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RESEARCH

Longitudinal analysis of liver transplant candidates for hepatocellular carcinoma in a single center

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Abstract

Background Wailitst lost is an critical issue and we investigated the long-term effect of insufficient liver functional reserve at liver transplantation evaluation on waitlist outcomes in patients with hepatocellular carcinoma (HCC).

Methods Clinical data of patients with HCC waitlisted for liver transplantation were retrospectively collected from a single hospital cohort during the period from 2014 to 2021. Parameters of liver reserve, including cirrhosis, Child–Pugh grade, and Model for End-Stage Liver Disease (MELD) scores, were analyzed for patient survival, after adjustment for tumor factors.

Results Of 292 eligible patients, 94.2% had cirrhosis, 55.8% had Child–Pugh grade B or C, and the median MELD score was 13.2. The median follow-up time was 2.2 years, with a dropout rate of 62.7%. Eighty-nine candidates (30.5%) eventually received liver transplant, including 67 from live donors. The estimated 1-year mortality rate reached 40.6% in 203 patients who remained on the waitlist without receiving a transplant, of whom 143 died. Most deaths were attributed to liver failure (37.1%) and cancer death (35.7%). After we adjusted for tumor confounders, including alpha fetoprotein, primary HCC stage, tumor number at evaluation, and sequential cancer treatment before and while waiting, hazard ratios (HRs) for patient survival were 1.69 (95% confidence interval, 1.18–2.41) for cirrhotic stage B or C, 1.07 (1.04–1.10) for MELD scores, and 1.14 (1.04–1.25) for tumor size at transplant evaluation. Transplantation was a protective disease modifier with adjusted HR 0.22 (0.14–0.33).

Conclusion Insufficient liver functional reserve poses more risk than expected to liver transplant waitlist outcomes with HCC.

Keywords Hepatocellular carcinoma · Liver transplantation · waitlist outcome · Reserve · Liver failure · Cirrhosis

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Abbreviations

ABI	Albumin-Bilirubin index
ACLF	Acute-on-chronic liver failure;
AFP	Alpha fetoprotein
BMI	Body mass index
CI	Confidence interval
DDLT	Deceased donor liver transplantation
DM	Diabetes mellitus
EV	Esophageal varices
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
IQR	Interquartile ranges
LDLT	Living donor liver transplantation
MELD	Model for End-Stage Liver Disease
RFA	Radiofrequency ablation
TACE	Trans-arterial chemoembolization
USCF	University of California San Francisco

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Introduction

Hepatocarcinogenesis results from a permissive microenvironment created by chronic liver disease [1]. Hepatocellular carcinoma (HCC), the most common form of primary liver cancer, typically develops against a background of chronic liver disease, with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol abuse, and nonalcoholic fatty liver disease being the major etiologies [2]. Apart from the cancer field effect, background liver functional reserve, which hosts HCC, largely determines HCC treatment choices and posttreatment recurrence, thus influencing survival [3–5]. Clearly, background liver condition plays a critical role in HCC outcomes.

Although HCC therapeutics depends largely on a relatively well-preserved liver to yield long-term survival, treatment options become considerably limited when liver reserve diminishes [3]. One curative treatment for HCC is liver transplantation, which also replaces the sick background liver. In HCC therapeutics, liver transplantation can be performed at an early stage of HCC (USA) [6], intermediate stage of HCC (Barcelona Clinic Liver Cancer classification) [7], and even at an advanced stage with poor liver reserve (Taiwan) [8]. The latter case, in which transplantation recommendation is shifted toward a later stage in the management spectrum of HCC therapeutics, [8] is usually preferred in situations of limited deceased donor livers to maximize overall transplant utility and individual benefit–risk ratio.

Although liver transplantation is a flexible and viable option for HCC cases with adequate liver reserve, it is limited by organ shortage and prolonged or unpredictable waiting times, thereby causing patient dropout due to tumor progression [1]. The effect of poor liver reserve on waitlist and survival outcomes has not been fully explored, although limited tumor progression beyond the Milan criteria did not result in irreversible impairment of survival in patients on the waiting list [9]. In this study, we examined the prognostic effect of background liver function in transplant candidates diagnosed as having HCC.

Methods

Patients

This study cohort included waitlisted adult patients who received a diagnosis of HCC in a university hospital between January 2014 and October 2021. HCC was diagnosed when imaging revealed a new lesion with features of HCC, either by pathology or by typical imaging of background liver in chronic hepatitis or cirrhosis [10]. The management policy of primary or recurrent HCC, including local treatment and surveillance, have been previously described and audited by our multidisciplinary tumor board [10, 11].

Liver transplantation was considered for either of the following conditions: resistance to an adequate local treatment modality against HCC or deterioration of liver function due to liver cirrhosis or its complications [5]. The University of California San Francisco (UCSF) criteria (single tumor < 6.5 cm, maximum of 3 total tumors with none > 4.5 cm, or cumulative tumor size < 8 cm without vascular invasion) were used for determining waitlist eligibility [5, 11, 12].

Demographic parameters

We collected demographic information, namely sex, age, body mass index, underlying liver diseases and comorbidities (presence HBV or HCV), alcohol use, presence of cirrhosis and cirrhotic grades, HCC status (primary TNM stages, tumor number, and largest tumor size at transplant evaluation), diabetes mellitus, hypertension, Model for End-Stage Liver Disease (MELD) scores [13], serum alpha fetoprotein (AFP), and other clinical variables at the time of transplant evaluation for the preclaim review. History of sequential HCC treatment, including resection, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE), was coded before transplant evaluation and after patients were waitlisted.

Primary HCC TNM stages were charted according to the American Joint Committee on Cancer Staging Manual applicable at the time of diagnosis. Cirrhotic stage was graded using the Child–Turcotte–Pugh scoring system [14, 15]. Acute-on-chronic liver failure (ACLF) was defined according to the consensus recommendations of the Asian Pacific Association for the Study of the Liver [16], namely the presence of acute hepatic insult, jaundice (bilirubin ≥ 5 mg/dL), and coagulopathy (international normalized ratio ≥ 1.5) complicated by ascites or encephalopathy or both within 4 weeks, with previously diagnosed or undiagnosed chronic liver disease [16, 17]. Antiviral therapy for HBV (nucleoside/nucleotide inhibitors of HBV polymerase) and HCV (interferon) were administered as per doctors' prescription. Transplant candidates were excluded from the waiting list when contraindications emerged or experts deemed the prospect of transplant as futile [18]. The transplantation panel retained the final decision for waitlist exclusion [18].

Outcome measurement

Patients were followed up until their death or April 2022, and the cause of death was recorded. The index date was

the date of waitlisting. The event date was the date of death, waitlist exclusion, liver transplantation, or last follow-up. The primary outcome was overall survival, and the secondary outcome was survival of patients on the waiting list.

Statistical analysis

Descriptive statistics are expressed as means ± standard deviation, medians (interquartile range [IQR]), or numbers (percentages) where appropriate. The Student *t* test, χ^2 test, Mann–Whitney U test, or Fisher exact test was used, where appropriate, to compare variables. Cumulative survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox regression modeling was employed for univariable and multivariable analyses. Sensitivity analysis was conducted in the subgroup of patients who did not undergo liver transplantation until the end of the study period. Statistical significance was indicated by a two-sided p value of < 0.05. Analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

Results

Demographics

Among 891 adult transplant candidates waitlisted during the study period, 292 candidates diagnosed as having HCC were included in the analysis (Fig. 1). Their clinical features are summarized in Table 1. Most of the candidates were male patients in their late fifties (71.9%) and HBV carriers (60.3%), had cirrhosis (94.2%) and esophageal varices (EV) (63.7%), had primary HCC stage 1 (56.1%), had underwent TACE (73.3%), had low (< 400 ng/mL) AFP level (90.1%), and had a low tumor burden at evaluation. Compared with patients with less advanced cirrhosis (Child A or less (no cirrhosis)), those with advanced cirrhosis (Child B or C) were frequently characterized with alcoholic cirrhotic liver, EV, ascites, and encephalopathy; had higher MELD scores; underwent more TACE and less curative treatments (resection or RFA) in previous cancer treatments; received less cancer treatment while waiting; and had higher rates of waitlist and overall mortality (all $p < 0.05$).

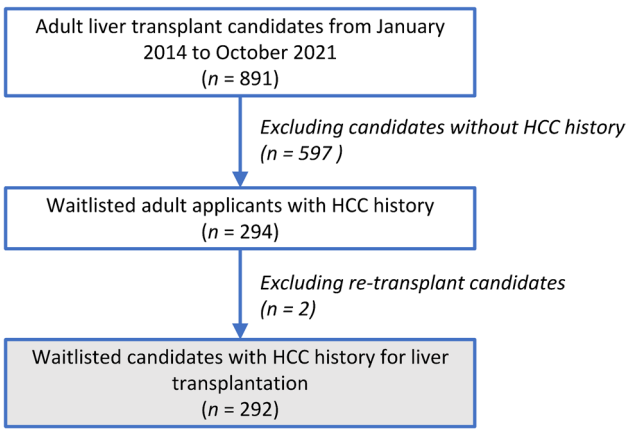

Fig. 1 Flowchart of patient selection. HCC, hepatocellular carcinoma

Among HBV carriers ($n = 176$), 108 received anti-HBV medications. Among candidates with positive anti-HCV serology ($n = 97$), 25 received interferon and 11 received direct-acting antiviral agents. Seven patients had malignancies in addition to HCC: two had lung adenocarcinoma; one, breast cancer; one, thyroid cancer; one, gastric B-cell lymphoma; one, buccal cancer; and one, transitional bladder cancer (developed while waiting). Furthermore, 81 patients (27.7%) had no viable HCC as revealed by imaging at evaluation, 27 (27/81, 33.3%) developed HCC recurrence while waiting, and 22 received at least one session of cancer treatment while waiting. Among 21 candidates who were tumor-free at evaluation but eventually received liver transplants, three received local treatment while waiting and all three had recurrent HCC in liver explants. Fourteen of the other 18 explants had recurrent HCC.

Eighty-nine candidates (30.5%) eventually received liver transplants, including 22 deceased donor liver transplants (DDLTs) and 67 live donor liver transplants (LDLTs). Compared with those with Child A cirrhosis, candidates with Child B or C cirrhosis had a higher tendency of receiving LDLT ($p = 0.07$, Table 1).

Survivals

The median survival time among all 292 candidates was 2.2 (IQR 0.7–NA) years, and among waitlisted patients who had not received a transplant, 1.4 (0.4–4.1) years. For all 292 candidates, the 6-month, 1-year, 2-year, and 3-year overall survival rates after placement on the waiting list were 79.5%, 69.9%, 53.0%, and 40.8%, respectively. Both overall and waitlist survival rates in patients with advanced cirrhosis (Child B or C) were inferior to those in the less advanced cirrhosis group (Child A or less) ($p < 0.001$, Figs. 2A and B).

The median time for liver transplantation after placement on the waiting list was 4.3 (2.8–8.7) months. Furthermore, although the advanced cirrhosis group was more likely to receive a liver transplant ($p = 0.08$, Fig. 2C), the overall survival between the advanced and less advanced cirrhosis group was not significant (Fig. 2D).

For those who did not undergo liver transplantation, the 6-month, 1-year, 2-year, and 3-year estimated mortality rates were 28.2%, 40.6%, 60.7%, and 71.8%, respectively. The advanced cirrhosis group had a lower overall survival

Table 1 Demographics of patients with hepatocellular carcinoma waitlisted for liver transplantation

	All	Child A or less	Child B or C	*p*
	n = 292	*n* = 129	*n* = 163	
Male gender (%)	210 (71.9)	90 (69.8)	120 (73.6)	0.513
Age (years)	59.0 (7.9)	58.9 (8.1)	59.1 (7.7)	0.834
Body mass index	25.6 (4.2)	25.3 (3.7)	25.8 (4.5)	0.309
Background liver				
Hepatitis B	176 (60.3)	83 (64.3)	93 (57.1)	0.229
Hepatitis C	97 (33.2)	41 (31.8)	56 (34.4)	0.708
Alcoholic	24 (8.2)	4 (3.1)	20 (12.3)	0.005
Cirrhosis	275 (94.2)	112 (86.8)	163 (100)	< 0.001
ACLF	14 (4.8)	3 (2.3)	11 (6.7)	0.100
MELD score (SD)	13.2 (6.8)	9.9 (4.9)	15.7 (6.9)	< 0.001
Diabetes mellitus	88 (30.1)	37 (28.7)	51 (31.3)	0.700
Hypertension	68 (23.3)	34 (26.4)	34 (20.9)	0.329
Primary HCC TNM stage				0.894
1	164 (56.1)	71 (55.0)	93 (57.1)	
2	109 (37.3)	50 (38.8)	59 (36.2)	
3	19 (6.5)	8 (6.2)	11 (6.7)	
Previous cancer treatment				
Resection	66 (22.6)	44 (34.1)	22 (13.5)	< 0.001
RFA	137 (46.9)	83 (64.3)	54 (33.1)	< 0.001
TACE	214 (73.3)	111 (86.0)	103 (63.2)	< 0.001
Viable HCC number, median	1 (0–2)	1 (0–2)	1 (0–2)	0.624
Largest HCC size (cm), median	1.5 (0–2.5)	1.5 (0–2.5)	1.5 (0–2.6)	0.582
AFP ng/mL (median)	7.9 (3.4–65.6)	9.6 (3.2–85.4)	7.7 (3.6–41.8)	0.680
AFP > 400 ng/mL	29 (9.9)	10 (7.8)	19 (11.7)	0.326
Cancer treatment at waiting	117 (40.2)	78 (60.5)	39 (24.1)	< 0.001
RFA	36 (12.4)	27 (20.9)	9 (5.6)	
TACE	73 (25.2)	48 (37.2)	25 (15.5)	
Others*	7 (2.4)	3 (2.3)	4 (2.5)	
EV	186 (63.7)	68 (52.7)	118 (72.4)	0.001
Ascites	133 (45.5)	38 (29.5)	95 (58.3)	< 0.001
Encephalopathy	65 (22.3)	11 (8.5)	54 (33.1)	< 0.001
Transplant	89 (30.5)	39 (30.2)	50 (30.7)	> 0.99
DDLT	23 (7.9)	15 (11.6)	8 (4.9)	0.071
LDLT	67 (22.9)	25 (19.4)	42 (25.8)	
Mortality				
Waitlist death	143 (49.0)	48 (37.2)	95 (58.3)	< 0.001
All	175 (59.9)	61 (47.3)	114 (69.9)	< 0.001

Median was compared with Mann–Whitney U test

*Include 3 sorafenib (2 in Child A or less), 2 immunotherapy (2 in Child B or C group), 1 radiotherapy (Child A or less), and 1 hepatic arterial infusion chemotherapy (Child B or C)

ACLF acute-on-chronic liver failure, *AFP* alpha fetoprotein, *EV* esophageal varices, *DDLT* deceased donor liver transplant, *HCC* hepatocellular carcinoma, *MELD* Model for End-Stage Liver Disease, *LDLT* living donor liver transplant, *RFA* radiofrequency ablation, *TACE* trans-arterial chemoembolization

rate than the less advanced group ($p < 0.001$, Fig. 2E). In the subgroups of HBV carriers and patients with positive anti-HCV serology, the use of antiviral agents did not produce any difference in survival (Fig. 2F and G) or cirrhotic stages (data not shown).

Cause of death

A total of 175 patients died in our study cohort, among whom 32 died after liver transplantation. Seventy-one patients died of cancer: 51 patients on the waitlist (including

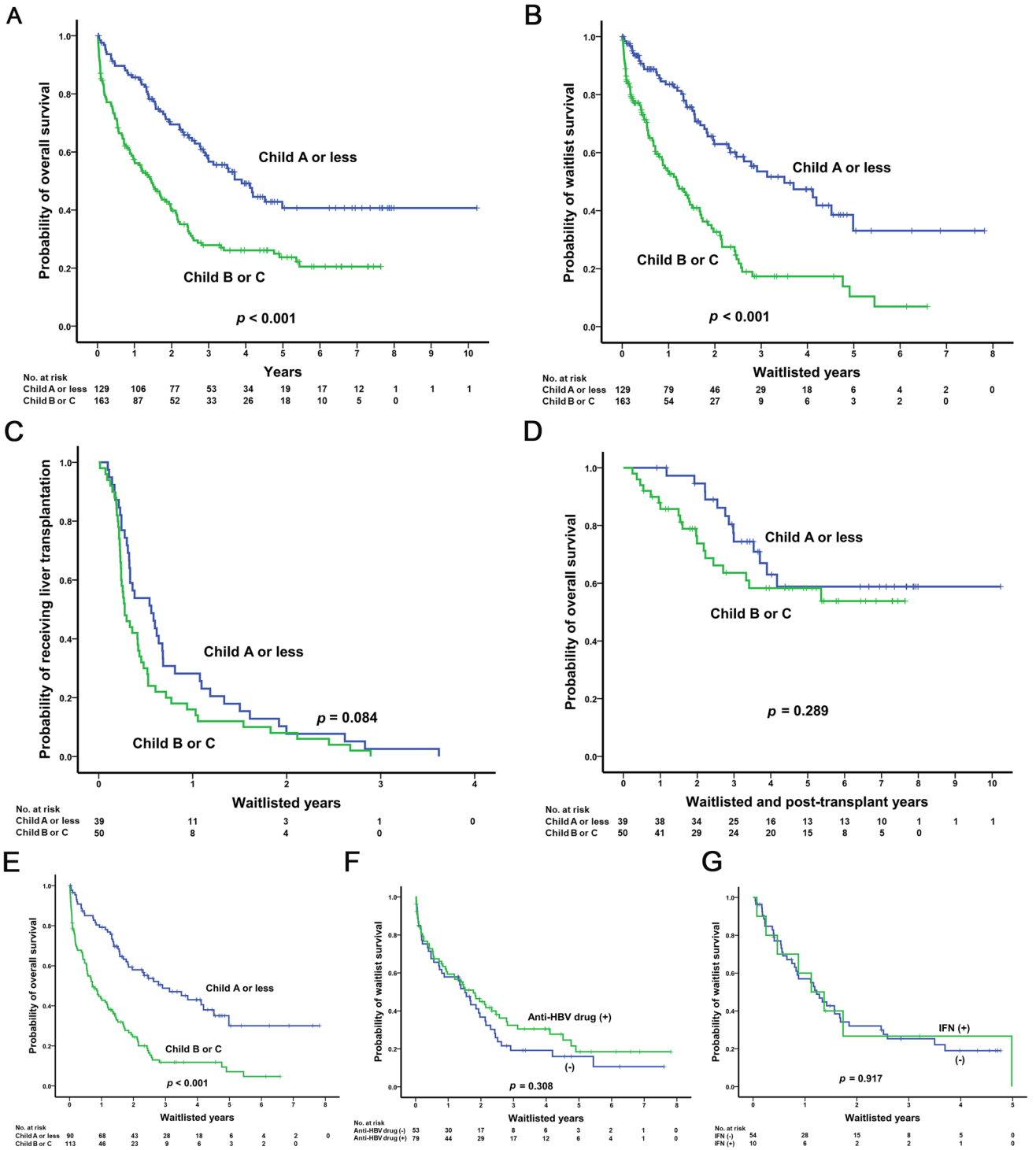

Fig. 2 Survivals in patients with hepatocellular carcinoma waitlisted for liver transplantation. Child B or C vs. Child A or less in overall (**A**) and waitlist survival (**B**). Probability of transplant (**C**) and overall survival (**D**) in candidates who eventually received liver transplantation. Overall survival in patients with hepatocellular carcinoma who did not undergo liver transplantation (**E**). HBV (**F**) and HCV (**G**) subgroups. IFN, interferon

one patient with rectal cancer and one with lung cancer) and 20 recipients after transplantation. Among the 143 candidates who died while on the waiting list, 53 deaths (53/143, 37.1%) were attributed to liver failure, and most deaths (43/53) were from the advanced cirrhosis group. Other causes included infection ($n = 19$), bleeding ($n = 5$), and nonliver etiologies ($n = 15$).

Dropout due to other reasons

Apart from the 143 candidates who died while waiting, 40 patients dropped out for other reasons. Of these, four patients exceeded the UCSF criteria during waitlist follow-up. One patient developed tuberculosis; one, cryptococcosis; one, total portal vein thrombosis; and one, bladder cancer. The remaining 32 were lost to follow-up. The overall dropout rate in this cohort was 62.7% (183/292).

Univariable and multivariable risk factor analyses of overall survival

Our univariable analysis revealed that HBV carrier state, presence of cirrhosis, advanced cirrhosis (Child B or C), increased MELD scores, ACLF, larger tumor size at evaluation, AFP and levels > 400 ng/mL, and encephalopathy were risk factors associated with poor survival (Table 2). By contrast, RFA before transplant evaluation or after placement on the waiting list and liver transplantation (LDLT or DDLT) were protective factors. In the multivariable analysis with backward selection of variables and $p < 0.1$, advanced cirrhosis (adjusted hazard ratio [aHR], 1.69; 95% confidence interval [CI], 1.18–2.41), increased MELD scores (aHR, 1.07; 95% CI, 1.04–1.10), and larger tumor size at evaluation (aHR, 1.14; 95% CI, 1.04–1.25) remained risk factors, and only transplantation (aHR, 0.22; 95% CI, 0.14–0.33) remained associated with superior patient survival (Table 2). ALCF and encephalopathy were borderline risk factors after adjustment.

Further sensitivity analysis of overall survival in waitlist patients who did not receive a liver transplant revealed that advanced cirrhosis (aHR, 1.95; 95% CI, 1.31–2.89), ACLF (aHR, 3.91; 95% CI, 1.56–9.84), increased MELD scores (similar effect size to that in Table 2), larger tumor size (similar effect size), and encephalopathy (adjusted HR, 1.68; 95% CI, 1.13–2.48) were associated risk factors (Table 3).

Discussion

The present cohort study yielded four main findings. First, the median survival time after placement on the waiting list was 2.2 years, and overall dropout rate was 62.7%. For patients who did not receive a transplant, the 1-year estimated mortality rate was 40.6%. Nearly 40% of deaths on the waiting list were due to liver failure. Second, although 81 patients (27.7%) had no viable HCC as revealed by imaging at evaluation, one-third developed HCC recurrence while waiting, and 22 received at least one session of cancer treatment. Third, both overall and waitlist survival in the advanced cirrhosis group (Child B or C) were inferior to those in the less advanced group (Child A or less). Finally, advanced cirrhotic stage, increased MELD scores, and larger tumor size at evaluation were adjusted risk factors associated with overall survival.

This study highlighted the role of poor liver functional reserve in waitlisted patients with HCC. Previous studies have similarly reported that cirrhosis and its parallel markers were risk factors for poor prognosis in nontransplant patients with HCC and that severe cirrhosis adversely affects long-term outcomes in HCC patients after hepatectomy or TACE [4, 5, 19–23]. MELD score and Child–Pugh (CP) grade were significant risk factors after other confounders were controlled for. Other noninvasive markers such as the albumin-bilirubin (ALBI) grade have demonstrated prognostic significance and performed as well as CP grade in HCC [24, 25]. The major advantage of the ALBI grade is that the Child A score in the ALBI grade comprises two classes with clearly different prognoses [24]. Compared with CP grade and MELD scores, the survival difference in the ALBI grade was not particularly obvious in patients with HCC receiving TACE who had less liver reserve than surgical patients [22]. Our waitlist cohort spanned a wide range of liver functional reserves; therefore, CP grade was used favorably to triage candidates according to liver reserve.

Our study also revealed that evidence of no tumor recurrence in imaging studies did not guarantee long-term free of recurrence, and most candidates (17/21, 81%) who eventually received transplants had HCC on explants. This temporary "cancer-free" status either may be due to previous noncurative treatments (inadequate treatment) or may be true, with new HCC developing later. Nonetheless, this finding echoes the fact that HCC carcinogenesis may occur in an altered microenvironment despite local tumor treatment. The interplay of various factors initiates the early steps of hepatocyte malignant transformation and HCC development [1]. These factors include genetic predisposition (genomic instability), reciprocal interactions between viral and nonviral risk factors, cellular microenvironment and various immune cells (cancer-associated fibroblast remodeling and immunoediting), and severity of underlying chronic liver disease [1, 2, 26]. Reliable evidence demonstrates that tumor clonal composition changes over time and after exposure to different treatments [2]. Currently, providing adequate liver cancer care without sequential evaluation of tumor response with imaging techniques or analysis of liver functional reserve with biochemical blood tests would be unrealistic [2].

Table 2 Risk factor analysis of overall survival in patients with hepatocellular carcinoma waitlisted for liver transplantation

	Univariable			Multivariable		
	HR	95CI	*p*	HR	95CI	*p*
Male gender	1.33	0.94–1.87	0.108			
Age	1.01	0.99–1.03	0.483			
BMI	1.01	0.98–1.05	0.445			
Background liver						
Hepatitis B	1.38	1.01–1.88	0.043	-		
Hepatitis C	1.04	0.76–1.42	0.795			
Alcoholic	0.86	0.49–1.52	0.606			
Cirrhosis	2.35	1.04–5.32	0.039	-		
Advanced cirrhosis (B or C)	2.20	1.61–3.00	< 0.001	1.69	1.18–2.41	0.004
ACLF	2.09	1.11–3.97	0.023	1.97	0.93–4.18	0.079
MELD score	1.10	1.07–1.12	< 0.001	1.07	1.04–1.10	< 0.001
Diabetes mellitus	1.06	0.76–1.46	0.748			
Hypertension	1.35	0.96–1.90	0.085	-		
Primary HCC stage						
1 Reference						
2	1.04	0.75–1.43	0.831			
3	1.56	0.92–2.64	0.101			
Previous cancer treatment						
Resection	0.88	0.62–1.26	0.493			
RFA	0.60	0.44–0.81	0.001	-		
TACE	0.82	0.59–1.13	0.229			
Viable HCC number	1.03	0.94–1.13	0.541			
Largest HCC size	1.20	1.09–1.33	< 0.001	1.14	1.04–1.25	0.003
AFP ng/mL	1.00	1.00–1.00	0.004	-		
AFP > 400 ng/mL	2.48	1.62–3.79	< 0.001	-		
Cancer treatment at waiting (no treatment as reference)						
RFA	0.39	0.22–0.68	0.001	-		
TACE	0.78	0.55–1.09	0.148			
Systemic	1.21	0.49–2.97	0.679			
Complications						
EV	1.29	0.94–1.76	0.112			
Ascites	1.26	0.93–1.69	0.133			
Encephalopathy	1.84	1.31–2.57	< 0.001	1.39	0.96–2.00	0.081
Transplant	0.28	0.19–0.41	< 0.001	0.22	0.14–0.33	< 0.001
LDLT	0.18	0.08–0.41	< 0.001	-		
DDLT	0.33	0.22–0.50	< 0.001	-		

-: variables not included in final model by backward selection process

ACLF acute-on-chronic liver failure, *AFP* alpha fetoprotein, *EV* esophageal varices, *DDLT* deceased donor liver transplant, *HCC* hepatocellular carcinoma, *MELD* Model for End-Stage Liver Disease, *LDLT* living donor liver transplant, *RFA* radiofrequency ablation, *TACE* trans-arterial chemoembolization

Moreover, different background livers may involve different drivers and prognoses [1, 2, 27–29]. To fully implement precision medicine, cancer specialists require new methods to sequentially monitor molecular alterations in cancer [2]. Whatever the case, liver transplantation can be the all-in-one solution to both HCC and microenvironmental deviation.

The present study had a few limitations. We conducted this study in areas with low deceased organ donation and high LDLT, thereby limiting the generalizability of our results. External validation with application in areas with high organ donation rates and high prioritization of patients with HCC in the organ sharing allocation policy is required. Although baseline AFP alone was not a risk to survival after adjustment of other variables, data regarding the changing trend of AFP were not available, as it has only recently been identified as a prognostic factor in waitlist and posttransplant survival [30, 31].

Table 3 Multivariable sensitivity analysis of overall survival in waitlisted patients with hepatocellular carcinoma without eventual liver transplantation

	Multivariable		
	HR	95CI	*p*
Advanced cirrhosis (B or C)	1.95	1.31–2.89	0.001
ACLF	3.91	1.56–9.84	0.004
MELD score	1.06	1.03–1.10	< 0.001
Largest HCC size	1.14	1.04–1.26	0.007
Encephalopathy	1.68	1.13–2.48	0.010

ACLF acute-on-chronic liver failure, *HCC* hepatocellular carcinoma, *MELD* Model for End-Stage Liver Disease

Nevertheless, it still may not greatly modify the effect of the "nontumor" background liver, which we have emphasized.

In conclusion, advanced liver cirrhosis poses a substantial risk to the survival of waitlisted transplant candidates with HCC, even adjusting tumor burdens. Issues of proper management of this subgroup are critical to reducing patient dropout, especially when cancer treatment is inadequate and timely transplant is not available.

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Authors' contributions HCM, CHY, HCY, and HRH collected the data, HCM drafted the manuscript, and HCM, HRH, and LPH designed the study. HCM, WYM, and HMC conducted data processing, and HCM and LPH performed data analysis. HCM and HRH were the directors responsible for general organization and instruction. All authors read and approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The Institutional Review Board of National Taiwan University Hospital approved this study (NTUH REC: 201701044RIND and 202004053RINB). Because this study retrospectively analyzed data through a chart review, the Institutional Review Board of National Taiwan University Hospital waived the need for informed consent. The research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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