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Spectrum of Gastric Carcinoma in a Tertiary Care Centre with Special Reference to PDL1 and Cyciln D1

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Gastric carcinoma is the fifth most frequently diagnosed tumor and the fourth leading cause of death. They represent a heterogenous group of tumors with multifactorial etiologies, both environmental and genetic. PD-L1 is a transmembrane protein, and a positive PD-L1 expression in gastric carcinoma may be a predictive biomarker of the response to PD-1/PD-L1 immune checkpoint inhibitors. Cyclin D1 is an important cell cycle regulatory protein and involved in the carcinogenesis of various cancers including gastric cancer.
Aims: The aim of this study is to find out the clinicopathological spectrum of gastric carcinoma and to show the immunohistochemical expression of Cyclin D1 and PD-L1 to evaluate their prognostic importance and their therapeutic impact.
Study Design: It is an observational cross-sectional study conducted in the Department of Pathology in collaboration with the Department of Surgery, in a tertiary care hospital. Partial and total gastrectomies were selected from January 2021 to July 2022 in a tertiary care hospital. Clinical history was collected in the study proforma. Immunohistochemical staining for Cyclin D1 and PD-L1 was performed.
Material and Methods: The clinicopathological parameters like age, gender, histological type, regional lymph node status, lymphovascular invasion, perineural invasion, and pathological stage were compared and correlated with Cyclin D1 and PD-L1 expression.
Results: Positive Cyclin D1 and PDL1 expression were found in 50% and 70% cases of gastric carcinoma, respectively. Cyclin D1 expression showed statistically significant correlation with anemia, regional lymph node status, and lymphovascular invasion. PD-L1 and Cyclin D1 expression showed statistically significant association between them (p value-0.0006).
Conclusion: Cyclin D1 and PDL1 are important biomarkers in gastric carcinoma. Their contribution towards prediction of progression and prognosis, along with newer therapeutic modalities, is of immense importace in these patients. A statistically significant correlation was found between these two markers.

Keywords: Combined positive score; cyclin D1; gastric carcinoma; gastrectomy; immunohistochemistry; PD-L1.

1. INTRODUCTION

"Gastric carcinoma (GC) is one of the most common cancers with mortality and morbidity worldwide" [1]. "Men are twice as commonly affected as women. This may be due to the protective effect of oestrogen against gastric cancer development" [2]. "GC is a multifactorial disease, 90% of which are sporadic, while 10% of the cases are familial. The genetic factors are usually the primary cause of Hereditary diffuse gastric cancer" [3]. "The GC is one of the common cancers in the north eastern and southern states of the Indian subcontinent, as per the National Cancer Registries. Its frequency in the north eastern states of India is higher than the rest of India" [4].

"The incidence shows a wide geographical variation, with more than 50% of the new cases occurring in the developing countries. Carcinoma stomach is the 5th common cause of carcinoma in the world. and 4th common cause of carcinoma death. It is very common in Asia, in China, Japan, Korea, etc. Previously, it was frequent in the United States and Europe, but its incidence has decreased in these countries" [5].

"Adenocarcinoma is the major histological subtype of GC, constituting 90-95% of all gastric malignancies. Environmental factors play a vital role in the incidence of GC, reflecting a characteristic geographical distribution" [5]. Death from stomach carcinoma is more frequent in Eastern Asia, South America, and parts of Europe [5].

"Helicobacter pylori (H. pylori) infection and certain environmental factors like consumption of preserved food containing carcinogenic nitrates, lifestyle, tobacco, alcohol, and obesity are some of the known eitiologic factors for GC" [5]. There is a general declining incidence of GC mainly due to higher standards of hygiene, improved food conservation, and *H. pylori* eradication. GC historically ranks among the worst malignancies, with 20%- 30% of the patients surviving for 5 years after diagnosis. There is some improvement in survival in Japan, Korea, and to some extent in China [5].

PD1 is expressed in lymphocytes and in various tumor cells. If the interaction between Progamed Death 1 (PD1) and Programed Death Ligand 1 (PDL1) can be stopped by anti PDL1, the antitumor response occurs [6-7].

Accumulation of genetic and molecular abnormalities occurs during the process of gastric carcinogenesis, in which oncogenes are activated, tumor suppressor genes, and DNA repair genes are inactivated. Overexpression of growth factor receptors, inactivation of DNA repair genes, and cell adhesion molecules also occur in this process [8-9]. The Cyclin D1 s increased in cases of gastric adenocarcinoma. Its overexpression is also related to the prognosis and overall survival of the patients. It is usually found in poorly differentiated tumors and related to decreased survival of the patients [10].

PDL1 is also assessed in cases of gastric carcinoma. It has an important therapeutic role. On the basis of PDL1 positive cells CPS (Combined Positive Score) is assessed, and therapy is started [11]. PDL1 expression was higher in adenocarcinoma and invasive carcinoma, and in those cases the diameter of the lesion in the gross specimen is more than 5 cm [12]. The combined study of gastric carcinoma and its association with Cyclin D1 and PDL1 are lacking. We undertook this study to ascertain the relationship among Gastric carcinoma, PDL1, and Cyclin D1. Immune checkpoint inhibition plays an important role in modern oncology. The PD-1 (Programed Death 1) receptor and its ligand PD-L1 (Programed Death ligand 1) are physiologically involved in immunomodulation. PD-1, a member of CD 28 superfamily, is an important immunosuppressive molecule, mainly expressed in T cells, NK cells and B cells surrounding tumor tissues. PD-L1 is a 40 kDa type 1 transmembrane protein and is a member of the B_7 protein family, which are expressed on a variety of cell types, including epithelium, B cells, mesenchymal stem cells, dendritic cells, macrophages, and mast cells [13]. Immune checkpoint inhibitors targeting PD1/PDL1 can aid the treatment of Gastric adenocarcinoma (GAC). However, the reported positive expression rate of PD-L1 in GAC is variable [14,15].

“The Cyclin D protein family interacts with cyclin dependent kinases (CDKs) 2,4, and 6 to regulate cell cycle progression. Cyclin D1, Cyclin D2, and Cyclin D3 are the three isoforms identified in humans. Cyclin D1 is a cell cycle regulator frequently involved in the G1/S transition. Deregulation of this pathway can result in aberrant cell cycle, resulting in carcinogenesis” [16,17].

2. MATERIAL AND METHODS

It is an observational cross-sectional study conducted in the Department of Pathology in collaboration with the Department of Surgery, in a tertiary care hospital. Fifty patients of Primary Gastric carcinoma diagnosed on partial and total gastrectomies were selected. The study was conducted over a period of 18 months from January 2021 to July 2022. Patients who received neo-adjuvant systemic therapy were excluded from this study.

After fixation, grossing was done. Different types of carcinoma were noted (Fig. 1 A,B,C). Total 798 blocks were made from the specimens. From the paraffin blocks, Hematoxylin & Eosin (H&E) and Immunohistochemical (IHC) staining were done for Cyclin D1 and PD-L1 expression in all these cases.

Four- micron sections were prepared from each formalin fixed and paraffin embedded tissue sample and stained with H&E and antibody against PD-L1(monoclonal Mouse anti human PD-L1, clone 22C3, DAKO, LOT-11431000, Expiry date:1/05/2024) and Cyclin D1(monoclonal rabbit anti-human, clone EP12, DAKO, LOT-R07035MA, Expiry date: 31.5.2024). Normal tonsil used as positive control and negative control was achieved by omission of primary antibody in PD-L1 and Cyclin D1.

2.1 Interpretation of Immunostaining

PD-L1: PD-L1 expression was evaluated using Combined Positive Score (CPS).

CPS = [Number of PD-L1 stained cells (tumor cells, lymphocytes, macrophages)/Total number of viable tumor cells] x100

Maximum CPS score is 100. A minimum of 100 viable tumor cells must be present for the specimen to be considered adequate for PD-L1 evaluation.

PD-L1 expression was considered positive for tumor cells if tumor cells showed complete and/or partial circumferential linear cellular membrane staining (brown) of any intensity where as tumor associated immune cells are considered PD-L1 positive if there is any staining (brown).

Results were considered PD-L1 negative if CPS was <1 and PD-L1 positive if CPS was >=1.

2.2 Tumor Infiltrating Lymphocytes (TILs)

Tumor infiltrating lymphocytes (TILs) are globally defined as the mean percentage of the invasive tumor area (including the tumor bed and peri-tumoral stroma), occupied by lymphocytes and plasma cells.

Based on this definition, the tumors included in this study were divided into three grades

Grade 1-(low, <=10%), considered TILs- low.
Grade 2-(moderate, 10-50%)
Grade 3-(high, >50%)

Patients with Grade 2 or 3, were considered TILs high.

2.3 Cyclin D1

Cyclin D1 immunohistochemical intensity and distribution were semi-quantitatively scored using the Allred score method. Only nuclear staining was considered specific. With this method, the intensity of immunohistochemical reaction as viewed under a light microscope (10 visual fields under high power objective, 400x) was recorded as 0 (negative); 1 (weak); 2 (moderate); and 3 (strong). The proportion of positive cells and intensity scores were then added to obtain a total score, which ranged from 0 to 8.

2.4 Statistical Analysis

All data were thoroughly maintained on a Microsoft Excel spreadsheet. Statistical analyses were performed using SPSS (software version 27.0; SPSS Inc.; Chicago, IL, USA) and Graph Prism version 5. The P value was found using a table of values from the Student's t-distribution. P value <=0.05 was considered statistically significant.

3. RESULTS

There were a total 50 cases, which includes 36 males and 14 females. The age of patients ranged from 31 to 80 years; the mean age (+/- standard deviation) of the patients was 55.0 +/- 11.76 years. The predominant age group (52%, 26 cases) is 41-60 years. The antral and pyloric region were most frequently involved (52% and 38%, respectively). The most, common symptoms were dyspepsia, vomiting, and weight loss, and predisposing factors were unhealthy food habits followed by smoking. The size of the tumors ranged from 1.5 cm to 8 cm. More than 50% of cases (29 cases -58%) were in T3 in the TNM group.

There were 22 cases (44%) of Tubular adenocarcinoma (the most common histological subtype) (Fig. 1 D,E) followed by 10 cases (20%) of Poorly cohesive carcinoma (Fig. 1 F,G). 8 cases (16%) of Mucinous adenocarcinoma (Fig. 1H), 5 cases (10%) of Mixed adenocarcinoma, 4 cases (8%) of Poorly cohesive carcinoma-signet ring cell type and 1 case of Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) (Fig. 1 H,I) . Intestinal type was the most prevalent Lauren's histological type (60%). Regional lymph nodes were involved by the tumor cells in 32 cases (64%) (Fig. 1 K). Lymphovascular invasion was present in 41 cases (82%). Perineural invasion was present in 14 cases (28%). 19 cases (38%) had Grade 1, 26 cases (52%) had Grade 2, and 5 cases (10%) had Grade 3 TILs (Fig. 1 L).

On Cyclin D1 immunohistochemical examination, 25 cases were Cyclin D1 negative (score 0 to 2) and 25 cases were Cyclin D1 positive (score 3 to 8) among which 7 cases had Cyclin D1 score 5 (moderate), 13 cases had Cyclin D1 score 6 (strong) and 5 cases had Cyclin D1 score 7 (strong) (Fig. 2 A,C,E,H,J).

On PD-L1 immunohistochemical examination, 15 cases were PD-L1 negative (CPS <1), 35 cases were PD-L1 positive (CPS >=1). Among PD-L1 positive cases, 20 cases had CPS between 1 to 4, 5 cases had CPS between 5 to 9 and 10 cases had CPS>= 10 (Fig. 2 B,D,F,G,I,K,L).

PD-L1 showed statistically significant correlation with anemia (p value-0.0117), TILs (p value-0.0021), lymph node status (p value-0.0007), lymphovascular invasion (p value-0.0080), Pathological stage (0.0111).

No statistically significant correlation was found between PD-L1 expression and age of patients, gender of patients, clinical features (other than anemia), predisposing factors, tumor location, tumor size, gross features, Lauren's classification, and histological subtype. Among histological subtypes , Tubular adenocarcinoma (moderately differentiated) showed maximum positive PD-L1 expression (15 cases), followed by poorly cohesive carcinoma-other cell type (8 cases). Out of 8 cases of Mucinous adenocarcinoma, 5 cases showed positive PD-L1 expression. Among 5 cases of Mixed

adenocarcinoma, 3 cases showed positive PD-L1 expression. There was a single case of MiNEN, which was negative for PD-L1 expression. PDL1 positive gastric carcinoma cases were associated with high TIL (grade 2 and 3).

Out of 22 cases of tubular adenocarcinoma, 11 cases were Cycin D1 (CCND1) positive. 4 cases of poorly cohesive signet ring cell type showed positive CCND1 expression. Among 10 cases of poorly cohesive carcinoma other cell type, 4 were positive for CCND1. 4 out of 8 cases of Mucinous adenocarcinoma showed positive Cyclin D1 expression. 2 out of 5 cases of Mixed adenocarcinoma showed positive Cyclin D1 expression. A single case of MiNEN was negative for Cyclin D1 expression.

Out of 30 cases of intestinal type, 15 cases were positive for Cyclin D1 expression, and 21 cases were positive for PD-L1 expression. Out of 14 cases of diffuse type, 8 cases were positive for Cyclin D1 expression, and 11 cases were positive for PD-L1 expression.

There was a statistically significant correlation between Cyclin D1 expression and age of patients (p value-0.0402), anemia (p value-0.0005), regional lymph node status (p value-0.0017), lymphovascular invasion (p value-0.0099), perineural invasion (p value - 0.0117), pathological stage (p value-0.0015).

There is a statistically significant association between PD-L1 and Cyclin D1 expression (p value- 0.0006). The correlation between clinico-pathological factors and Cyclin D1 and PD-L1 expression is summarised in Tables 1 and 2. Cyclin D1 score 5 (moderate), 13 cases had Cyclin D1 score 6 (strong), and 5 cases had Cyclin D1 score 7 (strong).

The relationship between Cyclin D1 and clinicopathological factors has been described in Table 1.

The relationship between PDL1 and Clinicopathological factors have been described in Table 2.

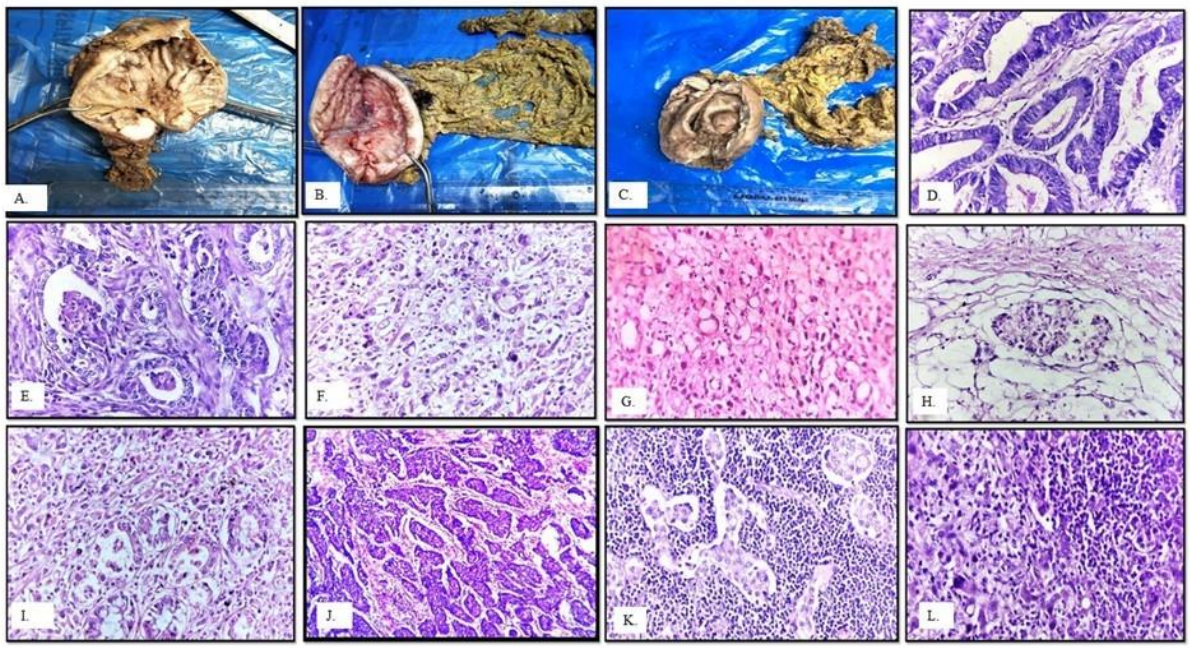

Fig. 1. Gross pictures of gastrectomy specimens showing, A. an ulcero-proliferative growth in the antro-pyloric region of stomach, B. a mucinous growth and C. a polypoid growth in the body of stomach. H&E (400X) from growth in stomach showing, D. well differentiated gastric adenocarcinoma, E. moderately differentiated gastric adenocarcinoma, F. poorly cohesive carcinoma (other cell type), G. poorly cohesive carcinoma (signet ring cell type), H. mucinous adenocarcinoma, I. mixed tubular and poorly cohesive carcinoma. H&E (100X) from growth in stomach showing, J. Gastric MiNEN. H&E (400X) showing K. lymph node metastasis from gastric adenocarcinoma and L. tumor infiltrating lymphocytes in a case of gastric adenocarcinoma

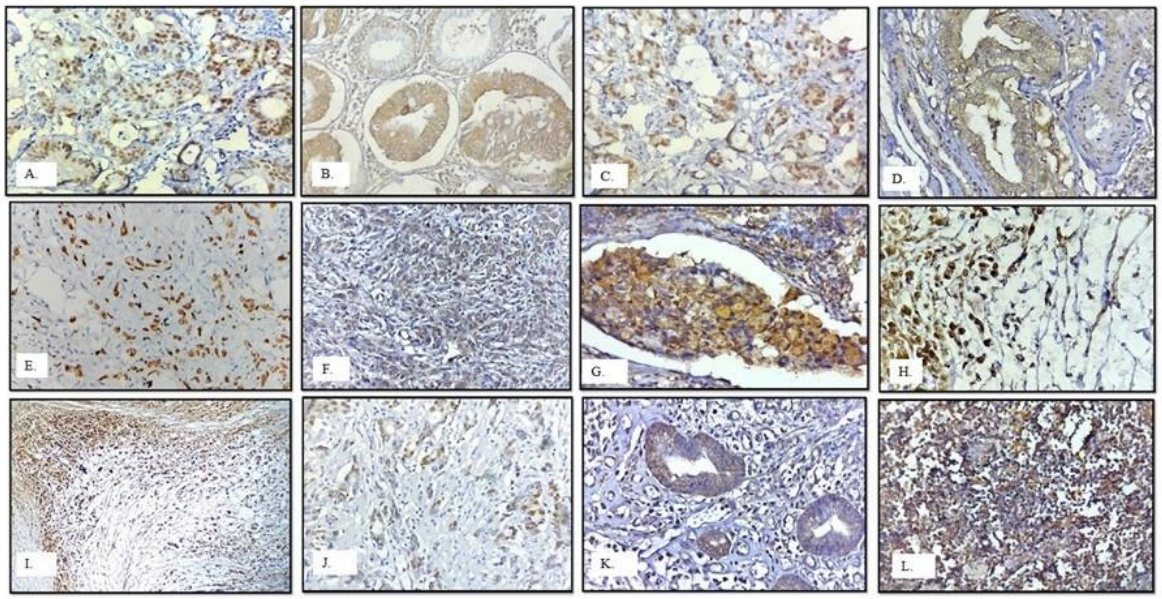

Fig. 2. Immunohistochemistry done in various subtypes of gastric adenocarcinoma showing A. (400X) Cyclin D1 expression in well differentiated gastric adenocarcinoma, B. (400X) PD-L1 expression in well differentiated gastric adenocarcinoma, C. (400X) Cyclin D1 expression in moderately differentiated gastric adenocarcinoma, D. (400X) PD-L1 expression in moderately differentiated gastric adenocarcinoma, E. (400X) Cyclin D1 expression in poorly cohesive carcinoma (other cell type), F. (400X) PD-L1 expression in poorly cohesive carcinoma (other cell type), G. (400X) PD-L1 expression in poorly cohesive carcinoma (signet ring cell type), H. (400X) Cyclin D1 expression in mucinous adenocarcinoma, I. (100X) PD-L1 expression in mucinous adenocarcinoma, J. (400X) Cyclin D1 expression in mixed tubular and poorly cohesive carcinoma, K. (400X) PD-L1 expression in mixed tubular and poorly cohesive carcinoma, and L. (400X) PD-L1 staining tumor infiltrating lymphocytes in gastric adenocarcinoma

4. DISCUSSION

GC is a disease with multiple outcomes that cannot be predicted by clinicopathological features alone. Consequently, the identification of molecular biomarkers that may allow further outcome stratification and treatment decisions is of critical importance. It is seen that elevated Cyclin D1 expression occurs in 50% cases of GC [18-19]. Cyclin D1 expression has been found to be associated with lymph node involvement, metastasis, poor prognosis, and lack of response to platinum treatment in gastric cancer. Cyclin D1 (CCND1) activation is induced by H. pylori infection in stomach [20]. Cyclin D1 overexpression can help tumor formation and facilitate metastasis. Inactivation of Cyclin D1 can help in control of cell division, cell migrtion, and metastasis and thus help in treatment [21,22].

PDL1 expression depends on the diameter of the lesion, and the depth of invasion of gastric carinoma, and anti PDL1 antibody can be used therapeutically [23-25].

In our study, we have studied two molecular biomarkers, namely, Cyclin D1 and PD-L1 on 50 patients. Understanding of the molecular events and pathways can lead to the application of molecular pathology in prevention, early diagnosis, tumor classification, and therapeutic intervention. The patients in this study presented with a mean age of 55 years, which was similar to the mean age procured in the study conducted by Saha et al. [26]. In our study, 52% of GC was in the age range of 41 to 60 years, and no cases of GC were found below 30 years of age. Also, the ratio of the male to female ratio was 2.5:1 in this study, which was nearly similar to that seen in the study of Saha et al. [26].

In our study, statistical correlation was found between age and Cyclin D1 expression (p value - 0.0402) which was contrary to the study of Gao et al. [18].

H. pylori infection has been reported to be an important risk factor for GC patients. Machida-Montani et al. [27], in their study, found a strong association of H. pylori infection and smoking with GC. Lee and Derakhshan found smoking and non vegetarian food habits, salty food, pickled vegetables, and excess salt intake were strong independent risk factors for GCs [28,29,30]. In our study, 54% of the patients were smokers, and 12% of the cases were on alcohol. Most of the cases were on unhealthy diets, i.e., excess salt and low fibre diets and non-vegetarian food. Here, H. pylori infection status among the patients was not studied separately. In our series, we did not find any statistical correlation between predisposing factors and PD-L1 and Cyclin D1 expression.

GC often produces nonspecific symptoms when it is superficial, although the majority of the patients may have nonspecific gastrointestinal complaints such as dyspepsia and anorexia. Some had dyshagia, reflux, fullness after a little meal, etc [31]. In our study too, the most common symptoms were dyspepsia (80%), vomiting (70%), and weight loss (70%). 60% of patients presented with anemia.

Table 1. Correlation between Cyclin D1 expression and clinicopathological (CP) factors

CP parameters	Clinicopathological (CP) factors	CyclinD1 expression		p-value
		Negative (0-2) (n=25)	Positive (3-8) (n=25)	
1) Age Group (in years)	<=40	7	0	0.0402
	41-50	5	8	
	51-60	6	7	
	>=61	7	10	
2) Sex	F	5	9	0.2077
	M	20	16	
3) Gross Tumor description	Type 1	3	2	0.7244
	Type 2	9	7	
	Type 3	9	13	
	Type 4	4	3	
4) Histologic Type	• Tubular adenocarcinoma (WD)	2	1	0.4248
	• Tubular adenocarcinoma (MD)	9	10	
	• PC CA-Signet ring cell type	0	4	
	• PC CA-Other cell type	6	4	
	• Mucinous Adenocarcinoma	4	4	
	• MiNeN	1	0	
	• Mixed adenocarcinoma	3	2	
5) Regional Lymph node status	Metaplastic Deposit	10	22	0.0017
	Reactive	13	3	
	Not found	2	0	
6) LVI	Absent	8	1	0.0099
	Present	17	24	
7) PNI	Absent	22	14	0.0117
	Present	3	11	
8) Pathological Stage	Ia	3	0	0.0015
	Ib	3	0	
	IIa	13	4	
	IIb	4	4	
	IIIa	2	8	
	IIIb	0	5	
	IIIc	0	1	
	IV	0	3	

WD – Well Differentiated, MD – Moderately Differentiated, PC CA – Poorly Cohesive Carcinoma, LVI- Lympho vascular invasion, PNI- Perineural invasion

Table 2. Correlation between PDL1 expression and clinicopathological (CP) factors

CP parameters	Clinicopathological (CP) factors	PD-L1-CPS Score (CPS Score ≥ ➡ 1 PD-L1+)		p-value
		<1 (n=15)	>=1(n=35)	
1) Age Group (in years)	<=40	4	3	0.2185
	41-50	3	10	
	51-60	5	8	
	>=61	3	14	
2) Sex	F	3	11	0.4094
	M	12	24	
3) Gross Tumor description	Type 1	3	2	0.3831
	Type 2	5	11	
	Type 3	6	16	
	Type 4	1	6	
4) Histologic Type	• Tubular adenocarcinoma (WD)	2	1	0.4283
	• Tubular adenocarcinoma (MD)	4	15	
	• PC CA-Signet ring cell type	1	3	
	• PC CA-Other cell type	2	8	
	• Mucinous adenocarcinoma	3	5	
	• MiNeN	1	0	
	• Mixed adenocarcinoma	2	3	
5) TILs	Grade 1	1	18	0.0021
	Grade 2	10	16	
	Grade 3	4	1	
6) Regional Lymph node status	Metaplastic Deposit	4	28	0.0007
	Reactive	9	7	
	Not found	2	0	
7) LVI	Absent	6	3	0.0080
	Present	9	32	
8) PNI	Absent	12	24	0.4094
	Present	3	11	
9) Pathological Stage	Ia	3	0	0.0111
	Ib	2	1	
	IIa	8	9	
	IIb	1	7	
	IIIa	1	9	
	IIIb	0	5	
	IIIc	0	1	
	IV	0	3	

WD – Well Differentiated, MD – Moderately Differentiated, PC CA – Poorly Cohesive Carcinoma, LVI- Lympho vascular invasion, PNI- Perineural invasion

Non Cardia stomach carcinoma is more common in developing countries and cardia carcinoma is common in developed countries [32]. In our study, 52% of the tumors were present in the antrum, followed by the pyloric region (38%).

According to Jun [33] Cyclin D1 overexpression indicates better prognosis in cases of small intestinal adenocarcinoma. Gao et al.'s [18] studies showed that Cyclin D1 is expressed in early and late GC. This is negative in gastric polyps. They also noted that Cyclin D1 positive GC cases have a worse prognosis. Some studies indicate that Cyclin D1 overexpression is present in 50% of GC. It is seen in poorly differentiated GC and results in poor prognosis [34,35]. In GC, Cyclin D1 forms a complex with CD kinase (CDK). This complex of Cyclin D1/CDK4/6 is target for therapy [36]. According to Shan et al. [10], CCND1 (Cyclin D1) expression was significantly increased in gastric intestinal type of adenocarcinoma of GC. In our study, out of 30 cases of intestinal type, 21 cases were positive for PD-L1 and 15 cases were positive for Cyclin D1, while out of 14 cases of diffuse type, 11 cases were positive for PD-L1 and 8 cases were positive for Cyclin D1.

In some studies, 57% Gastric tumors showed PDL1 positivity and 42% tumors were PDL1 negative [37]. In other studies there was 37.8% PDL1 positivity in gastric carcinoma. Xing et al noted that PDL1 is usually positive in non metastatic GC [38].

There is a difference of opinion regarding the prognosis of PDL1 in GC. It has been seen that PDL1 expression indicates better prognosis in GC [39]. Junttila et al. [40] in their study, found that PD-L1 positive tumor cells seem to be slightly more common in intestinal types, and the prognosis of PDL1 positive GC patients is worse than that of PDL1 negative patients.

Shen et al. [41] and Burr et al. [42] did not show any association between PDL1 and CD8+ lymphocytes. In another study, it was found that CD8+ T cells influence tumor immunity by differentiating into cytotoxic T lymphocytes. CD8+ T cell infiltration has been shown to correlate with PD-L1 expression in tumor cells and stroma [43]. CD8+ T cell infiltration correlates with PD-L1 expression and poor prognosis in GC. Dislich et al. [44], in their study also stated that PD-L1 positivity was associated with higher Tumor Infiltrating Lymphocyte (TIL) count, which also supported previous studies. In our study also we have seen that PDL1 positive cases were associated with high TIL grades (grade 2 and 3). So we experienced the positive correlation between PDL1 and density of TIL like other studies.

There are 55% to 65% PDL1 positivity in GC [45]. PDL1 positivity differs in resected samples and biopsy samples. Yamashita et al. found in their series PDL1 positive tumors 46% to 70% in the resected and biopsy specimens of GC respectively [46]. CPS score more than one was seen in 43.6% cases of GC was seen by Markiefka et al. [47] In our study there was a statistically significant correlation between PD-L1 expression (PD-L1 CPS score) and TIL (p value = 0.0021). In our study, we found PD-L1 positivity (CPS >=1) in 70% of the cases, which almost corroborated with the study of Yamashita et al. [46].

Thus, our study revealed the clinicopathological spectrum of GC and its association with Cyclin D1 and PD-L1 expression. Both Cyclin D1 and PDL1 are important prognostic markers and can be used to guide clinicians regarding targeted therapy.

5. CONCLUSION

The tumor marker analysis may reflect the various stages of the carcinoma and may assist the Clinicians in the planning and monitoring of the treatment. One of the most intractable challenges in clinical treatment of GC is that only a part of GC patients get benefit from traditional chemical treatment strategy. There are other elements that also affect the clinical outcome.

Inhibition of Cyclin D1 using specific therapy is a novel gastric cancer therapy. PD1/PDL1 immune checkpoint inhibitor therapy also used for treatment. PDL1 is also an independent prognostic predictor. Emerging evidence concerning experimental investigations and clinical trials suggested promising application of PD1/PDL1 blockade in these malignancies.

(PD-1) and its ligand Programmed death ligand 1 (PD-L1) cause immunomodulation by T cell inactivation and progression of cancer. So blocking the PD1/PDL1 pathway is helpful for control of GC and many other solid tumors.

CONSENT

Written informed consents were obtained from the patients for publication of this article and accompanying images.

ETHICAL APPROVAL

The approval for this study was obtained from the Institutional Ethics Committee.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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