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ABOUT COVER

Editorial Board of *World Journal of Gastroenterology*, Dr. Dario Sorrentino is a Professor of Medicine at Virginia Tech – Carilion School of Medicine and Research Institute (since 2013). His career research experience has ranged from the bench to the bedside focusing on IBDs, and carried out on three different continents. Fifteen years ago, he and his professional colleagues proposed a groundbreaking strategy to prevent post-surgical recurrence of Crohn's disease that has evolved into today's standard-of-care. More recently, he and his team developed a novel approach for diagnosing and treating pre-clinical Crohn's disease, representing a revolutionary approach to IBD management and research. Dr. Sorrentino has published > 150 high-quality publications and delivered speeches on his own research worldwide. His recent work in the United States has garnered awards of research funds exceeding 2 million dollars from major foundations and private sources. (L-Editor: Filipodia)

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Neutrophil to lymphocyte ratio and albumin bilirubin grade in hepatocellular carcinoma: A systematic review

Ayman Bannaga, Ramesh P Arasaradnam

ORCID number: Ayman Bannaga 0000-0003-4814-7864; Ramesh P Arasaradnam 0000-0002-2231-3062.

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Ayman Bannaga, Ramesh P Arasaradnam, Department of Gastroenterology and Hepatology, University Hospital Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, West Midlands, United Kingdom

Ayman Bannaga, Ramesh P Arasaradnam, Warwick Medical School, University of Warwick, Coventry CV4 7HL, West Midlands, United Kingdom

Corresponding author: Ayman Bannaga, MBBS, MRCP, Research Fellow, Department of Gastroenterology and Hepatology, University Hospital Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, West Midlands, United Kingdom.
aymanbannaga@yahoo.com

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a frequent cause of cancer related death globally. Neutrophil to lymphocyte ratio (NLR) and albumin bilirubin (ALBI) grade are emerging prognostic indicators in HCC.

AIM

To study published literature of NLR and ALBI over the last five years, and to validate NLR and ALBI locally in our centre as indicators of HCC survival.

METHODS

A systematic review of the published literature on PubMed of NLR and ALBI in HCC over the last five years. The search followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses. Additionally, we also investigated HCC cases between December 2013 and December 2018 in our centre.

RESULTS

There were 54 studies describing the relation between HCC and NLR and 95 studies describing the relation between HCC and ALBI grade over the last five years. Our local cohort of patients showed NLR to have a significant negative relationship to survival ($P = 0.011$). There was also significant inverse relationship between the size of the largest HCC nodule and survival ($P = 0.009$). Median survival with alpha fetoprotein (AFP) < 10 KU/L was 20 mo and with AFP > 10 KU/L was 5 mo. We found that AFP was inversely related to survival, this relationship was not statically significant ($P = 0.132$). Mean survival for ALBI grade 1 was 37.7 mo, ALBI grade 2 was 13.4 months and ALBI grade 3 was 4.5

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mo. ALBI grades performed better than Child Turcotte Pugh score in detecting death from HCC.

CONCLUSION

NLR and ALBI grade in HCC predict survival better than the conventional alpha fetoprotein. ALBI grade performs better than Child Turcotte Pugh score. These markers are done as part of routine clinical care and in cases of normal alpha fetoprotein, these markers could give a better understanding of the patient disease progression. NLR and ALBI grade could have a role in modified easier to learn staging and prognostic systems for HCC.

Key words: Hepatocellular carcinoma; Albumin bilirubin Grade; Neutrophil to lymphocyte ratio; Alpha fetoprotein; Prognosis; Survival

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Core tip: This review examined the current evidence over the last five years concerning the use of neutrophil to lymphocyte ratio (NLR) and albumin bilirubin (ALBI) as prognostic indicators in Hepatocellular carcinoma (HCC) from a clinical point of view. We also validated NLR and ALBI as prognostic indicators for HCC in a small cohort of patients in our centre. NLR and ALBI provide ways to prognosticate for HCC patients and should be used in addition to other conventional methods to aid in clinical judgment.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the final sequel of chronic liver disease (CLD) with increasing incidence worldwide. The most common causes of chronic liver disease are related to alcohol abuse and chronic viral hepatitis infections (B and C). In the western hemisphere, the incidence is notably increasing following the rise of non-alcoholic fatty liver disease. Early noninvasive diagnostic methods to identify HCC are lacking in primary care. Most of the patients present late with an advanced stage of the disease, which is manifested in poor clinical outcomes^[1,2].

The main system used to estimate the liver function in HCC patients is the Child Turcotte Pugh (CTP). This score was created in the early 1970s as a method for prognostication of CLD^[3,4]. CTP scoring rely on five parameters namely, Bilirubin, Albumin, International Normalised Ratio, Ascites, and Encephalopathy. The last two parameters are dependent on physical examination; this is of course is quite variable between clinicians. While CTP score can be useful in prognostication, a score like the Model For End-Stage Liver Disease (MELD) was shown to have better prognostic value in CLD^[5,6].

HCC prognostic staging systems integrated CTP in addition to imaging results and the comorbid status of the patient. The main staging systems used in HCC include the Barcelona Clinic Liver Cancer (BCLC), Cancer of Liver Italian Program, Hong Kong Liver Cancer staging system, the Japanese Tumour Node Metastasis staging system for primary liver cancer^[1,2].

HCC literature continues to report on studies from around the world aiming to find simpler prognostic markers for the disease. Linear predictive models generated from large data sets were shown to be able to prognosticate for HCC patients^[7,8]. Indeed, simpler prognostic ways are required given the complexity of the intermediate stage of HCC^[9]. The emerging literature describes two new markers in HCC prognosis, the Neutrophil to Lymphocyte Ratio (NLR) and the Albumin Bilirubin (ALBI) grade.

NLR is a simple and generic way to look into the cellular immune response and is considered a measure of the physiologic response of the body to different stressful factors^[10]. NLR was described to be a prognostic factor in many liver diseases. In non-

alcoholic fatty liver disease, NLR was associated with inflammatory activity and different histological fibrotic grades^[11-15]. In chronic viral hepatitis B and C, NLR predicted response to anti-viral therapy^[16-21]. In cirrhosis, NLR was associated with worse outcomes^[22-27]. In alcoholic hepatitis, NLR predicted mortality and identified patients likely to require steroid treatment^[28,29]. In primary biliary cholangitis, NLR predicted one-year mortality^[30,31]. NLR was also studied in liver transplantation and found to be correlated with poor prognosis and graft dysfunction^[32-38]. It is also important to note that NLR was also described to be prognostic in the gastrointestinal, renal tract, lung, and breast cancers^[39-56]. Furthermore, miscellaneous studies identified NLR to be associated with colorectal adenoma, tinnitus, hyperemesis gravidarum, hypertensive renal disease, acute appendicitis, and bacterial and viral infections^[57-65].

Albumin Bilirubin grade was described in 2015 by Johnson *et al*^[66]. It is a mathematical model for assessment of liver function in patients with hepatocellular carcinoma based on data from 1313 Japanese patients. ALBI uses the numerical values of both albumin and bilirubin to measure the distance/relation of these values to the overall prognosis of HCC. Johnson *et al*^[66], identified that $ALBI = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, where bilirubin is in $\mu\text{mol/L}$ and albumin in g/L . ALBI has three grades; $ALBI \leq -2.60$ or Grade 1, $ALBI > -2.60$ to ≤ -1.39 or Grade 2 and $ALBI > -1.39$ or grade 3.

This systematic review aimed to evaluate the studies published over the last five years in relation to the use of NLR and ALBI grade as prognostic indicators in HCC. Additionally, we also evaluated the performance of NLR and ALBI locally in our centre.

MATERIALS AND METHODS

We searched PubMed using the following MeSH Terms “neutrophil to lymphocyte ratio liver” and “albumin bilirubin grade” on February 5, 2020 covering the last 5 years. Following the initial search, all articles were retrieved. The checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was instituted in this review. We further applied the Problem, Intervention, Comparison Outcome (PICO) criteria to filter the retrieved articles, by identifying the problem as HCC patients, interventions as NLR/ALBI, comparators as conventional prognostic scores/systems and outcome as the described prognosis in the clinical studies.

In addition to the systematic search, we also looked into our local results concerning HCC, NLR, and ALBI in our centre. We retrospectively analysed all HCC cases between December 2013 and December 2018. The analysis was done using the IBM SPSS Statistics software version 25. We looked into the baseline characteristics of the patients. Survival analysis was performed using the Kaplan-Meier method and the log-rank test. Bivariate analysis was performed to detect the correlation between different variables and survival using the Independent Samples *t*-test to compare the means between independent groups. We also performed receiver operating characteristic analysis between the ALBI grades, and CTP scores and death from HCC.

RESULTS

NLR and ALBI in HCC

The initial systematic search revealed 430 articles related to NLR. After applying the PICO criteria 376 NLR articles were excluded, leaving 54 studies describing the relation between HCC and NLR (Table 1)^[67-121]. Furthermore, there were 348 articles related to ALBI and after applying the PICO criteria, 253 articles were excluded leaving 95 studies describing the relation between HCC and ALBI (Table 2)^[66,122-216].

HCC outcomes and validation of NLR and ALBI in our centre

Given the strong evidence around NLR and ALBI as demonstrated in (Table 1 and Table 2), we aimed to validate these prognostic indicators in our patients. Between December 2013 and December 2018, a total of 121 HCC patients was identified using the hospital informatics systems. We evaluated their clinical notes, test results, treatment, survival post treatment and overall survival since the diagnosis was made. Overall survival was calculated for each patient by calculating the time when the case was first discussed in the local hepato-pancreaticobiliary (HPB) multidisciplinary team (MDT) meeting till the end of collecting the data on September 3, 2019. The HPB-MDT

Table 1 studies describing the relation between hepatocellular carcinoma and Neutrophil to Lymphocyte Ratio in the last 5 years

Ref.	Type	Patients/Studies (n)	Summary of main clinical points
Kong <i>et al</i> ^[67]	Retrospective	292 patients	Combined preoperative fibrinogen with NLR was an independent predictor OS and DFS in patients with surgically resectable HCC
Hong <i>et al</i> ^[68]	Retrospective	441 patients	NLR was found to be predictive factor of long-term survival and able to identify patients with resectable HCC who benefit from neoadjuvant TACE
Cruz <i>et al</i> ^[69]	Retrospective	190 patients	Elevated baseline NLR was associated with higher rates of HCC tumour progression at two month follow-up imaging after TACE
Uchinaka <i>et al</i> ^[70]	Retrospective	176 patients	Combination of platelet count and neutrophil-lymphocyte ratio (COP-NLR) was an independent predictor for prognosis of HCC patients after hepatic resection
McVey <i>et al</i> ^[71]	Retrospective	422 patients	The objective of this retrospective study was to characterize the NLR on the transplantation waitlist and determine its prognostic utility in LT for HCC. NLR demonstrated a positive correlation with MELD-Na at LT ($P < 0.001$). However, NLR lost its statistical significance when MELD-Na was added to the Cox regression model (OS: HR = 1.46, $P = 0.098$) (recurrence: HR = 1.40, $P = 0.115$). NLR was a volatile marker on the waitlist that demonstrated a significant correlation and collinearity with MELD-Na temporally and at the time of LT. These characteristics of NLR bring into question its utility as a predictive marker in HCC patients
Sun <i>et al</i> ^[72]	Retrospective	47 patients	Pre-treatment NLR ≥ 3.09 is related to poor prognosis of young HCC patients implemented minimally invasive treatment (TACE/RFA). However, it is not an independent indicator for prognosis
Kabir <i>et al</i> ^[73]	Retrospective	132 patients	The preoperative NLR in combination with platelet to lymphocyte ratio was predictive of both OS and recurrence free survival in patients with HCC undergoing curative liver resection
Wong <i>et al</i> ^[74]	Retrospective	789 patients	Elevated NLR is associated with advanced cancer stage and aggressive tumour characteristics, such as large size, rupture, and invasion. NLR ≥ 3 was associated with early and overall recurrence after resection but varied with aetiology
Chon <i>et al</i> ^[75]	Retrospective	1697 patients	The tumour size, tumour number, AFP level, vascular invasion, CTP score, objective response after TACE, and NLR were selected as predictors of OS <i>via</i> multivariate Cox's regression model, incorporated into a 14-point risk prediction model called SNAVCORN score. The prognostic performance of the SNAVCORN score including NLR in patients with HCC treated with TACE was remarkable, much better than those of the conventional scores
Hong <i>et al</i> ^[76]	Retrospective	82 patients	A change in NLR after sorafenib therapy was associated with a better prognosis in patients with advanced HCC
Hu <i>et al</i> ^[77]	Retrospective	565 patients	NLR correlated with the BCLC stages, CTP score and tumour size. However, it was not correlated with Edmondson-Steiner histological grades for HCC
Shiraki <i>et al</i> ^[78]	Retrospective	478 patients	An elevated NLR (> 3.2) is predictive of a poor survival in patients with primary HCC showing normal AFP levels
Uchinaka <i>et al</i> ^[79]	Retrospective	135 patients	NLR was an independent predictor for OS in hepatectomy treated HCC
Hu <i>et al</i> ^[80]	Retrospective	545 patients	AFP and NLR offers better diagnostic performance than either marker alone for differentiating HCC from liver disease
Wu <i>et al</i> ^[81]	Retrospective	344 patients	HCC patients who receive radical liver resection, postoperative NLR ≥ 2.29 implicates poor prognosis. Moreover, postoperative NLR ≥ 2.41 suggests early recurrence, while NLR ≥ 2.15 suggests late recurrence
Wang <i>et al</i> ^[82]	Meta-analysis	17 studies	Elevated preoperative NLR had a close relationship with the OS, RFS and DFS of HCC. Additionally, preoperative NLR was associated with vascular invasion and tumour size
Gauln	Retrospective	109 patients	Prognostic value of NLR was confirmed in noncirrhotic HCC patients who underwent curative-intent liver surgery. In HCC patients with cirrhosis, the prognostic role of

<i>et al</i> ^[83]			NLR was not confirmed
Qi <i>et al</i> ^[84]	Meta-analysis	20475 patients; 90 studies	Low baseline NLR was significantly associated with better OS, RFS and DFS. Low post treatment NLR was significantly associated with better OS. Decreased NLR was significantly associated with OS, RFS and DFS
Tan <i>et al</i> ^[85]	Retrospective	402	Pre-ablation NLR was a valuable predictor in locally advanced HCC patients treated with RFA. NLR ≥ 2.2 indicated a poor prognosis
Najjar <i>et al</i> ^[86]	Systematic review	7902 patients with liver resection; 2929 patients with liver transplantation	Pretransplant NLR was most often predictive of HCC recurrence, RFS and OS. NLR was, however, more variably and less clearly associated with worse outcomes following liver surgical resection
Xu <i>et al</i> ^[87]	Meta-analysis	13 studies 1936 patients	Elevated pretransplant NLR had a close association with the OS, RFS DFS of patients undergoing liver transplantation for HCC, respectively. In addition, elevated NLR was associated with the presence of vascular invasion and Milan criteria
Chen <i>et al</i> ^[88]	Retrospective	287 patients	The combination of the NLR and the PLR, for predicting the survival time of patients with HCC who had received RFA was associated with developing distant intrahepatic recurrence, extrahepatic metastasis, shorter OS and RFS
Lué <i>et al</i> ^[89]	Retrospective	154 patients	NLR was found to be an independent prognostic indicator for OS in HCC patients treated with sorafenib
Liu <i>et al</i> ^[90]	Retrospective	760 patients	Combination of the NLR to the aspartate aminotransferase-to-alanine aminotransferase ratio was found to be an independent marker of poor prognosis in patients with HCC receiving TACE
Margetts <i>et al</i> ^[91]	Retrospective	1168 patients	Neutrophils alone, rather than lymphocytes, were independently associated with outcome
Min <i>et al</i> ^[92]	Meta-analysis	12979 patients	Elevated NLR had a close relationship with OS and DFS of liver cancer. It was also associated with tumour vascular invasion, multiple tumours, AFP ≥ 400 ng/mL, presence of HBV S Ag and cirrhosis
Liu <i>et al</i> ^[93]	Retrospective	793 patients	NLR plus prognostic nutritional index score had superior discriminative abilities, compared with either the NLR or PNI alone in predicting the outcomes of patients with unresectable HCC after TACE
Hung <i>et al</i> ^[94]	Retrospective	672 patients	In patients who had curative liver resection for HCC, NLR > 2.5 had larger tumour size, higher histology grade, and higher rates of tumour multiplicity and vascular invasion. After a median follow up of 76.3 mo, 437 (65.0%) patients had tumour recurrence. When patients had tumour recurrence, 5-year post-recurrent survival was best in the patients staying with NLR ≤ 2.5
Li <i>et al</i> ^[95]	Retrospective	724 patients	In HCC patients undergoing curative resection a prognostic index model, NylLR = [neutrophil count ($10^9/L$) \times γ -glutamyl transpeptidase (U/L)]/[lymphocyte count ($10^9/L$) \times U/L], was selected. Elevated NylLR predicted a worse OS and progression-free survival (PFS) for HCC patients
Jin <i>et al</i> ^[96]	Retrospective	556 patients	Platelet times neutrophil to lymphocyte ratio in hepatitis B related HCC within BCLC stage A was found to be a prognostic indicator of poor outcomes
Zhang <i>et al</i> ^[97]	Retrospective	756 patients	Investigated the outcome of synchronous hepatectomy and splenectomy in HCC. Splenectomy and NLR were found to be significant independent prognostic factors
Li <i>et al</i> ^[98]	Retrospective	81 patients	The preoperative NLR is a prognostic predictor after hepatectomy for HCC patients with portal/hepatic vein tumour thrombosis. NLR > 2.9 indicated poorer OS and DFS
Liu <i>et al</i> ^[99]	Prospective	160 patients	Elevated NLR is associated with the pathogenesis and progression of HBV related HCC. The study also identified that there was also reduced thymic output and hyperactivation of T lymphocytes which may contribute to the decrease of T lymphocytes, which could be also related to the pathogenesis of HBV related HCC
Son <i>et al</i> ^[100]	Retrospective	56 patients	Low NLR was significantly associated with better PFS and OS in patients with locally advanced HCC treated with radiotherapy
Taussig <i>et al</i> ^[101]	Prospective	86 patients	In 86 HCC treatment-naïve patients who had chemoembolization or radioembolization, NLR was found to be associated with early progressive disease after intra-arterial therapy of HCC
Yang <i>et al</i> ^[102]	Retrospective	1020 patients	NLR found to be independent prognostic factor for DFS in HCC patients undergoing hepatectomy

Personeni <i>et al</i> ^[103]	Prospective	98 patients	A study that randomized HCC patients to tivantinib or placebo. High NLR was associated with hazard ratio for overall survival (OS) of 1.58 [95% confidence interval (CI) 1.01; 2.47; $P < 0.046$], corresponding to median OS of 5.1 months <i>vs</i> 7.8 mo in patients with low NLR ($P = 0.044$). In contrast, time to progression was not significantly affected by NLR ($P = 0.20$). Multivariable model confirmed that both NLR > 3 ($P = 0.03$) and presence of vascular invasion ($P = 0.017$) were negatively associated with OS. After adjustment for vascular invasion, NLR independently predicted survival in both the placebo and the tivantinib cohort
Fu <i>et al</i> ^[104]	Retrospective	130 patients	Combination of preoperative Fibrinogen and NLR enlarges the prognostic accuracy of testing in HCC patients who underwent liver transplantation
Ji <i>et al</i> ^[105]	Retrospective	303 patients	Combining the preoperative aspartate aminotransferase to neutrophil ratio index and NLR increases the prognostic accuracy of testing in patients who underwent curative resection for HCC
Yang <i>et al</i> ^[106]	Retrospective	526 patients	Preoperative NLR ≥ 2.81 is an indicator of poor DFS and OS in patients with HCC undergoing surgery
D'Emic <i>et al</i> ^[107]	Retrospective	339 patients	Study evaluated the association between NLR and clinical outcomes in patients receiving SIRT. The results confirm that pre- and/or post-treatment NLR is predictive of clinical outcomes
Arai <i>et al</i> ^[108]	Retrospective	42 patients	Elevated preoperative NLR is an independent predictive risk factor for patients undergoing two-stage treatment combining reductive surgery and percutaneous isolated hepatic perfusion for multiple HCC with portal vein tumour thrombus. The median survival of patients with a preoperative NLR > 2.3 was 14.9 mo, whereas that of patients with a preoperative NLR ≤ 2.3 was 26.1 mo
Hu <i>et al</i> ^[109]	Retrospective	213 patients	Elevated preoperative NLR was found to be a reliable biomarker for assessing early recurrence of HCC after the initial hepatectomy
Lu <i>et al</i> ^[110]	Retrospective	963 patients	NLR is an independent predictor of OS and tumour recurrence after potentially curative resection in HCC patients of BCLC stages 0/A or B
Sun <i>et al</i> ^[111]	Meta-analysis	1687 patients 10 studies	Elevated NLR was significantly associated with poorer OS and poorer DFS in HCC patients treated with LT. In addition, poor prognosis was not altered by cut off values of NLR or types of LT
Tajiri <i>et al</i> ^[112]	Retrospective	163 patients	Pre RFA treatment NLR > 2.5 was significantly associated with recurrence in HBV-HCC
Huang <i>et al</i> ^[113]	Retrospective	1659 patients	NLR measurements were associated with worse OS from HCC patients who had liver resection with curative intent
Wang <i>et al</i> ^[114]	Retrospective	248 patients	NLR > 4 was associated with early tumour recurrence in HCC patients treated with LT
Xiao <i>et al</i> ^[115]	Retrospective	305 patients	NLR > 4 showed recurrence-free survival rates when compared to NLR ≤ 4 in HCC patients treated with LT
Liao <i>et al</i> ^[116]	Retrospective	222 patients	Preoperative NLR is a prognostic marker in HCC after curative resection
Li <i>et al</i> ^[117]	Retrospective	263 patients	The postoperative NLR predicted outcomes of hepatitis B virus-related HCC patients within Milan criteria after liver resection
Sukato <i>et al</i> ^[118]	Retrospective	176 patients	HCC patients with a normal NLR were found to have longer survival than individuals with a high NLR. HCC patients with BCLC stage C disease with elevated NLR may not derive benefit from yttrium-90 radioembolization
Gao <i>et al</i> ^[119]	Retrospective	825 patients	NLR ≥ 2.7 was a significant predictor of poor OS, and the survival period of patients with an NLR ≥ 2.7 decreased with more advanced BCLC and tumour node metastasis stage
Fan <i>et al</i> ^[120]	Retrospective	132 patients	High NLR and was associated with poor prognosis and metastasis in recurrent HCC patients treated with TACE
Okamura <i>et al</i> ^[121]	Retrospective	256 patients	NLR was an independent prognostic factor for overall, and recurrence-free survival in patients who undergo hepatectomy for HCC with curative intent

NLR: Neutrophil to lymphocyte ration; OS: Overall survival; DFS: Disease free survival; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; LT: Liver transplantation; MELD-Na: Model for end-stage liver disease-Na; RFA: Radiofrequency ablation; PLR: Platelet to lymphocyte ratio; RFS: Recurrence free survival ; CTP: Child Turcotte Pugh score ; BCLC: Barcelona clinic liver cancer staging system; AFP: Alpha fetoprotein; HBV: Hepatitis B virus; SIRT: Selective internal radiation therapy.

meeting is formed by HPB surgeon, hepatologist, oncologist, histopathologist and interventional liver radiologist.

HCC diagnosis was based on the identification of the typical hallmarks of HCC, which differed according to the imaging techniques or contrast agents used. All patients had an initial abdominal ultrasound scan either in our hospital or from a referring centre (general practice centre or district hospital). Initial computed tomography scan was used to make the radiological diagnosis. In case of any uncertainty, a dynamic contrast-enhanced MRI was done. 54 patients (44.6%) were diagnosed by HCC features on computed tomography scan while 67 (55.4%) patients were diagnosed with liver MRI features.

Commonest symptoms that patients presented with were abdominal pain and weight loss. Raised alpha fetoprotein (AFP) was found in 68 patients (> 10 KU/L). 82 patients (67.8%) had radiological features of liver cirrhosis. Majority of the patients had relatively good liver function as per CTP score (Table 3). Oesophageal varices and ascites were present in 36 patients (29.8%) and 29 patients had splenomegaly (24%). Patients were staged using the BCLC system (Table 3). Raised AFP (> 10 KU/L) was found in 68 patients (33 patients with AFP > 100KU/L, and 33 patients > 300KU/L). Normal AFP (AFP < 10 KU/L) was found in 53 patients. 50 patients had confirmatory histology for HCC leaving the sensitivity of AFP in comparison to histology to be low at 44%. Morphological characteristics of the HCC are described in (Table 3).

Current HCC treatment modalities available at our centre include liver surgery, radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), palliative chemotherapy (Sorafenib). For the liver transplant, patients were transferred to a nearby national transplant centre and then followed up in our hospital. Curative treatment (liver resection, RFA and/or liver transplant) was done in 13.2% of the patients. Non curative treatment (TACE and Sorafenib) was done in 41.3% of the patients. The rest of the patients (45.5%) were offered the best supportive care due to their late presentation at the time of diagnosis.

There were 10 patients that were referred for a liver transplant, 4 were transplanted. Among the other 6 liver transplant referrals two were denied a transplant because continued alcohol consumption. Three patients were denied a liver transplant because the tumour size increased while waiting for a transplant assessment. One patient died while on the waiting list for a liver transplant. On reviewing the clinical notes, it is important to note that both TACE and RFA were used as a bridge for liver transplant and liver resection in 3 cases. Three patients were offered TACE but declined to have any treatment. Few more cases were offered Sorafenib but declined to have chemotherapy for HCC following discussion with a specialised oncologist.

We divided patients into two groups treated and not treated. The treated group

Table 2 Studies describing the relation between hepatocellular carcinoma and albumin bilirubin grade in the last 5 years

Ref.	Type	Patients/Studies (n)	Summary of main clinical points
Johnson <i>et al</i> ^[66]	Retrospective	6410	ALBI was developed as a simple model to assess liver function, based on 1,313 patients with HCC of all stages from Japan that involved only serum bilirubin and albumin levels. ALBI was then tested using similar cohorts from other geographical regions (<i>n</i> = 5097). The ALBI grade was found to offer a simple, evidence-based, objective, and discriminatory method of assessing liver function in HCC. ALBI was tested in an international setting. ALBI eliminated the need for subjective variables such as ascites and encephalopathy, a requirement in the conventional CTP grade
An <i>et al</i> ^[122]	Retrospective	251	ALBI grade predicted long-term outcomes for HCV-related HCC patients after ultrasound-guided percutaneous microwave ablation (US-PMWA)
Ni <i>et al</i> ^[123]	Retrospective	546	ALBI grade resulted in reliable efficacy for prediction of individualized OS in patients with intermediate-stage HCC after transarterial chemoembolization combined with microwave ablation (TACE-MWA)
Geng <i>et al</i> ^[124]	Meta-analysis	11365 patients 20 studies	In patients with HCC after liver resection, higher ALBI grade was associated with poorer OS and RFS. Correlation between ALBI grade and poor long-term survival was not altered in different geographical areas, sample sizes, follow-up duration, and quality scores
Huang <i>et al</i> ^[125]	Prospective randomized controlled trial	830	ALBI grade was used to stratify patients to compare the clinical application values of contrast-enhanced ultrasound, computed tomography/magnetic resonance-CEUS, and three-dimensional ultrasound-CEUS. Fusion imaging (FI) techniques in the assistance of thermal ablation for HCC. The FI techniques were more suitable in patients with ALBI grade 2 and 3
Soydal <i>et al</i> ^[126]	Retrospective	86	Patients with low ALBI and NLR survive longer after TACE for unresectable HCC
Palmer <i>et al</i> ^[127]	Prospective randomized controlled trial	85	Tumour burden and liver function represented in the ALBI grade are useful tools in HCC patient selection for selective internal radiation therapy
Hatanaka <i>et al</i> ^[128]	Retrospective	93	ALBI grade was a good predictive factor affecting the incidence of fatigue and decreased appetite in HCC patients treated with Lenvatinib
Xu <i>et al</i> ^[129]	Meta-analysis	19805 patients 8 studies	The ALBI grade has the potency of becoming an independent prognostic factor in patients with HCC
Ho <i>et al</i> ^[130]	Retrospective	2186	Newly proposed ALBI-HOME model; is based on ALBI grade, serum AFP, total tumour volume, ascites, performance status, and vascular invasion or metastasis. It was associated with the best prognostic ability among different HCC staging systems to predict survival in patients beyond Milan criteria; its ability remained consistently stable in different treatment subgroups and viral aetiologies
Wu <i>et al</i> ^[131]	Retrospective	134	In HBV related HCC, ALBI grades were significantly associated with OS and RFS. Multivariate analyses further revealed ALBI grades were independent predictors for survival
Mai <i>et al</i> ^[132]	Retrospective	1055	In HBV-related HCC patients who underwent hepatectomy, ALBI- aspartate aminotransferase-platelet ratio index (APRI) score is a novel and effective predictive model of PHLF for HBV-related HCC patients, and its accuracy in predicting the risk of PHLF is better than that of CTP, ALBI and APRI scores
Kornberg <i>et al</i> ^[133]	Retrospective	123	Posttransplant HCC recurrence rates were 10.5%, 15.9%, and 68.2% in ALBI grade 1, 2, and 3, respectively. ALBI grades 1 or 2 were identified as an independent predictor of RFS. ALBI grade 3 proved to be the strongest indicator of microvascular invasion (MVI). ALBI grade provided the best discriminative capacity in selecting liver recipients with low oncological risk profile
Lin <i>et al</i> ^[134]	Retrospective	383	Independent predictors for HCC recurrence were ALBI grades 2 and 3. Independent risk factors for poor survival were ALBI grades 2 and 3. Patients whose deteriorated ALBI grades 5 years after resection had adverse RFS outcomes compared to those with constant and improved ALBI grades. In subgroup analysis, patients with post-operative 5 th -year ALBI grades 2 and 3 had significantly poorer RFS and OS than those with grade 1 among patients with low post-operative 5 th -year AFP (< 15 ng/mL)
Ye <i>et al</i> ^[135]	Retrospective	300	Postoperative ALBI grade could predict the prognosis of patients with HCC after hepatectomy

Zhang <i>et al</i> ^[136]	Retrospective	544	Combination of ALBI grade and the fibrosis-4 index (FIB-4) predicted HCC patient outcomes after liver resection. A high ALBI-FIB-4 score was associated with a high incidence of postoperative recurrence and mortality
Ho <i>et al</i> ^[137]	Retrospective	123	A comparison among ALBI grades at the start of Lenvatinib for treatment for unresectable HCC identified decline in hepatic function in the early stage (≤ 4 weeks, especially within 2 weeks)
Hiraoka <i>et al</i> ^[138]	Retrospective	3690	A proposed ALBI-based nomogram of BCLC system was found to be a feasible strategy to estimate the survival of individual HCC patient except for very early stage patients
Takada <i>et al</i> ^[139]	Retrospective	190	Baseline ALBI was a predictor to direct candidates for second-line treatment after sorafenib in unresectable HCC
Ni <i>et al</i> ^[140]	Retrospective	349	Platelet ALBI (PALBI) grade demonstrated significant greater area under the curve values than ALBI grade or CTP class in predicting 1-, 3- and 5-year OS in patients with large HCCs after transarterial chemoembolization combined with microwave ablation (TACE-MWA)
Nguyen <i>et al</i> ^[141]	Retrospective	110	Baseline ALBI grade is an independent predictor of survival in patients treated with sorafenib
Ho <i>et al</i> ^[142]	Retrospective	1655	ALBI grade is feasible in predicting survival in HCC patients within the Milan criteria, and helps identify high-risk patients who need timely liver transplantation
Lee <i>et al</i> ^[143]	Retrospective	570	ALBI is associated with survival in BCLC stage B HCC patients undergoing TACE. ALBI can be applied to select patients who can get most benefit from TACE
Hiraoka <i>et al</i> ^[144]	Retrospective	84	Good hepatic function represented by the ALBI grades at introduction of the initial tyrosine kinase inhibitor (TKI) is a requirement for improved prognosis of unresectable HCC undergoing TKI sequential therapy, including Lenvatinib (LEN)
Elshaarawy ^[145]	Retrospective	1910	Validation study for the proposed modified albumin-bilirubin-TNM (mALBI-T) grade as a prognostic model for patients with HCC. ALBI-T grade was a superior prognostic tool that selects patients with HCC who have better liver reservoir and tumour stage
Ueshima <i>et al</i> ^[146]	Retrospective	82	Patients with CTP score of 5 and ALBI grade 1 predicted a higher response rate and lower treatment discontinuation due to adverse events by Lenvatinib treatment
Sonohara <i>et al</i> ^[147]	Retrospective	305	Platelet-albumin-bilirubin (PALBI) grade can be used for assessing perioperative risks for hepatectomy for HCC
Antkowiak <i>et al</i> ^[148]	Retrospective	1000	Median OS for ALBI 1, 2, and 3 grades was 46.7, 19.1, and 8.8 months, respectively. Median OS for CTP A, B, and C was 21.7, 11.3, and 6.0 mo, respectively. ALBI outperforms CTP in survival prognosis in yttrium-90 radioembolization (Y90) treated patients. On sub-analyses, serum albumin (not bilirubin) appears to be the main driver of survival prediction
Honmyo <i>et al</i> ^[149]	Retrospective	1270	ALBI and Albumin-Indocyanine Green Evaluation (ALICE) grading systems could estimate the liver function of patients with HCC. Regarding hepatectomy patients, the ALICE grade was a more suitable model than the ALBI grade
Khalid <i>et al</i> ^[150]	Retrospective	71	Mean ALBI score in the study 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 mo (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 statistically significant association
Luo <i>et al</i> ^[151]	Retrospective	132	Combined albumin- bilirubin (ALBI) grade and aspartate aminotransferase-to-platelet count ratio index (APRI) score and presence of microvascular invasion correlated with postoperative mortality. The area under the curve for ALBI-APRI score was significantly higher than either ALBI or APRI alone for predicting both postoperative recurrence and mortality. ALBI-APRI score may be a predictor for the prognosis of patients with HCC within Milan criteria following liver resection
Lu <i>et al</i> ^[152]	Retrospective	2038	Study aimed to identify liver function reserve in CTP class A HCC patients. The platelet-albumin-bilirubin (PALBI) was discriminatory for risk stratification of PHLF grade B/C and OS in CTP class A HCC patients following resection
Lee <i>et al</i> ^[153]	Retrospective	6669	The median OS durations of PALBI grade1 (38.4%), grade2 (33.2%), and grade3 (28.4%) patients were 81, 30, and 5 mo, respectively ($P < 0.001$). The PALBI grade had a larger area under the receiver operator characteristic curve (AUC) than did the CTP class, MELD score, and ALBI grade. Moreover, the PALBI and ALBI grades enabled sub-classification of CTP A patients ($P < 0.001$). In a multivariate analysis, the PALBI and ALBI grades were significant risk factors for OS ($P < 0.05$). According to treatment modality, the PALBI grade was predictive of OS in patients receiving TACE or supportive care. The ALBI grade was predictive of OS in patients undergoing surgical resection or radiofrequency ablation
Su <i>et al</i> ^[154]	Retrospective	594	In HCC after stereotactic body radiation therapy CTP class was significantly related to OS, with a median OS of 29.9 mo in CTP-A, 11.5 in CTP-B. ALBI grade was also significantly related to OS, with a median OS of 53.0 mo in ALBI-1, 19.5 mo in ALBI-2, and 6.5 mo in ALBI-3. The ALBI score was a more objective, discriminatory and

			evidence-based approach in CTP-A groups
Mai <i>et al</i> ^[155]	Retrospective	1044	The preoperative aspartate aminotransferase-to-platelet-ratio index (APRI) score for predicting PHLF was significantly more accurate than CTP, MELD, or ALBI scores
Chen <i>et al</i> ^[156]	Retrospective	271	In patients with very early stage HCC after radiofrequency ablation (BCLC stage 0 HCC). ALBI grade 2 or 3 were the independent risk factors predicting worse OS. Multivariate analysis showed that ALBI grade 2 or 3 was the only one independent risk factor associated with poor recurrence-free survival (RFS) after RFA. Most of the subgroup analyses also demonstrated that patients with ALBI grade 2 or 3 had poorer OS and RFS than those with ALBI grade 1
Zhong <i>et al</i> ^[157]	Retrospective	838	ALBI grade performs at least no worse than CTP score regarding survival prediction for HCC receiving TACE
Sonohara <i>et al</i> ^[158]	Retrospective	273	Combined albumin-bilirubin-TNM (ALBI-T) score in CTP class A HCC could predict perioperative risk in hepatectomy such as longer operation time and excessive intraoperative blood loss
Xu <i>et al</i> ^[159]	Systematic review	22911 patients; 32 studies	High pre-treatment ALBI is associated with poor OS and poor DFS. 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. High ALBI should be treated as an ideal predictor during HCC therapy
Lee <i>et al</i> ^[160]	Retrospective	465	Following HCC surgical therapy, ALBI grade ≥ 2 was demonstrated to be an independent risk factor for early recurrence
Tada <i>et al</i> ^[161]	Retrospective	567	Time-dependent receiver operating characteristic analysis showed that ALBI grade was better than CTP score in predicting overall survival in patients with advanced HCC who received sorafenib therapy
Russolillo <i>et al</i> ^[162]	Retrospective	400	In HCC patients treated with resection, the albumin-indocyanine green evaluation (ALICE) model, correlated better with ALBI than with CTP score. It can be used as measure for liver function
Mohammadi <i>et al</i> ^[163]	Retrospective	124	ALBI is a more sensitive marker of liver function than CTP in the setting of mild dysfunction. Using ALBI identified a subset of patients that have significantly better outcomes from Y-90 radioembolization than previously identified with CTP in HCC patients
Fang <i>et al</i> ^[164]	Retrospective	2285	Patients with single large HCC (SLHCC) had an overall survival rate intermediate to those of the BCLC-A and BCLC-B groups. It is suggested that the SLHCC group could be classified as occupying a different stage from the BCLC stages A and B. ALBI was able to stratify SLHCC into a different prognostic group
Ho <i>et al</i> ^[165]	Retrospective	1038	ALBI was a feasible marker for HCC tumour recurrence after resection
Casadei Gardini, <i>et al</i> ^[166]	Retrospective	416	ALBI score identified patients with higher risk of HCC after treatment with DAAs
Zhang <i>et al</i> ^[167]	Retrospective	338	The ALBI grade showed good predictive ability for PHLF in HCC patients across different BCLC stages. However, the ALBI grade was only a significant predictor of OS in BCLC stage 0/A patients and failed to predict OS in BCLC stage B/C patients
Mohammed <i>et al</i> ^[168]	Retrospective	123	ALBI score before TACE provided objective prognostication for development of acute-on-chronic liver failure (ACLF)
Carling <i>et al</i> ^[169]	Retrospective	49	Platelet-albumin-bilirubin index (PALBI) grade 1 and 2 differentiated survival in CTP-A patients treated with TACE
Jaruvongvanich <i>et al</i> ^[170]	Retrospective	900	Platelet-albumin-bilirubin index (PALBI) was found to be the most accurate prognostic models among to predict mortality and recurrence in HCC patients when compared to CTP score, Fibrosis-4 (FIB-4) score, model for end-stage liver disease (MELD) score, ALBI and AST to platelet ratio index (APRI)
Amisaki <i>et al</i> ^[171]	Retrospective	136	In HCC patients who underwent curative resection Pre- and post-operative ALBI grade predicted patients' overall survival, and recurrence-free survival. Post-operative ALBI grade was associated with patients' surgical factors of repeated hepatic resection, intra-operative bleeding and surgery duration. Post-operative ALBI grade, rather than pre-operative ALBI grade, was an independent predictive factor of long-term outcome of CTP class A patients with HCC
Cai <i>et al</i> ^[172]	Retrospective	389	The Cancer of the Liver Italian Program (CLIP) score is commonly used for prognosis prediction of HCC. Combined ALBI-CLIP scoring system retained the prognostic value of the CLIP in HBV-related HCC treated with TACE therapy
Li <i>et al</i> ^[173]	Retrospectives	475	A high combined ALBI- platelet-to-lymphocyte ratio (ALBI-PLR) score is associated with a high incidence of postoperative recurrence and mortality in HBV-related HCC patients after liver resection

Ho <i>et al</i> ^[174]	Retrospective	174	Among CTP class A HCC patients receiving radiotherapy, the PALBI and ALBI grade were better prognostic tools than the CTP score
Murray <i>et al</i> ^[175]	Retrospective	102	The baseline ALBI grade was more discriminating than the CTP score in predicting OS and toxicity in patients with CTP class A liver disease patients with HCC treated with stereotactic body radiation therapy (SBRT)
Okuda <i>et al</i> ^[176]	Retrospective	38	ALBI grade was a prognostic factor for survival from brain metastases in HCC patients
Luo <i>et al</i> ^[177]	Retrospective	785	The prognostic significance of the PALBI grade for postoperative recurrence and mortality was maintained when stratified by the TNM stage. The preoperative PALBI grade is a surrogate marker for the postoperative prognosis in patients with HBV-related HCC after liver resection
Ho <i>et al</i> ^[178]	Retrospective	645	ALBI revealed the highest homogeneity and lowest value among twelve invasive models, indicating a better prognostic performance
Lei <i>et al</i> ^[179]	Retrospective	395	ALBI scores exhibited parallel tendencies to the CTP and MELD scores in HBV-ACLF, HBV-LC, and HBV-HCC patients; thus, ALBI grading may be a simple but applicable method for the evaluation of the functional status of patients with HBV-related end-stage liver diseases
Na <i>et al</i> ^[180]	Retrospective	2099	ALBI grade provided better prognostic performance in survival analysis and better distribution of the grades than C-P grade in HCC, suggesting that ALBI grade could be a good alternative grading system for liver function in patients with HCC
Chong <i>et al</i> ^[181]	Retrospective	63	Liver resection offered superior disease-free survival to microwave ablation (MWA) in patients with HCC. The ALBI grade could identify patients with worse liver function who might gain survival advantage from MWA
Gkika <i>et al</i> ^[182]	Retrospective	40	In HCC patients with BCLC classification stage B or C who were treated with SBRT in 3-12 fractions. A higher ALBI grade and CTP at baseline correlated with a higher incidence of acute and late radiation toxicities
Chen <i>et al</i> ^[183]	Retrospective	887	In patients with HCC with compensated liver function, a combination of albumin-bilirubin grade and platelet count (ALBI-PLT) score of 2 predicted a very low risk of variceal haemorrhage; therefore, endoscopic screening for esophageal varices is not recommended for these patients
Hiraoka <i>et al</i> ^[184]	Retrospective	46681	Study compared between Japan Integrated Staging (JIS), consisting of CTP classification and TNM staging (TNM), modified JIS (m-JIS), consisting of liver damage grading and TNM, and ALBI-TNM (ALBI-T), consisting of ALBI grading and TNM. The predictive value for prognosis of ALBI-T was found to be equal to that of JIS and m-JIS
Yoh <i>et al</i> ^[185]	Retrospective	207	A preoperative prognostic model using objective variables involving two parameters 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) and the albumin-bilirubin (ALBI) grade was useful for estimating the prognosis of selected patients with solitary HCC
Dong <i>et al</i> ^[186]	Retrospective	654	ALBI grade significantly influenced the overall survival and cumulative recurrence rates. Furthermore, the ALBI score was significantly related to the degree of liver cirrhosis and serum γ -glutamyl transpeptidase (GGT) concentration in solitary HCC cases within the Milan criteria and CTP A cirrhosis. Additionally, the combination of the ALBI score and serum GGT concentration contributed to the prognosis prediction in this cohort
Li <i>et al</i> ^[187]	Retrospective	258	Postoperative worsening of ALBI grade was associated with increased recurrence and poorer overall survival for patients with HBV-related HCC within the Milan criteria
Hsu <i>et al</i> ^[188]	Retrospective	1935	Risk Assessment for early Mortality (RAM) scoring system is a developed tool for assessing early mortality after hepatectomy for HCC. RAM score was obtained by the summation of the scores of 6 independent variables, namely diabetes mellitus (1), albumin \leq 3.5 g/DL (2), α -fetoprotein > 200 ng/ML (2), major resection (1), blood loss > 800ML (1), and major surgical complications (3). RAM classes were developed by visual inspection of the Kaplan-Meier survival curves, and RAM class I, II, and III corresponded to RAM scores of 0-6, 7-9, and 10, respectively. This study demonstrated that RAM score is an effective and user-friendly bedside scoring system to predict early mortality and early recurrence after hepatectomy for HCC. In addition, the predictive capability of RAM score is superior to ALBI and MELD scores
Hiraoka <i>et al</i> ^[189]	Retrospective	647	Study 1 comprised of 212 Barcelona clinic liver cancer stage-B (BCLC-B) HCC patients classified as CTP-A who had received repeated TACE treatments (r-TACE) (naïve: recurrence = 66:146). Study 2 comprised of 435 patients with unresectable HCC classified as CTP-A in whom sorafenib was introduced (naïve:recurrence = 37:398). The rate of patients with downgraded hepatic function with repeated TACE procedures, especially with regard to ALBI-grade, was not low. ALBI-grade was shown to be a better hepatic function assessment tool than CTP in patients receiving sorafenib treatment. Strict judgment of TACE-refractory status in patients with unresectable HCC is needed to improve prognosis before downgrading the hepatic function
Pinato <i>et al</i> ^[190]	Retrospective	387	Multi-centre retrospective study, the albumin-bilirubin grade highlights the interplay between liver reserve and immune dysfunction as prognostic determinants in HIV-associated HCC
Oh <i>et al</i> ^[191]	Retrospective	368	Among patients with very early-stage HCC treated with RFA, ALBI grade was a good stratifying biomarker. ALBI grade was better tool for assessing liver function than CTP

			score for very early-stage HCC treated with RFA
Lo <i>et al</i> ^[192]	Retrospective	152	ALBI was a predictor for both survival and liver toxicity. Complementary use of CTP and ALBI score could predict the risk of post stereotactic ablative radiation therapy (SABR) liver toxicity. Further prospective studies are necessary before use of the ALBI score can become part of daily practice
Chong <i>et al</i> ^[193]	Retrospective	488	Liver resection offered superior survival to RFA in patients with BCLC stage 0/A HCC. The ALBI grade could identify those patients with worse liver function who did not gain any survival advantage from curative liver resection
Lee <i>et al</i> ^[194]	Retrospective	404	ALBI can stratify the patients with advanced HCC for the second-line trials or salvage therapy
Hansman <i>et al</i> ^[195]	Retrospective	180	ALBI grades are accurate survival metrics in high-risk patients undergoing conventional TACE for HCC
Zou <i>et al</i> ^[196]	Retrospective	229	The ALBI score showed superior predictive value of post-operative outcomes over CTP score
Ho <i>et al</i> ^[197]	Retrospective	881	ALBI grade served as an objective and feasible surrogate to predict the prognosis of HCC patients undergoing TACE
Hiraoka <i>et al</i> ^[198]	Retrospective	3495	ALBI grade is a useful and easy classification system for assessment of hepatic function for therapeutic decision making
Kao <i>et al</i> ^[199]	Retrospective	622	ALBI grade offered personalized long-term survival data for patients with early-stage HCC who undergo RFA
Gui <i>et al</i> ^[200]	Retrospective	117	ALBI grade demonstrated clear survival discrimination that is superior to CTP class among HCC patients treated with radio-embolization, particularly within the subgroup of CTP class A patients
Kuo <i>et al</i> ^[201]	Retrospective	260	ALBI grade at baseline and also ALBI grade change during treatment predicted the prognosis of advanced HCC patients who received sorafenib
Waked <i>et al</i> ^[202]	Retrospective	3030	The ALBI grade categorised patients receiving TACE into three clear prognostic groups, thereby emphasising the importance of underlying liver function in the outcome of TACE
Pinato <i>et al</i> ^[203]	Retrospective	447	The ALBI grade at sorafenib discontinuation identified a subset of patients with prolonged stability of hepatic reserve and superior survival. This may allow improved patient selection for second-line therapies in advanced HCC
King <i>et al</i> ^[204]	Retrospective	448	Patients with ALBI grade > 1, CTP class B or poor performance status seem to derive limited benefit from sorafenib treatment
Li <i>et al</i> ^[205]	Retrospective	491	The ALBI grade added superior prognostic value compared to CTP class in patients with HCC who underwent liver resection
Ma <i>et al</i> ^[206]	Retrospective	318	ALBI grade predicted OS in patients with early-HCC. Reclassification of CTP class according to ALBI grade might improve the management of HCC
Liu <i>et al</i> ^[207]	Retrospective	3182	ALBI grades assess liver dysfunction in HCC. The PALBI grade is consistently better in all patients, in patients with minimally decreased liver function, and in patients receiving different aggressive therapies
Pinato <i>et al</i> ^[208]	Retrospective	2426	In this large, multi-centre retrospective study, the ALBI grade satisfied the criteria for accuracy and reproducibility following statistical validation in Eastern and Western HCC patients, including those treated with TACE. Consideration should be given to the ALBI grade as a stratifying biomarker of liver reserve in routine clinical practice
Hiraoka <i>et al</i> ^[209]	Retrospective	754	ALBI grade is simple and useful for prediction of prognosis and therapy decision-making in the heterogeneous population of BCLC stage B patients
Chan <i>et al</i> ^[210]	Retrospective	1973	The ALBI grade performs as well as the CTP grade when integrating into the CLIP system
Edeline <i>et al</i> ^[211]	Retrospective	1019	ALBI should be a stratifying factor in trials of systemic therapy
Hickey <i>et al</i> ^[212]	Retrospective	428	ALBI grade outperforms CTP class at discriminating survival in patients receiving TACE or (90) Y radioembolization. ALBI grade is also valuable in patients with moderate liver dysfunction and BCLC stage B disease
Wang <i>et al</i> ^[213]	Retrospective	1242	The ALBI grade predicted PHLF and OS in patients with HCC undergoing liver resection with curative intent more accurately than the CTP class

Chan <i>et al</i> ^[214]	Retrospective	3696	The ALBI grade performed as well as CTP class when integrated into the BCLC staging system in terms of predicting clinical outcome of HCC regardless of regions, aetiology, and treatment options
Hiraoka <i>et al</i> ^[215]	Retrospective	2584	ALBI grade was found to be superior for distinguishing patients with better hepatic function. ALBI-TNM scoring may be a better total prognostic scoring system for predicting survival of Japanese patients with HCC
Ogasawara <i>et al</i> ^[216]	Retrospective	89	Sorafenib may be indicated for all patients with advanced HCC and ALBI grade 1 and for some with ALBI grade 2. The subdivision of patients with ALBI grade 2 increases the utility of ALBI in identifying patients indicated for sorafenib therapy

ALBI: Albumin bilirubin grade; HCC: Hepatocellular carcinoma ; CTP: Child turcotte pugh score; HCV: Hepatitis C virus; US-PMWA: Ultrasound-guided percutaneous microwave ablation; TACE-MWA: Transarterial chemoembolization combined with microwave ablation; OS: Overall survival; RFS: Recurrence free survival; CEUS: Contrast-enhanced ultrasound; NLR: Neutrophil lymphocyte ratio; SIRT: Selective internal radiation therapy; PHLF: Post-hepatectomy liver failure; BCLC: Barcelona clinic liver cancer staging system; MELD: Model for end-stage liver disease; RFA: Radiofrequency ablation; DAAs: Direct-acting antivirals; PALBI: Platelet-albumin-bilirubin index; FIB-4: Fibrosis-4 ; APRI: AST to platelet ratio index; CLIP: Cancer of the liver Italian program; DFS: Disease free survival; HBV: Hepatitis B virus; AUC: Area under the curve.

included curative and non-curative modalities. The mean and median survival for the treated group was 29.7 mo and 18 mo, respectively. The mean and median survival for the non-treated group was 7.7 mo and 4 mo, respectively. This can be observed in the Kaplan-Meier survival curves for the treated and non-treated groups in (Figure 1A). Mean survival for resection was 47.8 mo, liver transplant was 23.2 mo, RFA was 12.29 months, TACE was 17.3 mo and Sorafenib was 4 mo.

CTP Score was also good in predicting overall survival. The mean and median survival for CTP (A) was 26.3 and 15 mo, CTP (B) 9.6 and 5 mo and CTP (C) 3.2 and 2 mo. This can be also observed in the survival curves (Figure 1B).

Overall survival per tumour number is shown in (Table 3). There was a negative significant relationship between the size of the largest HCC tumour/nodule detected on imaging and survival ($P = 0.009$). Our study also showed that BCLC is a good staging system when it comes to survival. The median survival for BCLC 0 was 50 mo, BCLC A was 40 mo, BCLC B was 21 mo, BCLC C was 6 mo and for BCLC D was 2 mo. Median survival with AFP < 10 KU/L was 20 mo and with AFP > 10 KU/L was 5 mo. We found that AFP was inversely related to survival, the higher the AFP the smaller number of months they live after HCC diagnosis. However, this relationship was not statically significant ($P = 0.132$).

NLR had a significant ($P = 0.011$) negative relationship, the higher the NLR the smaller number of months patients live after HCC diagnosis. NLR was categorised to < 3 and > 3 as previously described literature (Figure 1C). The mean and median survival with NLR < 3 was 24.5 and 11 mo respectively and with NLR > 3 the mean was 12.1 mo and the median survival was 6 mo.

We also calculated the ALBI grades at diagnosis and compared them to overall survival. The mean and median survival for ALBI grade 1 were 37.7 and 26 mo, ALBI grade 2 were 13.4 and 6 mo and for ALBI grade 3 were 4.5 and 3 months (Figure 1D).

Visually the Kaplan Meier curves showed better discriminative performance for ALBI grade than CTP score. To further evaluate this, we performed a comparison between receiver operating characteristics curves of CTP and ALBI. The area under the curve showed that ALBI was better than CTP in detecting death from HCC (Figure 2).

Table 3 Characteristics of hepatocellular carcinoma in University Hospital, Coventry, United Kingdom between December 2013 and December 2018

CTP Score	Patients (n)	Percentage
A	78	64.5%
B	29	24%
C	14	11.5%
BCLC stage	Patients (n)	Percentage
Stage 0	2	1.7%
Stage A	16	13.2%
Stage B	44	36.4%
Stage C	22	18.2%
Stage D	37	30.6%
Number of HCC nodules	Patients (n)	Percentage
1 nodule ¹	60	49.6%
2 nodules	11	9.1%
3 nodules	5	4.1%
> 3 nodules	45	37.2%
Number of HCC nodules	Mean survival	Median survival
1 nodule	23.8 mo	11 mo
2 nodules	26 mo	24 mo
3 nodules	26 mo	36 mo
> 3 nodules	9.7 mo	5 mo

¹Largest nodule mean size was 7.08 cm (SD 4.17 cm, minimum 1 cm to maximum 26 cm). The table shows child turcotte pugh score, barcelona clinic liver cancer stage, morphological characteristics of the hepatocellular carcinoma, mean and median overall survival. CTP: Child turcotte pugh score; BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma.

DISCUSSION

Our systematic search identified many studies describing NLR and ALBI in HCC over the last 5 years. Indeed, they are simple to use and they are also done routinely in HCC patients. It is important to note that NLR was proposed to be a surrogate marker of inflammation and immunological status in many diseases not just solely in HCC, it was also reported to add prognostic value in various other cancers. Only a few studies in this review found NLR not an independent indicator for prognosis^[71,72], while many studies associated NLR with HCC progression and metastatic spread. In particular, our review identified that NLR was associated with tumour vascular invasion and large tumour size and raised NLR (> 3) was associated with early and overall recurrence and survival after resection in HCC patients. Our local cohort also revealed that patients with high NLR (> 3) had an inversely significant relationship with survival.

In this review, the ALBI results described in (Table 2) showed better discriminative performance than CTP class as an indicator for survival after HCC diagnosis in many studies. ALBI was validated in large cohorts and was shown to be a good prognostic model in HCC. ALBI was shown to be able to stratify the choice of therapeutic interventions in HCC, in addition to the morphological features of HCC.

Our local cohort demonstrated typical characteristics for the HCC patient, being frequently in males and that two thirds of the patients had liver cirrhosis. Commonest presenting symptoms were abdominal pain and weight loss. In addition to this incidental diagnosis and hepatic decompensation were also common. This suggests that there was variability in the clinical presentation. Biochemical liver abnormality was commonly detected with serum Alkaline phosphatase being markedly raised in comparison to Alanine transaminase.

We would like to highlight that nearly 50% of the patients in our study had normal

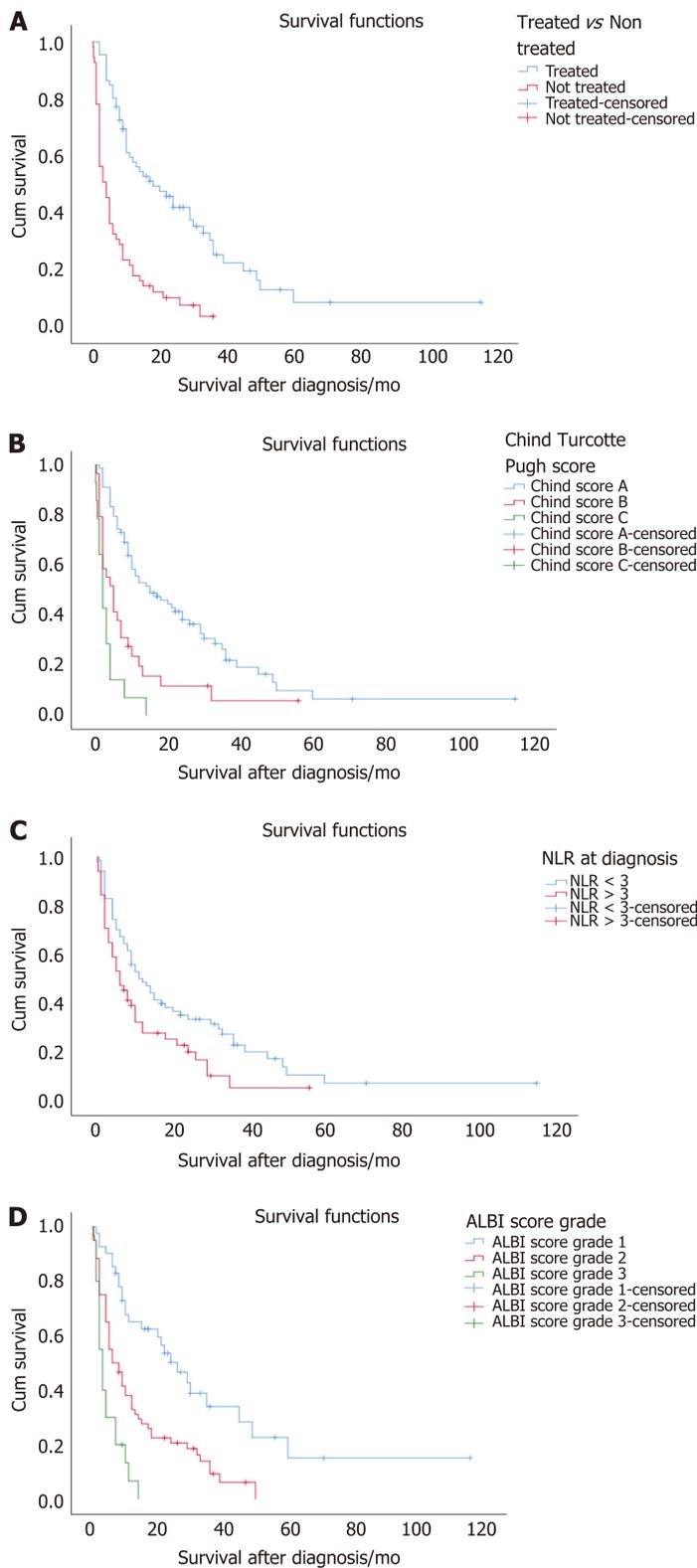


Figure 1 Hepatocellular carcinoma survival curves. A: Survival curve between the treated and non-treated group; B: Survival curve between different stages of the child Turcotte Pugh score; C: Survival curve comparing low and high neutrophil to lymphocyte ratio; D: Survival curve comparing different albumin bilirubin grades. NLR: Neutrophil to lymphocyte ratio. ALBI: Albumin bilirubin.

AFP. This suggests its poor sensitivity and specificity. International guidelines advised on not using AFP routinely in screening patients at risk of developing HCC^[1,2]. As in the literature, we found that in secretory HCC the serum AFP increases with the tumour growth and can predict poor survival and hence AFP can be considered a predictor of survival in patients who already had raised AFP at time of the diagnosis.

We found that patients who were treated with surgical resection have survived

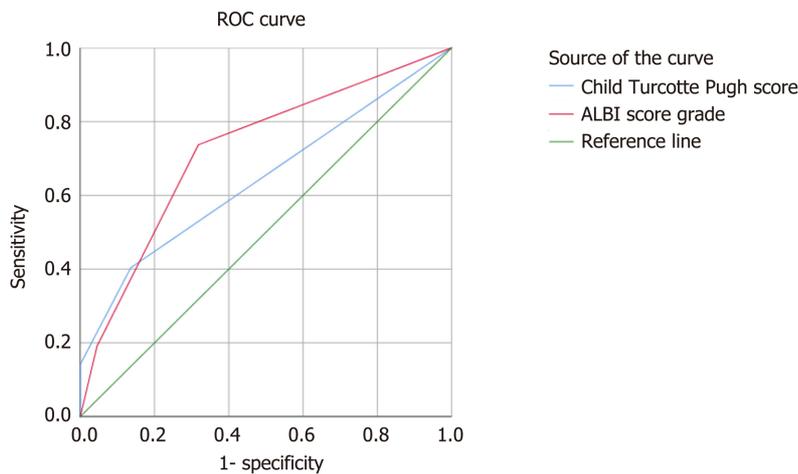


Figure 2 Receiver operating characteristic curves comparing between child turcotte pugh score and albumin bilirubin grading system.

The area under the curves represents death from hepatocellular carcinoma. ROC: Receiver operating characteristic.

more than patients who had a liver transplant. However, this is not significant given that only 4 patients underwent liver transplantation in our cohort. RFA and TACE were used in some cases as bridge therapy while awaiting transplantation. Some patients who underwent chemotherapy by Sorafenib often developed side effects and were not able to continue with the chemotherapy.

This review was limited to 5 years only and hence not inclusive of all data around NLR and HCC. Nevertheless, studies concluded in (Table 1) are sufficient to formulate a clinical opinion that NLR is a generic marker of inflammation in HCC and is associated with the overall prognosis. On the other hand, the review included all studies published since the first paper describing ALBI. Another limitation is that nearly all studies were retrospective, however, many had large numbers of HCC patients.

Many HCC patients are diagnosed radiologically in this era. The cancer HPB-MDT involved need to adequately prognosticate and stage patients. NLR and ALBI can aid by eliminating variable judgement between clinicians. Given the evidence from this systematic search, we argue that ALBI can be incorporated in staging HCC rather than CTP and that NLR can be used as an additional marker for severity of HCC in case of normal AFP. This will be required to be looked into by the interested stakeholders in the care of HCC patients.

CONCLUSION

NLR and ALBI are validated easy cost-effective markers that can predict survival and help in stratifying therapeutic interventions. They should be included in modified staging systems for HCC. They can be used for monitoring inflammation status and liver function in HCC patients in addition to overall functional status and radiological features.

ARTICLE HIGHLIGHTS

Research background

Neutrophil to lymphocyte ratio (NLR) and albumin bilirubin (ALBI) are emerging prognostic indicators in hepatocellular carcinoma (HCC). This review aimed to evaluate the use of these indicators in published clinical studies over the last 5 years.

Research motivation

HCC staging systems are complex and include many parameters to determine the overall therapeutic goals and prognosis. There is a need for a simple way to prognosticate for these patients. ALBI and NLR are numerical values that can be obtained easily from patient records.

Research objectives

To study the published literature of NLR and ALBI from a clinical point of view.

Research methods

Systematic search over the last 5 years of published literature on NLR and ALBI, and validation of these markers in a retrospective cohort locally in our centre.

Research results

NLR is a generic measure of inflammation in infection, cancer and the critically ill. Raised NLR predicted HCC prognosis and survival. ALBI was better than CTP score in predicting overall survival and liver function in HCC patients. NLR and ALBI can be used in prediction of HCC recurrence after surgery, ablation and chemo/radioembolisation.

Research conclusions

NLR and ALBI can be used in staging and prognosis of HCC.

Research perspectives

Stakeholders interested in HCC care should consider the use of NLR and ALBI in staging systems for HCC.

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