Original Article

CD3+ Tumor Infiltrating Lymphocytes (TILs) in Gastric Adenocarcinoma

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ABSTRACT

Gastric cancer is the fifth most common cancer worldwide. Early and proper diagnosis and proper assessment of prognosis is one of the most important things for treatment response. The presence and activity of tumor-infiltrating lymphocytes (TILs) is a key parameter related to the antitumor immune response. The role of CD3+ TIL as a prognostic marker as well as the role in targeted immunotherapy has been studied in many cancers including adenocarcinoma of the stomach. A cross-sectional study was conducted in the Department of Pathology, Sir Salimullah Medical College, Dhaka, Bangladesh, from March 2022 to February 2024, to evaluate the expression of CD3+ tumor infiltrating lymphocytes in gastric adenocarcinoma and their association with histological grade and pathological stage. This. A total of 50 gastrectomy samples with histopathologically confirmed diagnosis of gastric adenocarcinoma were included in this study. The expression of CD3+ in TILs were evaluated in formalin-fixed and paraffin embedded specimens by immunohistochemistry. The CD3+ TILs were categorized as positive and negative expressions. The mean age of the participants was 54.98±12.10 years. Most of the tumors were located in the lesser curvature (34%), while most of the tumors were intestinal type (60%). On staging of tumors, 52% cases were in stage T3, followed by stage T1 (22%), stage T2 (14%) and stage T4 (12%). CD3+ intratumoral and stromal TIL expression was positive in 34(68%) and 28(56%) cases respectively. Significant association was found between intratumoral CD3+ TILs and tumor grade, pathological stage and nodal status ($p<0.05$). However, no association was observed between the stromal CD3+ TILs and tumor grade, pathological stage and nodal status ($p>0.05$). As part of tumor microenvironment, CD3+ 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.

Keywords: *Adenocarcinoma, stomach cancer, tumor infiltrating lymphocytes, immunohistochemistry.*

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INTRODUCTION

Gastric cancer is the seventh most common cancer worldwide and the fifth most frequently diagnosed.[1] Gastric adenocarcinoma is the term for cancer that develops in the stomach's epithelium lining. Over a million cases of gastric cancer are detected globally each year. Approximately 75.3% of gastric cancer cases in Asia.[2] The most common type of stomach cancer, adenocarcinoma, originates in the glandular tissue of the stomach and accounts for 90–95% of all stomach cancer cases. Stomach cancers are classified based on the type of tissue in which they originate.[3] It frequently involves a combination of environmental

and genetic factors, making it multifactorial. Diet, H. pylori and EBV infection, smoking, alcohol, prior stomach surgery, atrophic gastritis, bile reflux, radiation exposure, race, ethnicity, and other environmental variables are all linked to the development of gastric cancer.[4] Despite advancements in diagnosis and treatment, the prognosis for patients with gastric cancer remains poor, with 5-year overall survival rates ranging from 28% to 51%.[5] Recent research indicates that this aggressive behavior can be attributed to the immune system during the progression of the cancer and therapeutic interventions. Approximately 60% of patients with stomach cancer exhibit late-stage cancer diagnosis. Over 40% of patients who underwent curative resection experienced recurrence within 2 years after surgery.[6]

The "Cancer immune editing Theory" states that tumors develop as a result of immune system failure, which happens when tumor development and immune surveillance are out of balance.[7] Generally, there is a correlation between the infiltration of immune cells within a tumor and tumor development. Therefore, the distribution of various immune cell types detected in gastric carcinoma may provide helpful information for patient's progress.[8,9] Blood and lymphoid tissue contain lymphocytes, which are immune cell types produced in the bone marrow. Tumor-infiltrating lymphocytes are white blood cells that have moved from the circulation to a tumor. The term "tumor-infiltrating immune cells" refers to a broader category of immune cells that include T-cells, B-cells, natural killer cells, macrophages, neutrophils, dendritic cells, mast cells, eosinophils, basophils, and other immune cells in varying proportions. Their frequency fluctuates according to the type and stage of the tumor and occasionally correlates with the prognosis of the illness.[10] T-cells aid in immune response regulation and tumor cell destruction. The cell membrane of TILs contains a variety of distinct antigens, including CD3, CD4, CD8, FOXP3, CD20, and CD57. Typically, distinct cell surface antigens attach to particular lymphocyte types. For instance, T-cells are bound by CD3, CD4, CD8, and FOXP3. Consequently, TILs regulate the immune response linked to tumors in both directions. The majority of the infiltrating T-cells are lymphocytes that are CD3 and CD8 positive. In an immunocompetent host, they either create a tumor microenvironment that promotes tumor propagation or selectively protects tumor cell survival. They play a crucial role in inhibiting tumor growth by decreasing their outgrowth or destroying cancer cells.[7] All mature lymphocytes in the peripheral circulation, including CD4+ and CD8+ cells, are classified as CD3+ T lymphocytes. These cells provide a comprehensive picture of T lymphocytes, including all of its subgroups. Analyzing CD3+ TILs in tumors may help us understand the overall T cell composition of the host immune response and tumor microenvironment.[11] The existence of tumor-infiltrating T-cell, cytotoxic T-cells has been linked to a survival advantage. Various studies demonstrate that high numbers of CD3+ T-cells in tumor are significantly associated with lower frequencies of lymph node metastasis or disease recurrence or longer survival.[12,13] Therefore, the immune response to gastric cancer may serve as a novel prognostic and therapeutic marker. This study aimed to evaluate CD3 expression in the tumor infiltrating lymphocytes in gastric adenocarcinoma specimens and to find out its association with histological grade and pathological stage.

METHODS

This cross-sectional study was conducted between March 2022 and February 2024. We studied on a total of 50 specimens. Thirty-five cases were fresh resected specimens and rest of the fifteen cases were paraffin blocks of resected and diagnosed cases of primary gastric adenocarcinoma, which were collected from the Department of Pathology of Sir Salimullah Medical College and Bangabandhu Sheikh Mujib Medical Univerity, Dhaka, Bangladesh. The patients were enrolled according to patients of any age group with histopathologically diagnosed cases of gastric adenocarcinoma. 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 and tumors other than adenocarcinoma were excluded from this study. Data was collected in approved data collection form and privacy of the patient's was maintained. All the cases were numbered chronologically and the same number was

given to histopathological as well as in immunohistochemical slides. 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 Hematoxylin & Eosin (H&E) stain. All the slides were thoroughly evaluated by microscopic examination and grading and staging were done. The collected paraffin blocks of fifteen cases were given re-cut and subsequent staining was done. Relevant information was collected from previous reports. After following standard protocols two slides were made from each tumor block. One slide was stained with Hematoxylin & Eosin (H&E) stain for reviewing the diagnosis and grading, while another one was used for immunohistochemical analysis with CD3+ immuno-marker.

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 CD3+ 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. Polyclonal Rabbit Anti-Human CD3+ (1:100, Code A0452, Dako Cytomation, Glostrup, Denmark) was used as primary antibody. Secondary antibody used as with DAKO REALTM En Vision TM (HRP RABBIT/MOUSE). An acute appendicitis specimen with positive lymphocytes was taken as a positive control. After that immunostained sections of CD3+was 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 CD3+ 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 CD3+ positive T-cells among total lymphocytes were calculated. The average values of five fields were taken as the density (%) of CD3+ TILs. Percentage of immunopositively cells among total cells was calculated as: 1=<1% of cells; 2=1–10% of cells; 3=11–33% of cells; 4=34–66% of cells; and 5=67–100% of cells. Then, intensity score was estimated as: 0 =negative/no staining;1+ =mild; 2+ =moderate; and 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 CD3+ expression.[13] Final score was calculated as: ≥ Median value (positive) = CD3+intra tumoral ≥5 (positive); stromal ≥6 (positive); and <Median value (negative) = CD3+intra tumoral <5 (negative); stromal <6 (negative).

Tumor staging was done was using TNM classification of gastric adenocarcinoma according to the American Joint Committee of Cancer (AJCC). Tumors were observe both for the depth of invasion of primary tumor (pT) and the involvement of regional lymph nodes by the tumor (pN).[14]

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 CD3+ tumor infiltrating lymphocytes with histological grade, stage and nodal status were evaluated using Chi-square test. A p-value ≤0.05 was considered statistically significant. Results were presented in the tabulated form.

RESULTS

Out of total 50 cases, the majority of the cases belonged to the age group of 50–59 years (32%) and 60–69 years (22%). The mean age was 54.98±12.10 years (Table-I). Most of the tumors were located in the lesser curvature 17(34%), followed by antrum 12(24%), body and greater curvature 6(12%) each, pylorus 5(10%) and fundus 4(8%). Most of the tumors were intestinal type 30(60%), followed by diffuse type 17(34%), mucinous type 3(6%). Regarding the staging of tumors, 26(52%) cases were in stage T3, followed by stage T1 11(22%),

stage T2 7(14%) and stage T4 6(12%) cases (Table-II). A significant association was found between intra tumoral CD3+ TILs and tumor grade (p=0.031), pathological stage (p=0.049) and nodal status (p=0.049). However, no significant association was seen between the stromal CD3+ TILs and tumor grade (p=0.145), pathological stage (p=0.085) and nodal status (p=0.826) (Table-III).

Table-I: *Distribution of the study subjects by age group (N=50)*

Age group (in years)	Frequency	Percentage
20–29	1	2.0
30–39	4	8.0
40–49	9	18.0
50–59	16	32.0
60–69	11	22.0
≥70	9	18.0

Mean±SD = 54.98±12.10 years
Range (Min–Max) (24–76 years)

Table-II : *Distribution of study subjects based tumor characteristics (N=50)*

Variables	Frequency	Percentage
Location of the tumor		
Fundus	4	8
Body	6	12
Greater curvature	6	12
Lesser curvature	17	34
Antrum	12	24
Pylorus	5	10
Histological types		
Intestinal	30	60
Diffuse	17	34
Mucinous	3	6
Pathological stage		
T1	11	22
T2	7	14
T3	26	52
T4	6	12

Table-III : Comparison between CD3+TILs distribution within intratumoral and stromal compartments

Variables	CD3+ Intratumoral TILs		p-value	CD3+ stromal TILs		p-value
	Positive	Negative		Positive	Negative	
Histological Grade						
G-I	3 (33.3%)	6 (66.7%)	0.031^{S}	3 (33.3%)	6 (66.7%)	0.145^{NS}
G-II	16 (69.6%)	7 (30.4%)		16 (69.6%)	7 (30.4%)	
G-III	15 (83.3%)	3 (16.7%)		9 (50%)	9 (50%)	
Pathological Stage						
T1 T2	6 (17.6%)	5 (31.3%)	0.049^{S}	6 (54.5%)	5 (45.5%)	0.085^{NS}
T3	4 (11.8%)	3 (18.8%)		7 (100%)	-	
T4	19 (55.9%)	7 (43.8%)		12 (46.2%)	14 (53.8%)	
	5 (14.7%)	1 (6.3%)		3 (50%)	3 (50%)	
Nodal involvement						
Present	25 (69.4%)	11 (30.5%)	0.049^{S}	20 (55.5%)	16 (44.5%)	0.826^{NS}
Absent	9 (71.4%)	5 (30.4%)		8 (57.1%)	6 (42.9%)	

Chi-square test was applied to reach p-value; S=significant, NS=not significant.

DISCUSSION

Gastric cancer is the fifth most commonly diagnosed malignancy and the third leading cause of cancer related mortality worldwide[15]. In this study, the ages of patients ranging from 24 to 76 years (mean age was 54.98±12.10 years), and we observed that 32% of patients were in the 50–59 years age group. These results are in congruence with another Indian study

done by Pramanik et al.,[16] as they found the mean age of gastric carcinoma patients 55.3±12.71 years, with age group ranged from 20 to 81 years. It is also consistent with the study of Abdel-Aziz et al.,[17] in which it was found that patient age ranged from 27 to 75 years and mean age was 54.04±11.98 years. Another study by Saeed & Saeed[18] reported that the mean age was 54 years and ranged between (30–72) years. Among the present study cases, 60% of gastric adenocarcinoma were intestinal type. Rest were diffuse type (34%) and mucinous type (6%). It aligns with the results of Abel-Aziz et al.,[17] which showed that among 32 cases of gastric adenocarcinoma 66.7% were intestinal subtype and 29.2% were diffuse subtype. However, our findings slightly differ with the findings of Kang et al.,[19] where the most common type of gastric adenocarcinoma was diffuse type (70%).

In the present study, most of the tumor located along the lesser curvature of the stomach 17(34%), followed by antrum 12(24%), body and greater curvature 6(12%) cases each, pylorus 5(10%) and fundus 4(8%). However, those findings are different from the findings of Kang et al.,[19] as they found that the most common site was the body of the stomach (74.2%). In our study, 26(52%) patients were in stage T3. Stage T1 comprised 11(22%) cases, stage T2 7(14%) cases and stage T4 were found in 6(12%) cases. It matches the results of Lu et al.,[13] as they found that most of the cases were in the stage 3 (50%).

We observed that 34(68%) cases were positive for intra tumoral CD3+ TILs and 16 (32%) were negative for intra tumoral CD3+ TILs. Whereas 28(56%) cases were positive for stromal CD3+ TILs and 22 (44%) were negative for stromal CD3+ TILs. This finding is in congruence with the results of Saeed & Saeed, as they found positive results for CD3 in 28(60.86%) out of 43 samples. Our results are also comparable to that of with Kang et al.,[19] where stromal TILs were positive in 60.83% cases and intra tumoral TILs were positive in 50% cases. Similar results were reported by Kim et al.[20] and Ishigami et al.[21] as they found higher levels of CD3 expressions in gastric cancer samples.

In search of the association of intra tumoral CD3+ TILs with histopathological grades of gastric adenocarcinoma, we observed that intratumoral CD3+ TILs positivity was mostly found in grade 3 tumors (83.3%) cases. Grade 2 tumors showed intra tumoral CD3+ TILs positivity in 69.6% cases and grade 1 tumors showed intratumoral CD3+ TILs positivity in 33.3% cases, which was statistically significant ($p<0.05$). Moreover, stromal CD3+ TILs positivity was mostly found in grade 2 tumors (69.6%). Grade 3 tumors showed stromal CD3+ TILs positivity in 50% cases and grade 1 tumors showed stromal CD3+ TILs positivity in 33.3% cases; however, the difference was not statistically significant ($p>0.05$). Similar results were found by Saeed & Saeed,[18] where CD3+ TILs were mostly positive in grade 3 tumors (50%), followed by grade 1 (35.71%) and grade 3 (14.29%). When considering the association of CD3+ TILs with pathological stage of gastric adenocarcinoma, we found that intratumoral CD3+ TILs positivity was mostly found in stage T3 tumors (55.9%), followed by stage T1 tumors in (17.6%), stage T4 tumors (14.7%) and stage T2 tumors (11.8%); the difference was statistically significant ($p<0.05$). Nonetheless, stromal CD3+ TILs positivity was mostly found in stage T2 tumors (100%), followed by stage T1 tumors (54.5%), stage T4 tumors (50.0%) and stage T3 tumors (46.2%); the difference was not statistically significant ($p>0.05$). Our findings are closely related to the findings of Saeed & Saeed,[18] where 71.43% CD3+ TILs positive tumors were in stage I–II and 28.57% were in stage III–IV. When assessing the association of nodal positivity with CD3+ TILs, we found that intra tumoral CD3+ TILs positivity was found mostly in the patients with no nodal involvement (71.4%) and intratumoral CD3+ TILs was positive in 69.4% of patients with lymph node involvement; the differences were statistically significant ($p<0.05$). Similar results were found regarding stromal TILs, as stromal CD3+ TILs positivity was found in 57.1% cases with no nodal involvement, while stromal CD3+ TILs were positive in 55.5% of the node involved cases; however, the difference was not statistically significant ($p>0.05$). Our findings are similar to that of Kang et al.,[19] as they observed both stromal and intratumoral TILs were mostly positive in the cases without lymph node involvement (83.3% and 79.5% cases respectively).

CONCLUSION

Our data suggests that expression of intratumoral CD3+ TILs is associated with tumor grade, pathological stage and nodal status of the patients. Such expression levels can be utilized as indicators of biological behavior and prognosis as well as in therapeutic purpose of gastric adenocarcinoma. To conclude, immunophenotyping and evaluation of TILs subsets might be considered as a valuable supplementary tool for predicting prognosis of

patients and further management by application of immunotherapy.

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Ethical Clearance: This study was approved by the Institutional Ethics Committee of Sir Salimullah Medical College, Dhaka, Bangladesh.

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