Medical Journal of
Viral Hepatitis (MJVH)

Original Article

Pentraxin 3 level as a Biomarker for Diagnosis of Hepatitis C Virus Related Hepatocellular Carcinoma

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Abstract

Background: *Pentraxin 3, referred to as tumor necrosis factor-stimulated gene 14, is an elongated pentraxin that belongs to the pentraxin superfamily.* ***Objectives:*** *To evaluate the clinical significance and potential role of Pentraxin 3 as a maker for diagnosis of hepatocellular carcinoma (HCC) related to HCV infection.* ***Subjects and methods.*** *The study included 78 patients and 26 healthy individuals from Mansoura University Hospital. Participants were divided into three groups: healthy individuals without HCV, chronic HCV patients with cirrhosis, and HCC patients with HCV. Pentraxin-3, AFP, and DCP levels were measured using ELISA. Diagnostic accuracy was evaluated using receiver operating characteristic curve analysis.* ***Results:*** *Pentraxin 3, AFP and DCP levels were significantly higher in cirrhosis and HCC patients compared to the healthy group, with HCC patients showing higher levels than cirrhosis patients. The ROC curve analysis for differentiating HCC from the healthy group revealed that, a cut-off value of 0.848 for Pentraxin 3 had superior sensitivity and specificity (81.8% and 88.5%, respectively), followed by DCP (81.8% and 73.1%, respectively) however, AFP had the lowest sensitivity and specificity. The combination of these three markers showed the highest sensitivity and specificity (95.5% and 96.2%, respectively). In distinguishing HCC from the cirrh-osis group, a cut-off value of 0.879 for DCP exhibited superior sensitivity and specificity (81.8% and 88.0%, respectively) followed by Pentraxin 3 (72.7% and 84.0%, respectively) however, AFP showed the lowest sensitivity (54.5%) and highest specificity 84.0%. The combination of these three markers showed the highest sensitivity and specificity (90.9% and 96.0%, respectively) in discriminating between HCC and cirrhotic groups, with an excellent AURC of 0.973.* ***Conclusion:*** *Pentraxin 3 is potential good a maker for diagnosis of HCC related to HCV infection.*

Introduction

Primary hepatocellular carcinoma (HCC) is the fourth most common tumor globally[1]. The main causes of HCC are cirrhosis, nonalcoholic steatohepatitis, and hepatitis B and C viruses. In Egypt, HCC is a growing health concern, making it important to establish screening and surveillance programs to detect small HCC cases early[2]. Early identification of HCC, is crucial for improving patient prognosis. Early diagnosis is often the only opportunity for long-term survival in HCC patients[3-5]. Commonly used methods for detecting HCC include serum alpha-fetoprotein (AFP) levels, abdominal ultrasound, computed tomography, and magnetic resonance imaging. However, distinguishing small HCC from cirrhotic nodules remains challenging with imaging techniques. Additionally, AFP, the primary biomarker for HCC, lacks specificity as elevated levels can be found in patients with both HCC and chronic hepatitis without cancer[6,7]. The majority of individuals with HCC are diagnosed at an advanced stage, often with chronic liver failure, making curative treatments impractical[8]. Pentraxin 3 (PTX3) is a key soluble pattern recognition molecule that plays a critical role in inflammation, tissue damage, and the innate immune response. It is also known as tumor necrosis factor-stimulated gene 14 and belongs to the pentraxin superfamily. PTX3 is involved in cancer, tissue repair, and innate immunity, serving a non-redundant role in humoral innate immunity against microbial infections. PTX3 may also play a role in cancer progression[9,10]. Many different types of cancer have been shown to be impacted by pentraxin 3 (PTX3), a pattern recognition receptor. But PTX3's precise clinical relevance in HCC has not been definitively established[11]. Plasma PTX3 is linked to liver diseases like nonalcoholic steatohepatitis[12]. In alcoholic hepatitis, both hepatic and plasma PTX3 levels are high, with PTX3 levels correlating with disease severity and short-term mortality[13]. Serum PTX3 is a validated marker for fibrosis in chronic hepatitis C, and increased plasma PTX3 levels raise the risk of developing liver cancer in chronic HCV infection[14]. PTX3 also promotes liver cancer progression, and high PTX3 levels in tumor tissues predict poor prognosis in liver cancer patients[15]. Despite these studies, the potential role of circulating PTX3 levels in chronic HCV infection remains to be further examined. The aim of this study was to evaluate the clinical significance and potential role of Pentraxin 3 as a marker for diagnosing HCC related to HCV infection.

Doi: 10.21608/mjvh.2024.380130
Keywords: Pentraxin 3, hepatocellular carcinoma, HCV infection
Received: 23-7-2024
Accepted: 7-9-2024
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Patients and Methods

From April 2022 to April 2023, a prospective case-control study was conducted involving 104 patients (between 18 and 80 years) from the tropical medicine department and outpatient clinics at Mansoura University Hospital. The participants were divided into three groups: 26 healthy individuals with no current or previous HCV infection, 52 chronic HCV patients with liver cirrhosis, and 26 patients with HCC associated with HCV infection. The grouping was based on a combination of history, clinical, laboratory, and radiological criteria. The diagnosis of liver cirrhosis is typically made through a combination of history, clinical examination, laboratory tests, and radiological imaging. The diagnosis of chronic HCV infection relies on the presence of positive anti-HCV antibodies for more than 6 months, which are confirmed by a positive PCR test. The diagnosis of HCC patients was identified based on Triphasic pelvi-abdominal CT or MRI findings consistent with HCC[16].

Exclusion criteria

Age under 18 or over 80 years old, non-HCV-related hepatocellular carcinoma, metastatic hepatic focal lesions (secondary liver malignancies), combined HCC with other malignancies, non-HCV-related liver cirrhosis including chronic HBV infection, non-alcoholic liver disease, autoimmune liver disease, metabolic liver diseases, and previously treated hepatocellular carcinoma.

Laboratory parameters.

After an overnight fast, venous blood samples were collected from all participants under strict aseptic conditions for CBC analysis using a Ruby electronic cell counter (USA), PT and INR, serum creatinine, aspartate aminotransferase, alanine aminotransferase, serum albumin, and serum bilirubin using commercially available kits from Spain.

Pentraxin-3 assay and des-gamma-carboxy-prothrombin assay.

Serum samples were stored at -80°C until analysis of Pentraxin-3 and Des-gamma Carboxyprothrombin using ELISA techniques from the Bioassay Technology Laboratory in China. Pentraxin-3 serum levels were measured using an ELISA kit from the same laboratory. The assay involved coating a 96-well plate with an antibody specific for Human Pentraxin-3. Standards and samples were added to the wells, where the immobilized antibody bound the Pentraxin-3 present in the sample. After washing, a biotinylated anti-Human Pentraxin-3 antibody was added, followed by Streptavidin-HRP to form a binding interaction. After incubation and washing, a substrate solution was added, and the color intensity increased with the concentration of Human PTX3. The reaction was stopped with an acidic solution, and the absorbance was measured at 450 nm within 10 minutes. Des-gamma-carboxy-prothrombin (DCP) serum levels were measured using an ELISA kit from Bioassay Technology Laboratory (China). The assay involved coating a 96-well plate with an antibody specific to Human DCP. Standards and samples were added to the wells, and the immobilized antibody captured the DCP present in the samples. After washing, a biotinylated anti-Human DCP antibody was added, followed by Streptavidin-HRP to form a complex. After washing off unbound components, a substrate solution was added, and the color intensity was measured at 450 nm. The reaction was stopped with an acidic solution, and absorbance was read within ten minutes.

Ethical considerations

Every individual who was involved in the research signed a written informed consent form after receiving permission from the Mansoura Faculty of Medicine's Institutional Research Board (IRB) Committee (code number: MS.21.12.1802.R1). The research was conducted in accordance with the basics of the Helsinki declaration.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 and MedCalc 12.0 software. Quantitative variables were reported as mean ± standard deviation or median with interquartile range, while categorical variables were presented as absolute or relative frequencies. Continuous variables were compared using analysis of variance, and categorical variables were compared using the Chi-Square test. Risk factors for HCC were assessed using multivariable logistic regression analysis. The predictive values of relevant parameters were evaluated using receiver operating characteristic (ROC) curve analysis to determine the area under the curve (AUC), 95% confidence interval (CI), optimal cut-off value, sensitivity, specificity, Yoden index, positive and negative predictive values, and positive and negative likelihood ratios. Statistical differences between AUCs were assessed using the Z-test. Propensity score matching (PSM) was conducted in a 1:1 ratio to minimize data bias and confounding variables. Significance was defined as a two-tailed P value < 0.05.

Results

Table 1 shows the demographic and laboratory data of the study groups. There were no significant differences among the groups in terms of age, sex, and total leukocyte count. However, significant differences were observed in hemoglobin levels, platelet count, ALT, AST, bilirubin, albumin, INR ratio, and serum creatinine. Pentraxin 3 levels were significantly higher in both cirrhosis and HCC patients compared to the healthy group, with HCC patients showing significantly higher levels than cirrhosis patients. Similarly, AFP and DCP levels were significantly elevated in both cirrhosis and HCC patients compared to the healthy group, with HCC patients exhibiting higher levels than cirrhosis patients. The ROC curve analysis in **table 2 and figure 1** shows that a cut-off value of 0.818 for Pentraxin 3 had optimal sensitivity (88%). This suggests that Pentraxin 3 could be a useful tool for identifying individuals with cirrhosis. AFP, with a cut-off value of 0.645, exhibited optimal specificity (73.1%), indicating its ability to exclude the disease in patients without cirrhosis. DCP showed intermediate sensitivity and specificity. Additionally, the combination of these three markers demonstrated the highest sensitivity and specificity (88% and 80%, respectively) in distinguishing between healthy and cirrhotic groups with excellent AURC (0.892). **Table 3 and figure 2** show that a cut-off value of 0.848 for Pentraxin 3 had superior sensitivity and specificity (81.8% and 88.5%, respectively) for differentiating HCC from healthy group, followed by DCP with sensitivity and specificity of 81.8% and 73.1%, respectively. AFP had the lowest sensitivity and specificity at 72.7% and 53.8%, respectively. Furthermore, the combination of these three markers demonstrated the highest sensitivity and specificity

(95.5% and 96.2%, respectively) in distinguishing between HCC and healthy group with an excellent AURC of 0.991. **Table 4 and figure 3** demonstrate that a cut-off value of 0.879, DCP exhibited superior sensitivity and specificity (81.8% and 88.0%, respectively) in distinguishing HCC from the cirrhosis group. Pentraxin 3 followed with sensitivity and specificity of 72.7% and 84.0%, respectively. AFP showed the lowest sensitivity (54.5%) but the highest specificity at 84.0%. Additionally, the combination of these three markers showed the highest sensitivity and specificity (90.9% and 96.0%, respectively) in discriminating between HCC and cirrhotic groups, with an excellent AURC of 0.973. Table 5 shows that Pentraxin-3, DCP, and AFP are statistically significant predictors of HCC. An increase of one unit in Pentraxin-3 raises the risk of HCC by 1.19, a one-unit increase in DCP raises the risk by 1.09, and an increase in AFP raises the risk by 1.04.

Table: 1 Demographic and of laboratory findings among the studied groups

	Healthy group N=26	Cirrhosis on top of HCV N=52	HCC on top of HCV N=26	Test of significance	Within group significance
Age/ years	58.15±6.33	58.69±9.13	60.69±6.49	F=1.43 P=0.238	P1= 0.785 P2= 0.200 P3= 0.312
Sex N (%) ▪ ***Male*** ▪ ***Female***	 15(57.7) 11(42.3)	 15(57.7) 11(42.3)	 22(84.6) 4(15.4)	 MC=5.777 P=0.123	P1=1.0 P2= 0.064 P3= 0.064
Hemoglobin (gm/dl)	12.79±1.21	11.45±1.92	11.28±1.77	F=6.30 P=0.001*	P1= 0.004* P2= 0.001* P3= 0.707
TLC	6.05(2.9-9.3)	5.4(1.9-14.1)	5.15(2.04-15.63)	KW=8.18 P=0.017*	P1= 0.792 P2=0.528 P3= 0.962
Platelet count	262 (190-412)	87 (39-296)	117 (30-320)	KW=40.81 P=0.001*	P1< 0.001* P2< 0.001* P3= 0.371
ALT	17.5 (12-24)	34 (15-152)	28.5 (17-420)	KW=37.37 P<0.001*	P12< 0.001* P23< 0.001* P3= 0.391
AST	12 (9-20)	55 (18-203)	44 (21-453)	KW=50.12 P<0.001*	P1< 0.001* P2< 0.001* P3= 0.341
Albumin	4.29±0.24	3.04±0.52	3.09±0.70	F=51.20 P<0.001*	P1< 0.001* P2< 0.001* P3= 0.690
Bilirubin	0.70 (0.50-1.0)	1.2 (0.40-10.3)	1.40(0.66-23.0)	KW=15.40 P<0.001*	P1< 0.001* P2< 0.001* P3= 0.184
INR	1.06±0.07	1.38±0.22	1.29±0.19	F=20.15 P<0.001*	P1<0.001* P2<0.001* P3=0.084
Serum Creatinine	0.70 (0.4-1.3)	1.05 (0.41-6.4)	0.815 (0.6-2.0)	KW=12.34 P=0.002*	P1= 0.002* P2= 0.02* P3= 0.119
Pentraxin 3	3.45 (2.15-23.21)	5.75 (2.7-33.05)	19.42 (1.11-35.15)	KW=16.38 P<0.0001*	P1= 0.001* P2= 0.001* P3= 0.001*
AFP	4.0 (2.46-10.8)	7.6 (1.3-64.8)	38.4 (1.3-11393.0)	KW= 6.56 P= 0.038*	P1= 0.059 P2= 0.002* P3= 0.04*
DCP	4.74 (2.0-15.46)	3.64 (2.0-8.29)	27.22 (1.68-110.2)	KW=7.65 P=0.02*	P1= 0.03* P2= 0.001* P3<0.001*

KW: *Kruskal Wallis test;* ***F:*** *one Way ANOVA test;* ***HCC:*** *hepatocellular carcinoma;* ***p1:*** *healthy group versus cirrhosis on top of HCV;* ***p2:*** *healthy group versus HCC on top of HCV;* ***p3:*** *cirrhosis on top of HCV versus HCC on top of HCV.*

Table 2: Validity of pentraxin 3, DCP and AFP in differentiating healthy group and from cirrhosis cases

	AUC (95%CI)	Cut off point	Sensitivity %	Specificity %	P value
Pentraxin3	0.818 (0.698-0.939)	3.73	88.0	61.5	<0.001*
DCP	0.675 (0.526-0.823)	4.66	76	50.0	0.03*
AFP	0.645 (0.490-0.817)	5.45	56.0	73.1	0.06
Combination#	0.892 (0.801-0.984)	0.422	88.0	80.8	0.001*

AUC: *Area under curve;* *******statistically significant; #retrived from saved probabilities by multivariate analysis*

Table 3: Validity of pentraxin 3 and AFP in differentiating healthy group from HCC cases

	AUC (95%CI)	Cut off point	Sensitivity %	Specificity %	P value
Pentraxin3	0.848 (0.719-0.977)	5.08	81.8	88.5	<0.001*
DCP	0.832 (0.695-0.970)	5.91	81.8	73.1	0.001*
AFP	0.760 (0.615-0.906)	4.25	72.7	53.8	0.002*
Combination#	0.991 (0.974-1.0)	0.382#	95.5	96.2	<0.001*

AUC: *Area under curve;* *******statistically significant; #retrived from saved probabilities by multivariate analysis*

Table 4: Validity of pentraxin 3, DCP and AFP in differentiating cirrhosis from HCC cases.

	AUC (95%CI)	Cut off point	Sensitivity %	Specificity %	P value
Pentraxin 3	0.749 (0.587-0.911)	8.98	72.7	84.0	0.003*
DCP	0.879 (0.762-0.996)	5.87	81.8	88.0	0.001*
AFP	0.675 (0.513-0.838)	22.73	54.5	84.0	0.04*
Combined	0.973 (0.932-1.0)	0.287#	90.9	96.0	0.001*

AUC: *Area under curve;* *******statistically significant.*

Table 5: Multivariate analysis of predictors of HCC among studied cases.

	β	p value	AOR (95% CI)
Pentraxin3	0.180	<0.001*	1.19 (1.11-1.29)
DCP	0.083	0.001*	1.09 (1.04-1.14)
AFP	0.04	0.003*	1.04 (1.01-1.07)

AOR: *Adjusted odds ratio;* ***CI:*** *Confidence interval;* ***β:*** *Regression coefficient*

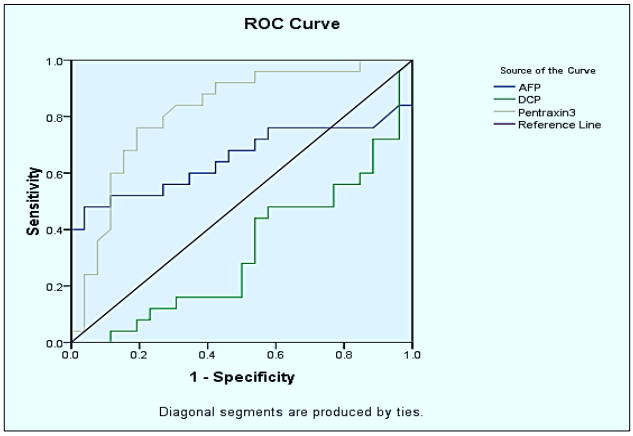

Figure 1: ROC Curve of pentraxin 3, DCP and AFP in differentiating healthy group from Cirrhosis cases.

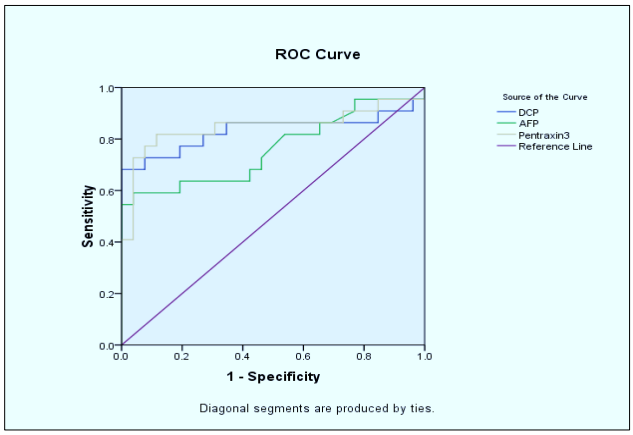

Figure 2. ROC Curve of pentraxin 3, DCP and AFP in differentiating healthy group from HCC.

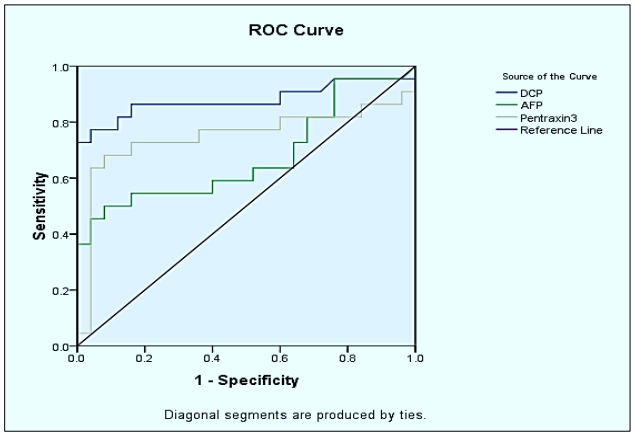

Figure 3: ROC Curve of pentraxin 3, DCP and AFP in differentiating Cirrhosis from HCC cases.

Discussion

This study found that levels of Pentraxin 3 (PTX3) were significantly higher in patients with cirrhosis and hepatocellular carcinoma (HCC) compared to the healthy control group. HCC patients had significantly higher PTX3 levels than cirrhosis patients. Additionally, levels of alpha-fetoprotein and des-gamma-carboxy prothrombin (DCP) were significantly elevated in both cirrhosis and HCC patients compared to the healthy group, with HCC patients showing higher levels than cirrhosis patients. These findings suggest a potential role of PTX3 in cancer development, as seen in other types of cancer such as breast cancer[17], gastric cancer[18], lung carcinoma[19], and pancreatic carcinoma[20]. According to our results, Carmo et al. found that an increased plasma level of PTX3 was a risk factor for the occurrence of HCC in chronic HCV infection[21]. Furthermore, PTX3 has been shown to promote HCC progression, and high PTX3 expression in tumor tissues has been associated with an unfavorable prognosis in HCC patients[22]. Additionally, PTX3 expression has been linked to disease severity and short-term mortality. Clinical studies have demonstrated that serum PTX3 has valid diagnostic accuracy as a marker of fibrosis in chronic hepatitis C virus (HCV) infection[23]. This study declared that, demonstrate that a cut-off value of 0.879, DCP exhibited superior sensitivity and specificity (81.8% and 88.0%, respectively) in distinguishing HCC from the cirrhosis group. Pentraxin 3 followed with sensitivity and specificity of 72.7% and 84.0%, respectively. AFP showed the lowest sensitivity (54.5%) but the highest specificity at 84.0%. Additionally, the combination of these three markers showed the highest sensitivity and specificity (90.9% and 96.0%, respectively) in discriminating between HCC and cirrhotic groups, with an excellent AURC of 0.973. A previous study evaluated the performance of PTX3 in identifying HCC using an ROC curve. The serum PTX3 cut-off value was set at ≥6.4 (ng/ml), which significantly differentiated HCC from cirrhotic patients without HCC, achieving a sensitivity of 80% and specificity of 74%. In comparison, the AFP cut-off value was ≥14 (IU/ml) with a sensitivity of 88% and specificity of 84%. Combining PTX3 with AFP enhanced the performance of both markers individually, resulting in a sensitivity of 92% and specificity of 76%[24]. PTX3 is believed to enhance HCC cell proliferation and trigger the epithelial-mesenchymal transition, a biological process closely associated with tumor cell invasion and

metastasis. This offers an additional rationale for the involvement of PTX3 in HCC[25]. Additionally, Deng et al. identified serum pentraxin 3 as a potential biomarker for hepatocellular carcinoma, demonstrating its utility as a diagnostic indicator for HCC. They also found that the diagnostic performance of PTX3 in distinguishing HCC from chronic HBV infection was superior to AFP[26]. A study demonstrated that pentraxin 3 and AFP levels were statistically significantly higher in the HCC group than in the cirrhotic group[27]. Based on our study, many reports from Eastern regions have emphasized the importance of DCP in diagnosing HCC and have thoroughly compared the progression of AFP and DCP as tumor markers[28]. Extensive evidence suggests that DCP has higher sensitivity than AFP, with reported sensitivities reaching up to 84%[29]. Our study had some limitations. We conducted this study on a small number of patients with HCV. The research was performed only on individuals with HCV. This study required a longer follow-up period for the included patients.

Conclusion

Our study concluded that, Pentraxin 3 is a good marker for diagnosing HCC related to HCV infection. Furthermore, Pentraxin 3 can be a simple marker for cirrhosis related to HCV.

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