed in cases with surgical site infection and sepsis. Acute rejection after LT was confirmed by pathologic biopsy results within 6 months after transplantation. Mortality was also evaluated in cases of deaths in the postoperative period before discharge.

Induction of anesthesia was performed with propofol and rocuronium or cisatracurium. Inhalation anesthesia was applied with sevoflurane or desflurane in an oxygen/air mixture with 40–50% inspired oxygen. Remifentanil (range 0.5–1 $\mu g.kg^{-1}.min^{-1}$) and a neuromuscular blocking agent (rocuronium [range 0.3–0.6 $mg.kg^{-1}.h^{-1}$] or cisatracurium [range 0.1–0.2 $mg.kg^{-1}.h^{-1}$]) were continuously infused. All patients underwent standard anesthetic monitoring, including electrocardiography and end-tidal carbon dioxide concentration, bispectral index, peripheral oxygen saturation, cerebral oxygenation using INVOS 5100 C (COVIDIEN, Mansfield, MA, USA), and invasive arterial blood pressure monitoring in the radial and femoral arteries. An oxygen monitoring central venous catheter (PreSep; Edwards Lifesciences, Irvine, CA, USA) was inserted and used to evaluate circulation using an EV1000 platform (Edwards Lifesciences) for monitoring cardiac output, cardiac index, stroke volume, stroke volume index, central venous oxygen saturation, and systemic vascular resistance. Transfusion was performed to maintain the hematocrit level at 25–30%. Norepinephrine (0.01–0.4 $\mu g.kg^{-1}.min^{-1}$) was used to maintain adequate blood pressure during surgery (systolic blood pressure > 90 mmHg, mean arterial pressure > 60 mmHg). If norepinephrine was not effective, dobutamine, vasopressin, and epinephrine were used, depending on the condition of the patient.

Data were analyzed using SAS (Statistical Analysis System version 9.3; SAS Institute, USA) and R software version 3.3.2 (R Project for Statistical Computing, Austria). All data are presented as the mean ± standard deviation, median (25th–75th percentile), or number of patients (%). The normality test was performed with the Shapiro-Wilk W-test or the Kolmogorov-Smirnov test. The independent *t*-test or Wilcoxon rank-sum test was used for continuous variables for comparison between the two groups. The chi-square test or Fisher's exact test was used for categorical variables. The survival difference was assessed by the log rank tests and Kaplan-Meier curves. A p-value < 0.05 was considered statistically significant.

The effect of the age on the death or not after LT using univariate analysis and multivariate analysis were analysed. Typical factors associated with the death after LT were analysed by univariate analysis, and multivariate analysis was performed using 8 factors with p-value < 0.1.

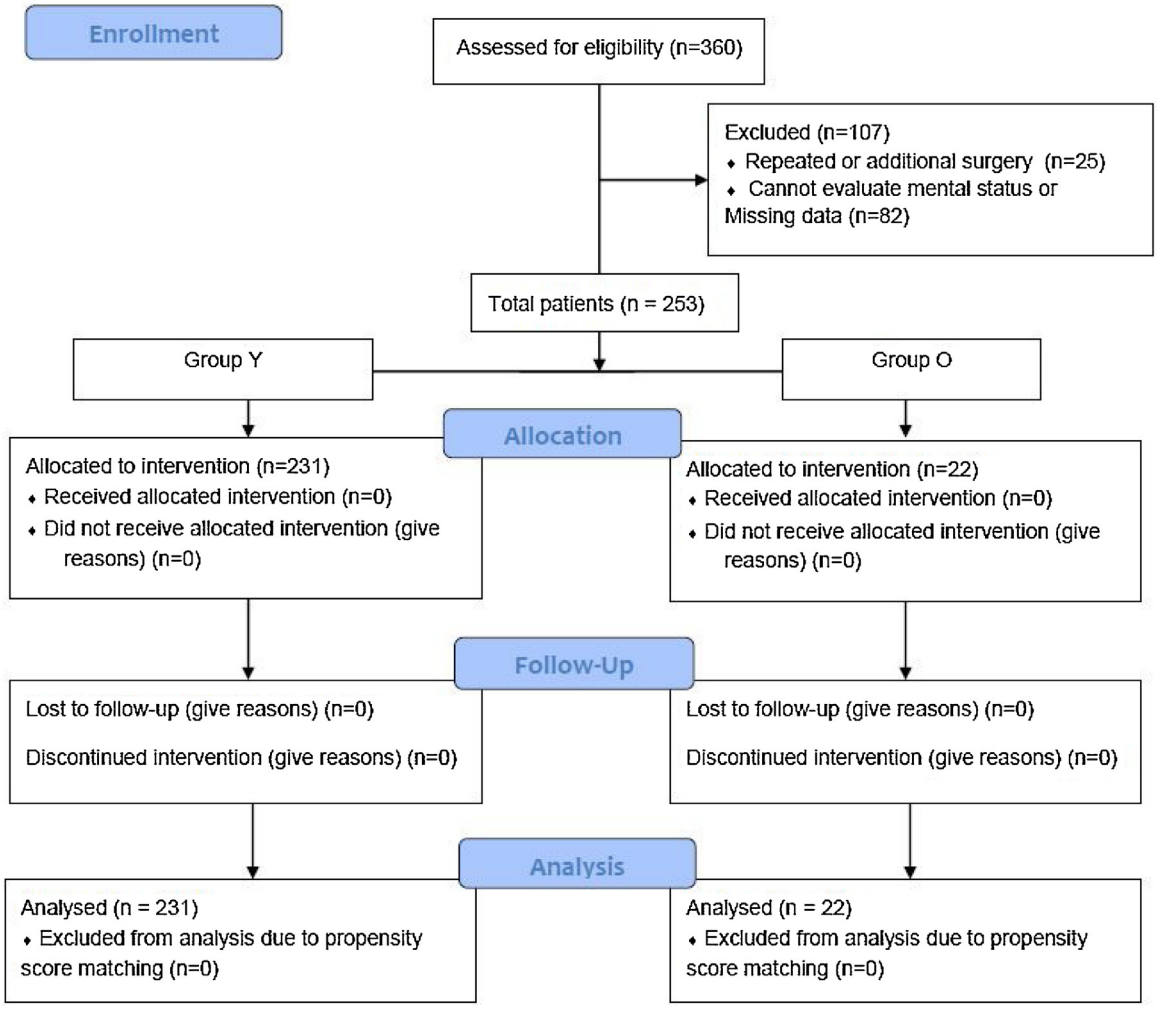

Figure 1 Flow diagram of the study.

Results

We retrospectively analyzed the data of 360 LT cases in Figure 1. Of these patients, 107 were excluded. Twenty-five patients were excluded due to repeated or additional surgery. Twenty patients were excluded as mental status could not be evaluated, while perioperative laboratory data were missing in 62 patients. Among the excluded patients, seven were aged 65 years or more: one patient was excluded due to repeated surgery, and six patients were excluded due to missing perioperative blood coagulation test data.

The preoperative characteristics of the patients are summarized in Table 1. The patients were divided into two groups: those aged < 65 years (group Y, n = 231) and those aged ≥ 65 years (group O, n = 22). The patients' characteristics, such as body mass index (BMI), use of diuretics or insulin, use of psychiatric medication, and underlying diseases, were not significantly different between group Y and group O. Moreover, the reasons for LT and the Model for End-Stage Liver Disease (MELD) scores also showed no difference between the two groups.

In the preoperative laboratory findings, most of the results showed no difference between the two groups, except for hemoglobin (p = 0.001), which was slightly lower in group O than in group Y (Table 2).

During the surgery, patients in group O had a longer anesthetic duration than patients in group Y (p = 0.033). In addition, the intraoperative estimated blood loss was higher in group O than in group Y (p = 0.027). The total amounts of infused fluid (p = 0.042) and packed red blood cells (p = 0.008) were higher in group O than in group Y (Table 3).

No notable differences in postoperative data were found between the two groups except for creatinine level. The plasma creatinine level after LT was higher in group O than in group Y (Table 4). However, there were no significant differences in the incidence of postoperative complications, including ICU stay and time from surgery to discharge.

Thirty-eight patients died after LT, five of whom were aged 65 years or older. In the group O, two patients died within 3 months of the liver transplant. One patient died of respiratory failure due to tuberculosis and the other died of multiple organ failure due to sepsis. In addition, there was no difference in the survival rate after liver transplantation depending on age using Kaplan-Meier curves (log-rank p-value = 0.20) as depicted in Figure 2. In the univariate analysis in Table 5, LDLT or CDLT, hypertension, diabetes

Table 1 Patients' characteristics.

Characteristics	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Age (y)	53 (22–64)	66 (65–74)	0.865
Sex (M/F)	62 (26.84)/169 (73.16)	8 (36.36)/14 (63.64)	0.340
Body mass index ($kg.m^{-2}$)	22.49 ± 3.21	21.09 ± 3.15	0.051
LDLT/CDLT	153 (66.23)/78 (33.77)	11 (50)/11 (50)	0.635
MELD score	18.32 ± 11.29	20.00 ± 9.93	0.500
Cause for LT			
Alcoholic cirrhosis	50 (21.65)	3 (13.64)	0.294
HBV and HCV	155 (67.10)	13 (59.09)	
NBNC LC	8 (3.46)	2 (9.09)	
Toxic hepatitis	13 (5.63)	3 (13.64)	
Primary biliary cirrhosis	5 (2.16)	1 (4.55)	
Ascites	76 (32.90)	10 (45.45)	0.235
Hepatic Encephalopathy	37 (16.02)	5 (22.73)	0.381
Varices	37 (16.02)	4 (18.18)	0.764
HRS	20 (8.66)	3 (13.64)	0.433
Hypertension	44 (19.05)	7 (31.82)	0.167
Diabetes mellitus	61 (26.41)	5 (22.73)	0.707
Ischemic heart disease	1 (0.43)	1 (4.55)	0.167

Values are presented as mean (standard deviation), median (range) or number (%). SD, standard deviation; LDLT, living donor liver transplantation; CDLT, cadaveric donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC LC, non-HBV non-HCV liver cirrhosis; HRS, hepatorenal syndrome; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.05$ compared between groups.

Table 2 Perioperative laboratory data in patients undergoing liver transplantation.

Variables	Preoperative data			Postoperative data		
	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Hb ($g.dL^{-1}$)	10.88 ± 2.29	9.65 ± 1.42	0.001[a]	8.93 ± 1.49	9.25 ± 1.31	0.331
Bilirubin ($\mu mol.L^{-1}$)	2.70 (1.30–1.80)	3.30 (1.80–7.00)	0.253	4.00 (2.10–6.80)	4.90 (3.00–7.50)	0.307
Protein ($g.dL^{-1}$)	5.97 ± 0.87	5.66 ± 0.84	0.108	5.27 ± 0.69	5.17 ± 0.55	0.470
Albumin ($g.dL^{-1}$)	3.13 ± 0.56	3.04 ± 0.50	0.446	3.64 ± 0.46	3.61 ± 0.39	0.731
K ($mmol.L^{-1}$)	3.98 ± 0.54	3.95 ± 0.61	0.817	3.99 ± 0.41	4.12 ± 0.49	0.166
Cr ($mg.dL^{-1}$)	0.78 (0.61–1.00)	0.90 (0.77–1.19)	0.099	1.04 ± 0.47	1.26 ± 0.54	0.044[a]
PT (INR)	1.55 (1.24–2.20)	1.75 (1.40–2.31)	0.203	1.79 ± 0.37	1.67 ± 0.30	0.139

Values are expressed as mean ± standard deviation or median (25th–75th percentile). Hb, hemoglobin; K, potassium; Cr, creatinine; PT, prothrombin time; INR, international normalized ratio; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.05$ compared between groups.

Table 3 Patients' perioperative factors.

Variables	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Anesthetic duration (h)	10.75 (9.20–12.50)	10.00 (8.50–11.00)	0.033[a]
Intraoperative EBL (L)	2.80 (1.50–5.00)	4.00 (2.50–6.00)	0.027[a]
Total fluid (L)	7.06 (5.32–10.09)	9.42 (6.40–13.26)	0.042[a]
pRBC (units)	4.00 (0.00–10.00)	7.00 (4.00–12.00)	0.008[a]
FFP (units)	4.00 (0.00–10.00)	6.50 (4.00–12.00)	0.076
Cryo (units)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.330
PLT (units)	0.00 (0.00–0.00)	0.00 (0.00–8.00)	0.257

EBL, estimated blood loss; pRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet; Group Y, patients < 65 years; Group O, patients ≥ 65 years. Values are expressed as mean ± standard deviation or median (25th–75th percentile).
[a] $p < 0.05$ compared between groups.

Table 4 Postoperative data of patients undergoing liver transplantation.

Variables	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
ICU stay (days)	8.00 (5.00–12.00)	14.00 (5.00–23.00)	0.112
Time from surgery to discharge (days)	28.00 (22.00–42.00)	34.00 (22.00–70.00)	0.118
Postoperative complication			
Cardiac complication	6 (2.60)	0 (0.00)	1.000
Atrial fibrillation	5 (2.16)		
Infectious endocarditis	1 (0.43)		
Respiratory complication	19 (8.23)	3 (13.63)	1.000
Neurologic complication			
Brain hemorrhage	0 (0.00)	1 (4.55)	0.087
Seizure	1 (0.43)	0 (0.00)	1.000
Brain injury	2 (0.87)	1 (4.55)	1.000
Delirium	31 (13.42)	5 (22.73)	0.215
Postoperative AKI	54 (23.38)	10 (45.45)	0.043[a]
Infectious complication			
Abscess	3 (1.31)	1 (4.55)	1.000
Sepsis	3 (1.31)	1 (4.55)	1.000
Reoperation	20 (8.66)	5 (22.73)	0.060
Acute rejection	6 (2.60)	0 (0.00)	1.000
Death during hospitalization	10 (4.32)	2 (9.09)	0.879

ICU, intensive care unit; AKI, acute kidney injury; Group Y, patients < 65 years; Group O, patients ≥ 65 years. Values are expressed as number (%) or median (25th–75th percentile).
[a] $p < 0.05$ compared between groups.

Table 5 Logistic Regression Analysis for death after liver transplantation.

Variables	OR	95% CI		*p*-value	OR	95% CI	*p*-value	
		Lower	Upper			Lower	Upper	
Age	1.025	0.980	1.071	0.283				
Age (Group Y/O)	1.765	0.610	5.109	0.295				
Sex	0.928	0.433	1.990	0.848				
Body mass index	0.989	0.888	1.101	0.836				
LDLT/CDLT	2.670	1.325	5.383	0.006[a]	1.808	0.741	4.41	0.193
Hypertension	2.422	1.137	5.160	0.022[a]	2.402	1.028	5.612	0.043[b]
Diabetes mellitus	2.742	1.342	5.603	0.006[a]	2.497	1.145	5.443	0.021[b]
Alcoholic cirrhosis	0.399	0.135	1.178	0.096[a]	0.309	0.096	0.999	0.050
MELD score	1.009	0.979	1.040	0.545				
Anesthetic duration	1.072	0.965	1.191	0.197				
Intraoperative EBL	1.078	0.974	1.193	0.146				
Total fluid	1.032	0.978	1.088	0.256				
pRBC	1.014	0.981	1.049	0.409				
Hb after surgery	1.195	0.958	1.492	0.114				
Cr after surgery	1.911	1.020	3.581	0.043[a]	0.966	0.421	2.217	0.935
ICU stay	1.064	1.031	1.098	< 0.001[a]	1.038	0.999	1.079	0.059
Cardiac complication	6.057	1.175	31.218	0.031[a]	4.669	0.456	47.828	0.194
Respiratory complication	1.765	0.610	5.109	0.295				
Postoperative AKI	2.209	1.071	4.559	0.032[a]	1.754	0.746	4.123	0.198
Infection	1.910	0.193	18.859	0.580				
Reoperation	1.477	0.518	4.209	0.465				
Acute rejection	2.931	0.518	16.593	0.224				

OR, odds ratio; CI, confidence interval; CDLT, cadaveric donor liver transplantation; MELD, Model for End-Stage Liver Disease; Hb, hemoglobin; Cr, creatinine; EBL, estimated blood loss; pRBC, packed red blood cells; ICU, intensive care unit; AKI, acute kidney injury; Group Y, patients younger than 65 years; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.1$ in univariate analysis.
[b] $p < 0.05$ in multivariate analysis.

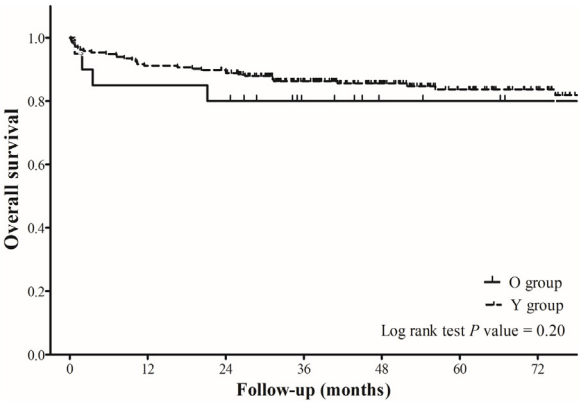

Figure 2 Overall survival rate according to the follow-up period in O and Y groups. Group Y, patients < 65 years; Group O, patients ≥ 65 years.

mellitus, alcoholic disease, ICU stay, cardiac complication, postoperative AKI showed lower *p*-values than 0.1. The multivariate analysis revealed that hypertension, diabetes mellitus were independent risk factors for death after LT ($p < 0.05$). However, age ($p = 0.283$) or groups classified by age ($p = 0.295$) were not related with death after LT.

Discussion

As the number of elderly patients undergoing transplantation has increased, we analyzed the data on the occurrence of age-related complications in liver transplant recipients. Although the preoperative hemoglobin level was lower and the requirement for blood transfusion was more common in the elderly patients, there were no notable differences in postoperative complications, including ICU stay and time from surgery to discharge, between the two groups. In addition, there was no difference in survival rate after liver transplantation based on age.

Early studies have reported higher mortality rates in elderly recipients than in younger patients because more complications occurred after transplantation in elderly recipients even when the MELD score was the same between the 2 groups.[5,6] The causes of high mortality in elderly recipients were as follows: comorbidities before surgery, malignancy, cardiovascular and/or neurological events after LT, renal failure, and secondary infections due to the use of immunosuppressants. The prognosis was poor in patients with renal insufficiency before surgery, especially in patients undergoing dialysis. Renal replacement therapy before surgery has been shown to have a strong association with poor outcomes.[13] Furthermore, the rate of bacterial or fungal infection, post-transplantation sepsis, and the duration of ICU stay also increased in recipients with renal insufficiency before surgery.[14] The second most influential comorbidity was cardiovascular diseases such as coronary artery disease, atherosclerosis in major vessels, and arrhythmia.[11] Niazi et al.[15] reported the impact of psychosocial factors on the outcomes associated with LT. Depression and anxiety are known to be related to poor outcomes after LT. In addition to these general complications, it was reported that elderly recipients had increased resource utilization owing to weak pulmonary function and low life expectancy.[9,11] Thus, many authors recommend screening elderly recipients with associated comorbidities and malignancy and performing LT only in elderly patients without significant comorbid conditions.[16–18]

Recently, with accumulated experience and successful LT cases, several studies have reported that graft survival and mortality did not differ significantly between young and elderly liver transplant recipients.[7,15,19–21] These studies suggested that functional status rather than chronological age had a greater impact on outcomes. Functional status depends not only on advanced patient age but also on behavioral factors, including exercise, BMI, smoking and alcohol use, and psychosocial factors. Moreover, regardless of age, high MELD scores, alcoholic liver disease, and medical comorbidities such as congestive heart failure, coronary artery disease, and renal insufficiency requiring dialysis were significantly associated with poor outcomes in liver transplant recipients.[11] Furthermore, the utilization of medical resources after transplantation was similar in the two groups.[22] However, those studies had limitations. They found that elderly liver transplant recipients had lower MELD scores, lower BMI, fewer comorbidities, and higher serum albumin than younger recipients. This shows that elderly patients with relatively preserved physiological conditions and low MELD scores selectively underwent LT.[23]

Blood transfusions are one of the known causes of postoperative complications such as infection, respiratory complications, myocardial infarction, and renal insufficiency.[24,25] Our study showed that group O had lower preoperative hemoglobin and more intraoperative transfusions than group Y. Blood transfusions are known to affect postoperative complications by directly increasing the plasma concentration of inflammatory mediators[26] and amplifying the inflammatory response induced by surgery.[27] However, our study showed that although there were differences in transfusion doses, there was no difference in the incidence of complications. Similar results have been obtained in other studies. Postoperative complications were reduced by the use of red blood cells that were irradiated or depleted of leukocytes by filtration during surgery.[28–31]

In our study, there was no significant difference in the occurrence of complications after LT between group O and group Y, and the patient characteristics, preoperative laboratory findings except for hemoglobin level, and comorbidities also did not differ significantly. The total amounts of infused fluid and packed red blood cells were higher, and the postoperative creatinine level was higher in the elderly group than in the younger group; however, there was no significant difference in the incidence of acute kidney injury after transplantation. Moreover, the ICU length of stay and time from surgery to discharge also showed no notable differences between the two groups. Altogether, these findings suggest that elderly patients may be considered adequate candidates for LT.

There are several risk factors for mortality after LT. Dialysis patients are known to have the highest risk of death regardless of age, and the number of fresh frozen plasma units transfused and re-transplantation have a statistically significant association with early death due to sepsis.[9,32] Previous studies have indicated that the risk of mortality is increased in liver transplant recipients aged ≥ 60

years-old, especially patients undergoing renal replacement therapy.[9,32] However, our study failed to demonstrate any association of advanced age and an increased mortality rate. Although this study has shown that the elderly group had a higher incidence of AKI after LT, serum creatinine levels were similar in both groups after surgery and any clinical difference between groups seems to be negligible.

This study has important limitations. The number of patients aged ≥ 65 years was small (22 patients); therefore, the outcomes of postoperative complications in elderly patients cannot be considered completely similar to those in younger patients. Because of the small number of ''exposed'' patients, the probability of type 2 error cannot be ignored, and the findings may not be sufficient to conclude that LT is safe in elderly patients.

Second, our study did not investigate long-term prognosis. It is an important issue that elderly recipients have a relatively short life expectancy and may have other critical diseases compared with younger patients, regardless of the severity of liver function before transplantation. Thus, long-term follow-up is necessary for a more accurate comparison between young and old patients.

Another limitation is our inability to collect data on vascular and biliary complications since the relevant data were missing. Vascular and biliary tract complications are known to be common in elderly patients,[33] increasing the risk of type 2 error in relation to the mortality rate.

In conclusion, despite the limitations imposed by the small number of patients, our study has demonstrated positive results for the safety indication of LT in elderly patients. Therefore, to improve the prognosis of elderly patients who require LT in the future, it is necessary to focus on the main strategies and new protocols in order to identify potential risk factors, and improve outcomes in elderly patients undergoing liver transplantation.

Conflict of interest

The authors declare no conflicts of interest.

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