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Research Article

Diagnostic performance of alpha-fetoprotein, YKL40 and GP73 in hepatocellular carcinoma Egyptian patients

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a primary malignancy of the liver. It is responsible for a large proportion of cancer deaths worldwide. Diagnosis of HCC often requires more sophisticated modalities and represents a challenge for physician.
Methods: This study aimed to compare the diagnostic performance of AFP, YKL40 and GP73 in patients' serum with hepatocellular carcinoma (HCC) in high-risk population in an attempt to justify the new, sensitive, specific and rapid measure for the diagnosis and detection of HCC. Serum YKL40, GP73 and alpha-fetoprotein (AFP) were compared in a total of 60 human subjects in this study, including 20 healthy adults, and 40 patients with HCC, The main outcome measures were the specificity and sensitivity of YKL40 and GP73 in patients at risk for the development of HCC.
Results: Using 4.4 relative units as a cut-off value, the sensitivity and specificity of serum GP73 for HCC were 85% and 90% compared with 77% and 60% for YKL40 using 21.06 ng/ml as a cut-off value. On the same context, the sensitivity and specificity of serum AFP at 8.5ng/ml cut-off were 82% and 95%. While that for the AFP and GP73 combined detection was up to 92% and 96%, justifying that the combined detection could prevent the false negative diagnosis by any marker alone and significantly improve the detection rate of HCC.
Conclusions: The current evidence indicates that serum GP73 has HCC diagnostic efficacy inferior to that of AFP and YKL40 and the clinical implementation of serum GP73 measurement as a standard test for HCC is recommended alone or in combination with AFP.

Keywords: Hepatocellular carcinoma, AFP, YKL40 and GP73

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world with high morbidity and mortality but its pathogenesis remains unclear.[1] Because primary liver cancer is a growing concern showing poor prognosis due to its rapid infiltrating power and complicating liver cirrhosis; more attention were given to address the causal risk factors that could be preventable and/or treatable.[2]

HCC is phenotypically and genetically heterogeneous tumor, reflecting in part the heterogeneity of etiologic factors involved in (i) the onset of HCC development that is also influenced by age, gender and ethnic differences, (ii) the complexity of hepatocyte functions and epigenome leading to neo-plastic transformation and (iii) the late stage of HCC development.[3]

Different forms of chronic viral hepatitis are associated with development of liver cirrhosis and hepatocellular

carcinoma (HCC). Indeed, approximately 80% of cases of hepatocellular carcinoma are associated with chronic HCV infections.[4]

The progression of liver disease into liver cancer is primarily monitored by serum levels of the oncofetal glycoprotein, α-fetoprotein (AFP). However, AFP can be produced under many circumstances, including other liver diseases, and is not present in all those with HCC.[5] Therefore, the use of AFP as a primary screen for HCC has been questioned and more sensitive serum biomarkers for HCC are desired. These screening tools should have an acceptable rate of accuracy and should be affordable.[6]

The major challenges in current cancer research are the discovery and justification of biomarkers that could be used to detect the initial stages of cancer whilst its development, to go after the succession or failure of cancer.[7]

An ideal image biomarker should be non-invasive, objectively quantitative, reproducible, readily available, validated and easy for clinical application to meet the expectations of regulatory authorities such as the FDA for using imaging as a surrogate end point of treatment response.

YKL40 is a 40 kD glycosylated chitinase like glycoprotein secreted by some specific in vivo cancers cells and several ex vivo cancer cell lines. The name YKL40 is based on its three N- terminal amino acids tyrosine (Y), lysine (K) and leucine (L) and 40 kDa of its molecular mass.[8]

YKL40 is an inflammatory marker and it is suggested that YKL 40 is a secreted protein and the sites of actions are most likely to be extracellular. Till today no specific cell-surface or soluble receptors for YKL40 have been identified. The role of YKL40 in cancer cells is still unclear, but several promising functions have been proposed.[9]

Elevated serum YKL40 levels were found in several primary and metastatic malignancies and serum YKL40 may serve as a valuable and independent prognostic biomarker of short survival.[10]

Golgi protein 73 (GP73), also named golgi phosphoprotein 2 (GOLPH2), is a 400 amino acid, 73 kDa trans-membrane glycoprotein that normally resides within the cis- golgi complex. Its mRNA was first identified in a search for unregulated hepatic genes in a patient with syncytial giant cell hepatitis. Subsequent studies revealed minimal GP73 expression in normal hepatocytes but marked expression in patients with acute and chronic hepatitis and liver cirrhosis.[11]

Since block and colleagues first demonstrated GP73 in serum and found increased GP73 levels in patients with hepatitis B virus-related hepatocellular cancer, more investigations on GP73 have been undertaken and GP73 has become a hotspot for its potent role in the diagnosis of HCC.[12]

Therefore this study was attempted to provide insight into the knowledge of the emerging role of GP73 and YKL40 as objective and reproducible biomarkers for diagnosis of HCC.

METHODS

Patients

A total of 40 HCC patients recruited from the hepatology and general internal medicine outpatient clinics, National cancer institute, Cairo University were enrolled in this study. They were diagnosed as HCC according to clinical examination, radiological investigations including abdominal ultrasonography, triphasic C.T and laboratory investigations. All patients were newly diagnosed cases and did not receive chemotherapy.

Additionally, 20 healthy subjects were included as a control group; they had normal values of serum alanine aminotransferase (ALT) and were seronegative for hepatitis B surface markers and HCV antibodies.

The protocol was conducted in accordance with guidelines approved by local research ethics committee and the subjects in this study were matched in regard to sex and age and in-formed consent was obtained from all the patients and volunteers.

Samples collection

Six milliliters of venous blood specimens were collected in dry clean centrifuge tubes after an overnight fast, left to clot for 30 minutes at 37°C, and then centrifuged at 3000 rpm for 10 minutes. The sera then were separated, divided into several aliquots, stored at -20°C to be thawed only once on demand for the biochemical analyses.

Biochemical analyses

Serum alanine and aspartate aminotransferase activities were determined by the method of Reitman and Frankel.[13] Enzymatic activity of alkaline phosphatase (ALP) was determined according to method of Kind and King.[14] Determination of serum total bilirubin was carried out according to colorimetric technique described by Perry et al.[15]

Serum AFP was quantitatively assessed using AFP commercial kit according to instruction included in the ELISA kits. The level of GP 73 was determined by ELISA kit provided by Uscn, Life Science (Inc-USA) and YKL 40 was measured using immunoassay kit (Stago, France) according to manufacturer's instructions included in the kit.

Data presentation and statistical analysis

All analyses were performed using the statistical package for the Social science (SPSS software version 22; SPSS INC., Chicago, USA). Results of biochemical studies were statistically analyzed using one way analysis of variance (ANOVA) and the data were expressed as mean±S.E. Receiver operating characteristic curves were plotted to define the optimal cut-off values and to identify the sensitivity and specificity. Pearson's correlation was performed to detect the relationship between different parameters studied.

RESULTS

Clinical laboratory data of the studied patients are shown in (Table 1) which elucidated a significant increase in ALT, AST, alkaline phosphatase activities in HCC group by 350%, 225% and 141% respectively when compared by their levels in control group. In contrast, non-significant changes in total bilirubin level in HCC patients in comparison with its level in nor-mal group.

Table 1: Descriptive data of the selected liver function tests in HCC and normal control groups.

Parameters	Groups	Mean	SE	P<value
ALT (U/L)	Control	19.95	2.12	0.001
	HCC	89.8	9.99	
AST (U/L)	Control	20.65	1.25	0.001
	HCC	67.28	6.63	
ALP (U/L)	Control	63.25	4.08	0.001
	HCC	152.63	16.5	
T-Bilirubin (mg/dl)	Control	0.45	0.03	NS
	HCC	1.59	0.43	

Also, data represented in Figure 1 showed a drastic elevation ($p<0.001$) in the levels of AFP, YKL40, and GP73 in patient group suffering from HCC when compared with their levels in normal control group.

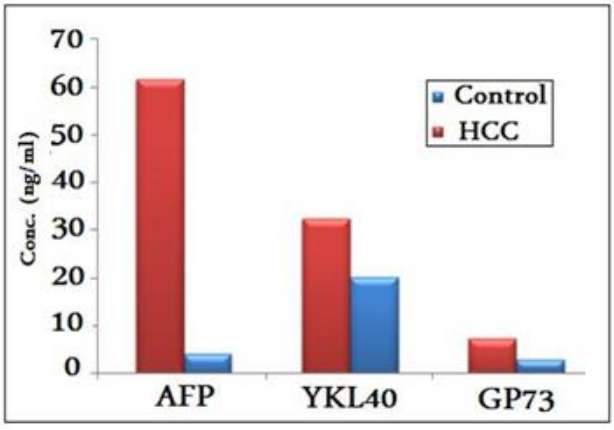

Figure 1: The levels of AFP, YKL40 and GP73 in HCC and control groups.

The obtained results presented in Table 2 revealed that, HCC diagnostic efficacy of AFP having sensitivity of 82%, specificity of 95% at a cut-off value of 8.5 ng/ml. In the meantime, the HCC diagnostic accuracy of YKL40 in the serum samples was 71% and in addition the parameter sensitivity was 77% and specificity was 60% at cut-off value of 21.06 ng/ml. At the cut off values of GP73 equivalent to 4.4 ng/ml; the accuracy for early diagnosis of HCC was 87% in the meantime the parameter sensitivity and specificity were 85% and 90% respectively.

Table 2: Sensitivity, specificity and accuracy of the targeted tumor markers for early diagnosis of HCC (n=40).

Variable	Cut-off value	Sensitivity	Specificity	Accuracy
AFP (ng/ml)	8.5 ng/ml	82%	95%	85%
YKL40 (ng/ml)	21.06 ng/ml	77%	60%	71%
GP73 (ng/ml)	4.4 ng/ml	85%	90%	87%
Combined AFP &GP73	AFP=85 ng/ml GP73=4.4 ng/ml	92%	96%	91%

The receiver–operator curve (ROC) of three individual markers is shown in Figure 2. The AUROC of AFP for the diagnosis of HCC was 0.866, which was superior to that of YKL40 (0.769) but inferior to GP73 (0.920). However, when GP73 used in combination with AFP for early detection of HCC, they increased sensitivity up to 92%, whereas, specificity was 96%.

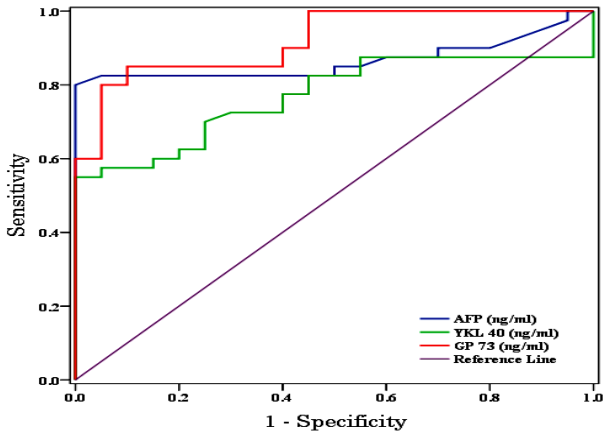

Figure 2: Receiver operating characteristic (ROC) curves dis-playing the accuracy of AFP, YKL40 and GP73 for HCC patients group.

Results of computing the correlation matrix between the targeted measured parameters in HCC group that

presented in Figure 3 showed highly significant positive correlation between YKL40 and GP73 (R^2= 0.171).

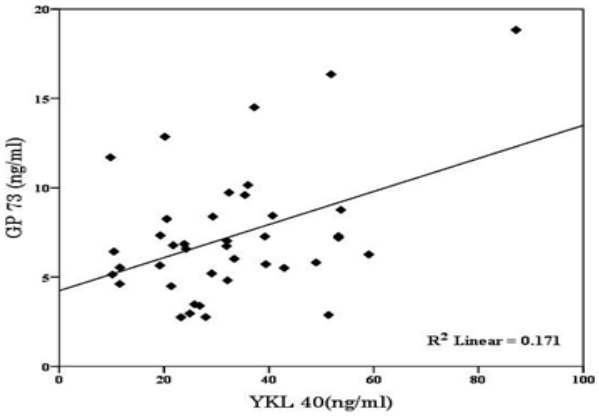

Figure 3: Graph dataset (correlations) between YKL4O and GP73 in HCC Patients.

DISCUSSION

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers worldwide. The disease is predominant in Asia and Africa, but its incidence is steadily increasing throughout the rest of the world.[16] Unlike other solid malignancies, the coexistence of inflammation and cirrhosis makes the early diagnosis and prognostic assessment of HCC much more difficult. This complication highlights the need to identify valuable biomarkers for the diagnosis and treatment of HCC.[17]

AFP, a specific glycoprotein produced primarily by the fetal liver has been the most practical and widely used serum biomarker for HCC diagnosis. AFP is expressed and secreted into the blood of approximately 70% of HCC patients. Thus, the blood AFP level is useful for early detection and differential diagnosis of HCC.[18] For patients who undergo curative hepatectomy for localized HCC, the AFP level is also helpful for recurrence detection and is associated with prognosis.[19] However, this is not considered common practice in light of the poor accuracy demonstrated in subsequent studies and in different populations.[20]

Other conventional clinical tumor associated biomarkers such as CEA, CA199, and CA724 etc. are not practical in the clinic because of their poor sensitivity and specificity. The present situation requires an urgent need to explore new markers to overcome these drawbacks in liver cancer diagnosis.[21]

The clinical usefulness of HCC biomarkers needs to be carefully evaluated and validated. So, an ideal serum biomarker should be both sensitive and specific for HCC detection at an early stage, and be easy to test, reproduce, as well as be non- invasive. Thus, we aimed to evaluate the utility of YKL 40 and GP 73 as biomarkers individually, as well as their combined application in the early detection of HCC and for their usefulness in therapeutic decision-making. With taking in consideration the comparison their efficacy as diagnostic markers with AFP that is used as well established marker for HCC diagnosis.

In the present study, the level of AFP was high significantly increased in HCC patient when compared with its normal level ($p<0.001$). Also, AFP has been detected in approximately 82% of HCC patients with cutoff value of 8.5 ng/ml. These results are in agreement with Tangkijvanich et al, Fujioka et al, Debruyne and Delanghe, Yamamoto et al and Saito et al who reported an increased level of AFP in HCC patients.[22-26] Elevated AFP levels were associated with larger tumor size, a later clinical stage, vascular invasion, poor tumor differentiation, and distant metastasis.[27]

There is a debate in defining the AFP cut off level for the diagnosis of the HCC.[28] An AFP value above 400ng/ml has been considered diagnostic for HCC in patients with cirrhosis. However, such cut off value is problematic in absolute diagnostic terms, since high levels of this magnitude are not as common in the presence of smaller tumors, furthermore; nor-mal AFP levels can be seen in approximately one-third of patients with HCC in this context.[29] A large multicenter study carried by Farinati et al based on both retrospecfic and prospective data collection, over a consecutive series of more than 1000 HCC patients, found that only 18% of studied patients had an AFP level >400 ng/ml, who also showed poor survival.[30] This discrepancy issue making detection and prognosis of HCC are very difficult.

In a search of new bone proteins, the glycoprotein YKL40 was identified in 1989 to be secreted in vitro in large amount by the human osteosarcoma cell line MG63. In the last few years there have been a growing number of publications concerning YKL40 and the "story about YKL40" has probably just started. The secreted protein; YKL40 is produced in humans by activated macrophages and neutrophils in different tissues with inflammation and increased remodeling of the ECM, by arthritic or injured chondrocytes, by fibroblast-like synovial cells, by vascular smooth muscle cells, and probably by hepatic stellate cells. The complete in vivo biological functions of YKL40 remains to be established, but it may have a function in inflammation and remodeling of the ECM.[31]

Data recorded in our study showed significant increase of YKL40 ($p<0.05$) in HCC group by 61%. The results of YKL40 assessment are in line with results of Yang et al, Ringsholt et al, and Johansen et al who illustrated the cancer progression that depends on the interplay between cancer cells and their microenvironment, particularly cells in the surrounding extracellular matrix.[32-34] It has been established that tumor-associated macrophages and leukocytes play important roles in tumor growth and metastasis because they produce growth and angiogenic factors, chemokines, metalloproteinases, and other

extracellular matrix-degrading enzymes. Previous studies have shown that YKL40 is expressed and secreted by activated neutrophils and macrophages, indicating that YKL40 may play a role in the inflammatory process around the tumor, stimulating angiogenesis, and remodeling of the extracellular matrix. Recent immunohistochemical analyses of biopsies from HCC patients demonstrated that overexpression of YKL40 was observed in primary HCC and their matched metastatic tumors.[32]

Golgi phosphoprotein 2 (GOLPH2) is a resident Golgi type-II membrane protein upregulated in liver disease. GP73 function is presently unknown. Multiple search algorithms for protein motifs have not revealed any obvious catalytic or enzymatic properties.[35] Recent gene knock-down studies in HepG2.2.15 cells demonstrated that GP73 inhibition is associated with a reduction in the surface area of the Golgi complex. Therefore, some researchers think that GP73 expression might be involved in maintaining the structural integrity of the Golgi complex during cellular stress.[36]

The obtained results clearly indicated that, GP73 level significantly increased in patients with HCC compared with healthy controls. These data were in agreement with Mao et al who compared serum GP73 and AFP levels in 4217 human subjects in a multicenter study in 2010, finding that the sensitivity and specificity of GP73 level for the detection of HCC were 74.6% and 97.4%, respectively, significantly higher than the corresponding values for AFP level.[37] El Shafie et al recently re-ported that in Egyptian patients the sensitivity and specificity of serum GP 73 for early detection of HCC were 95% each, thus GP73 was a promising diagnostic marker.[38] A recent meta-analysis also indicated that GP73 level was superior to AFP level for the early diagnosis and screening of HCC.[39]

The results of our analysis suggested that the combination between AFP and GP73 in the diagnosis of hepatocellular carcinoma has strong predictive values in differentiation of HCC and non HCC patients. These results are in line with Tian et al and Wang et al who found that, combined measurement of GP73 and AFP could further increase the sensitivity for the detection of HCC.[40,41]

From aforementioned results, GP73 might be as useful marker in the diagnosis and screening of potential HCC patients when used alone or in combination with AFP and we need to be evaluated further in future studies using stricter criteria where significant difficulties for interpreting the present studies arose due to different cutoff values, and study populations.

CONCLUSION

The current evidence indicates that serum GP73 has HCC diagnostic efficacy inferior to that of AFP and YKL40 and the clinical implementation of serum GP73 measurement as a standard test for HCC is recommended alone or in combination with AFP.

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