Article

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Prognostic Value of IKK/NF-κB Pathway Activation in Hepatocellular Carcinoma: A Retrospective Study

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide, with a high mortality rate that is closely associated with chronic inflammation and aberrantly activated signaling pathways in the tumor microenvironment. As a central regulator of inflammatory responses, the IκB kinase (IKK)/nuclear factor-κB (NF-κB) signaling pathway plays a critical role in the proliferation, invasion, and immune escape of HCC. This study analyzes the clinical significance of the IKK/NF-κB pathway in predicting the prognosis of HCC patients.

Methods: A total of 206 HCC patients from 2022 to 2025 were included in this study and divided into the death group (n = 117) and the survival group (n = 89) according to their survival status. The content of IKK, NF-κB p65 and downstream proteins interleukin-6 (IL-6) and cyclin D1 were analyzed using enzyme-linked immunosorbent assay (ELISA). Combined with the clinicopathological characteristics, Kaplan–Meier survival analysis and Cox proportional hazards model were used to evaluate the association between pathway activity and the risk of patient death.

Results: There was no significant difference in the baseline data between the two groups of patients ($p > 0.05$). The serum content of IKK and NF-κB p65 in the death group was significantly higher than that in the survival group ($p < 0.05$). Survival analysis showed that the high expression of IKK and NF-κB p65 was significantly associated with reduced overall survival (OS) in patients ($p < 0.05$). Multivariate Cox regression showed that IKK, NF-κB p65 and IL-6 were independent predictors of poor prognosis ($p < 0.05$).

Conclusion: Aberrant activation of the IKK/NF-κB signaling pathway is associated with death risk in HCC patients, serving as an independent prognostic marker.

Keywords: hepatocellular carcinoma; NF-κB; IκB kinase; IL-6; retrospective analysis; risk factors

Introduction

As one of the most life-threatening, aggressive malignancies, hepatocellular carcinoma (HCC) contributes considerably to the global healthcare burden [1,2]. The development of HCC is highly dependent on chronic liver injury-inducing factors such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [3]. Notably, these factors serve as the "exclusive triggers" for the abnormal activation of the IκB kinase (IKK)/nuclear factor-κB (NF-κB) signaling pathway. In the context of HBV-associated HCC, the X protein (HBx) encoded by the HBV genome exhibits strong targeting ability. It can directly bind to IKKγ, the regulatory subunit of the IKK complex, and activate the phosphorylation activity of IKKα/β through conformational changes [4,5].

The chronic inflammatory state within the tumor microenvironment (TME) serves as a critical driver of HCC initiation and progression, during which multiple inflammation-related signaling pathways are aberrantly activated, contributing to key processes such as tumor cell proliferation, invasion, metastasis, and immune evasion [6,7]. The IKK/NF-κB signaling pathway is a central regulator of inflammatory responses. Under physiological conditions, NF-κB remains sequestered in the cytoplasm by inhibitory IκB proteins, existing in an inactive complex [8]. Upon stimulation by inflammatory cytokines or oxidative stress, IKK is activated, leading to phosphorylation and subsequent degradation of IKK. This allows NF-κB to translocate into the nucleus, where it initiates the transcription of various target genes involved in inflammation, cell proliferation, apoptosis, and immune responses, upregulating transcription of anti-apoptotic genes (B-cell lymphoma 2 (*Bcl-2*) and X-linked inhibitor of apoptosis protein (*XIAP*)) and cell cycle regulatory genes (cyclin D1 (*cyclin D1*) and cellular myelocytomatosis oncogene (*c-Myc*)) that are highly expressed in HCC [9,10]. In HCC, persistent activation of the IKK/NF-κB pathway contributes to the regulation of malignant phenotypes [11,12].

It has been reported that IKK mediates liver inflammatory responses in mice and may affect the progression of non-alcoholic fatty liver disease [13]. However, there are relatively few studies on how this pathway affects the clinical prognosis of patients. Therefore, this study aims to evaluate the clinical significance of the IKK/NF-κB pathway in predicting prognosis in HCC patients by detecting the serum level of related markers and conducting a retrospective analysis of clinical data, providing new insights and potential therapeutic targets for precision treatment of HCC.

Methods

Study Design Population

In this retrospective analysis, a total of 206 HCC patients treated in The People's Hospital of Pingyang County between 2022 and 2025 were enrolled. According to their survival status, the patients were divided into two groups: a death group and a survival group.

Inclusion criteria of this study are as follows: (1) diagnosed with HCC, as confirmed by pathology or imaging approaches; (2) aged 18–80 years old; and (3) having complete clinical data and follow-up information. Patients were excluded if they met any of the following criteria: (1) presence of other malignant tumors, severe cardiovascular diseases, autoimmune diseases, mental disorders or other diseases that seriously affect survival; (2) secondary or recurrent HCC; (3) pregnant or lactation; and (4) death not attributed to HCC.

Sample Size Estimation

Sample size estimation was conducted using G*Power software (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany). This estimation was conducted taking into account an effect size of 0.8, an alpha error probability of 0.05, a power of 0.95, and an N2/N1 allocation ratio of 0.8. To obtain statistically significant results, at least 86 samples are required.

Data Collection

Baseline data were collected, including gender, age, tumor size, tumor count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), China Liver Cancer Staging (CNLC), Barcelona Clinic Liver Cancer (BCLC) staging, and history of liver cirrhosis, HBV or HCV infection.

Enzyme-linked Immunosorbent assay (ELISA)

Fasting peripheral venous blood (5 mL) was collected from patients before any treatments were given. After being left to stand at room temperature for 30 min, the blood samples were centrifuged at 3000 rpm for 10 min, and the serum obtained was separated and stored at –80 °C for subsequent analysis. The expression levels of serum IKK (ab284617, Abcam, Shanghai, China), NF-κB (JL19458, Jonlnbio, Shanghai, China), IL-6 (ab178013, Abcam, Shanghai, China), and cyclin D1 (KE00344, Proteintech, Wuhan, China) were detected by means of ELISA in accordance with the manufacturer's protocol. The optical density (OD) value of each well was measured at 450 nm to calculate the concentrations of IKK and NF-κB p65 in the samples.

Statistical Analysis

Data analysis was conducted using the SPSS 26.0 statistical software (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate the normal distribution of collected data. Continuous data are expressed as mean $\pm$ standard deviation, and the *t*-test was used for comparison analysis between the two groups. Categorical data are expressed as the number of cases and percentages (%), and the χ^2 test was used for comparison between groups. The survival curves were plotted using the Kaplan–Meier method, and the log-rank test was used to compare the survival differences between groups. Univariate and multivariate analyses were conducted using the Cox proportional hazards model to evaluate the association between the activity of the IKK/NF-κB pathway and the risk of patient death. The Bonferroni correction was utilized to reduce the false positive rate. A *p*-value of less than 0.05 was considered statistically significant.

Results

Baseline Data

Among the 206 HCC patients, 117 cases were classified into the death group and 89 cases into the survival group. There were no significant differences between the two groups of patients in terms of baseline characteristics such as gender, age, tumor size, tumor count, CNLC stage, BCLC stage, and history of liver cirrhosis or HBV/HCV infection ($p > 0.05$), indicating good comparability, as shown in Table 1.

Comparison of Protein Expression Related to the IKK/NF-κB Pathway

The serum level of proteins related to the IKK/NF-κB pathway in the patients was analyzed by means of ELISA. The results showed that the content of IKK, NF-κB p65 and downstream proteins such as IL-6 and cyclin D1 in the death group was significantly higher than that in the survival group ($p < 0.001$), indicating the close association of serum IKK and NF-κB p65 levels with death risk in HCC patients (Table 2).

The Relationship Between the Expressions of IKK and NF-κB and the Overall Survival in HCC Patients

The Kaplan–Meier survival analysis was employed to evaluate the impact of IKK and NF-κB p65 expression on

Table 1. Comparison of baseline characteristics between survival and death groups.

Characteristics	Survival group (n = 89)	Death group (n = 117)	χ^2/T	p-value
Gender (male/female)	61/28	82/35	0.057	0.811
Age (years)	57.8 ± 8.7	58.6 ± 9.2	0.633	0.527
Tumor size (cm)	5.5 ± 2.1	5.7 ± 2.3	0.642	0.521
Tumor count (single/multiple)	70/19	91/26	0.023	0.880
ALT (U/L)	46.3 ± 19.8	48.7 ± 21.5	0.821	0.412
AST (U/L)	50.1 ± 21.7	52.6 ± 23.4	0.778	0.438
AFP (ng/mL)	458.3 ± 98.4	482.5 ± 121.6	1.534	0.126
CNLC stage (I/II/III/IV)	5/29/31/24	6/34/47/30	0.642	0.887
BCLC stage (0/A/B/C)	4/28/30/27	5/32/45/35	0.615	0.904
History of liver cirrhosis (yes/no)	76/13	98/19	0.103	0.749
History of HBV infection (yes/no)	79/10	102/15	0.119	0.730
History of HCV infection (yes/no)	6/83	8/109	0.001	0.978

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2. Comparison of serum levels of IKK and NF-κB between survival and death groups.

Group	IKK (pg/mL)	NF-κB (ng/mL)	IL-6 (pg/mL)	Cyclin D1 (ng/mL)
Survival group (n = 89)	351.76 ± 32.22	1.98 ± 0.35	61.06 ± 5.30	1.02 ± 0.05
Death group (n = 117)	436.94 ± 51.37	3.96 ± 0.24	83.25 ± 6.44	2.56 ± 0.38
T	13.72	48.11	26.40	37.96
p-value	<0.001	<0.001	<0.001	<0.001

Abbreviations: IKK, IκB kinase; IL-6, interleukin-6; NF-κB, nuclear factor-κB.

overall survival (OS) in patients. Patients were divided into high-expression and low-expression groups based on the median expression levels of IKK and NF-κB p65. The results showed that the median OS was 25.46 months and 49.01 months in the high-expression and low-expression groups for IKK, respectively, with a significant difference between the two groups (log-rank $\chi^2 = 63.39$, $p < 0.001$), indicating that high IKK expression is significantly associated with shorter OS in HCC patients (Fig. 1A). Similarly, for the high NF-κB p65 expression group, the median OS was 25.19 months, notably shorter compared to 49.01 months in the low expression group (log-rank $\chi^2 = 62.20$, $p < 0.001$), suggesting that elevated NF-κB p65 expression is also correlated with poorer survival outcomes in patients (Fig. 1B).

Analysis of Risk Factors in HCC Patients

Univariate and multivariate analyses were conducted using the Cox proportional hazards model to evaluate the predictive performance of IKK and NF-κB p65 in the prognosis of HCC patients. The results of univariate analysis showed that high expression of IKK, high expression of NF-κB p65, tumor size, tumor count, and expression level of downstream proteins such as IL-6 and cyclin D1 were all significantly associated with death risk in HCC patients ($p < 0.05$), as shown in Table 3.

Factors that showed statistically significant results in the univariate analysis were included and analyzed in the multivariate Cox regression model. The analysis showed that the high expressions of IKK, NF-κB p65 and IL-6 remained independent predictors of poor prognosis in HCC patients ($p < 0.05$). This means that after excluding the influence of other clinicopathological factors, the expression level of NF-κB p65 can independently predict the risk of death for patients. Its high expression indicates a poor prognosis for patients, providing an important molecular marker for the clinical assessment of prognosis in HCC patients (Table 4).

Discussion

This study retrospectively analyzed 206 HCC patients to systematically investigate the clinical significance of the IKK/NF-κB signaling pathway in prognosis. The results demonstrated that the serum levels of IKK and NF-κB p65 were significantly higher in the death group compared to the survival group. High expression of these proteins was significantly associated with shorter overall survival and identified as independent predictors of poor prognosis in HCC patients. Moreover, activation of the IKK/NF-κB pathway promotes tumor progression by upregulating the expression of downstream proteins, including pro-inflammatory cytokines and anti-apoptotic proteins, thereby contributing to the malignant behavior of HCC.

Aberrant activation of the IKK/NF-κB signaling pathway in HCC may be attributed to multiple factors. Chronic HBV or HCV infection is one of the major risk factors for HCC development. Viral infection can acti-

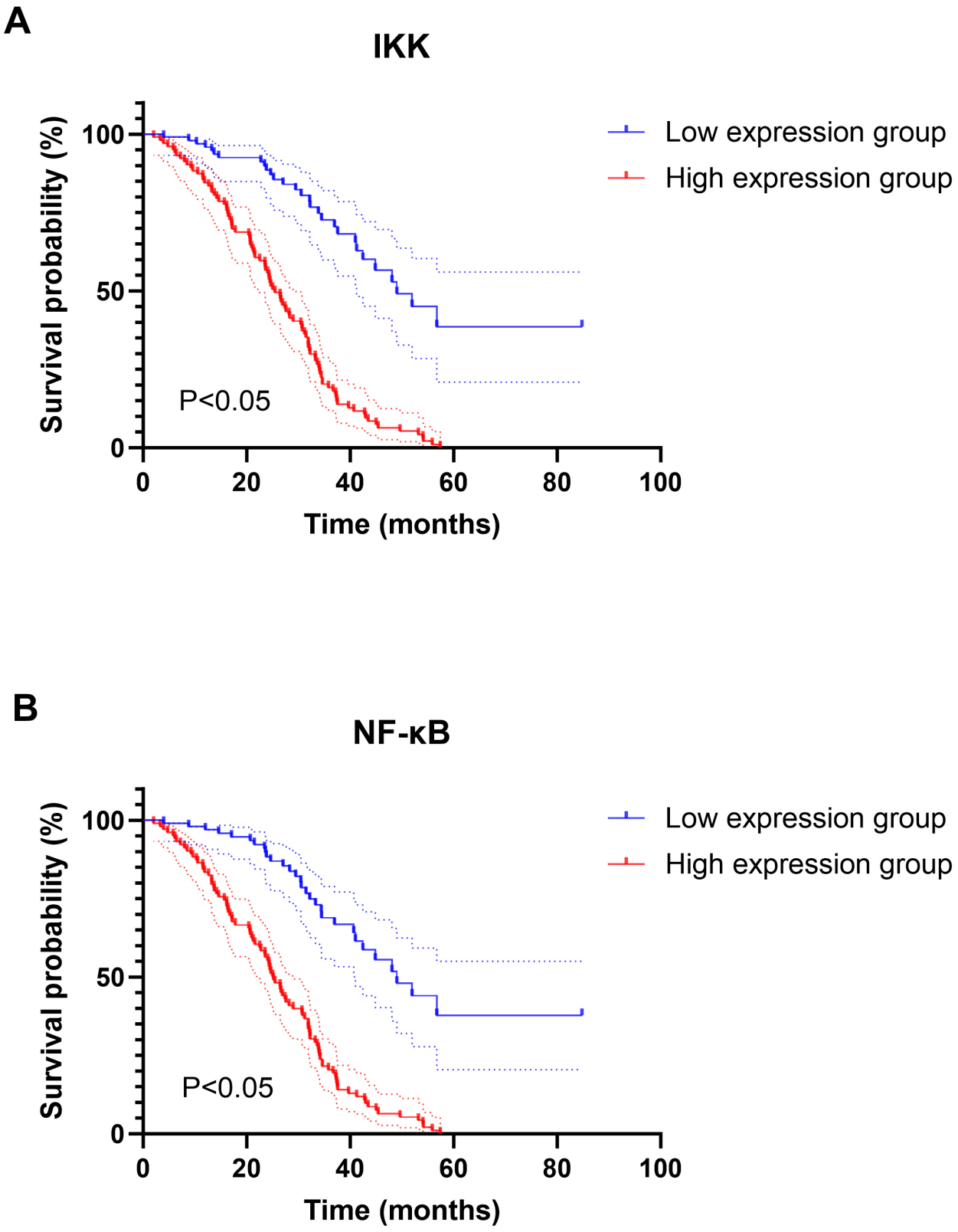

Fig. 1. Kaplan–Meier curves of overall survival in patients classified based on IKK (A) and NF-κB expression (B). Abbreviations: IKK, IκB kinase; NF-κB, nuclear factor-κB.

vate hepatic inflammatory cells, leading to the release of pro-inflammatory cytokines that subsequently trigger the IKK/NF-κB pathway [14,15]. Following tumor initiation, the cancer cells can further activate this pathway themselves

Table 3. Univariate Cox regression analysis of risk factors associated with death risk in HCC patients.

Variable	B	SE	Wald	HR (95% CI)	*p*-value
Gender	0.184	0.195	0.890	1.202 (0.820–1.761)	0.345
Age	–0.009	0.009	1.031	0.991 (0.973–1.009)	0.310
Tumor size	0.097	0.043	5.099	1.102 (1.013–1.199)	0.024
Tumor count	0.547	0.211	6.739	1.728 (1.143–2.612)	0.009
ALT	0.003	0.005	0.307	1.003 (0.994–1.012)	0.580
AST	0.002	0.005	0.198	1.002 (0.993–1.011)	0.656
AFP	0.000	0.000	0.101	1.000 (0.999–1.001)	0.751
CNLC stage	0.533	0.420	1.608	1.704 (0.748–3.883)	0.205
BCLC stage	0.201	0.223	0.812	1.222 (0.790–1.892)	0.368
History of liver cirrhosis	–0.063	0.241	0.069	0.938 (0.585–1.505)	0.792
History of HBV infection	–0.117	0.255	0.209	0.890 (0.540–1.467)	0.648
History of HCV infection	–0.222	0.348	0.408	0.801 (0.405–1.584)	0.523
IKK	0.008	0.001	38.664	1.008 (1.006–1.011)	<0.0001
NF-κB p65	0.984	0.126	60.950	2.675 (2.089–3.424)	<0.0001
IL-6	0.791	0.097	66.125	2.205 (1.823–2.668)	<0.0001
Cyclin D1	0.939	0.122	59.606	2.557 (2.015–3.245)	<0.0001

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IKK, IκB kinase; IL-6, interleukin-6; NF-κB, nuclear factor-κB.

Table 4. Multivariate Cox regression analysis of risk factors related to death in HCC patients.

Variable	B	SE	Wald	HR (95% CI)	*p*-value
Tumor size	–0.201	0.286	0.493	0.818 (0.467–1.434)	0.483
Tumor count	0.207	0.237	0.766	1.23 (0.773–1.958)	0.382
IKK	0.346	0.133	6.768	1.413 (1.089–1.834)	0.009
NF-κB p65	1.995	0.797	6.271	7.352 (1.543–35.036)	0.012
IL-6	0.726	0.302	5.779	2.067 (1.143–3.735)	0.016
Cyclin D1	0.187	0.290	0.416	1.205(0.682–2.128)	0.519

Abbreviations: HCC, hepatocellular carcinoma; IKK, IκB kinase; IL-6, interleukin-6; NF-κB, nuclear factor-κB.

by secreting inflammatory and growth factors, establishing a positive feedback loop that drives tumor progression [16].

Then we analyzed the expression of its downstream target genes. Our findings indicate that the expression of pro-inflammatory cytokines is upregulated in HCC patients. As a key cytokine, IL-6 can promote tumor cell proliferation, invasion, and metastasis while inhibiting apoptosis through activation of the JAK-STAT3 signaling pathway [17,18]. Moreover, IL-6 modulates the function of immune cells in the TME, promoting the polarization of tumor-associated macrophages toward the M2 phenotype, which exerts pro-tumorigenic effects and suppresses anti-tumor immunity, thereby facilitating tumor growth and metastasis [19,20]. Notably, Myojin *et al.* [21] reported that IL-6 levels serve as a novel prognostic biomarker for advanced HCC patients receiving combination immunotherapy. In addition, the IKK/NF-κB pathway regulates the expression of anti-apoptotic proteins such as cyclin D1. Cyclin D1 is a key regulator of the cell cycle, and its overexpression accelerates the transition from G1 to S phase, enhancing tumor cell proliferation [22]. Furthermore, cyclin D1 exhibits anti-apoptotic properties, reducing tumor cell sensitivity to chemotherapy and radiotherapy, thereby contributing to tumor progression and drug resistance [23].

The expression levels of IKK and NF-κB p65 can serve as independent prognostic markers, aiding in more accurate clinical assessment of patient prognosis and development of personalized treatment plans. For patients manifesting high expression of proteins associated with the IKK/NF-κB pathway, combining conventional treatments with IKK inhibitors or NF-κB inhibitors may help block aberrant pathway activation and inhibit tumor progression. Previous studies have shown that NF-κB inhibitors can modulate the function of immune cells within the tumor microenvironment, thereby boosting the body's anti-tumor immune response [24]. Additionally, IKK inhibitors can effectively suppress tumor cell proliferation, invasion, and metastasis, while enhancing chemosensitivity [25].

The current study has a few limitations. First, this single-center retrospective study has a relatively small sam-

ple size and is prone to selection bias, necessitating further validation through multicenter, prospective studies with larger cohorts. Second, although this study has explored the association between the IKK/NF-κB pathway and patient prognosis at the clinical level, the molecular mechanisms underlying this pathway in HCC development and progression remain unclarified and thus require further fundamental mechanistic investigations. For instance, future research should clarify the crosstalk between the IKK/NF-κB pathway and other signaling pathways, as well as its role in tumor stem cell regulation and the development of drug resistance in HCC.

Conclusion

Activation of the IKK/NF-κB pathway may lead to poor prognosis in HCC patients by upregulating the expression of downstream target proteins such as pro-inflammatory cytokines and anti-apoptotic proteins. The expression levels of proteins associated with this pathway are associated with mortality risk in HCC patients and can serve as independent prognostic biomarkers. Therefore, targeting the IKK/NF-κB pathway may offer a novel strategy for precision therapy in HCC.

Availability of Data and Materials

The data supporting the findings of this study are included within the article. During the study period, data may be made available from the corresponding author upon reasonable request.

Author Contributions

XHC and LLZ designed the research study and wrote the first draft. XHC and SL performed the research. RJZ and LLZ analyzed the data. All authors contributed to the critical revision of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study has been approved by The People's Hospital of Pingyang County Ethics Review Committee (Approval No. LW-2025-043) and strictly adheres to the Declaration of Helsinki. All enrolled patients have signed informed consent forms to use their routine clinical test data and residual biological samples for the study.

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Conflict of Interest

The authors declare no conflict of interest.

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