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Serum PARP2 as a Potential Diagnostic Biomarker for Hepatocellular Carcinoma: Postprint

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver. In recent years, the incidence of HCC has been increasing. Alpha-fetoprotein (AFP) is a classic serum marker in HCC diagnosis, but its sensitivity is low. There is an urgent need to develop novel molecular biomarkers for early diagnosis of HCC.

Objective: To detect the serum protein expression level of poly(ADP-ribose) polymerase 2 (PARP2) in HCC patients and explore whether it can serve as a potential diagnostic marker for HCC.

Methods: PARP2 mRNA levels were analyzed in 50 healthy individuals and 371 HCC patients from the TCGA database, and receiver operating characteristic (ROC) curves for HCC diagnosis were plotted based on PARP2 expression to evaluate diagnostic efficacy. PARP2 mRNA and protein expression levels were detected in HCC cells and normal hepatocytes. Serum samples were collected from 38 newly diagnosed HCC patients and 38 healthy individuals at the First Affiliated Hospital of Xinjiang Medical University between March 2021 and July 2022. Serum PARP2 protein levels were measured using enzyme-linked immunosorbent assay (ELISA). The correlation between serum PARP2 protein levels and clinical characteristics in HCC patients was analyzed. The efficacy of serum PARP2 expression level for HCC diagnosis and for diagnosis of alpha-fetoprotein (AFP)-negative HCC (AFP<20 ng/mL) was analyzed. The efficacy of combined serum PARP2 and AFP for diagnosing HCC patients versus healthy individuals was evaluated.

Results: Based on big data analysis from TCGA, PARP2 mRNA expression was higher in tumor tissues than in adjacent non-cancerous tissues ($P<0.001$). PARP2 mRNA and protein expression levels were higher in HCC HepG2 cells than in normal WRL68 hepatocytes ($P<0.05$). Serum PARP2 protein expression level was higher in HCC patients than in healthy individuals ($P<0.001$).

Serum PARP2 expression levels differed significantly among patients with different lymphatic metastasis status and tumor numbers ($P<0.05$). The area under the ROC curve (AUC) for HCC diagnosis based on serum PARP2 expression level was 0.92, with a sensitivity of 76.32%, specificity of 97.37%, and a cutoff value of 19.45 ng/mL. Among the 38 HCC patients, 21 were AFP-negative HCC based on serum AFP testing. The AUC of serum PARP2 protein level for diagnosing AFP-negative HCC was 0.95 (95%CI=0.88~1.00), with a sensitivity of 85.71%, specificity of 97.37%, and a cutoff value of 19.59 ng/mL. Furthermore, the diagnostic efficacy of PARP2 combined with AFP was evaluated using a parallel combination diagnostic model. The results showed that the combined diagnosis of HCC achieved a sensitivity of 92.11%, specificity of 94.74%, and AUC of 0.9342; for AFP-negative HCC patients, the combined diagnosis achieved a sensitivity of 85.71%, specificity of 94.74%, and AUC of 0.9023.

Conclusion: PARP2 is highly expressed in HCC and can serve as a biomarker for HCC screening, particularly for AFP-negative HCC.

Full Text

Investigating Serum PARP2 as a Potential Diagnostic Biomarker for Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common malignant liver tumor, and its incidence has been rising in recent years. Alpha-fetoprotein (AFP) is the classic serum marker for HCC diagnosis, but its low sensitivity underscores the urgent need for novel molecular biomarkers to enable early detection of HCC.

Objective: To measure serum poly(ADP-ribose) polymerase 2 (PARP2) protein expression levels in HCC patients and evaluate its potential as a diagnostic biomarker for HCC.

Methods: PARP2 mRNA levels from 50 healthy individuals and 371 HCC patients were analyzed using The Cancer Genome Atlas (TCGA) database, and receiver operating characteristic (ROC) curves were generated based on PARP2 expression to assess diagnostic performance. PARP2 mRNA and protein expression were also examined in HCC cells and normal hepatocytes. Serum samples were collected from 38 newly diagnosed HCC patients and 38 healthy controls at the First Affiliated Hospital of Xinjiang Medical University between March 2021 and July 2022. Serum PARP2 protein levels were measured by enzyme-linked immunosorbent assay (ELISA), and correlations with clinical characteristics were analyzed. The diagnostic performance of serum PARP2 for HCC and AFP-negative HCC (AFP < 20 ng/mL) was evaluated, and the efficacy of combined PARP2 and AFP testing was assessed.

Results: TCGA data analysis revealed significantly higher PARP2 mRNA expression in tumor tissues compared to adjacent non-tumor tissues ($P < 0.001$). HCC HepG2 cells exhibited higher PARP2 mRNA and protein expression levels than normal WRL68 hepatocytes ($P < 0.05$). Serum PARP2 protein levels were significantly elevated in HCC patients compared to healthy controls ($P < 0.001$). Statistically significant differences in serum PARP2 expression were observed based on lymph node metastasis and tumor number ($P < 0.05$). The ROC curve for serum PARP2 in HCC diagnosis yielded an area under the curve (AUC) of 0.92, with 76.32% sensitivity, 97.37% specificity, and a cutoff value of 19.45 ng/mL. Among the 38 HCC patients, 21 were AFP-negative. For diagnosing AFP-negative HCC, serum PARP2 achieved an AUC of 0.95 (95% CI = 0.88-1.00), 85.71% sensitivity, 97.37% specificity, and a cutoff of 19.59 ng/mL. Using a parallel combination approach, PARP2 and AFP together demonstrated 92.11% sensitivity, 94.74% specificity, and an AUC of 0.9342 for HCC diagnosis; for AFP-negative HCC, the combined approach showed 85.71% sensitivity, 94.74% specificity, and an AUC of 0.9023.

Conclusion: PARP2 is highly expressed in HCC and can serve as a biological marker for HCC screening, particularly for AFP-negative HCC.

Keywords: Liver neoplasms; PARP2; Alpha-fetoprotein; Diagnostic biomarkers; Wilcoxon rank sum test

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor, accounting for 45.3% of new global liver cancer cases in China. Despite recent advances, HCC treatment outcomes have not improved substantially, primarily because HCC develops insidiously and early diagnosis remains challenging. Enhancing early diagnostic capabilities is therefore critical for timely treatment and improved survival rates. Alpha-fetoprotein (AFP) is the classic serum marker for HCC diagnosis, but its sensitivity is low. Most HCC patients maintain low AFP expression throughout their disease course (this study defines AFP-negative HCC as AFP < 20 ng/mL), making them susceptible to missed diagnosis. Consequently, there is an urgent clinical need for effective molecular biomarkers to enable early HCC diagnosis, particularly for AFP-negative patients.

Poly(ADP-ribose) polymerase 2 (PARP2), a member of the PARP family, is an essential protein-modifying enzyme in DNA damage repair that also regulates fundamental biological processes including cell growth, proliferation, and apoptosis. PARP2 plays a crucial role in DNA repair and maintenance of genomic stability, while DNA damage represents a significant factor in HCC development and progression. The PARP family has been extensively studied as a therapeutic target in BRCA1/2-mutated breast and ovarian cancers. However, the expression and diagnostic value of PARP2 in HCC remain underexplored, and its ability to identify AFP-negative HCC patients has not been established. This study aims to measure serum PARP2 protein levels in HCC patients and healthy individuals, analyze its relationship with clinical features, and investigate the clinical significance and diagnostic efficacy of serum PARP2, particularly for early identification of AFP-negative HCC patients.

Methods

1.1 Serum Sample Collection and Inclusion/Exclusion Criteria We collected serum samples from 38 newly diagnosed HCC patients and 38 healthy individuals undergoing physical examinations at the First Affiliated Hospital of Xinjiang Medical University between March 2021 and July 2022. All HCC serum samples were obtained prior to treatment initiation. Clinical and pathological data were recorded, including gender, age, tumor size (maximum diameter) and number, TNM stage, lymph node metastasis, distant metastasis, AFP levels, hepatitis B surface antigen (HBsAg) status, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) for downstream analysis.

Inclusion criteria for HCC patients were: (1) pathologically and radiologically confirmed HCC diagnosis according to the Practice Guidelines for Pathological Diagnosis of Primary Liver Cancer (2015 Edition); (2) no prior HCC-related treatment; and (3) complete clinical records. Exclusion criteria included: history of other malignant tumors, autoimmune diseases, and hematologic disorders. Healthy controls were selected from individuals undergoing routine physical examinations at the same hospital, with complete medical records, no major medical history, and normal examination results. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval number: K202107-15).

1.2 Bioinformatics Analysis of PARP2 Expression in HCC Progression Using mRNA expression profiles from the TCGA database (https://www.cancer.gov/ccg/research/genome-sequencing/tcga) comprising 50 healthy individuals and 371 HCC patients, we analyzed PARP2 mRNA expression across various cancers to preliminarily assess its potential as a tumor marker. We examined differential PARP2 expression in paired and unpaired HCC samples to identify expression differences between tumor and normal tissues, and generated ROC curves based on PARP2 expression to evaluate diagnostic performance, sensitivity, and specificity.

1.3 RT-PCR Detection of PARP2 mRNA in HCC HepG2 Cells and Normal WRL68 Hepatocytes Total RNA was extracted from normal hepatocyte cell line WRL68 (gifted by Professor Li Jinyao, Xinjiang University) and HCC cell line HepG2 (purchased from Procell) using the Trizol method. RNA concentration was measured using a NanoDrop 1000 spectrophotometer, and RNA was reverse transcribed to cDNA using a TAKARA reverse transcription kit. Real-time quantitative PCR was performed to detect GAPDH and PARP2 mRNA expression levels according to the instrument protocol, with relative quantification using the $2\hat{}(-\Delta\Delta CT)$ method.

1.4 Western Blot Detection of PARP2 Protein Expression in HCC HepG2 Cells and Normal WRL68 Hepatocytes HepG2 and WRL68 cells were cultured in 6 cm dishes with DMEM medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin at 37°C in a 5% CO_2 incubator. Once cells reached stable growth, they were washed twice with sterile PBS, lysed on ice for 15 minutes with RIPA buffer containing protease inhibitors and PMSF, and scraped into Ep tubes. After 15 minutes of standing, samples were centrifuged at 12,000 rpm for 15 minutes at 4°C, and supernatants were transferred. Total protein was quantified using the BCA method, loading buffer was added, and proteins were boiled at 100°C for 10 minutes. Proteins were loaded onto SDS-PAGE gels, electrophoresed, and transferred to PVDF membranes. After blocking with 5% skim milk, membranes were incubated overnight at 4°C with primary antibodies: GAPDH (1:5,000) and PARP2 (1:2,000). The next day, membranes were washed three times with TBST, incubated with corresponding secondary antibodies (1:5,000) for 1 hour at room temperature, and visualized using an ECL chemiluminescence substrate kit. Band intensities were quantified using Image J software.

1.5 ELISA Detection of Serum PARP2 Protein Serum PARP2 protein levels were measured using an enzyme-linked immunosorbent assay (ELISA) with a human PARP2 ELISA kit (catalog number EH2530, Wuhan Fine Biotech) according to the manufacturer' s instructions.

1.6 Determination of Diagnostic Cutoff Value ROC curve analysis was used to determine the diagnostic cutoff value for serum PARP2 protein levels. The cutoff was established at the point of maximum Youden index (sum of sensitivity and specificity).

1.7 Statistical Methods Statistical analysis was performed using SPSS 21.0 software. Normally distributed continuous data were expressed as mean ± standard deviation and compared between groups using t-tests. Non-normally distributed data were presented as median (P25, P75) and compared using the Wilcoxon rank-sum test. Correlation analysis was performed using Spearman' s rank correlation. Diagnostic efficacy was evaluated using ROC curve analysis to obtain the area under the curve (AUC). A P-value < 0.05 was considered statistically significant.

Results

2.1 Analysis of PARP2 mRNA Expression in HCC and Adjacent Tissues Using TCGA Database TCGA database analysis revealed that PARP2 mRNA expression in adjacent non-tumor tissues was (2.28 ± 0.34), significantly lower than in tumor tissues (3.44 ± 0.63) ($t = -12.85$, $P < 0.001$). The ROC curve based on PARP2 expression for diagnosing HCC in 50 healthy individuals and 371 HCC patients showed an AUC of 0.9523, with 74.93% sensitivity and 98% specificity [Figure 1: see original paper].

2.2 PARP2 mRNA and Protein Expression Levels in HCC Cells and Normal Hepatocytes RT-PCR analysis demonstrated that PARP2 mRNA expression in HepG2 cells was (3.35 ± 0.91), significantly higher than in WRL68 cells (1.00 ± 0.61) ($t = -3.70$, $P < 0.05$). Western blot results showed that PARP2 protein expression in HepG2 cells (5.25 ± 0.55) was significantly higher than in normal WRL68 hepatocytes (0.67 ± 0.24) ($t = -15.27$, $P < 0.001$) [Figure 2: see original paper].

2.3 Serum PARP2 Protein Levels in HCC Patients Serum PARP2 expression in HCC patients was 33.22 (19.21, 53.77) ng/mL, significantly higher than in healthy controls [11.01 (7.26, 15.09) ng/mL] ($Z = -6.244$, $P < 0.001$).

2.4 Relationship Between Serum PARP2 and HCC Clinicopathological Features No statistically significant differences in serum PARP2 expression were observed based on gender, age, TNM stage, distant metastasis, HBsAg status, tumor size, or AFP levels ($P > 0.05$). However, significant differences were found in serum PARP2 levels according to lymph node metastasis and tumor number ($P < 0.05$) .

2.5 Diagnostic Efficacy of Serum PARP2 for HCC and Combined Diagnosis ROC curve analysis based on PARP2 expression for HCC diagnosis yielded an AUC of 0.92 (95% CI = 0.85-0.98), with 76.32% sensitivity, 97.37% specificity, and a cutoff value of 19.45 ng/mL. No significant correlation was observed between serum PARP2 expression and AFP levels in HCC patients ($r = -0.2106$, $P > 0.05$). Serum AFP testing identified 21 of 38 HCC patients as AFP-negative (AFP < 20 ng/mL). The ROC curve for serum PARP2 in diagnosing AFP-negative HCC versus healthy controls showed an AUC of 0.95 (95% CI = 0.88-1.00), with 85.71% sensitivity, 97.37% specificity, and a cutoff of 19.59 ng/mL.

For comparison, AFP alone yielded an AUC of 0.80 (95% CI = 0.70-0.91), 60.53% sensitivity, 97.37% specificity, and a cutoff of 8.145 ng/mL. These results indicate that PARP2 demonstrates superior sensitivity compared to AFP, particularly for AFP-negative HCC patients. Further evaluation using a parallel combination model showed that combined PARP2 and AFP testing achieved 92.11% sensitivity, 94.74% specificity, and an AUC of 0.9342 for HCC diagnosis. For AFP-negative HCC patients, the combined approach showed 85.71% sensitivity, 94.74% specificity, and an AUC of 0.9023 [Figure 3: see original paper].

Discussion

Hepatocellular carcinoma develops insidiously, necessitating improved early diagnostic methods and novel biomarkers, particularly for AFP-negative HCC patients, to enable timely diagnosis and treatment. This study identified significant PARP2 upregulation in HCC tissues through TCGA database analysis and validated these findings at the cellular level. In our local cohort, HCC patients exhibited significantly higher serum PARP2 protein levels than healthy controls, and serum PARP2 could effectively diagnose AFP-negative HCC patients. Furthermore, combining PARP2 with AFP substantially improved diagnostic performance, demonstrating that serum PARP2 can function as a biomarker for HCC diagnosis.

In clinical practice, serum-based screening of high-risk populations requires exceptionally high sensitivity to identify potential cases for further evaluation. While serum AFP is the most widely used HCC biomarker globally, its diagnostic sensitivity of approximately 60% risks substantial missed diagnoses, highlighting the need for more sensitive biomarkers, especially for patients without elevated AFP. Other HCC biomarkers include des-γ-carboxy prothrombin (DCP), Golgi protein 73 (GP73), glypican 3 (GPC3), and AFP-L3. Studies report DCP diagnostic sensitivity of 62.50% and specificity of 85.50%, both lower than PARP2 performance in our study. GPC3 is also expressed in other tumor types such as liposarcoma and lung squamous cell carcinoma. Although these markers serve as HCC biomarkers, none fully meet clinical diagnostic requirements. Our study found PARP2 sensitivity of 76.32% for HCC screening, superior to GPC3 and DCP, indicating favorable diagnostic efficacy. For AFP-negative HCC screening, serum PARP2 achieved 85.71% sensitivity, and combination with AFP further enhanced detection rates, suggesting strong diagnostic performance in this challenging subgroup. Additionally, the correlation between serum PARP2 levels and clinical indicators such as lymph node metastasis and tumor number suggests potential prognostic value for HCC patients.

PARP2, a member of the PARP protein family comprising 17 members involved in diverse cellular processes, plays central roles in DNA repair, replication, and transcription. DNA repair defects represent a common cancer hallmark. Previous studies have reported PARP2 overexpression in BRCA1/2-deficient breast and ovarian cancers, highlighting its potential as a novel therapeutic target. However, serum PARP2 protein expression in HCC has not been previously reported. Tumorigenesis is associated with accumulated DNA damage, making DNA repair mechanisms a promising target for cancer therapy. The PARP family is crucial for DNA damage repair and transcriptional regulation; PARP1 and PARP2 are the earliest discovered and most important DNA damage sensors. When DNA strand breaks occur, PARP2 becomes activated and can effectively ADP-ribosylate DNA gaps to protect cells from DNA damage. Our findings of significantly upregulated PARP2 in HCC tissues and cell lines, along with elevated serum PARP2 in HCC patients, suggest that oxidative stress-induced DNA damage and tumor cell proliferation in cancer tissues may activate PARP2, leading to increased expression.

This study has several limitations. First, we only investigated serum PARP2 expression in HCC patients and have not evaluated its levels in other benign liver diseases such as hepatitis B, cirrhosis, or hepatic hemangioma. Second, our sample size was relatively small, requiring larger cohorts to validate our conclusions.

In summary, serum PARP2 can serve as a diagnostic biomarker for HCC screening, particularly for AFP-negative HCC patients, and substantially improves diagnostic sensitivity when combined with AFP.

Author Contributions

MAIERHABA · Maimaitiaili performed the main experiments and drafted the manuscript. ZHANG Kainan conducted the bioinformatics analysis and statistical analysis. ZHAO Hui collected and organized the data. YAKUFU · Tuoheti and YE Jianwei collected serum samples. LYU Guodong conceived and designed the study, performed quality control and review, and supervised the overall project.

Conflicts of Interest

The authors declare no conflicts of interest.

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