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Prognostic Efficacy of the Albumin-Bilirubin Score and Treatment Outcomes in Hepatocellular Carcinoma: A Large-Scale, Multi-Center Real-World Database Study

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Keywords
Hepatocellular carcinoma · Treatment outcomes · Albumin-bilirubin score · Real-world evidence · Electronic health records

Abstract

Introduction: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality globally, with treatment outcomes closely tied to liver function. This study evaluates the prognostic utility of the albumin-bilirubin (ALBI) score compared to the traditional Child-Pugh (CP) grading, leveraging real-world evidence from a large-scale, multi-center database. ***Methods:*** The Liver Cancer IN Korea (LINK) research network, a multi-center initiative, retrospectively collected electronic health records from three academic hospitals in South Korea, encompassing HCC patients diagnosed between 2015 and 2020. Inclusion criteria mandated at least one HCC treatment and excluded patients with other primary cancer diagnoses. The study followed patients until death, the last visit, or June 2021, employing standardized data processing and rule-based algorithms for data consistency. The prognostic efficacy of ALBI scores and CP scores was compared through time-dependent receiver operating characteristic (ROC) curves and the inverse probability censoring weighting method. ***Results:*** From 25,248 newly diagnosed patients, 10,297 were included, with 65.82% having hepatitis B etiology and a mean follow-up of 27.49 months. Patients' classification by modified ALBI (mALBI) grade at diagnosis revealed: grade 1

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(48.87%), 2a (20.50%), 2b (24.54%), and 3 (5.17%), with a minimal percentage missing (0.92%). Transarterial therapy (54.07%) and tyrosine kinase inhibitors (84.14% as the first-line systemic therapy) were predominant treatments. The ALBI score demonstrated greater prognostic efficacy than the CP score in long-term outcomes, with time-dependent area under the ROC curve analysis showing a score of 0.71 for ALBI versus 0.67 for CP at 60 months. Furthermore, higher mALBI grades were significantly associated with poorer survival outcomes, as indicated by both univariate and multivariate Cox proportional regression model analyses ($p < 0.001$). ***Conclusions:*** The study confirmed the ALBI score's superior prognostic ability over the CP score, especially evident in long-term outcomes, suggesting a shift toward more nuanced liver function assessment tools in real-world clinical practice.

Introduction

Liver cancer, primarily hepatocellular carcinoma (HCC), is a major global health challenge, ranking as the sixth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide. In 2020, liver cancer was responsible for over 905,000 new cases and 830,000 deaths, underscoring its lethal nature [1, 2]. Particularly in South Korea, HCC is a predominant concern, being the second leading cause of cancer deaths and notably frequent in diagnoses [3]. Despite advancements in the therapeutic landscape of HCC, the prognosis for affected patients remains poor, emphasizing the critical need for a deeper understanding of real-world treatment patterns and outcomes [3].

Recent years have seen significant progress in HCC treatment options, including the advent of emerging therapies that have reshaped the treatment landscape [4, 5]. However, a critical gap persists in the literature regarding the analysis of real-world treatment patterns and outcomes with more recent data. This study aims to bridge this gap by providing a comprehensive analysis of the HCC treatment landscape, leveraging real-world evidence to inform healthcare decisions.

The management of HCC is closely linked to the hepatic function of patients, highlighting the importance of employing accurate clinical grading systems for outcome prediction and treatment optimization [6]. While the Child-Pugh (CP) classification has been traditionally utilized, its reliance on subjective assessments introduces variability [7]. Alternatively, the albumin-bilirubin (ALBI) score offers an evidence-based, objective approach, demonstrating accuracy in reflecting hepatic function [8]. Moreover, the modified ALBI (mALBI) grading system, which divided the ALBI score into four subgrades, enables more precise, discriminative classification of patient prognoses compared to the ALBI grades [9–12]. Recognizing these advantages, the 2022 update to the Barcelona Clinic Liver Cancer (BCLC) strategy also incorporated the ALBI and Model for End-Stage Liver Disease scores, moving beyond the conventional CP staging to assess liver function with greater granularity [13].

This study validates the prognostic value of the ALBI score using a large-scale real-world data by developing a longitudinal cohort of newly diagnosed HCC patients in South Korea. Through this, it seeks to elucidate current treatment patterns and outcomes, offering vital insights into the efficacy of clinical grading systems in a real-world context, ultimately aiming to improve HCC management.

Methods

Study Database and Populations

The Liver Cancer IN Korea (LINK) research network was established to generate real-world evidence on HCC from three leading academic hospitals in South Korea [14]. LINK operates as a large-scale longitudinal database that is regularly updated to include ongoing treatment data for existing patients and to capture newly diagnosed HCC patients. All adult patients (≥18 years) registered in the participating hospitals' database with newly diagnosed HCC between January 1, 2015, and December 31, 2020, were included in the LINK database. Of those patients, patients were excluded if they had no treatment record for HCC within 4 months of the index date or until June 30, 2021, had only surgical records, had the International Classification of Diseases for Oncology-Third Edition (ICD-O-3) code for the diagnosis other than HCC, or had any other primary cancer. The initial date of HCC diagnosis was defined as the index date. The follow-up period for assessing real-world overall survival (rwOS) was from the index date to the earliest of event (or death), end of data period (June 30, 2021), or last known visit. Patients without event or death were censored at their last known activity.

Source Data Selection and Feasibility

A comprehensive feasibility assessment was performed to confirm the availability and validity of data for this study. Initially, questionnaires were distributed to evaluate the logistics and data accessibility across potential sources, aiming to align with our research goals. This preliminary step was supplemented by an in-depth qualitative and quantitative evaluation of each data source, focusing on key metrics such as the annual volume of HCC patients treated and the presence of essential clinical characteristics as structured entries in electronic health records (EHRs).

Upon meticulous evaluation, the clinical research data warehouses (CDWs) of Asan Medical Center (AMC), Samsung Medical Center (SMC), and Severance Hospital (SVC) were selected to contribute to the LINK database. These institutions are

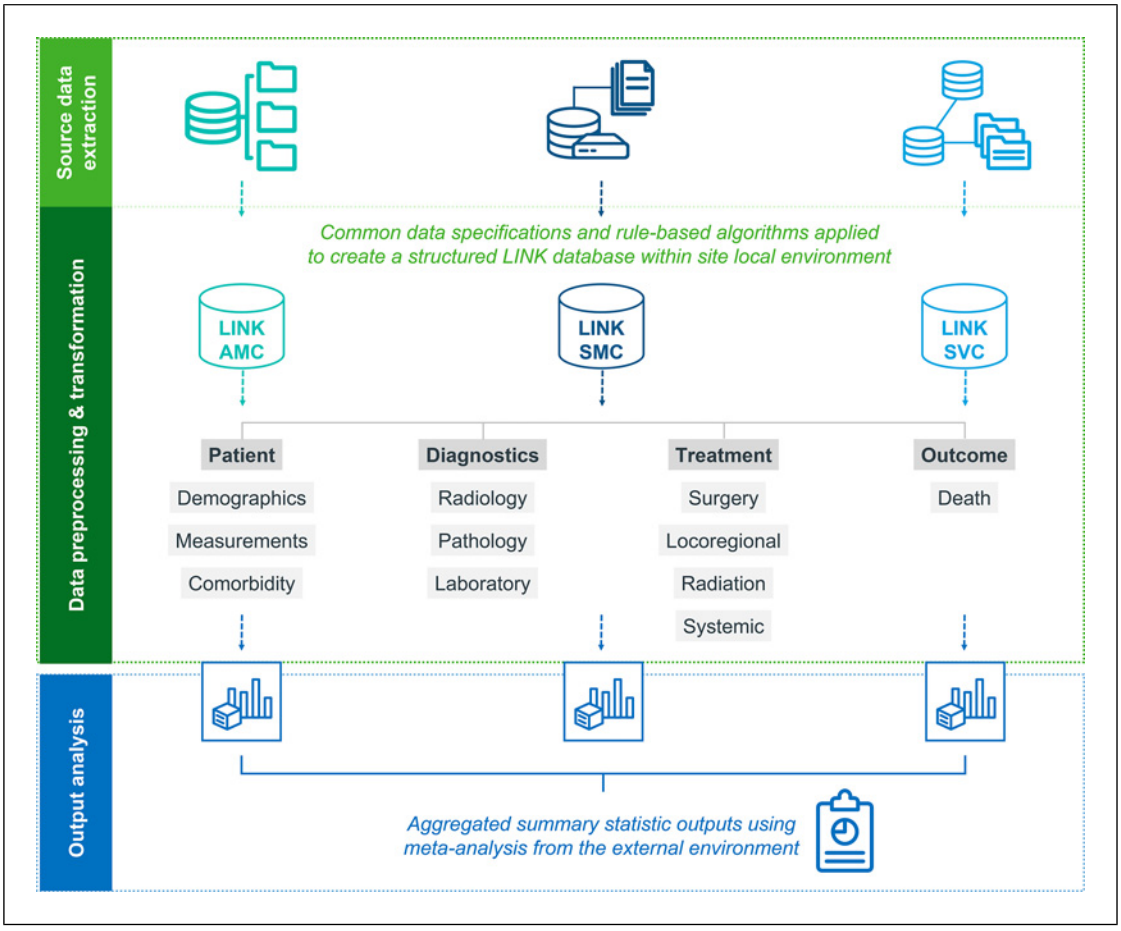

Fig. 1. Overview of the LINK research network design. LINK, Liver Cancer IN Korea; AMC, Asan Medical Center; SMC, Samsung Medical Center; SVC, Severance Hospital.

distinguished tertiary healthcare centers, with bed capacities ranging between approximately 2,200 to 2,700, providing comprehensive care from outpatient services to end-of-life support for cancer patients. Notably, all three institutes utilize an integrated EHR system that mirrors clinical data into the CDW. This setup ensures that the CDW serves as a centralized repository for de-identified patient data across various modalities, thereby serving as a pivotal resource for secondary research analyses.

Data Pre-Processing and Transformation

Data from each hospital's CDW were harmonized for inclusion in the LINK database, with structured data directly extracted and unstructured data enhanced through rule-based algorithms designed to accurately classify and interpret clinical information (Fig. 1). An analytical framework was established to ensure data consistency across sites, guided by common data specifications and programming scripts for data quality assessment, including conformance, completeness, and plausibility checks [15]. Discrepancies were addressed through medical adjudication and technology-based data abstraction. Data handling adhered to de-identification protocols per institutional policies.

To categorize initial HCC treatments and systemic anti-cancer therapy (SACT) lines of therapy (LoTs), rule-based algorithms were developed reflecting local guidelines. These were rigorously tested and refined in consultation with clinical experts to ensure they accurately mirrored real-world practices. Initial treatment modalities covering both surgical and non-surgical interventions were classified as in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539724). SACT LoT identification followed algorithms accounting for drug class, combination therapies, and gap days detailed in online supplementary Figure 1 using prescription data of drugs listed in online supplementary Table 2.

Statistical Analysis and Data Access Model

Descriptive statistics described patient characteristics and treatment patterns, with Sankey diagrams visualizing SACT sequences. The prognostic efficacy of ALBI scores and CP scores was compared using time-dependent ROC curves and the inverse probability censoring weighting method. Sensitivity and specificity were calculated using the Youden index. The Kaplan-Meier method assessed rwOS, with differences evaluated via the log-rank test and

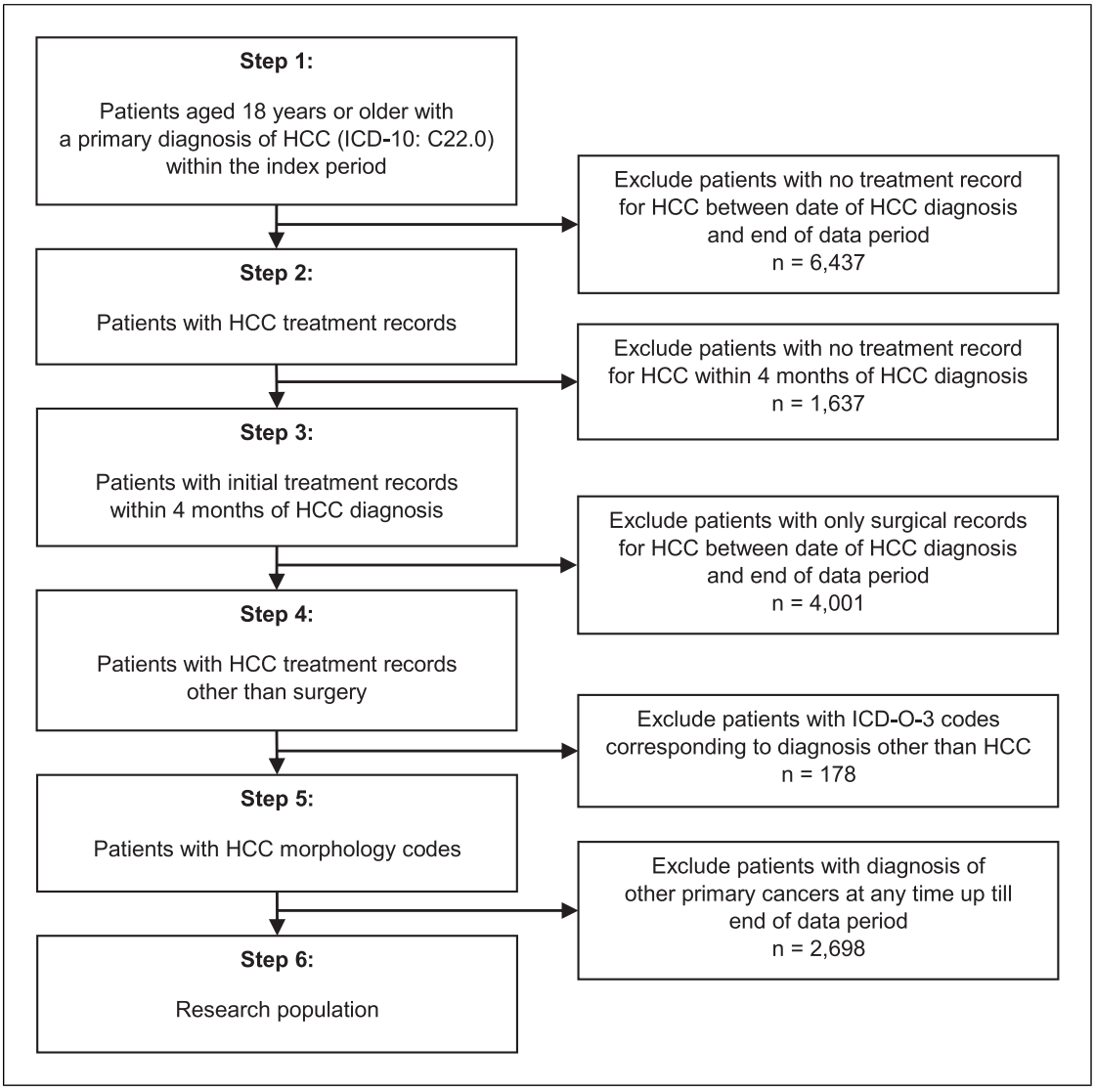

Fig. 2. Patient selection flow. HCC, hepatocellular carcinoma; ICD-10, International Classification of Diseases-10th Edition; ICD-O-3, International Classification of Diseases for Oncology-3rd Edition.

Benjamini-Hochberg correction. Cox proportional hazards models estimated hazard ratios for risk factors related to rwOS. All statistical analyses were performed using R, with two-sided tests employed and a significance level set at 0.05.

The analysis utilized a distributed research network model across three hospitals, enhancing data security by retaining patient-level data on-site and analyzing only aggregated statistics. This approach effectively minimizes the need to share confidential or proprietary information since the distributed research network's querying capability enables research partners to provide results primarily as aggregated data counts. This remote querying method significantly reduces legal, regulatory, privacy, and technical challenges associated with data sharing for research purposes. Such a strategy is especially relevant for studies employing common data models (e.g., Sentinel Common Data Model, Observational Medical Outcomes Partnership (OMOP) Common Data Model), where datasets are not publicly accessible but data codes are available [16–18].

Results

Demographic and Clinical Characteristics at Diagnosis

Our study identified 25,248 patients newly diagnosed with HCC between January 1, 2015, and December 31, 2020. Of these, 10,297 patients met the inclusion criteria

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Table 1. Demographic and clinical characteristics of HCC patients in LINK database

Variables	Total		mALBI grade 1		mALBI grade 2a		mALBI grade 2b		mALBI grade 3		Unknown/missing	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
	10,297	100.00	5,032	48.87	2,111	20.50	2,527	24.54	532	5.17	95	0.92
Age												
Mean (SE)	60.18 (0.10)		59.72 (0.15)		61.13 (0.23)		60.72 (0.20)		58.33 (0.41)		59.42 (0.98)	
Median (Q1–Q3)	60.00 (53.00–67.00)		60.00 (53.00–67.00)		61.00 (54.00–68.00)		60.00 (54.00–68.00)		57.00 (51.00–66.75)		58.00 (53.00–64.00)	
Sex												
Male	8,316	80.76	4,070	80.88	1,691	80.10	2,030	80.33	439	82.52	86	90.53
Female	1,981	19.24	962	19.12	420	19.90	497	19.67	93	17.48	9	9.47
BMI												
<18.5	224	2.18	94	1.87	45	2.13	63	2.49	21	3.95	1	1.05
18.5–22.9	3,086	29.97	1,444	28.70	654	30.98	811	32.09	169	31.77	8	8.42
23.0–24.9	2,599	25.24	1,305	25.93	502	23.78	653	25.84	135	25.38	4	4.21
≥25.0	4,176	40.56	2,145	42.63	873	41.35	950	37.59	202	37.97	6	6.32
Unknown/missing	212	2.06	44	0.87	37	1.75	50	1.98	5	0.94	76	80.00
Smoking status												
Never smoked	3,831	37.21	1,909	37.94	791	37.47	935	37.00	185	34.77	11	11.58
Former smoker	4,338	42.13	2,167	43.06	891	42.21	1,017	40.25	236	44.36	27	28.42
Current smoker	1,852	17.99	882	17.53	376	17.81	483	19.11	100	18.80	11	11.58
Unknown/missing	276	2.68	74	1.47	53	2.51	92	3.64	11	2.07	46	48.42
Drinking status												
Not a drinker	3,279	31.84	1,638	32.55	682	32.31	819	32.41	132	24.81	8	8.42
Former drinker	5,112	49.65	2,436	48.41	1,057	50.07	1,280	50.65	304	57.14	35	36.84
Current drinker	1,643	15.96	890	17.69	321	15.21	340	13.45	86	16.17	6	6.32
Unknown/missing	263	2.55	68	1.35	51	2.42	88	3.48	10	1.88	46	48.42
Clinical trial participation												
Yes	377	3.66	256	5.09	71	3.36	46	1.82	2	0.38	2	2.11
No	2,447	23.76	1,092	21.70	502	23.78	692	27.38	124	23.31	37	38.95
Did not receive SACT	7,473	72.57	3,684	73.21	1,538	72.86	1,789	70.80	406	76.32	56	58.95
Follow-up duration, months												
Mean (SE)	27.49 (0.21)		31.12 (0.29)		27.57 (0.44)		22.08 (0.39)		19.15 (0.85)		17.01 (1.71)	
Median (Q1–Q3)	22.67 (9.63–41.89)		25.53 (12.14–47.10)		18.40 (7.84–35.77)		15.05 (5.60–30.16)		10.32 (4.30–31.92)		14.72 (7.18–33.71)	
ECOG PS												
0	3,832	37.21	2,394	47.58	663	31.41	682	26.99	93	17.48	0	0.00
1	1,513	14.69	609	12.10	291	13.78	503	19.91	106	19.92	4	4.21
2	255	2.48	102	2.03	38	1.80	83	3.28	32	6.02	0	0.00
3	38	0.37	6	0.12	3	0.14	17	0.67	12	2.26	0	0.00
4	12	0.12	2	0.04	0	0.00	7	0.28	3	0.56	0	0.00
Unknown/missing	4,647	45.13	1,919	38.14	1,116	52.87	1,235	48.87	286	53.76	91	95.79
BCLC stage												
Stage 0	456	4.43	337	6.70	73	3.46	44	1.74	2	0.38	0	0.00
Stage A	679	6.59	414	8.23	112	5.31	135	5.34	18	3.38	0	0.00
Stage B	180	1.75	99	1.97	41	1.94	36	1.42	4	0.75	0	0.00
Stage C	3,259	31.65	1,644	32.67	610	28.90	852	33.72	145	27.26	8	8.42
Stage D	191	1.85	8	0.16	3	0.14	50	1.98	130	24.44	0	0.00
Unknown/missing	5,532	53.72	2,530	50.28	1,272	60.26	1,410	55.80	233	43.80	87	91.58
CP class												
Class A	7,635	74.15	4,423	87.90	1,809	85.69	1,398	55.32	4	0.75	1	1.05
Class B	1,595	15.49	86	1.71	157	7.44	961	38.03	391	73.50	0	0.00
Class C	146	1.42	0	0.00	0	0.00	26	1.03	120	22.56	0	0.00
Unknown/missing	921	8.94	523	10.39	145	6.87	142	5.62	17	3.20	94	98.95
Disease etiology												
Hepatitis B	6,778	65.82	3,519	69.93	1,371	64.95	1,545	61.14	312	58.65	31	32.63
Hepatitis C	936	9.09	382	7.59	208	9.85	287	11.36	50	9.40	9	9.47
Alcohol liver disease	1,490	14.47	520	10.33	335	15.87	467	18.48	147	27.63	21	22.11
Others	369	3.58	254	5.05	48	2.27	62	2.45	5	0.94	0	0.00
Unknown/missing	1,275	12.38	531	10.55	279	13.22	341	13.49	82	15.41	42	44.21

Table 1 (continued)

Variables	Total		mALBI grade 1		mALBI grade 2a		mALBI grade 2b		mALBI grade 3		Unknown/missing	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
	10,297	100.00	5,032	48.87	2,111	20.50	2,527	24.54	532	5.17	95	0.92
Comorbidities												
Liver cirrhosis	1,463	14.21	694	69.19	271	76.99	399	79.01	98	88.29	1	11.11
Hypertension	481	4.67	246	24.53	86	24.43	121	23.96	20	18.02	8	88.89
Diabetes mellitus	402	3.90	192	19.14	68	19.32	115	22.77	27	24.32	0	0.00
Number of tumors												
1	4,227	41.05	2,216	44.04	906	42.92	920	36.41	179	33.65	6	6.32
2	1,164	11.30	582	11.57	250	11.84	268	10.61	56	10.53	8	8.42
3	367	3.56	173	3.44	85	4.03	83	3.28	26	4.89	0	0.00
4–5	124	1.20	42	0.83	33	1.56	34	1.35	13	2.44	2	2.11
6+	30	0.29	9	0.00	11	0.05	7	0.03	3	0.06	0	0.00
Unknown/missing	4,385	42.59	2,010	39.94	826	39.13	1,215	48.08	255	47.93	79	83.16
Presence of metastasis												
No	9,554	92.78	4,716	93.72	1,957	92.70	2,304	91.18	503	94.55	74	77.89
Yes	743	7.22	316	6.28	154	7.30	223	8.82	29	5.45	21	22.11
AFP, ng/mL												
Mean (SE)	5,776.52 (323.90)		4,208.56 (340.33)		9,182.69 (927.11)		6,919.12 (787.37)		8,470.82 (1,731.25)		26,740.47 (20,578.56)	
Median (Q1–Q3)	22.20 (5.50–435.85)		17.70 (4.80–256.60)		38.61 (8.16–985.06)		31.00 (7.20–654.02)		30.78 (8.35–215.22)		9,194.15 (1,884.63–34,050.00)	
N	10,103	98.12	4,995	99.26	2,090	99.01	2,492	98.61	522	98.12	4	4.21
Unknown/missing	194	1.88	37	0.74	21	0.99	35	1.39	10	1.88	91	95.79
AFP group, ng/mL												
<200	7,143	69.37	3,684	73.21	1,448	68.59	1,649	65.26	362	68.05	0	0.00
≥200	2,960	28.75	1,311	26.05	642	30.41	843	33.36	160	30.08	4	4.21
Unknown/missing	194	1.88	37	0.74	21	0.99	35	1.39	10	1.88	91	95.79

SE, standard error; BMI, body mass index; Q1, first quartile; Q3, third quartile; SACT, systemic anti-cancer therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; mALBI, modified albumin-bilirubin; AFP, alpha fetoprotein.

Table 2. Distributions of initial treatments options

Total	mALBI grade											
	total		grade 1		grade 2a		grade 2b		grade 3		unknown/ missing	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
	10,297	100.00	5,032	48.87	2,111	20.50	2,527	24.54	532	5.17	95	0.92
Initial treatment												
Hepatectomy	1,515	14.71	1,089	21.64	275	13.03	133	5.26	14	2.63	4	4.21
LT	628	6.10	206	4.09	109	5.16	225	8.90	83	15.60	5	5.26
Local ablation therapy	1,294	12.57	793	15.76	225	10.66	233	9.22	37	6.95	6	6.32
Transarterial therapy	5,568	54.07	2,514	49.96	1,243	58.88	1,475	58.37	285	53.57	51	53.68
EBRT	163	1.58	50	0.99	26	1.23	58	2.30	29	5.45	0	0.00
SACT	1,129	10.96	380	7.55	233	11.04	403	15.95	84	15.79	29	30.53

mALBI, modified albumin-bilirubin; LT, liver transplantation; EBRT, external beam radiation therapy; SACT, systemic anti-cancer therapy.

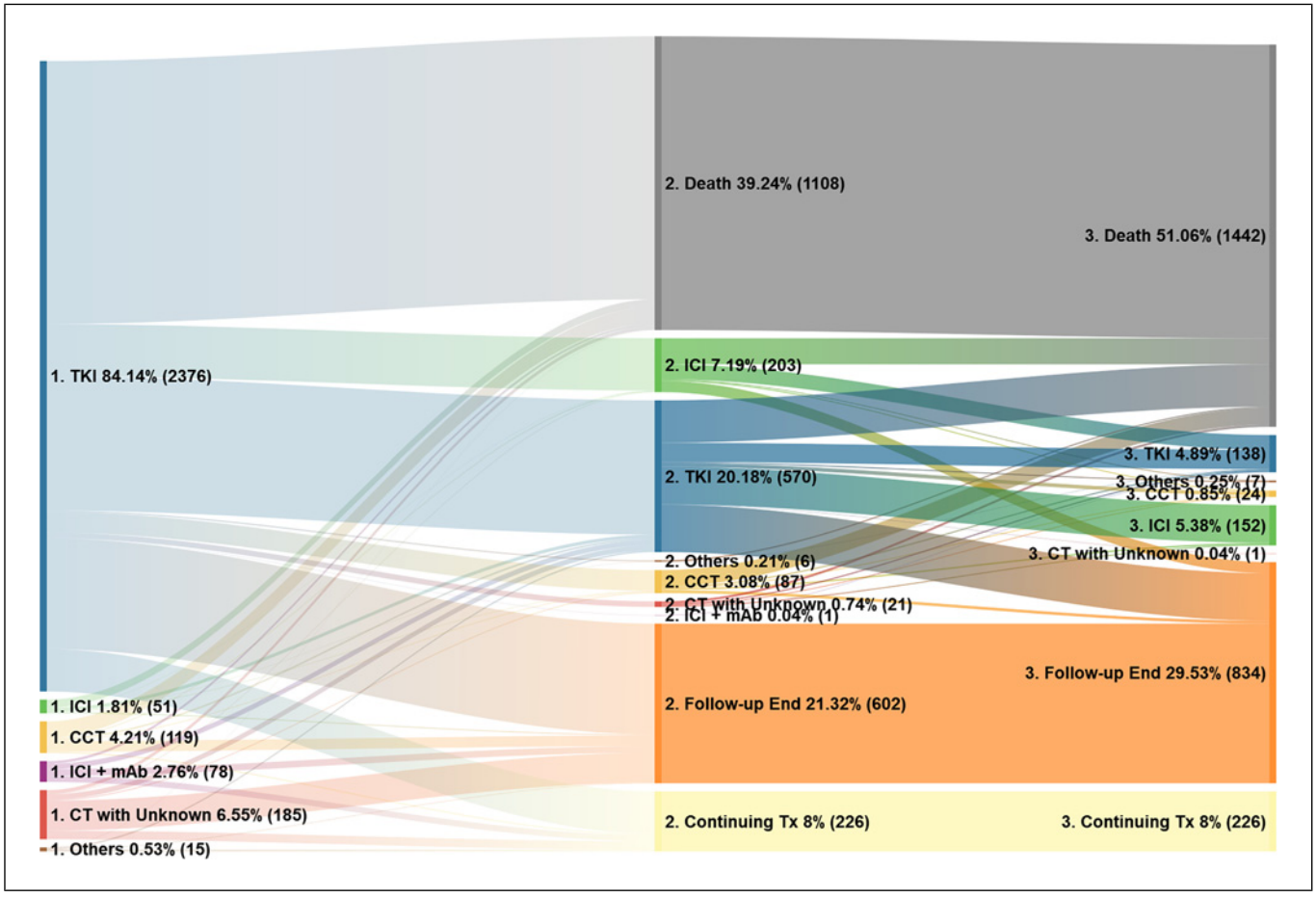
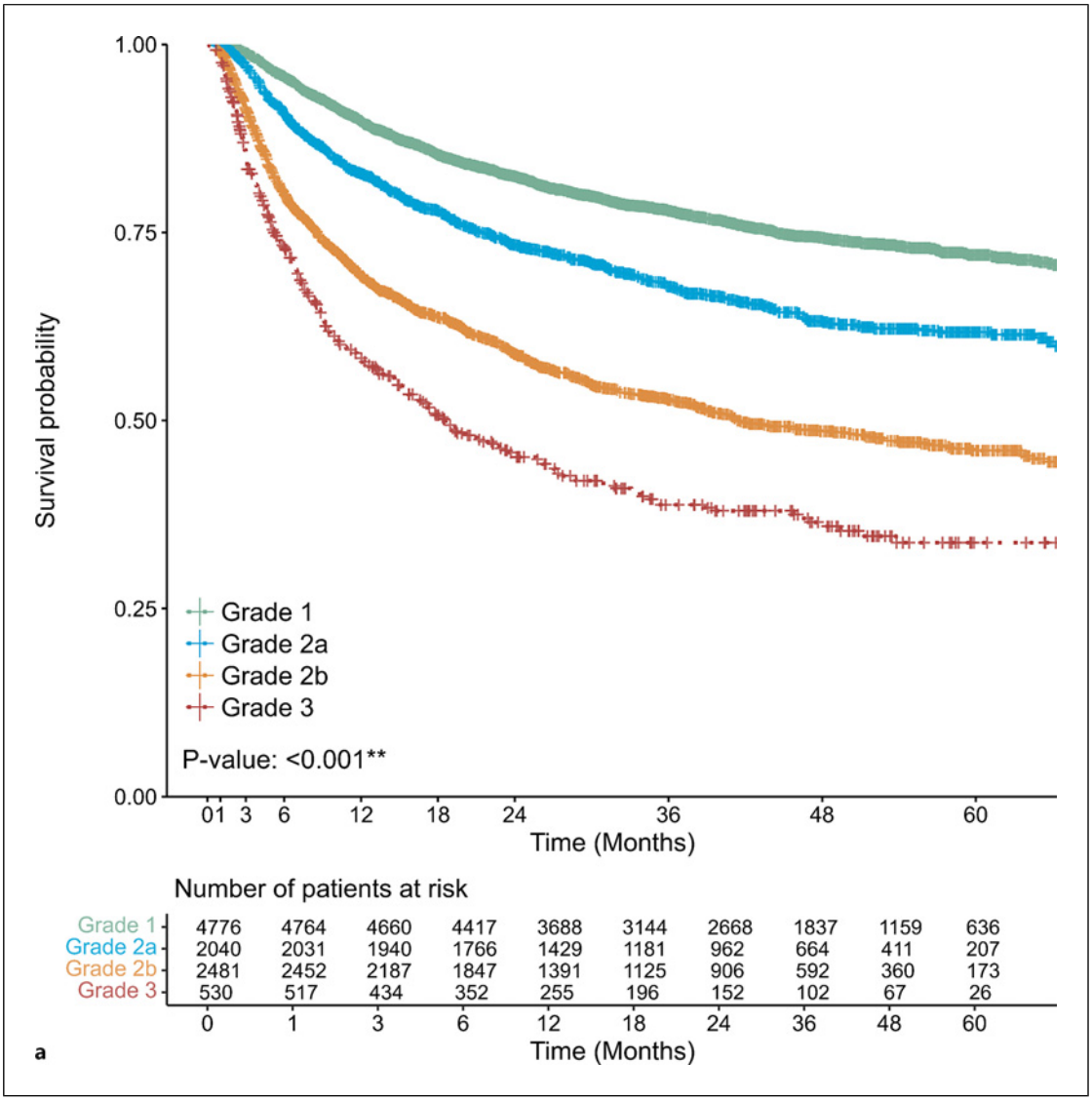


Fig. 3. Sankey diagram for SACT treatment sequence by drug class. TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CCT, cytotoxic chemotherapy; mAb, monoclonal antibody; CT, clinical trials; Tx, treatment.



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and were included into the LINK database, as detailed in Figure 2.

The baseline characteristics of patients at diagnosis within the LINK database are summarized in Table 1. The cohort predominantly comprised male patients (80.76%, n = 8,316), with a median age of 60 years (interquartile range: 53–67). The majority (65.82%) had a disease etiology of hepatitis B, with liver cirrhosis (14.21%), hypertension (4.67%), and diabetes mellitus (3.90%) as prevalent comorbidities. Metastasis was present in 7.22% of patients, and 28.75% had alpha fetoprotein (AFP) levels greater than 200 ng/mL. The average follow-up duration was 27.49 months (standard error: 0.21).

The distribution of CP class was highly skewed, where most patients were classified as CP class A (74.15%), followed by class B (15.49%), with very few in class C (1.42%). The distribution of mALBI grade was relatively more spread out than that of the CP class or traditional ALBI grade, with mALBI grade 1 (48.87%), grade 2a (20.50%), grade 2b (24.54%), and grade 3 (5.17%) at diagnosis.

The variables Eastern Cooperative Oncology Group (ECOG) performance score and number of tumors had a significant portion of missing data, 45.13% and 42.59%, respectively. This led to a high missing rate for the BCLC stage, which is commonly used as a reference staging system in clinical trials.

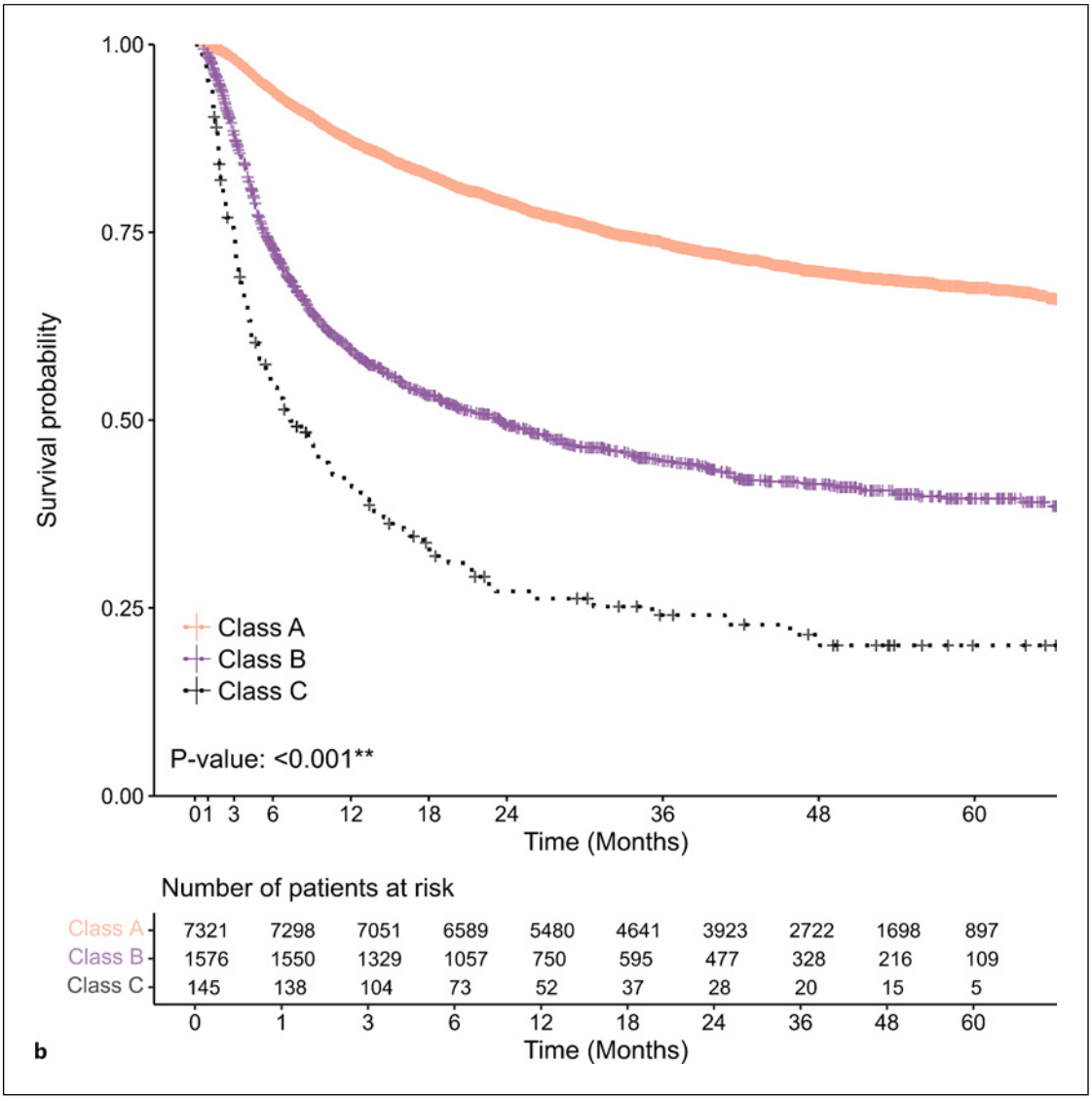


Fig. 4. rwOS of HCC patients by mALBI grade (**a**) and by CP class (**b**). mALBI, modified albumin-bilirubin.

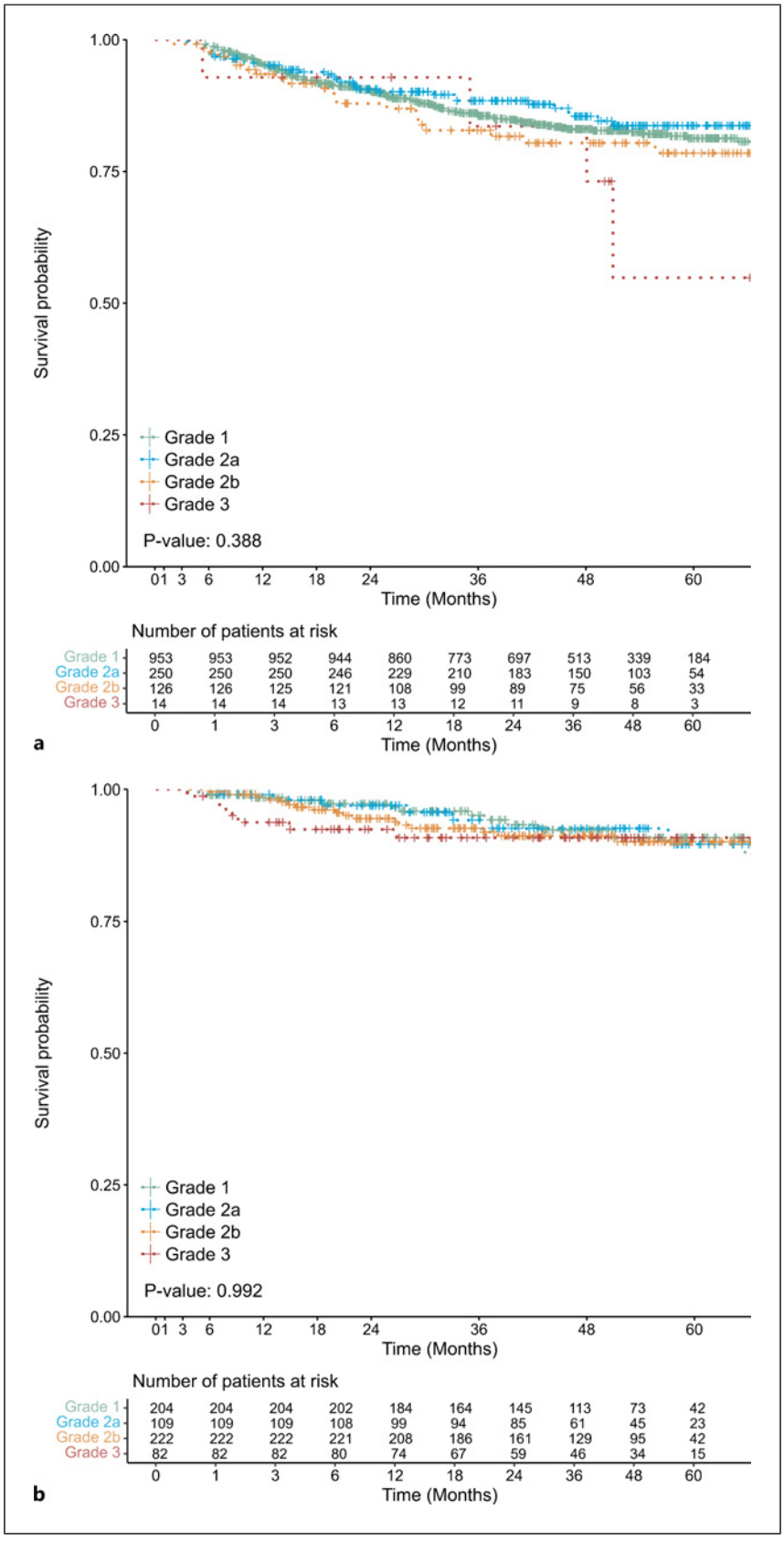
Initial Treatment Options and Systemic Therapy Regimens

Transarterial therapy was identified as the most common initial treatment (54.07%), followed by hepatectomy (14.71%) and local ablation therapy (12.57%), as outlined in Table 2. Transarterial therapy was prevalent across all mALBI grades, with hepatectomy being more common in grades 1 and 2a, while SACT was more frequent in grades 2b and 3.

Among the 2,824 patients who received at least one line of SACT during the follow-up period, tyrosine kinase inhibitors were the preferred regimen class for both LoT1 and LoT2. At LoT1, sorafenib (63.42%) was the most frequently received regimen, followed by lenvatinib (19.12%) and atezolizumab + bevacizumab (1.27%). For LoT2 (n = 888), regorafenib (41.55%) emerged as the leading choice, with nivolumab (18.47%) and sorafenib (17.23%) also commonly selected (Fig. 3).

Real-World Outcome of HCC Patients by mALBI Grades

The median rwOS was not reached for patients classified as mALBI grade 1 and 2a during the follow-up period, whereas patients with mALBI grade 2b and 3



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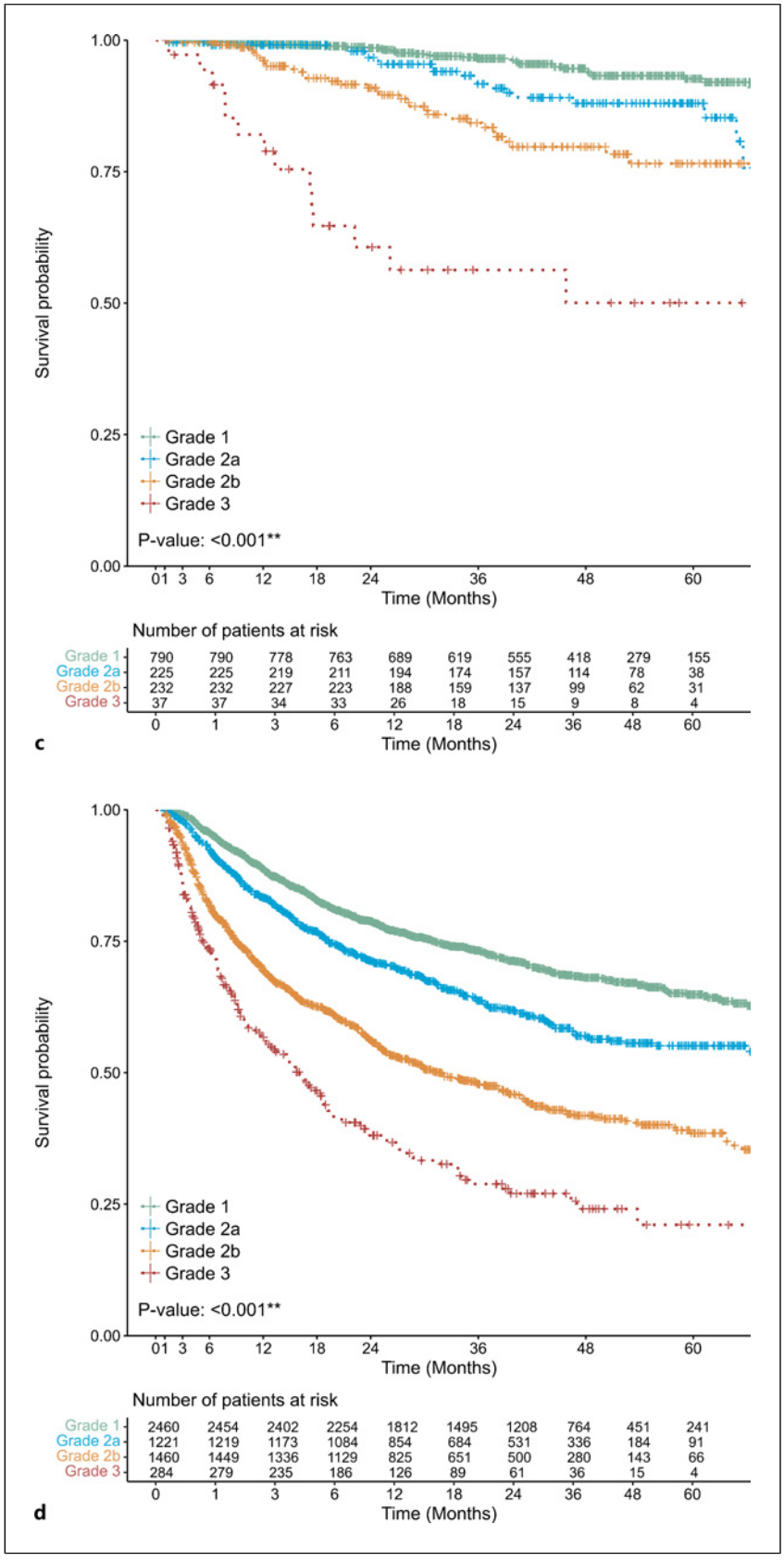

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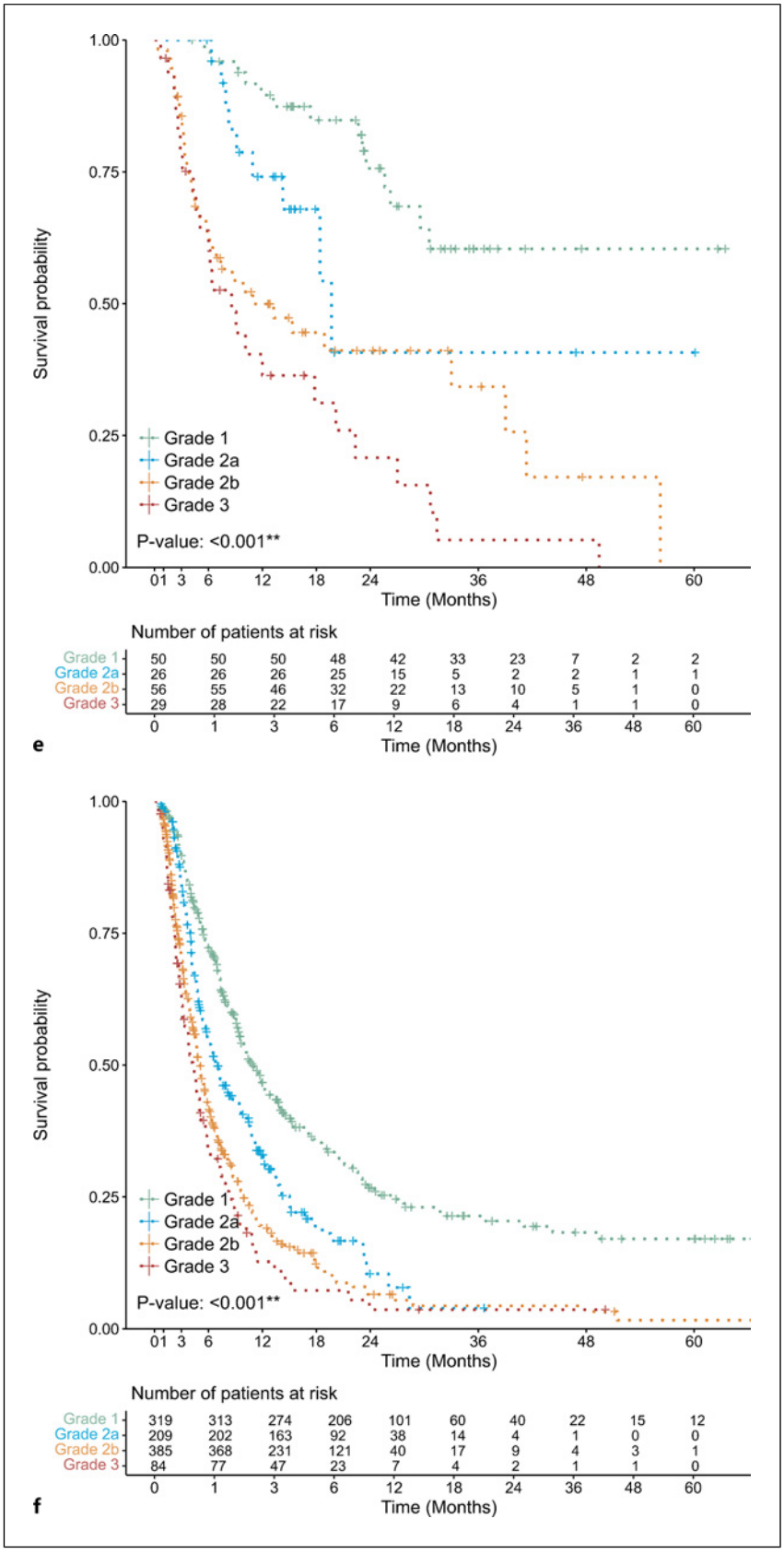

Fig. 5. rwOS of HCC patients by mALBI grade according to initial treatments modality. Surgical interventions include hepatectomy (**a**) and LT (**b**); and non-surgical interventions include local ablation therapy (**c**), transarterial therapy (**d**), EBRT (**e**), and SACT (**f**).

Table 3. mALBI multiple comparison log-rank tests within each initial treatment options

Initial treatment	*p* values for mALBI multiple comparison					
	1 versus 2a	1 versus 2b	1 versus 3	2a versus 2b	2a versus 3	2b versus 3
Hepatectomy	0.470	0.480	0.470	0.470	0.470	0.470
LT	0.960	0.910	0.910	0.910	0.910	0.910
Local ablation therapy	0.002**	<0.001***	<0.001***	0.032*	<0.001***	<0.001***
Transarterial therapy	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
EBRT	0.036*	<0.001***	<0.001***	0.036*	0.005**	0.090
SACT	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***	0.158

mALBI, modified albumin-bilirubin; LT, liver transplantation; EBRT, external beam radiation therapy; SACT, systemic anti-cancer therapy. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

exhibited median rwOS of 41.36 months (95% confidence interval [CI]: 37.75–52.96) and 18.53 months (95% CI: 15.21–25.69), respectively. Significant differences in rwOS were observed across all mALBI grades ($p < 0.001$, Fig. 4), with a significant difference in post hoc pairwise comparisons among all grade combinations, including mALBI 2a versus 2b, using Bonferroni corrections ($p < 0.001$). This indicates a clear segregation and difference in survival outlook between mALBI grade 2a and 2b, which is grouped together as grade 2 in the original ALBI grade system. When categorized by CP class, median rwOS also varied significantly ($p < 0.001$), not reached for class A, 23.46 months for class B (95% CI: 18.96, 28.29), and 7.33 months for class C (95% CI: 5.09, 12.75).

Cumulative rwOS curves indicated no significant differences across mALBI grades for patients undergoing surgical treatments such as hepatectomy or liver transplantation. However, significant disparities were observed in non-surgical interventions, with cumulative rwOS varying by mALBI grade across all treatment groups ($p < 0.001$), as shown in Figure 5. Multiple comparisons using the Benjamini-Hochberg method confirmed significant differences between each grade, except for mALBI grade 2b versus 3 in the EBRT and SACT category (Table 3).

Prognostic Efficacy of ALBI Score Compared to CP Score

The distribution of mALBI score within the CP score revealed a trend: as CP score increased from 5 to 14, there was a corresponding general escalation in mALBI grades (Fig. 6). Notably, within individual CP classes, a wide distribution of mALBI grades was observed, exhibiting considerable heterogeneity. For example, among patients with a CP score of 5, the majority were classified as mALBI grade 1 or 2a (72% and 24%, respectively), with a small fraction (3%) falling into grade 2b. Contrastingly, at CP score of 6, the majority (61%) were classified with grade 2b, with significant decrease in the proportions of grade 1 and 2a to 17% and 22%, respectively. This variability was also evident within CP class B, where a notable proportion of patients had higher mALBI grades, indicating heterogeneous liver function even among patients sharing the same CP classifications.

Time-dependent area under the receiver operating characteristic curve (AUROC) analysis favored the ALBI score's long-term prognostic efficacy for predicting rwOS over the CP score. Initially, the CP score showed a slightly better predictive ability for timepoints up to approximately 12 months (AUROC = 0.73), but the ALBI score's prognostic capability became more pronounced over time, remaining consistent after 15 months post-diagnosis (Fig. 7). The AUROC for the ALBI score consistently remained around 0.71, while the AUROC for the CP score dropped to 0.67 at the 60-month mark.

For the overall patient population, both univariate and multivariate Cox proportional hazards regression model analysis showed that higher CP class was significantly associated with decreased rwOS. Likewise, higher mALBI grades also had a significant association with less favorable survival outcome in both univariate and multivariate Cox proportional regression model analysis (Table 4). Furthermore, within the subgroup of patients with CP class A, both univariate and multivariate Cox proportional hazards regression model analyses indicated that mALBI grade 2a/2b was significantly associated with poor rwOS, suggesting that even within the same CP class A group, patients with different mALBI grades faced significantly different risks in terms of rwOS.

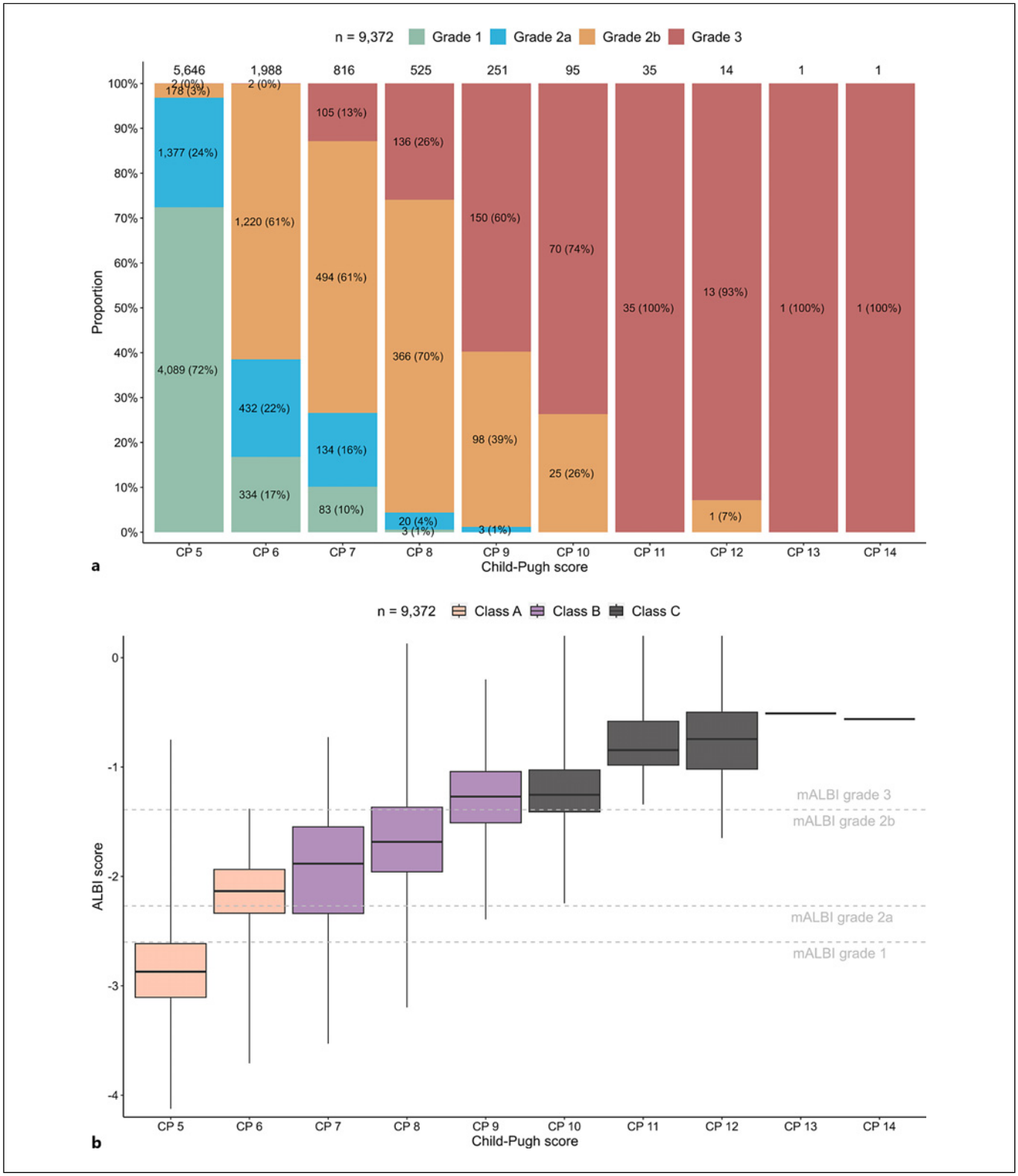

Fig. 6. a Distribution of mALBI grades across CP scores. **b** Side-by-side boxplots of ALBI score distributions within each CP score. mALBI, modified albumin-bilirubin; ALBI, albumin-bilirubin.

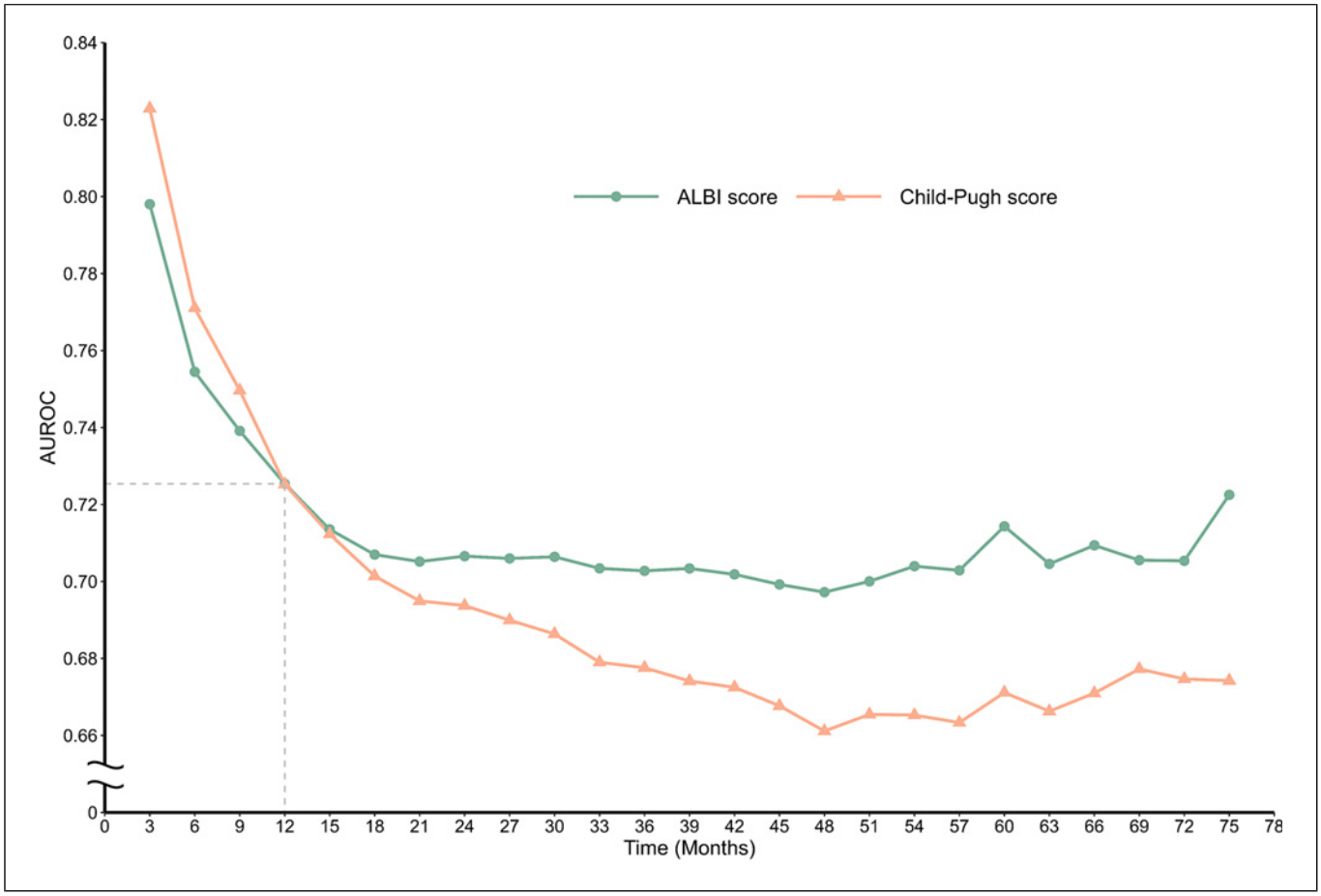

Fig. 7. Time-dependent AUROCs of ALBI score and CP score for predicting rwOS in HCC patients. AUROC, area under the receiver operating characteristic curve; ALBI, albumin-bilirubin.

Discussion

This study leverages a large-scale, multi-center database to generate fast and reliable real-world evidence in HCC patients through systematic data extraction from EHR, providing a comprehensive analysis of HCC management. Our findings not only corroborate the superior long-term prognostic efficacy of the ALBI score over the CP score, as established in previous studies [8, 12, 19], but also introduce new insights into its applicability for liver function assessments in a real-world setting.

The observed heterogeneity in mALBI grades within the same CP score categories emphasizes the intricate complexity of liver function assessment in HCC patients, indicating that the use of CP scores may not be consistent across different contexts and settings. This inconsistency is particularly notable with the subjective grading of ascites and encephalopathy [20], suggesting that mALBI may offer additional granularity that could refine prognostic evaluations and treatment stratifications beyond what CP scores alone can provide. Despite a broader distribution of ALBI grade being more evenly spread out among grade 1 and grade 2 compared to the traditional CP class, it was still practically a dichotomous categorization system with very few patients identified as grade 3, a trend also noted in prior research [12]. The subdivision of grade 2 into subcategories 2a and 2b in mALBI allows for distinguishing between patient groups who otherwise might be homogenously grouped, offering distinct survival outcomes and underscoring the potential of the mALBI score to identify subtler distinctions in liver function that may have significant implications for patient management and outcomes.

As an objective measure, especially in the context of multi-center comparisons, the mALBI score could serve a similar role to that of the Model for End-Stage

Table 4. Univariate and multivariate Cox proportional hazards regression model analyses of CP class and mALBI grade at diagnosis

	Number of events/patients, *n*	Univariate analysis			Multivariate analysis[a]		
		HR	95% CI	*p* value	HR	95% CI	*p* value
(Overall patients)	2,234/7,773						
CP class B	649/1,310	3.10	(2.02, 4.76)	<0.001***	3.03	(2.33, 3.94)	<0.001***
CP class C	89/128	3.87	(1.16, 12.93)	0.028*	4.37	(1.87, 10.23)	<0.001***
Ref: CP class A	1,496/6,335	1.00			1.00		
(Overall patients)	2,234/7,773						
mALBI grade 2a	451/1,604	2.07	(1.84, 2.34)	<0.001***	1.88	(1.66, 2.13)	<0.001***
mALBI grade 2b	804/1,958	3.34	(2.29, 4.85)	<0.001***	3.38	(2.62, 4.36)	<0.001***
mALBI grade 3	232/422	4.67	(2.60, 8.37)	<0.001***	4.93	(3.10, 7.83)	<0.001***
Ref: mALBI grade 1	747/3,789	1.00			1.00		
(CP class A)	1,496/6,335						
mALBI grade 2a	386/1,479	2.09	(1.69, 2.58)	<0.001***	1.77	(1.42, 2.20)	<0.001***
mALBI grade 2b	393/1,137	2.85	(2.30, 3.53)	<0.001***	2.71	(2.18, 3.38)	<0.001***
mALBI grade 3	1/2	2.53	(0.35, 18.03)	0.356	1.75	(0.24, 12.86)	0.585
Ref: mALBI grade 1	716/3,717	1.00			1.00		

HR, hazard ratio; CI, confidence interval; CP, Child-Pugh; mALBI, modified albumin-bilirubin. [a]Covariates including age, sex, BMI, drinking status, smoking status, etiology, metastasis, and AFP group were adjusted. *$p < 0.05$. ***$p < 0.001$.

Liver Disease score used for liver transplant organ allocation [21]. The variation in mALBI grades within CP classes, particularly the notable shift in grade distributions between CP class A and B, advocates for incorporating the ALBI score more systematically in clinical practice to enhance the precision of prognosis and potentially guide more tailored therapeutic approaches.

This is further evidenced by our time-dependent AUROC analysis and the distinctive stratification of HCC patient prognosis across mALBI grades. The time-dependent AUROC analysis indicated that the ALBI score has a better long-term prognostic value than the CP score. This finding aligned with the previous studies where the predictive ability of the ALBI score was initially comparable but superior to that of CP grade at long-term time points [22]. Furthermore, the rwOS curves demonstrated distinctive stratification for the prognosis of HCC patients with each mALBI grade, including grade 2a and 2b, showing significant differences across the mALBI grades. This indicates that the mALBI grade could provide a more detailed assessment of hepatic function and prognosis for HCC patients compared to the ALBI grades [10, 23, 24]. Such findings advocate for the broader adoption of the ALBI grade in clinical settings [25], despite the current Korean reimbursement criteria's reliance on the CP system [26].

Contrary to findings from the Liver Cancer Study Group of Japan [25, 27], our study revealed that the mALBI grade's stratification performance was especially effective in non-curative modality (non-surgical interventions) but not in curative/surgical modality such as hepatectomy or transplantation. This discrepancy might highlight the overriding significance of surgical interventions over liver function grading by mALBI at diagnosis and invite further investigation into the mALBI grading system's role across different HCC management strategies. We also demonstrated the significant retention of ALBI's relevance when comparing multiple modalities simultaneously, maintaining its significance across a broad spectrum of noncurative treatment modalities. This offers novel insights into the prognostic utility of liver function assessments in real-world settings where various treatment modalities coexist, suggesting that the ALBI score is particularly useful in such contexts. The median rwOS was notably longer for patients with lower mALBI grades, highlighting the grade's utility in prognostication. These findings provide a valuable benchmark for comparing the effectiveness of different treatment strategies and feature the potential of mALBI grades in guiding treatment decisions.

Our findings also highlight the LINK database's capability to accurately mirror real-world treatment patterns, disease prognosis, and patient outcomes for HCC. The comprehensive longitudinal cohort dataset, developed through a meticulously organized ETL (extract, transform, load) process, underpins the LINK database's

role as a sustainable research platform, ensuring ongoing data relevance with continuous updates. Significantly, it covers a broad spectrum of treatment options, both surgical and non-surgical, thereby enriching the decision-making process for patient care. The representativeness of the LINK database for HCC patients in South Korea is underscored by its coverage of approximately a quarter (26.72%) of the nation's newly diagnosed cases [28].

We observed that the choice of systemic therapy regimens aligns with clinical practice and reimbursement guidelines in Korea [26, 29] with sorafenib being the predominant first-line treatment for advanced unresectable HCC since 2007 [30]. However, newer treatments like lenvatinib and the combination of atezolizumab and bevacizumab, approved in 2018 and 2020, respectively [31, 32], suggest evolving treatment landscapes. Our database platform is an EHR-integrated patient registries that automate efforts to aggregate updated data on an interval basis [33, 34], which reflects launching of EHR-based registry across multiple institutes. As the present study spans data from 2015 to 2020, it has been iterated to include annual data to reflect newer therapies and warrant further investigation as treatment guidelines continue to change.

Despite these strengths, it is critical to recognize the inherent limitations associated with database studies, such as potential delays in incorporating the latest treatments and capturing out-of-hospital death data. While the LINK network undergoes annual updates, there is typically 1–2 year lag in extracting and integrating new data. Consequently, our current findings might not fully reflect the adoption of newer treatment regimens and may overestimate survival rates due to the absence of records on out-of-hospital deaths.

However, supporting evidence from recent studies using updated regimens suggests that our results remain relevant and robust. For instance, previous studies incorporating relatively recent regimens such as lenvatinib or atezolizumab + bevacizumab have shown similar outcomes to our findings, with a marked decrease in overall survival associated with higher mALBI grades in HCC patients. These studies reported a significant difference in survival outcomes for patients using lenvatinib ($p < 0.001$) [35] and for those using atezolizumab + bevacizumab ($p < 0.001$) [36], thereby validating the utility of the mALBI grade in reflecting patient outcomes across diverse treatment advancements.

Furthermore, database studies are limited to the information recorded in the EHR, meaning actual adherence to prescribed treatments or changes in regimen due to unforeseen adverse events might not be accurately captured or updated in the prescription data. Consequently, this limitation can lead to potential misclassification of LoT in some instances. Despite employing algorithms to categorize SACT treatments into LoTs and to identify patients' initial treatments, it should be noted that not every scenario could be accounted for by these algorithms, leaving room for possible misclassification. Moreover, the heterogeneity across participating centers and the variable completeness of EHR data, as indicated by the presence of high percentages of missingness in certain variables, pose challenges to ensuring data consistency and reliability in interpretation.

In conclusion, the LINK database not only fills a critical gap in real-world HCC research but also serves as a foundational platform for ongoing and future studies aimed at refining treatment strategies and improving patient outcomes in South Korea. By continually updating and expanding its dataset, LINK supports the ongoing refinement of HCC management guidelines, ensuring they remain aligned with the latest evidence and therapeutic advancements. This study, therefore, establishes a solid basis for more nuanced, data-informed decision-making in HCC management, demonstrating the invaluable role of real-world evidence in bridging the gap between clinical research and everyday clinical practice.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Boards of Asan Medical Center (AMC, S2022-0110-0001), Samsung Medical Center (SMC, 2022-01-132), and Severance Hospital (SVC, 4-2022-0010). This study has been granted an exemption from requiring written informed consent by the Institutional Review Boards of Asan Medical Center (AMC, S2022-0110-0001), Samsung Medical Center (SMC, 2022-01-132), and Severance Hospital (SVC, 4-2022-0010).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kyu-Pyo Kim contributed to the conception of the work, design of the work, and interpretation of data for the work.

Kang Mo Kim, Baek-Yeol Ryoo, Mira Kang, Dong Hyun Sinn, and Do Young Kim contributed to design of the work and interpretation of data for the work.

Won-Mook Choi contributed to design of the work and acquisition of data for the work.

Won Chul Cha and DongKyu Kim contributed to the conception of the work.

Myung Ji Goh contributed to design of the work.

Min Ji Lee, Subin Lim, and Kyoungdae Baek contributed to acquisition of data for the work.

Joohyun Kim contributed to design of the work, acquisition of data for the work, analysis of data for the work, and interpretation of data for work.

Eui Jun Choi contributed to acquisition of data for the work and analysis of data for the work.

Doik Lee contributed to interpretation of data for the work.

Jung-Ae Kim and Ki-Hun Kim contributed to conception of the work and interpretation of data for the work.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Access to anonymized patient-level data is restricted to participating site staff who are registered and approved by Institutional Review Boards, and such data will be provided either as encrypted files or within an encrypted system. Aggregated data outputs, however, are available from the authors [Kyu-Pyo Kim, Won Chul Cha, Do Young Kim] upon reasonable request and with permission from Data Review Boards [DFIT@amc.seoul.kr; http://www.e-irb.com; irb@yuhs.ac].

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