**Clinical Utility of Albumin Bilirubin Grade as a Prognostic Marker in Patients with Hepatocellular Carcinoma undergoing Transarterial Chemoembolization: A Systematic Review and Meta-Analysis.**

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**Short Title:** ALBI grade as prognostic marker in HCC treated with TACE.

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**ABSTRACT**

**Background:** Hepatic functional reserve is a key prognostic marker in patients with hepatocellular cancer (HCC) undergoing transarterial chemoembolization (TACE) and is central to appropriate patient selection. The ALBI grade is an emerging model of hepatic function measurement and its clinical utility has been investigated in several published studies in patients undergoing TACE.

**Objective:** To investigate the clinical utility of the ALBI grade in patients with HCC undergoing TACE via ameta-analysis of published studies.

**Methods:** Publications including full text articles and abstracts regarding ALBI grade were sourced by two independent researchers from databases including, PubMed, EMbase, Medline, and Cochrane Library. Studies analysing patients with HCC undergoing TACE treatment were systematically screened utilising the PRISMA tool for data extraction and synthesis, after exclusion of duplicates, non-relevant studies and overlapping cohorts. The primary outcome was overall survival (OS), as determined by ALBI grade and assessed by hazard ratio (HRs) with 95% confidence intervals (CIs), with analysis of collated data using Comprehensive Meta-analysis, version 3.0 software.

**Results:** Eight studies were eligible for inclusion, with a pooled population of 6538 HCC who underwent TACE. Higher pre-treatment ALBI was associated with poor OS, with median OS of 12.0 months (P<0.001) in ALBI grade 3, compared to 33.5 months in ALBI grade 1 (P<0.001). Significant heterogeneity within each ALBI grade was associated with age and tumour size (P<0.001) in ALBI grade 1 and 2. In contrast, age and alcohol-related liver disease were significant in the ALBI grade 3 group (p<0.001).

**Conclusions:** High pre-treatment ALBI grade is associated with poor prognosis in patients with HCC undergoing TACE therapy. This study demonstrates the ALBI grade is a useful clinical prognostication tool to aid clinical decisions on patient selection and treatment allocation.

**INTRODUCTION**

Hepatocellular carcinoma (HCC) is a major and rapidly increasing cause of global premature morbidity and mortality. It is the fifth most common cancer globally and the second leading cause of cancer-related mortality [1,2]. In managing HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is a widely adopted system used to stage patients and guide therapeutic decisions [3]. According to the BCLC system, subjects with intermediate stage (BCLC B) HCC should undergo transarterial chemoembolization (TACE)[4,5]. Indeed, TACE is the most commonly prescribed treatment for patients with HCC as the majority of patients present with disease that is not amenable to potentially curative therapies [6-8]. TACE not only improves the overall survival in such patients, but also has an adjunctive role in controlling disease before liver transplantation as well increasing patient eligibility for other treatments such as ablation and surgery [9,10].

However, patient outcomes with TACE are quite heterogeneous with median survival rates varying between 20 and 45 months [11,14] This is due, in part, to the wide spectrum of liver dysfunction observed in BCLC stage B patients [15-17]. Patient selection, therefore, plays an important role in treating patients with TACE as severity of pre-treatment liver dysfunction predicts both post-treatment complications and overall survival [18-20] Several models have been proposed to assess hepatic reserve [19,21-23], however their clinical utility is limited by variation in both objectivity and sensitivity in stratifying stages of hepatic dysfunction [7,24-26].

The ALBI score, derived from both serum albumin and bilirubin levels, was recently proposed by Johnson et al. as an objective measure of liver reserve in patients with HCC [27]. Subsequently, multiple studies have shown it to have significant discriminatory power in patients undergoing TACE [28-40]. In particular, it has been found to have equivalent or superior prognostic power to the Child-Pugh score that also includes subjective markers such as ascites and hepatic encephalopathy, as well as the model of end stage liver disease (MELD) score[24,28-30]. We, therefore, undertook a systematic review and meta-analysis of published studies to determine the role of ALBI grade as a prognostic determinant in HCC patients undergoing TACE.

**METHODS**

**Literature search strategy**

A comprehensive and systematic literature search was carried out in databases including PubMed, Embase, Medline, Web of Science, and Cochrane library (up to July 1, 2019). The following search terms were combined as key words: (hepatocellular or liver) and (tumor or cancer or carcinoma or malignant) and (chemoembolization or chemoembolisation or embolisation or embolization) and (albumin to bilirubin ratio or albumin/bilirubin or albumin to bilirubin or ALBI or albumin and bilirubin).

**Inclusion criteria**

The inclusion criteria included: (i) patients with HCC; (ii) prognostic value of ALBI was evaluated on overall survival (OS); (iii) 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; and (iv) studies were full text **or conference abstract**. Studies were excluded based on the following criteria: (i) case reports, reviews, letters, and comments; (ii) inclusion of patients undergoing liver transplantation; (iii) studies without sufficient data to calculate HR with 95% CI; and (iv) studies where we were unable to obtain missing data after contacting the corresponding author(s). Studies were included or excluded following consensus between two authors (GM and AM).

**Data extraction**

All the studies were systematically screened and reviewed by two independent researchers (GM, AM). Data extraction included, 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. Any incongruence in data extraction encountered between reviewers was resolved by a third investigator through discussion.

**Statistical analysis**

The ALBI score was calculated as a linear predictor = (log10 bilirubin µmol/L x 0.66)  +  (albumin g/L x -0.085) and stratified as follows: grade 1: $\leq $−2.60; grade 2: > −2.60 to $\leq $ −1.39; and grade 3: > −1.39 [27]. Pooled HRs with their corresponding 95% CI were calculated for each ALBI grade to assess the prognostic value of ALBI on OS in patients with HCC treated with TACE. A high ALBI was closely associated with poor survival outcome when the HR was > 1. We tested heterogeneity with Cochran’s Q statistic and Higgins I2 statistics quantified the degree of heterogeneity using the I2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity [41]*. I2* values of 25%, 50%, and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively [42]. If there was no heterogeneity (<50%, P > .1), fixed-effect model would be used. Otherwise, the random-effect model was applied. We quantified publication bias using the Egger’s regression model [43]. The result was defined as statistically significant if P < .05. All analyses were performed using Comprehensive Meta-analysis, version 3.0, Biostat, Englewood, NJ (2014). This is a systematic review and meta-analysis, which does not need to be approved by the institutional review board or Ethics committee.

**RESULTS**

**Literature search**

Of the 309 articles initially identified related to ALBI grade, 33 studies that included both full text and conference abstracts were eligible for inclusion after exclusion of duplicates (n=106) and review of records and removal of irrelevant articles (n=73). Of these, 12 studies fulfilled all inclusion criteria after removal of those with overlapping cohorts (n=5) and those that did not include TACE as a treatment cohort (n=20) or have OS data available as either HR with 95%CI or Kaplan Meier curves. In studies that provided incomplete OS data as either HR with 95% CI or Kaplan Meier curves the corresponding author was contacted for further data including baseline demographic data stratified by ALBI grade. Based on the data available from original studies and further data provided by study author correspondence a total of 8 studies were included for final analysis (see Figure 1).

**Clinical studies and cohort characteristics**

Characteristics of the eight included studies are presented in Tables 1 and 2. The studies covered a variety of geographical regions including two large multicenter international studies [28.34] that included populations from USA, Europe, Japan, South Korea and Egypt. The remaining studies included two smaller cohorts [35,36] from the US, one from UK [37], one from Norway [39] one from Japan[38] and one study from Taiwan [32]. The study cohort size ranged from 49 to 3030. In total, there were 6538 patients with OS data who had HCC and underwent TACE pooled from the eight eligible studies. The baseline population data derived from these studies are outlined in Table 1 and 2 with additional demographic data provided by the corresponding authors shown in Table 3.

The majority of patients were male (74%) with median age ranging from 55 to 75 years. The majority of patients had Child-Pugh A (n=4410) 66% or B (n=1839) 30% liver disease. Pinato’s multicenter study [28] and the Japanese paper [38] had mainly Child-Pugh A and B patients, while the smaller study from Norway [39] had exclusively Child Pugh A patients. Child-Pugh C patients were seen in the other studies but their overall numbers were small, n=176 (3%).

BCLC staging data was not available on patients from three studies [34,37,40]. Based on the data available from the remaining studies (N= 2209), 24% were BCLC A, 61% were BCLC B and 13% BCLC C. A relatively smaller cohort were BCLC D 1%, all being derived from a single population in Hansmann’s study [35]. The etiology of liver disease data was available in 86% (n=5590) of the entire cohort, and was not available in three studies [35-37] and multiple aetiologies were grouped together in one study [39]. The most common cause of liver disease was HCV (n=2717), found in 42% of the entire cohort, whilst both HBV, and ETOH had similar incidence at 15%. Other aetiologies including HBV/HCV co-infection occurred in 10% of the total cohort.

The median tumour size was 4.25 cm and varied widely from a median of 1cm to 19.4cm especially in the two large multicentre studies [28,34]. Macrovascular invasion (MVI) data were available in all cohorts except for one study [37] with MVI present in 11% of the overall cohort with the highest rate of 30% in the Japanese cohort of Waked’s multicenter study [34]. Extrahepatic spread (EHS) was present in 38 cases, (1%) of overall cases and derived mainly from the Japanese and South Korean cohort of Pinato’s multicenter study [28] and the small Norwegian cohort study [39].

**Effect of ALBI grade on overall survival**

A random effects model was used to analyse the aggregated data, to account for significant heterogeneity in the studies included. ALBI grade was able to stratify patients in to distinct overall survival groups with 33.5 months, (95% CI[26.1-­41.0], P<0.001) in ALBI grade 1, compared to 19.1 months (95% CI[16.3-­21.9], P<0.001) in ALBI grade 2, and 12.01 months (95% CI[8.71-­15.3], P<0.001) in ALBI grade 3 (Fig. 2 and 3).

**Subgroup analysis**

Stratification into subgroups (Table 3), found heterogeneity in the ALBI grade 1 and 2 groups was significantly associated with age and tumour size (P<0.001), while BCLC­ stage B (p<0.001) was an additional factor in the ALBI grade 1 group (Supplementary Fig 1A-E). In contrast, age and alcohol-related liver disease were associated with heterogeneity in the ALBI grade 3 group (p<0.001) (Supplementary Fig. 1F-G).

**Comparative subgroup analysis of ALBI grade with current prognostic tools**

The ALBI grade had superior prognostic ability to the Child Pugh class in the large multinational study by Waked et al, when applied to the cohort from Europe and China (C-index 0.5749 vs 0.5446) and (C-index 0.5898 vs 0.5684) respectively. Similarly, Hickey et al showed that the ALBI grade had superior discriminatory ability to the Child Pugh class (C-index 0.584 vs. 0.524). In addition, further sub-stratification with ALBI grade significantly improved the prognostic ability of the Child Pugh class and BCLC stage in both small single center and large multinational studies included in our meta-analysis. In particular, Huo et al demonstrated improvement in patients with BCLC stage B and Child Pugh A disease at baseline. Similarly, Hansman et al demonstrated the BCLC stage B had highest discriminatory ability with the application of ALBI grade (C-index 0.917), in addition to BCLC stage A (C-index 0.867) and Child Pugh B (C-index 0.892). Complete comparative data with the MELD score was only available in one study (Huo et al) and demonstrated the ALBI grade (C-index 0.544) had a better discriminatory index compared to the CPC (C-index 0.527) and MELD (C-index 0.497). The BCLC stage had the highest discriminatory index in this cohort (C-index 0.575), likely reflecting the influence of key tumour burden parameters that are incorporated in the BCLC staging system.

**Publication Bias**

The Eggers regression analysis was not significant for publication bias for the studies included for analysis in each ALBI grade (ALBI 1 p=0.33; ALBI 2 p=0.16; ALBI 3 p=0.75) (Supplementary Figure 2).

**DISCUSSION**

Accurate staging of HCC is an essential step towards improving patient survival for this cancer[2] that has a very high mortality [44]. The two main staging factors that contribute to HCC mortality, namely the underlying severity of liver dysfunction and tumour burden, make HCC unique in its category and are critical determinants upon which treatment decisions are based [6,7,21,22,45]. In this context, the ALBI score has emerged as a key grading system to facilitate prognostication and survival of patients with this inherently heterogenous disease [15,27,46]. Notably, the ALBI score overcomes many of the inherent differences in patient populations at a global level by using objective markers of liver function rather than other traditional markers such as the Child-Pugh score which are influenced by subjective clinician assessment [24,46,47]. Comparative studies between Child-Pugh and MELD scores in patients undergoing TACE for HCC have found Child-Pugh score correlated better with OS, particularly the albumin component [26,48-52].

Multiple international cohort studies have demonstrated the ALBI score has good discriminatory power and good prognostic function often equivalent and at times superior to current prognostic scoring systems that have variable performance when applied to populations beyond their original derivation cohort [53-55]. The main findings of our meta-analysis of these cohort studies is the demonstration that ALBI grade is a robust prognostic marker in HCC patients undergoing TACE with high pre-treatment ALBI grade associated with a poor prognosis. Importantly, we found that the ALBI score performed well across major global populations with ALBI grades 1, 2, and 3, identifying three populations with significantly different overall survivals of 33.5, 19 and 12 months respectively.

Moreover, the characteristics of the overall cohort in our study are consistent with previous studies of patients with HCC undergoing TACE [6,18,23]. The significant majority (74%) of patients were male with a median age ranging from 55 to 75 years old, with 66% having Child-Pugh A and 30% Child-Pugh B liver disease. However, while over half (n=1358) of the patients with available data (n=2209) had BCLC B stage HCC, they consisted of only 21% of the entire cohort of 6538 patients due to the relatively low 34% rate of reporting of BCLC stage across studies. Thus, accurate and robust conclusions regarding the impact of BCLC stage characteristics are difficult to make. In contrast, there was a high 87% reporting of data on the etiology of liver disease of patients and a wide range covered in the median tumour size (1-19.4cm), while rates of reporting of MVI and EHS varied across the different cohorts.

The significant heterogeneity in our overall cohort resulting from the differences in baseline demographic features within each study population likely reflect in part the variations in HCC classification and treatment guidelines between Eastern and Western populations [16,53-56]. The distribution of the ALBI grade on subgroup analysis varies across Europe and Asia and across ALBI grades, with the overall heterogeneity decreasing in patients classified as ALBI 3 compared to ALBI 1 and ALBI 2 (supplementary figure 3).

The main factors accounting for heterogeneity among the different ALBI grade groups included age, which was present for all ALBI grade groups, and tumour size for ALBI grade 1 and 2 groups. BCLC ­B stage and alcohol related liver disease were additional factors associated with heterogeneity in the ALBI grade 1 and ALBI grade 3 groups respectively. These factors may reflect the baseline demographics and tumour stage of each population group at the time of TACE therapy with patients in the Asian cohorts presenting at an older age, with higher rates of underlying HBV related HCC and lower tumour burden as defined by both BCLC stage and smaller median HCC diameter.

Heterogeneity is also seen within the included Asian cohorts with key differences noted in baseline cohort characteristics. For example, the frequency of MVI was 18% in the study by Lui et al [40], and as high as 30% in the Japanese cohort in Waked’s study, [34] while another study from a single centre Japanese cohort[38] included only patients with intermediate stage BCLC B disease without MVI or EHS. In addition, HCV related liver disease was more common in both the Japanese and Western cohorts, however patients from the Western cohorts were younger and also had a greater proportion of alcohol related liver disease particularly from Europe and the USA. Interestingly, patients within the European cohort also underwent TACE at a more advanced stage compared to the North American cohort. Further subgroup analysis is limited however due to the significant number studies with missing variables such as BCLC staging data as noted above. There is, however, evidence that patients from the Liu et al. study [40] had more advanced HCC stage as almost 50% presented with HCC > 5cm, and mean AFP levels and rates of macrovascular invasion were higher.

Recently, Xu et al.[57] published a meta-analysis of the prognostic value of pre-treatment ALBI in patients with HCC who underwent various treatments including TACE. The final 32 studies included in their meta-analysis were mainly derived from Asia (n=22) with significant heterogeneity (I2=83.7%, P=.000) in their overall cohort. Utilising the random effects model in their analysis they found high concordance between high ALBI grade and poor OS (HR = 1.577, 95%CI: 1.464–1.691, P =.000) on multivariate analysis, with liver failure associated with mortality in 63.1% of cases. With regards to TACE, Xu et al. [57] performed treatment stratified analysis that included only one TACE specific study, although many of the 32 studies included in their MA had subgroups with TACE treatment reflecting limitations of available data for analysis. The authors acknowledged these difficulties with many studies providing HRs with 95%CI from univariate analysis or as Kaplan Meier curves requiring extraction of data using the Engauge Digitizer software to convert graphs into numerical data, further increasing the heterogeneity of their overall cohort. Univariate analysis of the TACE specific data found significant correlation between ALBI grade and post TACE overall survival (HR =1.59, 95% CI(1.39–1.78), P=.000), however further subgroup analysis is limited due to the small sample size.

Our study also included a subgroup analysis of the performance of the ALBI grade in comparison to currently used prognostic tools including the Child Pugh class and the BCLC stage. Notably, the ALBI grade had superior prognostic ability to the Child Pugh grade in some but not all studies.[34-36, 40] Whilst these results are encouraging it is important to consider the variation in sample size in each the cohorts, and in particular the small number of patients with each cohort included in the sub stratification of the CP class and BCLC stage according to ALBI grade (Supplementary table 4). In addition, heterogeneity existed among studies with Pinato et al finding that the discriminatory ability of the ALBI grade, BCLC stage, and CPC were similar.[28] Still, the results of the comparative analysis are limited in their interpretability in most studies due to the small number of patients within certain subgroups. In particular, there were very few patients in the groups reflective of advanced liver disease and tumour burden, classified as ALBI grade 3, BCLC stage C and CPC-C across all included studies.

The ALBI grade also had a variable performance in improving the discriminatory function of the BCLC and CP class, ranging from significant (C-index 0.917), [35] to below adequate cut off for clinical use (C-index 0.65). [28] These results suggest that incorporation of parameters reflective of tumour burden including, tumour size, macrovascular invasion, extrahepatic spread and tumour markers such as AFP remain important prognostic factors as has been demonstrated in several multi-variate analyses. [28, 34, 36,38,39]

Overall, the ALBI grade is an adjunct tool in the assessment of prognosis in patients with HCC having TACE as post TACE hepatic dysfunction is one of the most common complications and a significant competing cause of mortality along with tumour burden. [10,18] In a comparative group of patients treated with repeat TACE prior to sorafenib commencement, Hiraoka et al demonstrated the ALBI grade was a more sensitive marker of worsening hepatic function compared to the CPC, and patients that were ALBI 1 grade prior to commencing Sorafenib had significantly better outcomes compared to patients that were ALBI grade 2, OS 10.9 vs. 10.04 months respectively (p = 0.001).[38] These results were also demonstrated in the multinational study by Pinato et al, and supports the utility ALBI grade as an objective tool for clinicians when assessing liver reserve in patients undergoing repeat TACE and facilitating timely stage migration to systemic therapies or enrollment into clinical trials. [28,38] Further large prospective studies analysing the role of the ALBI grade with repeat TACE therapy are required to determine the prognostic role of the ALBI score and the impact of the degree of ALBI score change on OS in comparison to currently used clinical tools.

The strengths of our study include a comprehensive search strategy, which involved searching four electronic databases and availability of a large pooled population derived from several geographical regions and variably sized cohorts for meta-analysis. Moreover, there was no evidence of publication bias associated with the studies included in the meta-analysis. In addition, comprehensive subgroup analysis was performed according to geographic region, and several other factors known to influence patients survival including age, tumour burden, HCC stage, and aetiology of liver disease. This enabled us to delineate the strengths and weaknesses of the ALBI scores prognostic value in patients having TACE with regards to several patient and tumour factors akin to what has been done in those undergoing potentially curative treatments. Our results are in concordance with the conclusion of Xu et al.’s meta-analysis [57] and further confirm the performance of ALBI grade in patients undergoing TACE across a larger cohort of TACE patients derived from a greater number of additional studies.

There were several limitations of our study that warrant more detailed discussion. Firstly, when assessing the correlation between factors such as HCC staging and grade of liver dysfunction with each ALBI grade and OS outcomes, we noted several examples of where data were variably reported and/or unable to be correctly separated. For example, in the study of Hansmann et al. [35], BCLC 0 and A were categorised together while data regarding underlying aetiology of liver disease, serum AFP levels and tumour nodule number and size were missing or variably reported. Secondly, while duplicates were removed during the screening process, we noted overlap in cohorts used in multiple publications, although this proved to be advantageous in some cases where missing data could be procured from the second publication [40,58].

 However, the subgroup analysis suggests errors in the reported data such as the breakdown of Child-Pugh categories, with the sum of each grade greater than the original TACE cohort in one particular study [40,58]. There were also differences due to loss of follow up in each study with slight reductions in sample size used to calculate OS and other baseline factors compared to the overall study population. Furthermore, the lack of overall survival data and cohort demographics was one of the key barriers to incorporation of additional studies relevant to this study [31,48,59]. As a result, these cohorts of patients who underwent TACE and had ALBI scores applied were excluded from our final analysis that may reduce the applicability of the pooled results. Finally, since the initial literature search Lee SK and colleagues published a study comparing the ALBI to PALBI (Platelet, Albumin, Bilirubin) grade in a large cohort of patients with HCC treated with TACE (n = 1715) [49]. Additional data were not forthcoming at the time of this publication despite efforts to contact corresponding authors.

In conclusion, we have shown in this meta-analysis incorporating multiple real-world international cohorts that ALBI grade is a useful clinical prognostication tool to aid clinical decisions on treatment allocation. A high pre­-treatment ALBI grade was associated with poor prognosis in patients with HCC undergoing TACE therapy. Further prospective studies are required to validate the ALBI grade in patients undergoing repeat TACE therapy and in those receiving TACE in combination with other treatment modalities.

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**Legends for figures and tables**

**Table 1** – Cohort Characteristics, Multicentre studies28,34

Footnotes:

Abbreviations – N/A (Not available), HCV – hepatitis C virus, HBV – Hepatitis B virus, ETOH – ethanol, AFP – Alfa feto protein, MVI – Macrovascular invasion, IQR – interquartile range.

\*Includes patient cohorts from Japan and South Korea.

**Table 2** – Cohort Characteristics – Single Centre studies 35–40

Footnotes:

Abbreviations – N/A (Not available), HCV – hepatitis C virus, HBV – Hepatitis B virus, ETOH – ethanol, AFP – Alfa feto protein, MVI – Macrovascular invasion, IQR – interquartile range.

\*Aetiology of liver disease were grouped in original data as, viral hepatitis / ETOH / or both (n=20 (41%)), NAFLD / other (n=17 (35%)), and cryptogenic (n=12 (24%)).

**Table 3.** Demographic and baseline tumour parameters stratified by ALBI grade28,34,38

Footnotes:

Abbreviations – OS – overall survival, N/A (Not available), HCV – hepatitis C virus, HBV – Hepatitis B virus, ETOH – ethanol, AFP – Alpha feto protein, MVI – Macrovascular invasion, SD – standard deviation, IQR – interquartile range.

**Fig. 1.** Study selection flowchart.

**Fig. 2.** Forest plots evaluating effect of ALBI grade 1 (A), grade 2 (B) and grade 3 (C) on overall survival.

**Fig. 3.** ALBI grade 1,2, and 3 association with overall survival in the study cohort.