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ARTICLE

ANALYSIS OF THE DIAGNOSTIC VALUE OF SEVERAL SEROLOGIC MARKERS FOR PRIMARY HEPATOCELLULAR CARCINOMA

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ABSTRACT

Objective: To investigate the clinical value of laboratory diagnostic indexes of alpha-fetoprotein (AFP), Golgi protein 73 (GP73), abnormal plasminogen (DCP), alpha-fetoprotein heterodimer ratio (GP73%), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and globulin (Alb) in the diagnosis of primary hepatocellular carcinoma (PHC). Method: Thirty patients with primary liver cancer (liver cancer group) and 41 controls were selected, including 30 patients with hepatitis and 11 patients with healthy physical examination. Compare the serum DCP, GP73, AFP, AFP-L3%, GGT, ALP, Alb levels of the three groups; compare the positive detection rate of each index for primary liver cancer; apply ROC curve to analyze the indexes, and meanwhile analyze and compare the diagnostic value of PHC in individual and We analyzed and compared the diagnostic value of individual and combined tests for PHC. Results: Patients in the hepatocellular carcinoma group had higher DCP, GP73, AFP, AFP-L3%, GGT, and ALP than patients in the liver disease group and the physical examination group, with statistically significant differences; DCP diagnosed the highest positive rate of primary hepatocellular carcinoma; the ROC curves showed that DCP had the largest AUCROC and the highest diagnostic value; the sensitivity of combined test was no difference with the detection of DCP alone. Conclusion: (1) DCP, GP73, AFP, AFP-L3%, GGT, and ALP can play an important role in disease screening for patients with primary hepatocellular carcinoma. (2) DCP is the most valuable single biological indicator for the diagnosis of primary hepatocellular carcinoma, and it has high sensitivity, specificity, and accuracy. (3) Combined assays improved the accuracy of the assays when tested individually but did not differ significantly from the assays for DCP alone.

KEYWORDS

Primary Hepatocellular Carcinoma, Serologic Markers, ROC, Co-Diagnosis

1. Introduction

Primaryhepaticcancer (PHC) has become the sixth most common malignant tumor in the world, with a high mortality rate that is the third highest among cancer-related deaths globally, and the second highest among the causes of tumor deaths in China (Bray et al., 2024), and a 5-year survival rate of only 14.1% (Allemani et al., 2018), with a poor overall prognosis. One of the key strategies to improve the prognosis is to accurately diagnose HCC at an early stage when surgical cure is still possible in order to improve the clinical outcome (Wang et al., 2023). Early diagnosis of HCC includes imaging, serum tumor marker, pathology and other testing methods. Serological biomarker testing is non-invasive, easy to operate, inexpensive, rapid and can be repeatedly monitored to understand the progress of the disease, etc. It is worthwhile to widely promote in the early screening stage of PHC, which has a greater value of clinical application. AFP is the most commonly used biomarker to diagnose hepatocellular carcinoma in China at the present stage, but the value of the AFP test is limited, and about 40% of the early stage hepatocellular carcinoma is AFP monitor negative (Tzartzeva et al., 2018), which is not suitable as a monitoring index for high-risk patients. Therefore, it is essential to find new liver cancer-related biomarkers to improve the accuracy of early diagnosis and reduce the rate of missed diagnosis. The sensitivity and specificity of single-indicator detection are difficult to reach a clinically satisfactory state, and it is worthwhile to investigate whether combined detection can further improve the diagnostic efficacy of the disease. In view of this, this study analyzes the diagnostic value of combined detection of DCP, AFP, GP73, GP73%, GGT, ALP, Alb in hepatocellular carcinoma, and is reported as follows.

2. Data and Methods

2.1 Subjects of the Study

Seventy-one patients admitted to the Affiliated Hospital of Hebei University from April 2024 to August 2024 were selected, with the pathologic or clinical diagnosis of PHC as the gold standard, and 30 of them with primary liver cancer and 30 patients with hepatitis and 11 healthy physical examination people who attended the clinic during the same period of time were selected as the study subjects for group comparison. Among them, there were 22 males and 8 females in the liver cancer group, aged 43-78 years old, with an average age of 66.13 years old; 20 males and 10 females in the hepatitis group, aged 36-77 years old, with an average age of 55.97 years old; and 6 males and 5 females in the physical examination group, aged 37-71 years old, with an average age of 54.55 years old; the difference in the age of the three groups was not statistically significant when compared with each other (P<0. 05). Inclusion criteria: ① all patients have a clear diagnosis, hepatitis cirrhosis diagnostic criteria refer to the "Viral Hepatitis Prevention and Control Program", HCC diagnostic criteria refer to the "Expert Consensus on Standardized Pathological Diagnostic Programs for Primary Liver Cancer" (Chen et al., 2020); ② complete clinical data.

2.2 Observation Index

① Observe the serum DCP, AFP, GP73, AFP-L3%, GGT, ALP, Alb test results of the three groups and compare them. ② Statistics on the positive detection rate of various tumor markers for the diagnosis of primary liver cancer. ③ Draw ROC curves to analyze the diagnostic efficacy of each index individually and in combination.

2.3 Statistical Methods

The data were statistically analyzed using SPSS22.0. Measurement data were expressed as mean ± standard deviation ± s and analyzed by one-way ANOVA; count data were expressed as rate (%) and χ^2 test was used. P < 0.05 was considered as statistically significant difference. Subjects' work characteristic curves (ROC) were plotted and area under the curve, sensitivity, specificity, and Jordon's index were calculated.

3. Results

3.1 The Results of 7 Serological Markers in the Liver Cancer Group and the Hepatitis Group and Physical Examination Group

The differences between DCP, AFP, GP73, AFP-L 3%, GGT and ALP in the liver cancer group and the other two groups were statistically significant (P< 0. 05), and the differences between Alb and the other two groups were not statistically significant, ALP were significantly higher than those in the liver disease group and the physical examination group. See Table 1.

3.2 Comparison of the Positive Detection Rate of Various Indexes in the Two Groups

30 patients with primary liver cancer and 41 patients with non-liver cancer were statistically analyzed, in which the highest positive rate of DCP diagnosis was 83.3%, and the differences were all statistically significant (P<0.05). See Table 2.

3.3 Diagnostic Efficacy of Each Index for Primary Liver Cancer

The ROC curve was used to analyze the efficacy of each index for diagnosing primary liver cancer. The results showed that when applying the indexes individually, the sensitivity (0.923) and specificity (0.970) of DCP were the highest, with a high predictive performance. When the six indexes were combined to diagnose, the sensitivity (0.900) and specificity (1.00) changed, but there was no statistically significant difference with the detection of DCP alone. Among the results of ROC analysis and characteristic parameters, DCP had the highest area under the curve, and the highest Jordon index, sensitivity, and specificity; ALP had the smallest area under the curve, and the lowest Jordon index, sensitivity, and specificity. See Figure 1 and Table 3.

Table 1: Comparison of tumor marker test results among the 3 groups (x ± s)

GROUP	DCP	GP73	AFP	GP73	GGT	ALP	Alb
Liver Cancer	7953.5±8755.1	183.7±107.3	106.6±175.0	10.2±4.7	228.3±270.3	211.3±264.0	31.3±6.7
Hepatitis	24.63±29.4	82.0±66.6	3.1±2.1	5.0±0.0	43.9±42.9	82.3±35.3	31.5±6.7
Physical Examination	17.0±5.4	72.5±68.8	3.8±2.3	5.7±2.2	224.3±11.7	78.3±20.2	28.7±4.0
F	16.7	12.3	7.1	22.2	8.2	4.0	0.8
P	<0.01	<0.01	<0.01	<0.01	<0.01	0.02	0.45

Table 2: Comparison of the positive detection rates of various tumor biomarkers between the two groups [n (%)]

Group	Number of examples	DCP	GP73	AFP	AFP-L3	GGT	ALP
Liver Cancer	30	25(83.30%)	15(50%)	20(66.70%)	15(50%)	24(80%)	18(60%)
Non-Liver Cancer	41	2(4.90%)	4(9.80%)	5(12.20%)	1(2.40%)	15(36.60%)	12(29.30%)
Chi-square value	/	45.2	14.3	22.5	22.4	13.1	6.7
P	/	<0.01	<0.01	<0.01	<0.01	<0.01	<0.05

Table 3: Area below the curve

Indicator	AUC	95% CI	Optimal cutoff value	Sensitivity	Specificity	Jordon's index
DCP	0.884	0.79~0.97	29.22	0.82	0.917	0.74
GP73	0.718	0.58~0.85	81.00	0.85	0.583	0.44
AFP	0.740	0.61~0.86	8.73	0.50	0.917	0.42
AFP-L3	0.714	0.58~0.84	9.13	0.47	0.958	0.43
GGT	0.729	0.59~0.86	59.50	0.76	0.708	0.47
ALP	0.733	0.59~0.86	76.50	0.85	0.583	0.44
Alb	0.506	0.35~0.65	35.00	0.82	0.833	0.66
Joint diagnosis 6	0.892	0.81~0.97	-	0.79	0.875	0.67
Joint diagnosis 2	0.881	0.80~0.96	-	0.32	0.875	0.20

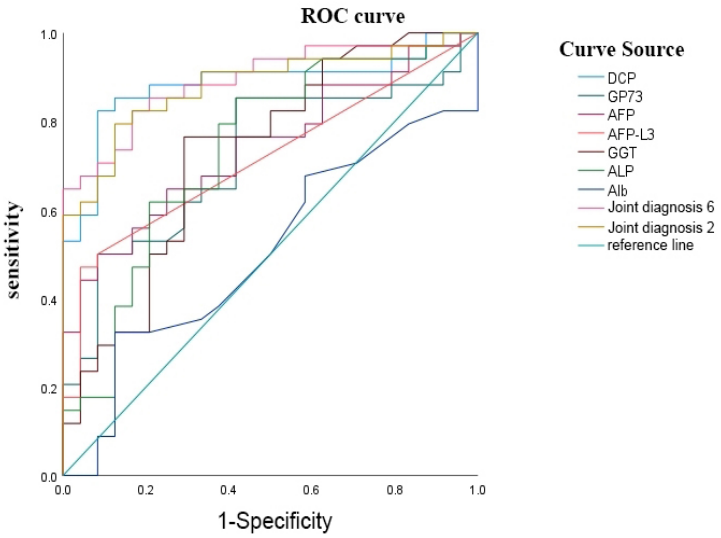

Figure 1: ROC curve

4. Discussion

As the largest metabolic organ in human body, liver undertakes various roles such as de-oxidization, synthesis of secretory proteins, storage of hepatic glycogen and so on. After the occurrence of hepatocellular carcinoma, many indicators related to the liver in the body may show abnormal changes, and the early diagnosis of the disease can be assisted by detecting the value of such indicators. Finding a simple, highly accurate and safe diagnostic method can help clinical screening, improve the early detection rate of hepatocellular carcinoma and improve the prognosis of patients.

AFP is one of the important indicators for early diagnosis of hepatocellular carcinoma, which is mainly synthesized in fetal stem cells, and yolk sacs, and the level of AFP in the body decreases rapidly after the birth of the fetus, and when hepatocellular carcinoma occurs in the patient, the cancer cells can stimulate the synthesis of AFP in large quantities and release it into the blood (Sun et al., 2023). AFP is not only persistently elevated in patients with hepatocellular carcinoma, but also the serum level of AFP in patients with chronic hepatitis, liver cirrhosis, gestation period, germinal embryonic-derived tumors and some of the patients with digestive tract tumors have abnormal serum AFP levels, which limits the clinical application of AFP (Zhou et al., 2023). During the invasion of tumor cells, heterogeneous changes in AFP sugar chain structure occur, and according to the affinity with lentil lectin (LCA), AFP can be classified into three types of heterodimers, i.e., AFP-L1, AFP-L2, and AFP-L3, which has the highest affinity with LCA, among which AFP-L3 is produced only by hepatocellular carcinoma cells, and it is not expressed in hepatitis and other chronic liver diseases (Wei et al., 2020). The percentage of AFP-L3 to total AFP is commonly used clinically as a diagnostic indicator of PHC, i.e., the alpha-fetoprotein heterodimer ratio (AFP-L3%), which is highly specific for HCC and reflects tumor characteristics such as poor differentiation or malignant invasion (Vipani et al., 2022).DCP is a type of abnormal prothrombin that does not have a clotting function. Under normal conditions hepatocytes can generate thromboplastin with the assistance of vitamin K to maintain the stability of the body's coagulation system. When hepatocellular carcinoma occurs, there is an obstacle in the process of prothrombin synthesis, which leads to a large amount of abnormal prothrombin generation and a substantial increase in DCP (Wang et al., 2020), whereas there is almost no abnormality in patients with hepatitis and cirrhosis (Piratvisuth et al., 2023). Currently, AFP, AFP-L3% and DCP have been listed as important indicators for the diagnosis of HCC by several domestic and foreign liver disease associations (Saeki et al., 2024).

Golgi protein 73 (GP73), a type II transmembrane glycoprotein, is found in the Golgi membrane. The level of GP73 is low in normal liver, but its level is significantly increased in liver diseases caused by HBV and HCV infections or non-viral-induced liver diseases (alcohol-induced liver disease, autoimmune hepatitis), but it is hardly expressed in normal hepatocytes (Liu et al., 2021), GP73 is associated with the invasive behavior of HCC, and it is a potentially promising molecular marker, and it may be an important target for future therapeutic strategies as well (Piñero et al., 2020); ALP and GGT belong to the commonly used indicators for clinical assessment of patients' liver function status, ALP is a hepatocyte metabolite, and the greater the degree of biliary dilatation when biliary excretion is impeded, the higher its serum level (Koneri et al., 2023), and serum ALP is elevated to varying degrees in patients with obstructive jaundice, acute and chronic jaundice hepatitis, hepatocellular carcinoma, and other hepatobiliary disorders (Li et al., 2022). GGT includes a variety of isoforms, which are expressed by the hepatic Kupffer cells and bile duct endothelial cells, which are secreted and involved in the synthesis and catabolism of glutathione, which is an important mechanism for tumor growth and resistance to injury. GGT is not a liver-specific enzyme, and almost all cell membranes have GGT, and high expression of GGT is not only found in hepatocellular carcinomas, but also in colon cancers, ovarian cancers, and tumors of the blood system, etc. The isoform of GGT, GGT II, is useful for the diagnosis of HCC with good sensitivity and specificity (Zheng et al., 2022). Serum albumin is an endogenous nutrient in the body, and is an indicator of hepatic protein synthesis and inflammatory response of the body. Hepatocellular carcinoma can lead to liver damage, which prompts an increase in the number of inflammatory cells, which in turn leads to an increase in the level of total protein in the body and inhibits the synthesis of albumin.

There are numerous existing PHC markers in the clinic, and each serum tumor marker has its unique advantages in diagnostic value as well as its limitations, and there is no single marker that can diagnose all PHC (Kim et al., 2023). Therefore, it is usually believed that the combined detection of several serum PHC markers can complement each other's advantages and improve the diagnostic efficiency, which is also the development trend of experimental diagnosis of primary liver cancer in recent years.

The results of this study showed that DCP, AFP, GP73, AFP-L3%, GGT, and ALP were higher in patients in the liver cancer group than in patients in the liver disease group and the physical examination group, which was statistically significant and helped in the differential diagnosis of benign and malignant liver diseases; while the difference between Alb and the other groups was not statistically significant, and it could not be used alone in the diagnosis of primary hepatocellular carcinoma. The positive detection rates of DCP, AFP, GP73, AFP-L3%, GGT and ALP for hepatocellular carcinoma in the hepatocellular carcinoma group were higher than those in the control group, in which the highest positive rate of DCP diagnosis was 83.3%, and the drawing of ROC curves showed that the areas under the curve of DCP, GP73, AFP, AFP-L3, GGT, ALP, and the combined detection for diagnosis of hepatocellular carcinoma were 0.959 respectively, 0.848, 0.823, 0.816, 0.853, 0.726, 0.977. This suggests that DCP, AFP, GP73, AFP-L3%, GGT, ALP, and the combined diagnosis

have a certain value in the diagnosis of hepatocellular carcinoma, among which DCP is the most valuable single biological indicator for diagnosing primary hepatocellular carcinoma, which has high sensitivity and specificity. The combined detection of the six indicators based on DCP and the detection of DCP alone, although its specificity and positive predictive value were elevated, the change was not significant, and the significance was very small, and further conclusions need to be verified by higher-quality meta-analysis or clinical trials.

5. Conclusion

In summary, serum DCP, GP73, AFP, AFP-L3%, GGT, and ALP can play an important role in disease screening for patients with primary liver cancer; DCP is the most valuable single biological indicator for diagnosing primary liver cancer, with high sensitivity, and specificity. The combined test improved the accuracy when tested alone, but did not differ significantly from DCP alone. This study has some limitations. First, the number of HCC patients included in the study was small (n=30), and the insufficient sample size may have led to a certain bias in our study. Secondly, this study was designed as a case-control study, which, while useful for initial hypothesis testing, has inherent limitations in establishing causality or long-term outcomes. To address these limitations, it is recommended to conduct prospective serologic follow-up studies on healthy control patients. Such studies would help to further clarify the diagnostic value of these serologic indexes in PHC and provide more comprehensive insights into their utility in early diagnosis, treatment, and prognosis of the disease. Moreover, extending the study duration and incorporating dynamic data analysis could significantly improve the understanding of how these biomarkers evolve over time in the Chinese population. This would not only enhance the accuracy of early diagnosis but also provide valuable information for monitoring disease progression and treatment efficacy. By addressing these limitations and expanding the scope of future research, the diagnostic and prognostic potential of these serum biomarkers in PHC can be more fully realized, ultimately leading to better patient outcomes and more effective clinical management strategies.

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