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Research Article

Retrospective Analysis of Epidermal Growth Factor Receptor (EGFR) in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) remains a major global health challenge with limited targeted therapy options. The epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor, plays a critical role in cell proliferation, differentiation, and survival, making it a potential biomarker and therapeutic target in GC. This retrospective study systematically evaluated the expression profile, clinical associations, and prognostic significance of EGFR in GC using data from the PubMed database. We analyzed 38 eligible studies published between 2015 and 2024, involving 7,542 patients. Our results showed that EGFR overexpression was detected in 34.2% of GC cases (95% confidence interval [CI]: 30.1%-38.3%). EGFR positivity was significantly associated with advanced TNM stage (odds ratio [OR] = 2.67, 95% CI: 2.15-3.31, P < 0.001), lymph node metastasis (OR = 2.89, 95% CI: 2.32-3.61, P < 0.001), vascular invasion (OR = 2.45, 95% CI: 1.92-3.13, P < 0.001), and poor differentiation (OR = 2.23, 95% CI: 1.81-2.75, P < 0.001). Moreover, EGFR overexpression predicted shorter overall survival (hazard ratio [HR] = 1.76, 95% CI: 1.53-2.02, P < 0.001) and disease-free survival (HR = 1.68, 95% CI: 1.42-1.99, P < 0.001). In patients receiving anti-EGFR therapy, EGFR positivity was associated with a higher objective response rate (31.5% vs. 12.3%, OR = 3.21, 95% CI: 2.18-4.73, P < 0.001). These findings confirm EGFR as a valuable prognostic biomarker and support its role as a therapeutic target in GC.

Keywords: Epidermal growth factor receptor; Gastric cancer; Transmembrane tyrosine kinase receptor

Introduction

Gastric cancer (GC) is characterized by aggressive biological behavior and poor prognosis, with limited effective treatment options for advanced disease[1]. The epidermal growth factor receptor (EGFR) signaling pathway is frequently dysregulated in GC, driving tumorigenesis through activation of downstream pathways such as RAS/RAF/MEK/ERK and PI3K/Akt/mTOR[2]. EGFR overexpression or amplification leads to uncontrolled cell proliferation, resistance to apoptosis, and enhanced invasion and metastasis[3].

Despite extensive research on EGFR in GC, inconsistencies exist regarding its prevalence, clinical associations, and prognostic value[4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify the expression pattern of EGFR in GC, its correlations with clinicopathological features, and its utility as a predictive biomarker for anti-EGFR therapy.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using

the terms («gastric cancer» OR «stomach neoplasm») AND («EGFR» OR «epidermal growth factor receptor») with filters for English-language articles, human studies, and publication dates between January 2015 and December 2024. The last search was performed on March 10, 2025.

Study selection criteria

Inclusion criteria were: (1) studies evaluating EGFR expression in GC tissues using immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR); (2) studies analyzing associations between EGFR expression and clinicopathological parameters (TNM stage, lymph node metastasis, differentiation, vascular invasion); (3) studies reporting survival outcomes (overall survival [OS], disease-free survival [DFS]) or response to anti-EGFR therapy; (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, EGFR detection method, cutoff value for positivity, 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. The pooled prevalence of EGFR overexpression with 95% CI was calculated. Pooled ORs (clinicopathology/therapy response) and HRs (survival) with 95% CIs were computed. 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

EGFR Expression Prevalence in GC

The pooled prevalence of EGFR overexpression in GC was 34.2% (95% CI: 30.1%-38.3%), with moderate heterogeneity ($I^2 = 47.6\%$, $P = 0.02$). Subgroup analysis showed higher prevalence in intestinal-type GC (38.5%, 95% CI: 33.2%-43.8%) compared to diffuse-type GC (27.3%, 95% CI: 22.1%-32.5%, $P = 0.01$).

Associations with clinicopathological parameters

EGFR positivity was significantly associated with advanced TNM stage (OR = 2.67, 95% CI: 2.15-3.31, $P < 0.001$), lymph node metastasis (OR = 2.89, 95% CI: 2.32-3.61, $P < 0.001$), vascular invasion (OR = 2.45, 95% CI: 1.92-3.13, $P < 0.001$), and poor differentiation (OR = 2.23, 95% CI: 1.81-2.75, $P < 0.001$). No significant associations were found with age or gender ($P > 0.05$).

Prognostic significance

EGFR overexpression predicted shorter OS (HR = 1.76, 95% CI: 1.53-2.02, $P < 0.001$) and DFS (HR = 1.68, 95% CI: 1.42-1.99, $P < 0.001$) in GC patients (Figure 3). Subgroup analyses showed consistent results across detection methods (IHC: HR = 1.72, 95% CI: 1.48-1.99; FISH: HR = 1.91, 95% CI: 1.45-2.52).

Correlation with Anti-EGFR therapy response

In studies evaluating anti-EGFR therapy (cetuximab or panitumumab), EGFR positivity was associated with a higher objective response rate (31.5% vs. 12.3%, OR = 3.21, 95% CI: 2.18-4.73, $P < 0.001$) and longer progression-free survival (HR = 0.62, 95% CI: 0.48-0.80, $P < 0.001$).

Discussion

This retrospective analysis demonstrates that EGFR is overexpressed in approximately one-third of GC cases and is associated with aggressive clinicopathological features and poor prognosis. EGFR activation promotes GC progression through multiple mechanisms: ligand binding induces receptor dimerization and autophosphorylation, activating downstream pathways such as RAS/ERK to enhance cell proliferation[6] and PI3K/Akt to inhibit apoptosis[7]. Additionally, EGFR-mediated epithelial-mesenchymal transition (EMT) contributes to lymph node metastasis, consistent with our finding of a strong association between EGFR and lymph node involvement[8].

The higher prevalence of EGFR overexpression in intestinal-type GC aligns with previous reports that intestinal-type tumours have more frequent activation of growth factor signalling pathways compared to diffuse-type GC [9]. This subtype-specific expression may help guide therapeutic stratification, as intestinal-type GC patients with EGFR overexpression may derive greater benefit from anti-EGFR therapy.

Clinically, our findings support EGFR as a prognostic biomarker. While anti-EGFR monotherapy has shown limited efficacy in unselected GC patients[10], our analysis indicates that EGFR-positive patients have a higher response rate, suggesting that EGFR expression can help identify candidates for such therapy. Combining anti-EGFR agents with chemotherapy or immune checkpoint inhibitors may further enhance efficacy by overcoming resistance mechanisms, such as KRAS mutations or PTEN loss[11].

Limitations include heterogeneity in EGFR detection methods and cutoff values for positivity. Standardized IHC protocols (e.g., using monoclonal antibodies like 31G7) and uniform cutoff criteria are needed for consistent clinical application[12]. Further studies should explore the correlation between EGFR mutations/amplifications and therapy response, as FISH-detected amplification may be a better predictor than IHC expression[13].

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