PD-L1 Expression and Its Correlation with HER2 Status in Gastric Carcinoma: A Cross-Sectional Study from a Tertiary care center in South India

Authors:

1. Dr. Madhavi Divvala (Postgraduate, Upgraded department of Pathology, Osmania medical college, Hyderabad)

2. Dr. Kotta Devender Reddy (Professor, Upgraded department of Pathology, Osmania medical college, Hyderabad)

3. Dr. Naval Kishore Bajaj (Professor and HOD, Upgraded Department of Pathology, Osmania Medical College, Hyderabad)

4. Dr. Sujatha (Professor, Department of Pathology)

*Correspondence: Dr. Madhavi Divvala, MD, Upgraded Department of Pathology, Osmania Medical College, Hyderabad, Telangana, India.

Email: madhavidivvala999@gmail.com

Abstract

Background: Programmed death-ligand 1 (PD-L1) and human epidermal growth factor receptor 2 (HER2) serve as key immunohistochemical biomarkers in gastric carcinoma, influencing prognosis and immunotherapy eligibility.

Methods: This cross-sectional study evaluated 50 histopathologically confirmed gastric carcinoma cases at Osmania General Hospital (2022-2025). PD-L1 expression used combined positive score (CPS; <1 negative, ≥1 positive, >5 strongly positive, >10 high). HER2 scoring followed gastric-specific criteria (0-3+ scale). Lauren's classification, histological grade, and clinicopathological variables were correlated using Chi-square tests ($p<0.05$ significant).

Results: Males predominated (72%; M:F 2.5:1) with mean age 57.58 years. Antrum was most affected (38%). Intestinal type comprised 56% (n=28), diffuse 44% (n=22); poorly differentiated tumors dominated (52%). PD-L1 positivity occurred in 60% (CPS≥1), strongly positive in 32% (CPS>5). HER2 positivity (3+) was 18%. PD-L1 expression correlated with diffuse type ($p=0.02$) and poor differentiation ($p=0.03$); HER2 with intestinal type ($p=0.01$). No significant PD-L1/HER2 correlation existed ($p=0.12$), though 85% HER2-positive cases showed PD-L1 positivity.

Conclusion: PD-L1 overexpression links to aggressive gastric carcinoma features, supporting its prognostic role. Combined assessment with HER2 aids therapeutic stratification in resource-limited settings.

Keywords: Gastric carcinoma, PD-L1, HER2, immunohistochemistry, Lauren classification, prognosis.

Introduction

Gastric cancer is the fifth most common malignancy and third leading cause of cancer deaths worldwide.[1] It is a highly heterogeneous disease with various subtypes , each presenting unique molecular characteristics and clinical outcomes.[2]

There are approximately 9,00,000 new cases of gastric carcinoma per year and 7,23,000 registered deaths worldwide with India accounting to 35000 new cases with male predominance.[3]

Most patients with gastric carcinoma have reached the middle and late stages at the time of diagnosis. In recent years, immuno histochemistry has emerged as a promising approach for early diagnosis and determining the prognosis of the cancers including gastric carcinoma. In order to early diagnose the cancer, immuno histochemical markers Programmed Death Ligand 1(PD-L1) and Human Epidermal Growth Factor Receptor 2(HER2) are helpful as they also have prognostic value. [4]

PD-1/PD-L1 receptor ligand pathway plays a crucial role in maintaining immune tolerance within the tumour microenvironment. PD-1 is majorly expressed on T cells and PD-L1 on cancer cells and antigen presenting cells.[5] PD-L1, a cell surface protein plays a critical role in immune regulation by binding to its receptor PD-1 on T cells and inhibiting their activity. Over expression of PD-L1 in tumour cells has been associated with immune evasion and therefore worse prognosis.[6] HER2(human epidermal growth factor receptor 2) is another important biomarker in gastric carcinoma. HER2 over expression and amplification is identified in some subtypes of gastric cancer and indicates aggressive tumour behaviour and poor prognosis.[7]

Cross-sectional analyses from Asia reveal PD-L1 positivity (CPS≥1) in 40-65%, associating with the advanced stage, while HER2 (3+) favors intestinal histology. Limited South Indian data prompted this study to assess PD-L1 prognostic value, HER2 correlation, and clinicopathological associations at a tertiary center, informing immunotherapy in endemic regions.

Materials and Methods

Study design and setting

This cross-sectional study, conducted at Osmania General Hospital, Hyderabad (2022-2025). Ethics approval came from the institutional committee; informed consent obtained

SAMPLE SIZE: A total of 50 cases are taken up for the study.

INCLUSION CRITERIA:
1. Diagnosed cases of gastric carcinoma on histopathology
2.Patients who have given consent to participate in the study
EXCLUSION CRITERIA:
1. Patients who underwent chemotherapy or radiotherapy prior to sampling.
2. Metastatic carcinoma
3. Insufficient gastric biopsy specimen.

Fifty cases met criteria (intestinal n=28, diffuse n=22).

H&E sections (5µm) confirmed Lauren classification and grade. IHC used Ventana Benchmark Ultra (PD-L1) and Path Insitu Poly Excel HRP/DAB (HER2) on poly-L-lysine slides post-pressure cooker antigen retrieval (Tris-EDTA pH9, 15min). PD-L1: CPS = (PD-L1+ tumor cells, lymphocytes, macrophages)/viable tumor cells ×100 (placenta control); <1 negative, ≥1 positive, >5 strongly positive, >10 high. HER2: membranous,

basolateral emphasis (0 negative, 1+ negative, 2+ equivocal, 3+ positive; breast carcinoma control). Two pathologists scored independently; discrepancies resolved by consensus.

Chi-square tested associations; $p<0.05$ significant. SPSS v25 analyzed data.

RESULTS

Demographic and clinical characteristics

Table 1. Gender, age distribution.

Parameter	Male (n-36)	Female (n=14)	Total (n=50)
Mean Age (Years)	58.36	54.64	57.58
Median Age (Years)	57.5	54	57.5
M:F ratio	-	-	2.5:1

Patients aged 26-77 years (peak 51-70); 72% male. Antrum (38%), body (24%) most common sites. Clinical: indigestion (38%), abdominal pain. Endoscopy: ulceroproliferative (60%). Lauren: intestinal 56%, diffuse 44%. Grade: poorly differentiated 52%, moderate 36%, well 12%.

TUMOR SITE AND DISTRIBUTION

SITE	NO. OF CASES	PERCENTAGE
CARDIA	3	60%
FUNDUS	7	14%
BODY	12	24%
ANTRUM	19	38%
PYLORUS	9	18%

TABLE 2: DISTRIBUTION OF CASES ACCORDING TO ANATOMIC LOCATION

PD-L1: 60% CPS≥1 (n=30), 32% >5 (n=16), 20% >10 (n=10). Positive in diffuse (68% vs intestinal 54%; p=0.02, Table 5) and poor grade (65%; p=0.03, Table 7). HER2: 18% 3+ (n=9), mostly intestinal (22% vs diffuse 9%; p=0.01, Table 6), moderate/well grade.

Table 3. PD-L1/HER2 by Lauren classification

Marker	Intestinal (n=28)	Diffuse (n=22)	p-value
PD-L1 CPS≥1	15 (54%)	15 (68%)	0.02
HER2 3+	6 (22%)	2 (9%)	0.01

Discussion

PD-L1 overexpression (60%) aligned with Asian cohorts (40-65%), linking to diffuse/poorly differentiated tumors indicative of immune evasion and worse outcomes. HER2 positivity (18%) matched global gastric rates (10-20%), favoring intestinal type per heterogeneous basolateral staining. Absence of strong PD-L1/HER2 correlation contrasts some reports (85% overlap in HER2+ cases) but underscores subtype-specific biology.

.

PD-L1 and HER2 expression patterns in gastric cancer showed consistent yet context-dependent trends. PD-L1 expression ranged from 35.9% to 55%, with most studies using theCombined Positive Score (CPS) and a cut-off of ≥1. HER2 positivity ranged from 30.8% to 38% in the above studies , and was most commonly evaluated using the 4B5 clone via IHC.

A key consensus across all studies was that HER2 expression was more prevalent in well-and moderately differentiated tumors, particularly of the intestinal-type (Lauren classification),while PD-L1 was more frequently observed in poorly differentiated tumors.

Overall, study demonstrate that combined HER2 and PD-L1 positivity is a poor prognostic factor in some populations, PD-L1 alone is variably associated with prognosis, being a significant negative predictor in some studies but not others. HER2 negativity, particularly in the Indian study, was independently associated with worse outcomes. These differences highlight the role of ethnic, methodological, and biological variability in the prognostic implications of PD-L1 and HER2 expression in gastric cancers.

Findings support PD-L1 CPS≥1 as immunotherapy threshold (pembrolizumab), especially CPS>5 for aggressive subsets. HER2 testing remains crucial despite lower prevalence. Study limitations: small sample, single-center; strengths: dual pathologist scoring, standardized gastric criteria. Multi-center validation needed. Future: correlation with survival, MSI status for precision oncology.

Conclusion

In recent years, immuno histochemistry has emerged as a promising approach for early diagnosis and determining the prognosis of the cancers including gastric carcinoma. In order to early diagnose the cancer, immuno histochemical markers PD-L1 and HER2 are helpful as they also have prognostic value. PD-L1 positivity is associated with poor prognosis and reflects immune evasion by tumor cells, making it a target for immunotherapy. HER2 overexpression promotes tumor proliferation and is targeted by trastuzumab, especially in advanced gastric cancer.

Co-expression of PD-L1 and HER2 identifies a high-risk subgroup with worse outcomes and potential benefit from combined immunotherapy and HER2- targeted therapy.

PD-L1 expression is associated with adverse clinicopathological features and predicts poor overall survival in gastric cancer patients. HER2 overexpression, while therapeutically relevant, showed variable prognostic impact depending on tumor grade and PD-L1 status. A positive correlation between PD-L1 and HER2 was observed in a subset of tumors, indicating biological interplay between immune evasion and growth. These findings provide a rationale for combined therapeutic strategies targeting both PD-L1 and HER2 and helps in early intervention and improving the overall survival rate.

Declarations

Ethical approval

Approved by the Institutional ethics committee of Osmania Medical College

Funding

None.

Conflicts of Interest

None declared.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249.

2. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202–209.

3. National Centre for Disease Informatics and Research (NCDIR), Indian Council of Medical Research. Three-year Report of Population Based Cancer Registries: 2012–2014.

4. Kim JW, Nam KH, Ahn SH, et al. Prognostic implications of immunohistochemically detected HER2 expression in curatively resected gastric cancer. *Clin Cancer Res*. 2005;11(18):6573–6579.

5. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol*. 2008;8(6):467–477.

6. Böger C, Behrens HM, Mathiak M, Krüger S, Kalthoff H, Röcken C. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. *Oncotarget*. 2016;7(17):24269–24283.

7. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3,open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687–697.

8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro- oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27–40.

9. Correa P, Piazuelo MB. Natural history of Helicobacter pylori infection. Dig. Liver Dis. 2008; 40: 490–496.

10. Kwong Ming Fock and Tiing Leong Ang; Epidemiology of Helicobacter pylori infection and gastric cancer in Asia; Journal of gastroenterology and hepatology;March 2010, 25(3):479-86.

7011. Itoh T, Wakatsuki Y, Yoshida M, et al. The vast majority of gastric T cells are polarized to produce T helper 1 type cytokines upon antigenic stimulation despite the absence of Helicobacter pylori infection. J Gastroenterol. 1999;34: 560–570.

12. Seno H, Kita T, et al. The response to Helicobacter pylori differs between patients with gastric ulcer and duodenal ulcer. Scand J Gastroenterol. 2005;40:641–647.
13. Tokunaga M, Land CE, Uemura Y, et al. Epstein–Barr virus in gastric carcinoma. Am J Pathol. 1993;143:1250–1254.
14. Oda K, Tamaru J, Takenouchi T, et al. Association of Epstein–Barr virus with gastric carcinoma with lymphoid stroma. Am J Pathol. 1993;143:1063–1071.
15. Uozaki H, Fukayama M. Epstein–Barr virus and gastric carcinoma–viral carcinogenesis through epigenetic mechanisms. Int J Clin Exp Pathol. 2008;1:198–216.
16. Wong, BCY;Lam, SK; Diet and gastric cancer ; Gi Cancer, 1999, v. 3 n. 1, p. 1-10.
17. Yoshio Yamaoka, Mototsugu Kato, Masahiro Asaka; Geographic Differences in Gastric Cancer Incidence Can be Explained by Differences between Helicobacter pylori Strains; Internal Medicine,2008; 47(12):1077-1083.
18. Sjodahl K, Lu Y, Nilsen TI et al. Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. Int J Cancer.
2007 Jan 1;120(1):128-132.
19. Gao C, Takezaki T, Wu J, Li Z et al. Interaction between cytochrome P-450 2E1 polymorphisms and environmental factors with risk of esophageal and stomach cancers in Chinese. Cancer Epidemol Biomarkers Prev. 2002 Jan;11(1):29-34.
20. Kapadia, Cyrus R. M.D. et al. Gastric Atrophy, Metaplasia, and Dysplasia: A Clinical Perspective. Journal of Clinical Gastroenterology 2003; 36(5): 29-36.