To determine the prognostic value of the albumin–bilirubin grade (ALBI) in patients underwent transarterial chemoembolization for unresectable hepatocellular carcinoma

Muhammad Ali Khalid, Inamullah Khan Achakzai, Farina M Hanif, Shoaib Ahmed, Zain Majid, Nasir Hassan Luck
Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, (SIUT), Karachi, Pakistan

ABSTRACT

Aim: We aimed at determining the prognostic value of the albumin–bilirubin grade (ALBI) in patients undergoing transarterial Chemoembolization for unresectable Hepatocellular carcinoma.

Background: Various noninvasive liver reserve markers are used to predict the severity of liver injury. The role and probability of these markers in predicting the prognosis of patients with hepatocellular carcinoma (HCC) is still unknown.

Methods: Patients who underwent TACE from 2013 to 2017 were included. Patient’s age, gender, cause of cirrhosis, ALBI Grade along with the site, size and number of tumors were recorded. Radiological response to TACE was assessed by CT scan at 1 and 3 months after the procedure, respectively. Survival assessment was performed and all patients were assessed for survival until the last follow-up.

Results: A total of 71 patients were included. Majority of them were male (80.3 %). The mean tumor size of 6 ± 3.9 cm. Majority of patients (54.9 %) had a single lesion and it was mostly localized to the right lobe (60.5 %). The most common cause of chronic liver disease was HCV (65.3%). Median Child class score (CTP) and MELD score were 7 and 10, respectively. Ascites was treated prior to TACE in 12 patients (16.9 %).

Mean ALBI score in the study population was -1.59 ± 0.69, with the majority (49.2 %) falling in grade 2. The mean duration of survival at the last follow up was of 12.1 ± 12.14 months (1- 49).

Univariate analysis showed serum albumin (p = 0.003), serum bilirubin (p = 0.018), CTP score (p = 0.019), ALBI grade (p = 0.001) and presence of varices (p = 0.04) to be the main predictors of 6 months survival after TACE. On Cox analysis, only ALBI score (p = 0.038) showed statistical significant association.

Conclusion: ALBI grade may serve as a surrogate marker in predicting the prognosis of HCC patients undergoing Transarterial Chemoembolization.

Keywords: Hepatocellular carcinoma, Unresectable disease, Transarterial chemoembolization, ALBI grade, CTP score, MELD score.

Introduction

Hepatocellular carcinoma (HCC) accounts for 70%-85% of major liver cancer burden globally (1). It is the sixth most common malignancy and the third most cause of cancer-related mortality worldwide (2) The incidence of HCC is higher in Southeast Asia and sub-Saharan Africa regions. In Pakistan, the prevalence of HCC varies from 3.7%-16% of malignant tumors, with about 87% of HCC being mainly due to viral hepatitis, that is Hepatitis C (68%) or B related cirrhosis (22%). The incidence of HCC in Pakistan is 7.6 per 100,000 persons per year for males and 2.8 per 100,000 persons per year for females (3,4).
HCC mostly develops on a milieu of chronic liver disease or cirrhosis (5,6). As a consequence, various degrees of liver functional insufficiency are typically present at the point of cancer identification. For patients with early stage and well preserved liver function, surgical resection and liver transplantation are usually suggested (7). As a result, in unresectable HCC, radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are the potential palliative modalities (8). Transarterial chemoembolization is commonly acknowledged as a palliative treatment option and improves survival in unresectable HCC (9, 10).

Parameters assessing liver function have been integrated into majority of the staging systems (11-14). However, the clinical management of HCC primarily depends upon its clinical stage of the disease (11). Nevertheless, the precision of the current ongoing staging systems in predicting the prognosis and guiding management is not satisfactory. It was recommended that the unsatisfactory prognostic performance of the staging systems could somewhat be explained by the inadequate liver function gauging system (14).

Among patients with chronic liver diseases of diverse etiologies as well as HCC, the Child–Pugh (C-P) class is generally used to approximate prognosis and disease severity (15). However in C-P class A patients, with apparently normal liver functions, prognosis varies widely (16,17) In addition, some of the variables in the C-P grade are interconnected (e.g., ascites and serum albumin levels), and the grading of ascites and encephalopathy can be highly subjective (17-19). Hence, the shortcomings of the C-P grading system leaves an area for the improvement of another liver function estimation systems.

In patients with chronic liver diseases, various noninvasive liver reserve markers like the model for end-stage liver disease (MELD), Lok index, cirrhosis discriminant index (CDS), fibrosis index based on 4 factors (FIB-4) and aspartate aminotransferase-to-platelet ratio (APRI), have been suggested to assess the degree of functional liver reserve (20). Recently, the albumin-bilirubin (ALBI) grade was introduced as a prognostic marker which was solely based on the serum albumin and bilirubin level (21).

Selecting the most favorable surrogate marker for these patients is contentious. Given all these choices, the role of these markers and their accuracy in foretelling the outcome of HCC patients remains largely uncertain. Thus the aim of this study was to evaluate the prognostic value of the new liver function assessment tool, the albumin–bilirubin (ALBI) grade, in patients with hepatocellular carcinoma undergoing TACE.

Methods

Definitions

The primary C-P score is divided into three sub classes (A= 5–6 points, B = 7–9 points, and C= 10–15 points).

The ALBI grade was calculated using the following formula: 0.66 × log (bilirubin mg/dl)_0.085 × (albumin g/dl). The cut-off points for ALBI grades 1–3 were: grade 1, less than -2.60; grade 2, -2.60 to -1.39; and grade 3, more than -1.39 (21).

Patient selection

All patients diagnosed as HCC according to the American Association Study of Liver Disease (AASLD) criteria 15 and found eligible for TACE were included in this study. The study period was of five years, i.e from September 2013 to December 2017. Those patients who presented within 6 months of any previous intervention such as RFA or surgical liver resection for HCC were excluded from this study.

Inclusion criteria

Patients of either sex, of all ages, diagnosed with non-resectable and non-ablatable HCC were enrolled in this study. We defined cases of HCC as non-resectable when any one or more of the following conditions were present: severe comorbidity that precluded the administration of general anesthesia; liver dysfunction and/or portal hypertension that contraindicated parenchyma loss during radical tumor resection.

Ablation therapy was not indicated when the maximum diameter of the tumor was >5 cm, when the tumor was in close proximity to major vascular or biliary structures, or if there was multifocal disease.

Methods

This was a retrospective observational study. Approval was obtained from the Ethical Review Committee (ERC) of Sindh Institute of Urology and Transplantation, Karachi, Pakistan (SIUT), with informed consent being obtained from the patients before enrollment. A total of 71 patients were included in this study. The TACE procedure was performed in the
Radiology Department of our institute with the procedure involving injection of a chemotherapeutic agent (doxorubicin) mixed with lipoidal into selectively or super selectively catheterized branches of the arteries feeding the tumor followed by injection of gelfoam particles to reinforce the effect of treatment. After the procedure, the patients were shifted to the Gastroenterology Ward for observation. A structured proforma was used to collect data and included demographics (age, gender), clinical (etiology), laboratory parameters [serum bilirubin, albumin, creatinine, international normalized ratio (INR), and alphafetoprotein (AFP)] and imaging (number of lesions, size, and lobe involved), the Child-Turcotte-Pugh (CTP) score and the Model of end-stage liver disease (MELD) score (22). At the end of 6 weeks, a computerized tomography (CT) scan of the abdomen was performed as per the TACE protocol. Response of TACE was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Inquiries were made through telephone calls to determine the patient's survival status.

Statistical analysis:
Data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) software version 20.0 (Chicago, IL, USA). Frequencies and percentages were computed for different categorical variables such as gender and cause of HCC. Mean and standard deviation were computed for age. We employed the two-sided Fisher’s exact test to analyze the dichotomous variables before and after TACE. Univariate analysis and multivariate analysis were also performed. A P-value of <0.05 was considered statistically significant. Survival analysis was done using the Kaplan-Meier estimates, with comparisons generated using the log rank test.

Results
A total of 71 patients were included in our study. Patients demographic and tumor characteristics are shown in Table 1. Majority of our patients were male i.e 57 patients (80.3 %) and a mean age of 51.9 ± 12.1 years (18 – 76 years) was observed. The mean tumor size was of 6 ± 3.9 cm. Majority of the patients (54.9 %) had a single lesion and these were mostly localized to the right lobe of the liver (60.5 %). The most common cause of chronic liver disease was HCV (65.3%) while a cryptogenic cause was documented in 10 patients (14.1%). The median Child class score (CTP) and MELD score were 7 and 10, respectively.

| Variables          | p-value |
|--------------------|---------|
| Age                | 0.215   |
| Male               | 0.37    |
| Serum Albumin      | 0.003   |
| Bilirubin          | 0.018   |
| INR                | 0.70    |
| MELD, median       | 0.21    |
| CTP score          | 0.019   |
| A                  | 33 (46.5%) |
| B                  | 35 (49.3%) |
| C                  | 3 (4.2%)  |
| Cause of liver disease |         |
| HCV                | 45 (63.4%) |
| HBV                | 8 (11.3%)  |
| HBV+HCV            | 5 (7.0%)   |
| HBV+HDV            | 1 (1.4%)   |
| HBV+HCV+HDV        | 2 (2.8%)   |
| Cryptogenic        |          |
| ALBI grade         | 0.001    |
| -2.60 and above    | 6 (8.4%)  |
| -2.59 to -1.39     | 35 (49.2%) |
| -1.38 to +1        | 30 (42.2%) |
| Varices, n (%)     | 0.04     |
| Present            | 30 (55.6%) |
| Absence            | 24 (44.4%) |
| Tumor size, mean   | 0.84     |
| Less than 5 cm     | 42       |
| More than 5 cm     | 29       |
| Lesions            |          |
| Single             | 39 (54.9%) |
| Two or more        | 32 (45.1)  |
| Lobes              | 0.48     |
| Right              | 43 (60.6%) |
| Left               | 17 (23.9%) |
| Both               | 11 (15.5%) |
| TACE session       |          |
| 1                  | 43 (60.6%) |
| 2                  | 17 (23.9%) |
| 3 or more          | 11 (15.5%) |
| Recurrence         | 47 (66.2%) |
| Survival           | 0.198    |
| Duration of survival | 12.1 ± 12.14 (1-49) |

Fifty four patients had consented for an EGD and esophageal varices were seen in 30 (55.6 %) patients. Ascites was treated prior to TACE in 12 of these patients (16.9 %).

The mean ALBI score in the study population was -1.59 ± 0.69, with majority (49.2 %) being in ALBI grade 2. While the mean duration of survival at the last follow up was 12.1 ± 12.14 months (1-49).
Univariate analysis showed that serum albumin ($p=0.003$), serum bilirubin ($p=0.018$), CTP score ($p=0.019$), ALBI grade ($p=0.001$) and the presence of varices ($p=0.04$) were significant predictors of 6 months survival post TACE. On Cox regression analysis, only ALBI score ($p=0.038$) showed statistical significant association.

Discussion

TACE has a considerable survival benefit in the management of non-resectable HCC. Llovet et al. (9) reported a 2 year survival in 63% of the patient while Lo et al. (10) showed a 26% three-year survival advantage in patients who underwent TACE. A recent meta-analysis also supported the advantage of chemoembolization in the selected patients (23). For these reasons, TACE has been established as a treatment of choice in patients with unresectable HCC. Chronic hepatitis C appears to be the major risk factor for the development of HCC which is consistent with our study population, where HCV has accounted for 63.7% of patients.

In our study we validated the prognostic ability of ALBI grade in patients with HCC who underwent TACE. We further discovered that ALBI Grade has gained a superior prognostic differentiating efficacy than that of C-P in HCC patients, which augmented the results by Johnson et al. (21). In the modern surgical era, reducing morbidity and mortality are still major concerns, numerous studies have recommended that precise evaluation of liver function reserve is indispensable for prognosticating the occurrence of morbidities and mortalities (24). The C-P score was usually calculated to estimate the risks (24). Our study shows that the ALBI score, could also be used to estimate the post TACE morbidities.

The survival outcome, morbidity, mortality and the treatment options in HCC are not only reliant on the tumor stage, but also on liver functional reserve compared with other solid tumors (24). The C-P score, which was originally evolved for patients with cirrhosis rather than HCC, is the most extensively acknowledged liver function assessment tool and thus is included in a number of tumor staging systems including BCLC12 and the CLIP (25). Several fundamental flaws of the C-P class exist. First, clinical assessment of ascites and hepatic encephalopathy can be highly biased. Presence or severity of ascites, by some practitioners, is determined by physical examination. Others may consider ascites only when it is detectable by radiological scanning. The tumor itself and the diuretic may also impact ascites. Encephalopathy may be equally difficult to grade, as many of the early symptoms may be shared by the HCC itself. Second, some of the indexes in the C-P class, such as ascites and serum albumin, are closely interconnected. In fact, the five items may not influence the clinical outcomes at an identical level.

Hiraoka et al. (26) compared the predictive value of ALBI grade and C-P score in 2584 Japanese HCC patients. The ALBI grade was found to be better for distinguishing patients with better hepatic function. In our study on univariate analysis the ALBI grade, CTP score and varices were closely related to overall survival of HCC patients but on multivariate Cox analysis, only ALBI grade ($p=0.038$) showed statistical significant association.

| Table 2. Association between ALBI grade and survival |
|---------------------------------|-----------------|---|
| 3 months                        | 55 (77.5%)      | 0.010 |
| 6 months                        | 39 (54.9%)      | 0.001 |
| 12 months                       | 31 (43.7%)      | 0.00 |

| Table 3. Multivariate Analysis on association of factors with 6 months Survival |
|---------------------------------|-----------------|----------------|
| Variables                       | Hazard Ratio    | p- value       |
| CTP score                       | 0.64            | 0.09           |
| ALBI grade                      | 3.06            | 0.038          |
| Varices                         | 0.97            | 0.64           |

Gastroenterol Hepatol Bed Bench 2019;12(2):110-115
test, which are available in almost every medical setup both in the rural and urban areas. Moreover, the ALBI grade get rides of the subjective items such as hepatic encephalopathy. The objectivity and accuracy of the grading system are merited.

Our study had some limitations. This was a single center study with retrospective data collection. Hepatocellular carcinoma was diagnosed on the basis of CT scan as per AASLD criteria. Although rare, the possibility of mixed HCC and cholangiocarcinoma (CC) could not be entirely excluded. Second, this study was limited to HCC patients undergoing TACE. Hence the accuracy of ALBI grade in patients receiving other therapies required further studies to recognize.

Our results signify that the ALBI grade is the most precise prognostic model among the other noninvasive liver reserve markers as supported by Shu-Yein Ho et al. (27). The ALBI grade may provide as an objective, discriminatory and evidence-based method in assessing liver functional reserve. The ALBI grade is clinically more useful due to is higher prognostic power in HCC patients undergoing TACE. Further studies are now needed to authenticate the practicability of ALBI grade in diverse clinical scenarios.

Conflict of interests
The authors declare that they have no conflict of interest.

References
1. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
3. Badar F, Mahmood S. Hospital-based cancer profile at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, pakistan. J Coll Physicians Surg Pak 2015;25:259-63.
4. Bhurgri Y, Bhurgri A, Hassan SH, Zaidi SH, Rahim A, Sankaranarayanan R, et al. Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. Int J Cancer 2000;85:325-9.
5. Lee MH, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH, et al. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatol 2013;58:546-54.
6. Schutte K, Bornschein J, Malfertheiner P. Hepatocellular carcinoma Epidemiological trends and risk factors. Dig Dis 2009; 27:80-92.
7. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatol 2005;42:1208-36.
8. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321-8.
9. Llovet JM, Rea ML, Montoya X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734-9.
10. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatol 2002;35:1164-71.
11. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
12. Forner A, Reig ME, De Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61–74.
13. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatol 1998;28:751–5.
14. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatol 2000;32:1224-9.
15. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC, and JIS) in Japan. Am J Gastroenterol 2005;100:1764-71.
16. Okajima C, Arii S, Tanaka S, Matsumura S, Ban D, Ochiai T, et al. Prognostic role of Child-Pugh score 5 and 6 in hepatocellular carcinoma patients who underwent curative hepatic resection. Am J Surg 2015;209:199-205.
17. Franco D, Capussotti L, Smeda C, Bouzari H, Meakins J, Kemeny F, et al. Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. Gastroenterol 1990;98:733-8.
18. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res 2009;39:107–16.
19. Hung HH, Chao Y, Chiu YY, Li CP, Lee RC, Huo TI, et al. Comparison of clinical manifestations and prognoses between patients with hepatocellular carcinoma and Child-Pugh scores of 5 or 6. Medicine 2014;93:e348.
20. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterol 2012;142:1293-302.
21. Johnson PJ, Berhane S, Kageyashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.

22. Abbas Z, Siddiqui AU, Luck NH, Hassan M, Mirza R, Naqvi A, et al. Prognostic factors of survival in patients with non-resectable hepatocellular carcinoma: hepatitis C versus miscellaneous etiology. J Pak Med Assoc 2008;58:602-7.

23. Llovet JM, Bruix J. Systematic review of randomize trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatol 2003;37:429-42.

24. De Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol 2012;56:S75–87.

25. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatol 1998;28:751-5.

26. Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1031-6.

27. Ho SY, Liu PH, Hsu CY, Hsia CY, Lee YH, Lee RC, et al. Prognostic role of noninvasive liver reserve markers in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. Plos One 2017;12:e0180408.