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Original Research

Influence of Recipient Age on Outcomes After Liver Transplantation for Hepatocellular Carcinoma

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Abstract

Objectives: Liver transplantation (LT) is being performed with increasing frequency in elderly patients in parallel with the aging population worldwide today. In this study, we aimed to analyze the outcomes of LT for HCC in patients aged ≥65 (Older) versus those <65 (Younger).

Methods: In total of 535 HCC patients undergone LT at İnönü University Liver Transplantation Institute between April 2006 and March 2025 were retrospectively reviewed from a consecutively and prospectively recorded database and were analyzed.

Results: 68 out of 535 LT's age were ≥65 (12.7%). The percentage of older HCC patients receiving LT increased over time: it was 6.3% from 2002-2010, 11.3% from 2011-2020, and 17.5% from 2021-2025, showing a significant upward trend (p=0.039). 1-5-, and 10-years OS was 89.1%, 66.8%, and 53.9% in Younger group, and 81.5%, 52.8%, and 39.7% in Older group (p=0.012). Age≥65years was an independent predictor of mortality in patients undergoing LT for HCC (HR = 1.65, 95% CI: 1.11–2.46, p = 0.013). DFS, recurrence rate, tumor characteristics, demographics were similar. Only the last creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group.

Conclusion: Older age was independently associated with worse post-transplant overall survival among patients undergoing LT for HCC. This inferior survival cannot attribute to the tumor-related factors. Future studies focusing on sarcopenia, frailty, causes of death, and post-transplant complications, immunosuppressive regimens to better define the mechanisms underlying poor survival outcomes in elderly liver transplant recipients and to improve patient selection and post-transplant management in this growing population.

Keywords: Older, elderly, younger, hepatobiliary, neoplasm, survival, recurrence

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Liver transplantation is being performed with increasing frequency in elderly patients in parallel with the aging population worldwide today. According to data from the United Network for Organ Sharing (UNOS) and the European Liver Transplant Registry (ELTR), between 2000 and 2015, the rates of waiting list registration and liver transplantation (LT) for patients aged 65-70 doubled.[1] In our country, according to the data of the Turkish Statistical Institute (TÜİK), the population aged 65 and over, considered the elderly population, increased by 20.7% from 7.5 million in 2019 to 9.1 million in 2024.[2]

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In our center, the proportion of elderly patients among the number of liver transplants we have performed over the years has also increased significantly. In our program, which started in 2002, the rate of transplant patients aged 65 and over was 2.5% (13/512) between 2002 and 2010, while this rate increased to 5.1% (121/2378) between 2011 and 2020, and to 9.4% (127/1358) between 2021 and 2025, showing a significant increase (p<0.001).

LT outcomes in older patients have shown mixed results, with some studies indicating similar survival rates to younger individuals[3] and others reporting poorer outcomes.[4] Furthermore, hepatocellular carcinoma (HCC) is considered an independent risk factor for poor outcomes in older patients.[1] However, some studies[5] report similar LT results for HCC patients aged 65 and over compared to younger individuals.

In this study, we aimed to analyze the outcomes of LT for HCC in patients aged 65 and over (Older) versus those under 65 years of age (Younger).

Patients and Methods

Study Population

Data from patients who underwent liver transplantation due to HCC at İnönü University Liver Transplantation Institute between April 2006 and March 2025 were retrospectively reviewed from a consecutively and prospectively recorded database. To focus on oncological outcomes, patients with a follow-up period of less than 90 days after transplantation were excluded, and patients who have HCC in explant pathology were included in the study. In total of 535 transplant patients with HCC were analyzed.

Patients' demographic data, tumor characteristics obtained from explant pathology, pre-transplant last laboratory parameters, Milan criteria status, Malatya criteria status and expanded Malatya criteria status,[6] and post-transplant survivals and recurrence status were recorded.

According to the Turkish Statistical Institute's age classification,[2] patients were divided into two groups: under 65 years of age (Younger) and 65 years and older (Older). The distribution of the liver transplant numbers we performed for older HCC patients was calculated according to 3 time periods (2002-2010; 2011-2020; 2021-2025).

Post-transplant overall survival (OS), disease-free survival (DFS), and recurrence rates were calculated and compared for each group. The demographic and tumor characteristics of both groups were then compared to investigate the possible reasons for the difference in survival.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the quantitative data. The Mann-Whitney U test was used for comparisons between two independent groups. Median, minimum, and maximum values were used to summarize the quantitative data. Distributions of the qualitative data were presented by count and percentage. Pearson chi-square test (asymptotic significance or exact significance) and the continuity-corrected chi-square test were applied for comparisons. The Kaplan-Meier method was used for survival estimations, and the Log-Rank test was used for survival comparisons between groups. Univariate Cox regression analysis was used to obtain the Hazard Ratios. In all analyses, the two-sided significance level was considered as <0.05. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Results

Patient Demographics

Patient demographics are presented in Table 1. The median age was 56 years (1–72), with 12.7% (68/535) of patients aged ≥65. Patients classified as CHILD B or C accounted for 63% (337/535). The proportion of patients within the Milan criteria was 51.4%, within the Malatya criteria was 63.6%, and within the Expanded Malatya criteria was 69%. The predominant underlying disease was viral hepatitis, accounting for 74.8% of cases.

Distribution of LT Numbers of Older Patients According to Time Periods

In our center, the proportion of elderly patients among the number of liver transplants we have performed over the years has increased significantly. In our program, which started in 2002, the rate of transplant patients aged 65 and over was 2.5% (13/512) between 2002 and 2010, while this rate increased to 5.1% (121/2378) between 2011 and 2020, and to 9.4% (127/1358) between 2021 and 2025, showing a significant increase (p<0.001).

The percentage of older HCC patients receiving LT also increased over time: it was 6.3% from 2002 to 2010, 11.3% from 2011 to 2020, and 17.5% from 2021 to 2025, showing a significant upward trend (p=0.039) (Table 2).

Overall Survival Functions of the Groups

Mean overall survival time for Younger group was 3793.5 days and 2497.5 days for Older group (Table 3). 1-5-, and 10-years OS was 89.1%, 66.8%, and 53.9% in Younger group, and 81.5%, 52.8%, and 39.7% in Older group. Survival difference was statistically significant with p=0.012 (Fig. 1).

Table 1. Patient demographics of all cohort

	n	Median (Min.-Max.)
AFP	530	12.1 (0.2-55000)
MTD (cm)	535	3 (0-26)
Number of nodules	535	2 (1-36)
BSA	535	1.92 (0.38-2.54)
BMI	535	26.1 (14.8-46.88)
NLR	535	2.59 (0.15-35.3)
PLR	535	84.15 (2.61-1092.31)
Platelets	535	101 (15-701)
INR	442	1.31 (0.82-4.1)
Albumin	534	3 (1.2-5.2)
Total Bilirubin	535	1.84 (0.23-44.7)
Creatin	535	0.8 (0.22-13.8)
Total protein	385	7 (1.01-9.4)
AST	533	58 (9-7789)
ALT	534	42 (7-3535)
ALP	533	118 (28-2327)
GGT	533	73 (11-1396)
LDH	451	232 (57-1538)
	n (%)	
Gender		
Female	69 (12.9)	
Male	466 (87.1)	
CHILD class		
A	198 (37)	
B	217 (40.6)	
C	120 (22.4)	
GGT		
≤104	343 (64.4)	
>104	190 (35.6)	
AFP		
≤200	450 (84.9)	
>200	80 (15.1)	
MELD		
<15	324 (60.6)	
≥15	211 (39.4)	
Recurrence		
None	441 (82.4)	
Yes	94 (17.6)	
TTD, cm		
≤8	390 (72.9)	
>8	145 (27.1)	
Differentiation		
Well/moderate	460 (86)	
Poor	75 (14)	
Venous invasion		
None	474 (88.6)	
Microscopic/Macroscopic	61 (11.4)	

Table 1. Patient demographics of all cohort (Cont.)

	n (%)
Milan Criteria	
In	275 (51.4)
Out	260 (48.6)
Malatya Criteria	
In	340 (63.6)
Out	195 (36.4)
Expanded Malatya Criteria	
In	369 (69)
Out	166 (31)
Etiology	
Viral hepatitis	400 (74.8)
Cryptogenic	88 (16.4)
Ethanol	11 (2.1)
Budd-Chiari	12 (2.2)
Metabolic	11 (2.1)
Others	13 (2.4)
GRWR	
≥0.8	470 (90)
<0.8	52 (10)

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BSA: Body surface area; GGT: Gamma glutamyl transferase; GRWR: Graft to recipient weight ratio; LDH: Lactate dehydrogenase; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; PLR: Platelet to lymphocyte ratio; TTD: Total tumor diameter.

Cox Proportional Hazards Regression Analysis for Age ≥65 Years

Age ≥ 65 years was an independent predictor of mortality in patients undergoing liver transplantation for hepatocellular carcinoma (HR = 1.65, 95% CI: 1.11–2.46, p=0.013), according to Univariate Cox regression analysis (Table 3).

Disease-Free Survival Functions of the Groups

Mean disease-free survival time for Younger group was 3711.4 days and 2483.6 days for Older group (Table 4). 1-5-, and 10-years OS was 84.2%, 63.9%, and 53.1% in Younger group, and 80%, 53.6%, and 40.3% in Older group. Survival difference was not statistically significant with p=0.066 (Fig. 2).

Tumor Recurrence

The overall HCC recurrence rate was 17.6% (94/535), with 13.2% (9/68) in the Older group and 18.2% (85/467) in the Younger group, showing no significant difference (p=0.404, Table 5). In the Older group, recurrences were liver-only 22% (2/11), extrahepatic-only 33% (3/11), or both 44% (4/11).

Table 2. Distribution of the LT numbers for HCC and all other indications according to time periods

Time period	All others n	All others Age <65 n (%)	All others Age ≥65 n (%)	p	HCC n	HCC Age <65 n (%)	HCC Age ≥65 n (%)	p
2002 – 2010	512	499 (97.5)	13 (2.5)	<0.001	63	59 (93.7)	4 (6.3)	0.039
2011 – 2020	2378	2257 (94.9)	121 (5.1)		301	267 (88.7)	34 (11.3)	
2021 – 2025	1358	1231 (90.6)	127 (9.4)		171	141 (82.5)	30 (17.5)	
Total	4248	3987 (93.9)	261 (6.1)		535	467 (87.3)	68 (12.7)	

Table 3. Overall survival and cox regression according to age 65

				Univariate Analysis	
OS	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p	HR (95% C.I.)	HR p
Age<65 (n=467)	3793.55±157.48	4451±762.33	0.012	reference	
Age≥65 (n=68)	2497.50±334.36	2184±919.77		1.653 (1.111-2.460)	0.013

HR: Hazard ratio; OS: Overall survival; SE: Standard error.

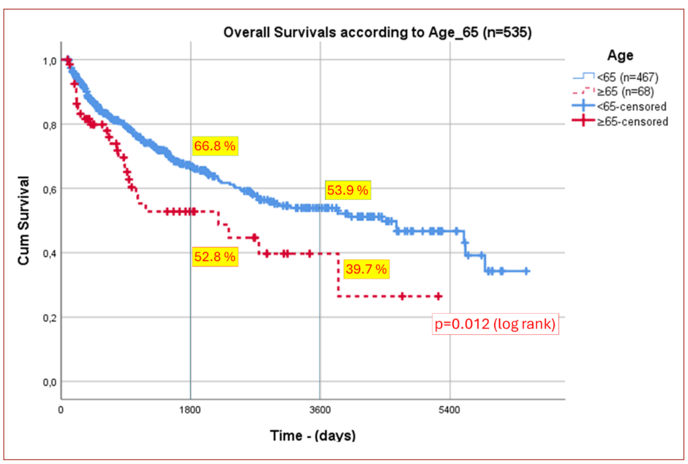

Figure 1. Overall survival function of LT patients with HCC according to age 65.

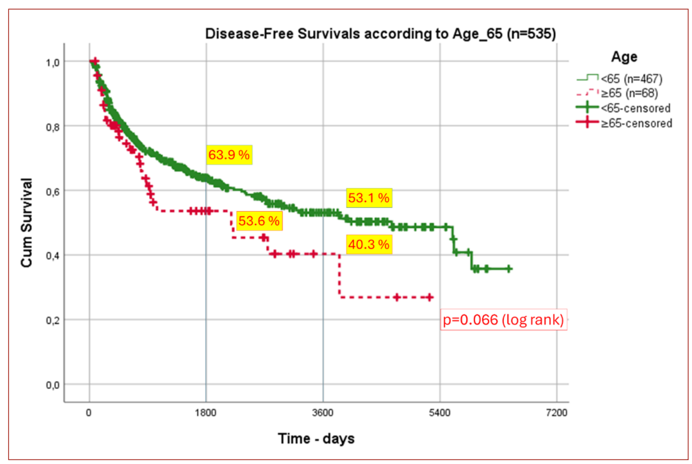

Figure 2. Disease-free survival function of LT patients with HCC according to age 65.

Table 4. Disease-free survival table according to age 65

DFS	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p
Age<65 (n=467)	3711.41±159.21	4655±918.12	0.066
Age≥65 (n=68)	2483.62±340.31	2184±871.69	

DFS: Disease-free survival; SE: Standard error.

In the Younger group, rates were 11.8% (10/85) liver-only, 48.2% (41/85) extrahepatic-only, and 40% (34/85) both.

Extrahepatic metastases occurred most frequently in the lungs (n=46), followed by bones (n=16), peritoneum (n=14), lymph nodes (n=12), adrenal glands (n=11), and brain (n=4).

Comparison of the Groups in Terms of Demographics and Tumor Parameters

Next, we made a comparison between the groups. Demographics, etiology, CHILD class, MELD score, recurrence rates, MTD, NN, differentiation grade, and vascular invasion status were similar between the groups. Only the last creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group.

Discussion

In our study, we demonstrated that the proportion of patients aged 65 years and older undergoing liver transplantation, both for all indications and specifically for HCC, increased significantly over time (Table 2). When analyzed by

Table 5. Comparison of the age groups

	Age<65		Age≥65		p
	n	Median (Min.-Max.)	n	Median (Min.-Max.)	
AFP	462	12.34 (0.2-55000)	68	10.5 (0.4-20179)	0.793
MTD (cm)	467	3 (0-26)	68	3.25 (0-16)	0.844
Number of nodules	467	2 (1-36)	68	2 (1-27)	0.072
BSA	467	1.92 (0.38-2.54)	68	1.92 (1.4-2.37)	0.972
BMI	467	25.96 (14.8-46.88)	68	26.85 (16.1-41)	0.125
NLR	467	2.59 (0.15-35.3)	68	2.59 (0.54-15.14)	0.997
PLR	467	82.7 (2.61-1092.31)	68	87.78 (34.06-298.68)	0.397
Platelets	467	96 (16-701)	68	110.5 (15-538)	0.152
INR	383	1.31 (0.82-3.67)	59	1.26 (0.9-4.1)	0.132
Albumin	466	3 (1.2-5.2)	68	3 (1.9-5.2)	0.242
Total Bilirubin	467	1.88 (0.23-44.7)	68	1.8 (0.3-10.7)	0.262
Creatin	467	0.8 (0.22-13.8)	68	0.88 (0.3-1.6)	0.003
Total protein	336	7 (1.5-9.4)	49	7 (1.01-9)	0.968
AST	465	59 (9-7789)	68	54 (14-268)	0.172
ALT	466	42.5 (10-3535)	68	40.5 (7-250)	0.281
ALP	465	121 (28-2327)	68	106.5 (46-367)	0.431
GGT	465	71 (11-1396)	68	88.5 (13-702)	0.070
LDH	391	235 (57-1538)	60	219 (149-401)	0.617

	Age<65 n (%)	Age≥65 n (%)	p
Gender			
Female	60 (12.8)	9 (13.2)	1.000
Male	407 (87.2)	59 (86.8)	
CHILD class			
A	171 (36.6)	27 (39.7)	0.763
B	189 (40.5)	28 (41.2)	
C	107 (22.9)	13 (19.1)	
GGT			
≤104	306 (65.8)	37 (54.4)	0.067
>104	159 (34.2)	31 (45.6)	
AFP			
≤200	391 (84.6)	59 (86.8)	0.782
>200	71 (15.4)	9 (13.2)	
MELD			
<15	282 (60.4)	42 (61.8)	0.828
≥15	185 (39.6)	26 (38.2)	
Recurrence			
None	382 (81.8)	59 (86.8)	0.404
Yes	85 (18.2)	9 (13.2)	
TTD			
≤8	344 (73.7)	46 (67.6)	0.370
>8	123 (26.3)	22 (32.4)	
Differentiation			
Well/moderate	400 (85.7)	60 (88.2)	0.699
Poor	67 (14.3)	8 (11.8)	

Table 5. Comparison of the age groups (Cont.)

	Age<65 n (%)	Age≥65 n (%)	p
Venous invasion			
None	416 (89.1)	58 (85.3)	0.476
Microscopic/Macroscopic	51 (10.9)	10 (14.7)	
Milan Criteria			
In	248 (53.1)	27 (39.7)	0.039
Out	219 (46.9)	41 (60.3)	
Malatya Criteria			
In	300 (64.2)	40 (58.8)	0.386
Out	167 (35.8)	28 (41.2)	
Expanded Malatya Criteria			
In	327 (70)	42 (61.8)	0.169
Out	140 (30)	26 (38.2)	
Etiology			
Viral hepatitis	350 (74.9)	50 (73.5)	0.347
Cryptogenic	73 (15.6)	15 (22.1)	
Ethanol	9 (1.9)	2 (2.9)	
Budd-Chiari	12 (2.6)	0 (0)	
Metabolic	11 (2.4)	0 (0)	
Others	12 (2.6)	1 (1.5)	
GRWR			
≥0.8	409 (89.7)	61 (92.4)	0.636
<0.8	47 (10.3)	5 (7.6)	

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BSA: Body surface area; GGT: Gamma glutamyl transferase; GRWR: Graft to recipient weight ratio; LDH: Lactate dehydrogenase; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; PLR: Platelet to lymphocyte ratio; TTD: Total tumor diameter.

indication, the proportion of elderly recipients was higher among patients transplanted for HCC compared with those transplanted for other indications. Advanced age is a well-established risk factor for the development of HCC; therefore, a higher proportion of elderly patients among those undergoing transplantation for HCC is an expected finding.

In the present study, we found that recipient age ≥65 years was independently associated with significantly worse post-transplant overall survival in patients undergoing liver transplantation for HCC (5-year OS 66.8% vs 52.8%, p=0.012). In the Cox regression analysis, the risk of mortality in the elderly group was found to be 1.65 times higher than that in the younger group (HR = 1.65, 95% CI: 1.11–2.46, p=0.013). These findings are highly consistent with the study by Xing et al.,[7] which compared locoregional therapy (LRT) in patients who underwent liver transplantation for HCC. In that study, advanced age (≥65 years) was identified as an independent risk factor for poor survival in patients with HCC (univariate analysis: HR 1.71, 95% CI: 1.44–2.94). Additionally, donor age, bridging LRT, and longer waiting time were identified as independent prognostic factors for survival.[7]

On the other hand, disease-free survival and recurrence rates were comparable between younger and older recipients. This finding suggests that the observed difference in overall survival among older patients cannot be explained by tumor recurrence. The impact of recipient age on liver transplantation outcomes has long been debated. While earlier studies suggested that chronological age alone should not preclude transplantation, more recent analyses indicate that selected elderly patients older than 65 and even 70 years benefit from LT as much as younger ones.[3, 5] But our findings are consistent with reports demonstrating inferior survival among elderly transplant recipients,[1, 4] even when tumor burden and transplant eligibility criteria are comparable between age groups.

When we compare the groups in terms of demographics, etiology, CHILD class, MELD score, recurrence rates, MTD, NN, differentiation grade, Malatya criteria status, Expanded Malatya criteria status and vascular invasion status we could not find significant difference. Only the last median creatin level before LT (0.88 vs 0.8, p=0.003) and beyond Milan criteria rate were significantly higher (39.7% vs 60.2%, p=0.039) in the Older group. In elderly

HCC patients with elevated creatinine levels, reassessing diuretic therapy, fluid status, and glomerular filtration rate during the pre-transplant preparation period to improve renal function may be beneficial in improving post-transplant survival outcomes. However, the significantly higher rate of beyond Milan criteria in elderly patients does not explain the current poor survival rate, as tumor recurrence rates, AFP levels, MTD, tumor differentiation, vascular invasion rates, and the rates of non-Milan criteria were similar in both groups. Age-related factors such as comorbidity, reduced cardiopulmonary reserve, frailty, and sarcopenia are well-recognized contributors to poor outcomes after major surgery. These conditions are not fully captured by conventional risk stratification tools or MELD-based allocation systems. Furthermore, immunosenescence in elderly recipients may predispose to infectious complications and impair long-term tolerance to immunosuppressive therapy, thereby contributing to late mortality independent of graft function or tumor recurrence. Comprehensive geriatric assessment, objective frailty indices, and detailed cardiopulmonary evaluation may help identify elderly patients who are most likely to derive long-term benefit from transplantation. In addition, individualized immunosuppressive regimens and closer post-transplant monitoring may be particularly important in this high-risk group. Further studies analyzing these parameters are needed.

This study has limitations inherent to its retrospective design, and age-related factors such as frailty, sarcopenia, or cause-specific mortality, immunosuppressive regimens, post-transplant complications which have potential contributors to poor outcomes were not analyzed.

The results of our study indicate that advanced age should be considered as a factor within risk stratification models for HCC transplant candidates, rather than used as an exclusion criteria.

Conclusion

In conclusion, the number of older patients (≥65 years) undergoing liver transplantation has increased significantly, both for HCC and for other indications. Older age was independently associated with worse post-transplant overall survival among patients undergoing liver transplantation for HCC. This inferior survival cannot attribute to the tumor-related factors. Future studies focusing on sarcopenia, frailty, causes of death, and post-transplant complications, immunosuppressive regimens to better define the mechanisms underlying poor survival outcomes in elderly liver transplant recipients and to improve patient selection and post-transplant management in this growing population.

Disclosures

Ethics Committee Approval: Ethical committee approval was not obtained because this study was retrospective in design.

Peer-review: Externally peer-reviewed.

Data Availability: The raw data used to support the findings of this study are available from the corresponding author upon request.

Informed Consent: No informed consent was requested from patients since this is a retrospectively designed study.

Conflict of Interest Statement: There is no conflict of interest

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Authorship Contributions: Concept – F.G., S.U., V.I.; Design – F.G., V.I.; Supervision – H.G.B, V.I.; Funding – None; Materials – None.; Data Collection and/or Processing – F.G., S.U., V.I.; Analysis and/or Interpretation – H.G.B; Literature Review – F.G., S.U., V.I.; Writing – F.G., S.U., V.I.; Critical Review – V.I.

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