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ORIGINAL ARTICLE

# Predictive Value of Protein Kinase C Delta as a Diagnostic Biomarker for Hepatocellular Carcinoma in Hepatitis C Virus-Related Cirrhosis

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## Abstract

**Background/Aim:** Hepatocellular carcinoma (HCC) is considered the 6th prevalent tumour and 3rd leading cause of cancer-associated mortality worldwide. Protein kinase C delta (PKCδ), released by liver cancer cells, has an effect in cell-proliferation and cancer formation, recommending PKCδ can serve as a good biomarker in HCC detection. The aim of this research was the assessment of predictive value of PKCδ as a diagnostic biomarker for HCC in hepatitis C virus (HCV)-related cirrhosis.

**Methods:** The study involved 180 participants, who were separated into three groups, the first control group included 45 healthy volunteers, the second cirrhotic without HCC group (non-HCC group) included 45 cirrhotic patients due to HCV and the third cirrhotic with HCC group (HCC group) included 90 cases with HCC on top of HCV-related cirrhosis. All participants were subjected to clinical examination, taking of history, radiological evaluation and routine laboratory investigations involving alpha-fetoprotein (AFP) assessment. PKCδ was assessed for all participants using Enzyme-Linked Immunosorbent Assay.

**Results:** AFP and PKCδ concentrations were greater in HCC than in non-HCC and controls. PKCδ ≥ 30.75 ng/mL showed excellent diagnostic performance for detecting HCC in HCV-related cirrhosis (AUC = 0.977, sensitivity 95.6 %, specificity 86.7 %, accuracy 92.6 %). Multivariate analysis identified PKCδ ≥ 30.75 ng/mL, AFP ≥ 9.4 ng/mL and current smoking as independent predictors of HCC.

**Conclusion:** PKCδ has a significant diagnostic ability for hepatocellular carcinoma (HCC), with good specificity and sensitivity in HCC prediction in patients with HCV-related liver cirrhosis.

**Key words:** Carcinoma, hepatocellular; Liver cirrhosis; Hepacivirus; Biomarkers; Protein kinase c-delta.

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## Introduction

Hepatocellular carcinoma (HCC) is the leading primary liver tumour and a major health challenge globally.[1] It usually develops in cirrhotic, chronically diseased livers commonly linked to HCV, hepatitis B virus (HBV), or metabolic dysfunction-associated steatotic liver disease (MASLD).[2]

HCC primarily presents as the most prevalent malignancy among men and the second prevalent among females in Egyptian population. It accounts for the highest rate of cancer-related death in the country, with the majority of cases attributed to HCV-related cirrhosis.[3, 4]

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Despite significant advances in screening and treatment, HCC remains a disease with a poor prognosis due to late-stage identification and high recurrence rates.[5] Early detection of HCC by using surveillance tools is crucial as it increases quality of life and patient survival by providing effective treatments.[6]

Current EASL (2024) and AASLD (2023) guidelines suggest HCC surveillance in high-risk groups utilising ultrasonography (US) and/or serum alpha-fetoprotein (AFP) every six months.[7, 8] Several studies showed that sensitivity of AFP for detecting early HCC ranges from 39-64 %, while other studies reported that the sensitivity of AFP combined with ultrasonography for early-stage HCC was only 63 % which is still unsatisfactory.[9]

Finding new non-invasive tools that can observe HCC early with high specificity and sensitivity is urgently needed.[10] Protein kinase C (PKC) is expressed across many cell types and is grouped based on domain structure and activation requirements into three subfamilies: classical (cPKCs), novel (nPKCs; including PKCδ) and atypical (aPKCs).[11, 12]

PKCδ is a protein that is mainly located in the nucleus and cytoplasm; however, its atypical extracellular release appears to be restricted to HCC cells and is not observed in normal hepatocytes or other gastrointestinal cancer cells.[13] Extracellularly secreted PKCδ functions similarly to growth factors by activating insulin-like growth factor 1 receptor (IGF1R) and epidermal growth factor receptor (EGFR) signalling pathways, which subsequently amplify extracellular signal-regulated kinase (ERK1/2) and signal transducer and activator of transcription 3 (STAT3) activity, thereby facilitating the advancement of HCC.[14, 15] Serum PKCδ would be become a novel biomarker for the diagnosis of HCC that complements the conventional markers, AFP and DCP and a useful tool for detecting very early-stage.[16]

Experimental evidence suggests that PKCδ silencing may influence AFP expression and secretion in HCC cell lines, supporting the concept that PKCδ may provide complementary diagnostic information beyond AFP alone.[17] The PKCδ levels did not significantly differ between HCC patients with HCV SVR and non-SVR. These findings indicate that serum PKCδ could be a reliable biomarker for HCV-related HCC, irrespective of viral clearance status.[18] This research aimed to assess the predictive value of PKCδ as a diagnostic biomarker for HCC in HCV-related cirrhosis.

## Methods

This was case-control research conducted in the Internal Medicine department, Specialised Medical Hospital (SMH), Mansoura University, Egypt, from October 2023 to October 2024. Research protocol has been submitted for approval by the Institutional Ethics Committee. Informed written consent has been attained from each participant in the research following assuring confidentiality.

The study included 180 participants aged above 18 years old, divided into three groups. Control group included 45 healthy volunteers, cirrhotic without HCC group (non-HCC group) included 45 cirrhotic patients (HCV-related cirrhosis) without HCC proved clinically, laboratory and radiologically by abdominal ultrasonography either decompensated or compensated and subgrouping was performed according to Child-Pugh score,[19] and cirrhotic with HCC group (HCC group) included 90 patients with newly diagnosed HCC on a background of HCV-related cirrhosis. Diagnosis was confirmed by triphasic abdominal CT using standard radiologic hallmarks arterial phase hyperenhancement (APHE) with washout on the portal venous or delayed phases.[8] Patients were then stratified using Barcelona Clinic Liver Cancer (BCLC) staging score,[20] TNM staging system,[21] Hong Kong Liver Cancer (HKLC) staging system,[22] Cancer of the Liver Italian Program (CLIP) scoring system[23] and Japan Integrated Staging (JIS) score.[24]

Participants with the following conditions were excluded: existence of other malignancies like bladder carcinoma, multiple myeloma, breast carcinoma and gastric carcinoma, existence of severe co-morbidity, morbid obesity (BMI ≥ 40 kg/m$^2$), severe psychosis and autoimmune illnesses.

All participants were subjected to clinical examination, detailed history taking and laboratory examinations involving: complete blood count (CBC), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin (total and direct), serum albumin, serum creatinine, international normalised ratio (INR), hepatitis B surface antigen (HBsAg), AFP

and PKCδ measurement using Enzyme-Linked Immunosorbent Assay.

Serum PKCδ levels were quantified utilising Human PKCδ kits (Bioassay technology laboratory Cat No: E6740Hu). To conduct the evaluation, 3 mL of venous blood gathered from all cases by clean venipuncture utilising plastic disposable syringes. Blood samples were allowed to clot, then centrifuged for ten minutes at (~3000) rpm. The separated serum was collected and stored at −20 °C until PKCδ measurement.

## Statistical analysis

Data were analysed using IBM SPSS Statistics. Variables were summarised as n (%) or mean ± SD/median (IQR). Groups were compared using chi-square and Kruskal–Wallis tests and associations assessed by Spearman's correlation. A p-value ≤ 0.05 was considered significant. Univariate/multivariate logistic regression estimated ORs (95 % CI) and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated.

# Results

There was a statistically significantly higher proportion of smokers among cirrhotic with HCC (HCC) group vs cirrhotic without HCC (non-HCC) group. Smokers showed significantly higher odds of HCC compared to non-smokers (1.6, 95 % CI = 1.3-1.9, p < 0.001). There was significantly higher WBC count in HCC group vs non-HCC and control groups, although within the normal laboratory range. Haemoglobin and serum albumin levels were significantly lower in non-HCC and HCC groups vs control group, statistically significantly higher AST, INR, serum total and direct bilirubin in non-HCC and HCC groups vs control group, significantly higher platelet count in control > HCC > non-HCC group and statistically significantly higher ALT, AFP and PKCδ in HCC > non-HCC > control group (Table 1, Figure 1).

*Table 1: Comparative analysis of demographic and laboratory variables among control, hepatocellular carcinoma (HCC) and non-HCC groups*

| Characteristic | Control (45) | | Non-HCC (45) | | HCC (90) | | p-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Sex | | | | | | | |
| Male | 29 | 64.4 | 29 | 64.4 | 71 | 78.9 | 0.099 |
| Female | 16 | 35.6 | 16 | 35.6 | 19 | 21.1 | |
| Current smoking | 12[a, b] | 26.7 | 5[b] | 11.1 | 38[a] | 42.2 | < 0.001 |
| | **Median** | **Q1-Q3** | **Median** | **Q1-Q3** | **Median** | **Q1-Q3** | |
| Age (years) | 61 | 57-65.5 | 64 | 58-67 | 64 | 60-68 | 0.057 |
| WBC count /mm³ | 5.5[a] | 4.9-6.2 | 5.8[a] | 4.7-7.5 | 7.1[b] | 5.9-8.5 | < 0.001 |
| Haemoglobin (g/dL) | 13.9[a] | 12.9-14.6 | 11[b] | 9.8-12.9 | 11.95[b] | 10.3-13.5 | < 0.001 |
| Platelet count /mm³ | 264[a] | 238-294 | 102[b] | 87-155 | 152[c] | 121-238 | < 0.001 |
| AST (IU/L) | 23[a] | 21-25.5 | 47[b] | 37-57 | 59[b] | 38-78 | < 0.001 |
| ALT (IU/L) | 21[a] | 20-22 | 30[b] | 20-39 | 35[c] | 27-48 | < 0.001 |
| Serum total bilirubin (mg/dL) | 0.8[a] | 0.8-0.9 | 1.3b | 0.9-2 | 1.15[b] | 0.8-1.7 | < 0.001 |
| Serum direct bilirubin (mg/dL) | 0.3[a] | 0.2-0.3 | 0.7b | 0.4-1.1 | 0.5[b] | 0.3-0.8 | < 0.001 |
| Serum albumin (g/dL) | 4.6[a] | 4.3-4.8 | 3.4[b] | 3-3.9 | 3.4[b] | 3.2-4 | < 0.001 |
| INR | 1[a] | 1-1 | 1.2[b] | 1.16-1.35 | 1.2[b] | 1.1-1.3 | < 0.001 |
| AFP (ng/mL) | 1.9[a] | 1.5-2.35 | 3.3[b] | 1.95-7.85 | 88[c] | 20.7-673 | < 0.001 |
| PKCδ (ng/mL) | 12[a] | 11-13.8 | 21[b] | 18.5-23 | 40.3[c] | 36.2-43.1 | < 0.001 |

*The test of significance is chi-square test for categorical variables and Kruskal-Wallis test for numerical variable. Values sharing the same letter (a, b, c) do not differ significantly from each other (p > 0.05), whereas different letters indicate statistically significant differences (p < 0.05) between groups; WBC: white blood count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalised ratio; AFP: alpha-fetoprotein; PKCδ: Protein kinase C delta;*

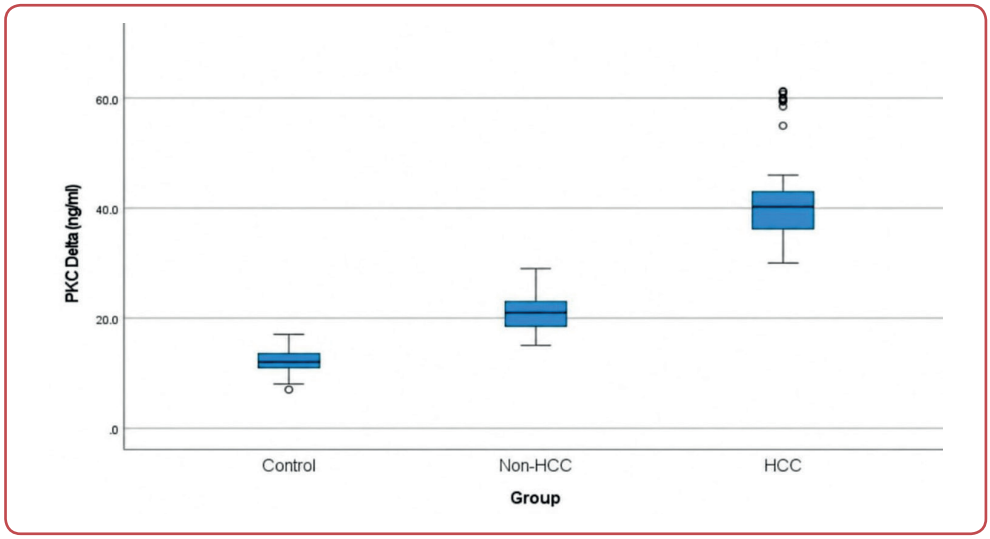


*Figure 1: Box-plot of serum protein kinase C delta (PKCδ) levels among the studied groups*

*Study groups: control, non-HCC and hepatocellular carcinoma (HCC); with median levels (12, 21 and 40.3 ng/mL), respectively and interquartile range (11-13.8, 18.5-23 and 36.2-43.1 ng/mL), respectively*

A statistically significant positive association was reported between AFP and PKCδ, ALT, AST, alkaline phosphatase and platelet count and statistically significant positive association between PKCδ and AFP, ALT, AST, alkaline phosphatase, WBC count and platelet count (Table 2). A statistically significant positive association was observed between AFP and BCLC, TNM, Hong Kong, CLIP, JIS staging systems and focal liver lesions size and number. Statistically significant positive association was demonstrated between PKCδ and ALBI grading within HCC group (Table 2).

Univariate binary logistic regression analysis showed that PKCδ ≥ 30.75 ng/mL, AFP ≥ 9.4 ng/mL, current smoking, AST ≥ 62 IU/L, ALT ≥ 25 IU/L, enlarged liver by abdominal ultrasonography and HCV treatment were significant predictors for HCC in cirrhotic cases. So, all these predictors were involved in a multivariate regression analysis which showed that PKCδ ≥ 30.75 ng/mL, AFP ≥ 9.4 ng/mL and current smoking remained statistically significant independent predictors. The regression model was statistically significant and correctly classified 93.3 % of cases with 93.5 % sensitivity, 92.85 % specificity, 96.7 % PPV and 86.7 % NPV (Table 3 , Figure 2).

*Table 2: Correlations of alpha-fetoprotein (AFP) and protein kinase C delta (PKCδ) with study parameters*

| Cirrhosis with and without HCC (HCC and non-HCC) groups | | | | |
|---|---|---|---|---|
| Parameter | AFP (rs) | p-value | PKCδ (rs) | p-value |
| AFP | - | - | 0.527 | < 0.001 |
| PKCδ | 0.527 | < 0.001 | - | - |
| ALT | 0.205 | 0.017 | 0.275 | 0.001 |
| AST | 0.285 | 0.001 | 0.251 | 0.003 |
| Haemoglobin | 0.015 | 0.865 | 0.104 | 0.229 |
| WBC count | 0.116 | 0.181 | 0.187 | 0.030 |
| INR | -0.115 | 0.182 | -0.275 | 0.071 |
| Platelet count | 0.417 | < 0.001 | 0.295 | 0.001 |
| Serum albumin | 0.072 | 0.409 | -0.014 | 0.870 |
| Alkaline phosphatase | 0.311 | < 0.001 | 0.285 | 0.001 |
| Serum total bilirubin | 0.070 | 0.420 | -0.003 | 0.971 |
| CTP classes | 0.020 | 0.821 | -0.023 | 0.788 |
| **Within HCC group (n = 90)** | | | | |
| AFP | - | - | -0.073 | 0.495 |
| PKCδ | -0.073 | 0.495 | - | - |
| BCLC | 0.276 | 0.008 | 0.116 | 0.277 |

| | | | | |
|---|---|---|---|---|
| TNM | 0.247 | 0.019 | 0.034 | 0.748 |
| ALBI score | 0.091 | 0.394 | 0.217 | 0.040 |
| Hong Kong | 0.286 | 0.006 | 0.152 | 0.153 |
| CLIP | 0.643 | < 0.001 | 0.043 | 0.689 |
| JIS | 0.359 | 0.001 | 0.124 | 0.243 |
| CT focal liver lesions (FLLs) number | 0.216 | 0.040 | -0.039 | 0.718 |
| CT FLLs size | 0.253 | 0.016 | 0.068 | 0.524 |

*Note: The test of significance is Spearman's correlation. The strength of association is considered low, medium and large if the coefficient equals 0.1-0.3, 0.3-0.5 and >0.5, respectively; CTP: Child-Turcotte-Pugh; WBC: white blood count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalised ratio; AFP: alpha-fetoprotein; PKCδ: Protein kinase C delta; ALBI: albumin-bilirubin; CLIP: Cancer of the Liver Italian Program; JIS: Japan Integrated Staging; HCC: hepatocellular carcinoma;*

*Table 3: Predictors of hepatocellular carcinoma (HCC) in cirrhosis (univariate and multivariate logistic regression)*

| Predictor | Univariate P | COR | 95 % CI | Multivariate P | AOR | 95 % CI |
|---|---|---|---|---|---|---|
| PKCδ ≥ 30.75 ng/mL | < 0.001 | 139.75 | 37.31–523.42 | < 0.001 | 319.318 | 19.80–5149.39 |
| AFP ≥ 9.4 ng/mL | < 0.001 | 30.06 | 10.89–82.98 | 0.001 | 78.336 | 5.79–1060.18 |
| Current smoking | 0.001 | 5.80 | 2.11–16.20 | 0.015 | 28.753 | 1.90–435.69 |
| AST ≥ 62 IU/L | < 0.001 | 8.97 | 2.96–27.13 | 0.076 | 22.871 | 1.23–426.51 |
| ALT ≥ 25 IU/L | 0.001 | 3.57 | 1.65–7.75 | 0.144 | 0.128 | 0.01–2.02 |
| Enlarged liver by US | 0.013 | 4.16 | 1.35–12.80 | 0.137 | 16.59 | 0.41–674.21 |
| HCV treatment | 0.001 | 4.05 | 1.82–8.97 | 0.170 | 3.970 | 0.55–28.50 |

*COR = crude odds ratio. AOR = adjusted odds ratio. CI = confidence interval. AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; PKCδ: Protein kinase C delta; HCV: hepatitis C;*

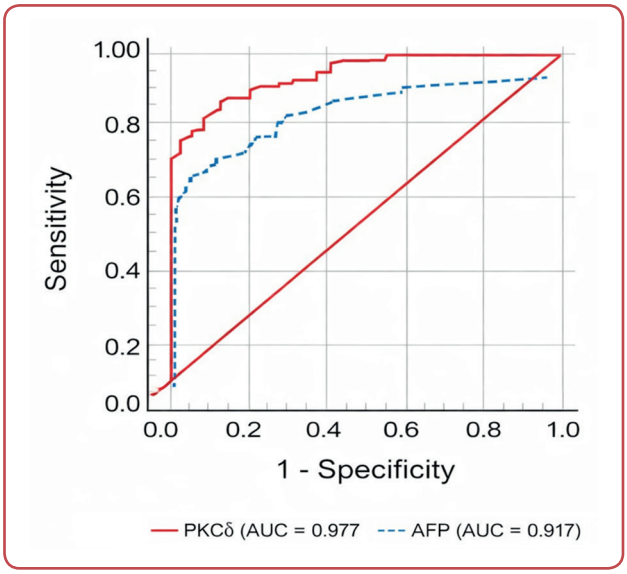


*Figure 2: ROC curve analysis showing delta protein kinase C delta (PKCδ) and alpha-fetoprotein (AFP) cut-off values and their diagnostic performance for discrimination of hepatocellular carcinoma (HCC) from non-HCC cirrhotic patients*

*PKCδ at a cut-off value of ≥ 30.75 ng/mL (using ROC curve) significantly discriminates HCC with cirrhosis from cirrhosis without HCC, with AUC = 0.977, sensitivity of 95.6%, specificity of 86.7 %, PPV of 93.5 %, NPV of 90.69 % and accuracy of 92.59 %. AFP at a cut-off value of ≥ 9.4 ng/mL (using ROC curve) significantly discriminates HCC with cirrhosis from cirrhosis without HCC, with AUC = 0.917, 82.2 % sensitivity, 86.7 specificity, 92.5 % positive predictive value (PPV), 70.9 % negative predictive value (NPV) and accuracy of 83.7 %.*

## Discussion

PKCδ is produced from hepatic tumour cells and is included in cell proliferation and tumour growth, so serum PKCδ might be a possible biomarker for screening or identifying HCC.[15] In the current study, HCC group comprised 71 males (78.9 %) and 19 females (21.1 %), this male predominance has been reported in previous studies.[4, 16] Males are more susceptible to HCC development due to variances in endogenous sex hormones, immune responses and epigenetics.[25]

In the current research, the proportion of smokers was significantly greater within the HCC group in comparison with the non-HCC group and smokers exhibited 1.6 times higher odds of developing HCC than non-smokers. This aligns with prior study that reported tobacco smoking as a significant risk factor for HCC.[26] Smoking promotes carcinogenesis through increased inflammatory cytokine, reactive oxygen species and exposure to carcinogenic compounds.[27] Moreover, a synergistic interaction among HBV and HCV infections and cigarette smoking further amplifies HCC risk.[28] Regarding laboratory findings,

white blood cell (WBC) counts were significantly greater in HCC cases, although within the normal range, this possibly suggests increased systemic inflammatory response associated with HCC tumour microenvironment.[29, 30]

Haemoglobin and serum albumin levels were significantly lower in both non-HCC and HCC groups in comparison to the control group. Anaemia in cancer patients may result from chronic inflammation, bone marrow suppression, hypersplenism and nutritional deficiencies.[31] Hypoalbuminemia indicating decreased hepatic protein synthesis, is recognised as a key marker of liver functional reserve and disease severity.[32]

In the current study, Thrombocytopenia was a common finding in cirrhotic patients, may be owing to direct viral interaction, portal hypertension, decreased thrombopoietin level and splenomegaly.[33] Patients with HCC showed relatively higher platelet counts than cirrhotic patients without HCC, possibly due to tumour-driven platelet production and activation.[34, 35] INR was significantly elevated in cirrhotic and HCC groups, suggesting reduced liver synthetic function.[36]

Moreover, ALT and AFP concentrations were significantly greater in HCC cases in comparison with non-HCC cases, with both groups showing higher levels than controls. Similarly, a significant rise in ALT concentrations between HCC against cirrhotic cases, reflecting increased liver cell injury in HCC patients.[36, 37] AFP is a well-established tumour indicator, significantly raised in HCC and its levels correlated with tumour burden, microvascular invasion and poor prognosis.[38, 39]

Regarding PKCδ, it was significantly higher in HCC cases than non-HCC cases, with both groups showing higher levels than controls, with median levels (40.3, 21 and 12 ng/mL) respectively. These findings are consistent with previous study involved 313 patients and demonstrated that serum PKCδ is markedly elevated in HCC group than non-HCC and control groups with median levels nearly comparable to our findings (46.9, 37.9 and 27.0 ng/mL) in HCC, non-HCC and control groups correspondingly.[16] Recent evidence indicates that PKCδ is significantly elevated in HCC, supporting its use as a biomarker for very early-stage detection and for HCV-related HCC, independent of viral clearance status.[18] In the present research, PKCδ at a cut-off value of ≥ 30.75 nanogram per millilitres showed excellent diagnostic performance for detecting HCC in HCV-related cirrhosis with AUC = 0.977, sensitivity 95.6 %, specificity 86.7 %, PPV 93.5 %, NPV 90.69 % and accuracy 92.59 %. These results are comparable to previous study reported that serum PKCδ distinguished HCC from cirrhosis at a cut-off point 57.7 ng/mL with high sensitivity, specificity and PPV of 95.3 %.[16]

There was moderate significant positive correlation among PKCδ and AFP in HCC and non-HCC groups, while no correlation among PKCδ and AFP within HCC group. This was previously reported with nearly similar correlations, suggesting that PKCδ is an independent and complementary biomarker.[16] Moreover, previous research illustrated that there is a functional relation between PKCδ expression and AFP production at the cellular level *in vitro* as the expression of PKCδ has been influenced by the variation of AFP.[17] Also, PKCδ silencing affects AFP expression and secretion in liver cancer cell lines.[17]

In the current study, PKCδ has positive association with ALT, AST and alkaline phosphatase. ALT and AST concentrations were significantly raised in HCC cases due to hepatocellular necrosis and inflammatory cytokine release.[31, 40] Increased AST and ALT levels are considered risk factors and indicators of HCC.[41]

In the present research, there was a positive association between AFP and ALT and focal liver lesions size and number. This is in agreement with prior studies.[39, 42]

In the present study, AFP levels showed a significant positive correlation with HCC staging systems such as BCLC, TNM, JIS, Hong Kong and CLIP. Higher AFP levels often indicate poorer prognosis as commonly observed in advanced tumour burden and poorer liver functions,[38, 43] reflecting worsening stage in HCC staging systems. Similarly, previous studies reported the positive correlation between AFP and both BCLC and TNM staging systems.[44, 45]

In the current study, PKCδ was positively correlated with Albumin-Bilirubin (ALBI) grading in HCC patients. To our knowledge, limited data are available regarding this association. The ALBI grade is a validated objective score widely used for evaluating liver function and prognosis in HCC, showing superior stratification than Child-Pugh in many studies.[46, 47]

Regarding multivariate regression analysis, PKCδ ≥ 30.75 ng/mL, AFP ≥ 9.4 ng/mL and current smoking were statistically significant independent predictors of HCC development in patients with HCV-related cirrhosis, the regression model was statistically significant and correctly classified 93.3 % of cases with 93.5 % sensitivity, 92.85 % specificity, 96.7 % PPV and 86.7% NPV. So, serum PKCδ may represent a promising biomarker for HCC detection in HCV-related liver cirrhosis.

Limitations of the study: The case-control design does not allow establishing causality and being performed at a single centre can limit generalisability of the outcomes. Moreover, the absence of follow-up prevents assessment of prognostic value of PKCδ. Larger multicentre studies are recommended for further validation.

## Conclusion

Serum PKCδ demonstrated strong diagnostic performance for detecting HCC in HCV-related cirrhosis. PKCδ and AFP were independent predictors of HCC. PKCδ given its high sensitivity and specificity may complement AFP in clinical practice; further prospective multicentre studies are warranted to evaluate their combined role.

## Ethics

The study was approved by the Institutional Ethics Committee of Faculty of Medicine, Mansoura University (Approval No MD.23.01.732, dated 14 March 2023). Written informed consent was obtained from all participants included in the study or their legal representatives after ensuring confidentiality. Written permission was obtained from all individuals acknowledged in the manuscript.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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# References

1. Lee MH. Public health strategies for hepatocellular carcinoma: from risk factors to prevention and control. J Liver Cancer. 2025;25(2):204-16. doi: 10.17998/jlc.2025.07.25.
2. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, et al. Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol. 2025;31(Suppl):S228-S254. doi: 10.3350/cmh.2024.0824.
3. Ezzat R, Eltabbakh M, El Kassas M. Unique situation of hepatocellular carcinoma in Egypt: a review of epidemiology and control measures. World J Gastrointest Oncol. 2021;13(12):1919-38. doi: 10.4251/wjgo.v13.i12.1919.
4. Ali AA, Gamal SE, Anwar R, Elzahaf E, Eskandere D. Assessment of clinico epidemiological profile of hepatocellular carcinoma in the last two decades. Egyptian J Intern Med. 2023;35(1):18.
5. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6. doi: 10.1038/s41572-020-00240-3.
6. Ibrahim M, El Raey F, Fathy N, El Bakrey K. Transthyretin as a novel biomarker for diagnosis of hepatocellular carcinoma in cirrhotic patients. Int J Med Arts. 2020;2(2):412-19. doi: 10.21608/ijma.2020.23373.1094.
7. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025 Feb;82(2):315-374. doi: 10.1016/j.jhep.2024.08.028.
8. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922-65. doi: 10.1097/HEP.0000000000000466.
9. Parikh ND, Mehta AS, Singal AG, Block T, Marrero JA, Lok AS. Biomarkers for the early detection of hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 2020;29(12):2495-503. doi: 10.1158/1055-9965.EPI-20-0005.
10. Zou W, Cui J, Ren Z, Leng Y. NRAGE is a potential diagnostic biomarker of hepatocellular carcinoma. Medicine (Baltimore). 2018;97(48):e13411. doi: 10.1097/MD.0000000000013411.
11. Lu HC, Chou FP, Yeh KT, Chang YS, Hsu NC, Chang JG. Expression of protein kinase C family in human hepatocellular carcinoma. Pathol Oncol Res. 2010;16(3):385-91. doi: 10.1007/s12253-009-9228-z.
12. Rehman A, Shabbir M, Badshah Y, Khan K, Trembley JH, Ashraf NM, et al. Elucidating the role of missense SNP of protein kinase C epsilon in HCV induced hepatocellular carcinoma. BMC Cancer. 2023;23(1):147. doi: 10.1186/s12885-023-10618-7.
13. Ueda K, Oikawa T, Yamada K, Tsubota A, Saeki C, Katagiri K, et al. Serum PKCδ is a useful biomarker to distinguish hepatocellular carcinoma from other gastrointestinal cancers. Biochem Biophys Res Commun. 2025 Mar 5;751:151431. doi: 10.1016/j.bbrc.2025.151431.
14. Yamada K, Oikawa T, Kizawa R, Motohashi S, Yoshida S, Kumamoto T, et al. Unconventional secretion of PKCδ exerts tumorigenic function via stimulation of ERK1/2 signaling in liver cancer. Cancer Res. 2021;81(2):414-25. doi: 10.1158/0008-5472.CAN-20-2009.
15. Yamada K, Kizawa R, Yoshida A, Koizumi R, Motohashi S, Shimoyama Y, et al. Extracellular PKCδ signals to epidermal growth factor receptor for tumor proliferation in liver cancer cells. Cancer Sci. 2022;113(7):2378-85. doi: 10.1111/cas.15386.
16. Oikawa T, Yamada K, Tsubota A, Saeki C, Tago N, Nakagawa C, et al. Protein kinase C delta is a novel biomarker for hepatocellular carcinoma. Gastro Hep Adv. 2022;2(1):83-95. doi: 10.1016/j.gastha.2022.07.020.
17. Ammoury R, Tahtouh R, Mahfouz N, Doumit R, Khalil C, Hilal G. Relationship between protein kinase C isoforms, telomerase and alpha fetoprotein through PI3K/AKT/mTOR pathway in hepatocellular carcinoma. MedPharmRes. 2021;5(4):12-26.
18. Nakagawa C, Oikawa T, Yamada K, Tsubota A, Saeki C, Katagiri K, et al. Protein kinase C delta enhances the diagnostic performance of hepatocellular carcinoma. Biomarkers. 2024;29(2):55-67. doi: 10.1080/1354750X.2024.2312990.
19. Pugh RN, Murray Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-49. doi: 10.1002/bjs.1800600817.
20. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681-93. doi: 10.1016/j.jhep.2021.11.018.
21. Kamarajah SK, Frankel TL, Sonnenday C, Cho CS, Nathan H. Critical evaluation of the American Joint Committee on Cancer (AJCC) 8th edition staging system for patients with hepatocellular carcinoma: a SEER analysis. J Surg Oncol. 2018;117(4):644-50. doi: 10.1002/jso.24908.
22. Hui RW, Mak LY, Cheung TT, Lee VH, Seto WK, Yuen MF. Clinical practice guidelines and real life practice on hepatocellular carcinoma: the Hong Kong perspective. Clin Mol Hepatol. 2023;29(2):217-29. doi: 10.3350/cmh.2022.0399.
23. Calderon-Martinez E, Landazuri-Navas S, Vilchez E, Cantu-Hernandez R, Mosquera-Moscoso J, Encalada S, et al. Prognostic scores and survival rates by etiology of hepatocellular carcinoma: a review. J Clin Med Res. 2023;15(4):200-7. doi: 10.14740/jocmr4902.
24. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging score (JIS score). J Gastroenterol. 2003;38(3):207-15. doi: 10.1007/s005350300038.
25. Arias IM, Alter HJ, Boyer JL, Eds. Epidemiology of hepatocellular carcinoma. In: The Liver: Biology and Pathobiology. Hoboken, US: Wiley 2020. pp. 758-72.
26. Jain D, Chaudhary P, Varshney N, Bin Razzak KS, Verma D, Khan Zahra TR, et al. Tobacco smoking and liver cancer risk: potential avenues for carcinogenesis. J Oncol. 2021;2021:5905357. doi: 10.1155/2021/5905357.
27. Li S, Saviano A, Erstad DJ, Hoshida Y, Fuchs BC, Baumert T, et al. Risk factors, pathogenesis, and strategies for hepatocellular carcinoma prevention: emphasis on secondary prevention and its translational challenges. J Clin Med. 2020;9(12):3817. doi: 10.3390/jcm9123817.

28. Shadi Y, Heshmati B, Poorolajal J. Interaction between hepatitis B, hepatitis C and smoking in the development of hepatocellular carcinoma: a systematic review and meta analysis. J Public Health (Oxf). 2024;46(1):51-60. doi: 10.1093/pubmed/fdad214.
29. Aasarey R, Yadav K, Kashyap BK, Prabha S, Kumar P, Kumar A, et al. Role of immunological cells in hepatocellular carcinoma disease and associated pathways. ACS Pharmacol Transl Sci. 2023;6(12):1801-16. doi: 10.1021/acsptsci.3c00216.
30. Seyhan D, Allaire M, Fu Y, Conti F, Wang XW, Gao B, et al. Immune microenvironment in hepatocellular carcinoma: from pathogenesis to immunotherapy. Cell Mol Immunol. 2025;22(10):1132-58. doi: 10.1038/s41423-025-01308-4.
31. Toqueer U, Manan A, Riyaz A, Zaman A, Shafi R, Anis R, et al. Correlation of liver enzymes and blood parameters with histopathological severity in benign and malignant liver lesions. Cureus. 2025;17(9):e92954. doi: 10.7759/cureus.92954.
32. Jeng LB, Chan WL, Teng CF. Prognostic significance of serum albumin level and albumin based mono and combination biomarkers in patients with hepatocellular carcinoma. Cancers (Basel). 2023;15(4):1005. doi: 10.3390/cancers15041005.
33. Bihari C, Rastogi A, Shasthry SM, Bajpai M, Bhadoria AS, Rajesh S, et al. Platelets contribute to growth and metastasis in hepatocellular carcinoma. APMIS. 2016;124(9):776-86. doi: 10.1111/apm.12574.
34. Zanetto A, Senzolo M, Campello E, Bulato C, Gavasso S, Shalaby S, et al. Influence of hepatocellular carcinoma on platelet aggregation in cirrhosis. Cancers (Basel). 2021;13(5):1150. doi: 10.3390/cancers13051150.
35. Gouda AM, Abd Elaziz MA, Mousa MA, Saad HM, Helaly NA. Evaluation of platelet indices in Egyptian cirrhotic patients. Afr J Gastroenterol Hepatol. 2024;7(1):163-84. doi: 10.21608/ajgh.2024.282311.1052.
36. Sharma P. Value of liver function tests in cirrhosis. J Clin Exp Hepatol. 2022;12(3):948-64. doi: 10.1016/j.jceh.2021.11.004.
37. Sheta T, Selim M, Sabry M, Saed A. Serum thioredoxin as a diagnostic marker for hepatocellular carcinoma in cirrhotic hepatitis C patients. Med J Viral Hepat. 2021;5(2):9-15. doi: 10.21608/mjvh.2021.158271.
38. Lee WC. Value of alpha fetoprotein in hepatocellular carcinoma. Transl Gastroenterol Hepatol. 2021;6:52. doi: 10.21037/tgh.2019.12.19.
39. Huang D, Zhang J, Xu J, Niu Q, Zhou D. Utility of alpha fetoprotein and ultrasound in the diagnosis and prognosis of patients with hepatocellular liver cancer. J Multidiscip Healthc. 2024;17:1819-26. doi: 10.2147/JMDH.S449276.
40. Che Noh I, Avoi R, Abdullah Nurul A, Ahmad I, Abu Bakar R. Analysis of serum and gene expression profile of cytokines (IL 6, TNF α and TGF β1) in chronic hepatitis C virus infection. PeerJ. 2022;10:e13330. doi: 10.7717/peerj.13330.
41. Qin S, Wang J, Yuan H, He J, Luan S, Deng Y. Liver function indicators and risk of hepatocellular carcinoma: a bidirectional mendelian randomization study. Front Genet. 2024;14:1260352. doi: 10.3389/fgene.2023.1260352.
42. Hanif M, Mobeen N, Huda N, Nagra MA, Hussain HA, Ahmed U, et al. Correlation of elevated serum alpha feto protein level with mean tumor size in hepatocellular carcinoma. Ann Punjab Med Coll. 2020;14(3). doi: 10.29054/APMC/2020.987.
43. Hanif H, Ali MJ, Susheela AT, Khan IW, Luna-Cuadros MA, Khan MM, et al. Update on the applications and limitations of alpha fetoprotein for hepatocellular carcinoma. World J Gastroenterol. 2022;28(2):216-29. doi: 10.3748/wjg.v28.i2.216.
44. Hamayun A, Anees S, Gardezi A, Khan Niazi N, Tirmizi SH, Rafique I, et al. Evaluation of co relation between BCLC stage of HCC and alpha fetoprotein levels. Pakistan J Med Health Sci. 2022;16(08):104. doi: 10.53350/PJMHS22168104.
45. Bai DS, Zhang C, Chen P, Jin SJ, Jiang GQ. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep. 2017;7(1):12870. doi: 10.1038/s41598-017-12834-1.
46. Feng D, Wang M, Hu J, Li S, Zhao S, Li H, et al. Prognostic value of the albumin bilirubin grade in patients with hepatocellular carcinoma and other liver diseases. Ann Transl Med. 2020;8(8):553. doi: 10.21037/atm.2020.02.116.
47. da Fonsecaa LG, de Melo MAZ, da Silveira THM, Yamamoto VJ, Hashizume PHS, Sabbaga J. Prognostic role of albumin bilirubin (ALBI) score and Child Pugh classification in patients with advanced hepatocellular carcinoma under systemic treatment. Ecancermedicalscience. 2024;18:1748. doi: 10.3332/ecancer.2024.1748.