Original Article

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Evaluation of CD8+ Tumor Infiltrating Lymphocytes (TILs) Association in Gastric Adenocarcinoma in a Tertiary Care Hospital inBangladesh

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Abstract

Background: Gastric cancer remains one of the most common types of cancer and a major cause of cancerrelated deaths. It ranks as the fifth most frequently diagnosed cancer and the fourth leading cause of mortality worldwide. The Tumor Microenvironment (TME) consists of tumor cells, extracellular matrix, immune cells, cytokines, and other components. Among these, immune cells- particularly T lymphocytes- plays a crucial role as regulatory factors in TME. In particular, T lymphocytes, especially CD8+ Cytotoxic T Cells (CTLs) are recognized as key anti-tumor immune cells. The aim of the study was to evaluate the expression of CD8+ tumor infiltrating lymphocytes in gastric adenocarcinoma and their association with histological grade and pathological stage.

Materials and methods: This cross-sectional observational study was conducted in the Department of Pathology, Sir Salimullah Medical College, Dhaka from March 2022 to February 2024. A total of 50 gastrectomy samples with a histologically confirmed diagnosis of gastric adenocarcinoma were included in this study. The expression of CD8+ in TILs were evaluated in formalin-fixed and paraffin embedded specimens by immunohistochemistry. The CD8+ TILs were categorized as positive and negative expressions. Histopathological results were analyzed and statistical analysis was done using Statistical Package for Social Science (version 26.0).

Results: In this study showed that among 50 cases, 68% (n=34) were male and 32% (n=16) were female. The major tumor type, poorly differentiated type of adenocarcinoma reported was 38%. CD8+ intra tumoral and stromal TIL expression was positive in 33 (66%) and 35 (61%) cases respectively. A significant association was found between intra tumoral CD8+ TILs and histological tumor grade (p value=0.037) pathological stage (p-value = 0.005) but no significant association was seen with nodal status (p value =0.759). Similarly, a significant association was observed between the stromal CD8+ TILs with histologic grades (p value= 0.012) and pathological stage (p value = 0.035) but not with nodal status (p value = 0.434).

Conclusion: As part of tumor microenvironment CD8+ TIL influence the progression and differentiation of gastric adenocarcinoma. These expression levels can be utilized as indicators of biological behavior and prognosis as well as in therapeutic purpose of gastric adenocarcinoma.

Key words: Gastric adenocarcinoma; Histological grading; Pathological staging; Tumor-Infiltrating Lymphocytes (TILs).

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Introduction

Gastric Adenocarcinoma (GAC) is a major health issue worldwide, contributing significantly to cancer-related mortality, particularly in East Asia and Eastern Europe.[1] The prognosis for advanced-stage GAC remains poor even though various treatment options such as surgery, chemotherapy and targeted therapies have advanced. This highlights the urgent need for innovative strategies to improve patient classification and treatment effectiveness.[2] Tumor-Infiltrating Lymphocytes (TILs) especially CD8+ T cells exhibit cytotoxicity by directly killing tumor cells or facilitating tumor destruction through the release of effector cytokines like interferon-c.[3] These cells are capable of identifying and destroying malignant cells by releasing cytolytic molecules like perforins and granzymes, thereby enhancing anti-tumor immunity.[4] Their efficiency is often regulated by the Tumor Microenvironment (TME) which can either promote or inhibit their cytotoxic function.[5] Several studies have shown that the presence of CD8+ Tumor-Infiltrating Lymphocytes (TILs) within both the tumor and stromal compartments of gastric adenocarcinoma is linked to better clinical outcomes.[6] A higher density of CD8+ TILs has been associated with longer overall survival and a lower risk of disease recurrence, indicating their potential as prognostic biomarkers.[2] Additionally, the spatial distribution of CD8+ TILs – whether within the tumor epithelium or infiltrating the tumor stroma has

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been found to influence patient prognosis differently.[5] Although CD8+ TILs play a crucial role in immune response, gastric adenocarcinoma cells often develop mechanisms to evade immune detection, one such mechanism involves the increased expression of immune checkpoint molecules like Programmed Death-Ligand 1 (PD-L1) which binds to the PD-1 Receptor on CD8+ T-cells exhaustion.[7] This interaction impairs the function of CD8+ TILs, reducing their ability to suppress tumor progression.[5] However, the use of Immune Checkpoint Inhibitors (ICIs) such as anti-PD-1 and anti-PD-L1 therapies, has emerged as a promising strategy to restore CD8+ T-cell function and enhance anti-tumor immunity.[4] Apart from PD-1/PD-L1 signaling, other elements such as regulatory T cells

(Tregs) Myeloid-Deprived Suppressor Cells (MDSCs) and Tumor-Associated Macrophages (TAMs) contribute to immunosuppression in gastric adenocarcinoma, these cells achieve this by secreting inhibitory cytokines and diminishing CD8+ T-cell activity.[6] Gaining a deeper understanding of these interactions within the Tumor Microenvironment (TME) is essential for designing combination immunotherapy strategies that can enhance CD8+ TIL- mediated tumor suppression.[1]

This study shows investigate the relationship between CD8+ TILs and the clinicopathological characteristics of gastric adenocarcinoma. By assessing the density, localization and functional state of CD8+ T cells, we seek to provide meaningful insights into their prognostic and therapeutic value. These findings could help guide the development of more effectiveness immunotherapeutic strategies for treating gastric cancer.

Gastric adenocarcinoma is one of the most prevalent cancer in Eastern Asia. Despite the combined use of surgery, chemotherapy and targeted agents, the great majority of patients with gastric adenocarcinomas will die of metastatic disease and thus new therapies with curative potentials are needed. Traditional prognostic models for GC patients depend on the TNM staging system. Even patients with the same stage of cancer may have very different prognoses. Tumor Infiltrating Lymphocytes (TILs) in GC are the key representators of tumor immune microenvironment. Combination of CD3+ and CD8+TILs and TNM stage can provide prognostic information for GC patients. TILs has the potential to be immune therapy biomarker.

Therefore, understanding the biology of TILs may help prognostic stratification of patients based on TIL status. In the upcoming years, it can guide doctors in adopting customized treatment plans according to individual patients' response. The purpose of the study to evaluate any association of CD8+ tumor infiltrating lymphocytes in gastric adenocarcinoma with its histologic grades and pathologic stages.

Materials and methods

This cross-sectional observational study was conducted among 50 cases of patient who underwent partial or total gastrectomy and diagnosed as gastric adenocarcinoma in the Department of Pathology in Sir Salimullah Medical College, Dhaka and Bangladesh Medical University, Dhaka during study period from March, 2022 to February, 2024 after receiving ethical approval from Institutional Ethics Committee (SSMC/2023/137, dated 15 January, 2023). Patients of any age group were included in the study.

In this study, exclusion criteria were as follows:

- Patients having prior radiotherapy or chemotherapy or both.
- Inadequate Formalin Fixed and Paraffin Embedded (FFPE) tissue block.
- Poorly preserved sample.
- Patients having secondary metastasis of stomach.
- Tumors other than adenocarcinoma.

Using the organized questionnaire, data were recorded on variables after taking informed written consent from the patient. Histological results were systematically recorded in the predesigned data sheet i.e. patient data sheet. All the cases were numbered chronologically and the same number was given to histopathological as well as in immunohistochemical slides.

In this study, among fifty (50) gastric adenocarcinoma cases, thirty-five (35) were fresh specimens. Rest of the fifteen (15) cases were paraffin blocks and relevant information' s was collected from previous reports.

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After receiving fresh samples (Partial and total gastrectomy) gross examination was done as per standard procedure. All the tissues were submitted for routine processing, paraffin embedding and the blocks were sectioned in 3-4 micrometer thickness and finally slides were stained with routine H & E stain. All the slides were thoroughly evaluated by microscopic examination and grading and staging were done. The collected paraffin blocks of fifteen (15) cases were given re-cut and subsequent staining was done. Relevant information's were collected from previous reports. After following standard protocols two slides were made from each tumor block. One slide was stained with H & E stain for reviewing the diagnosis and grading, one slide for immunohistochemical analysis of CD8+ immunomarker.

For immunohistochemistry, 3-4 micrometer sections of formalin-fixed, paraffin embedded tissues were mounted on poly-L-lysine coated slides. The sections were deparaffinized in xylene and rehydrated in a descending ethanol series. Sections were incubated for five minutes in 3% hydrogen peroxide to block endogenous tissue peroxidase. The sections were incubated with primary antibodies against CD8+ in appropriate dilutions. Mouse anti-human monoclonal primary antibodies against the said antigens were used. Standard immunohistochemical method was applied for subsequent staining. For visualizing the section, DAKO En Vision+ HRP (Horseradish peroxidase) system was used. Each assay included a positive control slide.

Primary antibody:

- For CD8: Mouse monoclonal anti-human CD8+ (Clone C8/144, code M7103, 1:100 dilution, DAKO) was used as primary antibody.

Secondary antibody: DAKO REALTM En Vision TM (HRP RABBIT/MOUSE)

Positive control slides:

Acute appendicitis specimen with positive lymphocytes was taken as a positive control.

Evaluation of immunostain:

Immunostained sections of CD8+ were examined under light microscope.

Immunopositively cells are defined as those showing partial or complete staining within the cytoplasm and/or plasma-membrane. The semi quantitative immunohistochemical grading of CD8+TILs were determined by high power microscopy. Five fields of view with the most abundant lymphocyte infiltration area was selected by the "hot spot" method. The percentage of CD8+ positive T-cells among total lymphocytes were calculated. The average values of five fields were taken as the density (%) of CD8+TILs.[8]

i) Percentage of immunopositively cells among total cells:

- ≤1% of cells
- 1-10% of cells
- 11-33% of cells
- 34-66% of cells
- 67-100% of cells

ii) Intensity score:

- 0 negative/no staining
- 1+ mild
- 2+ moderate
- 3+ intense

Finally, scores (Ranging from 1 to 8) were calculated by adding the percentage positivity scores and the intensity scores for each section. The cases were divided into two groups using the median value, with negative or positive CD8+ expression.[8]

iii) Final score:

- ≥ Median value (Positive)- CD8+ intra tumoral ≥ 4 (Positive); stromal ≥ 5 (Positive)
- ≤Median value (negative)- CD8+ intra tumoral <4 (Negative); stromal < 5 (Negative)

The statistical analysis was conducted using Statistical Package for Social Sciences version 28.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Qualitative variables were expressed as frequency (Percentile). Continuous variables were expressed as mean± SD and range. The association of CD8+ a TINs with histological grade, stage and nodal status were evaluated using Chi Square Test. The results were calculated by using descriptive statistical formulas and were presented in tables, figures and diagrams. p value <0.05 was considered as statistically significant.

Results

In this study, among the 50 patients, 68% (n=34) patients were male, and 32% (n=16) patients were

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female. Among 50 cases, most were poorly differentiated type 19 (38%), followed by tubular 14 (28%) and mixed 12 (24%) type. Rest were papillary 2 (4%) and mucinous type 3 (6%) (Figure 02). Figure 03 depicts, the distribution of the study population according to histopathological grade of the tumor. It reveals that among the 50 cases, 23 (46%) patients were grade II. Grade I comprised 09 (18%) cases and Grade III were found in 18 (36%) cases. Among the 50 cases, 36 (72%) were nodal positive. N1 comprised 16 (32%) cases, N2 were 15 (30%) cases and N3 were found in 5 (10%) cases (Figure 04). A significant association was observed between intra tumoral CD8+ TILs expression with tumor grade (p-value = 0.037) and pathological stage (p-value = 0.005) but not with nodal status (p-value = 0.759). Similarly, a significant association was observed between stromal CD8+ TILs expression with tumor grade (p- value = 0.012) and pathological stage (p-value = 0.035) but not with nodal status (p value = 0.434).

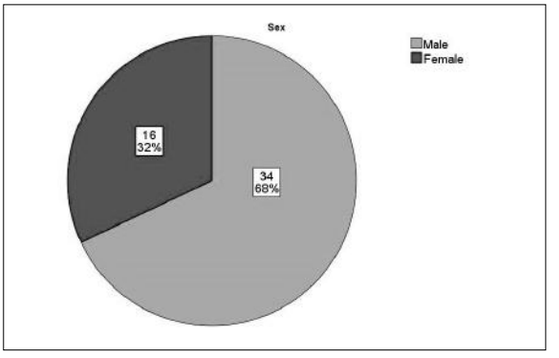

Figure 1 Distribution of patients according to gender (n=50)

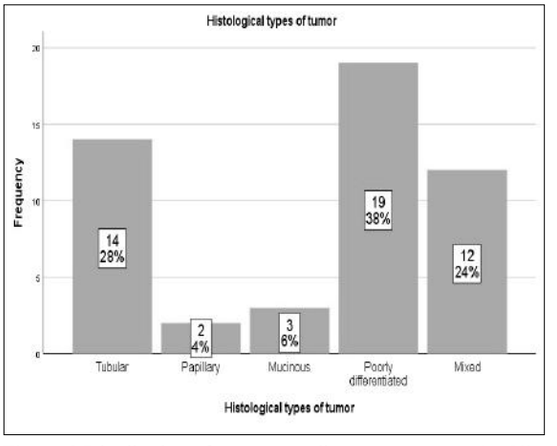

Figure 2 Distribution of cases according to tumor type (n=50)

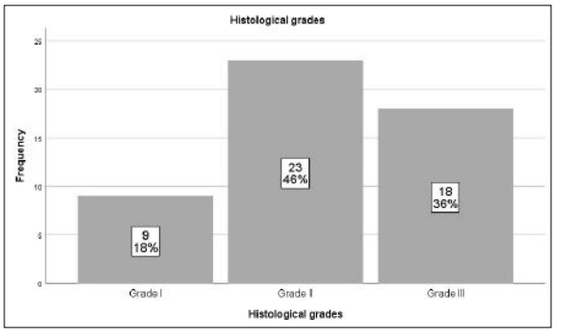

Figure 3 Distribution of cases according to tumor grade (n=50)

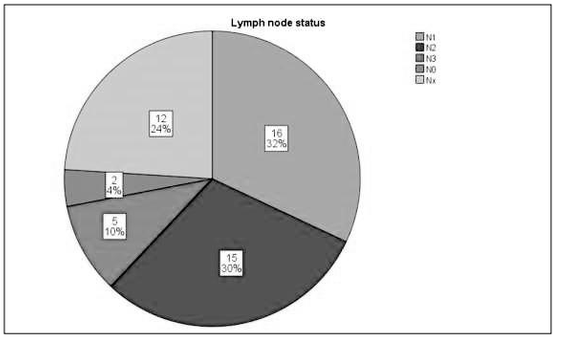

Figure 4 Distribution of cases according to nodal status (n=50)

Table I Comparison between CD8+TILs distribution within intratumoral and stromal compartments

Characteristics	CD8+ Intra tumoral TILs		p-value	CD8+ stromal TILs		p-value
	Positive	Negative		Positive	Negative	
Histological Grade: G-I	05 (55.6%)	04 (44.4%)	0.037	03 (33.3%)	06 (66.7%)	0.012
G-II	12 (52.2%)	11 (47.8%)		16 (69.6%)	07 (30.4%)	
G-III	16 (88.9%)	02 (11.1%)		16 (69.6%)	02 (11.1%)	
Pathological Stage: T1	05 (45.5%)	06 (54.5%)	0.005	04 (36.4%)	07 (63.6%)	0.035
T2	05 (71.4%)	02 (28.6%)		05 (71.4%)	02 (28.6%)	
T3	22 (84.6%)	04 (15.4%)		22 (84.6%)	04 (15.4%)	
T4	01 (16.7%)	05 (83.3%)		04 (66.7%)	02 (33.3%)	
Nodal Involvement:						
Present	24 (66.7%)	12 (33.3%)	0.759	25 (69.4%)	11 (30.6%)	0.434
Absent	9 (71.4%)	05 (30.4%)		10 (71.4%)	04 (28.6%)	

Discussion

Gastric adenocarcinoma is one of the most common neoplasms encountered in our modern world, ranking 6th as the cancer related mortality.[9] It is an inflammation related cancer characterized by a large degree of multinuclear and monocyte infiltration, including lymphocytes and macrophages. Tumor-associated immune cells affect complex microenvironments, with prognostic

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value in previous studies. To date, several markers are found for TILs, such as CD3, CD4, CD8, Foxp3 and Granzyme B. In the present study, CD8+ on T cells, were stained on gastric adenocarcinoma cases in order to determine their association with tumor grade and pathological stage. A sum of 50 cases of formalin fixed paraffin embedded tissue blocks diagnosed with gastric adenocarcinoma were collected from the Department of Pathology of SSMC during the period from March 2022 to February 2024 for these purposes. The socio-demographic data, histopathological findings and immunohisto-chemical expression were noted in a preformed data sheet.

In the study, 68% of the studied cases were male and 32% were female. Similarly, Abdel-Aziz et al, have reported that among the 48 cases of gastric carcinoma, 30 were male patients (62.5%) and 18 were female patients (29.2%).[10] In another study conducted by Pramanik et al. there was a male preponderance (69.2%) with male to female ratio 2.3:1.[11] Lu et al. showed that in their study, among 401 patients 271 male (67.6%), 130 females (32.4%).[8]

Among the present study cases, 38% of gastric adenocarcinoma were poorly differentiated type. Rest were papillary type (4%) and mucinous type (6%). This finding slightly differs from the study of Kang et al. where most common type of gastric adenocarcinoma was diffuse type (70%).[12]

As per histological grade of gastric adenocarcinoma, the current study revealed that among the 50 cases, 46% of patients were grade II. Grade I comprised 18% of cases and grade III were found in 36% cases. It almost matches the results of Paramanik et al. in which most of the cases, poorly differentiated were 51.9% (Grade III) followed by 40.4% moderately differentiated (Grade II) and 7.7% well differentiated (Grade I).[11]

It shows that among the 50 cases of the present study, 36 (72%) were nodal positive. N1 comprised 16 (32%) cases, N2 were 15 (30%) cases and N3 were found in 5 (10%) cases. This result is according to the result of Lu et al. which shows that 66.8% cases were nodal positive.[8]

In the present study showed that intra tumoral CD8+ TILs positivity in grade I tumors with 5 (55.6%) cases, grade II tumors showed intra tumoral CD8+ TILs positivity with 12 (52.2%) cases and intra tumoral CD8+ TILs positivity was mostly found in grade III tumors, with 16 (88.9%) which was statistically significant (p-value <0.05). This finding resembles the findings of Lu et al. which showed that CD8+ TILs were mostly positive in higher grade tumors (57.7% cases).[8] Another study by Huda et al. also found similar result which demonstrated that 7 (36.84%) grade I, 1 (5.26%) grade II and 11(57.89%) grade III tumors were positive for CD8+ TILs.[13]

The current study describes that intra tumoral CD8+ TILs positivity was mostly found in stage T3 tumors with 22 (84.6%) cases followed by stage T2 tumors in 5 (71.4%) cases, stage T1 tumors in 5 (45.5%) cases and stage T4 tumors in 1 (16.7%) case, which was statistically significant (p-value <0.05). Whereas stromal CD8+ TILs positivity was mostly found in stage T3 tumors, 22 (84.6%) cases followed by stage T2 tumors in 5 (71.4%) cases, stage T4 tumors in 4 (66.7%) cases and stage T1 tumors in 4 (36.4%) cases, which was statistically significant (p-value <0.05). Similar results were also described by Lu et al.[8] They found that CD8+ TILs positivity was highest in stage III (41% cases). But current study slightly differs from the finding of Huda et al. which concluded that positive CD8+ TILs were mostly seen in stage I-II (68.42% cases) compared to stage III-IV (31.58% cases).[13] Haas et al. also conducted a study where no correlation between the infiltration of CD8+T-Cells and clinical outcome was found.[14]

In the present study intra tumoral CD8+ TILs positivity was mostly found in the cases with no nodal involvement, in 9 (71.4%) cases and intra tumoral CD8+ TILs were positive in 24 (66.7%) of node involved cases, which was not statistically significant (p-value > 0.05). Also, stromal CD8+ TILs positivity was mostly found in the cases with no nodal involvement, in 10 (71.4%) cases and stromal CD8+ TILs were positive in 25 (69.4%) of node involved cases, which was not statistically significant (p-value >0.05). This finding slightly contradicts the findings of Lu et al. where CD8+ TILs positivity was higher in the cases with lymph node metastasis (54.6%) in comparison with the cases with no nodal involvement (45.4%).[8]

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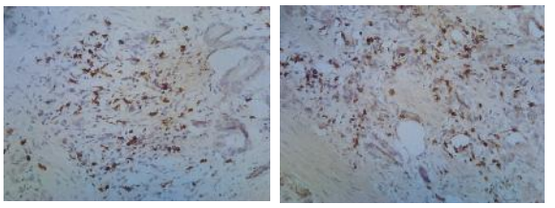

Image 1 PHOTOMICROGRAPH SHOWING NEGATIVE CD8 IT-TIL EXPRESSION IN GRADE II GASTRIC ADENOCARCINOMA (Left) and NEGATIVE CD8 PT-TIL IN GRADE II GASTRIC ADENOCARCINOMA (Right)

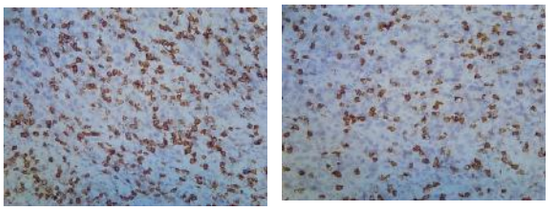

Image 2 PHOTOMICROGRAPH SHOWING POSITIVE CD8 IT-TIL EXPRESSION IN GRADE III GASTRIC ADENOCARCINOMA (Left) and POSITIVE CD8 PT-TIL IN GRADE III GASTRIC ADENOCARCINOMA (Right)

Limitations

- Relatively small sample size.
- Extensive research including all the subsets of TILs could not be possibly done due to lack of available resources.
- Pathological staging was done on the basis of tumor size (pT) and lymph node involvement (pN). Metastasis (pM) was not included.

Conclusion

Stromal CD8+ TILs revealed that the significant association with histological grade and pathological stage (pTN). It can be stated that high levels of TILs are associated with a positive prognosis and TILs reflect the protective host antitumor immune response.

Recommendations

It will be better to conduct a further study with larger sample size.

- CD8 immunostain for TILs can be utilised as a tool for assessment ofprognosis of the patients of gastric adenocarcinoma.
- Application of immunotherapy through evaluation of TILs may be helpful in control ofprogression of gastric adenocarcinoma.
- Long term follow-up of the patients to correlate TILs with progressionand recurrence of the disease and survival of the patients would be beneficial toestablish its prognostic and therapeutic role.

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Contribution of authors

UQT-Acquisition of data, data analysis, drafting & final approval.

JA-Data analysis, interpretatin of data & final approval.

FE-Design, data analysis, interpretation of data drafting & final approval.

SA-Interpretation of data, critical revision & final approval.

SR-Interpretation of data, drafting & final approval.

SDG-Concept, design, interpretation of data, critical revision & final approval.

SB-Concept, design, critical revision & final approval.

Disclosure

All the authors declared no conflict of interest.

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