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# Outcomes Between Elderly and Young Hepatocellular Carcinoma Living Donor Liver Transplantation Recipients

## *A Single-Center Experience*

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**Abstract:** Although older age theoretically might be a negative risk factor for liver transplantation (LT) outcomes, age alone should not exclude a patient from waiting list. This study is to investigate the outcomes of elderly hepatocellular carcinoma (HCC) living donor liver transplantation (LDLT) recipients which meet Milan criteria.

A retrospective study was performed in a single liver transplantation center. Demographic and clinical data of 110 HCC LDLT recipients from January 2004 to December 2012 were collected and analyzed, including 31 elderly recipients in group E (≥60 years) and 79 younger recipients in group Y (<60 years).

Recipients' age between 2 groups were significantly different ($65.4 \pm 4.8$ vs $49.9 \pm 5.9$, $P = 0.000$). There was no significant difference in preoperative demographic data as well as postoperative liver function. Complication rates, length of ICU and hospital stay, graft loss, and mortality were similar in both groups, as well as the 1-, and 3-year overall and disease-free survival rates (77.4%, and 64.5% vs 82.8%, and 44.6%, $P = 0.458$; 94.7%, and 80.7% vs 98.6%, and 85.9%, $P = 0.661$). When recipients were further stratified into group E1, E2, Y1, and Y2, no significant difference was found in 1-, and 3-year overall and disease-free survival rates. In multivariate analysis, recipients' age was not a predictor for long-term survival.

Following rigorous listing criteria, if overall clinical conditions and comorbidities allowed, elderly HCC recipients achieved similar LDLT outcomes and survival rates with the younger HCC recipients.

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**Abbreviations**: AFP = alpha-fetoprotein, BMI = body mass index, CIT = cold ischemia time, HCC = hepatocellular carcinoma, LDLT = living donor liver transplantation, LT = liver transplantation, MELD = model for end-stage liver disease, OLT = orthotopic liver transplantation, TACE = transarterial chemoembolization, WIT = warm ischemia time.

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## INTRODUCTION

Although older age theoretically might be a negative risk factor for liver transplantation (LT) outcomes, age alone should not exclude a patient from the waiting list.[1] However, some other reports suggested that elderly recipients might yields worse outcomes than that of younger individuals in LT.[2,3] Due to the prevalence of end-stage liver disease in older age patients,[4] it was likely that more LTs would be performed in such part of population. It was not well defined whether the outcomes of elderly living donor liver transplantation (LDLT) recipients with hepatocellular carcinoma (HCC) were comparable to the younger individuals who were candidates for LDLT.

In this retrospective study, the outcomes between elderly and young HCC LDLT recipients, which met Milan criteria, were evaluated and discussed.

## PATIENTS AND METHODS

We retrospectively analyzed data of 233 consecutive LDLT recipients from January 2004 to December 2012. LDLT indications included: HCC meeting UCSF criteria, decompensated liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic, sclerosing cholangitis reason, autoimmune hepatitis, and liver echinococcosis. MELD score was used as the listing criteria. For HCC recipients who met Milan criteria, additional 25 score were added to total score in the waiting list in our transplant center[5,6] and uploaded to *China Liver Transplant Registry*. AFP, CPEX testing, and stress echo were not used to select recipients. Inclusion criteria were (1) diagnosed with HCC within Milan criteria with/without decompensated liver cirrhosis; (2) age >18 years old. After excluding cases of patients diagnosed with HCC beyond Milan criteria and pediatric recipients, there were 130 patients included. Patients with incomplete follow-up data were excluded from analysis. Eventually, there were 110 recipients enrolled in this study (Figure 1).

The diagnosis of HCC was made according to the EASL criteria in 2012.[7] The operative procedures were similar to those performed in other major medical centers.[8] Patients were divided into 2 groups: age ≥ 60 years (Group E, n = 31) and age <60 years (Group Y, n = 79). In subgroup analysis, patients were further stratified into 4 groups as follows: Group E1 (age>70 years, n = 7), Group E2 (age: 60–70 years, n = 24), Group Y1 (age: 40–60 years, n = 74), and Group Y2 (age<40 years, n = 5). The following variables were considered for analysis—(1) recipients: sex, age, BMI, etiology of the underlying liver disease, Child-Pugh scores, model for end-stage liver

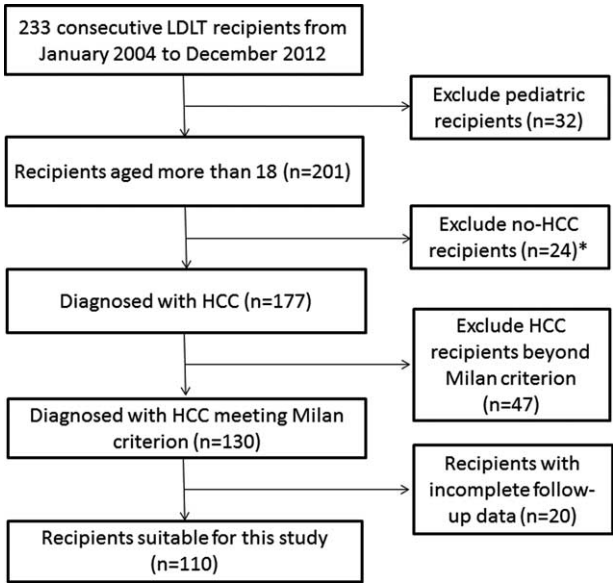


**FIGURE 1.** Recipients selection. Asterisk (∗) denotes recipients diagnosed with decompensated alcoholic cirrhosis (n = 12), sclerosing cholangitis (n = 5), autoimmune hepatitis (n = 4), and liver echinococcosis (n = 1).

disease (MELD) scores, serum AFP levels, number of HCC nodules, total tumor size, size of the dominant HCC nodule, preoperative and postoperative complications, preoperative neoadjuvant therapy, number of TACE procedures before transplantation, ICU and hospital stay, operation and waiting list time; (2) donor: age, sex, BMI, cold ischemia time (CIT), warm ischemia time (WIT), and graft type.[9] The definitions used for complications were adapted from the Clavien grading system for negative outcomes.[10,11]

Long-term outcomes were assessed by patient 1- and 3-year survival rates. Follow-up of all individuals including abdominal and chest CT scans as well as assessment of serum AFP levels performed every 3 to 6 months until the third year after LDLT for the detection of HCC recurrence.

## Ethics Statement

All clinical investigations were in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval was obtained from the Committee of Ethics in West China Hospital of Sichuan University. Liver donations were voluntary and altruistic in all cases, and written informed consent was obtained from both donors and recipients specifically to be involved in this study.

## Statistical Analysis

Statistical analyses were performed using SPSS version 16.0 (SSPS Inc, Chicago, IL). $P$ values $< 0.05$ were considered to be significant. The differences between groups were analyzed by independent sample Student's $t$ test for quantitative descriptive variables and by the chi-square test or Fisher's exact text for categorical variables. Kaplan–Meier survival analysis and the log-rank tests were used to calculate and compare patients' survival between groups. A multivariate analysis using Cox proportional hazards model was adopted to detect the predictors for survival.

# RESULTS

## Donors and Recipients Characteristics

The preoperative characteristics of the donors, grafts, and recipients are summarized in Table 1. Donor gender between the 2 groups were significantly different (men: 64.5% vs 35.4%, $P = 0.006$). There was no significant difference in donor age ($35.1 \pm 8.6$ vs $36.3 \pm 11.2$, $P = 0.609$), donor BMI ($23.5 \pm 2.6$ vs $23.0 \pm 2.7$, $P = 0.461$), graft type (right lobe: 96.8% vs 97.5%, $P = 1.000$), WIT ($45.1 \pm 5.7$ vs $51.5 \pm 6.1$, $P = 0.171$), and CIT ($2.5 \pm 5.3$ vs $4.9 \pm 8.9$, $P = 0.154$) between 2 groups.

The recipient age between the 2 groups were significantly different ($65.4 \pm 4.8$ vs $49.9 \pm 5.9$, $P = 0.000$). Recipient gender (men: 80.6% vs 91.1%, $P = 0.125$), recipient BMI ($23.4 \pm 2.8$ vs $22.8 \pm 3.3$, $P = 0.397$), etiology (HBV infection: 87.1% vs 92.4%, $P = 0.384$; HCV infection: 3.2% vs 1.3%, $P = 0.486$; others: 9.7% vs 6.3%, $P = 0.841$), Child-Pugh grade (A: 61.3% vs 44.3%, $P = 0.109$; B: 32.3% vs 46.8%, $P = 0.164$; C: 6.5% vs 8.9%, $P = 0.978$), serum AFP levels ($909 \pm 2448$ vs $1205 \pm 3948$, $P = 0.699$), number of HCC nodules ($1.5 \pm 1.2$ vs $1.6 \pm 0.9$, $P = 0.897$), total tumor size ($3.8 \pm 1.0$ vs $3.9 \pm 1.4$, $P = 0.527$), size of the dominant HCC nodule ($4.1 \pm 2.5$ vs $3.8 \pm 3.0$, $P = 0.228$), postoperative pathological portal vein invasion (16.1% vs 22.8%, $P = 0.440$), serum creatinine (before transplant: $88.1 \pm 12.7$ vs $83.6 \pm 15.5$, $P = 0.926$; after transplant: $79.5 \pm 14.3$ vs $73.9 \pm 17.1$, $P = 0.634$), renal dysfunction rates (before transplant: 1/31 vs 6/79, $P = 0.398$; after transplant: 2/31 vs 2/79, $P = 0.323$), pretransplantation complications (encephalopathy: 3.2% vs 1.3%, $P = 0.486$; uncontrolled ascites: 6.5% vs 6.3%, $P = 1.000$; peritonitis: 3.2% vs 2.5%, $P = 1.000$; variceal bleeding: 0% vs 1.3%, $P = 1.000$), preoperative neoadjuvant therapy (19.4% vs 6.3%, $P = 0.090$), No. of TACE ($1.8 \pm 1.1$ vs $1.8 \pm 1.7$, $P = 0.834$), waiting time to transplantation ($20.0 \pm 15.0$ days vs $27.4 \pm 44.4$ days, $P = 0.363$), operation time ($11.1 \pm 2.3$ h vs $10.7 \pm 2.4$ h, $P = 0.464$), total blood loss ($558 \pm 201$ mL vs $611 \pm 185$ mL, $P = 0.331$), and red blood cell transfusion ($431 \pm 117$ mL vs $484 \pm 137$ mL, $P = 0.527$) were similar in comparison of Groups E and Y (Table 1). Most of the patients were diagnosed with HBV virus infection. And the decompensated liver cirrhosis rates between 2 groups were comparable (14/31 vs 44/79, $P = 0.319$).

For 47 patient transplanted for HCC who were outside Milan criteria but within UCSF criteria, the average age was $53.7 \pm 7.9$ years. HBV infection was the most seen etiology in this group patient (46/47). The MELD score was $9.6 \pm 3.7$, number of HCC nodules was $1.3 \pm 1.5$, total tumor size was $5.6 \pm 1.1$, size of the dominant HCC nodule was $4.4 \pm 1.2$, waiting time to transplantation was $29.4 \pm 34.7$ days, and operation time was $11.2 \pm 2.0$ h. There were 8 patients aged $\geq$ 60 years, whereas 39 patients aged $<$60 years. Donor characteristics were not significantly different. Recipients' demographic data were comparable between 2 group patients, including BMI ($23.1 \pm 2.3$ vs $22.3 \pm 3.3$, $P = 0.455$), etiology (HBV infection: 100% vs 97.4%, $P = 1.000$), MELD score ($9.9 \pm 3.3$ vs $9.7 \pm 4.1$, $P = 0.993$), serum AFP levels ($1023 \pm 2477$ vs $1180 \pm 3368$, $P = 0.357$), number of HCC nodules ($1.4 \pm 1.7$ vs $1.6 \pm 1.1$, $P = 0.221$), total tumor size ($5.5 \pm 1.7$ vs $6.1 \pm 1.1$, $P = 0.721$), size of the dominant HCC nodule ($4.1 \pm 1.7$ vs $4.7 \pm 2.7$, $P = 0.568$), waiting time to transplantation ($27.3 \pm 22.1$ days vs $30.8 \pm 41.0$ days, $P = 0.143$), operation time ($11.5 \pm 2.2$ h vs $11.2 \pm 1.9$ h, $P = 0.574$). And there were no significant difference in recipients' serum

**TABLE 1.** Donor and Recipient Characteristics

| | Group 1 | Group 2 | *P* Value |
|---|---|---|---|
| Donor characteristics | | | |
| Donor age, y | 35.1 ± 8.6 | 36.3 ± 11.2 | 0.609 (NS) |
| Donor gender (male) | 64.5% (20/31) | 35.4% (28/79) | 0.006 |
| Donor BMI | 23.5 ± 2.6 | 23.0 ± 2.7 | 0.461 (NS) |
| Cytotoxic antibody (positive) | 0% (0/31) | 0% (0/79) | - |
| Graft type | | | |
| Right lobe | 96.8% (30/31) | 97.5% (77/79) | 1.000 (NS) |
| WIT, min | 45.1 ± 5.7 | 51.5 ± 6.1 | 0.171 (NS) |
| CIT, min | 2.5 ± 5.3 | 4.9 ± 8.9 | 0.154 (NS) |
| Recipients characteristics | | | |
| Recipient age, y | 65.4 ± 4.8 | 49.9 ± 5.9 | 0.000 |
| Recipient gender (male) | 80.6% (25/31) | 91.1% (72/79) | 0.125 (NS) |
| Recipient BMI | 23.4 ± 2.8 | 22.8 ± 3.3 | 0.397 (NS) |
| Recipient MELD | 10.5 ± 4.0 | 10.5 ± 4.1 | 0.996 (NS) |
| Etiology | | | |
| HBV | 87.1% (27/31) | 92.4% (73/79) | 0.384 (NS) |
| HCV | 3.2% (1/31) | 1.3% (1/79) | 0.486 (NS) |
| Others | 9.7% (3/31) | 6.3% (5/79) | 0.841 (NS) |
| Child–Pugh grade | | | |
| A | 61.3% (19/31) | 44.3% (35/79) | 0.109 (NS) |
| B | 32.3% (10/31) | 46.8% (37/79) | 0.164 (NS) |
| C | 6.5% (2/31) | 8.9% (7/79) | 0.978 (NS) |
| Serum AFP levels | 909 ± 2448 | 1205 ± 3948 | 0.699 (NS) |
| Number of HCC nodules | 1.5 ± 1.2 | 1.6 ± 0.9 | 0.897 (NS) |
| Total tumor size, cm | 3.8 ± 1.0 | 3.9 ± 1.4 | 0.527 (NS) |
| Size of the dominant HCC nodule, cm | 4.1 ± 2.5 | 3.8 ± 3.0 | 0.228 (NS) |
| Postoperative pathological portal vein invasion | 16.1% (5/31) | 22.8% (18/79) | 0.440 (NS) |
| Serum creatinine, μmol/L | | | |
| Before transplant | 88.1 ± 12.7 | 83.6 ± 15.5 | 0.926 (NS) |
| After transplant | 79.5 ± 14.3 | 73.9 ± 17.1 | 0.634 (NS) |
| Renal dysfunction | | | |
| Before transplant | 1/31 | 6/79 | 0.398 (NS) |
| After transplant | 2/31 | 2/79 | 0.323 (NS) |
| Pretransplant complications | | | |
| Encephalopathy | 3.2% (1/31) | 1.3% (1/79) | 0.486 (NS) |
| Uncontrolled ascites | 6.5% (2/31) | 6.3% (5/79) | 1.000 (NS) |
| Peritonitis | 3.2% (1/31) | 2.5% (2/79) | 1.000 (NS) |
| Variceal bleeding | 0% (0/31) | 1.3% (1/79) | 1.000 (NS) |
| Preoperative neoadjuvant therapy | 19.4% (6/31) | 6.3% (5/79) | 0.090 (NS) |
| No. of TACE | 1.8 ± 1.1 | 1.8 ± 1.7 | 0.834 (NS) |
| Waiting time to transplantation, d | 20.0 ± 15.0 | 27.4 ± 44.4 | 0.363 (NS) |
| Operation time, h | 11.1 ± 2.3 | 10.7 ± 2.4 | 0.464 (NS) |
| Total blood loss, mL | 558 ± 201 | 611 ± 185 | 0.331 (NS) |
| Transfusion (RBC, mL) | 431 ± 117 | 484 ± 137 | 0.527 (NS) |

AFP = alpha-fetoprotein, BMI = body mass index, CIT = cold ischemia time, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, RBC = red blood cell, TACE = transarterial chemoembolization, WIT = warm warm ischemia time.

creatinine (pre- and post-transplant) and renal dysfunction rates (pre- and post-transplant) ($P > 0.05$).

## Postoperative Outcomes

There was no significant difference in postoperative complications rates between Groups E and Y (22.6% vs 16.5%, $P = 0.454$). Totally, 7 recipients in Group E and 13 recipients in Group Y suffered postoperative complications. Postoperative renal dysfunction (E: n = 2, Y: n = 2), pneumonia (E: n = 4, Y: n = 5), and hepatic artery thrombosis (E: n = 1, Y: n = 1) were seen in both groups. There were 3 patients suffered fluid collection in Group Y, whereas 1 patient for biliary complication and 1 patient for intraperitoneal bleeding. Graft loss, the length of ICU and hospital stay, and mortality were similar ($P > 0.05$) (Table 2). It was not significantly different when using the Clavien score to grade the severity of postoperative complications ($P > 0.05$).

**TABLE 2.** Postoperative Complications and Clinical Outcome of Recipients

| | Group 1 | Group 2 | *P* Value |
|---|---|---|---|
| Complications (n) | 22.6% (7/31) | 16.5% (13/79) | 0.454 (NS) |
| Clavien score | | | |
| Grade I | 6.5% (2/31) | 6.3% (5/79) | 0.981 (NS) |
| Grade II | 0% (0/31) | 2.5% (2/79) | 1.000 (NS) |
| Grade III | 0% (0/31) | 0% (0/79) | – |
| Grade IV | 0% (0/31) | 0% (0/79) | – |
| Grade V | 16.1% (5/31) | 7.6% (6/79) | 0.323 (NS) |
| Length of ICU stay | 12.9 ± 12.5 | 11.2 ± 6.0 | 0.330 (NS) |
| Length of hospital stay | 20.7 ± 8.5 | 21.7 ± 11.1 | 0.098 (NS) |
| Graft loss | | | |
| Within hospital | 3.2% (1/31) | 1.3% (1/79) | 0.486 (NS) |
| Late | 6.5% (2/31) | 7.6% (6/79) | 1.000 (NS) |
| Mortality | | | |
| Within hospital | 16.1% (5/31) | 7.6% (6/79) | 0.323 (NS) |
| Late | 38.7% (12/31) | 45.6 (36/79) | 0.514 (NS) |
| Follow-up, y | 1.8 ± 2.3 | 1.5 ± 1.8 | 0.545 (NS) |

ICU = intensive care unit.

## Survival Analysis

The median follow-up time were similar (Group E: 1.8 ± 2.3 years vs Group Y: 1.5 ± 1.8 years, $P = 0.545$) (Table 2). The overall survival rates were similar between 2 groups (1 year: 77.4% vs 82.8%; 3 year: 64.5% vs 44.6%) ($P = 0.458$). The 1- and 3-year disease-free survival rates between groups were 94.7%, and 80.7% vs 98.6%, and 85.9% ($P = 0.661$) (Figure 2). In the subgroup analysis, the 1- and 3- year overall survival rates were 71.3% and 71.3% in Group E1, 78.0% and 60.7% in Group E2, 79.0% and 40.6% in Group Y1, and 99.7% and 50.0% in Group Y2 ($P = 0.838$). The 1- and 3-year disease-free survival rates were 66.7% and 66.7% in Group E1, 92.1% and 80.5% in Group E2, 96.3% and 83.9% in Group Y1, and 100% and 100% in Group Y2 ($P = 0.745$). Recipients' age, AFP, postoperative pathological portal vein invasion, and HCC recurrence did not predict the overall and disease-free survival rates after a multivariate analysis ($P > 0.05$) (Tables 3–4).

**TABLE 3.** Risk Factors Multivariate Analysis for Overall Survival

| Covariate | HR | 95.0% CI | *P* Value |
|---|---|---|---|
| AFP | 1.000 | (1.000, 1.000) | 0.662 |
| Portal vein invasion | 0.934 | (0.462, 1.890) | 0.850 |
| HCC recurrence | 0.318 | (0.043, 2.346) | 0.261 |
| Recipients age | 1.012 | (0.959, 1.066) | 0.670 |

AFP = alpha-fetoprotein, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio.

## DISCUSSION

As a result of an increasing life expectancy with an aging population, the demand for LT in elderly patients is expected to increase. Numerous studies have confirmed that LT can be performed safely in elderly patients.[12,13] However, in unadjusted analysis, elderly patients were found to have worse overall survival. These conflicting results were based on orthotopic liver transplantation. In this study, our data supported a result that age should not preclude LDLT when this is a choice of treatment for HCC recipients, which met the Milan criteria.

Donors' and recipients' demographic data analysis showed no significant difference between groups, as well as the postoperative outcome. With the development in technique, advancement in management of postoperative complications, and immunosuppressive drugs, in this study, there was no significant difference in the postoperative complication rates after LDLT between groups. Pneumonia was seen in both groups and still the first cause of postoperative morbidity and mortality. Due to the improvements of perioperative intensive care, including continued support of respiration and circulation, the adoption of effective antirejection therapy and powerful antibiotics, dynamic observation of bedside ultrasound for transplanted liver, and necessary adoption of artificial liver supporting system and dialysis treatment,[11] length of ICU and hospital stay were not significantly different. HCC LDLT recipients who met the Milan criteria were selected into this analysis, in order to exclude the influence of No. of HCC nodules and size of HCC nodules on postoperative HCC recurrence risks. In survival analysis, the 1-, and 3-year overall

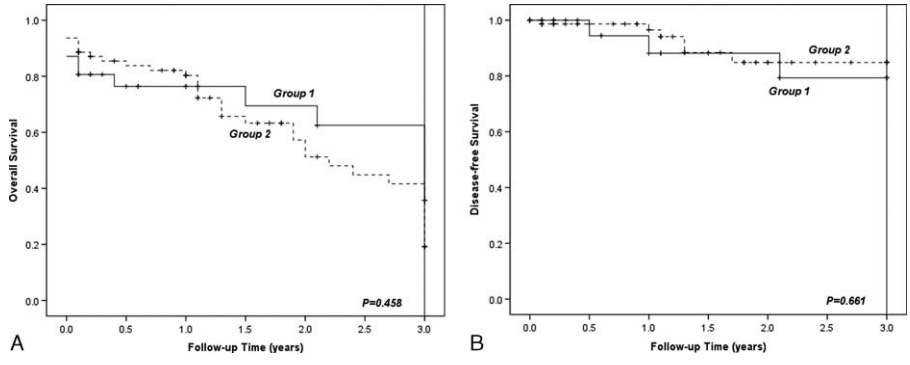


**FIGURE 2.** (A) Comparison of the 1- and 3-year overall survival rates between groups ($P = 0.458$); (B) comparison of the 1- and 3-year disease-free survival rates between groups ($P = 0.661$).

**TABLE 4.** Risk Factors Multivariate Analysis for Disease-free Survival

| Covariate | HR | 95.0% CI | *P* Value |
|---|---|---|---|
| AFP | 1.000 | (1.000, 1.000) | 0.502 |
| Portal vein invasion | 0.457 | (0.056, 3.745) | 0.466 |
| Recipients age | 1.120 | (0.967, 1.297) | 0.129 |

AFP = alpha-fetoprotein, CI = confidence interval, HR = hazard ratio.

and disease-free survival rates were similar, and comparable results were achieved in subgroup analysis as well. But there seem to be a trend that younger recipients had a lower overall survival rates than older ones in longer observation time. This might be that the elderly recipients had a relatively shorter natural life expectancy in such observation time. It was reported that patients with early stage HCC and relatively good liver function had excellent outcomes in excess of 80% 5-year survival at most centers. Our results showed a relatively lower survival rates. It might be that there was an unsolvable problem in medical insurance and social insurance in the subsequent treatments (antihepatitis drugs and antirejection drugs) after LDLT in China, especially in West of China, even though the antihepatitis treatment was routinely recommended for all patients who were diagnosed with HBV or HCV. And the first cause of death in these patients who met the Milan criteria after LDLT was recurrence of hepatitis, whereas the second was HCC recurrence. Chronic lethal rejection could also be seen in some patients. And for patients who suffered HCC recurrence, radiofrequency ablation, TACE, and/or Sorafenib were considered. The MELD severity score has been used in the USA to prioritize adult patients on the waiting list for liver transplantation.[14] Several risk factors which might affect recipients' survival rates were selected and a Cox proportional hazard model was used to detect the predictors for long-term survival. As a result, due to our rigorous listing criteria, recipients' age, MELD scores, AFP, postoperative pathological portal vein invasion, and HCC recurrence did not predict the overall and disease-free survival rates.

The small sample size and the retrospective design were a significant bias. And longer follow-up time might provide different results than those presently reported. However, our study was the first research on outcomes between elderly and young HCC LDLT recipients. LDLT was feasible among candidates aged $\geq$60 years with HCC which met the Milan criteria. Following rigorous listing criteria, if overall clinical conditions and comorbidities allowed, elderly recipients achieved similar LDLT outcomes and survival rates with younger HCC recipients.

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