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Immunohistochemical Expression of Programmed Death Ligand- 1 (PD-L1) in Gastric Adenocarcinoma and Non- Neoplastic Gastric Epithelium

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ABSTRACT

Background: Tumor progression is heavily influenced by immune evasion strategies such as the expression of Programmed Death Ligand-1 (PD-L1), which also presents as a promising target for cancer therapies. This study aimed to investigate the immunohistochemical presence of PD-L1 in gastric adenocarcinoma tissues and to compare it with non-cancerous gastric mucosa, and explore its relationship with various clinicopathological factors.

Methods: This comparative analytical cross-sectional study was conducted at the Histopathology Division, Department of Pathology, Peshawar Medical College, Riphah International University, Islamabad, over one year (March 2022–February 2023). A total of 60 formalin-fixed, paraffin-embedded (FFPE) samples were analyzed, comprising 30 gastric adenocarcinoma specimens from gastrectomies and 30 non-neoplastic gastric mucosa samples from endoscopic biopsies. Samples were selected using non-probability consecutive sampling. PD-L1 expression was assessed by standardized immunohistochemistry, scored for intensity and proportion of positive cells, and reviewed independently by two pathologists. Statistical analysis was performed using SPSS version 20.0; Chi-square and Fisher's exact tests were applied, with $p < 0.05$ considered significant. Although a smaller comparison group (e.g., 2:1 ratio) could suffice to demonstrate absence of PD-L1 in non-neoplastic tissue, an equal ratio (1:1) was chosen to strengthen comparability and analysis.

Results: PD-L1 expression was detected more frequently in 14 out of 30 neoplastic gastric tissues (46.6%) compared to 2 out of 30 non-neoplastic samples (6.6%), although this difference was not statistically significant (p=0.171). No significant associations were found between PD-L1 expression and patient age, sex, tumor location, histological subtype, tumor grade, stage, lymph node involvement, or presence of perineural or vascular invasion.

Conclusion: PD-L1 is commonly expressed in gastric adenocarcinoma; however, its expression does not appear to be significantly linked to major clinicopathological characteristics. Multicenter studies with larger study population are warranted to better understand the prognostic value and therapeutic potential of PD-L1 in gastric cancer.

Keywords: Gastric Neoplasms, Adenocarcinoma, Programmed Death-Ligand 1, Immunohistochemistry, Biomarkers

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INTRODUCTION

Gastric adenocarcinoma is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide, accounting for an estimated 1,089,000 new cases and approximately 769,000 deaths in 2020 alone[1,2]. The burden of this disease is disproportionately high in Eastern Asia, Latin America, and Eastern Europe, where incidence rates exceed 30 cases per 100,000 population annually[3]. Despite advances in diagnostic techniques and therapeutic options, the overall 5-year survival rate for advanced gastric cancer remains below 30%, largely due to late-stage diagnosis and the complex biological heterogeneity of tumors[4]. Understanding the tumor microenvironment and mechanisms of immune evasion has become critical for developing new therapeutic strategies aimed at improving patient outcomes.

Immunological evasion is made easier by programmed death ligand-1 (PD-L1), a transmembrane protein expressed on immunological and tumor cells that interacts with T-cells' PD-1 receptor to inhibit the anti-tumor immune response[5,6]. In a number of cancers, including gastric cancer, this PD-1/PD-L1 pathway has become a crucial immunological checkpoint and therapeutic target[7]. To forecast how well patients with gastric cancer might have responded to immune checkpoint inhibitors such as pembrolizumab and nivolumab, which had already demonstrated encouraging outcomes, the immunohistochemical (IHC) identification of PD-L1 expression in tumour tissues was considered essential[8,9]. However, due to a variety of factors, including tumor heterogeneity, the use of antibody clones, scoring criteria, and ethnic variances, the expression of PD-L1 in gastric adenocarcinoma differs greatly between studies[10,11].

Moreover, the expression of PD-L1 in non-neoplastic gastric epithelium is less studied but important to understand the baseline expression and the changes that accompany malignant transformation[12]. Some studies have suggested that chronic inflammation and Helicobacter pylori infection can induce PD-L1 expression in the gastric mucosa, which may contribute to immune tolerance and carcinogenesis[13,14]. Understanding PD-L1 expression patterns in both neoplastic and non-neoplastic gastric tissues can provide insights into gastric carcinogenesis and help identify patients who might benefit from immunotherapy[15].

While the therapeutic significance of PD-L1 in gastric adenocarcinoma is well-recognized, limited data compare its expression in malignant versus non-neoplastic gastric epithelium within the same population. Clarifying this differential expression through immunohistochemical studies could improve the understanding of immune evasion mechanisms during gastric tumorigenesis and guide patient selection for PD-1/PD-L1 targeted therapies. The present study aimed to evaluate and compare the immunohistochemical expression of PD-L1 in gastric adenocarcinoma tissues and non-neoplastic gastric epithelium, and to assess its potential role in tumor immune evasion and therapeutic targeting.

METHODS

This comparative analytical cross-sectional study was carried out over a one-year period from March 1, 2022, to February 28, 2023, at the Histopathology Division of the Department of Pathology, Peshawar Medical College, Peshawar, Riphah International University, Islamabad. Ethical clearance was granted by the Institutional Review Board (IRB) of the Prime Foundation, Pakistan (Approval No: Prime/IRB/2022-387, dated January 17, 2022).

The sample size was calculated using OpenEpi software, based on PD-L1 expression rates reported in gastric tissues. An Asian cohort study provide data comparable to our target population, reporting PD-L1 positivity of 45% in gastric adenocarcinoma and 5% in non-neoplastic gastric mucosa [16]. Using these assumptions and aiming for 80% study power at a 95% confidence interval, the minimum required sample size was 27 cases per group; therefore, 30 cases of gastric adenocarcinoma (gastrectomy specimens) and 30 non-neoplastic gastric mucosa samples (endoscopic biopsies) were included, totalling 60 cases.

Subsequent studies have reported heterogeneous PD-L1 expression rates due to differences in methodology, scoring criteria, and antibody clones. One study demonstrated that different PD-L1 antibody clones (SP142, 28-8, E1L3N) yielded variable staining patterns, with SP142 showing the highest positivity in stromal/immune cells and significant prognostic value [17]. A recent study reported PD-L1 positivity in 45.6% of gastric cancer patients with peritoneal metastasis (CPS $\geq$ 1) and 14.3% with high expression (CPS $\geq$ 10), showing prognostic significance for survival outcomes [18]. These variations confirm that reported PD-L1 frequencies depend strongly on technical and biological factors. Thus, the Asian study dataset was considered most appropriate for sample size estimation in our local context [16], while we cited more recent studies to contextualise our findings.

Cases were selected using non-probability consecutive sampling. Only well-preserved FFPE blocks with verified gastric adenocarcinoma diagnoses and comprehensive clinical and pathological data

were included. Samples showing poor fixation or inadequate antigen retrieval potential were excluded from the analysis.

Gastric adenocarcinoma specimens, including partial, distal, and total gastrectomy samples, were retrieved from the electronic laboratory records. Corresponding FFPE blocks were sectioned at 5 to 7 microns and stained with Hematoxylin and Eosin (H&E) for detailed histopathological evaluation. This examination assessed parameters such as tumor histological subtype, depth of gastric wall invasion, presence of lymphovascular and perineural invasion, lymph node metastasis, and surgical margin status. All findings were systematically documented using a structured proforma.

The study variables encompassed patient demographics, histological tumor subtype and grade, tumor site, invasion depth, lymph node status, vascular and perineural invasion, as well as PD-L1 expression determined by immunohistochemistry. PD-L1 staining was performed using the Dako universal detection kit with a Rabbit Monoclonal PD-L1 primary antibody, following the manufacturer's protocol. To ensure unbiased evaluation, two independent pathologists, blinded to clinical information, examined the slides at 40x magnification, focusing on cytoplasmic and membranous staining in tumor and epithelial cells.

For PD-L1 scoring, the methodology was employed due to its simplicity and reproducibility[19]. The proportion of positive tumor cells was categorized into four groups: less than 5%, 5% to less than 25%, 25% to 50%, and greater than 50%. Staining intensity was graded on a scale from 0 (no staining) to 3 (strong staining). The sum of the percentage and intensity scores formed a staining index, where an index of 4 or higher was classified as high (positive) PD-L1 expression, and less than 4 as low (negative) expression.

SPSS version 20.0 was used to analyze the data. While categorical data like gender, tumor grade, location, and PD-L1 expression were shown as frequencies and percentages, continuous variables like age were shown as mean ± standard deviation. Variables including age groups, tumor site, and depth of invasion were subjected to stratified analyses. PD-L1 expression in neoplastic and non-neoplastic gastric mucosa was compared using chi-square and Fisher's exact tests. Additionally, correlations between PD-L1 expression and pathological characteristics such as tumor grade, stage, vascular invasion, and perineural invasion were investigated. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Table 1: Clinicopathological Parameters for Gastric Adenocarcinoma Cases (n=30)

Parameter	Category	n (%)
Gender	**Male**	22 (73.3%)
	Female	8 (26.7%)
	M: F Ratio	2.7:1
Age	**> 50 years**	25 (83.3%)
	< 50 years	5 (16.7%)
	Mean Age (years)	60.36 ± 11.78
Gastric Adenocarcinoma Subtype	**Intestinal Type**	17 (56.6%)
	Diffuse Type	13 (43.3%)
Histological Grade	**Low Grade**	11 (36.7%)
	High Grade	19 (63.3%)
Tumor Location	**Upper Stomach** (Fundus/Body)	13 (43.3%)
	Lower Stomach (Antrum/Pylorus)	17 (56.6%)
Tumor Invasion (pT Stage)	**Low Stage** (pT2)	1 (3.3%)
	High Stage (pT3, pT4)	29 (96.6%)
Lymph Node Metastasis (pN Stage)	**pN0**	5 (16.6%)
	pN1, pN2, pN3	25 (83.3%)

The clinicopathological profile of gastric adenocarcinoma cases in this study revealed a marked male predominance, with males comprising over two-thirds of the patients and a male-to-female ratio of 2.7:1. The majority of cases occurred in individuals older than 50 years, with the average age being approximately 60 years. Histologically, the intestinal subtype was slightly more prevalent than the diffuse type. Most tumors were high grade and predominantly located in the lower part of the stomach. The vast majority of cases were diagnosed at an advanced tumor invasion stage (pT3 or pT4). Lymph node metastasis was also common, present in over 80% of the cases, indicating a

significant degree of regional disease spread at diagnosis (Table 1). In addition, 30 non-neoplastic gastric mucosa samples were analysed as a reference control group to validate PD-L1 expression patterns between malignant and non-malignant tissues.

Representative hematoxylin and eosin (H&E) sections of gastric adenocarcinoma are shown in Figures 1A to 1C. These illustrate the histological spectrum of differentiation and corresponding PD-L1 immunohistochemical staining patterns. Figure 1A demonstrates strong membranous and cytoplasmic PD-L1 expression in a well-differentiated intestinal-type gastric adenocarcinoma, confirming its immunohistochemical positivity. Figure 1B highlights diffuse high-intensity PD-L1 staining in moderately differentiated gastric adenocarcinoma, emphasizing tumor heterogeneity in immune checkpoint expression. Figure 1C shows intense PD-L1 positivity in poorly differentiated gastric adenocarcinoma, supporting the role of immune checkpoint activation across tumor grades.

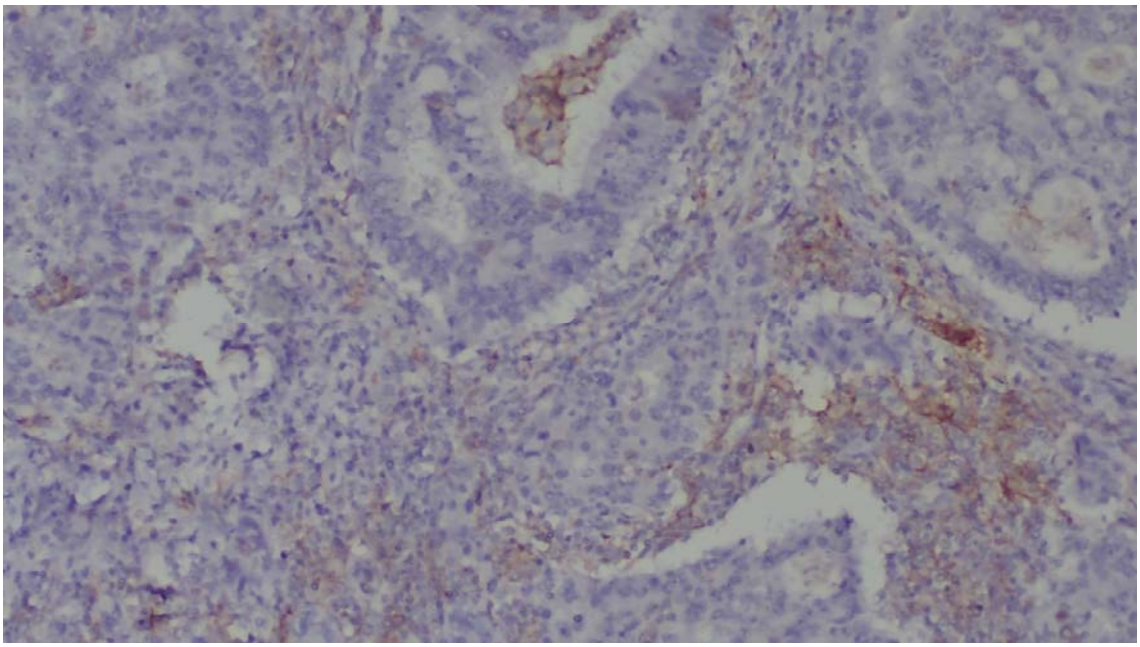

Figure 1A: Well Differentiated Gastric Adenocarcinoma showing high intensity PD-L1 immunohistochemical staining (20× magnification).

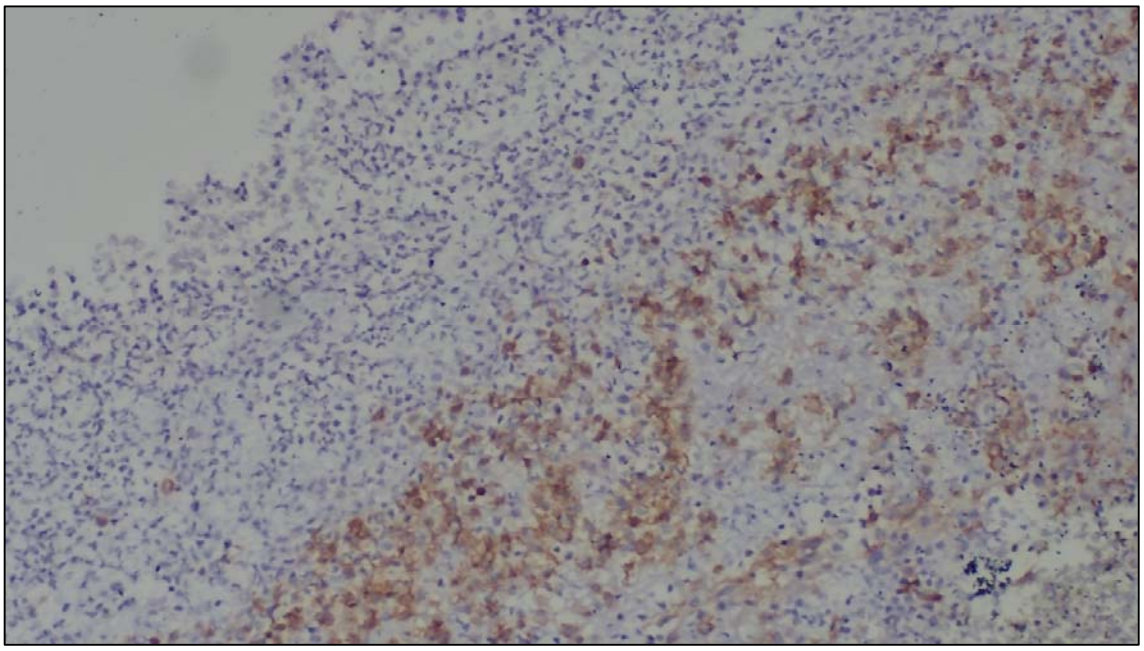

Figure 1B: Moderately Differentiated Gastric Adenocarcinoma showing high intensity PD-L1 immunohistochemical staining (10× magnification).

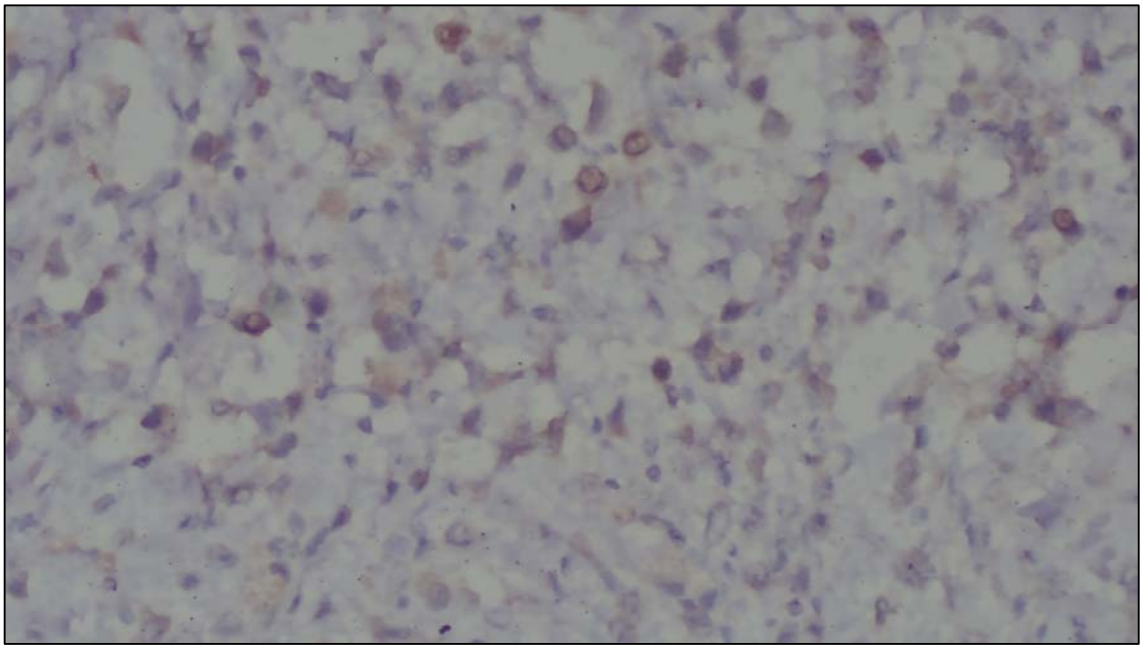

Figure 1C: Poorly Differentiated Gastric Adenocarcinoma showing high intensity PD-L1 immunohistochemical staining (40× magnification).

The analysis of PD-L1 expression showed a higher frequency of positivity in neoplastic gastric mucosa compared to non-neoplastic tissue; however, this difference was not statistically significant. When stratified by clinical and pathological parameters such as gender, age, tumor location, and histological subtype, PD-L1 expression did not demonstrate significant variation. Similarly, no

meaningful association was found between PD-L1 status and tumor grade, pathological stage, lymph node metastasis, or the presence of perineural and perivascular invasion. These findings suggest that PD-L1 expression in gastric adenocarcinoma may be independent of these conventional clinicopathological factors. (Table 2)

Table 2: Comparison of PD-L1 Expression in Gastric Adenocarcinoma (GAC) Cases Based on Various Clinical Parameters

Parameter	Category	PD-L1 Expression		p-value
		Negative n (%)	Positive n (%)	
Non-Neoplastic vs Neoplastic Mucosa	**Non-Neoplastic Gastric Mucosa**	28 (93.3%)	2 (6.6%)	0.171
	Neoplastic Gastric Mucosa	16 (53.3%)	14 (46.6%)	
Gender	**Male**	12 (40.0%)	11 (36.7%)	0.818
	Female	4 (13.3%)	3 (10.0%)	
Age	**< 50 Years**	3 (50%)	3 (50%)	0.713
	≥ 50 Years	14 (58.3%)	10 (41.7%)	
Tumor Location	**Upper Stomach** (Fundus/Body)	7 (53.8%)	6 (46.2%)	0.785
	Lower Stomach (Pylorus)	10 (58.8%)	7 (41.1%)	
Lauren's Subtypes	**Intestinal Type**	10 (58.8%)	7 (41.1%)	0.785
	Diffuse Type	7 (53.8%)	6 (46.1%)	
Grade of Gastric Adenocarcinoma	**Low Grade**	8 (72.7%)	3 (27.2%)	0.179
	High Grade	8 (42.2%)	11 (57.8%)	
AJCC Pathological Stage (pT)	**pT2**	1 (100%)	0 (0%)	0.432
	pT3, pT4	15 (51.7%)	14 (48.3%)	

Lymph Node Metastasis (pN)	**Without Lymph Node Mets (pN0)**	4 (80%)	1 (20%)	0.190
	With Lymph Node Mets (pN1-3)	12 (48%)	13 (52%)	
Perineural Invasion	**With Perineural Invasion**	10 (50%)	10 (50%)	0.605
	Without Perineural Invasion	6 (60%)	4 (40%)	
Perivascular Invasion	**With Perivascular Invasion**	9 (45%)	11 (55%)	0.196
	Without Perivascular Invasion	7 (70%)	3 (30%)	

Representative non-neoplastic gastric mucosa is shown in Figure 2. This figure illustrates non-neoplastic gastric mucosa with absent PD-L1 staining, serving as a negative control and validating the specificity of tumor-associated expression.

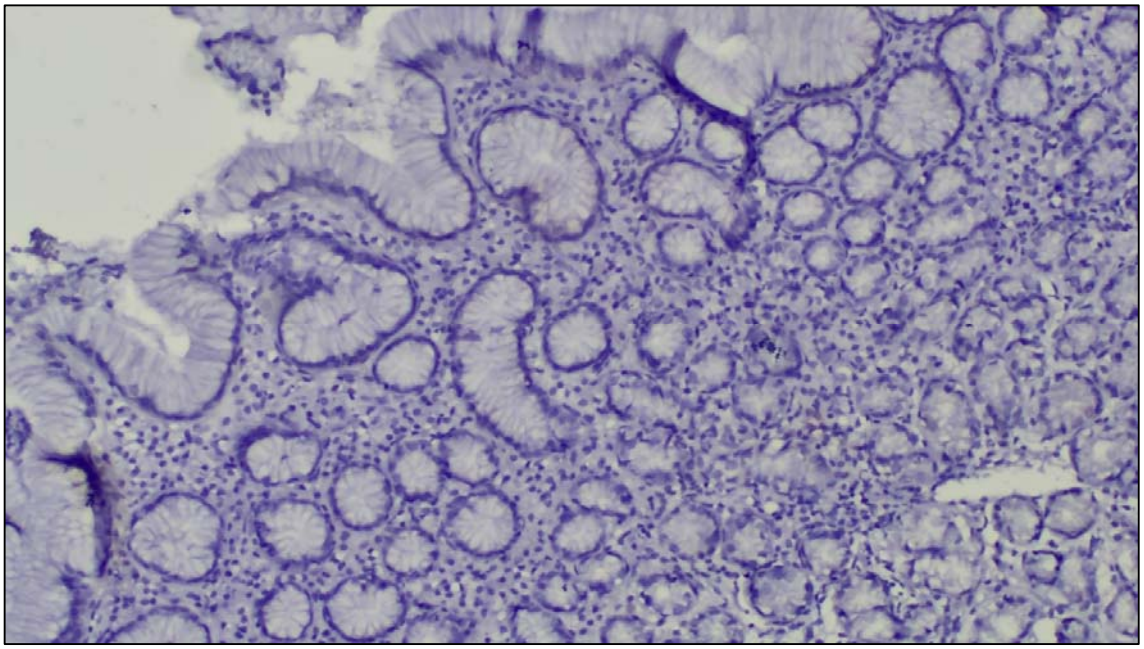

Figure 2: Moderate Active Gastritis showing negative PD-L1 staining (20× magnification).

DISCUSSION

In this study, comparing 30 cases of gastric adenocarcinoma with 30 samples of non-neoplastic gastric mucosa, no statistically significant difference was observed in PD-L1 expression between cancerous and non-cancerous tissues. Furthermore, PD-L1 expression showed no meaningful variation when analyzed according to patients' gender, age categories, tumor site, histological subtype, tumor grade, depth of invasion, lymph node involvement, or the presence of perineural and vascular invasion.

The male predominance observed aligns with a finding reported locally but contrasts with a study showing female predominance in younger age groups[20,21]. Tumor location predominantly involved the lower stomach, similar to Turkish cohorts[22], while Western studies report upper or middle stomach predominance[23]. PD-L1 expression in GAC was higher than in non-neoplastic mucosa. According to a Malaysian study, there was no discernible relationship between Lauren's histological subtypes and PD-L1 expression[24]. Similarly, a study reported that PD-L1 expression is not significantly correlated with clinicopathological criteria, including tumor grade, stage, or lymph node involvement[25]. Nevertheless, a study indicated a function for PD-L1 in tumor development and dissemination by demonstrating strong correlations between PD-L1 expression and advanced tumor stage or lymph node metastases[26]. A study also reported differential PD-L1 expression between histological subtypes[27]. Variations in methodology, sample sizes, and geographic differences may account for these conflicting findings.

The findings of this study indicate that PD-L1 expression is present in a significant proportion of gastric adenocarcinoma cases but does not correlate strongly with traditional clinicopathological features such as tumor grade, stage, or lymph node involvement. This suggests that PD-L1 expression alone may not serve as a reliable prognostic biomarker in gastric cancer. However, given its role in immune evasion, assessing PD-L1 status could still provide valuable information for identifying patients who may benefit from immune checkpoint inhibitor therapies. Incorporating PD-L1 testing into routine pathological evaluation might help guide personalized immunotherapy strategies, especially as targeted treatments become more widely available.

This study has several limitations that should be acknowledged. The relatively small sample size of 30 gastric adenocarcinoma cases limits the statistical power and generalizability of the findings. Additionally, the cross-sectional design precludes assessment of patient outcomes or survival about PD-L1 expression. Variations in antibody clones, scoring systems, and interpretation criteria for PD-L1 immunohistochemistry may also affect comparability with other studies. Lastly, because the study

was only carried out at one location, the findings might not be as applicable to larger, more varied populations. To confirm these results and investigate the prognostic and predictive significance of PD-L1 in gastric cancer, larger, multicenter prospective studies are required in the future.

In conclusion, our results highlight the intricacy of PD-L1's role in tumor biology by indicating that its expression in gastric adenocarcinoma may not be closely associated with conventional clinicopathological criteria. To fully understand the prognostic and therapeutic implications of PD-L1 in gastric cancer, especially in the age of immunotherapy, larger, multicenter studies are necessary.

CONCLUSION

Although PD-L1 expression was observed more frequently in neoplastic gastric tissues compared to non-neoplastic samples, this difference did not reach statistical significance. In our analysis, PD-L1 expression showed no significant association with various clinicopathological factors such as tumor subtype, patient age and gender, tumor location, histological grade and stage, presence of perineural or lymphovascular invasion, or lymph node metastasis in gastric adenocarcinoma cases. These findings suggest that while PD-L1 is commonly expressed in gastric cancer, its usefulness as a prognostic biomarker may be limited. Therefore, further research is necessary to clarify its role and potential value in guiding personalized immunotherapy strategies.

ETHICAL APPROVAL

The study received ethical approval from the Ethical Review Committee, under reference number (Ethical Approval No: Prime/IRB/2022-387, Dated: 17th January, 2022.

FUNDING

None.

CONFLICT OF INTEREST

None

AUTHORS CONTRIBUTIONS

FR developed the study concept and design, supervised the project, and provided administrative, technical, and material support. **SF** and **DK** collected and analysed the data, interpreted the results, and drafted the manuscript. **MT** and **SS** contributed to data acquisition and critically reviewed the manuscript, while DK and SS also provided further critical revisions.

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