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Serum beta-2 microglobulin in patients with chronic hepatitis C virus with or without hepatocellular carcinoma

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Objectives

To investigate serum beta-2 microglobulin (B2M) as a noninvasive marker for disease progression in chronic hepatitis C virus (HCV)-infected patients and to study its role as a tumor marker in diagnosis of hepatocellular carcinoma (HCC).

Background

HCV is a hepatotropic RNA virus that causes progressive liver damage, which might result in liver cirrhosis and HCC.

Patients and methods

From January 2020 to January 2022, this prospective study was carried on 136 participants who were classified into four groups: group I, 22 patients with noncirrhotic chronic hepatitis C; group II, 70 HCV-related cirrhotic patients; group III, 25 patients with HCC on top of HCV; and group IV, 19 healthy controls. Serum B2M was quantitatively measured in all of the studied groups.

Results

B2M was significantly higher in diseased groups than the control group, and it was significantly higher in cirrhosis and HCC groups than the chronic HCV group (P<0.001). The B2M cutoff value for HCC with cirrhosis group was 7.35, with sensitivity of 72.4% and specificity 60.1%, whereas the cutoff value for cirrhosis with chronic HCV group was 6.25. The sensitivity for HCC diagnosis increased upon combining B2M and alpha-fetoprotein, to be 96.4%, and specificity was 80%.

Conclusion

Serum B2M level was elevated in HCV-related chronic liver diseases and may be used as a marker for HCV disease progression toward cirrhosis and HCC.

Keywords:

alpha-fetoprotein, beta-2 microglobulin, cirrhosis, hepatitis C virus, hepatocellular carcinoma

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Introduction

Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver damage, which might result in liver cirrhosis and hepatocellular carcinoma (HCC). Globally, between 64 and 103 million people are chronically infected. Major risk factors for this blood-borne virus infection are unsafe drug injection and unsterile medical procedures (iatrogenic infections) in countries with high HCV prevalence [1]. Egypt has the highest prevalence of HCV infection in the world (~14.7%). Approximately 10–15% of HCV-infected persons will advance to cirrhosis within the first 20 years. The incidence of HCC is expected to grow in the next two decades, largely owing to HCV-related cirrhosis, and detection of HCC at an early stage is critical for a favorable clinical outcome [2]. Serum markers have been proposed as a simple and convenient means to estimate chronic liver disease progression. Although some markers may be effective, the clinical utility of these markers is still limited [3]. Detection of a simple, noninvasive, accurate, and reliable marker that is linked to clinically important milestones in liver disease progression, such as cirrhosis and HCC, is currently an area of active investigation [4]. Beta-2 microglobulin (B2M), a nonglycosylated polypeptide composed of 99 amino acids, is one of the components of HLA class I molecules on the surfaces of all nucleated cells. A high serum level of B2M was detected in many infectious diseases including HCV [5]. Serum B2M was elevated in HCV-infected patients and HCV-related HCC when compared with HCV-negative patients or healthy donors [6].

Therefore, the aim of the study was to investigate serum B2M as a noninvasive marker for disease progression in chronic HCV-infected patients and to study its role as a tumor marker in diagnosis of HCC.

Patients and methods

This prospective cross-sectional study was carried out at Tropical Medicine Department, Menoufia University hospitals, in the period between January 2020 and January 2022. The study included 136 participants, and they were classified into four groups: group I, 22 patients with chronic hepatitis C; group II, 70 patients with HCV-related liver cirrhosis, who were subdivided into three subgroups according to Child–Pugh classification as group IIa (20 patients with Child A), group IIb (25 patients with Child B), and group IIc (25 patients with Child C); group III, 25 patients with HCC on top of HCV; and group IV, 19 healthy controls of comparable age and sex. Chronic HCV (GI) was identified by detection of HCV antibody for more than 6 months and no evidence of cirrhosis in pelviabdominal ultrasonography. Triphasic computed tomography abdomen was required to confirm HCC diagnosis in group III (wash out lesions). Patients with hepatic focal lesions other than HCC and had liver disease other than HCV such as chronic hepatitis B, autoimmune hepatitis, metabolic hepatitis, and history of alcohol consumption or hepatotoxic drug use were excluded from this study. All participants were volunteers. All of them signed a written informed consent after explaining to them the aim of study before study initiation. Approval of the study protocol was obtained from the Ethical Scientific Committee of Faculty of Medicine, Menoufia University (Approval No. 32016TROP). Patient and controls were subjected to careful history taking, clinical examination, routine laboratory investigations [complete blood count, liver function tests, renal function tests, alpha-fetoprotein (AFP), serological tests for viral markers by ELISA using hepatitis C virus antibodies and hepatitis B virus surface antigen (Murex HBsAg, anti-HCV Version 3, South Africa)], and pelviabdominal ultrasonography. In the studied groups, B2M was estimated by the IMX B2MG assay using fully automated IMX system (Abbott Laboratory, Abbott Park, Illinois, United States), based on the microparticle immunoassay, and its normal level is 0.7–1.8 μg/ml.

Sample collection, preparation, and storage

Blood samples were collected by sterile venipuncture and divided into four parts: the first part was transferred into dipotassium EDTA vacutainer tube for complete blood count analysis. The second part was transferred into a sodium citrate vacutainer tube for prothrombin time and international normalized ratio (INR) measurement. The third part was transferred into a plain vacutainer tube, left to clot, and then centrifuged to separate sera used for assessment of liver and kidney functions tests, as well as and anti-HCV antibody assay. The fourth part was transferred into another plain vacutainer tube, left to clot, and then centrifuged at 3000 rpm for 10 min. Sera, separated for estimation of AFP and B2M, were kept frozen at −20°C until analysis.

Sample size calculation

The sample size was calculated as follows: 95% power and 90% noninferiority margin, based on the overall adverse event rate of 15% on chronic HCV in a previous study [5]. So, the required sample size was calculated to be 20 patients per group.

Statistical analysis

The data analysis was conducted using SPSS (Statistical Package for the Social Sciences (IBM, Chicago, Illinois, USA) program, version 13 for Windows. Descriptive statistics were used in which qualitative data were presented in the form numbers and percentages, and quantitative data were presented in the form of SD, mean, and range. Statistical significance was demonstrated for results ($P < 0.05$) using analysis of variance (F) test and Kruskal–Wallis (K) test. χ^2 test was used to study the association between two qualitative variables.

Results

There was no significant difference among the studied groups regarding to age and sex ($P = 0.08$ and 0.76, respectively), and there was a statistically highly significant difference among the studied groups regarding jaundice, pallor, ascites, encephalopathy, lower limb edema, and ecchymosis ($P < 0.001$) (Table 1).

There was a statistically highly significant difference among the studied groups regarding complete blood count ($P < 0.001$). Serum alanine transaminase (ALT) and aspartate transaminase (AST) levels were significantly increased among Child C and HCC than other studied groups, whereas serum albumin level was significantly higher among chronic HCV and Child A patients than other groups. Moreover, INR was significantly increased among Child C patients than other studied groups, whereas AFP was significantly increased among patients with HCC than chronic HCV and cirrhosis patients. Regarding ultrasonographic findings, there were highly statistically significant differences among the studied groups regarding liver size, echogenicity, and portal vein diameter ($P < 0.001$) (Table 2).

B2M was significantly higher in diseased groups than the control group, and it was significantly higher in cirrhosis and HCC groups than the chronic HCV

Table 1 Demographic and clinical data of studied groups

Data	Chronic HCV (*n*=22) [*n* (%)]	Cirrhosis				Control (*n*=19) [*n* (%)]	Test of significance	*P*
		Child A (*n*=20) [*n* (%)]	Child B (*n*=25) [*n* (%)]	Child C (*n*=25) [*n* (%)]	HCC (*n*=25) [*n* (%)]			
Age (years)								
Mean±SD	52.2±10.4	52.5±11.8	52.9±17.7	58±11.1	61.6±15.6	52.2±10.4	*F*=2.1	0.08
Range	35-77	33.5-71.5	33-80	40-76	33-85	35-77		
Sex								
Male	13 (59.1)	13 (65)	16 (64)	20 (80)	18 (72)	13 (68.4)	χ^2=1.93	0.76
Female	9 (40.1)	7 (35)	9 (36)	5 (20)	7 (28)	6 (31.6)		
Jaundice								
Yes	0	5 (25)	16 (64)	15 (60)	18 (72)		χ^2=73.5	<0.001
No	22 (100)	15 (75)	9 (36)	10 (40)	7 (28)	-		
Pallor								
Yes	2 (9.1)	4 (20)	4 (16)	5 (20)	8 (32)		χ^2=65.5	<0.001
No	20 (90.9)	16 (80)	21 (84)	20 (80)	17 (68)	-		
Ascites								
Yes	0	3 (15)	13 (52)	20 (80)	19 (76)		χ^2=59.4	<0.001
No	22 (100)	17 (85)	12 (48)	5 (20)	6 (24)	-		
Encephalopathy								
Yes	0	0	18 (72)	18	14 (56)		χ^2=93.1	<0.001
No	22 (100)	20 (100)	7 (28)	7 (100)	11 (44)	-		
LL edema								
Yes	0	0	14 (56)	20 (80)	19 (76)		χ^2=93.1	<0.001
No	22 (100)	20 (100)	11 (44)	5 (20)	6 (24)	-		
Ecchymosis								
Yes	0	0	7 (28)	12 (48)	10 (40)		χ^2=93.1	<0.001
No	22 (100)	20 (100)	18 (72)	13 (52)	15 (60)			

F, analysis of variance test; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LL, lower limb; χ^2, χ^2 test.

group (P<0.001). Moreover, B2M was higher in Child C than Child A and Child B (Fig. 1).

There were significantly negative correlations between B2M and platelets and serum albumin in group I and between B2M and platelets only in group IIC (P < 0.001). There were positive correlations between B2M and white blood cell (WBCs), ALT, AST, INR, and AFP in group I. In group IIA and group IIB, B2M was significantly correlate with hemoglobin, ALT, AST, serum albumin, and INR. Moreover, B2M was significantly correlated with most parameter among group IIC. In HCC group (GIII), there were positive correlations between B2M and hemoglobin, WBCs, AST, ALT, and AFP (Table 3).

The diagnostic yield of B2M for cirrhosis with chronic HCV group had a sensitivity of 86.4% and specificity of 42.9% at area under the curve (AUC) of 0.773, with a cutoff value of 6.25 (Fig. 2a). B2M had a sensitivity of 82.3% and specificity of 60.9% at AUC of 0.63, with cutoff value of 6.85 among for patients of Child B and C from Child A (Fig. 2b). Moreover, it had a sensitivity of 72.4% and specificity of 60.1% at AUC of 0.581 with a cutoff value of 7.35 for patients with HCC from cirrhotic patients (Fig. 2c). The diagnostic yield of AFP among cirrhosis with HCC had a sensitivity of 70.1% and a specificity of 45.2% at AUC of 0.562 with a cutoff value of 8.35 (Fig. 2d). The AUC increased significantly to 0.953 after combining B2M and AFP in the estimation for HCC diagnosis, with sensitivity of 96.4% and specificity of 80% (Fig. 2e and Table 4).

Discussion

HCV infection is a major cause of advanced hepatic fibrosis and cirrhosis with significantly increased risk for development of HCC [7]. Early detection of HCC leads to improved survival; however, current early detection strategies for HCC surveillance are ineffective. Thus, there has been interest in developing biomarkers to aid in the early detection of HCC [8]. A high serum level of B2M was detected in many infectious diseases including HCV. Serum B2M was elevated in HCV-infected patients and HCV-related HCC when compared with HCV-negative patients or healthy donors [6,9]. In the present study, AFP was significantly increased among HCC (1327 ± 309.1) patients than cirrhotic patients and healthy group. Elnakeeb *et al.*[10] found that, regarding of AFP, there was a highly significant difference between patients with HCC and those with liver cirrhosis, where the mean was 210.93 ng/ml in patients with HCC and 8.48 ng/ml in patients with liver cirrhosis. This was in agreement with Liu *et al.* [11], who stated that AFP

Table 2 Laboratory and ultrasonographic findings of studied groups

Data	HCV (*n*=22)		Child A (*n*=20)		Child B (*n*=25)		Child C (*n*=25)		HCC (*n*=25)		Test	*P*
Hb (g/dl)												
Mean±SD	12.4±1.5		12.9±1.3		11.2±1.4		11.1±1.2		10.1±1.2		*F*=10.6	<0.001
WBCs (×10^3)												
Mean±SD	6.9±1.6		6.7±0.98		9.5±1.4		8.5±2.2		6.9±1.4		*F*=13.1	<0.001
Platelets (×10^3)												
Mean±SD	286±22.5		179±11.8		134.7±19.9		96±22.1		121.7±31.8		*F*=13.1	<0.001
ALT (IU/l)												
Mean±SD	30±11.2		46.5±17.7		45±14.7		59±22.1		57±22.1		*K*=21.4	<0.001
AST (IU/l)												
Mean±SD	30.6±10.3		46.7±17.3		41.3±8.6		53.3±15.9		57.4±22.7		*K*=22.5	<0.001
Albumin (g/dl)												
Mean±SD	3.9±0.54		4.04±0.44		3.6±0.70		2.5±0.64		2.8±0.59		*F*=27.4	<0.001
INR												
Mean±SD	1.15±0.14		1.27±0.22		1.65±0.27		2.01±0.27		1.54±0.44		*F*=27.5	<0.001
Alpha-fetoprotein (ng/ml)												
Mean±SD	1.13±0.21		4.4±1.30		6.2±1.10		5.9±1.03		1327±309		*F*=405.5	<0.001
Urea (mg/dl)												
Mean±SD	22.8±8.4		27.4±8.3		28.3±9.5		24.7±8.4		23.8±7.1		*K*=5.46	0.141
Creatinine (mg/dl)												
Mean±SD	0.94±0.33		1.11±0.26		0.96±0.23		1.08±0.30		1.01±0.25		*K*=5.08	0.166
Liver												
Normal	19	100	15	75	6	24	4	16	0	0	196.5	<0.001
Enlarge	0	0	5	25	4	16	0	0	0	0	χ^2	
Shrunk	0	0	0	0	15	60	21	84	25	100		
Spleen												
Normal	19	100	4	20	0	0	0	0	0	0	119.7	<0.001
Enlarge	0	0	15	75	23	92	21	84	22	88	χ^2	
Remove	0	0	1	5	2	8	4	16	3	12		
Echogenicity												
Homogenous	19	100	0	0	0	0	0	0	0	0	χ^2=114	<0.001
Cirrhotic	0	0	20	100	25	100	17	0	0	0		
Heterogeneous	0	0	0	0	0	0	8	100	25	100		
PV diameter												
Mean±SD	11.8±1.2		11.8±0.81		16.1±2.6		18.1±1.1		14.3±2.8		*F*=13.1	<0.001

ALT, alanine transaminase; AST, aspartate transaminase; *F*, one way analysis of variance test; Hb, hemoglobin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; *K*, Kruskal-Wallis test; PV, portal vein; WBCs, white blood cells; χ^2, χ^2 test.

Table 3 Correlation between beta-2 microglobulin and other parameters among the studied patients

	Beta-2 microglobulin									
	GI		GIIA		GIIB		GIIC		GIII	
	Rho	*P*	Rho	*P*	Rho	*P*	Rho	*P*	Rho	*P*
Age	0.200	0.078	0.16	0.085	0.13	0.68	0.23	0.047	0.11	0.90
Hemoglobin	0.018	0.852	0.331	0.002*	0.018	0.852	0.23	0.027	0.98	0.001
WBCs	0.241	0.010	0.151	0.087	0.241	0.010	0.65	0.001	0.38	0.001
Platelets	−0.363	<0.001	0.01	0.98	0.198	0.42	−0.41	0.001	0.08	0.90
ALT	0.689	<0.001	0.55	<0.001	0.79	<0.001	0.24	0.02	0.70	0.001
AST	0.460	<0.001	0.78	<0.001	0.39	<0.001	0.411	0.001	0.208	0.042
Serum albumin	−0.323	<0.001	0.41	<0.001	−0.323	<0.001	0.15	0.57	0.17	0.54
Creatinine	0.128	0.174	0.15	0.164	0.028	0.94	0.01	0.93	0.07	0.32
Urea	0.168	0.074	0.18	0.063	0.08	0.86	0.09	0.81	0.12	0.79
INR	0.332	<0.001	0.26	0.011	0.332	<0.001	0.32	0.02	0.12	0.934
Alpha-fetoprotein	0.391	<0.001	0.21	0.51	0.19	0.76	0.32	0.004	0.43	0.001

ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; WBCs, white blood cells.

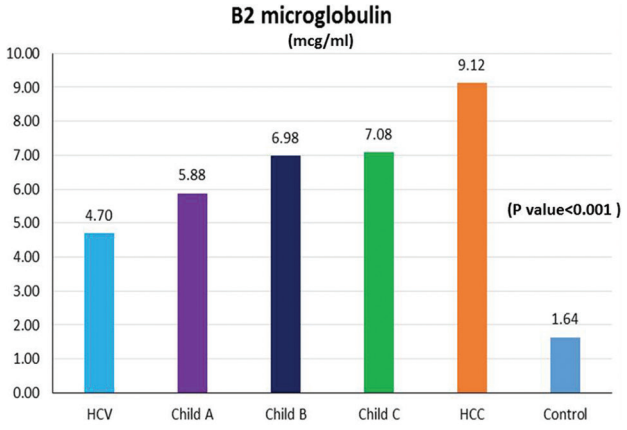
levels significantly differed in patients with HCC, having a mean 250.65 nm/ml, and patients with liver cirrhosis, with a median of 2.32 ng/ml. In this current study, B2M was significantly higher in diseased groups than the control group, and it was significantly higher in cirrhosis and HCC groups than the HCV group. This

Table 4 Validity of beta-2 microglobulin as a marker for disease progression

Groups	AUC	*P*	Cutoff point	Sensitivity	Specificity	NPV	PPV
Cirrhosis with CHCV	0.773	<0.001*	6.25	86.4	42.9	93%	42%
Child A with child B and C	0.63	0.027*	6.85	82.3%	60.9%	95%	26%
Cirrhosis with HCC	0.581	0.162	7.35	72.4%	60.1%	80%	39%
AFP among cirrhosis with HCC	0.562	0.035*	8.35	70.1%	45.2%	87%	30%
AFP combined B2M among cirrhosis with HCC	0.953	<0.001*	5.80	96.4%	80%	98%	45%

AFP, alpha-fetoprotein; AUC, area under the curve; B2M, beta-2 microglobulin; CHCV, chronic hepatitis C virus; HCC, hepatocellular carcinoma; NPV, negative predictive value; PPV, positive predictive value.

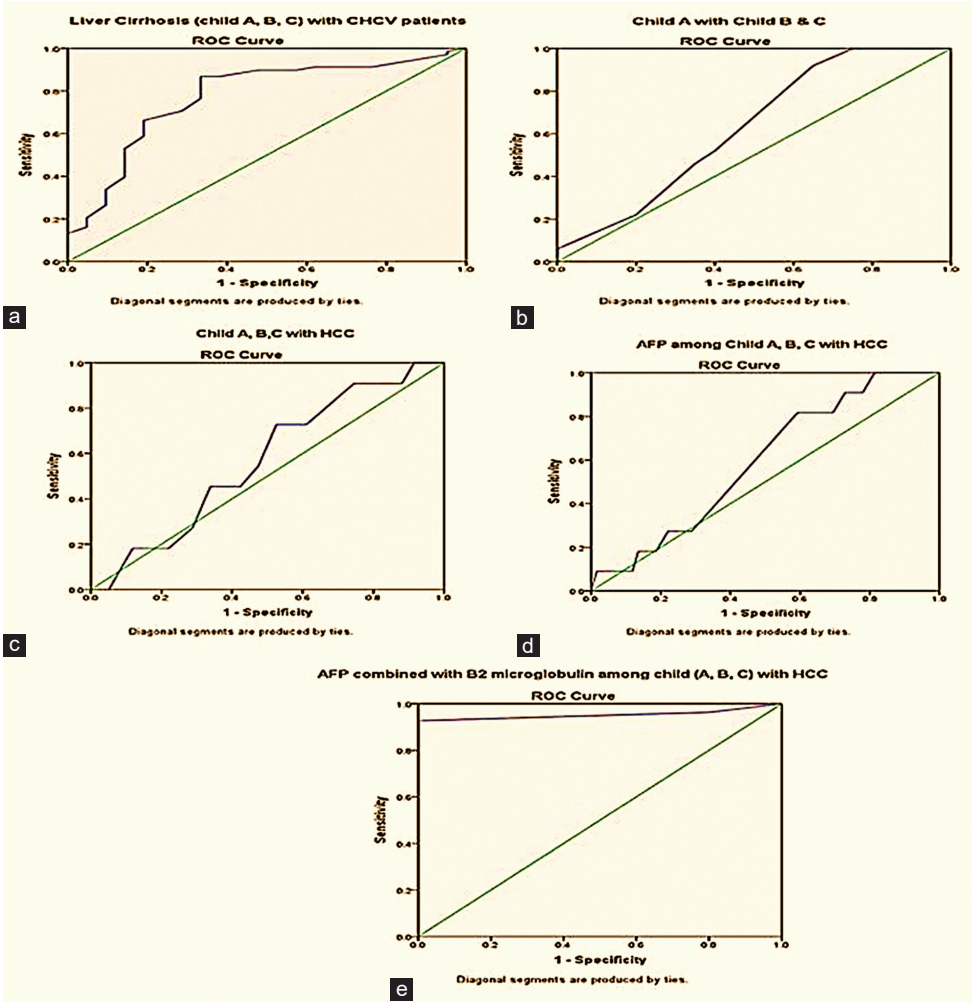
Figure 1



Serum beta-2 microglobulin of studied groups.

goes with Huckans *et al.* [6], who found that B2M levels were higher in patients with HCV (n = 39) than those without HCV (n = 40). This might be attributed to the increased endogenous production of interferons and other cytokines associated with HCV infection. [12]. High serum B2M level is associated with an activated immune response and release by activated lymphocyte, so increase in its level might indicate increasing HCV replication-related apoptosis. In chronic HCV, many expressed genes involved in the pathways of immune system, fibrosis, proliferation, cell growth, and cell death have been found to be up-regulated, including major histocompatibility and B2M genes [13,14]. Moreover, Ouda *et al.*[5] demonstrated that serum B2M level was significantly higher in the HCC group (6.62 ± 2.49) than the chronic HCV group (4.25 ± 1.48). Other studies reported high serum B2M in patients with HCC on top of chronic HCV and suggested that the B2M in plasma could be used as an early marker to detect imaging-invisible HCC [15,16]. Moreover, Malaguarnera *et al.*[17] found that patients with HCC showed higher serum B2MG levels than did chronic hepatitis C patients (36 ± 16.5 pg/ml vs. 2.3 ± 0.8 mg/ml) or healthy participants (36 ± 16.5 vs. 1.6 ± 0.4 μg/ml). As in normal liver histology, HLA class 1 antigens were mainly expressed on liver sinusoidal lining cells rather than on hepatocytes. The reason why normal hepatocytes have no or only weak HLA class 1 antigen expression, though liver cancer cells strongly express HLA class antigens, may be related to the unique lymphocyte distribution in liver and natural killer cell escape. Therefore, re-expression of HLA class 1 antigens on HCC cells would be helpful for inhibiting the nonspecific cytotoxicity of NK cells through their inhibitory KIR receptors [18]. In this study, there were significant negative correlations between B2M and platelets and serum albumin in group I and with platelets only in group IIC, and positive correlations with WBCs, ALT, AST, INR, and AFP among group I. In group IIA and group IIB, B2M was significantly correlate with hemoglobin, ALT, AST, serum albumin, and INR. Moreover, B2M was significantly correlated with most parameters among group IIC. In HCC group (GIII), there were positive correlations between B2M and hemoglobin, WBCs, AST, ALT, and AFP. This goes with Malaguarnera *et al.* [17], who found a significant positive correlation between B2M and AFP in their HCC patients, and this correlation confirms the role of both polypeptides as tumor markers, as shown in other studies. This role for B2MG is further expressed by the significant correlation to size and nodular features of the neoplasm. Some humoral factors related to the inflammation have been already indicated as responsible for the increase of B2M. It seems that B2M is shed in serum by oncogenic ally transformed hepatocytes stimulated by cytokines such as interleukin-6, a proinflammatory cytokine involved in different tumor types because of its pleiotropic actions. In contrast, Ouda *et al.* [5] found that there was no significant correlation between B2M and serum AFP level. In this study, ROC curve analysis showed that the diagnostic yield of B2M increased with disease progression and the AUC increased significantly to 0.953 among combined B2M and AFP estimation for HCC diagnosis. This finding was in agreement with Ouda *et al.* [5] who reported that combined AFP and B2M estimation improved AUC for HCC diagnosis from 0.74 to 0.93. Malaguarnera *et al.* [17] confirmed that serum B2M levels were significantly higher in HCC patients than in chronic hepatitis C patients and healthy controls. Altered expression of HLA antigens could be the method adopted by tumor cells to avoid immunological response. This goes with Ward *et al.* [19], where B2M was the most significantly HCC-associated proteomic finding in their study. They mentioned that B2M might

Figure 2



(a) Diagnostic performance of B2M for cirrhotic from chronic HCV patients. (b) Diagnostic performance of B2M for Child B, Child C from Child A patients. (c) Diagnostic performance of B2M for HCC from cirrhotic patients. (d) Diagnostic performance of AFP for HCC from cirrhotic patients. (e) Diagnostic performance of combined B2M and AFP for HCC. AFP, alpha-fetoprotein; B2M, beta-2 microglobulin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

add power to a multi-marker HCC diagnostic panel and concluded that combined estimation of AFP and B2M might add a significant yield rather than B2M values alone for diagnosis of HCC.

This study has some limitations that should be mentioned. First, the cross-sectional design of this single-center study limits our ability to establish causal associations between B2M levels and disease progression of chronic HCV patients. Second, the sample size of our study was small. Third, serum B2M level needs to be explored further by close monitoring of patients with chronic active HCV and cirrhosis who are at high risk of HCC and also repeated B2M serum profiling to reach more confirmatory results.

Conclusion

Serum B2M level is elevated in HCV-related chronic liver diseases and may be used as a marker for HCV disease progression toward cirrhosis and HCC. Moreover, its value was higher in Child C than Child A and Child B. Combined estimation of AFP and B2M might add a significant yield rather than B2M values alone for diagnosis of HCC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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