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Research Article

Retrospective Analysis of Claudins in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) is characterized by disrupted epithelial integrity, and claudins, key components of tight junctions, play a critical role in maintaining epithelial barrier function. Dysregulation of claudins contributes to tumor progression, metastasis, and chemotherapy resistance. This retrospective study systematically evaluated the expression patterns, clinical correlations, and prognostic significance of claudins in GC using data from the PubMed database. We analyzed 37 eligible studies published between 2015 and 2024, involving 6,842 patients. Our results showed that claudin-1, -3, -4, and -7 were frequently overexpressed in GC (pooled positivity rates: 58.7%, 42.3%, 51.6%, and 47.9%, respectively), while claudin-5 and -18 were downregulated (23.5% and 31.2%). Overexpression of claudin-1 (odds ratio [OR] = 2.89, 95% confidence interval [CI]: 2.31-3.62, P < 0.001), -3 (OR = 2.15, 95% CI: 1.76-2.62, P < 0.001), and -4 (OR = 2.47, 95% CI: 1.98-3.08, P < 0.001) was significantly associated with lymph node metastasis. Reduced claudin-18 expression predicted poor overall survival (hazard ratio [HR] = 1.87, 95% CI: 1.56-2.24, P < 0.001), while high claudin-7 was associated with shorter overall survival (HR = 1.63, 95% CI: 1.35-1.97, P < 0.001). These findings highlight claudins as potential biomarkers and therapeutic targets in GC.

Keywords: Disrupted epithelial integrity; Gastric cancer; Claudin-18

Introduction

Gastric cancer (GC) remains a leading cause of cancer-related mortality, with invasion and metastasis being major determinants of poor prognosis[1]. Tight junctions (TJs) are essential for epithelial polarity and barrier function, and their disruption is a hallmark of epithelial-mesenchymal transition (EMT) and tumor progression[2]. Claudins, a family of transmembrane proteins (27 members identified to date), are core components of TJs, regulating paracellular permeability and cell-cell adhesion[3].

Dysregulated claudin expression has been reported in various cancers, including GC, but inconsistencies exist regarding specific isoforms, their clinical associations, and prognostic value[4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify the expression patterns of claudins in GC, their correlations with clinicopathological features, and their utility as prognostic biomarkers.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using the terms («gastric cancer» OR «stomach neoplasm») AND («claudin» OR «claudins») with filters for English-language

articles, human studies, and publication dates between January 2015 and December 2024. The last search was performed on May 10, 2025.

Study selection criteria

Inclusion criteria were: (1) studies evaluating claudin expression in GC tissues using immunohistochemistry (IHC); (2) studies analyzing associations between claudin expression and clinicopathological parameters (TNM stage, lymph node 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. Exclusions: 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, claudin isoform, detection method, positivity rate, and associations with clinicopathology/survival. 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 claudin isoform. 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

Claudin expression patterns in GC

Claudin-1 (58.7%, 95% CI: 53.2%-64.2%), -3 (42.3%, 95% CI: 36.8%-47.8%), -4 (51.6%, 95% CI: 46.1%-57.1%), and -7 (47.9%, 95% CI: 42.0%-53.8%) were frequently overexpressed in GC, while claudin-5 (23.5%, 95% CI: 18.6%-28.4%) and -18 (31.2%, 95% CI: 25.9%-36.5%) were downregulated.

Associations with clinicopathological parameters

Overexpression of claudin-1 (OR = 2.89, 95% CI: 2.31-3.62, $P < 0.001$), -3 (OR = 2.15, 95% CI: 1.76-2.62, $P < 0.001$), and -4 (OR = 2.47, 95% CI: 1.98-3.08, $P < 0.001$) was strongly associated with lymph node metastasis. Claudin-1 and -4 were also associated with advanced TNM stage (OR = 2.36, 95% CI: 1.89-2.95 and OR = 2.01, 95% CI: 1.62-2.49, respectively). Reduced claudin-18 was associated with poor differentiation (OR = 1.92, 95% CI: 1.51-2.44, $P < 0.001$).

Prognostic significance

CLDN18 downregulation predicted shorter OS (HR = 1.82, 95% CI: 1.53-2.17, $P < 0.001$) (Figure 3A). High CLDN7 correlated with shorter OS (HR = 1.59, 95% CI: 1.33-1.90, $P < 0.001$).

Discussion

This analysis identifies distinct expression patterns of claudins in GC, with claudin-1, -3, -4, and -7 frequently upregulated and claudin-5 and -18 downregulated. Overexpression of claudin-1, -3, and -4 correlates with lymph node metastasis, consistent with their role in promoting EMT and invasion[6]. Claudin-4, for example, interacts with TGF-β signaling to induce EMT, enhancing metastatic potential[7].

Claudin-18, a stomach-specific isoform, maintains gastric epithelial integrity; its downregulation disrupts TJs, facilitating tumor dissemination[8]. The strong prognostic value of claudin-18 (HR = 1.87) aligns with preclinical data showing that claudin-18 loss accelerates GC progression[9]. Conversely, claudin-7 overexpression predicts poor prognosis, possibly by stabilizing β-catenin to activate Wnt signalling[10].

Clinically, claudins offer potential biomarkers and therapeutic targets. Claudin-18.2-targeted antibodies (e.g., zolbetuximab) have shown efficacy in GC[11], validating its clinical relevance. Claudin-4 inhibitors may reverse chemotherapy resistance[12], while claudin-1 targeting could suppress metastasis[13].

Limitations include heterogeneity in IHC cutoffs and claudin isoform selection. Standardized detection protocols are needed. Future studies should explore claudin interactomes to identify combinatorial therapeutic strategies.

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