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Monocyte/granulocyte to lymphocyte ratio and the MELD score as predictors for early recurrence of hepatocellular carcinoma after trans-arterial chemoembolization

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ABSTRACT

Background: The first-line treatment option for intermediate-stage hepatocellular carcinoma is trans-arterial chemoembolization (TACE). Blood indices, such as lymphocyte/monocyte ratio (LMR), lymphocyte count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte-granulocyte/lymphocyte ratio (MGLR) and red blood cell distribution width (RDW), are prognostic biomarkers in certain diseases. The model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores have been designed for patients with cirrhosis waiting for liver transplantation and in patients with hepatocellular carcinoma. We hypothesized possible roles for these blood indices, and the MELD and CTP scores as predictors for early recurrence of hepatocellular carcinoma after TACE.

Methods: Routine laboratory indices determined the NLR, LMR, MGLR, RDW, PLR, as well as MELD and CTP scores in 147 patients. Sensitivity and specificity of the indices for hepatocellular carcinoma recurrence 36 months after TACE were estimated by receiver operator characteristic curve.

Results: In multivariate regression analysis, only male sex, the lymphocyte count, CTP, the MGLR and the MELD score significantly ($P < 0.01$) predicted recurrence. The area under curve (AUC) for detection of recurrence for MGLR at a cut-off value 2.75 was 0.63 (95% CI 0.54–0.72) with sensitivity 70.7%, specificity 59.2% and accuracy 63%. The MELD score at cut-off value 9.5 had diagnostic performance with AUC 0.71 (0.63–0.79), sensitivity 80% and specificity 55.8% and accuracy 71.3%.

Conclusions: High MGLR and MELD scores are linked to increasing frequency of hepatocellular carcinoma recurrence after TACE and could be used as novel, simple, non-invasive prognostic tests.

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KEYWORDS
Blood indices; MELD score; prognosis; hepatocellular carcinoma; trans-arterial chemoembolization

Introduction

Hepatocellular carcinoma is the most common primary malignant tumour of the liver, constituting about 90% of all primary liver cancers and a leading cause of cancer-related death [1]. The most important risk factors for this disease are chronic viral hepatitis, exposure to aflatoxin B1 and excessive intake of alcohol [2]. The overall outcome of patients is poor. In early stages of the tumour, which account for ≤30% of patients, hepatic resection, liver transplantation and locoregional therapy may be curative. Trans-arterial chemoembolization (TACE) constitutes the first-line treatment option for intermediate-stage hepatocellular carcinoma [3]. TACE improves survival in most patients with intermediate or advanced stages of the disease [4], leaving room for improved scoring methods that will identify those patients that are more likely to have better prognosis [5].

The model for end-stage liver disease (MELD) is a scoring system built on three laboratory parameters (creatinine, total bilirubin and international normalized ratio [INR]), each variable has its specific prognostic effect [6]. It has been designed for patients with cirrhosis waiting for liver transplantation and in patients with hepatocellular carcinoma to evaluate hepatic dysfunction [7]. The Child-Turcotte-Pugh (CTP) score has been the standard assessment of the severity of liver cirrhosis [8]. It relies on three objective laboratory parameters (total bilirubin, albumin and INR) and two subjective variables (ascites and hepatic encephalopathy). The CTP has been widely used to predict the surgical risks [9] and mortality-related post-transcatheter arterial embolization [10].

Indices such as lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), C-reactive protein and platelet/lymphocyte ratio (PLR), have been identified as prognostic biomarkers in several cancers [11,12]. Alterations in other blood indices such as

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monocyte-granulocyte/lymphocyte ratio (MGLR) and red blood cell distribution width (RDW) have also been reported as survival biomarkers [13,14]. We hypothesize that the different blood indices NLR, MGLR, RDW, lymphocyte count and PLR, in comparison to the MELD and CTP scores, can predict the outcome of hepatocellular carcinoma after TACE.

Patients and methods

We tested our hypothesis on 147 patients diagnosed with HCV-related hepatocellular carcinoma treated with conventional TACE, between September 2012 and November 2016 at Tropical Medicine Department, Diagnostic and Intervention Radiology Department, Faculty of Medicine, Mansoura University, Egypt. Written informed consent was obtained from all patients, and the study was approved by the ethical committee of Mansoura Faculty of Medicine. The diagnosis of hepatocellular carcinoma made by European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer criteria [15]. All patients underwent conventional TACE by injecting a mixture of lipidol and doxorubicin powder (according to body surface area): only those with evidence of complete response with good lipidol uptake of the tumours were recruited [16]. Other inclusion criteria were CTP score class A or B cirrhosis, no extrahepatic metastasis, no portal vein thrombosis, prothrombin time ratio >50%, platelet count >50,000/mm^3, size of the tumour <6 cm and no prior treatment before TACE.

A full blood count, prothrombin time, liver function tests, albumin and α-fetoprotein were obtained by standard routine methods prior to the TACE. The size of the tumour was determined by ultrasound. These indices provide NLR, MGLR (white cell count minus lymphocyte count vs. the lymphocyte count) and PLR. The CTP score was calculated by the Pugh score modification [17]. The MELD score was calculated using the following formula: MELD score = 0.957 × log (creatinine mg/dL) + 0.378 × $\log_e$ (bilirubin mg/dL) + 1.120 × $\log_e$ (INR) + 6.43 [18].

Follow-up by Triphasic CT and/or MRI was done 1 month after treatment. For patients with evidence of complete response, follow-up was done every 3 months over 36 months using ultrasound imaging. Data were analysed by SPSS version 17 (SPSS Inc., Chicago, IL). Subjects were dichotomized by outcome and predictors sought by *t* test, Mann–Whitney *U* test or chi-squared test as appropriate. Those indices significant at $P < 0.05$ were taken forward to a logistic multivariate Cox regression analysis.

Results

Table 1 shows patients' baseline characteristics. At follow-up, 75 had recurrence of their cancer: 72 were free of recurrence. The cumulative free recurrence periods at 12, 24 and 36 months were 100%, 76% and 40%, respectively. Univariate and multivariate analyses of the prognostic factors for recurrence after TACE were performed (Table 2). In univariate analysis, male gender, the CTP score, lymphocyte count, platelet count, albumin, α-fetoprotein, MGLR and MELD score all predicted outcome. In multivariate analysis only male gender, the CPT score, lymphocyte count, α-fetoprotein, MGLR and the MELD score were retained as being independently associated with recurrence. However, of these, only MGLR and MELD had ROC/AUC significance at $P < 0.05$: the lymphocyte count failed to reach significance (Table 3, Figure 1). Table 3 also shows sensitivity, specificity, positive predictive value, negative predictive value and accuracy for these indices.

Discussion

Cytokines and inflammatory cells found in tumours are likely to contribute to tumour growth, progression and immunosuppression [19]. In cancer patients, haematological markers of systemic inflammation have been shown to have prognostic value [20]. We hypothesized that certain blood indices (RDW, NLR, MGLR, PLR, lymphocyte count) are comparable to the MELD and CTP scores as prognostic predictors for early recurrence of hepatocellular carcinoma after TACE. We found that the MGLR and the MELD score were both significant predictors of outcome. This result supports the finding of Zhou et al. [14]

Table 1. Baseline characteristics of the patients.

Variables	Value
Age (years)	56.2 (6.3)
Gender N (%)	Male 111 (75.5%)
	Female 36 (24.5%)
Child-Pugh-Turcoitt Class N (%)	A: 123 (83.7%)
	B: 24 (16.3%)
Albumin (g/dL)	3.5 (0.6)
Bilirubin (mg/dL)	1.3 (0.6)
ALT (IU/L)	53.2 (20.2)
AST (IU/L)	50.8 (17.6)
INR	1.3 (0.1)
AFP (ng/mL)	250 (110–420)
Total leucocyte count (10^9/L)	6.8 (2.5)
Neutrophils(10^9/L)	4.1 (1.7)
Lymphocytes (10^9/L)	1.8 (0.8)
Platelets (10^9/L)	114 (41.5)
NLR	2.4 (0.9)
MGLR	2.98 (1.2)
PLR	74.8 (3.8)
RDW (fL)	49.14 (6.26)
MELD score	11.04 (2.86)
Diameter of the largest tumour (cm)	4.1 (1.4)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; MELD: model for end stage liver disease; AFP: alpha fetoprotein; NLR: neutrophil lymphocyte ratio; MGLR: monocyte granulocyte lymphocyte ratio; RDW: red cell distribution width; PLR: platelet lymphocyte ratio, fL: femtoliters. Numerical data mean (SD) or median (IQR).

Table 2. Univariate and multivariate analysis of clinical, laboratory and demographic data.

	Univariate analysis			Multivariate analysis	
Parameter	No recurrence	Recurrence	*P* value	Hazard ratio (95% CI)	*P* value
Sex (M/F)	60 (83.3%) 12 (16.7%)	51 (68.0%) 24 (32.0%)	0.031	4.6 (1.67–12.94)	0.003
CPT score	5.45 (0.57)	6.0 (1.0)	0.001	2.36 (1.16–4.8)	0.02
Age	56.4 (6.5)	55.9 (6.1)	0.17		
WBCs	6.6 (2.2)	7.1 (2.8)	0.065		
Neutrophils	3.9 (1.6)	4.3 (1.7)	0.27		
Lymphocytes	1.7 (0.6)	1.9 (0.9)	0.002	2.49 (1.28–4.87)	0.007
Platelets	108 (36)	120 (45)	0.007	1.00 (0.99–1.02)	0.31
Albumin	35 (5.5)	34 (7.3)	0.001	0.99 (0.43–2.25)	0.96
Bilirubin	1.17 (0.45)	1.40 (0.61)	0.057		
AST	53 (21)	49 (13)	0.069		
ALT	55 (24)	52 (16)	0.087		
INR	1.27 (0.11)	1.36 (0.11)	0.607		
AFP	160 (28–170)	320 (142–455)	0.001	1.0 (1.0–1.004)	0.01
Tumour diameter	3.82 (1.38)	4.36 (1.44)	0.053		
NLR	2.31 (0.81)	2.52 (1.01)	0.14		
MGLR	2.94 (0.83)	3.02 (1.39)	0.017	1.92 (1.32–2.8)	0.005
PLR	70.9 (34.9)	78.4 (41.2)	0.15		
RDW	48.5 (5.7)	49.6 (6.7)	0.061		
MELD score	9.87 (2.3)	12.16 (2.8)	0.004	3.3 (1.08–1.57)	0.001

Abbreviations and units as per Table 1.

Table 3. Area under ROC curve and cut-off values of MGLR, MELD score and lymphocyte count.

	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy
MGLR	0.63 (0.54–0.72)	2.75	70.7%	59.2%	71.5%	58.9%	62.9%
MELD score	0.71 (0.63–0.79)	9.5	80%	55.8%	69%	52%	71.3%
Lymphocyte count	0.55 (0.45–0.64)	1.77	60%	55%	63%	58%	55%

ROC: receiver operating characteristic; MGLR: monocyte granulocyte lymphocyte ratio; MELD: model for end stage liver disease; AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.

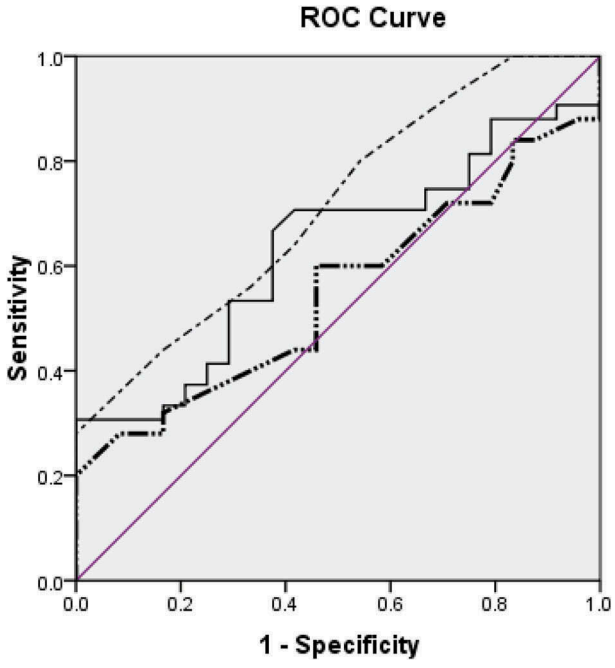

Figure 1. AUC analyses of lymphocyte (▬··), MGLR (——), and MELD score (– – –). The solid line is reference.

that MGLR predicts outcome, but we fail to support their finding that MGLR is comparable to the NLR. However, we extend their work in showing that the MGLR is comparable to the MELD score and is superior to the CTP score.

Cancer development may occur as a result of chronic systemic inflammation, as this can encourage tumour progression by many mechanisms [21,22]. Increased number of neutrophils in the circulation may enhance the level of proteases and growth factors, circulating angiogenesis-regulating chemokines, matrix metallopeptidase 9, vascular endothelial growth factor and intercellular adhesion molecule 1 [23–25]. Each of these mechanisms can lead to cancer progression by regulating angiogenesis, cell growth or inflammation, so potentially leading to poor survival in hepatocellular cancer [26,27]. Lymphocytes play key roles in production of cytokines that inhibits tumour proliferation and metastatic competence [28]; therefore, weaker lymphocytic infiltration in hepatocellular cancer patients would in theory be linked to a bad prognosis [29]. A high monocyte count had been linked to poor prognosis in different cancers: circulating monocytes may promote growth of the tumour and help tumour cells escape immune surveillance [30]. Tumour-associated macrophages have been found to infiltrate the hepatocellular carcinoma matrix promoting proliferation, metastasis, angiogenesis and immunosuppression [31,32]. Alpha-fetoprotein (AFP) is an important biological marker of liver cancer, and a high level is associated with poorer outcomes [33]. Previous studies reported that ~50% of hepatocellular carcinomas secrete AFP [34]. AFP has oncogenic effects as it had been shown to promote cell proliferation [35], invasive growth and stimulates cell motility of some HCC cell lines *in vitro* [36]. Therefore, AFP is an independent prognostic factor as it

correlates with vascular invasion and histopathological grading [37].

Although high AFP in our patients predicted outcome in a multivariate setting, MELD and MGLR were better predictors. Nevertheless, these data support the view that the patient's liver function at diagnosis of hepatocellular carcinomas is predictive for recurrence. This appears to have been largely driven by deterioration of liver functions by the more aggressiveness of the tumour, a view in agreement with two previous studies that found that advancing stage of hepatocellular carcinomas influenced patient's survival when stratified by treatment subgroups [38,39]. The MELD score represents the extent of liver damage, which is logically closely related to hepatocellular carcinoma prognosis than other variables such as the NLR and lymphocyte count, and it has been shown to have a reliable prediction value for all patients with advanced liver disease, regardless of the underlying aetiology [40].

The present study is constrained by a number of limitations which include the sample size (relatively small due to the rigorous eligibility criteria for patient selection), that it is a single-institution, retrospective study, that only patients with post-viral hepatitis C cirrhosis and subsequent hepatocellular carcinomas were recruited and that only patients treated with TACE were recruited. Therefore, a prospective large-scale validation study is required to confirm our results.

The laboratory is coming to the fore in providing clinicians with useful scoring information regarding outcome in the liver disease that follows hepatitis virus infections, and other aetiologies [40–43]. This study represents an advance in biomedical science because it shows that higher MGLR (obtained from a single platform – the full blood count) and the MELD score (requiring two platforms – creatinine/bilirubin and coagulation) were associated with increasing frequency of cancer recurrence after TACE and can be used as novel, simple, non-invasive prognostic tests in hepatocellular carcinoma.

Summary table

What is known about this subject?
- Hepatocellular carcinoma is the most common primary malignant tumour of the liver.
- TACE improves survival in patients with intermediate or advanced stages of this cancer.
- Non-invasive methods focusing on blood markers are common.

What this paper adds
- A high MGLR and MELD score are both associated with increasing hepatocellular carcinoma recurrence after TACE.

Disclosure statement

No potential conflict of interest was reported by the authors.

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