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Research Article

Pattern of Serum Interleukin-10 Level in Patients with Liver Cirrhosis Versus Patients with Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma is a common morbid condition in our country, due to various reason, however the current surveillance protocols which depend on Alfa-fetoprotein and ultrasound could not predict early cases in many situations.

Aim: To evaluate the pattern of serum interleukin-10 in patients with cirrhotic liver versus patients with hepatocellular carcinoma.

Methods: We compared the level of Interleukin-10 in 44 patients with liver cirrhosis versus 36 patients with HCC.

Results: patients with HCC have significantly higher IL-10 than cirrhotic group (10.86 ± 4.48, 7.005 ± 6.1) respectively (p = 0.002*). Our results also shows that the best cut off value of IL-10 for detection of HCC among HCV patients is > 7.5 with sensitivity of 86% and specificity of 75% (p = 0.0001*); IL-10 was significantly negatively correlated with albumin (p = 0.003*), and positively correlated to WBC count (p = 0.001*).

Conclusion: Serum IL-10 levels may serve as complementary tumor markers and contribute to the differential diagnosis in HCC patients.

Keywords: *HCC; Interleukin-10; Liver cirrhosis*

Introduction

Being the fifth most common cancer in the world and the third most frequent cause of cancer-related death, Hepatocellular carcinoma (HCC) represents the most common primary malignant tumor of the liver and is one of the major causes of death among patients with cirrhosis [1], nevertheless, its incidence is increasing all over the world [1,2]. One of the main problems that HCC is frequently diagnosed after the development of clinical deterioration at which time survival is measured in months, whereas Long-term survival requires detection of small tumors, often present in asymptomatic individuals, which may be more amenable to invasive therapeutic options. In our practice detection of HCC depends mainly on Surveillance for high-risk individuals with liver cirrhosis using the serum marker AFP often in combination with ultrasonography [3-5], however, AFP is insensitive for the early cancer detection [6].On the other hand Interleukin-10

(IL-10) is a small protein cytokine that functions as an important regulator of the immune system as inhibitor of cytokine production and the accessory functions of macrophages during T cell activation [7,8].It was noticed that IL-10 concentrations were substantially higher in patients with HCC as compared with that of healthy controls [9], but this was not true in non-tumor patients with virally, autoimmune- or alcohol-induced cirrhotic or non-cirrhotic liver disease [10,11], moreover Increased serum levels of interleukin (IL)-10 have been associated with poor prognosis in patients with hepatocellular carcinoma [12,13]. So, whether IL-10 can be used as a diagnostic or prognostic marker in cirrhotic patients with or without HCC, this is our main concern.

Aim of the work

To evaluate the pattern of serum interleukin-10 in patients with cirrhotic liver versus patients with hepatocellular carcinoma.

Subject and Methods

The study performed as a comparative study aiming to determine IL-10 level in the serum of cirrhotic patients and hepatocellular carcinoma patients at the out-patient clinics and In-patient department of Suez Canal University Hospitals, Ismailia, Egypt. All patients fulfilled the following criteria: Age 18 - 80 years old, both sexes and patient with HCC according to Barcelona clinic of liver cancer (Bclc) staging system criteria [14,15]. The exclusion criteria were: Patients with other neoplasms, Patients with gastrointestinal hemorrhage, Patients with spontaneous bacterial peritonitis (SBP). The study groups divided into two groups: 44 Patients with liver cirrhosis (group 1), and 36 patients who are diagnosed to have HCC by the Barcelona clinic of liver cancer (Bclc) staging system criteria (group 2). Data collected for all patients included: Full medical history taking, complete clinical examination, laboratory investigations (ALT, AST, S. albumin, and S. bilirubin, prothrombin time, complete blood picture, fasting blood sugar, S. creatinine and Alpha-fetoprotein level), abdominal ultrasound, and triphasic CT abdomen). Finally, IL-10 assay evaluated for all patients by ELISA (Sandwich-Technique) as follows: 1- Blood samples collected in plane tubes from a peripheral vein; 2-The serum separated immediately by centrifugation (2000g for 10 min) and stored at -20˚C until assayed.

Data Analysis

The data obtained from the records coded, organized and the final study results stated using the SPSS (statistical package for social sciences) version 16 and data presented through tables and graphs. Data are compared by using Chi-square test for qualitative variables while independent t-test used for quantitative variables. Statistical significance is considered at P-value < 0.05 and highly significant at P-value < 0.01.

Results

The range of age in study population was between 23 - 72 years; mean of age in cirrhosis group was 49.75, while mean of age in HCC group was 56.7, so HCC group has significantly higher mean age than cirrhosis group. 66% of study population were males and 33% were females, 18% lived in urban area and 56% lived in rural area, no statistically significant difference was noted between two groups regarding sex and residence (Table 1). Regarding the values of IL-10 in both group Table 2 shows that patients with HCC have significantly higher IL-10 than cirrhotic group (10.86 ± 4.48, 7.005 ± 6.1) respectively (p = 0.002*). Our results also shows that the best cut off value of IL-10 for detection of HCC among HCV patients is > 7.5 with sensitivity of 86% and specificity of 75% (p=0.0001*) (Figure 1). Table 3 also shows that 86.11% of HCC patients have IL-10 values more than 7.5 while only 25% of cirrhotic patients have IL-10 values above this value with statistically significant difference, while the odds of having HCC if IL-10 was estimated to be more than 7.5 is 18.6 times the odds if IL-10 is lower than this value (p = 0.002*). Regarding the levels of IL-10 and others laboratory markers, Table 4 shows that IL-10 was significantly correlated with albumin (negative correlation) (p = 0.003*), and WBC count (positive correlation) (p = 0.001*). But there was no significant correlation between IL-10 and other laboratory measures including alfa fetoprotein.

		Cirrhosis group (n = 44)		HCC group (n = 36)		p-value
Age	Mean ± SD	49.75 ± 9.97		56.7 ± 6.95		0.001*
	Range	23 – 60		44 – 72		
Sex	Male	26	59.09%	27	75%	0.1 (NS)
	Female	18	40.91%	9	25%	
Residence	Urban	18	40.91%	17	47.22%	0.6 (NS)
	Rural	26	59.09%	19	52.78%	

Table 1: *Demographic characteristics among the studied patients in both groups.*

**Statistically significant difference*

NS: no statistically significant difference

		Cirrhosis group (n = 44)	HCC group (n = 36)	p-value
IL-10	Mean ± SD	7.005 ± 6.1	10.86 ± 4.48	0.002*
	Range	2.4 – 40.2	3.1 -0 28	

Table 2: *Interleukin-10 values among the studied patients in both groups.*

**Statistically significant difference*

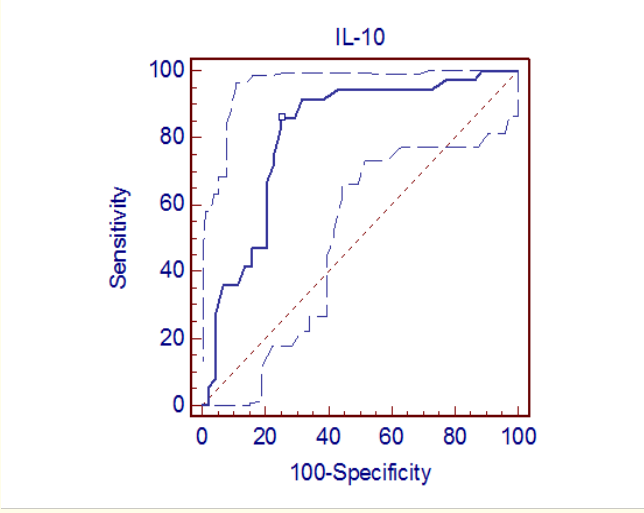

Figure 1: *ROC curve of IL-10 for differentiation between HCC patients and cirrhotic patients.*

		Cirrhosis group (n = 44)		HCC group (n = 36)		p-value	OR (95% CI)
IL-10	≤ 7.5	33	75%	5	13.89%	0.002*	18.6 (5.2 – 73.5)
	> 7.5	11	25%	31	86.11%		

Table 3: *Relation between Interleukin-10 values and presence of HCC according to determined value by ROC curve.*

OR: odds ratio, CI: confidence interval

**Statistically significant difference*

	Total		Cirrhosis group (n = 44)		HCC group (n = 36)	
	r	p-value	r	p-value	r	p-value
Hb (g/dl)	-0.1	0.3 (NS)	-0.06	0.7 (NS)	-0.001	0.9 (NS)
WBC (×10^3)	0.3	0.003*	0.1	0.5 (NS)	0.5	0.002*
Platelet (×10^3)	-0.06	0.6 (NS)	-0.2	0.1 (NS)	0.3	0.05 (NS)
ALT	-0.08	0.5 (NS)	-0.2	0.3 (NS)	-0.09	0.6 (NS)
AST	-0.06	0.6 (NS)	-0.2	0.1 (NS)	-0.04	0.8 (NS)
Total bilirubin	0.04	0.7 (NS)	-0.1	0.5 (NS)	0.2	0.1 (NS)
Direct bilirubin	0.02	0.9 (NS)	-0.1	0.4 (NS)	0.2	0.2 (NS)
Albumin (g/dl)	-0.4	0.001*	-0.3	0.07 (NS)	-0.09	0.6 (NS)
PT (sec)	0.2	0.07 (NS)	0.2	0.2 (NS)	0.1	0.4 (NS)
Creatinine	0.1	0.2 (NS)	0.2	0.3 (NS)	0.1	0.5 (NS)
α-FP	0.04	0.8 (NS)	-0.1	0.4 (NS)	-0.1	0.5 (NS)

Table 4: *Correlation between IL-10 and other laboratory measures.*

**Statistically significant*

NS: no statistically significant

Discussion

No doubt that HCC is one of the most common malignant tumors, representing more than 5% of all cancers and ranks as the fifth most common cancer in the world [1]; above all being related to liver cirrhosis due to viral hepatitis B or C, which are common in our community, this represents a major health problem we have to deal with. Long-term survival for patients with HCC requires detection of small tumors, mostly show no symptoms at that stage, and may be more amenable to invasive therapeutic options. Although surveillance of high-risk individuals for HCC is commonly performed using the serum marker AFP often in combination with ultrasonography, unfortunately serum AFP can be helpful if levels are markedly elevated, which occurs in fewer than half of cases at time of diagnosis [16,17] moreover, it is insensitive for the early cancer detection [6,17]. Another problem that ultrasonography is both machine and operator dependent. These make AFP and ultrasonography unsatisfactory for screening, and suggest the need for novel biomarkers for the detection of early HCC. IL-10 is multifunctional cytokines produced by a range of cells and play a central role in host defense mechanism and modulation of immune response [7,18]. An increasing body of evidence indicates a key role of IL-10 in the process of liver damage and carcinogenesis [19,20]. In our study we aimed to evaluate the pattern of interleukin 10 in cirrhotic patients with and without HCC. The study included 80 patients

cirrhotic, their ages between 23 - 72 years, divided into two groups, first group contained 44 patients with no HCC, and second group contained 36 HCC patients. It was demonstrated that serum IL-10 is significantly elevated in HCC patients in comparison to those without HCC. The range of age in study population was between 23 - 72 years, mean of age in cirrhosis group was 49.75, mean of age in HCC group was 56.7 so HCC group has significantly higher mean age than cirrhosis group (p = 0.001*). 66% of study populations were males and 33% were females, 18% lived in urban area and 56% lived in rural area, no statistically significant difference was noted between two groups regarding sex and residence. There was no statistically significant between HCC and cirrhosis group as regarding all basic laboratory investigations except for albumin. HCC group patients have significantly lower albumin values compared to cirrhosis group patients range was between 1.4 – 3.2 mean 2.32 ± 0.49 (p = 0.001*) and this matched with study conducted by H.A. Metwaly., *et al* [21].

In our study serum levels of AFP were significantly elevated in HCC group compared with cirrhosis group (2954.9 ± 7061.6, 6.97 ± 6.9) respectively (p = 0.01*), and this matched with many studies which concluded that Alfa-fetoprotein is an important marker for HCC. Our results showed that HCC group patients have significantly higher IL-10 than cirrhosis group (10.86 ± 4.48, 7.005 ± 6.1) respectively (p = 0.002*) and this matched with study of M. Othman 2013 [22] and another recent study [23]. More interestingly, our study determined the best cut off value of IL-10 for detection of HCC among HCV patients is > 7.5 with sensitivity of 86% and specificity of 75%and this also matched with the other study [22] as The AUROC for IL-10 was 0.914(95%CI: 0.829 - 0.965), with a sensitivity of 80%, specificity 96.67% and accuracy 92.5% and optimal cutoff value 9.7 pg/ml (p = 0.0001).more analysis of our study showed that 86.11% of HCC patients have IL-10 values more than 7.5 while only 25% of cirrhotic patients have IL-10 values above this value with statistically significant difference, and the odds of having HCC if IL-10 was estimated to be more than 7.5 is 18.6 times the odds if IL-10 is lower than this value (p = 0.002) this make IL-10 as a good diagnostic tool for HCC specially in screening and in doubtful cases. IL-10 also was significantly correlated with albumin (negative correlation) (p = 0.003*) and WBC count (positive correlation) (p = 0.001*); this may reflect the pathophysiological conditions of those patients with liver cirrhosis and HCC. Finally, there was significant correlation between IL-10 and other laboratory measures including Alfa fetoprotein and this matched with the other studies [21-23].

Conclusion

High levels of IL-10 are observed in HCC patients, may be helpful to identify a subset of HCC patients with questionable AFP levels and also can aid in screening for HCC.

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