Application of the Albumin-Bilirubin Grade in Predicting the Prognosis of Patients With Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. The albumin-bilirubin (ALBI) grade has exhibited an equal excellence with the Child-Pugh (C-P) grade in predicting overall survival (OS) of patients with hepatocellular carcinoma (HCC). However, available published results of the ALBI grade in predicting the prognosis of HCC are still limited. The goal of this study is to perform a systematic review and meta-analysis of the available data to comprehensively evaluate the ALBI grade in predicting OS of patients with HCC.

Methods. Multiple databases were systematically searched for eligible studies. Studies analyzing the relationship between the ALBI grade and survival outcome were identified. Hazard ratio (HR) with 95% confidence interval (CI) was calculated to assess the risk. All statistical analyses were conducted by R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results. A total of 8 studies were enrolled in the meta-analysis. The pooled estimates demonstrated a significant relationship between elevated ALBI grade and inferior OS in patients with HCC (grade 1 vs 2: HR = 1.71, 95% CI: 1.52-1.92; grade 1 vs 3: HR = 3.81, 95% CI: 2.75-5.29.). In addition, the same tendency was observed when performing subgroup analysis, including treatment strategies (surgical resection, transcatheter arterial chemoembolization, radiofrequency ablation, and sorafenib) and study regions (Japan, Europe, China, and the USA). Moreover, the ALBI grade was able to classify patients with C-P grade A into 2 distinct prognostic cohorts—ALBI grade 1 and ALBI grade 2—with distinguishing survival outcomes (surgical resection: grade 1 vs 2: HR = 1.74, 95% CI: 1.55-2.06, $P < .001$; sorafenib: grade 1 vs 2: HR = 1.54, 95% CI: 1.30-1.82, $P < .001$).

Conclusion. The ALBI grade has the potency of becoming an independent prognostic factor in patients with HCC. More well-designed studies should be performed to evaluate the ALBI grade as a complementary prognostic tool to current staging systems in routine clinical practice.

HEPATOCELLULAR carcinoma (HCC) has been ranked as the sixth most common malignancy and the second leading cause of cancer death on a global scale [1]. In contrast to most solid tumors, the prognosis of HCC is influenced by several factors, including tumor stage, underlying liver function, and performance status. Conventionally, liver function is graded according to the Child-Pugh (C-P) grade, which was originally established to assess the prognosis in patients with cirrhosis and portal hypertension undergoing surgery for variceal bleeding [2,3]. While having been widely adopted, the C-P grade still has

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limitations in predicting the prognosis of HCC. In fact, a large number of patients with HCC do not have cirrhosis but rather a range of liver pathology from mild abnormalities to advanced fibrosis [4]. In addition, some of the variables considered in the C-P grade (eg, ascites and serum albumin level) are often interrelated, and the grading of ascites and encephalopathy can be highly subjective [5]. In addition, owing to the arbitrary cutoff points for objective laboratory variables including albumin and bilirubin, patients with bilirubin of 55 μM who have a better prognosis are classified equally as those with a bilirubin of 250 μM, which is the similar situation in which the C-P grade does not differentiate the prognosis between patients with an albumin of 17 g/L versus 25 g/L, leading to the so-called "ceiling effects" and "floor effects" [6,7]. As a result, the accuracy of the C-P grade in prognostication has been limited [8]. Moreover, it has been commonly recognized that the C-P grade fails to offer a wide degree of discrimination among patients with HCC, the majority of whom fall into the C-P grade A. However, since the level of liver function has always been related to the prognosis of HCC, the C-P grade has become widely used in clinical trials and staging systems, despite the fact that establishment of this grading system was solely based on several dichotomous variables without formal statistical grounding.

Recently, a new model based solely on albumin and bilirubin, known as "albumin-bilirubin (ALBI) grade," has been adopted for assessing liver function in patients with HCC [9]. This model is composed of a simple formula involving only albumin and bilirubin, which can stratify patients with HCC into 3 prognostic groups: ALBI score $\leq$ -2.60 (ALBI grade 1), -2.60 to -1.39 (ALBI grade 2), and ALBI score $\geq$ -1.39 (ALBI grade 3). According to the previous study [9], the ALBI grade exhibited an equal excellence with the C-P grade in predicting overall survival (OS) of patients with HCC from different geographic and etiologic populations. Owing to fact that the available published results of the ALBI grade in predicting the prognosis of HCC are still limited, the goal of the current study is to perform a systematic review and meta-analysis of the available data to comprehensively evaluate the value of the ALBI grade in predicting OS of patients with HCC.

METHOD

Search Strategy

We identified literature published up to September 31, 2018, by searching the following databases: MEDLINE, EMBASE, Cochrane Library, Web of Science, ChinaInfo, and Chinese National Knowledge Infrastructure. Terms used in our search involved "albumin-bilirubin grade," "prognosis," and "hepatocellular carcinoma." In addition, a manual search in published articles was conducted to identify additional relevant articles. After removing duplicate publications, 2 reviewers (Liao and Xu) independently assessed the results by checking the titles and abstracts. Studies associated with the topic were considered for further full-text assessment. Meanwhile, the references listed in all reviewed articles were also screened to identify additional related articles. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart was adopted to depict the study selection.

Study Selection

Studies included fulfilled the following criteria: diagnosis of HCC was based on pathological examination or the current ongoing clinical guidelines and data of OS were presented separately in each ALBI grade. Once overlapping populations existed among the studies included, only the one with higher confidence was involved for further analysis. The excluded studies were abstracts, letters, editorials, expert opinions, reviews, case reports, and articles without sufficient reported data for analysis. The quality of the observational studies included were reviewed independently by 2 authors (Xu and Wu) and validated by a third (Lu), with discrepancies resolved by a consensus decision.

Data Extraction

A standardized data-extraction table was adopted to extract data from each study. The following information was extracted from each article: first author's last name, year of publication, accrual period, collaboration of study, regions, age, sex, sample size, etiology of liver disease, ALBI grade, treatment strategy, clinicopathological features, and hazard ratios (HRs) with 95% confidence interval (95% CI). In addition, the qualities of the studies included were assessed by the Newcastle-Ottawa scale. All the data were independently checked by 2 investigators (Xu and Wu). Any disagreements were resolved by consensus or by consultation with a third reviewer (Yang).

Statistical Analysis

HRs for OS were either directly extracted form studies or reconstructed by the using relevant data or Kaplan-Meier curves in the included articles by using the methods claimed by Parmar et al and Tierney et al [10,11]. HRs from multivariable analysis was preferred for they are more reliable than those from univariable analysis, which was followed by those extracted from Kaplan-Meier curves. Fixed-effects models were used to pool the rate estimate when heterogeneity among studies was considered statistically insignificant. Otherwise, the random-effects model was applied to integrate the results. The standard Cochran's Q test with a significance level of $\alpha = 0.10$ was used to identify heterogeneity between these studies. We also examined heterogeneity with the I^2 statistic, which quantifies inconsistency across studies to assess the impact of meta-analysis heterogeneity. An I^2 statistic of 50% or more indicates a considerable level of heterogeneity. Publication bias was detected by using the Egger's tests. "Trim and fill" analysis was additionally conducted once the publication bias was identified [12]. All statistical tests were 2 sided, with a P value $< .05$ considered to be statistically significant. R version 3.3.1 (The R Foundation for Statistical Computing, Parametric Technology Corporation, Vienna, Austria) was employed to conduct all statistical analysis.

RESULTS

Search Results

A total of 1168 articles were identified, and 253 duplicates were removed during the initial search (Fig 1). After screening the titles and abstracts, 17 articles were further assessed for eligibility. Subsequently, 9 of these records were

excluded from our study due to their insufficient data for us to generate the estimated HRs. Finally, a total of 8 studies were involved [9,13-19]. The characteristics of these 8 studies are described in Table 1.

ALBI Grade and Overall Survival

All the studies included presented with data stratifying time of overall survival regarding to the ALBI grades. It was noticeable that there were overlapping study populations among the study of Johnson et al and of Toyoda et al [9,18]. Considering that both of these studies were multicenter studies covering regions around the world, overlapping study populations from the one with higher confidence was included, while the other was excluded according to the criteria we set. Finally, all the study populations reported by Toyoda et al were included for further analysis, while the study population from the USA in the study of Johnson et al was also involved for pooled analysis. A significant relationship between elevated pretreatment ALBI grades and inferior OS with high heterogeneity was demonstrated in Fig 2 (grade 1 vs 2: HR = 1.71, 95% CI: 1.52-1.92, $P < .001$, $I^2 = 75.40\%$, P value of Q test for heterogeneity (Ph) < .001; grade 1 vs 3: HR = 3.81, 95% CI: 2.75-5.29, $P < .001$, $I^2 = 88.70\%$, Ph < .001.).

Subgroup analysis was performed according to the treatment strategies (Fig 3 and Table 2) and study regions (Fig 4 and Table 2). There was a tendency that the elevated ALBI grade turned to inferior OS in these subgroups.

ALBI Grade Within Child-Pugh A

According to the previous study, the ALBI grade was able to classify patients with C-P grade A into 2 distinct prognostic cohorts—ALBI grade 1 and ALBI grade 2 [9]. In the current study, 5 of the included studies identified these 2 prognostic categories among C-P grade A patients [12,15-18]. Distinguishing survival outcome was observed when comparing these 2 groups of patients. (surgical resection: grade 1 vs 2: HR = 1.74, 95% CI: 1.55-2.06, $P < .001$; sorafenib: grade 1 vs 2: HR = 1.54, 95% CI: 1.30-1.82, $P < .001$; Fig 5 and Table 2).

Sensitivity Analysis

In order to reveal the influence of the individual data on our results, every single study involved in our work was deleted each time to perform a sensitivity analysis. Fortunately, no significant deviation was detected among these studies.

Publication Bias

In the current study, the Begg's funnel plot was used for detecting the risk of publication bias. Whilst substantial publication bias was detected in the Begg's test in pooled estimates for OS between ALBI grades 1 and 2, no obvious bias was observed between ALBI grades 1 and 3. Then the "trim and fill" analysis was performed, and the results showed that at least 2 relevant studies concerning OS between ALBI grades 1 and 2 were unpublished. Fortunately, the strength of our pooled results was upheld by the filled

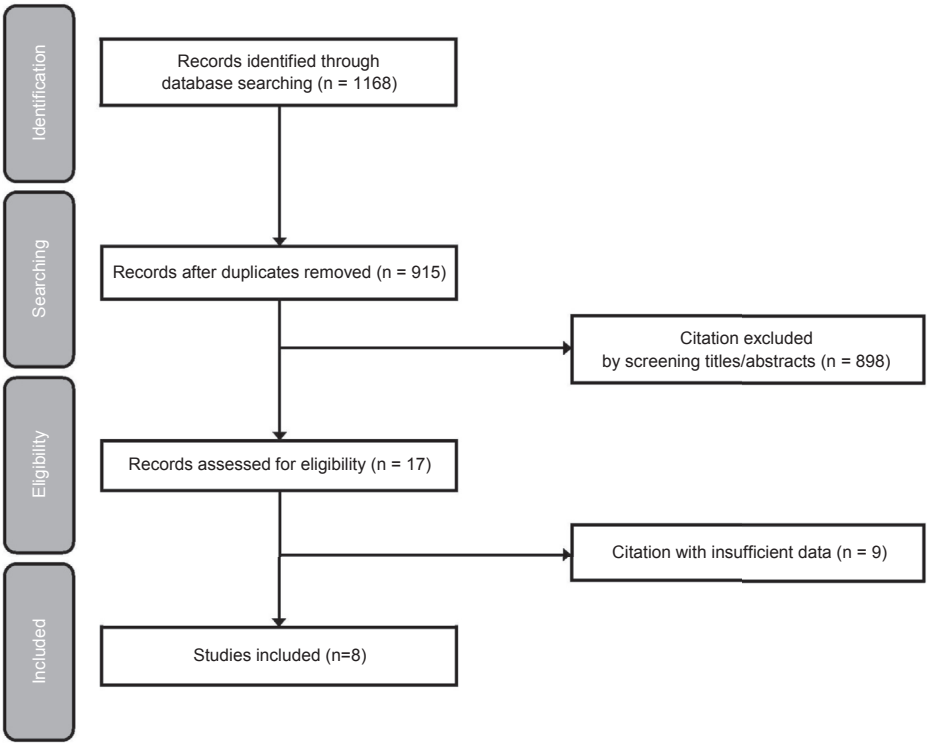

Fig 1. Trial identification, inclusion, and exclusion.

Table 1. Baseline Characteristics of Studies Included

Main Characteristics of the Studies Included in the Meta-Analysis								
Author, year	Johnson et al 2014	Pinato et al 2016	Edeline et al 2016	Liu et al 2016	Wang et al 2016	Ma et al 2016	Toyoda et al 2016	Li et al 2016
Accrual period (y)	24 (1990-2014)	24 (1989-2013)	11 (2004-2014)	12 (2002-2014)	6 (2007-2013)	1 (2012-2013)	20 (1994-2014)	7 (2000-2007)
Collaboration	multicenter	multicenter	multicenter	single center	single center	single center	multicenter	single center
Region	Europe, Asia, USA	Europe, Asia, USA	Europe	Taiwan	Mainland China	Mainland China	Europe, Asia	Mainland China
Age	63 ± 11.5	NA	67 (17-89)	65 (55-75)	NA	NA	63 ± 10.4	54.5 ± 11.2
Number of patients								
Total	8568	2426	1019	3182	1242	318	2559	491
Male*	6604	1866	810	2440	1072	261	1955	435
Etiology of liver disease*								
Viral	NA	1611	245	2554	NA	NA	1893	438
Nonviral	NA	746	603	152	NA	NA	NA	NA
Noncharacterized	NA	69	258	476	NA	NA	NA	NA
Albumin (g/L)*	NA	NA	37 (17-61)	37 ± 6	41.0 ± 4.4	NA	NA	41.3 ± 4.6
Bilirubin (μmol/L)*	NA	NA	15 (3-436)	25.6 ± 46.2	12.3 (2.7-66.8)	NA	NA	16.0 ± 7.3
Treatment	SR, Chem	SR, TACE, Chem	Chem	SR, TACE, RFA, Chem, LT	SR	SR	SR, RFA, LT	SR
ALBI grade*								
1	2441	569	327	1199	850	226	74	327
2	4338	1617	574	1670	390	92	15	164
3	812	240	61	313	2	0	0	0
Child-Pugh grade*								
A	5633	1639	722	2324	1189	304	2079	491
B	1730	600	NA	702	53	NA	360	0
C	468	63	NA	156	0	NA	81	0
BCLC								
0-A	NA	809	120	1001	731	409	NA	409
B	NA	1169	178	503	219	82	NA	82
C	NA	448	711	1282	292	0	NA	0
D	NA	0	10	396	0	0	NA	0
Number of lesions*								
Single	NA	NA	NA	NA	NA	297	1776	414
Multiple	NA	NA	NA	NA	NA	21	689	NA
Macroscopic vascular invasion*	1794	NA	NA	806	NA	214	124	51
Extrahepatic metastasis*	NA	NA	338	295	NA	NA	NA	NA
Survival outcome	OS	OS	OS	OS	OS	OS	OS	OS
HR extracting	E(U)	R(M)	E(U)	E(U)	E(U)	E(U)	R(M)	E(U)
NOS	7	7	6	6	7	5	6	5

Data are number of patients, mean ± standard deviation, median (range), or as otherwise indicated.

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; Chem, chemotherapy; E(U), estimated(univariate); HR, hazard ratio; LT, liver transplantation; NA, not available; NOS, Newcastle-Ottawa Scale; OS, overall survival; RFA, radiofrequency ablation; R(M), reported(multivariate); SR, surgical resection; TACE, transcatheter arterial chemoembolization.

*With available data.

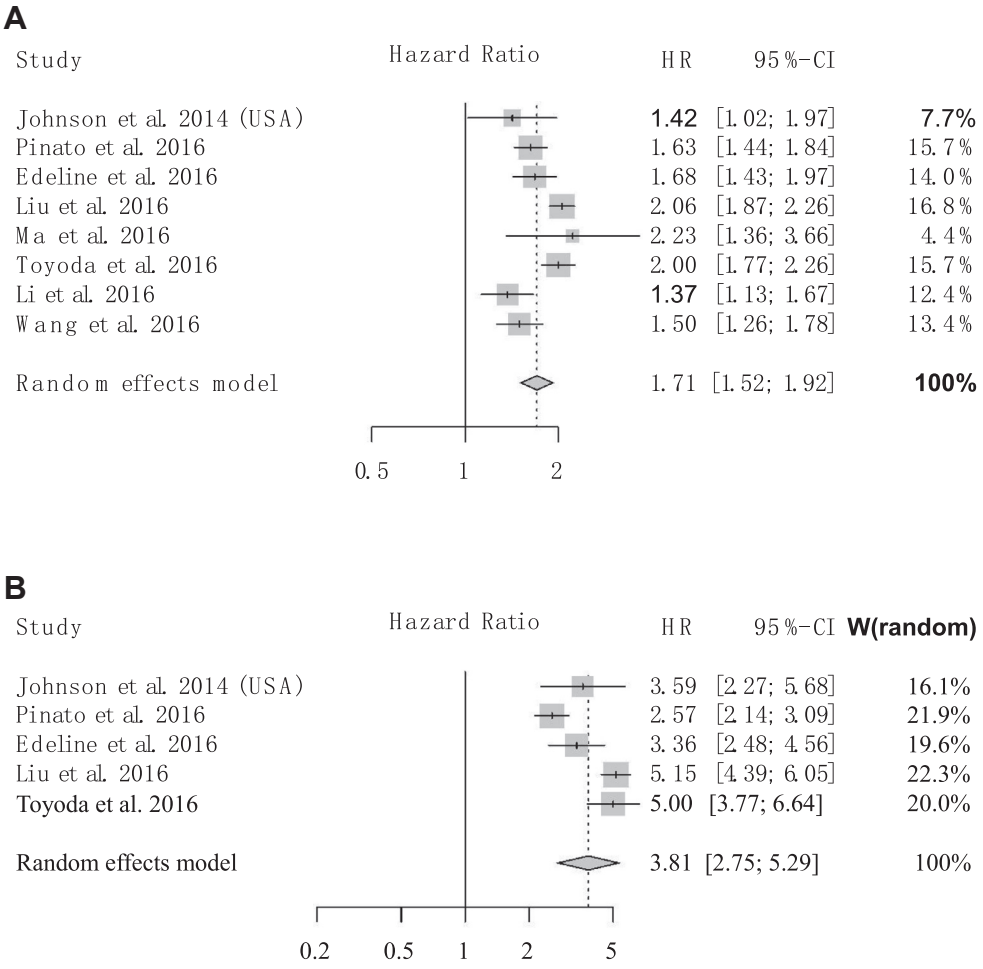

Fig 2. Hazard ratio for the association between elevated ALBI grade and overall survival in patients with hepatocellular carcinoma. **(A)** ALBI grade 1 vs 2; **(B)** ALBI grade 1 vs 3.

meta-analysis (HR = 1.81, 95% CI: 1.61-2.04, $P < .001$, $I^2 = 77.90\%$, Ph < .001; Fig 6).

DISCUSSION

At this time, numerous staging systems on HCC have been compared and reviewed, among which the most widely recognized is the Barcelona Clinic Liver Cancer system (BCLC) [20,21]. This system links tumor stage, performance status or cancer-related symptoms, and liver function to a current evidence-based treatment algorithm based on the results of randomized control trials and cohort studies. The BCLC system can provide physicians with guidance for treatment strategies and help evaluating the condition of patients during clinical trials. What should be highlighted is that the grading of liver function, which is a key component of the BCLC staging system, is assessed by the C-P grade. Thus, the limitations of the C-P grade we mentioned above became the incentive for the establishment of the ALBI grade by Johnson et al [9]. To our knowledge, the current study we conducted is the first meta-analysis to evaluate the ALBI grade on predicting the prognosis of patients with HCC. The pooled estimate of 8 studies from various regions across the world shows that elevated ALBI grade resulted in inferior survival outcome in these participants. Subgroup analyses stratified by treatment, regions, and patients within C-P grade A further validated the significant relationship between the ALBI grade and OS.

Besides the tumor itself, underlying liver function is another important factor affecting survival in patients with HCC [22,23]. In the current study, the ALBI grade stratifies patients undergoing the same treatment into different liver function risk categories, including ALBI grades 1, 2, and 3. The results show that patients with ALBI grade 1 had a higher OS rate than those with ALBI grade 2 after different curative treatments, including surgical resection, transcatheter arterial chemoembolization, radiofrequency ablation, and sorafenib. However, high heterogeneity was observed when comparing OS in patients with ALBI grades 1 and 3 ($I^2 = 88.70\%$, Ph < .001, Table 2). According the

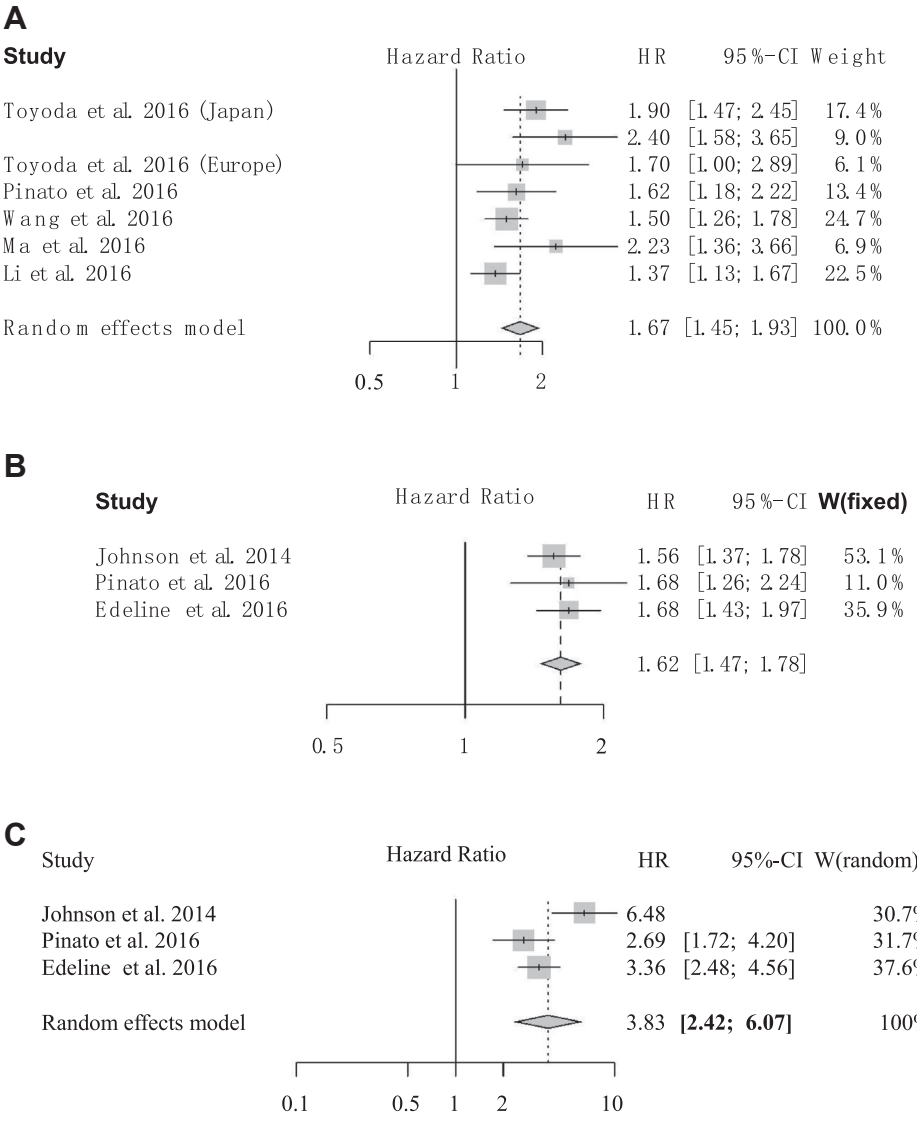

Fig 3. Hazard ratio for the association between elevated ALBI grade and overall survival in patients receiving different treatments. **(A)** ALBI grade 1 vs 2 in patients treated with surgical resection; **(B)** ALBI grade 1 vs 2 in patients treated with sorafenib; **(C)** ALBI grade 1 vs 3 in patients treated with sorafenib.

results of Wang and co-workers [16], the incidence and severity of post-hepatectomy liver failure (PHLF) would increase with a higher ALBI grade, thus affecting the survival outcome of patients falling into ALBI grade 3. Provided with these facts, further studies evaluating different treatments on patients falling into ALBI grade 3 should be performed to validate our findings.

In terms of the study regions, 1 study has provided us with survival data of populations from different regions, including China, Japan, Europe, and the USA [9]. As we expected, the same tendency was observed when applying the ALBI grade in comparing OS of populations from different regions. The Japanese data set recruited patients from 5 institutions in the western part of Japan, from which the etiology was predominantly hepatitis C virus (HCV), while in China the etiology was predominantly hepatitis B virus (HBV) [24,25], indicating that the ALBI grade was applicable in both HBV- and HCV-dominant areas. Meanwhile, although 4 included studies recruited patients from institutions in western countries (USA, Spain, the UK, etc), elevated ALBI grade still turned to inferior OS in these groups of participants, suggesting that the distinguishing ethnic backgrounds and lifestyles of the study populations did not significantly alter the overall results. Hence, our findings may promote the progression of the ALBI grade becoming a global tool for evaluating the prognosis of patients with HCC in the perspective of liver function.

In order to avoid the short-term complications associated with poor liver function, current guidelines suggest that curative treatments, other than liver transplantation, should be confined to those with C-P grade A [26,27]. However, the previous study shows that a clear separation between survival outcomes of ALBI grade 1 and ALBI grade 2 persists

Table 2. Summary of the Meta-Analysis Results

					Heterogeneity					
			HR (95% CI)		ALBI Grade 1 vs 2			ALBI Grade 1 vs 3		
Analysis	N	References	ALBI Grade 1 vs 2	ALBI Grade 1 vs 3	*P*	I^2	Ph	*P*	I^2	Ph
Overall survival	8	9, 13-19	1.71 (1.52-1.92)	3.81 (2.75-5.29)	<.001	75.40%	<.001	<.001	88.70%	<.001
Treatment										
SR	5	13, 16-19	1.68 (1.45-1.95)		<.001	41.60%	.11			
Sorafenib	3	9, 13, 14	1.62 (1.47-1.78)	3.83 (2.42-6.07)	<.001	0.00%	.75	<.001	74.50%	<.05
RFA	1	18	1.79 (1.41-2.27)	4.79 (2.52-9.17)	<.001	0.00%	.82	<.001	40.10%	.19
TACE	1	13	1.60 (1.28-2.00)	2.25 (1.72-2.93)	<.001	48.60%	.14	<.001	19.50%	.29
Total			1.65 (1.53-1.77)	3.25 (2.02-5.23)	<.001	0.00%	.87	<.001	71.50%	<.05
Region										
Japan	1	9	1.6 (1.40-1.84)	4.98 (4.07-6.08)	<.001					
Europe	1	9	1.9 (1.69-2.13)	3.86 (3.23-4.62)	<.001					
China	1	9	2.08 (1.80-2.41)	3.08 (2.62-3.63)	<.001					
USA	1	9	1.42 (1.02-1.97)	3.59 (2.27-5.68)	<.001					
Total			1.79 (1.55-2.06)	3.83 (3.04-4.83)	<.001	67.90%	<.05	<.001	77.60%	<.05
Child-Pugh A										
SR	6	13, 15-19	1.74 (1.55-2.06)		<.001	41.60%	.11			
Sorafenib	1	14	1.54 (1.30-1.82)		<.001					
Total			1.64 (1.43-1.88)		<.001	15.30%	.28			

Abbreviations: CI, confidence interval; HR, hazard ratio; Ph, *P* value of Q test for heterogeneity; RFA, radiofrequency ablation; SR, surgical resection; TACE, transcatheter arterial chemoembolization.

in patients defined as C-P grade A [9]. In this study, the results also show that within C-P grade A, there are 2 distinct subgroups as classified by the ALBI grade. For patients receiving surgical resection, inferior OS was observed when patients were stratified into ALBI grade 2, indicating that the ALBI score can evaluate preoperative liver functional reserve more accurately than the C-P grade. Similar results were obtained for those undergoing sorafenib therapies with curative intent. These findings suggest that a very significant fraction of the mortality in HCC after potentially curative therapies, even in C-P grade A patients, is attributable to liver dysfunction. Considering that C-P grade A is a standard inclusion criterion for patients undergoing surgical resection [28], our results may have implications for stratification in patients' survival after this curative treatment.

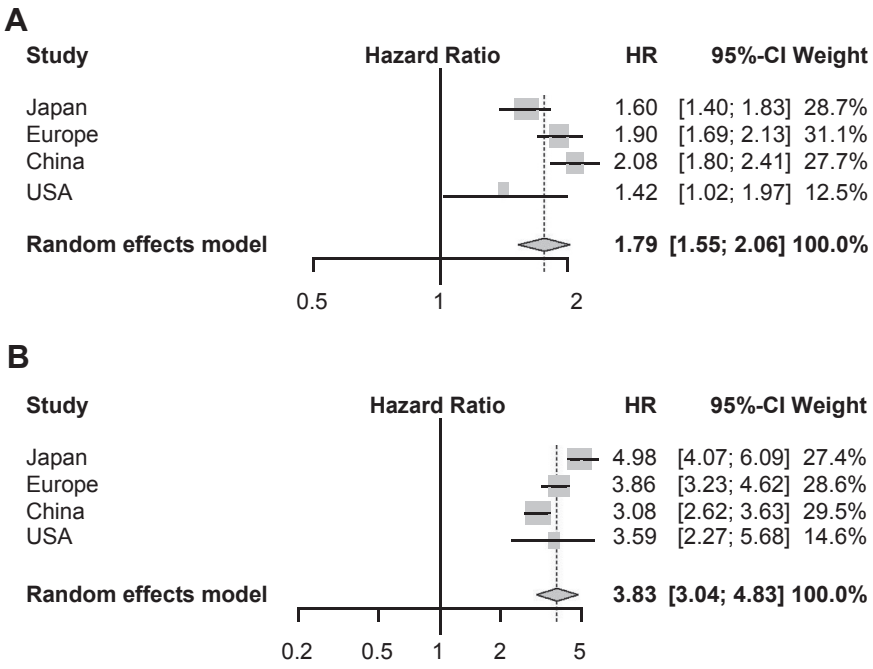

Fig 4. Hazard ratio for the association between elevated ALBI grade and overall survival in patients from different regions. **(A)** ALBI grade 1 vs 2; **(B)** ALBI grade 1 vs 3.

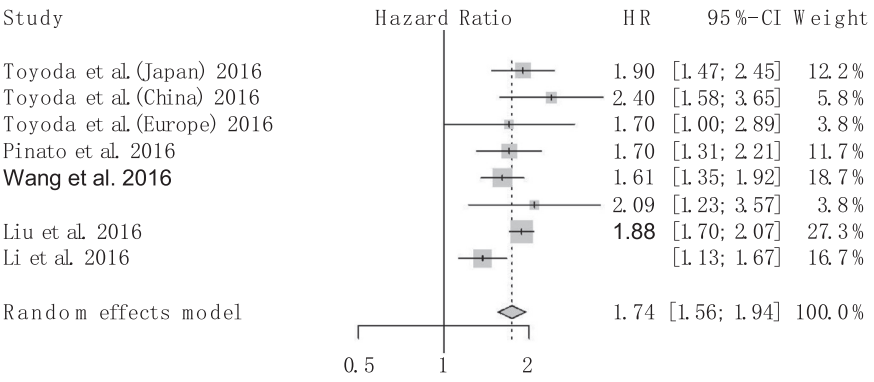

Fig 5. Hazard ratio for the association between elevated ALBI grade and overall survival in patients (treated with surgical resection) within C-P grade A.

Owing to the fact that the ALBI grade has become a potential substitute for the C-P grade, there are several studies incorporating the ALBI grade into staging systems for HCC. In the study of Chan et al [29], for instance, the ALBI grade was integrated into the BCLC stage system. The results showed that the ALBI grade performed as well as the C-P grade when integrated into the BCLC staging system in terms of predicting clinical outcome of HCC. In another study reported by Shao et al [30], modification of the Cancer of the Liver Italian Program score with ALBI retained its prognosis prediction for patients with advanced HCC. These studies will definitely inspire more work on integrating the ALBI grade into other staging systems to further promote its application in various liver diseases.

Finally, the limitations of our work should be discussed. The first one that should be mentioned is the variations in the treatment details, baseline characteristics of the study population, and the follow-up information in these included studies, which may contribute to the high heterogeneities in the current work. Moreover, since all the included studies were conducted retrospectively, the susceptible biases could not be ignored. The other limitation is that HRs from 6 out of 8 included studies were extracted from Kaplan-Meier curves, thus less accuracy might exist when compared with those generated from reported multivariate analyses. In addition, high heterogeneity was observed when performing the pooled analysis. Since only 8 studies were involved in the current work, meta-regression analysis wasn't adopted to find out the sources of heterogeneity. According to the subgroup analyses, the treatment strategy and study region were 2 main sources of heterogeneity. However, it cannot be ignored that there are still other factors that might contribute to the high heterogeneity in this study. In the study of Toyoda et al, HBV-positive patients had a significantly better prognosis than HCV-positive patients in the Japanese, Hong Kong, and European cohorts [18]. Due to the shortage of available data, further investigation on summarizing other sources of heterogeneity couldn't be conducted.

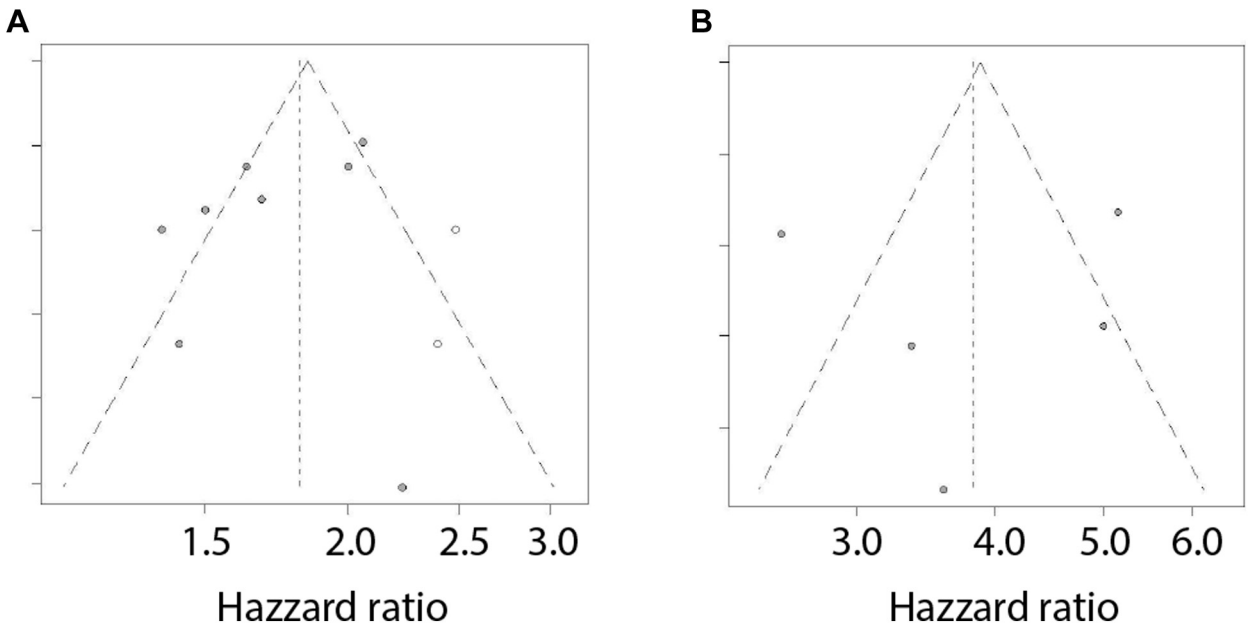

Fig 6. The Begg's funnel plot for overall survival in patients with hepatocellular carcinoma. **(A)** ALBI grade 1 vs 2; **(B)** ALBI grade 1 vs 3.

CONCLUSION

In the current study, we presented the first systematic review and meta-analysis to evaluate the ALBI grade as a tool in predicting the prognosis of patients with HCC. Despite of the limitation in available studies, the results showed that this model was able to distinguishingly classify patients into groups with different survival endpoints by using 2 easily obtained indexes—albumin and bilirubin. More clinical trials focusing on this topic are still needed to validate what we found in the current work. We believe that the ALBI grade will someday become a complementary prognostic tool to current staging systems in routine clinical practice.

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