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Malondialdehyde and C-reactive protein as prognostic markers of hepatocellular carcinoma

S Elbaz[a], N Mousa[b], T Besheer[b], T Sheta[c], K Taha[c], M Awad[c], N Effat[d], A Elgamal[e] and A Abdel-Razik[b]

[a]Endemic Diseases and Gastroenterology Department, Aswan University, Aswan, Egypt; [b]Tropical Medicine Department, Mansoura University, Mansoura, Egypt; [c]Internal Medicine Department, Mansoura University, Mansoura, Egypt; [d]Clinical Pathology Department, Mansoura University, Mansoura, Egypt; [e]Department of Tropical Medicine, Menoufia University, Mansoura, Egypt

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Hepatocellular carcinoma(HCC) is the most common type of liver cancer. Many factors are related to progression of cirrhosis to HCC and poor outcomes in patients with chronic hepatitis C virus(HCV) infection, including genetic variants [1,2]. Oxidative stress leads to peroxidation of membrane lipids, and this process generates a variety of lipid oxidation products such as malondialdehyde (MDA), a low-molecular weight aldehyde produced by the attack of free radicals to polyunsaturated fatty acids during cellular membrane phospholipid degradation. Studies have reported higher serum levels of MDA in HCC patients [3]. Serum C-reactive protein (CRP) parallels carcinogenesis possibly as an expression of the host defence reaction or as paraneoplastic syndrome [4]. The serum CRP has been investigated as a risk factor and prognostic tool in various human malignancies, including HCC [5]. Despite the advances in the treatment and diagnosis of HCC, the prognosis of patients is still poor [6,7]. Therefore, the aim of this study is to evaluate MDA and CRP as prognostic markers in cirrhotic patients with HCV infection, suffering from HCC and its links with Child-Pugh, and MELD score and tumour size.

We recruited 180 patients with HCC and chronic HCV infection (positive anti-HCV antibodies, and PCR) and 180 age and sex matched cirrhotic chronic HCV patients free of HCC. All patients were recruited from Tropical medicine and Internal Medicine departments, Mansoura University, Tropical medicine Menufia University and Endemic Diseases and Gastroenterology Department, Aswan University during the period from March 2017 to June 2018. Patients were classified according to the Child–Pugh classification into A (n = 50), B (n = 62) and C (n = 68), and according to size of HCC into 66 patients with a tumour size of ≤ 5cm and 114 patients with a tumour size > 5cm. According to the Model for End-Stage Liver Disease (MELD), patients were classified into 64 with MELD ≤ 15 and 126 with MELD > 15 [8]. Patients with any inflammatory conditions that may affect serum levels of CRP or MDA (e.g. infection, collagen disorders or malignancies other than HCC) were excluded. The diagnosis of HCC was made according to the Barcelona-2000 conference on the clinical management of HCC. Peripheral venous blood samples were obtained from patients and controls in the morning following an overnight fast. The samples were collected in sterile tubes and allowed to coagulate for 1 hour at room temperature. Then, serum samples were aliquoted in smaller containers and stored at −80 °C. CRP was assessed by particle-enhanced immunoturbidimetric assay. MDA was determined by the thiobarbituric acid method. Serum albumin, bilirubin, alpha-fetoprotein (AFP), creatinine, prothrombin time and aminotransferases were measured by standard routine techniques. HBsAg and anti-HCV antibodies were detected by ELISA. All patients included in the study were subjected to full medical history and thorough clinical examination and imaging using ultrasound scan and triphasic CT. Data are presented as mean [SD]. Differences between two groups were analysed by t test, three groups by ANOVA. $p < 0.05$ is taken to be significant.

Table 1 shows the demographic and clinical characteristics of the studied patients. There was no significant difference between studied groups as regard, age, sex, serum albumin, or ALT. However, a significant increase in serum CRP, MDA, bilirubin, AST level, INR and serum AFP were found in HCC. Both CRP and MDA were the strongest differentiators of the two groups, exceeding bilirubin, AST and AFP.

Table 2 shows a significant progressive increase in serum MDA and CRP from Child-Pugh A to C (both $p < 0.001$, ANOVA) with significant differences between stages (all $p < 0.02$). Serum MDA was significantly higher in patients with HCC > 5cm in size versus patients with HCC ≤ 5cm in size (7.7 [1.4] nmol/ml v 5.5 [1.3] nmol/ml, $P < 0.001$). Similarly, CRP was higher in HCC ≤ 5cm in size (7.1 [1.8] mmol/ml versus 6.1 [2.1] mmol/ml, $P < 0.001$). The same pattern was present in

CONTACT N Mousa mousa_medic@yahoo.com Tropical Medicine, Faculty of Medicine, Mansoura University, Ahmed Maher Street, Dakahlya, Mansoura, Egypt

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Table 1. Demographic and clinical characteristics of the studied patients.

	Patients with HCC (n = 180)	Cirrhotic control (n = 180)	P value
Age/years	54.5 [4.7]	53.9 [6.5]	0.32
Sex (M/F)	96/84	99/81	0.75
CRP (mmol/L)	6.9 [1.9]	5.9 [2.6]	<0.001
MDA (nmol/ml)	6.8 [1.8]	6.1 [1.5]	<0.001
Albumin mol/dL	32 [14]	33 [16]	0.53
Bilirubin µmol/L	80 [10]	50 [9]	0.001
ALT (IU/L)	118 [27]	115 [6]	0.19
AST (IU/L)	58 [27]	70 [21]	0.001
INR	1.2 [0.2]	1.3 [0.4]	0.002
AFP nmol/L	576 [171]	211 [67]	0.008

Data mean/SD. MDA, Malondialdehyde; CRP, C-Reactive Protein; ALT, alanine transaminase; AST, aspartate transaminase; AFP, Alpha-Fetoprotein.

Table 2. MDA and CRP in HCC patients according to the Child-Pugh classification.

	Child-Pugh A (n = 50)	Child-Pugh B (n = 62)	Child-Pugh C (n = 68)	P value
MDA (nmol/ml)	5.5 [1.7]	7.0 [1.4]	7.7 [1.5]	P1 < 0.001 P2 < 0.001 P3 = 0.013
CRP (mmol/L)	5.6 [1.9]	6.9 [1.6]	7.8 [1.5]	P1 = 0.012 P2 < 0.001 P3 < 0.001

P1 = A versus B; P2 = A versus C; P 3 = B versus C.
Data mean [SD]. MDA, Malondialdehyde; CRP, C-Reactive Protein

those with a low (≤15) versus a high (>15) MELD score: MDA 5.8 [1.5] v 7.4 [1.5] nmol/L ($p < 0.001$) and CRP 6.3 [1.9] v 7.0 [1.2] nmol/L ($p < 0.001$) respectively.

Increased risks of certain cancers were shown in patients with hepatitis C virus infection, however, HCC is the most common [9]. In this study, serum MDA levels were higher in patients with HCC versus the control cirrhotic group and showed a significant increase with progression from Child-Pugh A to Child-Pugh C score and from MELD ≤ 15 to MELD > 15. In addition, MDA was higher in HCC patients with tumour size > 5cm in comparison with patients with tumour size < 5cm. Metabolism of various endogenous and exogenous compounds generates reactive oxygen species, which could be involved in the pathogenesis of different liver diseases, including cirrhosis and HCC. Different studies in agreement with our results reported higher levels of MDA in patients with HCC than cirrhotic patients. Czeczot et al [10] investigated MDA level in supernatants prepared from cirrhotic, cancer and adjacent normal liver tissues and indicated a higher MDA content in cancer tissue compared to control tissue or cirrhotic tissue. Recurrence and poor prognosis of HCC are linked to MELD score and Child-Pugh score even after transarterial chemoembolization [11]. The level of MDA progressively increased from Child-Pugh A to Child-Pugh C score, with MELD score and with increasing tumour size. This finding can be explained by the increase in free radical production with the clinical progression of the disease, causing increased lipid peroxidation which involves the oxidative conversion of polyunsaturated fatty acids to a product known as malondialdehyde.

The same pattern was found for levels of serum CRP. These results suggest CRP is also an indicator of poor prognosis among patients with HCC. Moreover, Hashimoto et al [5] demonstrated that the serum CRP level was correlated significantly with unfavourable tumour factors, such as tumour size and portal vein invasion. However, Lin et al concluded that, serum CRP is not a good marker for HCC, although very high values of CRP in cirrhotic patients suggested the presence of a diffuse-type HCC [12]. Several mechanisms have been proposed for the relationship between CRP and cancer. First, tumour growth can cause tissue inflammation and hence increase CRP levels [13]. Second, CRP could be an indicator of an immune response to tumour antigens [14]. Third, there is evidence that cancer cells can increase the production of inflammatory proteins, explaining the increased CRP in patients with cancer. Some cancerous cells have been found to express CRP and cancer cell lines have been shown to secrete IL-6 and IL-8, which in turn induce the production of CRP [15].

This study represents an advance in biomedical science because it shows that, combined MDA and CRP (which requires only routine laboratory tests) may be used as simple, non-invasive prognostic markers for HCC diagnosis, so helping management.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

N Mousa http://orcid.org/0000-0001-8329-2587
T Besheer http://orcid.org/0000-0002-0583-8860
T Sheta http://orcid.org/0000-0001-9257-8018

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