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Research Article

Retrospective Analysis of AKT in Gastric Cancer Expression Profiling, Clinical Relevance, and Therapeutic Potential

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ABSTRACT

AKT, a serine/threonine kinase, is a central mediator of the PI3K/AKT/mTOR pathway, regulating cell survival, proliferation, and metabolism. Dysregulation of AKT is frequently observed in gastric cancer (GC) and contributes to tumor progression. This retrospective study systematically evaluated the expression patterns, clinical associations, and prognostic significance of AKT in GC using data from the PubMed database. We analyzed 43 eligible studies published between 2017 and 2024, involving 8,126 patients. Results showed that phosphorylated AKT (p-AKT), a marker of activation, was overexpressed in 59.4% of GC cases (95% confidence interval [CI]: 54.7%-64.1%). p-AKT overexpression was significantly associated with advanced TNM stage (odds ratio [OR] = 3.27, 95% CI: 2.70-3.96, P < 0.001), lymph node metastasis (OR = 3.62, 95% CI: 2.96-4.43, P < 0.001), distant metastasis (OR = 2.98, 95% CI: 2.39-3.71, P < 0.001), and poor differentiation (OR = 2.78, 95% CI: 2.29-3.37, P < 0.001). Moreover, p-AKT overexpression predicted shorter overall survival (hazard ratio [HR] = 2.11, 95% CI: 1.82-2.44, P < 0.001) and disease-free survival (HR = 1.98, 95% CI: 1.69-2.32, P < 0.001). In patients receiving AKT inhibitors, high p-AKT expression was associated with a higher objective response rate (40.2% vs. 16.3%, OR = 3.75, 95% CI: 2.68-5.23, P < 0.001). These findings confirm AKT as a critical oncogenic driver and potential therapeutic target in GC.

Keywords: Dysregulation; Tumor progression; Phosphorylated AKT; Lymph node metastasis

Introduction

Gastric cancer (GC) is a leading cause of cancer-related mortality worldwide, with limited targeted therapeutic options for advanced disease[1]. AKT, also known as protein kinase B (PKB), is a key downstream effector of the PI3K pathway, playing a pivotal role in cell survival, proliferation, and metabolism[2]. Aberrant AKT activation, primarily through phosphorylation at Ser473 and Thr308, is frequently observed in GC and contributes to tumor initiation, progression, and resistance to therapy[3].

Despite extensive research on AKT in GC, inconsistencies exist regarding its expression patterns, clinical associations, and prognostic value[4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify the role of AKT in GC and validate its utility as a biomarker and 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 («AKT» OR «protein kinase B» OR «phospho-AKT») with filters for English-language articles, human studies, and publication dates between January 2017 and December 2024. The last search was performed on September 10, 2025.

Study selection criteria

Inclusion criteria were: (1) studies evaluating AKT expression/activation (total AKT or p-AKT) in GC tissues using immunohistochemistry (IHC) or Western blot; (2) studies analyzing associations between AKT status and clinicopathological parameters (TNM stage, metastasis, differentiation); (3) studies reporting survival outcomes (overall survival [OS], disease-free survival [DFS]); (4) studies providing sufficient data to calculate ORs, HRs, or pooled positivity rates 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, AKT isoform (AKT1/2/3), detection method, p-AKT phosphorylation site, positivity rate, and associations with clinicopathology/survival/therapy response. Discrepancies were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS), with scores ≥ 6 indicating high quality.

Statistical analysis

Meta-analyses were performed using Stata 17.0 software. Pooled positivity rates with 95% CIs were calculated for each AKT isoform and p-AKT. Pooled ORs (clinicopathological associations) and HRs (survival) with 95% CIs were computed. Heterogeneity was assessed via I^2 statistic and Q-test; a random-effects model was used for $I^2 > 50\%$. Publication bias was evaluated via Egger's test and funnel plots. $P < 0.05$ was considered significant.

Results

AKT expression patterns in GC

p-AKT (Ser473) overexpression was detected in 59.4% (95% CI: 54.7%-64.1%) of cases, with moderate heterogeneity ($I^2 = 51.2\%$, $P = 0.01$). AKT1 was overexpressed in 43.2% (95% CI: 38.3%-48.1%), while AKT2 and AKT3 showed lower prevalence (34.6% and 30.1%, respectively).

Clinicopathological associations

p-AKT overexpression strongly correlated with advanced TNM stage (OR = 3.27), lymph node metastasis (OR = 3.62), distant metastasis (OR = 2.98), and poor differentiation (OR = 2.78) (all $P < 0.001$). AKT1 overexpression showed similar associations (ORs 2.56-3.12).

Prognostic significance

p-AKT overexpression predicted shorter OS (HR = 2.11, 95% CI: 1.82-2.44, $P < 0.001$) and DFS (HR = 1.98, 95% CI: 1.69-2.32, $P < 0.001$). AKT1 overexpression was also associated with poor OS (HR = 1.85, 95% CI: 1.57-2.18, $P < 0.001$).

Correlation with AKT inhibitor response

In 9 studies evaluating AKT inhibitors (e.g., ipatasertib, capivasertib), patients with high p-AKT expression had a higher objective response rate (40.2% vs. 16.3%, OR = 3.75, 95% CI: 2.68-5.23, $P < 0.001$) and longer progression-free survival (HR = 0.56, 95% CI: 0.45-0.69, $P < 0.001$).

Discussion

This analysis confirms frequent AKT activation in ~59% of GC cases, with p-AKT (Ser473) being the most prevalent marker. The strong associations with advanced stage and metastasis align with preclinical data showing that activated AKT promotes epithelial-mesenchymal transition (EMT) via Snail and Twist upregulation[6], and angiogenesis through VEGF induction[7].

AKT1, the most commonly overexpressed isoform, drives proliferation via mTORC1 activation[8], while p-AKT (Ser473) is a robust prognostic marker (HR = 2.11) due to its role in chemotherapy resistance through MDR1 and Bcl-2 upregulation[9]. The 3.75-fold higher response rate to AKT inhibitors in p-AKT-positive patients supports its utility as a predictive biomarker[10].

Clinically, AKT inhibitors (e.g., capivasertib) are being evaluated in combination with chemotherapy or immune checkpoint inhibitors[11]. Standardized p-AKT (Ser473) testing could improve patient stratification. Limitations include variable IHC protocols; harmonized assays are needed for clinical implementation[12].

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