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Research Article

Retrospective Analysis of CD8+ T Cells in Gastric Cancer Prognostic Significance and Clinical Implications

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ABSTRACT

Gastric cancer (GC) is a highly aggressive malignancy with limited therapeutic options, emphasizing the need for reliable prognostic biomarkers and novel therapeutic targets. CD8+ T cells, key mediators of adaptive anti - tumor immunity, have emerged as critical players in the tumor microenvironment (TME) of GC. This retrospective study aimed to systematically evaluate the clinical significance of CD8+ T cell infiltration in GC using data from the PubMed database. We analyzed 38 eligible studies published between 2015 and 2024, focusing on the association between CD8+ T cell density, clinicopathological features and patient survival outcomes. Our results showed that high CD8+ T cell infiltration in GC tissues was significantly associated with early TNM stage (odds ratio [OR] = 0.42, 95% confidence interval [CI]: 0.32 - 0.55, P < 0.001), absence of lymph node metastasis (OR = 0.38, 95% CI: 0.29 - 0.50, P < 0.001) and improved overall survival (hazard ratio [HR] = 0.63, 95% CI: 0.55 - 0.72, P < 0.001). Subgroup analyses revealed that intraepithelial CD8+ T cells had a more pronounced prognostic impact than stromal CD8+ T cells. These findings highlight CD8+ T cell infiltration as a favorable prognostic biomarker in GC and support its potential role in guiding immunotherapeutic strategies.

Keywords: Gastric cancer; Tumor microenvironment; Adaptive anti - tumor immunity

Introduction

Gastric cancer (GC) remains the fifth most common cancer globally, with approximately 1 million new cases and 768,000 deaths annually[1]. Despite advancements in surgical resection, chemotherapy and targeted therapy, the 5 - year survival rate for advanced GC remains below 30%[2]. The emergence of immunotherapy has revolutionized cancer treatment, but responses in GC are limited to a subset of patients, underscoring the need to identify biomarkers that predict therapeutic efficacy and prognosis[3].

CD8+ T cells, also known as cytotoxic T lymphocytes, play a central role in anti - tumor immunity by recognizing and eliminating cancer cells expressing tumor - associated antigens[4]. Their infiltration into the TME has been linked to favorable outcomes in various cancers, including melanoma and colorectal cancer[5]. In GC, accumulating evidence suggests that CD8+ T cell density correlates with prognosis, but inconsistencies exist regarding the optimal anatomical location (intraepithelial vs. stromal) and cutoff values for defining “high” infiltration. This retrospective analysis synthesizes data from PubMed - indexed studies to clarify the prognostic value of CD8+ T cells in GC and

their potential clinical applications.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using the terms («gastric cancer» OR «stomach neoplasm») AND («CD8» OR «CD8+ T cell» OR «cytotoxic T lymphocyte») with filters for English - language articles, human studies and publication dates between January 2015 and July 2024. The last search was performed on July 15, 2024.

Study selection criteria

Inclusion criteria were: (1) studies quantifying CD8+ T cell infiltration in GC tissues using immunohistochemistry (IHC); (2) studies analyzing associations between CD8+ T cell density and clinicopathological parameters (e.g., TNM stage, lymph node metastasis, differentiation); (3) studies reporting survival outcomes (overall survival [OS], disease - free survival [DFS]) based on CD8+ T cell levels; (4) studies providing sufficient data to calculate ORs or HRs with 95% CIs. Exclusion criteria included reviews, case reports, preclinical studies and studies with overlapping patient cohorts.

Data extraction and quality assessment

Two independent reviewers extracted data, including first author, publication year, country, sample size, anatomical location of CD8+ T cell assessment (intraepithelial, stromal or combined), IHC antibody clone, cutoff value for high/low infiltration and associations with clinicopathology and 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 ORs with 95% CIs were calculated for clinicopathological associations and pooled HRs with 95% CIs for survival outcomes. Heterogeneity was assessed via the I^2 statistic and Cochran's Q test; a random - effects model was used for $I^2 > 50\%$ or $P < 0.10$, otherwise a fixed - effects model was applied. Publication bias was evaluated using Egger's test and funnel plots. $P < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

Of 527 retrieved articles, 38 studies (n = 7,245 patients) were included after screening. The characteristics of included studies are summarized. Most studies were conducted in Asia (27/38), with sample sizes ranging from 56 to 620. CD8+ T cells were assessed in intraepithelial regions (18/38), stromal regions (12/38) or both (8/38). The most commonly used antibody clone was SP16 (22/38), with cutoff values defined by median (21/38) or quartile (11/38) infiltration. The median NOS score was 7 (range 6 - 9), indicating high study quality.

CD8+ T cell infiltration and clinicopathological parameters

High CD8+ T cell infiltration was significantly associated with early TNM stage (OR = 0.42, 95% CI: 0.32 - 0.55, $P < 0.001$), absence of lymph node metastasis (OR = 0.38, 95% CI: 0.29 - 0.50, $P < 0.001$) and well/moderate differentiation (OR = 0.67, 95% CI: 0.52 - 0.86, $P = 0.002$) . No significant association was found with age, gender or tumor size ($P > 0.05$).

Prognostic significance of CD8+ T cells

High CD8+ T cell infiltration predicted improved OS (HR = 0.63, 95% CI: 0.55 - 0.72, $P < 0.001$) and DFS (HR = 0.68, 95% CI: 0.58 - 0.80, $P < 0.001$). Subgroup analyses showed that intraepithelial CD8+ T cells had a stronger prognostic effect (OS: HR = 0.57, 95% CI: 0.47 - 0.69) compared to stromal CD8+ T cells (OS: HR = 0.71, 95% CI: 0.59 - 0.86).

Discussion

This retrospective analysis demonstrates that high CD8+ T cell infiltration in GC is associated with favorable clinicopathological features and improved survival, confirming the critical role of cytotoxic immunity in GC progression. The protective effect of CD8+ T cells aligns with their ability to recognize and eliminate tumor cells via perforin - and granzyme - mediated cytotoxicity[6]. Intraepithelial CD8+ T cells, which are in direct contact with cancer cells, showed a more pronounced prognostic impact, highlighting the importance of assessing T cell localization within the TME[7].

The association between CD8+ T cells and early TNM stage suggests that robust anti - tumor immunity may limit tumor growth and metastasis. Mechanistically, CD8+ T cells can suppress epithelial - mesenchymal transition (EMT) by secreting interferon - γ (IFN - γ), which downregulates EMT - promoting factors such as Snail and Twist[8]. Additionally, high CD8+ T cell infiltration correlates with microsatellite instability (MSI) in GC[9], a subtype associated with better response to immune checkpoint inhibitors (ICIs)[10]. This supports the potential of CD8+ T cell density as a predictive biomarker for ICI efficacy in GC.

Clinically, our findings validate CD8+ T cell infiltration as a favorable prognostic marker, which could be integrated into existing staging systems to refine risk stratification. For example, combining CD8+ T cell counts with TNM stage may better identify patients who could benefit from adjuvant immunotherapy. Ongoing trialsare evaluating ICIs in GC and CD8+ T cell density may help select responders.

Limitations include heterogeneity in CD8+ T cell assessment methods and cutoff values, which could affect comparability between studies. Standardization of IHC protocols and cutoff definitions is needed for clinical translation. Additionally, the retrospective nature of the included studies prevents causal inference and prospective validation is required.

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