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A STUDY OF THE UTILITY OF A NOVEL SERUM MARKER PIVKA-II (DES-GAMMA-CARBOXY PROTHROMBIN) ALONG WITH CONVENTIONAL SERUM MARKER ALPHA FETO PROTEIN (AFP) IN THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA AT A TERTIARY REFERRAL CENTRE

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ABSTRACT

BACKGROUND Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver with a very poor prognosis. Early diagnosis and effective treatment of HCC remain a challenge. The role of biomarkers for early detection, invasiveness, metastasis, and recurrence has generated a great deal of research interest. As the magnitude of the burden of HCC in India continues to be high and the search for an effective biomarker for early diagnosis of HCC continues, there is an urgent need to search for different biomarkers, including des-gamma-carboxy prothrombin (DCP) in HCC.

METHODS This was a cross-sectional study conducted in the department of gastroenterology, Kurnool medical college, Kurnool. The objective was to assess the role of DCP and AFP as adjunctive diagnostic markers in detection of HCC. All patients of age greater than 18 years with HCC diagnosed on contrast-enhanced CT or MRI abdomen were included in the study and blood samples were taken at the same time for measurement of serum AFP, DCP and sent to a standard laboratory.

RESULT: The study included 50 patients with HCC, out of which PIVKA II/DCP was positive in 48 patients and AFP was positive in 21 patients. The combined sensitivity of both DCP and AFP was 98% which was higher than that of either test alone.

CONCLUSION: PIVKAII/DCP was more sensitive in the diagnosis of HCC compared to AFP. Levels of PIVKAII/DCP increase significantly with all stages of HCC, whereas levels of AFP does not increase significantly with stages of HCC.

KEYWORDS : HCC, PIVKA II/DCP, AFP

INTRODUCTION

Hepatocellular carcinoma (HCC) has been estimated to be 3rd common cause of death due to cancers globally. Liver cirrhosis, hepatitis B virus (HBV), hepatitis C virus (HCV) infection, excessive alcohol consumption, ingestion of aflatoxin B1, and nonalcoholic steatohepatitis (NASH) are important risk factors for HCC development[1-4]. In Asia, chronic hepatitis B virus (HBV) infection is the primary cause of HCC[5]. Early diagnosis and effective treatment of HCC remain a challenge as most patients remain asymptomatic and clinical presentation occurs at advanced stages of the disease. If detected very early, HCC can actually be cured with an excellent long-term prognosis and a 5-year survival rate is above 70%. Diagnosis is based on the identification of the typical hallmarks of HCC, which differ according to imaging techniques or contrast agents[6]. With advances in the understanding of tumor biology, along with the development of cellular and molecular techniques, the role of biomarkers related to early detection, invasiveness, metastasis, and recurrence has generated a great deal of research interest[4].

AFP is a serum glycoprotein that was first recognized as a marker for HCC more than 50 years ago and has since been described to detect preclinical HCC[7]. Usually, a serum AFP level of >400 ng/mL is considered as a cut-off value to differentiate HCC from non-HCC[4]. Serum AFP level has a high false-negative rate for the detection of small/ early-stage tumors and even with advanced HCC[8,9].

Serum des-gamma-carboxy prothrombin (DCP), also known as prothrombin-induced by vitamin K absence-II (PIVKA-II), was first reported by Liebman et al. in 1984[10]. Its value has been confirmed in the diagnosis of HCC in a series of clinical trials[11,12]. However, the sensitivity, specificity, and cut-off points in previous studies have been inconsistent.

METHOD:

This cross-sectional study was conducted in patients greater than 18 years with HCC due to various causes admitted in department of gastroenterology, Kurnool medical college, Kurnool. Patients with suspected nodule but inconclusive of HCC on triple phase CT/MRI abdomen, other malignancies of liver were excluded

All the patients were subjected to baseline blood investigations and Upper gastrointestinal endoscopy. Imaging studies like Chest X-ray, Ultrasound abdomen, contrast-enhanced CT abdomen, or MRI abdomen were done.

HCC was diagnosed based on typical imaging characteristic features in CECT abdomen /MRI abdomen. Blood samples of all patients included in the study were taken at the same time for measurement of serum AFP ,DCP and sent to a standard laboratory.

RESULTS:

50 patients were included in the study, mean age of patients with HCC was 58.18±4.83 years.

Sensitivity of PIVKA-II/DCP and AFP in the diagnosis of HCC:

The sensitivity of PIVKA-II/DCP at the cut-off level of 54 (mAU/ml) was 96%, and the sensitivity of AFP at the cut-off level of 400 (ng/ml) was 42%.

The difference in sensitivity between the two markers was found to be highly significant statistically.

($p<0.001$)i.e., DCP is more sensitive as compared to AFP in diagnosis of HCC.

Table 1: Sensitivity of PIVKA-II/DCP and AFP in the diagnosis of HCC

	PIVKA-II/DCP (mAU/ml)		AFP(ng/ml)		P value
	N	%	N	%	<0.001**
Positive	48	96	21	42	
Negative	2	4	29	58	
Total	50	100	50	100	

P<0.001: highly significant

Table 2: Comparison of sensitivity (%) of serum PIVKA-II/DCP and AFP based on stages of HCC

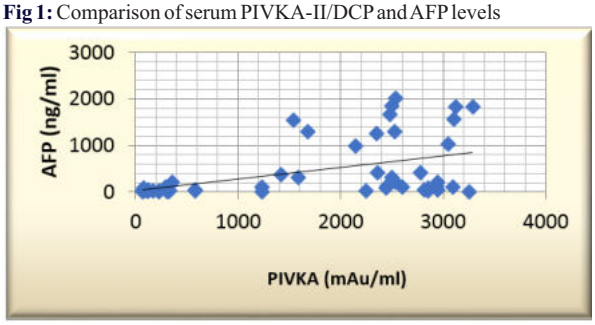
Sensitivity (%)	stage 0	stage A	stage B	stage C	p-value
DCP>54	75	88.88	100	100.00	<0.001**
AFP>400	0	0	50	36.36	

P<0.05**:** Statistically Significant

Correlation between Serum PIVKA/DCP and serum AFP:

A weak positive correlation was observed between Serum PIVKA/DCP and serum AFP values, r=0.461

Fig 1: Comparison of serum PIVKA-II/DCP and AFP levels



DISCUSSION

In hepatocellular carcinoma (HCC), the stage at diagnosis is the most important prognostic factor. Alpha-fetoprotein (AFP) is the most widely used biomarker for hepatocellular carcinoma (HCC) during the past several decades. AFP levels are not increased in 80% of small HCCs.

Des-γ-carboxyprothrombin (DCP) also called prothrombin induced by vitamin K absence-II (PIVKA II), is an abnormal form of prothrombin. Upregulation of DCP has been found to correlate with the degree of malignancy of HCC, as DCP-positive tumors are characterized by increased likelihoods of intrahepatic metastasis and portal venous invasion[13].

In the present study, the sensitivity of PIVKA-II/DCP at cut off level of 54 (mAU/ml) was 96%, and the sensitivity of AFP at cut off level of 400(ng/ml) was 42% and combined sensitivity of DCP and AFP was 98%. DCP is more sensitive in the diagnosis of HCC as compared to AFP ($p<0.001$). In the present study mean DCP levels increased significantly with advancing stages of HCC compared to AFP levels. DCP was more sensitive compared to AFP in the diagnosis of early stages of HCC indicating that DCP was more accurately predictive of early stages of HCC. Comparable findings have been reported by Fei X et al., where in the early-stage HCC patients, sensitivity for PIVKA-II is 74.5% and 60.9% for AFP. In the study by Fei X et al. where AFP and PIVKA-II were used in combination, the diagnostic accuracy significantly improved in the whole HCC cohort. Serum PIVKA-II was obviously superior to AFP for HCC screening; it provides further evidence that "AFP + PIVKA-II" was an effective blood-based biomarker facilitating diagnoses of HCC.

Thus, measurement of des-gamma-carboxy prothrombin combined with alpha-fetoprotein is useful for detecting hepatocellular carcinoma in chronic liver disease patients and for monitoring recurrence after treatment of hepatocellular carcinoma

CONCLUSION:

PIVKAII/DCP is more sensitive in the diagnosis of HCC compared to AFP and Levels of PIVKAII/DCP increase significantly with stages of HCC, whereas levels of AFP do not increase significantly with stages of HCC. A combination of AFP and DCP as biomarkers can significantly improve the detection of HCC.

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