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Liver Transplantation and Survival in Hepatocellular Carcinoma and Viral Hepatitis: A 19-Year Nationwide Cohort from Taiwan

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Abbreviations:

LT: liver Transplantation; HCC: Hepatocellular Carcinoma; TORSC: Taiwan Organ Registry and Sharing Centre; HBsAg: Hepatitis B Surface Antigen; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus.

1. Abstract

1.1. Background

Liver transplantation (LT) is the definitive therapy for end-stage liver disease and hepatocellular carcinoma (HCC). However, in HBV-endemic regions, the allocation-relevant implications of the viral hepatitis status, waiting time, age, and donor type remain incompletely defined in real-world transplant systems.

1.2. Methods

We analysed 19 years of nationwide data (2005–2024) from the Taiwan Organ Registry and Sharing Centre (TORSC). Survival outcomes were stratified by HCC status, hepatitis B surface antigen (HBsAg) status, anti-HCV status, waiting time, age, and donor type to evaluate their roles as allocation-relevant variables using Kaplan-Meier analysis and Cox proportional hazards models.

1.3. Results

LT was associated with markedly improved survival compared to non-transplantation (5-year survival: 77.9% vs. 30.6%; $p < 0.0001$). Among HCC recipients, viral serostatus did not significantly affect the long-term survival. In contrast, among non-HCC recipients, HBsAg positivity was associated with superior survival ($p = 0.0002$), whereas anti-HCV positivity predicted worse outcomes ($p = 0.001$). A longer waiting time was associated with reduced mortality among transplant recipients but increased mortality among non-transplant candidates. Advanced age increased the post-transplant mortality risk; nevertheless, recipients aged ≥70 years achieved substantially better survival than non-transplant patients. Living-donor liver transplantation conferred a significant survival advantage over deceased-donor transplantation (HR, 0.783; $p < 0.001$).

1.4. Conclusions

This nationwide cohort study demonstrated that LT prolongs survival across patient subgroups. Viral serostatus, waiting time, age, and donor type function as dynamic context-dependent allocation variables rather than fixed prognostic labels. These findings provide real-world evidence to inform transplant allocation and donor strategies in HBV-endemic aging societies.

2. Introduction

Liver transplantation (LT) is the definitive treatment for end-stage liver disease and is used to select patients with hepatocellular carcinoma (HCC). In regions with a high prevalence of chronic viral hepatitis, such as Taiwan, hepatitis B virus (HBV) and hepatitis C virus (HCV) remain the leading etiologist of cirrhosis and HCC, accounting for the majority of transplant indications and liver-related mortalities. As a result, liver transplantation in HBV-endemic societies operates under conditions of sustained disease burden, severe organ scarcity, and increasing demand from the aging populations [1-4].

Advances in antiviral therapy have fundamentally altered the natural history of hepatitis B virus (HBV)- and HCV-related liver diseases. Potent nucleus(t)ide analogy and direct-acting antivirals have markedly reduced viral replication, graft reinfection, and post-transplant complications [5-7]. Nevertheless, viral serostatus, particularly HBsAg positivity, continues to be perceived as an adverse prognostic factor in transplant decision making, despite growing evidence that its clinical significance may differ in the contemporary antiviral era. How the viral hepatitis status should be interpreted as a prognostic and allocation-relevant variable in real-world transplant systems remains unclear.

Several non-biological factors play critical roles in transplant outcomes and allocation. Waiting time before transplantation reflects both disease progression and selection processes within transplant systems, yet its relationship with post-transplant survival is complex and context dependent [8-11]. Similarly, advanced recipient age is often viewed as a relative contraindication to transplantation, although improvements in surgical techniques and perioperative care have expanded the eligibility of older adults [12]. Donor type, particularly living donor liver transplantation (LDLT), has emerged as a structural response to organ shortage, but its survival advantage and policy implications vary across healthcare systems [13-15].

Most existing studies addressing these issues originate from Western transplant systems and focus on single dimensions such as viral status, HCC, or age, rather than their combined effects within a unified allocation framework. Moreover, evidence from HBV-endemic regions with universal health insurance coverage and extensive reliance on LDLT is limited.

Using 19 years of nationwide registry data from the Taiwan Organ Registry and Sharing Centre (TORSC), we aimed to evaluate how viral hepatitis status, HCC, waiting time, age, and donor type influence survival outcomes of liver transplantation. Rather than treating these factors as fixed risk labels, this study examined their behaviour as dynamic, context-dependent variables within a real-world transplant allocation system. In doing so, we provide population-level evidence.

3. Materials and Methods

Data were obtained from the Taiwan Organ Registry and Sharing Centre (TORSC) and included all liver transplant candidates registered between 2005 and 2024. The primary outcome was overall survival from listing and transplantation. Variables of interest included hepatocellular carcinoma (HCC) status, viral serostatus (hepatitis B surface antigen [HBsAg] and anti–hepatitis C virus [anti-HCV]), age at listing, waiting time, and donor type.

Survival was assessed using the Kaplan–Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Ethics approval was waived because the TORSC data were de-identified and publicly available (TMU-JIRB Certificate No: N202501024).

4. Statistical Analysis

All statistical analyses were performed using R version 4.3.1 (R Core Team, Vienna, Austria). Categorical variables are presented as numbers and percentages, and continuous variables as mean ± standard deviation (SD). Baseline characteristics and outcomes were compared using the chi-square or Fisher's exact tests for categorical variables and analysis of variance for continuous variables.

Kaplan–Meier analysis with the log-rank test was used to compare the cumulative survival among the groups. Crude hazard ratios (CHRs), adjusted hazard ratios (AHRs), and corresponding 95% CIs were derived from Cox regression models. Follow-up commenced at the time of listing. Statistical significance was defined as a two-sided p-value < 0.05.

5. Results

5.1. Baseline Characteristics

Among transplant recipients, patients with HCC were significantly older than those without HCC (mean age 56.0 vs. 48.5 years; $p < 0.001$; Table 1), consistent with the epidemiological profile of HCC in Taiwan. HBsAg and anti-HCV positivity were more prevalent among HCC recipients than among non-HCC recipients (both $p < 0.001$; Table 1).

5. 2. Overall Survival Benefit of Liver Transplantation

A survival advantage associated with transplantation was observed across all age groups, although it was less pronounced among patients with HCC (Tables 2A, 2 B).

Kaplan–Meier analysis demonstrated that liver transplantation was associated with significantly higher 5-year survival than non-transplantation (77.9% vs. 30.6%; $p < 0.0001$), with consistent survival benefits across patient subgroups (Figure 1A). Among transplant recipients, the 10-year survival was higher in non-HCC patients than in HCC patients (70.5% vs. 62.8%; $p < 0.0001$; Figure 1B).

5. 3. Impact of HCC and Viral Hepatitis Status on Post-Transplant Survival

Among HCC recipients, neither HBsAg positivity ($p = 0.24$) nor anti-HCV positivity ($p = 0.57$) was significantly associated with long-term survival (Figure 1C). Among non-HCC recipients, HBsAg positivity was associated with improved survival compared to HBsAg negativity ($p = 0.0002$), whereas anti-HCV positivity was associated with worse survival compared to anti-HCV negativity ($p = 0.001$; Figure 1D).

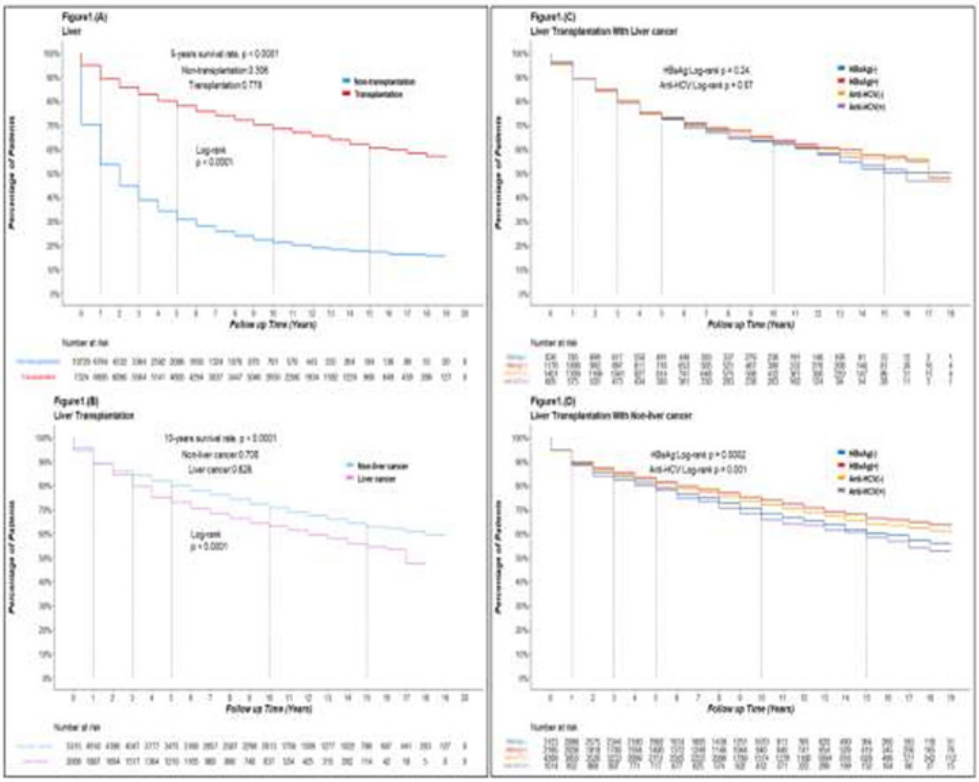

Figure 1: Kaplan–Meier survival analyses:
(A) Survival comparison between patients with and without liver transplantation.
(B) Survival among liver transplant recipients with versus without hepatocellular carcinoma (HCC).
(C) Survival by HBsAg and anti-HCV status in HCC transplant recipients.
(D) Survival by HBsAg and anti-HCV status in non-HCC transplant recipients.
Transplantation is associated with significantly improved survival, which is modified by the HCC status and viral status.

(A)	Transplantation (n = 7324)	Non-transplantation (n = 10729)	p-value	(B)	Liver cancer (n = 2009)	Non-liver cancer (n = 5315)	p-value
[2] Enrollment age (mean±sd)	50.54 ± 14.53	52.45 ± 11.82	<0.001		56.02 ± 8.22	48.47 ± 15.80	<0.001
Median (IQR)	54 (14)	55 (14)			57 (10)	53 (13)	
(Q1, Q3)	(46, 60)	(47, 61)			(52, 62)	(45, 58)	
Range (Min-Max)	0-84	0-79			1-76	0-84	
[1] <20	429 (5.9)	244 (2.3)	<0.001		3 (0.1)	426 (8.0)	<0.001
20-29	103 (1.4)	148 (1.4)			7 (0.3)	96 (1.8)	
30-39	422 (5.8)	789 (7.4)			78 (3.9)	344 (6.5)	
40-49	1523 (20.8)	2375 (22.1)			288 (14.3)	1235 (23.2)	
50-59	2981 (40.7)	4035 (37.6)			864 (43.0)	2117 (39.8)	
60-69	1793 (24.5)	2934 (27.3)			746 (37.1)	1047 (19.7)	
≥70	73 (1.0)	204 (1.9)			23 (1.1)	50 (0.9)	
Liver Cancer			<0.001				
No	5315 (72.6)	8046 (75.0)			-	-	
Yes	2009 (27.4)	2683 (25.0)			-	-	
HBsAg			0.083				<0.001
Negative(-)	3953 (54.0)	5655 (52.7)			830 (41.4)	3123 (58.8)	
Positive(+)	3361 (46.0)	5071 (47.3)			1176 (58.6)	2185 (41.2)	
Missing	10	3			3	7	
Anti-HCV			0.950				<0.001
Negative(-)	5690 (77.8)	8340 (77.8)			1401 (69.8)	4289 (80.9)	
Positive(+)	1619 (22.2)	2380 (22.2)			605 (30.2)	1014 (19.1)	
Missing	15	9			3	12	

Table 1: Baseline characteristics of patients with end-stage liver disease, stratified by (A) transplantation status and (B) presence of hepatocellular carcinoma among transplant recipients. Differences in age, viral hepatitis status, and cancer prevalence are presented.

	N	1 year	p	3 years	p	5 years	p	10 years	p	15 years	p
Age<20											
Non-transplantation	244	0.645	<0.001	0.570	<0.001	0.558	<0.001	0.514	<0.001	0.467	<0.001
Transplantation	429	0.915		0.885		0.877		0.861		0.837	
Age 20-29											
Non-transplantation	148	0.681	0.016	0.603	<0.001	0.545	<0.001	0.392	<0.001	0.364	<0.001
Transplantation	103	0.825		0.815		0.769		0.703		0.677	
Age 30-39											
Non-transplantation	789	0.571	<0.001	0.441	<0.001	0.384	<0.001	0.300	<0.001	0.288	<0.001
Transplantation	422	0.902		0.838		0.802		0.729		0.690	
Age 40-49											
Non-transplantation	2375	0.554	<0.001	0.412	<0.001	0.345	<0.001	0.237	<0.001	0.197	<0.001
Transplantation	1523	0.913		0.858		0.802		0.705		0.641	
Age 50-59											
Non-transplantation	4035	0.521	<0.001	0.364	<0.001	0.278	<0.001	0.185	<0.001	0.143	<0.001
Transplantation	2981	0.889		0.831		0.780		0.678		0.575	
Age 60-69											
Non-transplantation	2934	0.518	<0.001	0.355	<0.001	0.257	<0.001	0.155	<0.001	0.097	<0.001
Transplantation	1793	0.873		0.786		0.733		0.617		0.516	
Age≥70											
Non-transplantation	204	0.487	<0.001	0.314	<0.001	0.238	<0.001	0.118	<0.001	0	<0.001
Transplantation	73	0.758		0.687		0.592		0.592		0.296	

[a]Chi-squared test used to compare survival rates between transplantation and non-transplantation groups.

Table 2. **(B)**Survival rate of population with liver cancer and non-liver cancer, stratified by age.

	N	1 year	p	3 years	p	5 years	p	10 years	p	15 years	p
Age<20											
Non-liver cancer	426	0.917	0.238	0.887	0.306	0.878	0.327	0.862	0.364	0.838	0.415
Liver cancer	3	0.667		0.667		0.667		0.667		0.667	
Age 20-29											
Non-liver cancer	96	0.822	1	0.811	1	0.763	1	0.706	1	0.676	1
Liver cancer	7	0.857		0.857		0.857		0.686		0.686	
Age 30-39											
Non-liver cancer	344	0.898	0.638	0.840	1	0.811	0.436	0.729	1	0.688	0.876
Liver cancer	78	0.923		0.832		0.764		0.731		0.705	
Age 40-49											
Non-liver cancer	1235	0.909	0.221	0.863	0.396	0.812	0.068	0.713	0.186	0.642	1
Liver cancer	288	0.933		0.841		0.763		0.672		0.641	
Age 50-59											
Non-liver cancer	2117	0.890	0.873	0.842	0.013	0.798	<0.001	0.694	0.006	0.592	0.005
Liver cancer	864	0.887		0.804		0.738		0.641		0.535	
Age 60-69											
Non-liver cancer	1047	0.869	0.611	0.798	0.171	0.752	0.037	0.640	0.018	0.544	0.003
Liver cancer	746	0.879		0.770		0.707		0.584		0.472	
Age≥70											
Non-liver cancer	50	0.794	0.448	0.722	0.463	0.690	0.017	0.690	0.017	-	-
Liver cancer	23	0.680		0.605		0.363		0.363		-	

[a]Chi-squared test used to compare survival rates between transplantation and non-transplantation groups; Fisher's exact test was used for the age <20 and age 20-29 subgroup.

Table 2 (A): Age-stratified survival rates at 1, 3, 5, 10, and 15 years for patients with and without liver transplantation. (B) Similar stratification among transplant recipients with and without HCC. Transplant recipients consistently demonstrate better survival across age groups.

	Transplantation group (N=7324)	Non-transplantation group			Transplantation group	
		All (N=10729)	Death (N=7045)	Dropout (N=3684)	Liver cancer (N=2009)	Non-liver cancer (N=5315)
Waiting time (year, mean±sd)	0.70 ± 1.54	2.52 ± 3.59	1.57 ± 2.39	4.35 ± 4.65	0.75 ± 1.46	0.68 ± 1.57

Table 3: Mean waiting time (years) in transplant and non-transplant groups, stratified by transplant status and presence of HCC. Longer waiting times were observed among patients who ultimately dropped out or died on the waitlist.

5. 4. Waiting Time and Survival

Mean waiting time was shorter among transplant recipients (0.70 ± 1.54 years) than among non-transplanted candidates (2.52 ± 3.59 years), while patients who dropped out of the waiting list had the longest waiting time (4.35 ± 4.65 years). Among transplant recipients, patients with HCC had a longer mean waiting time than those without HCC (0.75 ± 1.46 vs. 0.68 ± 1.57 years; Table 3).

Each additional year of waiting time was associated with a reduced mortality risk among transplant recipients (adjusted HR, 0.955; 95% CI, 0.928–0.982; p = 0.001). The association was most pronounced among recipients with waiting times of 6–10 years (adjusted HR 0.693; p = 0.028), consistent with the selection of candidates with greater physiological reserves. In contrast, a longer waiting time was associated with increased mortality among non-transplant candidates (adjusted OR, 1.007 per year; p < 0.001; Table 4A).

When stratified by HCC status, waiting time was not significantly associated with survival among HCC patients (adjusted HR 0.969; p = 0.226), whereas among non-HCC patients, a longer waiting time was associated with improved survival (adjusted HR 0.945; p = 0.002; Table 4B).

(A)	N	Crude Model (HR)	p	Adjusted Model [a]	p	**(B)**	N	Crude Model (HR)	p	Adjusted Model [a]	p
Transplantation						**Liver cancer**					
Waiting time (per year)		0.941 [0.915, 0.968]	<0.001	0.955 [0.928, 0.982]	0.001	Waiting time (per year)		0.950 [0.903, 0.999]	0.046	0.969 [0.920, 1.020]	0.226
<1	6329	Ref		Ref		<1	1694	Ref		Ref	
2	386	0.812 [0.670, 0.983]	0.033	0.823 [0.680, 0.997]	0.046	2	138	0.772 [0.568, 1.050]	0.099	0.806 [0.593, 1.096]	0.170
3	210	1.024 [0.810, 1.293]	0.844	1.042 [0.825, 1.317]	0.729	3	71	1.058 [0.728, 1.537]	0.767	1.102 [0.759, 1.602]	0.610
4	148	0.765 [0.564, 1.039]	0.086	0.792 [0.583, 1.075]	0.135	4	44	0.605 [0.342, 1.072]	0.085	0.634 [0.358, 1.124]	0.119
5	86	1.043 [0.743, 1.465]	0.807	1.110 [0.790, 1.558]	0.547	5	14	1.358 [0.702, 2.628]	0.363	1.493 [0.771, 2.890]	0.235
6-10	143	0.617 [0.445, 0.854]	0.004	0.693 [0.500, 0.961]	0.028	6-10	47	0.791 [0.501, 1.250]	0.315	0.941 [0.592, 1.495]	0.797
≥11	22	0.264 [0.085, 0.819]	0.021	0.333 [0.107, 1.035]	0.058	≥11	1	-	-	-	-
		Crude Model (OR)	p	Adjusted Model [b]	p			Crude Model (HR)	p	Adjusted Model [a]	p
Non-transplantation						**Non-liver cancer**					
Waiting time (per year)		0.791 [0.780, 0.802]	<0.001	1.007 [1.003, 1.011]	<0.001	Waiting time (per year)		0.933 [0.901, 0.966]	<0.001	0.945 [0.912, 0.979]	0.002
<1	6197	Ref		Ref		<1	4635	Ref		Ref	
2	1168	0.526 [0.460, 0.601]	<0.001	0.523 [0.457, 0.598]	<0.001	2	248	0.798 [0.625, 1.021]	0.072	0.811 [0.635, 1.037]	0.095
3	772	0.433 [0.371, 0.507]	<0.001	0.434 [0.372, 0.508]	<0.001	3	139	0.969 [0.718, 1.309]	0.837	0.986 [0.730, 1.332]	0.926
4	506	0.413 [0.343, 0.498]	<0.001	0.412 [0.342, 0.497]	<0.001	4	104	0.837 [0.583, 1.202]	0.336	0.866 [0.603, 1.244]	0.436
5	436	0.285 [0.234, 0.348]	<0.001	0.287 [0.236, 0.350]	<0.001	5	72	0.993 [0.668, 1.475]	0.970	1.033 [0.695, 1.534]	0.874
6-10	1080	0.191 [0.167, 0.219]	<0.001	0.194 [0.170, 0.223]	<0.001	6-10	96	0.479 [0.301, 0.763]	0.002	0.532 [0.334, 0.848]	0.008
≥11	570	0.054 [0.042, 0.068]	<0.001	0.057 [0.044, 0.071]	<0.001	≥11	21	0.298 [0.010, 0.925]	0.036	0.359 [0.115, 1.114]	0.076

[a]Adjusted Model were estimated using cox model adjusted for age.

[b]Adjusted Model were estimated using logistic regression adjusted for age.

Table 4 (A): Adjusted hazard ratios for mortality associated with waiting time in transplant versus non-transplant patients. (B) Separate analysis of HCC and non-HCC recipients for mortality associated with waiting time.

5. 5. Age-Dependent Outcomes and Donor Type Effects

Recipient age was independently associated with posttransplant mortality. Each additional year of age at transplantation was associated with an increased mortality risk (HR, 1.018; 95% CI, 1.014–1.022; $p < 0.001$), with the highest risk observed among recipients aged ≥70 years (HR, 4.119 compared with recipients aged <20 years; $p < 0.001$; Table 5A). The association between age and mortality was less pronounced in HCC recipients (Table 5B).

Living-donor liver transplantation was independently associated with better survival than deceased donor liver transplantation (HR, 0.783; 95% CI, 0.716–0.855; $p < 0.001$). These findings underscore the importance of age-sensitive risk stratification and the role of living donor transplantation in optimizing outcomes, particularly in non-HCC recipients with prolonged waiting times (Table 5A).

(A)	N	Hazard Ratio	p
Transplant group			
Transplant age (per year)		1.018 [1.014, 1.022]	<0.001
<20	419	Ref	
20-29	98	2.235 [1.429, 3.496]	<0.001
30-39	371	2.119 [1.546, 2.906]	<0.001
40-49	1414	2.047 [1.562, 2.683]	<0.001
50-59	2954	2.471 [1.906, 3.203]	<0.001
60-69	1973	2.954 [2.272, 3.842]	<0.001
≥70	95	4.119 [2.727, 6.221]	<0.001
Deceased donor	2135	Ref	
Living donor	5172	0.783 [0.716, 0.855]	<0.001
Enrollment age (per year)		1.019 [1.015, 1.023]	<0.001
<20	429	Ref	
20-29	103	2.203 [1.419, 3.421]	<0.001
30-39	422	1.930 [1.418, 2.626]	<0.001
40-49	1523	2.113 [1.622, 2.754]	<0.001
50-59	2981	2.481 [1.922, 3.203]	<0.001
60-69	1793	3.013 [2.323, 3.909]	<0.001
≥70	73	4.595 [2.925, 7.217]	<0.001
Non-transplant group			
Enrollment age (per year)		1.013 [1.010, 1.015]	<0.001
<20	244	Ref	
20-29	148	1.132 [0.839, 1.528]	0.418
30-39	789	1.579 [1.283, 1.943]	<0.001
40-49	2375	1.796 [1.480, 2.180]	<0.001
50-59	4035	2.047 [1.691, 2.477]	<0.001
60-69	2934	2.121 [1.750, 2.571]	<0.001
≥70	204	2.315 [1.802, 2.975]	<0.001

(B)	N	Hazard Ratio	p
Liver cancer			
Transplant age (per year)		1.022 [1.012, 1.033]	<0.001
<20	3	Ref	
20-29	4	1.486 [0.135, 16.39]	0.746
30-39	64	0.993 [0.133, 7.421]	0.995
40-49	266	0.915 [0.127, 6.583]	0.930
50-59	830	1.195 [0.168, 8.516]	0.859
60-69	805	1.427 [0.200, 10.17]	0.723
≥70	37	2.205 [0.293, 16.58]	0.442
Deceased donor	511	Ref	
Living donor	1498	0.970 [0.819, 1.150]	0.728
Enrollment age (per year)		1.024 [1.014, 1.034]	<0.001
<20	3	Ref	
20-29	7	0.864 [0.078, 9.538]	0.906
30-39	78	0.838 [0.113, 6.232]	0.863
40-49	288	0.995 [0.139, 7.142]	0.996
50-59	864	1.213 [0.170, 8.645]	0.847
60-69	746	1.442 [0.202, 10.28]	0.715
≥70	23	3.173 [0.409, 24.60]	0.269
Non-liver cancer			
Transplant age (per year)		1.016 [1.012, 1.020]	<0.001
<20	415	Ref	
20-29	94	2.189 [1.381, 3.468]	<0.001
30-39	306	2.102 [1.512, 2.924]	<0.001
40-49	1146	2.040 [1.546, 2.691]	<0.001
50-59	2119	2.369 [1.818, 3.089]	<0.001
60-69	1160	2.765 [2.104, 3.633]	<0.001
≥70	58	3.541 [2.113, 5.936]	<0.001

Table 5 (A): Association between transplant age, donor type (living vs. deceased), and survival, along with enrollment and dropout age in non-transplanted patients, but living donor transplantation offers a protective benefit. (B) Similar analysis stratified by HCC status among transplant recipients. Older age increases mortality risk in non-HCC recipients.

6. Discussion

In this nationwide, long-term cohort study from an HBV-endemic society, we demonstrated that liver transplantation confers a consistent and substantial survival benefit across disease categories, viral serostatus, age groups, and donor types. Beyond confirming the survival advantage of transplantation, our findings highlight how traditionally defined risk factors-viral hepatitis status, waiting time, and advanced age-function as dynamic context-dependent variables within a real-world transplant allocation system.

In Taiwan, the scarcity of deceased donor organs has led to widespread adoption of LDLT. For DDLT, patient selection followed the Milan criteria, which limits eligibility to patients with a single tumour ≤5 cm or up to three tumours ≤3 cm, without macrovascular invasion or extrahepatic spread. For LDLT, broader criteria, such as the UCSF guidelines, are often applied, allowing a single tumour ≤6.5 cm or up to three nodules with the largest diameter ≤4.5 cm and a total diameter ≤8 cm [16-19]. Taiwan's National Health Insurance (NHI) requires transplant recipients to meet either the Milan or UCSF criteria for reimbursement, emphasizing cost-effectiveness and fairness in allocation.

Consistent with previous studies, transplant recipients with HCC exhibited lower long-term survival than those without HCC, reflecting the oncological burden inherent to malignancy [20]. Nevertheless, liver transplantation remains associated with a marked survival advantage in HCC patients compared with non-transplanted individuals, supporting its role as a definitive therapy in appropriately selected candidates [21]. In contrast, among non-HCC recipients, post-transplant outcomes appeared to be more strongly influenced by systemic and virological factors than by tumour-related considerations.

Viral serostatus demonstrated differential prognostic implications according to the HCC status. Among HCC recipients, neither HBsAg nor anti-HCV positivity significantly affected long-term survival, suggesting that tumour biology and recurrence risk outweigh virological factors in this population. However, among non-HCC recipients, HBsAg positivity was associated with superior survival, whereas anti-HCV positivity predicted worse outcomes. These findings should not be interpreted as a protective effect of hepatitis B itself, but rather as evidence that, in the contemporary antiviral era, HBsAg status may serve as a marker of well-controlled chronic viral disease within a structured transplant and post-transplant management system. In contrast, the adverse impact of anti-HCV positivity likely reflects residual comorbidity and history of disease burden despite antiviral treatment.

Beyond transplantation, the clinical significance of HBsAg levels is being radically reinterpreted, providing a plausible biological explanation for our findings. Traditionally, high HBsAg levels have been considered a marker of an increased risk of HCC. However, emerging evidence has suggested a more nuanced relationship. A landmark study by Tseng et al. found that among patients with inactive CHB (HBeAg-negative, normal ALT, HBV DNA <2000 IU/mL), an HBsAg level <100 IU/mL identified a large subgroup with an annual HCC risk of 0.08%, which is not only below the recommended surveillance threshold, but also comparable to the non-HBV/non-HCV general population [22]. This defines the state of "partial cure." Intriguingly, this inverse relationship between HBsAg level and risk was also observed in specific high-viremia populations. Another study by the same group found that among HBeAg-positive immune-tolerant patients, those with HBsAg ≥10,000 IU/mL had a delayed development of HCC compared to those with lower levels [23]. This suggests that a high HBsAg level in the absence of liver injury might be a biomarker for a

more genuine and stable immune-tolerant phase characterized by less aggressive viral integration and hepatocarcinogenesis.

In the context of transplantation, our HBsAg-positive non-HCC recipients likely represent a population with effectively controlled viral replication (via NA therapy) and potentially favorable viral-host dynamics, akin to the "immune-tolerant" or "inactive carrier" state described above. Their superior survival reflects a lower burden of underlying metabolic comorbidities compared with the HBsAg-negative group, coupled with a virological profile that is now well-controlled and less carcinogenic.

These results also highlight the importance of individualized virological management of transplant candidates. For non-HCC patients, rigorous viral suppression, such as lifelong HBV prophylaxis and DAA therapy for HCV, is crucial for improving the long-term outcomes. For patients with HCC, the surveillance of tumour recurrence remains a priority. Given Taiwan's large cohort of patients with HBV- and HCV-related HCC, these observations are clinically meaningful and valuable for international comparisons. For patients with hepatitis B virus (HBV) awaiting liver transplantation, submission of medical data to the Taiwan Organ Registry and Sharing Centre (TORSC) does not require HBV DNA levels as a mandatory field. As a result, there remains significant room for further research to elucidate the impact of hepatitis B on liver transplantation outcomes in non-hepatocellular carcinoma (non-HCC) cases.

Waiting time before transplantation showed a bidirectional association with survival, depending on transplant status [24,25]. Among transplant recipients, a longer waiting time is associated with reduced post-transplant mortality. This relationship should be understood not as a causal benefit of delay, but as a selection mechanism whereby candidates with stable disease biology and preserved physiological reserves are more likely to survive transplantation and achieve favourable outcomes. Conversely, a prolonged waiting time was associated with increased mortality among non-transplant patients, underscoring the detrimental consequences of delayed access to definitive therapy. These findings illustrate the dual role of waiting time as both a risk indicator and system-level selection tool within allocation frameworks [26,27].

Recipient age was independently associated with post-transplant mortality; however, even patients aged ≥ 70 years derived a substantial survival benefit from transplantation compared with non-transplanted individuals. This observation supports the view that chronological age alone should not be treated as a fixed exclusion criterion but rather as a component of a broader, outcome-oriented assessment incorporating physiological reserve and system capacity [28]. In parallel, living donor liver transplantation was independently associated with superior survival compared to deceased donor transplantation, highlighting its role as a structural solution to organ scarcity, particularly in aging societies with limited deceased donor supply [29-31].

Taken together, these results indicate that viral serostatus, waiting time, age, and donor type should be interpreted as allocation-relevant variables, whose prognostic significance is shaped by antiviral effectiveness, system design, and selection processes, rather than static risk labels. In HBV-endemic settings with severe organ scarcity, such as Taiwan, transplant policies that integrate these dynamic factors and strategically expand living donor programs may optimize both equity and outcomes in liver transplantation.

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