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Research Article

Retrospective Analysis of Circular RNAs (CircRNAs) in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) is a highly lethal malignancy with limited early diagnostic biomarkers and poor prognosis. Circular RNAs (circRNAs), a class of covalently closed non-coding RNAs, have emerged as key regulators of GC progression and potential biomarkers due to their stability and tissue-specific expression. This retrospective study aimed to systematically evaluate the expression patterns, clinicopathological associations, and diagnostic/prognostic significance of circRNAs in GC using data from the PubMed database. We analyzed 45 eligible studies published between 2015 and 2024, involving 7,326 patients. Our results showed that 28 circRNAs were significantly upregulated in GC tissues (pooled standardized mean difference [SMD] = 2.14, 95% confidence interval [CI]: 1.78-2.50, P < 0.001), while 17 circRNAs were downregulated (SMD = -1.86, 95% CI: -2.23 to -1.49, P < 0.001). Upregulated circRNAs were associated with advanced TNM stage (odds ratio [OR] = 3.21, 95% CI: 2.53-4.07, P < 0.001), lymph node metastasis (OR = 3.45, 95% CI: 2.69-4.42, P < 0.001), and poor differentiation (OR = 2.87, 95% CI: 2.22-3.71, P < 0.001). Moreover, elevated levels of oncogenic circRNAs predicted shorter overall survival (hazard ratio [HR] = 2.03, 95% CI: 1.75-2.35, P < 0.001). The combined diagnostic value of circRNA panels showed high accuracy (area under the curve [AUC] = 0.86, 95% CI: 0.82-0.89). These findings confirm that circRNAs are valuable diagnostic and prognostic biomarkers in GC, with potential as therapeutic targets.

Keywords: Gastric cancer; Highly lethal malignancy; Prognostic biomarkers

Introduction

Gastric cancer (GC) remains a leading cause of cancer-related mortality globally, with over 769,000 deaths in 2020[1]. Late diagnosis and limited therapeutic options contribute to its poor prognosis, highlighting the need for novel biomarkers and therapeutic targets[2]. Circular RNAs (circRNAs), generated by back-splicing of pre-mRNA, are characterized by their closed-loop structure, resistance to RNases, and stable expression in tissues and body fluids[3]. They exert biological functions by sponging microRNAs (miRNAs), regulating gene expression, and interacting with proteins, thereby influencing GC cell proliferation, invasion, and metastasis[4].

Numerous studies have identified dysregulated circRNAs in GC, but inconsistencies exist regarding their specific roles and clinical significance[5,6]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify the expression patterns of circRNAs in GC, their associations with clinicopathological features, and their diagnostic/prognostic value.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using the terms («gastric cancer» OR «stomach neoplasm») AND («circRNA» OR «circular RNA») with filters for English-language articles, human studies, and publication dates between January 2015 and December 2024. The last search was performed on January 20, 2025.

Study selection criteria

Inclusion criteria were: (1) studies comparing circRNA expression between GC tissues and adjacent normal mucosa; (2) studies analyzing associations between circRNA expression and clinicopathological parameters (TNM stage, lymph node metastasis, differentiation); (3) studies reporting diagnostic accuracy (sensitivity, specificity, AUC) or survival outcomes (overall survival [OS], disease-free survival [DFS]) based on circRNA levels; (4) studies providing sufficient data to calculate ORs, HRs, SMDs, or AUCs 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, circRNA name, detection method (quantitative real-time PCR [qRT-PCR], RNA sequencing), expression trend (up/downregulated), and associations with clinicopathology/diagnosis/survival. Discrepancies were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS) for prognostic studies and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic studies.

Statistical analysis

Meta-analyses were performed using Stata 17.0 software. Pooled SMD with 95% CIs was calculated for circRNA expression comparisons. Pooled ORs (clinicopathology), HRs (survival), and AUCs (diagnosis) 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

Study selection and characteristics

Of 628 retrieved articles, 45 studies (n = 7,326 patients) were included after screening (Figure 1). The characteristics of included studies are summarized in Table 1. Most studies were conducted in Asia (38/45), with sample sizes ranging from 52 to 638. A total of 45 unique circRNAs were analyzed, with 28 upregulated and 17 downregulated in GC. Detection methods included qRT-PCR (40/45) and RNA sequencing (5/45). The median NOS score was 7 (range 6-9) for prognostic studies, and QUADAS-2 assessment indicated low risk of bias for most diagnostic studies.

CircRNA expression in GC tissues

Upregulated circRNAs showed significantly higher expression in GC tissues compared to normal mucosa (SMD = 2.14, 95% CI: 1.78-2.50, $P < 0.001$), with high heterogeneity ($I^2 = 78.3\%$, $P < 0.001$) (Figure 2A). Downregulated circRNAs showed significantly lower expression (SMD = -1.86, 95% CI: -2.23 to -1.49, $P < 0.001$), with high heterogeneity ($I^2 = 75.6\%$, $P < 0.001$).

Associations with clinicopathological parameters

Upregulated circRNAs were strongly associated with advanced TNM stage (OR = 3.21, 95% CI: 2.53-4.07, $P < 0.001$), lymph node metastasis (OR = 3.45, 95% CI: 2.69-4.42, $P < 0.001$), and poor differentiation (OR = 2.87, 95% CI: 2.22-3.71, $P < 0.001$). Downregulated circRNAs showed inverse associations with these parameters ($P < 0.05$).

Diagnostic value

Individual circRNAs showed moderate diagnostic accuracy (AUC = 0.79, 95% CI: 0.75-0.83), while circRNA panels (≥2 circRNAs) exhibited higher accuracy (AUC = 0.86, 95% CI: 0.82-0.89). The most promising panel included hsa_circ_0000190, hsa_circ_0001649, and hsa_circ_002059 (AUC = 0.91, 95% CI: 0.88-0.94).

Prognostic significance

Elevated levels of upregulated circRNAs predicted shorter OS (HR = 2.03, 95% CI: 1.75-2.35, $P < 0.001$) and DFS (HR = 1.98, 95% CI: 1.67-2.35, $P < 0.001$). Downregulated circRNAs were associated with longer OS (HR = 0.52, 95% CI: 0.43-0.63, $P < 0.001$).

Publication bias

Funnel plots and Egger's test revealed no significant publication bias for OS ($P = 0.21$) or diagnostic AUC ($P = 0.26$), supporting the robustness of the findings.

Discussion

This retrospective analysis identifies 45 dysregulated circRNAs in GC, with most upregulated circRNAs acting as oncogenes and associated with aggressive disease and poor prognosis. CircRNAs exert their functions primarily through the "sponge effect," sequestering miRNAs to derepress their target genes. For example, hsa_circ_0000190 sponges miR-34c-5p to upregulate Bcl-2, promoting GC cell survival[7], while hsa_circ_002059 targets miR-182-5p to activate the PI3K/Akt pathway, enhancing invasion[8].

The strong association between upregulated circRNAs and lymph node metastasis aligns with their role in epithelial-mesenchymal transition (EMT), as several circRNAs (e.g., hsa_circ_001680) regulate EMT transcription factors such as Snail and Twist[9]. The higher diagnostic accuracy of circRNA panels compared to individual circRNAs highlights the importance of combinatorial biomarkers, as GC is a heterogeneous disease with multiple dysregulated pathways.

Clinically, our findings support circRNAs as promising diagnostic and prognostic tools. Their stability in plasma/serum makes them ideal non-invasive biomarkers for early GC detection[10]. Targeting oncogenic circRNAs with siRNAs or antisense oligonucleotides has shown preclinical efficacy in reducing GC tumor growth[11], warranting further clinical development.

Limitations include heterogeneity in circRNA detection

methods and patient populations. Standardized protocols for circRNA quantification and validation in large multicenter cohorts are needed. Further studies should explore the mechanisms of circRNA-miRNA-mRNA networks to identify therapeutic vulnerabilities.

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