

Prognostic value of pretreatment albumin to bilirubin ratio in patients with hepatocellular cancer

A meta-analysis

Yi-Xin Xu, MD, Yi-Bo Wang, MD, Yu-Lin Tan, MD, Cheng Xi, MD, Xue-Zhong Xu, MD*

Abstract

Background: Hepatic function is closely associated with prognosis in patients with hepatocellular cancer (HCC). In this study, a meta-analysis of the published studies was performed to assess the prognostic value of ALBI grade in HCC patients.

Methods: Databases, including PubMed, EMBase, Web of Science, and Cochrane Library were retrieved up to August 2018. The primary outcome was OS and secondary outcome was DFS, the prognostic impact of which was assessed by using hazard ratio (HRs) with corresponding 95% confidence intervals (CIs). The enrolled studies were analyzed by using STATA version 12.0 software.

Results: A total of 22,911 patients with HCC in 32 studies were included. Our results demonstrated that high pretreatment ALBI is associated with poor OS (HR = 1.719, 95%CI: 1.666–1.771, $P = .000$, univariate results; HR = 1.602, 95%CI: 1.470–1.735, $P = .000$, multivariate results) and poor DFS (HR = 1.411, 95%CI: 1.262–1.561, $P = .000$, univariate results; HR = 1.264, 95%CI: 1.042–1.485, $P = .000$, multivariate results). Meanwhile, when the analysis was stratified into subgroups, such as treatment methods, sample size, geographic area, and ALBI grade, the significant correlation in ALBI and poor long-term survival was not altered.

Conclusion: High pretreatment ALBI is closely associated with poor prognosis in HCC, and High ALBI should be treated as an ideal predictor during hepatocellular therapy.

Abbreviations: ALBI = albumin-to-bilirubin ratio, CIs = confidence intervals, DFS = disease-free survival, HCC = hepatocellular cancer, HRs = hazard ratio, OS = overall survival.

Keywords: albumin to bilirubin ratio, hepatic function, hepatocellular cancer, prognostic factor

1. Introduction

Hepatocellular cancer is the fifth most common aggressive malignancies in the world, which leads to the second cancer-related mortality.^[1] The prognosis of hepatocellular patients was assessed according to several factors, such as hepatic function, tumor burden, hepatitis virus type, and performance status. The liver function was mostly defined by Child-Pugh's class, while Barcelona Clinic Liver Cancer staging system was used to provide guidelines for HCC treatment frequently.^[2] Due to the high recurrence and mortality rate, various molecular markers have been reported to show prognostic importance in patients with HCC.^[3] Among them, the ALBI (calculate as $\log_{10} \text{bilirubin} * 0.66 + \text{albumin} * 0.085$) was first proved to be not only a marker to assess

hepatic function but also a prognostic factor to predict long-term survival in HCC patients in 2015.^[4] Different from Child-Pugh's class, ALBI grade only contains two parameters, including albumin and bilirubin. Recently, several studies have confirmed that the ALBI grade successfully predicted the OS and DFS in HCC patients after curative hepatectomy, radiotherapy, transarterial chemo-embolization, and sorafenib.^[5–8]

However, there is still no consensus on the clinical value of ALBI grade. Because of that, the Child-Pugh's class is the only tool to assess the hepatic function. Therefore, we performed this meta-analysis to evaluate the prognostic role of ALBI grade in patients with HCC.

2. Methods

2.1. Literature search strategy

A systematic literature search was performed in PubMed, EMBase, Web of Science, and Cochrane library (up to August 1st, 2018). In each database, the following terms were combined as key words: (hepatocellular or liver) and (tumor or cancer or carcinoma or adenocarcinoma or malignant) and ("albumin to bilirubin ratio" or "albumin/bilirubin" or "albumin to bilirubin" or "ALBI" or "albumin and bilirubin"), as well as ("overall survival" or "disease-free survival" or recurrence or mortality, prognosis or prognostic or predict).

2.2. Inclusion criteria

The inclusion criteria were as follows: (1) patients with hepatocellular carcinoma; (2) prognostic value of ALBI was

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Department of General Surgery, Wujin Hospital Affiliated to Jiangsu University, Changzhou, Jiangsu Province, China.

* Correspondence: Xue-Zhong Xu, Wujin Hospital Affiliated to Jiangsu University, Changzhou, Jiangsu 213002, China (e-mail: xxz197001@sina.com).

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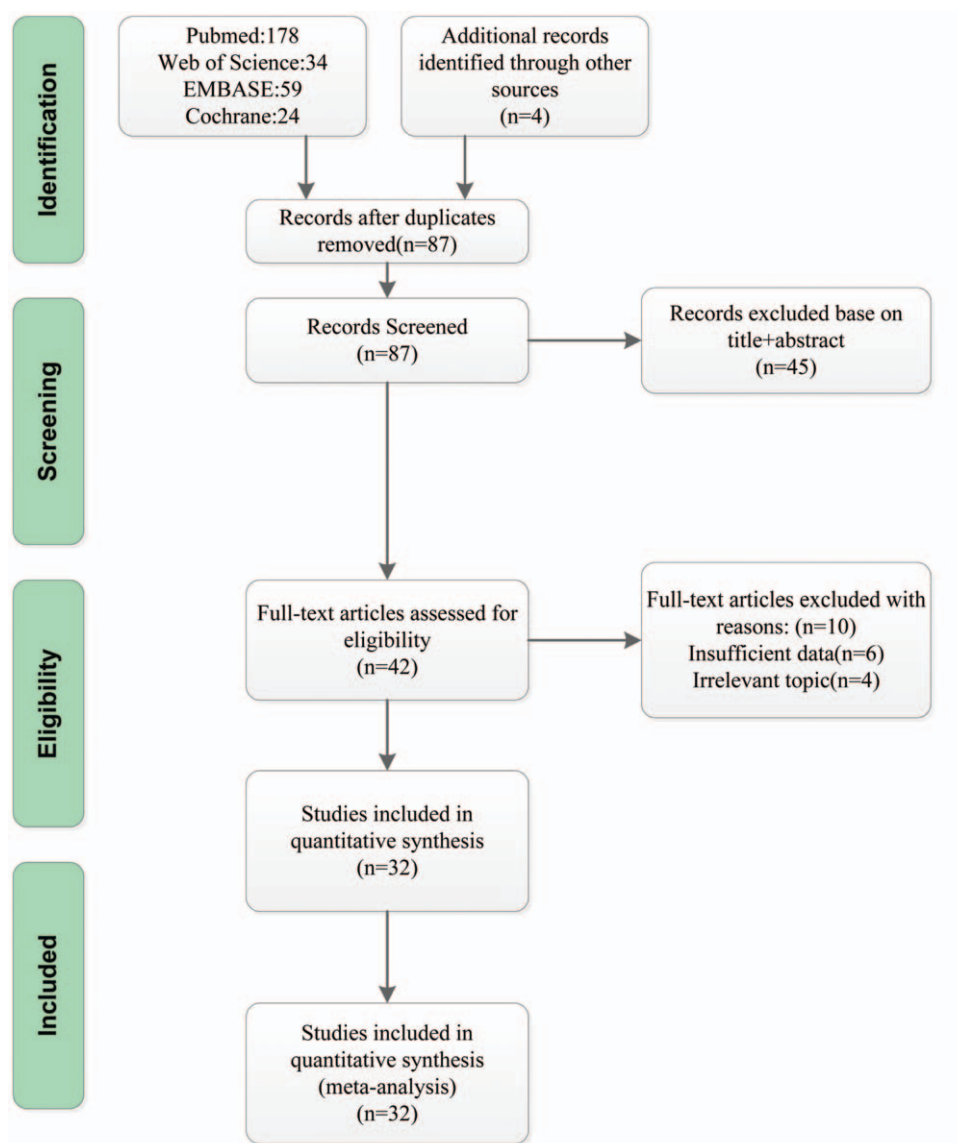


Figure 1. Flow diagram for study selection.

evaluated on overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), mortality or recurrence rate; (3) the survival outcomes were measured by hazard ratio (HRs) with 95% confidence interval (CIs), Kaplan–Meier curve, or data for calculating HR with its corresponding 95%CI; (4) studies were full text and published in English. The studies would be excluded if they met the following criteria: (1) case reports, reviews, letters, and comments; (2) studies could not provide sufficient data to calculate the HR with 95%CI; (3) researches were not performed on human beings; (4) non-English publications.

2.3. Data extraction

All the studies were carefully reviewed, and data were extracted from each study, including study ID (first author’s name and publication year), country, sample size, cancer stage, treatment method, survival outcome, analysis model, data source, and follow-up period by two independent researchers. The

inconsistencies between reviewers were resolved by a third investigator through discussion. If studies could only provide Kaplan–Meier curve, the HRs for OS and DFS were extracted from them by using Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>). In this study, we extracted prognostic data as much as possible both from univariate and multivariate analyses.

2.4. Statistical analysis

In this study, we used STATA version 12.0 (Stata Corporation, Collage Station, TX, USA) to perform meta-analysis. HRs with corresponding 95%CI were used to assess the prognostic value of ALBI on OS and DFS in patients with HCC. The heterogeneity between studies was tested by Cochran’s Q and Higgins I^2 statistics. If there was no heterogeneity ($<50\%$, $P > .1$), fixed-effect model would be used. Otherwise, the random-effect model was applied. The high ALBI was closely associated with poor survival outcome when $HR > 1$. Publication bias was measured by Begg’s test and Egger’s test with graph. Normally, the result

Table 1
Characteristics of studies included in the analysis.

Study	Year	Country	Sample size	Median Age	Cancer stage	ALBI grade	Treatment methods	Survival outcome	HR (95%CI) (data source)	Model for HR	Follow-up period (months)
Amisaki M	2018	Japan	133	68	I-III (AJCC)	I-II	Surgery	OS	1.69 (1.09–2.63) (curve) 1.394 (0.523–3.721) (direct)	U M	Median 51.5
Xu QD	2018	China	151	51	0-C (BCLC)	I-III	Surgery	OS	1.552 (0.826–2.914) (direct)	M	Median 33.8 (1–86)
							DFS	1.751 (1.178–2.604) (direct) 1.131 (0.783–1.632) (direct)	U U		
Li C	2018	China	475	51	A (BCLC)	I-II	Surgery	OS	2.035 (1.472–2.811) (direct)	U	Median 36.4
								DFS	1.601 (1.239–2.068) (direct)	U	
Ho CH	2018	China	174	62	B-C (BCLC)	I-II	Radiotherapy	OS	1.41 (1.00–1.99) (direct)	U	Median 21.7
									1.72 (1.20–2.48) (direct)	M	
Murray LJ	2018	Canada	102	69	B-C (BCLC)	I-II	Radiotherapy	OS	1.809 (1.157–2.827) (direct)	U	Median 50.9
									1.79 (1.14–2.80) (direct)	M	
Liao R	2018	China	536	52	A-C (BCLC)	I-III	Surgery	DFS	1.727 (1.217–2.450) (direct)	U	Up to 80
Luo HM	2018	China	785	51	I-III (AJCC)	I-II	Surgery	OS	1.460 (1.184–1.801) (direct)	U	Median 33.9
								DFS	1.324 (1.010–1.592) (direct)	U	
Ho SY	2018	China	645	61	n/a	I-III	Surgery	OS	1.526 (1.231–1.891) (direct)	U	Median 55
									1.439 (1.158–1.790) (direct)	M	
Na SK	2018	Korea	2099	58	I-IV (AJCC)	I-III	Multiple	OS	2 nd vs 1 st : 2.421 (2.084–2.813); 3 rd vs 1 st : 5.136 (4.243–6.217) (direct)	U	Median 16.2
									2 nd vs 1 st : 1.518 (1.285–1.794); 3 rd vs 1 st : 1.764 (1.332–2.337) (direct)	M	
Kim JH	2018	Korea	951	64	C (BCLC)	I-III	Chemotherapy	OS	2 nd vs 1 st : 1.61 (1.25–2.07); 3 rd vs 1 st : 4.3 (2.44–7.57) (direct)	U	Median 36
									2 nd vs 1 st : 1.77 (1.37–2.3); 3 rd vs 1 st : 7.11 (3.98–12.7) (direct)	M	
Gkika E	2018	Germany	40	69	A-C (BCLC)	I-II	Radiotherapy	OS	2 nd vs 1 st : 2.157 (0.790–5.887); 3 rd vs 1 st : 0.941 (0.181–4.901) (direct)	U	Median 14.3
Chen PH	2017	China	887	65	A-C (BCLC)	I-III	Multiple	OS	2 nd vs 1 st : 2.036 (1.690–2.453); 3 rd vs 1 st : 3.486 (2.772–4.383) (direct)	U	Median 11 (3–23)
									2 nd vs 1 st : 1.684 (1.372–2.066); 3 rd vs 1 st : 2.115 (1.560–2.867) (direct)	M	
Yoh T	2017	Japan	207	69	n/a	I-II	Multiple	OS	1.966 (1.349–2.884) (direct)	M	Median 58.8
Dong ZR	2017	China	654	n/a	0-A (BCLC)	I-II	Surgery	OS	2.07 (1.63–2.63) (curve)	U	Up to 80
									1.359 (1.026–1.800) (direct)	M	
									1.341 (1.047–1.718) (curve)	U	
									2.268 (1.227–4.189) (direct)	M	
Hsu HY	2017	China	1935	n/a	n/a	I-II	Multiple	OS	2.309 (1.577–3.383) (direct)	M	Median 41.9
Oh IS	2017	Korea	368	58	n/a	I-II	RFA	OS	2.78 (1.7–4.57) (direct)	U	Median 61.2
									2.32 (1.35–3.99) (direct)	M	
									1.27 (0.96–1.69) (direct)	U	
									1.06 (0.79–1.43) (direct)	M	
Lo CH	2017	China	152	64	0-D (BCLC)	I-II	Radiotherapy	OS	2.09 (1.26–3.46) (direct)	U	Medina 10
									1.68 (0.98–2.9) (direct)	M	
Lee PC	2017	China	310	62	0-C (BCLC)	I-III	Multiple	DFS	G1: 2 nd vs 1 st : 2.023 (1.213–3.373); 3 rd vs 1 st : 6.188 (3.412–11.220) (direct)	U	Median 5.8
									3 rd vs 1 st : 3.238 (1.539–6.813) (direct)	M	
									G2: 2 nd vs 1 st : 1.989 (1.155–3.428); 3 rd vs 1 st : 4.946 (2.735–8.944) (direct)	U	
									3 rd vs 1 st : 2.441 (1.155–5.158) (direct)	M	
Ho SY	2017	China	881	68	n/a	I-III	TACE	OS	2 nd vs 1 st : 1.678 (1.421–1.981); 3 rd vs 1 st : 1.501 (1.251–1.801) (direct)	U	Up to 156

(continued)

Table 1
(continued).

Study	Year	Country	Sample size	Median Age	Cancer stage	ALBI grade	Treatment methods	Survival outcome	HR (95%CI) (data source)	Model for HR	Follow-up period (months)
									2 nd vs 1 st : 1.531 (1.285–2.823); 3 rd vs 1 st : 1.525 (0.976–2.382) (direct)	M	
King J	2016	UK	448	68	A-C (BCLC)	I-II	Radiotherapy	OS	1.92 (1.51–2.44) (direct)	U	Up to 48
Li MX	2016	China	491	55	0-B (BCLC)	I-II	Surgery	OS	1.394 (1.146–1.696) (direct)	U	Median 57
Jaruvongvanich V	2018	USA	900	63	0-D (BCLC)	I-III	Multiple	OS	1.371 (1.127–1.668) (direct)	M	
								2 nd vs 1 st : 1.75 (1.45–2.11); 3 rd vs 1 st : 3.5 (2.66–4.61) (direct)	U	Median 19.8	
								DFS	2 nd vs 1 st : 1.34 (1.05–1.72); 3 rd vs 1 st : 2.28 (1.41–3.68) (direct)	U	
Edelin J	2016	UK	905	67	A-D (BCLC)	I-III	Sorafenib	OS	2 nd vs 1 st : 1.55 (1.36–1.78); 3 rd vs 1 st : 4.28 (2.86–6.40) 3 rd vs 2 nd : 1.67 (1.21–2.29) (direct)	U	Up to 96
Wang YY	2016	China	1242	n/a	n/a	I-II	Surgery	OS	1.84 (1.54–2.20) (direct)	U	Up to 60
Ma XL	2016	China	318	n/a	0-A (BCLC)	I-II	Surgery	OS	3.72 (2.34–5.89) (direct)	U	Medina 44
Johnson PJ	2015	UK	1313	n/a	n/a	I-III	Multiple	OS	Japanese: 2 nd vs 1 st : 1.64 (1.46–1.84); 3 rd vs 1 st : 7.79 (6.13–9.90); 3 rd vs 2 nd : 3.61 (2.95–4.43) (direct)	U	Up to 100
								European: 2 nd vs 1 st : 1.85 (1.65–2.06); 3 rd vs 1 st : 5.35 (4.22–6.78); 3 rd vs 2 nd : 1.87 (1.55–2.26) (direct)			
								Chinese: 2 nd vs 1 st : 1.97 (1.71–2.27); 3 rd vs 1 st : 5.48 (4.12–7.28); 3 rd vs 2 nd : 1.81 (1.45–2.26) (direct)			
								US: 2 nd vs 1 st : 1.61 (1.22–2.12); 3 rd vs 1 st : 3.37 (2.28–4.98); 3 rd vs 2 nd : 1.80 (1.30–2.50) (direct)			
Toyota H	2017	Japan	1669	70	0-D (BCLC)	I-II	Multiple	OS	3.32 (2.07–3.71) (direct)	U	Up to 20
Ogasawara S	2015	Japan	89	n/a	n/a	I-II	Sorafenib	OS	1.86 (1.10–3.15)(curve)	U	Median 11.1
Samawi HH	2018	Canada	681	n/a	I-IV	I-III	Radiotherapy	OS	2 nd vs 1 st : 1.54 (1.26–1.89); 3 rd vs 1 st : 3.23 (1.66–6.26); 3 rd vs 2 nd : 1.42 (0.84–2.38) (curve)	U	Up to 125
Pinato DJ	2016	London	386	71	C (BCLC)	I-III	Sorafenib	OS	2 nd vs 1 st : 1.56 (1.06–2.31); 3 rd vs 1 st : 1.99 (1.40–2.84); 3 rd vs 2 nd : 1.65 (1.32–2.06) (curve)		Up to 60
Pinato DJ	2017	London	387	54	A-D (BCLC)	I-III	Multiple	OS	2 nd vs 1 st : 1.96 (1.46–2.65); 3 rd vs 1 st : 3.00 (2.20–4.11); 3 rd vs 2 nd : 1.82 (1.43–2.33) (curve)		Up to 120
Waked I	2017	Egypt	3030	63	n/a	I-III	TACE	OS	2 nd vs 1 st : 1.37 (1.25–1.50); 3 rd vs 1 st : 2.40 (2.05–2.82); 3 rd vs 2 nd : 1.52 (1.33–1.74) (curve)	U	Up to 60

AJCC=American joint committee on cancer, ALBI=albumin-to-bilirubin ratio, BCLC=Barcelona clinic liver cancer, CI=confidence interval, DFS=disease-free survival, HR=hazard ratio, M=multivariate analysis, OS=overall survival, RFA=radiofrequency ablation, TACE=transarterial chemoembolization, U=univariate analysis.

was defined as statistically significant if $P < .05$. The ALBI score was calculated as $\log_{10} \text{bilirubin} * 0.66 + \text{albumin} * 0.085$, and stratified as follows: grade 1: < -2.60 ; grade 2: -2.60 to -1.39 ; and grade 3: > -1.39 .

This is a systematic review and meta-analysis, which does not need to be approved by the institutional review board or Ethics committee.

3. Results

3.1. Study search

A total of 299 articles were identified after searching four databases (PubMed, Embase, Web of Science and Cochrane library) and their reference lists. Eight-seven articles remained after duplicates were removed. Then, 45 articles were removed

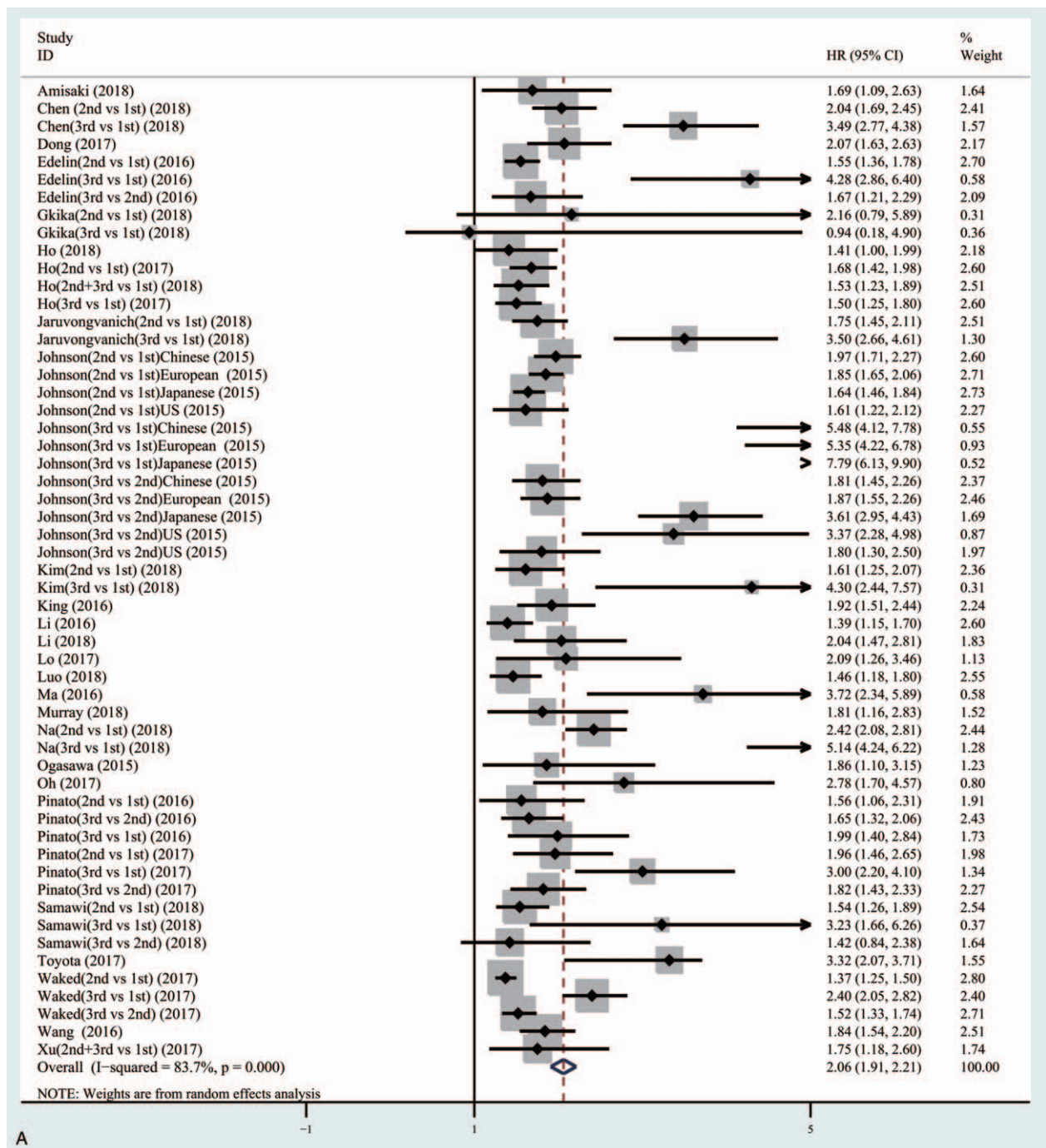


Figure 2. Meta-analysis forest plots for correlation of albumin-to-bilirubin ratio (ALBI) and overall survival (OS) based on univariate analysis results (A) and multivariate analysis results (B).

after reading the title and abstract. After reading the full-text articles, those which could not provide HRs with 95%CI (n=6) and irrelevant topic (n=4) were extracted. Finally, 32 articles were included in this meta-analysis (Fig. 1).

3.2. Cohort characteristics

32 studies were finally included in our analysis.^[4-35] The sample size varied from 40 to 3030. With respect to the study region, 15 studies were performed in China, 5 in United Kingdom, 4 in Japan, 3 in Korea, 2 in Canada, 1 in Germany, 1

in Egypt and 1 in United States. The publication date ranged from 2015 to 2018. Twenty-three studies provided overall survival (OS), 2 provided disease-free survival (DFS) and 7 provided both OS and DFS. Other information including cancer stage, treatment method, and follow-up period were presented in Table 1.

3.3. Meta-analysis on OS

The prognostic value of ALBI on OS was identified by both univariate and multivariate analyses. Because of the severe

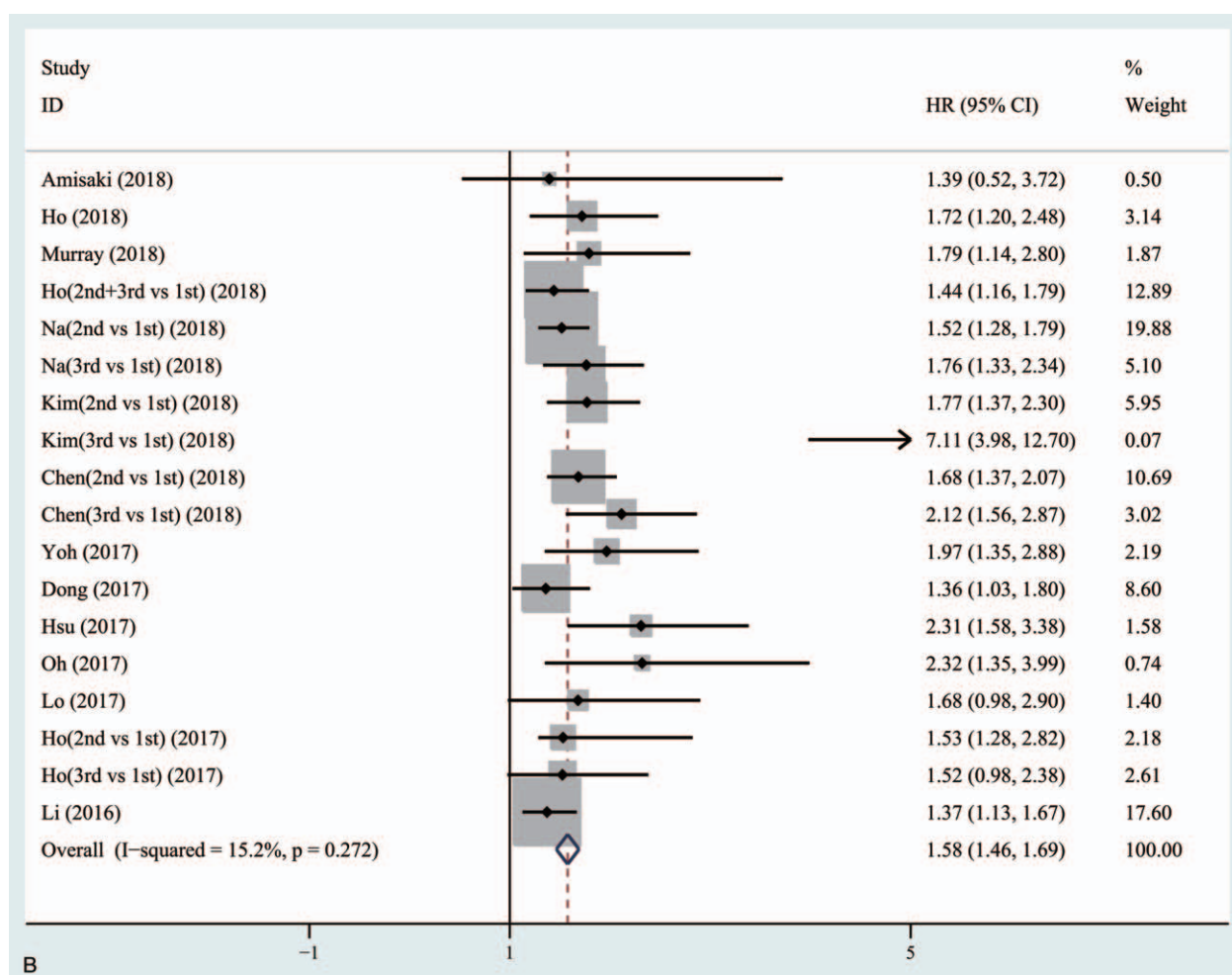


Figure 2 (Continue).

heterogeneity ($I^2 = 83.7\%$, $P = .000$), the random-effect model was used. We found that high ALBI grade was associated with poor OS (HR=2.060, 95%CI: 1.909–2.211, $P = .000$). Besides, the multivariate analysis group showed similar result (HR=1.577, 95%CI: 1.464–1.691, $P = .000$). The fixed-effect model was performed because of the low heterogeneity ($I^2 = 15.2\%$, $P = .272$). These results illustrated that HCC patients with high ALBI grade suffered from poor long-term survival (Fig. 2A and B).

3.4. Meta-analysis on DFS

Nine studies with 4312 HCC patients were included for analysis of disease-free survival (DFS). Due to the low heterogeneity (univariate group: $I^2 = 49.5\%$, $P = .031$; multivariate group: $I^2 = 31.6\%$, $P = .199$), the fixed-effect model was used in both groups. The univariate group (HR=1.411, 95%CI: 1.262–1.561, $P = .000$) and multivariate group (HR=1.264, 95%CI: 1.042–1.485, $P = .000$) showed that HCC patients with high ALBI grade were closely associated with early tumor recurrence (Fig. 3A and B).

3.5. Subgroup meta-analysis according to potential confounding factors

We performed subgroup meta-analysis when severe heterogeneity was found in OS univariate analysis group. The OS univariate

analysis group was stratified into four parameters, including treatment method, geographic area, sample size, and ALBI grade. The subsequent result (high ALBI grade is associated with poor OS) was not altered (Table 2).

3.6. Publication bias

Publication bias was confirmed both in OS univariate analysis group (Egger’s test $P = .015$, Begg’s test $P = .018$) and multivariate analysis group (Egger’s test $P = 0.028$, Begg’s test $P = .081$). Because the numbers of articles were <10 in DFS group, the publication bias was not performed (Fig. 4A and B).

4. Discussion

To the best of our knowledge, this is the first meta-analysis assessing the prognostic value of the ALBI grade in patients with HCC. In this research, 32 studies were conducted to investigate the relationship between ALBI grade and long-term survival in HCC patients. The result consistently indicated that the high ALBI grade was significantly associated with poor survival and early recurrence in patients with HCC.

Hepatic dysfunction was closely associated with high incidence of tumor recurrence and poor long-term survival of patients with HCC.^[36] The liver failure rate was about 63.1% in patients with

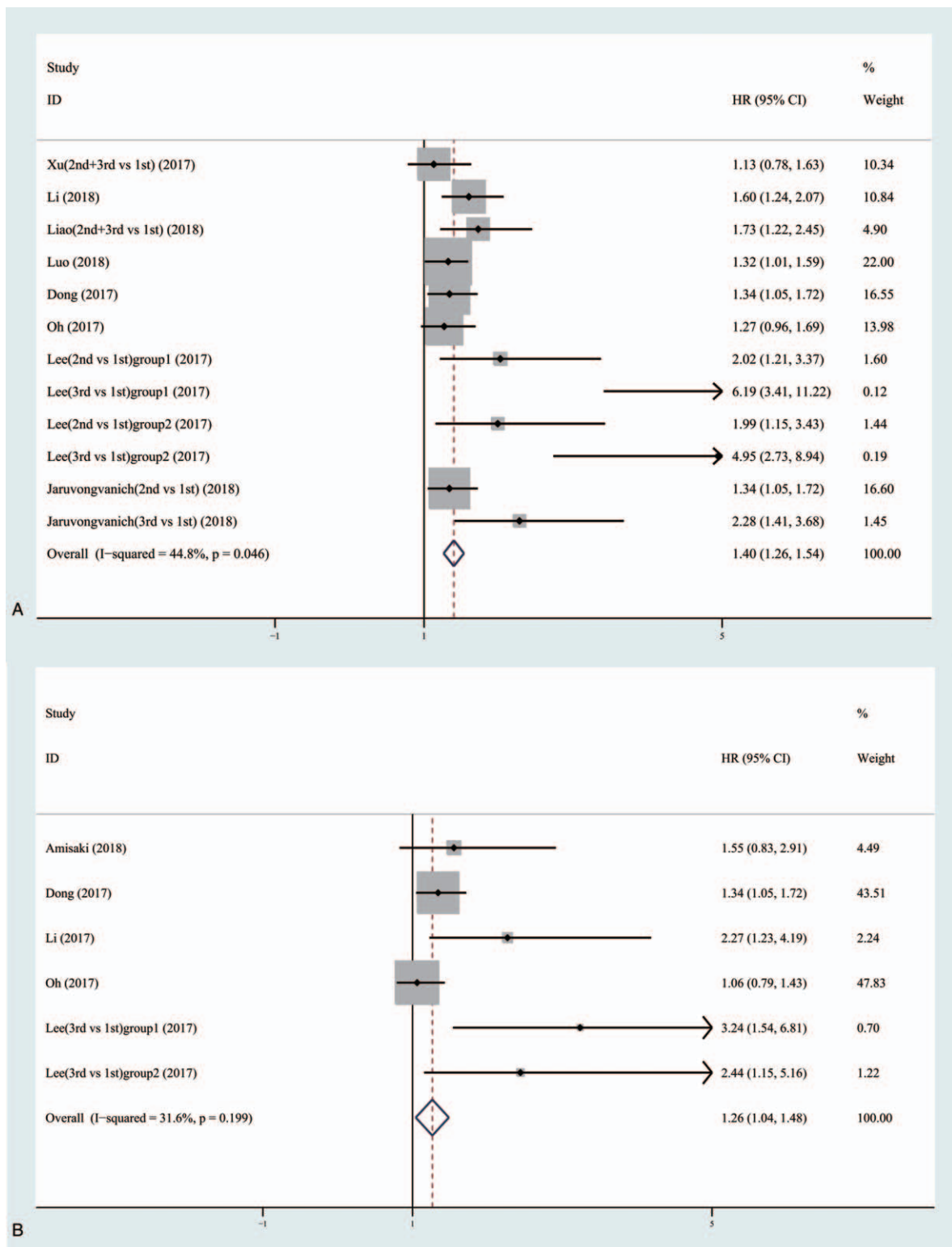


Figure 3. Meta-analysis forest plots for correlation of albumin-to-bilirubin ratio (ALBI) and disease-free survival (DFS) based on univariate analysis results (A) and multivariate analysis results (B).

mortality. Those who had cancer progression without hepatic failure account for a minority. The result clearly indicated the importance of hepatic function for the long-term survival of HCC patients. Therefore, various types of tools using to assess hepatic function were proposed to manage treatment of HCC patients.

The Child-Pugh's class was first proposed by Child in 1964. Five parameters of patients, including general condition, ascites, serum bilirubin, serum albumin, and prothrombin time, were divided into three levels scoring 1, 2, and 3, respectively. The hepatic function was divided into three levels (A, B, and C)

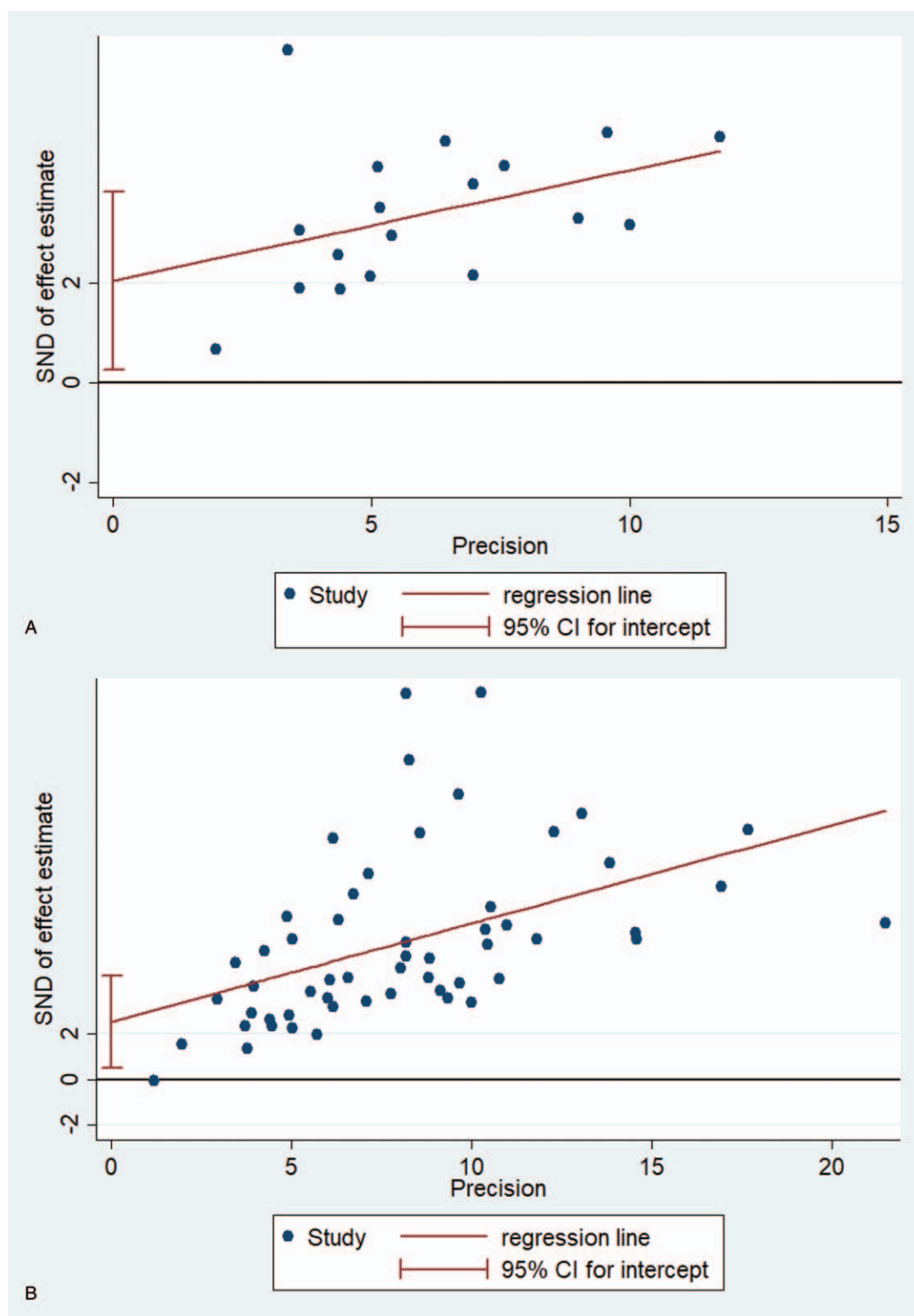


Figure 4. Egger's test for the evaluation of potential publication bias in overall survival (OS) univariate analysis (A) and multivariate analysis (B) groups.

according to the sum score, which indicated different severity of liver damage. However, the general condition of patients was often difficult to measure, so Pugh proposed to replace the general condition with the presence or absence of hepatic encephalopathy. Finally, the Child-Pugh class, most frequently used in clinic, was formed.

The ALBI grade has been proved to be a simple, evidence-based tool to assess the hepatic function of patients. Compared to the Child-Pugh's class, the ALBI grade only involves two items including albumin and bilirubin ($\log_{10}\text{bilirubin} \times 0.66 + \text{albumin} \times 0.085$). As first mentioned by Johnson in 2015,^[4] the ALBI grade has been evaluated for long-term survival and disease

Table 2
Stratified meta-analysis based on overall survival (OS) univariate analysis.

Stratified analysis	No.of studies	Pooled HR (95%CI)	P-value	Heterogeneity	
				I ²	P-value
Treatment methods					
Surgery	11	1.844 (1.583–2.105)	.000	72.6	.000
Radiotherapy	6	1.681 (1.453–1.909)	.000	0.0	.648
Chemotherapy	2	1.747 (1.373–2.121)	.000	86.7	.000
TACE	1	1.588 (1.392–1.784)	.000	0.0	.377
Sorafenib	3	1.714 (1.446–1.982)	.000	42.3	.109
Multiple	5	2.642 (2.311–2.973)	.000	89.9	.000
Sample size					
<500	14	1.815 (1.639–1.990)	.000	29.7	.104
>500	14	2.170 (1.975–2.366)	.000	88.8	.000
Geographic area					
East	19	2.025 (1.789–2.262)	.000	81.1	.000
West	9	2.060 (1.909–2.211)	.000	85.7	.000
ALBI grade					
2nd vs. 1st	27	1.777 (1.651–1.903)	.000	67.4	.000
2nd+3rd vs. 1st	1	1.526 (1.196–1.856)	.000	–	–
3rd vs. 1st	12	3.623 (2.861–4.385)	.000	91.2	.000
3rd vs. 2nd	7	1.849 (1.567–2.131)	.000	73.9	.000

ALBI=albumin-to-bilirubin ratio, TACE=transarterial chemoembolization.

recurrence in HCC patients in recent years. There are many methods to treat hepatic cancer, including curative resection, chemotherapy, transarterial chemoembolization, and radiotherapy.^[6,18,19,30] No matter how treatment methods changed, the ALBI grade system consistently showed significantly prognostic value for OS and DFS in patients with HCC. In the present studies, ALBI grade showed better predicted value and distribution in survival prognosis of patients with HCC than Child-Pugh's class.^[22,31] Our research further confirmed that the ALBI was a good alternative grading system to assess the long-term survival and tumor recurrence in patients with HCC.

There are some limitations which should be declared here. First, the HRs with 95%CI were extracted from articles, because the original data were not available. Second, all of the studies conducted were retrospective. Most of them only provided HRs with 95%CI from univariate analysis and some only provide Kaplan–Meier curve. For that, we had to extract the survival data by using the Engauge Digitizer. Due to these, the heterogeneity in OS univariate group was severe. Third, the publication bias was found both in OS univariate and multivariate analyses groups. Only published articles were included in this meta-analysis, which might be partly responsible for that. Finally, the number of articles to assess the prognostic value of DFS was quite few, which may threaten the reliability of pooled results in that regard. Therefore, further investigations were required to confirm the prognostic value of ALBI grade in patients with HCC.

5. Conclusion

This meta-analysis consistently indicated that the high ALBI grade was significantly associated with poor long-term survival and early tumor recurrence in patients with HCC. ALBI grade can be used as a prognostic biomarker in HCC patients in clinical work. However, the large prospective studies should be performed to identify the predict value of the ALBI grade.

Author contributions

Conceptualization: Yixin Xu, Xuezhong Xu.

Validation: Yulin Tan, Yibo Wang.

Writing – original draft: Cheng Xi.

Writing – review & editing: Xuezhong Xu.

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