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Diagnostic role of Golgi protein 73 and IL-17 in Egyptian cirrhotic rather than hepatocellular carcinoma patients

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third cause of cancer mortality worldwide. This study aimed to pursue changes in serum interleukin-17 and Golgi protein 73 in both cirrhotic and HCC patients, as predictive tools for disease progression, cirrhosis was considered as the major risk prior to HCC. Fifty HCC patients were recruited from Mansura Oncology Center, Mansura University, Egypt, against 30 cirrhotic patients and 8 healthy subjects. Serum level of Golgi protein 73 was significantly increased in HCC and cirrhotic patients than control, but HCC group showed non-significant difference from cirrhotic group. Serum interleukin-17 increased significantly only in HCC patients. In HCC patients, a significant positive correlation was found between serum IL-17 to poor performance, presence of ascites, distant metastasis, portal vein thrombosis, Barcelona-Clinic Liver Cancer (BCLC) and Child scoring. IL-17 showed sensitivity of 54% and specificity of 60.5% in HCC patients, while AFP showed a sensitivity of 50% and specificity of 100%. IL-17 was positive in 48% of AFP-negative HCC patients. Combined determination of AFP and IL-17 had a sensitivity of 74% in HCC patients. Serum Golgi protein 73 is not a valuable diagnostic marker for HCC, serum IL-17 can be used as a better marker, related to HCC stages with poor prognostic criteria and metastasis. So it can be recommended as a new diagnostic marker. Combination of AFP and IL-17 increases the positive predictive value for HCC diagnosis and it is more helpful in diagnosing cirrhosis than HCC.

INTRODUCTION

HCC is the fifth cancer and third common cause of cancer mortality worldwide (Li *et al*., 2014; Zhuang *et al*., 2014), accounting for about 90% of primary liver cancer in most countries (Sun *et al*., 2014). The global incidence of HCC is increasing annually. It shows nearly 600,000 deaths per year (Maida *et al*., 2014; Scaggiante *et al*., 2014; Tsoulfas *et al*., 2012). In Egypt, HCC is the second and fifth most common malignancy in males and females, respectively (Gomaa *et al*., 2014). Formerly, it was reported roughly that, 14% of the population in Egypt has HCV infection who were assumed to suffer from a chronic liver disease (Deuffic-Burban *et al*., 2006; Goldman *et al*., 2009).

Due to the lack of symptoms during early stages of HCC, it is usually detected at late and advanced stages, which precludes the use of curative surgical therapy (El-Tayeh *et al*., 2012). Early diagnosis of HCC is the most critical step in liver cancer management (Abdel-Hamid, 2008). Ultrasonography and serum α-fetoprotein (AFP) levels are the most commonly used methods for diagnosing HCC (Liu *et al*., 2013). Although serum AFP is the most widely used tumor marker in HCC and considered as the golden standard compared to other markers (Stefaniuk *et al*., 2010), it was found to be normal in up to 40% of patients with HCC, particularly during the early stages of HCC. Also it may be elevated in patients with cirrhosis or exacerbations of chronic hepatitis and a variety of other malignancies (Ba *et al*., 2012). Golgi protein 73 (GP73), also known as Golph2 and GOLM1, is a resident Golgi type II transmembrane protein with a single N-terminal transmembrane domain and an extensive C-terminal coiled-coil domain. It is encoded by the GOLM1 gene located on chromosome 9q21.33 (Kladney *et al*., 2000; Norton *et al*., 2008).

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GP73 expression is significantly increased in different kinds of cancer, including seminomas (Fritzsche *et al*., 2010), renal cell cancer (Fritzsche *et al*., 2008), and lung adenocarcinoma (Zhang *et al*., 2010), however, it is closely associated with hepatic disease (Zhao *et al*., 2013), being highly up-regulated in liver disease due to viral infection with HBV and HCV, autoimmune hepatitis, alcohol-induced liver disease, liver cirrhosis, and HCC (Iftikhar *et al*., 2004; Riener *et al*., 2009; Schwegler *et al*., 2005).

It was demonstrated that the activated hepatic stellate cells are a potential source of GP73 (Iftikhar *et al*., 2004). As activated hepatic stellate cells are considered the most important feature of liver fibrosis, it has been suggested that GP73 is a useful indicator for the evaluation of liver impairment or fibrosis (Maitra and Thuluvath, 2004).

Moreover, GP73 expression was significantly elevated in liver disease as a result of viral infection (Kladney *et al*., 2002). This might suggest its probable association with the direct response of hepatocytes to viral injury and HCC patients (Hu *et al*., 2010; Iftikhar *et al*., 2004).

Several studies presented that GP73 level is significantly elevated in patients with primary hepatic carcinoma (PHC) (Kristiansen *et al*., 2008; Shi *et al*., 2011).

The human IL-17 gene was linked to human chromosome 6p12. The gene product is a protein consisting of 150 amino acids with 15 kDa molecular weight. It is secreted as a disulfide linked homodimer of 30–35 kDa glycoproteins (Awasthi and Kuchroo, 2009). It stimulates granulopoiesis (Jovcic *et al*., 2007) in tumor models. Some studies have shown that high expression of IL-17 associates with prognosis and development of tumor (Zhang *et al*., 2014).

Cumulative evidence has shown that IL-17 has an effect on different types of cancer models (Murugaiyan and Saha, 2009) such as colorectal cancer (Le Gouvello *et al*., 2008), NSCLC (Chen *et al*., 2010), prostate cancer (Sfanos *et al*., 2008), breast cancer (Zhu *et al*., 2008), ovarian cancer (Miyahara *et al*., 2008), and HCC (Zhang *et al*., 2009).

Tumor growth is mainly dependent on the process of angiogenesis which needs continuous new vessel growth (Kolls and Linden, 2004). Fibroblasts are considered as a crucial source of proangiogenic factors, such as vascular endothelial growth factor (VEGF) during hypoxia, inflammation and tumor growth and they markedly enhance inflammatory and tumor angiogenesis (Cho *et al*., 2000; Volpert *et al*., 1997). IL-17 was found to be able to enhance the up-regulation of VEGF, prostaglandins, MIP-2, and Nitric Oxide (NO) production by fibroblasts. So IL-17 has the ability to stimulate the production of proangiogenic factors and promotes fibroblast-induced neovessel formation in inflammation and tumors (Kotake *et al*., 1999; Ziolkowska *et al*., 2000).

The present work aims to estimate the level of GP73, IL-17 and AFP in both HCC and cirrhotic patients, compared to normal subjects, in a trial to find more sensitive tool/tools to expect progression of HCC among risk holders of liver cirrhosis.

MATERIALS AND METHODS

Subjects

The present study was conducted on 80 patients, 50 patients with HCC (40 males and 10 females; aged 38-76 years with a mean ± SE of 58.84 ± 1.15) , selected from the out-patient clinics of the Oncology Centre , Faculty of Medicine, Mansoura University, Mansoura, Egypt. A control group comprised of 8 healthy individuals (5 males and 3 females; aged 45 – 65 years with a mean ± SE of 53.75 ± 2.45) with no apparent evidence of active disease or medical disorders was selected. All patients had signed a written informed consent to share in the study through their respective physicians. Since the majority of HCC patients in this study have cirrhosis as an underlying liver disorder and to nullify the effect of cirrhosis on the level of the measured parameters, a group of 30 cirrhotic patients, (17 males and 13 females.; aged 32-81years with a mean ± SE of 57.8±1.85), without any evidence of HCC was adopted from the in-patient clinics of the Specialized Medical Hospital, Mansoura University, Mansoura, Egypt. Cirrhosis was considered as the major risk prior to HCC. All cases involved in this study were clinically, radiologically and pathologically examined by the physicians in the same center. HCC was diagnosed by abdominal ultrasonography and serum AFP, with or without triphasic computed tomography scan and/or liver histopathology. The severity of liver disease was assessed by the Child–Pugh classification (Pugh *et al*., 1973). The stage and management were defined according to the Barcelona-Clinic Liver Cancer Group diagnostic and treatment strategy (BCLC) (Llovet *et al*., 2004). Patients with advanced organ failure, other types of malignancy, active infection and advanced medical co-morbidity were excluded from the study.

Blood sampling

The blood samples were collected before any treatment at the period from March to September 2014, after confirmed diagnostic procedures. Five CC of blood were collected from each individual and divided into two portions. One containing citrate for INR determination, the rest was used as serum for other determinations. Blood samples were left for about 30 minutes and centrifuged for 10 minutes at 1500 rpm. The sera were maintained at −80°C right biochemical analysis.

Biochemical Analysis

Routine tests as ALT, AST, albumin and total bilirubin were determined colorimetrically, using Randox kits (UK).Serum α-fetoprotein was measured using a commercially available ELISA kit from Bio Check Company (USA), serum Golgi protein 73 level was measured using a commercially available ELISA kit from Wuhan USCN, China and serum Interleukin-17 level was measured using a commercially available ELISA kit from eBioscience, Inc (USA), following the manufacturer's instructions. Other routine investigations were purchased from local suppliers (Egypt).

Statistical Analysis

Statistical computations were done on a personal computer using the computer software SPSS version 18 (Chicago, IL, USA). Statistical significance was taken at P< 0.05. The results were calculated as mean values ± standard error (SE). For correlation, Pearson correlation was used. Both sensitivity and specificity were calculated according to the following formulae:

Sensitivity= TP/ (TP+FN), where TP = true positive, and FN = false negative

Specificity: the capacity of the test to correctly exclude individuals who are free of the disease "true negatives". The greater the specificity, the fewer "false positives" will be included.

Specificity= TN/ (TN+FP), where TN = true negative, and FP = false positive.

RESULTS AND DISCUSSION

The demographic characteristics of cirrhotic and HCC patients' groups, as well as, tumor characteristics of HCC are summarized in Table 1.

Table 1: Demographic characteristics of the studied patient groups.

		HCC (n=50)	Cirrhotic (n=30)
Sex	Male	40 (80%)	17 (56.66%)
	Female	10 (20%)	13 (43.33%)
Ascites	No	34 (68%)	5 (16.67)
	Yes	16 (32%)	25 (83.33%)
Child Pugh Classification	A	38 (76%)	10 (33.3%)
	B	9 (18%)	8 (26.7%)
	C	3 (6%)	12 (40%)
BCLC	A	10 (20%)	
	B	19 (38%)	
	C	17 (34%)	
	D	4 (8%)	
Performance status	0-1	34 (68%)	
	2-3	16 (32%)	
Number of lesions	Single	17 (34%)	
	Multifocal	33 (66%)	
Metastasis	Absent	42 (84%)	
	Present	8 (16%)	
Portal vein	Patent	37 (74%)	
	Thrombosed	13 (26%)	

BCLC: Barcelona-Clinic Liver Cancer Group diagnostic and treatment strategy.

Table 2: Liver function tests, α-fetoprotein, Golgi protein 73 and interleukin-17 serum levels in patients with cirrhosis and HCC, compared to control subjects.

Variables (mean ±SE)	Control group (n=8)	Cirrhotic group (n=30)	HCC group (n=50)
ALT (U/L)	17.26±2.28	40.5±5.1$^{\$}$	55.7 ± 4.9$^{\$\#}$
AST (U/L)	16.05 ±1.9	58.2±5.9$^{\$}$	69.6±5.9$^{\$}$
Total bilirubin (mg/dl)	0.7 ±0.1	6.3 ± 1.3$^{\$*}$	2.2± 0.3
Albumin (g/dl)	3.5 ± 0.3	2.4 ± 0.09$^{\$*}$	3.1 ±0.1
INR	1.0± 0.01	1.4 ± 0.05$^{\$*}$	1.2 ± 0.03$^{\$}$
α-fetoprotein (ng/ml)	4.01 ± 0.2	6.7 ± 0.9	571.8± 89.4 $^{\$\#}$
Golgi protein 73(ng/ml)	8.02±1.3	20.3±1.5$^{\$}$	19.09±1.4$^{\$}$
Interleukin-17 (pg/ml)	1.8±0.2	3.7±0.9$^{\$}$	8.7±1.2$^{\$\#}$

n = Number of subjects; **$** = Significant against control (P<0.05); ***** = Significant against HCC group (P<0.05); # = Significance against cirrhotic group (P<0.05).

The activity of both ALT and AST, in addition to AFP and IL-17 were significantly elevated in HCC patients, INR showed a significant elevation in cirrhotic than HCC patients, however, GP73 was elevated in both cirrhotic and HCC patients (Table 2).

In our study, variations relevant to cut off values in AFP, GP- 73 and IL-17 among HCC patients, showed that GP73 and IL-17 values were concomitant to AFP cut off values up and down (Table 3).

Table 3: AFP, GP73 and IL – 17 values in HCC patients at different cut off values (numbers in the Table indicate number of patients) , comparison was made only among patients, not control.

AFP (ng/ml)	Golgi 73 (ng/ml)			IL – 17 (pg/ml)		
	≥ 16	< 16	Total	≥ 3	< 3	Total
AFP ≥ 200	15	10	25	15	10	25
AFP < 200	13	12	25	12	13	25
Total	28	22	50	27	23	50

Although the sensitivity of GP73 is higher than that of AFP , the latter's specificity is still the best at higher cut off values (Table 4).

Table 4: Sensitivity and specificity values for AFP, IL-17 and Golgi protein 73 in HCC patients.

Markers	Sensitivity	Specificity	Positive predictive value	Negative predictive value
AFP ≥200(ng/ml)	50 %	100 %	100 %	60 %
AFP< 200 (ng/ml)				
IL - 17 ≥ 3(pg/ml)	54%	60.5%	64.2%	50%
IL - 17 < 3(pg/ml)				
Golgi 73 ≥ 16(ng/ml)	56%	42.1%	56%	42.1%
Golgi 73 < 16(ng/ml)				

This study elucidated no correlation between serum AFP and IL-17 in HCC, although, only a significant correlation was found between AFP and GP 73 among cirrhotic patients (Table 5).

Table 5: Correlation between serum AFP (ng/ml) and IL-17and GP 73 in cirrhotic and HCC patients.

Parameters	Cirrhotic patients		HCC patients	
	r	P	r	P
IL- 17 (pg/ml)	- 0.11	0.5	0.08	0.54
Golgi 73 (ng/ml)	0.4	0.02*	0.14	0.3

IL-17 was significantly correlated to tumor staging, distant metastasis, ascites, portal vein thrombosis and deteriorated performance of HCC patients rather than Golgi and AFP, although the three variables were not significantly indicative in cirrhotic patients (Table 6). HCC is one of the most common aggressive cancers, accounting for more than two-thirds of all primary liver cancers (Sherman, 2010). It is considered as one of the least curable malignancies due to lack of specific biomarkers for the detection in early stages and also as a result of high recurrence rate after curative therapy (Sun *et al*., 2007).

Table 6: Relation between serum AFP (ng/ml), GP 73 (ng/ml) and IL-17 (pg/ml) into tumor stages in HCC patients, (values are expressed as: mean ± SE).

		Serum AFP Level (mean ± SE)	Serum GP 73 Level (mean ± SE)	IL-17 Level (mean ± SE)
Performance status	0-1 (n= 34)	488.6±103.4	18.6± 1.6	6.5±1.2*****
	2-3 (n= 16)	748.6±169	16.1±2.6	13.3±2.6*****
Ascites	Absent (n= 34)	674.3±111.5	17.4±1.7	6.5±1.2*****
	Present (n= 16)	352.6±137	19.1±2.3	13.2±2.7*****
Cirrhosis	Absent (n= 5)	80.7±64.5	13.4±4.5	8.6±4.9
	Present (n= 45)	626.3±95.7	18.4± 1.4	8.7±1.3
Number of lesions	Single (n= 17)	422.6±145.4	18.6± 2.4	7.8±2.3
	Multifocal (n= 33)	648.6±112.06	17.5± 1.7	9.1±1.5
Distant Metastasis	Absent (n= 42)	576.3±100.2	18.6±1.5	7.1±1.2*****
	Present (n= 8)	547.9±201.6	14.3±2.8	16.9±3.5*****
Portal vein	Patent (n= 37)	560.2±101.9	18.1± 1.6	7.1±1.4*****
	Thrombosed (n= 13)	604.9±191.5	16.5± 2.5	13.1±2.4*****
BCLC stage	A-B (n= 29)	578.4±115.8	20.01±1.7	4.01±0.8*******
	C-D (n= 21)	562.7±143.7	15.1±2.1	15.2±2.1*******
Child score	A (n = 38)	566.2±103.5	16.2±1.6	6.5±1.1*******
	B (n = 9)	349.5±181.4	21.4±3.5	12.2±3.4*******
	C (n = 3)	1308.7±105.2	20.01± 4.4	25.7±4.8*******

n = Number of subjects, *= Significant (P< 0.05), **= Significant (P< 0.01), ***= Significant (P< 0.001).

Nowadays, differentiation of HCC from liver cirrhosis has become challenging as in liver cirrhosis regenerative nodules may mimic tumors, in addition to increased levels of AFP in patients with cirrhotic liver (Ressom *et al*., 2012; Stefaniuk *et al*., 2010). In the present study, serum concentration of AFP was significantly increased in HCC patients in comparison to cirrhotic patients and control group. Altered AFP level is still a hallmark of HCC development (Eissa *et al*., 2013; Ghazy *et al*., 2012; Hou *et al*., 2013; Kikuchi *et al*., 2009; Montaser *et al*., 2012). AFP serum concentration is normal in up to 40% of small HCCs, as not all tumors secrete AFP (Colombo *et al*., 1991), the sensitivity of AFP for detection of HCC is low (20-65%) (El-Serag, 2011) and it's utility for the differentiation between HCC and benign hepatic diseases has been limited as a result of high false positive and negative rates (Zhao *et al*., 2015). In addition, the elevated INR among cirrhotic than HCC patients, despite the elevated ALT and AST activities in the latter, indicates that the liver synthetic power is depressed more in cirrhosis.

Golgi protein 73 (GP73) is a novel Golgi trans-membrane protein, usually expressed in human epithelial cells (Kladney *et al*., 2000). In normal human liver, GP73 is primarily expressed by biliary epithelial cells, but its expression by healthy hepatocyte was limited or even absent. However, in case of viral infection, the expression of GP73 is highly up-regulated by hepatocytes (Kladney *et al*., 2002; Riener *et al*., 2009). Several experimental and clinical studies have shown that serum level of GP73 was significantly increased in liver disease including HCC (Comunale *et al*., 2004). Subsequent studies revealed that serum level of GP73 is elevated in different viral and non-viral hepatic diseases, cirrhosis and HCC; even, it is elevated in non-liver malignances (Hu *et al*., 2010; Li *et al*., 2009; Willyard, 2007).

Our study showed that serum GP73 level was significantly increased in HCC and cirrhotic patients, compared to control group. GP73 levels in cirrhotic patients tend to be higher than in HCC patients, but the difference was not statistically significant. This was in accordance with Gu *et al*. and Morota *et al*., (Gu *et al*., 2009; Morota *et al*., 2011). Other studies (Gu *et al*., 2009; Morota *et al*., 2011; Shan *et al*., 2013; Tian *et al*., 2011) reported that serum GP73 level was significantly elevated in HCC and cirrhotic patients than healthy individuals. However, the serum GP73 level in the liver cirrhosis group was significantly higher than in the HCC group. The expression of GP73 was absent or decreased in normal and healthy hepatocytes, indicating that its expression was considered as a feature of the giant-cell transformation. Consequently, the high expression of GP73 was observed in hepatocytes of patients suffering from decompensate liver cirrhosis (Kladney *et al*., 2002). Iftikhar *et al*., (Iftikhar *et al*., 2004) suggested that there are two mechanisms for GP73 regulation; one triggered during acute hepatocellular injury and the second during chronic tissue remodeling and fibrogenesis. Our results elicited a significant positive correlation between serum GP73 and AFP levels in cirrhotic patients. Golgi protein 73 was high in both cirrhotics and HCCs. This didn't affect its utility in predicting transformation into HCC. The minor depression after HCC progression, shares AFP and some other cancer proteins in being of peak value which may down by time. AFP is an ideal marker for these proteins, this is why it is considered as acute phase marker.

Interleukin 17 (IL‑17) was primarily identified as a transcript from a rodent T‑cell hybridoma by 1993 (Liu *et al*., 2014). It was defined as a pro inflammatory cytokine produced by innate and adaptive immune cells (Cua and Tato, 2010; Hirota *et al*., 2010; Korn *et al*., 2009). IL-17 producing cells are engaged in several liver diseases (Bertolino, 2008) and detected in the tumor microenvironment (Su *et al*., 2010; Zhang *et al*., 2008). Since IL-17 receptor (IL-17R) is expressed on all types of liver cells (Lafdil *et al*., 2010), IL-17 producing cells were mainly involved in the crosstalk with various liver-resident cells in HCC (Liao *et al*.,

2013). It was previously published that the levels of IL-17 producing cells were significantly increased in tumors of HCC patients, compared with corresponding non-tumor regions (Wang *et al*., 2010; Zhang *et al*., 2009). It was published that serum IL-17 level was markedly increased in HCV-infected patients(El Husseiny *et al*., 2012) and patients with HCC(Liu *et al*., 2014). In the present study, serum IL-17 level was significantly elevated in HCC, compared to cirrhotic patients and control group. This was in agreement with some other reports (Hammad *et al*., 2013) who observed that serum IL-17 level was significantly increased in HCC patients in comparison to cirrhotic patients and healthy control group. Unlike Ghazy *et al*., (Ghazy *et al*., 2012) who reported that serum IL-17 level was correlated with serum AFP level, our study elucidated no correlation between these two serum levels. This is possibly because the present work was executed on 84% of participants with primary HCC (Wu *et al*., 2012). This study elucidated significant negative correlation between serum IL-17 level and overall survival rates in HCC patients and this was in consistent with elsewhere results (Liao *et al*., 2013; Wu *et al*., 2012; Zhang *et al*., 2009).

CONCLUSION

Serum Golgi protein 73, unlike some previous observations, is not a valuable diagnostic marker for HCC due to its low sensitivity and low specificity. It can only be used as an additional marker for cirrhosis. Serum IL-17 can be used as a useful HCC staging marker. It was significantly related to HCC stages and other poor prognostic criteria like portal vein invasion, presence of distant metastasis and low survival. So it can be used as a potential diagnostic marker. Combined use of AFP and IL-17 increases the positive predictive value for HCC diagnosis. Golgi protein 73 shows a correlative value to AFP in cirrhotic, rather than HCC patients. Although correlations were low, the next Table (6) clarified the contributory roles of the 3 parameters in different pathologic phase from cirrhosis into HCC development and stages.

CONFLICT OF INTEREST:

None.

ETHICAL APPROVAL

The whole work was early approved by the Committee of Research and Ethics and the study was approved by the committee for clinical studies in the university.

AUTHORS' CONTRIBUTIONS

All authors equally contributed to the article, however, the corresponding author is the team leader and suggested the research goal.

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