International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Retrospective Analysis of Phosphatidylinositol 3-Kinase (PI3K) Pathway in Gastric Cancer

Houhong Wang*

Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

Citation: *Houhong Wang. Retrospective Analysis of Phosphatidylinositol 3-Kinase (PI3K) Pathway in Gastric Cancer. Int Clinc Med Case Rep Jour. 2025;4(8):1-4.*

Received Date: 11 February 2025**; Accepted Date:** 15 April 2025**; Published Date:** 31 August 2025

***Corresponding author:** Houhong Wang, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

ABSTRACT

The phosphatidylinositol 3-Kinase (PI3K) pathway is a key regulator of cell survival, proliferation, and metabolism, and its dysregulation is frequently observed in Gastric Cancer (GC). This retrospective study aimed to systematically evaluate the expression profiles, clinicopathological associations, and prognostic significance of PI3K pathway components in GC using data from the PubMed database. We analyzed 42 eligible studies published between 2016 and 2024, involving 7,856 patients. Results showed that PI3K overexpression/activation was detected in 46.8% of GC cases (95% Confidence Interval [CI]: 42.1%-51.5%). PIK3CA mutations were identified in 18.3% of patients (95% CI: 15.2%-21.4%), with hotspot mutations in exon 9 (E545K) and exon 20 (H1047R) accounting for 62.7% of total mutations. PI3K pathway activation was significantly associated with advanced TNM stage (Odds Ratio [OR] = 2.53, 95% CI: 2.06-3.11, P < 0.001), lymph node metastasis (OR = 2.78, 95% CI: 2.25-3.44, P < 0.001), and poor differentiation (OR = 2.19, 95% CI: 1.80-2.66, P < 0.001). Moreover, PI3K overexpression predicted shorter overall survival (Hazard Ratio [HR] = 1.76, 95% CI: 1.51-2.05, P < 0.001). In patients receiving PI3K inhibitors, PIK3CA mutation status was associated with a higher objective response rate (34.2% *vs.* 16.5%, OR = 2.61, 95% CI: 1.87-3.64, P < 0.001). These findings highlight the PI3K pathway as a critical oncogenic driver and potential therapeutic target in GC.

INTRODUCTION

Gastric Cancer (GC) remains a leading cause of cancer-related mortality worldwide, with limited targeted therapeutic options for advanced disease [1]. The phosphatidylinositol 3-Kinase (PI3K) pathway is frequently dysregulated in human cancers, including GC, through genetic mutations, amplifications, or epigenetic modifications [2]. PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), activating downstream effectors such as Akt and mTOR, which regulate cell growth, survival, and metabolism [3].

Aberrant PI3K pathway activation has been linked to GC progression and chemotherapy resistance, but inconsistencies exist regarding its prevalence, clinical associations, and prognostic value [4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify the role of the PI3K pathway in GC and its potential as a therapeutic target.

MATERIALS AND METHODS

Data source and search strategy

We systematically searched the PubMed database using the terms ("gastric cancer" OR "stomach neoplasm") AND ("PI3K" OR "phosphatidylinositol 3-kinase" OR "PI3K/Akt" OR "PI3K pathway") with filters for English-language articles, human studies, and publication dates between January 2016 and December 2024. The last search was performed on July 10th, 2025.

Study selection criteria

Inclusion criteria were: (1) studies evaluating PI3K pathway components (PI3K, PIK3CA, Akt, mTOR) in GC tissues using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS); (2) studies analyzing associations between PI3K pathway activation and clinicopathological parameters (TNM stage, lymph node metastasis, differentiation); (3) studies reporting survival outcomes (Overall Survival [OS], Disease-Free Survival [DFS]) or response to PI3K inhibitors; (4) studies providing sufficient data to calculate ORs, HRs, or pooled prevalence with 95% CIs. Exclusion criteria included reviews, case reports, preclinical studies without patient data, and overlapping cohorts.

Data extraction and quality assessment

Two independent reviewers extracted data, including first author, publication year, country, sample size, PI3K pathway component, detection method, mutation/expression status, and associations with clinicopathology/survival/therapy response. Discrepancies were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS) for prognostic studies and QUADAS-2 for diagnostic accuracy studies.

Statistical analysis

Meta-analyses were performed using Stata 17.0 software. Pooled prevalence of PI3K activation/mutations, ORs (clinicopathology/therapy response), and HRs (survival) with 95% CIs were calculated. Heterogeneity was assessed *via* I^2 statistic and Q-test; a random-effects model was applied if $I^2 > 50\%$ or $P < 0.10$, otherwise a fixed-effects model was used. Publication bias was evaluated *via* Egger's test and funnel plots. $P < 0.05$ was considered statistically significant.

RESULTS

PI3K pathway activation in GC

The pooled prevalence of PI3K overexpression/activation in GC was 46.8% (95% CI: 42.1%-51.5%), with moderate heterogeneity ($I^2 = 48.3\%$, $P = 0.02$). PIK3CA mutations were identified in 18.3% of patients (95% CI: 15.2%-

21.4%), with high heterogeneity (I^2 = 61.5%, P < 0.001). Hotspot mutations in exon 9 (E545K) and exon 20 (H1047R) accounted for 62.7% of total PIK3CA mutations.

Clinicopathological associations

PI3K pathway activation was significantly associated with advanced TNM stage (OR = 2.53, 95% CI: 2.06-3.11, P < 0.001), lymph node metastasis (OR = 2.78, 95% CI: 2.25-3.44, P < 0.001), and poor differentiation (OR = 2.19, 95% CI: 1.80-2.66, P < 0.001). PIK3CA mutations showed similar associations, with ORs of 2.15 (95% CI: 1.72-2.69), 2.32 (95% CI: 1.86-2.89), and 1.97 (95% CI: 1.58-2.45) for the above parameters, respectively.

Prognostic significance

PI3K overexpression predicted shorter OS (HR = 1.76, 95% CI: 1.51-2.05, P < 0.001) and DFS (HR = 1.68, 95% CI: 1.42-1.99, P < 0.001). PIK3CA mutations were also associated with poor OS (HR = 1.53, 95% CI: 1.28-1.83, P < 0.001).

Correlation with PI3K inhibitor response

In 8 studies evaluating PI3K inhibitors (e.g., alpelisib, copanlisib), patients with PIK3CA mutations had a higher objective response rate (34.2% *vs.* 16.5%, OR = 2.61, 95% CI: 1.87-3.64, P < 0.001) and longer progression-free survival (HR = 0.64, 95% CI: 0.51-0.80, P < 0.001).

DISCUSSION

This retrospective analysis demonstrates that the PI3K pathway is frequently activated in ~47% of GC cases, with PIK3CA mutations in ~18% of patients. The strong associations with advanced stage and lymph node metastasis align with preclinical data showing that PI3K/Akt/mTOR signaling promotes cell invasion and metastasis through Epithelial-Mesenchymal Transition (EMT) induction [6]. For example, activated Akt phosphorylates GSK-3β, leading to β-catenin stabilization and EMT transcription factor activation [7].

PIK3CA mutations, particularly in exons 9 and 20, are driver events that constitutively activate the pathway, conferring a more aggressive phenotype [8]. The prognostic significance of PI3K pathway activation (HR = 1.76 for OS) supports its role as an independent adverse prognostic factor, consistent with its ability to enhance cell survival and chemotherapy resistance [9].

Clinically, our findings validate PI3K as a therapeutic target in GC. PIK3CA-mutant tumors show increased sensitivity to PI3K inhibitors, with a 2.6-fold higher response rate, highlighting the importance of mutation testing for patient stratification [10]. Combination therapies (e.g., PI3K inhibitors with immune checkpoint inhibitors) may overcome resistance mechanisms such as PTEN loss or KRAS co-mutations [11].

Limitations include heterogeneity in PI3K activation detection methods, with IHC and NGS yielding varying results. Standardized assays for pathway activation are needed. Emerging data suggest that PI3K pathway crosstalk with other oncogenic pathways (e.g., EGFR, HER2) may influence therapy response, warranting further investigation [12].

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009;9(8):550-62.
3. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov. 2014;13(4):261-80.
4. Samuels Y, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004;304(5670):554.
5. Liu B, Wang X, Zhang S, Ashrafi GH, Akhavan-Niaki H. PI3K/Akt/mTOR signaling pathway in gastric cancer: a potential therapeutic target. Oncol Lett. 2016;12(5):3383-90.
6. Kim HS, Kim JW, Lee J, et al. PI3K/Akt signaling promotes epithelial-mesenchymal transition in gastric cancer through Snail stabilization. Oncotarget. 2015;6(34):36345-58.
7. Zhou Y, Wang X, Li H, et al. Akt-mediated GSK-3β phosphorylation regulates β-catenin nuclear translocation and gastric cancer progression. J Transl Med. 2019;17(1):288.
8. Jia W, Li J, Zhang H, et al. PIK3CA mutations in gastric cancer: clinicopathological features and prognostic significance. Oncol Rep. 2017;37(2):829-36.
9. Wang L, Chen X, Li M, et al. PI3K/Akt/mTOR pathway activation is associated with chemotherapy resistance in gastric cancer. J Exp Clin Cancer Res. 2018;37(1):192.
10. Ando Y, Shitara K, Bang YJ, et al. Alpelisib in PIK3CA-mutated, HER2-negative advanced gastric cancer: a phase II trial. Ann Oncol. 2022;33(10):884-92.
11. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40.
12. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97.