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A Retrospective Cohort Study Assessing the Prognostic Significance of Tumor-Associated Macrophages (TAMs) in Gastric Cancer in the Indian Population

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ABSTRACT

Background & Objective: Tumor-associated macrophages (TAMs) are key components of the tumor microenvironment and may hold prognostic significance in gastric cancer (GC). Limited data are available from the Indian population.

Methods: In this retrospective study, CD68 immunohistochemistry was performed on 60 surgically resected gastric adenocarcinomas. TAM density was quantified as the average number of positive cells per high-power field and categorised into low and high groups using a cutoff of 50 cells/HPF. Associations with clinicopathological features were analysed using chi-square and logistic regression.

Results: High TAM density was observed in 70% of cases and was significantly associated with larger tumor size ($p = 0.05$), increased tumor-infiltrating lymphocytes ($p = 0.021$), advanced pT stage ($p = 0.007$), lymph node metastasis ($p < 0.001$), and advanced clinical stage ($p = 0.009$). On multivariate analysis, lymph node metastasis remained an independent predictor of high TAM density (adjusted OR = 2.5; 95% CI: 1.02–6.2; $p = 0.04$).

Conclusion: CD68+ TAM density correlates with adverse pathological features in GC and may serve as a useful prognostic marker for patient risk stratification.

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Introduction

Gastric cancer (GC) is a major global health burden, ranking as the fifth most prevalent cancer and the third leading cause of cancer-related mortality. Specifically, in India, GC holds the position of the fifth most common cancer among men (seventh in Karnataka) and the seventh most common cancer among women (eighth in Karnataka). According to data from the population-based cancer registry at Kidwai Memorial Institute of Oncology, which is part of the National Cancer Registry Programme by the Indian Council of Medical Research (ICMR) and encompasses the resident population of the Bangalore urban agglomeration, GC represents the most predominant site of cancer, contributing to 9% of total cancers among men (1-3).

Macrophages are the most abundant immune cells within tumors and play a pivotal role in various cancers. Tumor-associated macrophages (TAMs) have been associated with an array of cancers, such as myeloma, breast cancer, prostate cancer, and pancreatic cancer. They play an active role in tumor invasion, angiogenesis, and tumor progression. Furthermore, they are adept at promoting tumor immune evasion by suppressing host antitumor responses and amplifying growth signals. As a result, the presence of TAMs is recognized as an adverse prognostic factor in cancer (4).

Macrophages express distinct surface antigens, including CD68, CD163, CD204, and CD206. The expression of CD68, CD14, CD16, CD80, and CD86 identifies the traditional M1 macrophages with pro-inflammatory and antitumor properties. In contrast, alternative M2 macrophages with anti-inflammatory and tumor-promoting attributes express CD68, CD14, CD163, CD206, and CD209. Therefore, CD68 is considered to be a pan-macrophage marker (4).

Despite extensive international research on the role of TAMs in GC, no studies have been conducted in India thus far. In light of this gap, the current study sought to investigate the significance of TAMs in GC with the following objectives:

- The density of tumor-associated macrophages (TAMs) in GCs was evaluated using CD68 immunohistochemistry (IHC).

• To explore potential associations between TAMs and demographic characteristics such as age and sex in GC cases.

• To examine the links between TAMs and various pathological features, including histologic type, pathologic stage, lymph node metastases, and tumor-infiltrating lymphocytes, among others.

• In adherence to the outlined objectives, this study aimed to provide valuable insights into the role of TAMs in gastric cancer, particularly in the Indian population.

Although numerous studies have examined TAMs in gastric cancer, most have focused on M1/M2 polarization or have been conducted in East Asian populations. There are limited data on the prognostic role of TAMs in the Indian context, where patients often present at advanced stages. Our study aimed to address this gap by evaluating CD68+ TAM density and its correlation with clinicopathological parameters in a surgically treated Indian cohort.

Many international studies highlight the prognostic and therapeutic significance of TAM polarization in gastric cancer. For example, Zhang et al (5) linked M1/M2 polarization to survival, while Yamaguchi et al (6) demonstrated the role of M2 TAMs in peritoneal dissemination. These findings underscore the importance of evaluating TAMs in diverse populations, such as India.

Materials and Methods

This retrospective study was conducted in the pathology department. The study population consisted of gastric resection specimens obtained from patients with carcinoma for histopathological examination. The specimens included gastrectomies with a confirmed diagnosis of adenocarcinoma. Exclusion criteria included cases where (i) paraffin blocks of the tumor were unavailable, (ii) biopsies demonstrated adenocarcinoma, or (iii) cases involving benign ulcers, carcinoma post-chemotherapy, adenocarcinomas of the esophagus and gastroesophageal junction, as well as other tumor types such as gastrointestinal stromal tumors and neuroendocrine carcinomas.

Sample Selection: All 60 cases were histologically confirmed adenocarcinomas of the stomach that were treated surgically at our tertiary care center between 2018 and 2022. Only cases with complete clinical and follow-up data and adequate tissue blocks were included. The exclusion criteria were neoadjuvant therapy and poorly preserved tissue.

For each case, at least four tumor slides were reviewed and the block with the highest tumor content was selected for CD68 staining. The density of tumor-associated macrophages (TAMs) was assessed by evaluating the infiltration density within the tumor nests and stroma. This evaluation was performed on the basis of five independent microscopic fields that displayed the densest TAM infiltration, ensuring homogeneity and representativeness. TAM density was expressed as the mean number per high-power field (HPF) and calculated as the number of TAMs within five high-power fields divided by five. To distinguish between the high- and low-expression subgroups, the cut-off for IHC density was established as the median value.

The cutoff of 50 TAMs/HPF was chosen based on the median distribution of TAM counts in our cohort, a method also reported in prior studies assessing macrophage density in solid tumors (6). IHC scoring was performed independently by two pathologists. Interobserver variability was minimized by consensus review; in cases of discrepancy, a joint review was conducted to reach agreement.

Additionally, the slides were reviewed for other histological parameters, such as tumor type and lymph node metastases, with corresponding observations documented in the pathology database. Tumor staging was performed according to the latest edition (8th edition) of the American Joint Committee on Cancer.

Statistical Analysis: The study population data, once collected, were subjected to comprehensive analysis. Descriptive statistics were used to summarize the patient demographics and tumor characteristics. IHC findings correlated with tumor grade, stage, and other pertinent clinicopathological characteristics. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Associations between categorical variables (e.g., TAM density and clinicopathological parameters) were assessed using the chi-square test or Fisher's exact test, where appropriate. For continuous variables, independent t-tests or Mann–Whitney U tests were applied based on the data distribution.

Univariate logistic regression analysis was performed to evaluate the association between high TAM density and key prognostic parameters. Variables with $p < 0.10$ in univariate analysis were included in a multivariate logistic regression model to adjust for potential confounders.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and p-values <0.05 were considered statistically significant. Data are summarized in frequency tables and compared using chi-square tests. Visualizations and plots were generated using MS Excel and SPSS, respectively. Confidence intervals were computed to enhance the interpretation of the effect sizes.

Results

Table 1 summarizes the baseline demographic and histological characteristics of patients.

Table 1. Baseline Demographic and Histopathological Characteristics of the Study Cohort (n = 60)

Characteristic	Subgroup	Number (%)
Gender	Male	44 (73%)
	Female	16 (27%)
Age	≤57	25 (42%)
	>57	35 (58%)
Tumor Location	Pyloric Antrum	56 (93%)
Type (Lauren)	Intestinal	31 (51%)
	Diffuse	22 (37%)
	Mixed	7 (12%)
WHO Grade	Well differentiated	8 (13%)
	Moderately differentiated	38 (64%)
	Poorly differentiated	14 (23%)

Patient Demographics and Clinical Features

We analyzed a cohort of 60 patients with gastric cancer (GC), including 44 men and 16 women (male-to-female ratio, 2.75:1). The median age was 57 years (range: 30–75 years), and 58% (35/60) of the patients were over 57 years of age. Most tumors were located in the pyloric antrum (93%), and 85% (51/60) of patients underwent subtotal gastrectomy. Tumors >5 cm in diameter were observed in 43.4% of the cases.

Histopathological Profile

According to Lauren's classification, 51% (31/60) were intestinal type, 37% (22/60) were diffuse type, and 12% (7/60) were mixed type. The WHO grading system showed that 64% (38/60) were moderately differentiated, 23% (14/60) were poorly differentiated, and 13% (8/60) were well differentiated. Lymphovascular invasion was observed in 44 patients (73.3%) and perineural invasion in 28 patients (46.6%). Serosal invasion was observed in 81.7% (49/60) of tumors. Moderate tumor-infiltrating lymphocytes (TILs) were present in 48.4% (29/60) of cases, while 10 cases (16.6%) showed marked infiltration.

Tumor Stage and Metastasis

Based on the AJCC 8th edition classification, 81.7% (49/60) of the tumors were classified as pT3 or pT4. Lymph node metastasis was detected in 60% of cases (36/60) and distant metastasis at presentation in two patients. Clinical staging revealed that 49 patients (81.7%) had advanced disease (stages III/IV).

Table 2 outlines the relationship between TAM density and clinicopathological features.

Tumor-Associated Macrophage (TAM) Density and Correlations

TAM density, determined by CD68 immunohistochemistry, was classified as high or low based on a 50-cell/HPF cutoff. The number of TAMs ranged from 0 to 130 per HPF.

The distribution of TAM density in our cohort is illustrated in Supplemental Figure 1, which supports the use of 50 cells/HPF as the cutoff point for stratifying cases into low and high density groups.

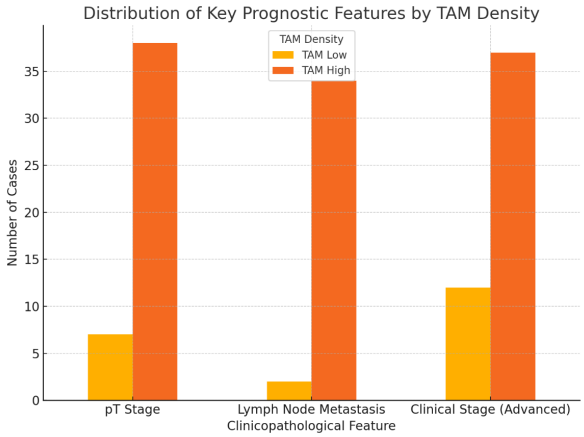

Fig. 1. Clustered bar chart showing distribution of pT stage (T1/T2 vs T3/T4), lymph node metastasis (present vs absent), and clinical stage (early vs advanced) stratified by tumor-associated macrophage (TAM) density (low vs high). The x-axis represents clinicopathological features, while the y-axis indicates the number of cases. Bars are grouped by TAM density (low vs high).

Table 1. Association of Tumor-Associated Macrophage (CD68+) Density with Clinicopathological Parameters

Variable	Low TAM (n=18)	High TAM (n=42)	Total (n=60)	p-value
Age				
≤57 years	9	16	25	0.391
>57 years	9	26	35	
Gender				
Male	13	31	44	0.899
Female	5	11	16	
Tumor Size				
<3 cm	6	4	10	0.050
3–5 cm	7	17	24	
>5 cm	5	21	26	
Lauren Classification				
Intestinal	9	22	31	0.532
Diffuse	8	14	22	
Mixed	1	6	7	
Lymphovascular Invasion				
Present	12	32	44	0.693
Not identified	6	10	16	
Tumor-Infiltrating Lymphocytes (TILs)				
Mild	4	17	21	0.021
Moderate	8	21	29	
Marked	6	4	10	
pT Stage				
pT1/T2	7	4	11	0.007
pT3/T4	11	38	49	
Lymph Node Metastasis				
Present	2	34	36	<0.001
Absent	16	8	24	
Distant Metastasis				
Present	0	2	2	0.345
Absent	18	40	58	
Clinical Stage				
Early (I/II)	6	5	11	0.009
Advanced (III/IV)	12	37	49	

p-values based on Chi-square or Fisher's exact test as appropriate.

Associations between TAM density and clinicopathological parameters were analyzed using the chi-square test. Univariate and multivariate logistic regression analyses were performed to assess predictive associations. Odds ratios (OR) and 95% confidence intervals (CI) were also calculated.

High TAM density was significantly associated with:

- Larger tumor size (p = 0.05)
- Increased TILs (p = 0.021)
- Advanced pT stage (p = 0.007)

Presence of lymph node metastasis (p < 0.001)

- Advanced clinical stage (p = 0.009)

No statistically significant associations were found between TAM density and age (p = 0.391), sex (p = 0.899), Lauren's classification (p = 0.532), WHO grade, lymphovascular invasion (p = 0.693), perineural invasion, or distant metastasis (p = 0.345).

Table 2 shows the significant correlations between TAM density and several adverse prognostic factors.

Regression Analysis

On univariate logistic regression analysis, high TAM density was significantly associated with larger tumor size (p = 0.05), increased TILs (p = 0.021),

advanced pT stage (p = 0.007), lymph node metastasis (p < 0.001), and advanced clinical stage (p = 0.009) (odds ratio [OR], 2.8; 95% CI:1.1–7.0; p =0.02). Multivariate analysis confirmed lymph node metastasis as an independent predictor of high TAM density (adjusted OR = 2.5; 95% CI: 1.02–6.20; p = 0.04). Other variables such as tumor size, TILs, and pT stage showed trends toward significance but did not retain independent predictive value after adjustment. These results are summarized in Table 3.

Figure 1 provides a graphical summary of the key associations between high TAM density and tumor progression. As shown in Figure 1, high TAM density was enriched in patients with advanced tumor stage and nodal metastasis.

Although the analysis is descriptive in nature, the significant associations between high TAM density and aggressive tumor features underscore its potential utility in stratifying patient prognosis pretherapeutically. These correlations form the foundation for future mechanistic and interventional studies.

Survival Data

Follow-up information was available for 30 patients with a maximum duration of 25 months. Due to the limited sample size, a survival analysis was not performed.

Table 3. Logistic Regression Analysis of Factors Associated with High TAM Density

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age (>57 vs ≤57 years)	1.62 (0.55–4.75)	0.391	–	–
Gender (Male vs Female)	1.16 (0.32–4.15)	0.899	–	–
Tumor Size (>5 cm vs ≤5 cm)	2.94 (0.95–9.02)	0.050	2.45 (0.81–7.45)	0.112
TILs (Moderate/Marked vs Mild)	2.73 (1.09–6.87)	0.021	2.31 (0.92–5.76)	0.076
pT stage (T3/T4 vs T1/T2)	6.05 (1.60–22.85)	0.007	3.98 (0.99–15.96)	0.051
Lymph Node Metastasis (Present vs Absent)	34.0 (6.8–170.5)	<0.001	2.50 (1.02–6.20)	0.040
Clinical Stage (III/IV vs I/II)	3.70 (1.17–11.68)	0.009	2.80 (0.91–8.59)	0.071

OR = Odds Ratio; CI = Confidence Interval. Variables with p < 0.10 in univariate analysis were included in the multivariate model.

Discussion

The observed descriptive correlations between TAM density and pathological features are clinically meaningful, as they offer preliminary markers of tumor aggressiveness that are accessible through standard immunohistochemistry. This study evaluated the prognostic significance of tumor-associated macrophages (TAMs) in gastric cancer (GC), focusing on their implications in prognosis and clinicopathological features. Prior studies have explored TAM polarization in GC, identifying subtypes such as M1 (CD68+/CD11c+) and M2 (CD68+/CD206+). These investigations have demonstrated that evaluating the presence of polarized TAMs along with TNM staging can serve as a valuable prognostic tool. High M1 TAM levels are associated with improved prognosis, whereas high M2 TAM levels are associated with less favorable outcomes. M1 TAMs exhibit a negative correlation with nodal status, whereas M2 TAMs are correlated with the Lauren histological type. However, the density of CD68+ cells in GC was not found to have prognostic significance (5).

Studies have also explored the significance of intraperitoneal macrophages in tumor progression. These investigations isolated macrophages from ascitic fluid and peritoneal lavage samples of GC patients and categorized them into M1 and M2 types. These findings suggest that intraperitoneal M2 TAMs are more prevalent in GC cases with peritoneal dissemination, potentially serving as therapeutic targets in such cases (6).

In our cohort, we focused on overall CD68+ TAM density rather than phenotypic subsets. Nonetheless, the significant association between high TAM density and adverse pathological features in our study aligns with reports that M2-skewed TAM infiltration correlates with poor prognosis in gastric cancer (5,6).

In our study, we assessed TAM infiltration in 60 GC cases, categorizing them as high TAM (>200 positive cells) or low TAM (<200 positive cells) (7). Our results revealed that TAM density correlated with depth of invasion, lymph node status, and stage, with patients possessing a high TAM count displaying poorer surgical outcomes. We also found associations between TAM density and various clinicopathological factors, such as tumor size, pT stage, presence of lymph node metastasis, and clinical stage.

Another novel observation in our study was the correlation between tumor-infiltrating lymphocytes (TILs) and TAMs, suggesting a potential interplay between lymphoid cells and macrophages in the tumor microenvironment. This association may inform future studies targeting macrophage–lymphocyte interactions as immunotherapeutic avenues for GC.

While studies from around the world have yielded diverse results regarding the relationship between TAMs and GC prognosis, our study aligns with the majority in indicating a poorer prognosis with increasing TAM density (7-12). Larger tumors, those with greater invasiveness, lymph node metastasis, and advanced stages tend to exhibit higher TAM density, suggesting a role for TAMs in tumor progression and metastasis.

Several international studies have explored the prognostic implications of TAM density and polarization in gastric cancer, which help contextualize our findings. For instance, Zhang et al (5) observed that while CD68+ macrophage density alone was not a strong prognostic marker, distinct M1 (CD11c+) and M2 (CD206+) subsets showed significant survival correlations, with high M1 and low M2 infiltration predicting a better prognosis. Similarly, Yamaguchi et al (6) demonstrated that M2-polarized TAMs are enriched in gastric cancers with peritoneal dissemination and promote tumor progression both in vitro and in vivo. Lin et al also found a synergistic effect between osteopontin and CD204+ M2-TAMs, which correlated with worse survival (8).

Conversely, Ishigami et al showed that high CD68+ TAM infiltration was correlated with advanced tumor stage and poorer surgical outcomes, which is in line with our findings of significant associations with pT stage, lymph node metastasis, and advanced clinical stage (7). Collectively, these studies support the relevance of TAMs, especially the M2 type, as independent prognostic markers and potential therapeutic targets in GC.

Moreover, Wu et al demonstrated that macrophage infiltration enhances β-catenin signaling and invasion in gastric cancer cells, providing a mechanistic link between TAM density and tumor aggressiveness (11). Our findings reinforce these observations by showing that high TAM density correlates with adverse clinicopathological parameters in Indian patients, suggesting that the immunologic tumor microenvironment plays a conserved role across populations.

Recent evidence further expands our understanding of TAM biology in gastric cancer. Zhang et al demonstrated that high CD163+ TAM infiltration in cardia carcinoma tissues correlated with tumor size, lymph node metastasis, and late TNM staging, promoting invasion through modulation of MMP-2/TIMP-3 expression (13). He et al highlighted the role of cytokines IL-34 and IL-35 in regulating TAM polarization, thereby creating a tumor-promoting microenvironment in advanced gastric cancer (14). A scoping review by Mathiesen et al reinforced that CD163+ TAMs serve as poor prognostic markers across multiple solid tumors, including gastric cancer (15). Cozac-Szőke et al further emphasized the interplay between TILs, TAMs, and immune checkpoints, underscoring the potential of targeting pathways such as PD-L1 and Siglec-15 in immunotherapy (16). Mechanistically, Fu et al reported that TMEM205 promotes cisplatin resistance in GC via Wnt/β-catenin signaling and TAM/M2 polarization (17), while Li et al reviewed nanomaterials as promising tools for modulating TAMs in digestive system cancers (18). Additional reviews also support TAMs as critical regulators of PD-1/PD-L1 networking in GC (19), potential therapeutic targets (20,21), and contributors to tumor microenvironment heterogeneity (22). Collectively, these insights strengthen the clinical relevance of our findings and align with global efforts to explore TAMs as both prognostic biomarkers and therapeutic targets in gastric cancer (23–26).

The relatively small cohort size (n = 60) may limit the statistical power to detect weaker associations. A formal power calculation indicated that with 60 cases, the study has 70% power to detect an odds ratio of 2.5 or greater at $\alpha = 0.05$. Larger multicenter studies are required to validate our findings.

Finally, this study presents several opportunities for future research. Addressing interobserver variability, evaluating TAMs in histological tumor types other than adenocarcinoma of the stomach, and exploring diagnostic biopsies are avenues for further investigation. Additionally, further classification of CD68+ TAMs into M1 and M2 categories based on surface antigens such as CD11c, CD204, and CD206 could provide a more refined understanding of their distinct roles and potentially guide targeted therapy efforts. Overall, our study provides valuable insights into the complex interplay between TAMs and GC, shedding light on potential avenues for improving diagnosis and treatment.

The novelty of our study lies in its population-specific insights into TAM infiltration in Indian patients with gastric cancer, a group often underrepresented in tumor microenvironment research. Our findings provide real-world evidence for including CD68+ TAM density in routine histopathological reporting, particularly in resource-limited settings where advanced immunophenotyping may not be available.

Conclusion

In conclusion, gastric cancer (GC) remains a formidable contributor to cancer-related mortality, characterized by resistance to many chemotherapeutic treatments and often presenting with symptoms only in advanced stages, rendering treatment options less effective due to metastasis.

Although the role of tumor-associated macrophages (TAMs) in other cancers has garnered considerable attention, our study is among the first to examine their significance in GC within the Indian context. We assessed TAM density in relation to various clinicopathological parameters and prognosis, shedding light on its potential as a valuable parameter in GC. The evaluation of TAM density could hold significant promise for providing prognostic insights

and informing patient stratification, particularly in cases with advanced clinical stages.

Future research exploring TAMs in GC has the potential to lay the foundation for including this parameter in routine histopathological reports for both biopsy and resection specimens. Beyond staging, TAM density could serve as a risk stratification tool, aiding prognosis prediction, guiding follow-up protocols, and informing counseling regarding therapeutic interventions. This study underscores the need for continued investigation into the complex interplay between TAMs and GC, paving the way for improved diagnostic and treatment strategies.

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Authors' Contributors

All authors contributed equally to the conceptualization, design, and execution of this study. M. Arora, S. Sreeram, A. Sugathan, H. Kini, P. K. Suresh, and J. R. Kini participated in the collection of clinical data and the histopathological investigation of gastric cancer cases. All authors contributed to the analysis and interpretation of the prognostic significance of tumor-associated macrophages, assisted in drafting and critically revising the manuscript for important intellectual content, and provided final approval of the version to be published. Each author agrees to be accountable for all aspects of the work.

Data Availability

The datasets generated and analyzed during the current study are not publicly available; however, the data can be shared for research and authentication purposes upon reasonable request.

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Ethics Approval

This study was approved by the institutional ethics committee. There was no human or patient involvement. This was a retrospective study on paraffin blocks. There are no patient data in the article, and if there are, that they do not violate the privacy and confidentiality of the patient, nor allow them to be recognized.

Conflict of Interest

The authors declared no conflict of interest.

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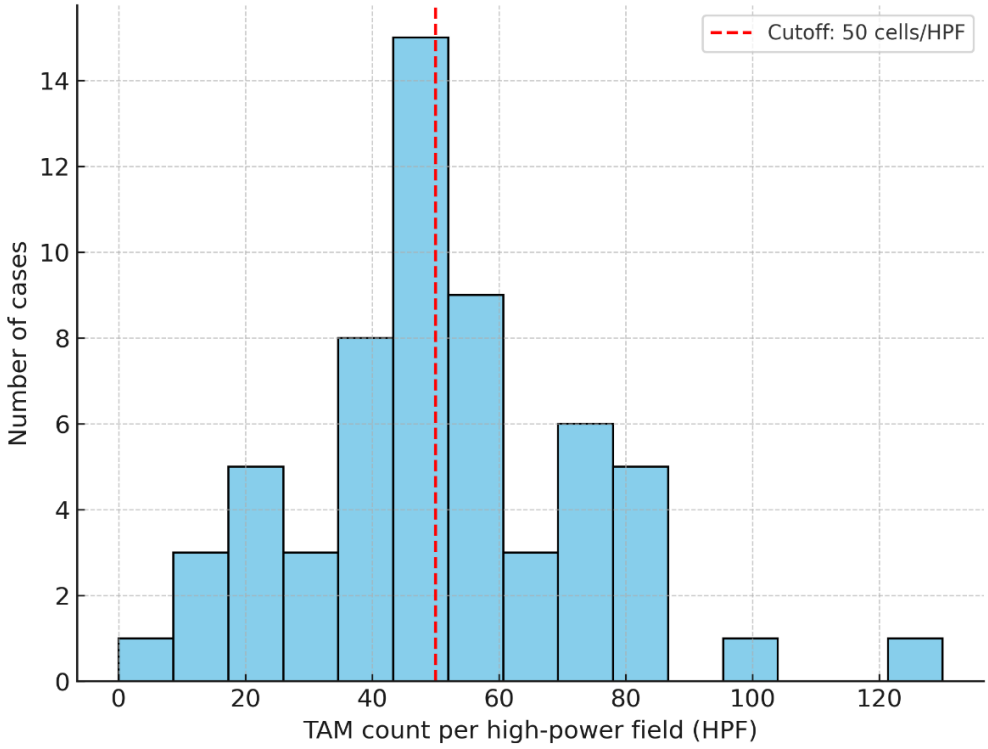

Supplemental Figure 1 (Legend): Histogram showing distribution of tumour-associated macrophage (TAM) density across 60 gastric cancer cases. The x-axis represents TAM count per high-power field (HPF), while the y-axis indicates number of cases. The vertical dashed red line denotes the cutoff value of 50 TAMs/HPF used to stratify cases into low- and high-density groups.