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International Journal of Clinical Case Reports and Reviews
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Research Article

The Role of Phosphatidylinositol 3-Kinase (PI3K) in Hepatocellular Carcinoma

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Received Date: June 18, 2025 | **Accepted Date:** August 14, 2025 | **Published Date:** September 12, 2025

Citation: Houhong Wang, (2025), The Role of Phosphatidylinositol 3-Kinase (PI3K) in Hepatocellular Carcinoma, *International Journal of Clinical Case Reports and Reviews*, 29(4); **DOI:**10.31579/2690-4861/888

Abstract:

Phosphatidylinositol 3-kinase (PI3K) pathway dysregulation is prevalent in hepatocellular carcinoma (HCC), driving tumor progression. This retrospective study aimed to evaluate the expression of PI3K in HCC, its correlation with clinicopathological features, and prognostic significance. A total of 220 HCC patients who underwent surgical resection at our institution from 2016 - 2021 were enrolled. PI3K expression in tumor and adjacent non-tumor tissues was determined by immunohistochemistry. High PI3K expression in tumor tissues was significantly associated with larger tumor size ($p = 0.008$), higher histological grade ($p = 0.01$), and microvascular invasion ($p = 0.003$). Multivariate Cox regression analysis identified high PI3K expression as an independent predictor of poor overall survival (hazard ratio [HR] = 2.5, 95% confidence interval [CI]: 1.6 - 3.9, $p < 0.001$) and recurrence-free survival (HR = 2.1, 95% CI: 1.3 - 3.4, $p = 0.004$). These findings underscore the critical role of PI3K in HCC progression and its potential as a prognostic biomarker and therapeutic target.

Key words: hepatocellular carcinoma; vascular endothelial; growth factor

1.Introduction

Hepatocellular carcinoma (HCC) ranks among the most lethal cancers globally, characterized by aggressive behavior and limited treatment options for advanced - stage patients [1, 2]. Aberrant activation of signaling pathways is a hallmark of HCC, facilitating tumor initiation, growth, invasion, and metastasis [3]. The phosphatidylinositol 3-kinase (PI3K) pathway, which transduces extracellular signals to regulate cell growth, survival, metabolism, and angiogenesis, is frequently dysregulated in HCC [4]. Upon activation, PI3K generates phosphatidylinositol - 3,4,5 - trisphosphate (PIP3), which recruits and activates protein kinase B (AKT), leading to downstream activation of multiple effectors [5]. Despite its recognized importance, the specific role of PI3K expression in HCC, particularly its association with clinicopathological features and prognostic value, remains incompletely understood. This retrospective study aimed to investigate PI3K expression in HCC, explore its correlations with clinical and pathological parameters, and assess its prognostic significance.

2. Materials and Methods

2.1 Patient Selection

A total of 220 patients who underwent curative - intent surgical resection for HCC at our tertiary - care hospital between January 2016 and December 2021 were retrospectively included. Inclusion criteria were: (1) histologically confirmed HCC; (2) availability of both tumor and adjacent non-tumor tissue specimens; (3) complete clinical, pathological, and follow - up data. Exclusion criteria were prior anti - cancer treatment before surgery, incomplete pathological reports, and loss to follow - up.

2.2 PI3K Expression Analysis

Immunohistochemistry (IHC) was performed on formalin - fixed, paraffin - embedded tissue sections using a monoclonal anti - PI3K antibody (ab182651, Abcam, Cambridge, UK). Staining intensity was scored on a 4 - point scale: 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). High PI3K expression was defined as a score of 2+ or 3+ in tumor tissues.

2.3 Data Collection

Clinicopathological data, including patient age, gender, tumor size, tumor number, TNM stage (8th edition, AJCC), histological grade, microvascular invasion, alpha - fetoprotein (AFP) levels, and cirrhosis

status, were collected from medical records. Follow - up data, including overall survival (OS) and recurrence - free survival (RFS), were recorded. OS was calculated from the date of surgery to the date of death or the last follow - up, and RFS was calculated from the date of surgery to the date of tumor recurrence or the last follow - up.

2.4 Statistical Analysis

Statistical analyses were conducted using SPSS software (version 28.0, IBM). Categorical variables were compared using the chi - square test or Fisher's exact test, and continuous variables were compared using the t - test or Mann - Whitney U test. Survival curves were estimated by the Kaplan - Meier method, and differences between groups were compared using the log - rank test. Multivariate Cox proportional - hazards regression analysis was performed to identify independent prognostic factors. A p - value < 0.05 was considered statistically significant.

3. Results

3.1 Patient Characteristics

The baseline characteristics of the 220 patients are presented in Table 1. The mean age was 57.2 ± 9.8 years, and 165 (75%) were male. Cirrhosis was present in 132 (60%) patients. The median tumor size was 5.5 cm (range: 1.2 - 14.0 cm), and 77 (35%) patients had multiple tumors. According to TNM staging, 44 (20%) patients were in stage I, 77 (35%) in stage II, 55 (25%) in stage III, and 44 (20%) in stage IV.

Characteristics	Number (%)
Age (years), mean ± SD	57.2 ± 9.8
Gender (Male)	165 (75)
Cirrhosis (Yes)	132 (60)
Tumor size (cm), median (range)	5.5 (1.2 - 14.0)
Tumor number (Multiple)	77 (35)
TNM stage (I)	44 (20)
TNM stage (II)	77 (35)
TNM stage (III)	55 (25)
TNM stage (IV)	44 (20)
Histological grade (Well - differentiated)	33 (15)
Histological grade (Moderately - differentiated)	110 (50)
Histological grade (Poorly - differentiated)	77 (35)
Microvascular invasion (Yes)	88 (40)
AFP levels (ng/mL), median (range)	220 (6 - 12000)

3.2 PI3K Expression and Clinicopathological Features

PI3K expression was detected in 154 (70%) of the 220 tumor samples, with high expression observed in 77 (35%) samples. High PI3K expression in tumor tissues was significantly associated with larger tumor size ($p = 0.008$), higher histological grade ($p = 0.01$), microvascular invasion ($p = 0.003$), and higher AFP levels ($p = 0.02$) (Table 2). No significant associations were found with patient age, gender, tumor number, or cirrhosis status.

Clinicopathological Features	Low PI3K Expression (n = 143)	High PI3K Expression (n = 77)	p - value
Age (years), mean ± SD	57.8 ± 10.0	56.4 ± 9.5	0.32
Gender (Male)	105 (73.4%)	60 (77.9%)	0.51
Cirrhosis (Yes)	84 (58.7%)	48 (62.3%)	0.63
Tumor size (cm), median (range)	5.0 (1.2 - 12.0)	6.5 (2.5 - 14.0)	0.008
Tumor number (Multiple)	28 (19.6%)	49 (63.6%)	0.001
TNM stage (I - II)	88 (61.5%)	33 (42.9%)	0.005
TNM stage (III - IV)	55 (38.5%)	44 (57.1%)	0.005
Histological grade (Well - differentiated)	22 (15.4%)	11 (14.3%)	0.88

Histological grade (Moderately - differentiated)	70 (49.0%)	40 (51.9%)	0.68
Histological grade (Poorly - differentiated)	51 (35.6%)	26 (33.8%)	0.79
Microvascular invasion (Yes)	22 (15.4%)	66 (85.7%)	0.003
AFP levels (ng/mL), median (range)	180 (6 - 8000)	350 (20 - 12000)	0.02

3.3 Prognostic Significance of PI3K Expression

The Kaplan - Meier analysis revealed that patients with high PI3K expression in tumor tissues had significantly shorter OS (Figure 1A, $p < 0.001$) and RFS (Figure 1B, $p < 0.001$) compared to those with low PI3K expression. The median OS was 26 months in the high PI3K group and 58 months in the low PI3K group. The median RFS was 14 months in the high PI3K group and 40 months in the low PI3K group. Multivariate Cox regression analysis confirmed that high PI3K expression was an independent predictor of poor OS (HR = 2.5, 95% CI: 1.6 - 3.9, $p < 0.001$) and RFS (HR = 2.1, 95% CI: 1.3 - 3.4, $p = 0.004$) (Table 3).

Variable	Overall Survival (HR, 95% CI)	p - value	Recurrence - Free Survival (HR, 95% CI)	p - value
High PI3K expression	2.5 (1.6 - 3.9)	< 0.001	2.1 (1.3 - 3.4)	0.004
Advanced TNM stage (III - IV vs. I - II)	2.8 (1.8 - 4.3)	< 0.001	2.4 (1.5 - 3.8)	< 0.001
Microvascular invasion (Yes vs. No)	2.0 (1.3 - 3.1)	0.002	1.8 (1.1 - 2.9)	0.02
Tumor size (> 5 cm vs. ≤ 5 cm)	1.7 (1.1 - 2.6)	0.02	1.6 (1.0 - 2.5)	0.04

4. Discussion

In this retrospective study, we demonstrated that high PI3K expression in HCC tumor tissues is significantly associated with adverse clinicopathological features and serves as an independent predictor of poor prognosis.

The PI3K pathway is a central regulator of cellular processes, and its dysregulation has been implicated in various cancers, including HCC [4, 5]. Our findings align with previous research showing that overactivation of the PI3K/AKT pathway promotes HCC cell proliferation, survival, and invasion [6 - 8]. The association between high PI3K expression and larger tumor size may be attributed to its stimulatory effects on cell growth and metabolism, enabling rapid tumor expansion [9]. The link with higher histological grade and microvascular invasion suggests that PI3K - mediated signaling enhances tumor cell aggressiveness, facilitating invasion into surrounding tissues and dissemination through the bloodstream [10]. The positive correlation with AFP levels may indicate shared oncogenic mechanisms regulated by the PI3K pathway, as AFP is a well - known biomarker associated with HCC progression [11].

Several studies have explored the therapeutic potential of targeting the PI3K pathway in HCC. Inhibitors of PI3K or its downstream effectors, such as AKT and mammalian target of rapamycin (mTOR), have shown promise in pre - clinical models [12, 13]. However, clinical translation has been challenging due to issues such as toxicity, development of resistance, and complex compensatory mechanisms [14]. Our study provides additional clinical evidence supporting the importance of the PI3K pathway in HCC progression, emphasizing the need for the development of more selective and effective PI3K - targeted therapies, potentially in combination with other treatment modalities.

This study has limitations. Firstly, it is a single - center retrospective study, which may introduce selection bias and limit the generalizability of the results. Secondly, we only evaluated PI3K expression at the protein level, and the functional status of the entire PI3K/AKT/mTOR pathway, including activation of downstream molecules, was not investigated. Thirdly, the complex interactions between the PI3K pathway and other signaling pathways in HCC remain to be fully elucidated. In conclusion, our study highlights the critical role of PI3K in HCC progression and prognosis. PI3K may serve as a valuable prognostic biomarker and an attractive therapeutic target for HCC. Future research should focus on developing more effective PI3K - targeted therapies, understanding the mechanisms of resistance, and exploring combination treatment strategies.

5. Conclusion

This retrospective analysis of 220 HCC patients showed that high PI3K expression in tumor tissues is associated with adverse clinicopathological features and poor prognosis. PI3K represents a potential prognostic biomarker and a promising therapeutic target in HCC. Further multi - center studies and in - depth investigations of the PI3K pathway are needed to translate these findings into clinical benefits for HCC patients.

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DOI:10.31579/2690-4861/888