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ORIGINAL RESEARCH

Role of Computed Tomography in Predicting Programmed Death Ligand-1 Positivity in Gastric Adenocarcinoma

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Objective: To examine the association between computed tomography (CT) imaging characteristics and programmed death ligand-1 (PD-L1) expression in patients with gastric adenocarcinoma (GAC), and to develop a nomogram model for prediction.

Methods: The patients were randomly allocated into a training set and a validation set at a ratio of 7:3. The training set was further divided into a PD-L1 positive group and a PD-L1 negative group, based on the combined positive score (CPS). Univariate and multivariate logistic regression analyses were performed to identify independent predictors of PD-L1 positivity. A nomogram was developed to assess the model's predictive performance, which was evaluated using the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA). It was also compared with the model established by previous study.

Results: Patients with PD-L1-positive gastric adenocarcinoma exhibited a higher prevalence of larger short diameters of lymph nodes (LNs) (≥ 1 cm), and lower CT attenuation values in the venous and delayed phases compared to those in the PD-L1-negative group. Short diameter of LNs, and CT attenuation values in the delayed phase were identified as independent predictors of PD-L1 positivity. The nomogram analysis indicated that CT attenuation values in the delayed phase were the most significant predictor of PD-L1 positivity, followed by short diameter of LNs.

Conclusion: The GAC prediction model based on the CT imaging features is effective in predicting PD-L1 expression levels and demonstrates strong clinical applicability.

Keywords: combined positive score, computed tomography, gastric adenocarcinoma, nomogram, programmed death ligand-1

Background

Gastric cancer is the most prevalent malignant tumor within the digestive system, ranking third globally in both incidence and mortality among cancers. Most cases are diagnosed at advanced stages, resulting in an overall five-year survival rate of less than 50%.[1] Immune checkpoint inhibitors have been employed in the treatment of various malignant tumors, with clinical trials validating their efficacy.[2–4] Currently, research is focused on the use of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors. PD-L1, a transmembrane protein from the B7 family, is commonly expressed on tumor cells and tumor-infiltrating immune cells. Initial reports in 2006 identified PD-L1 expression in gastric cancer tissues.[5] In 2021, clinical treatment guidelines incorporated immunotherapy into the first-line treatment for gastric cancer, highlighting the importance of detecting the immune checkpoint PD-L1 in current research.[6,7] At present, combined positive scores (CPS) for patients are typically determined through endoscopic biopsy prior to surgery. However, advancements in the spatial resolution of computed tomography (CT) imaging and the use of

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multiplanar reconstruction techniques have enhanced CT's ability to provide a comprehensive assessment of the tumor, including the delineation of tumor boundaries and adjacent tissue vessels. This makes CT a critical tool for preoperative staging in gastric cancer patients. Emerging research suggests that CT features may also help predict PD-L1 expression levels, offering potential benefits for cases with limited biopsy samples.[8–10] Therefore, this study aims to develop a prediction model for PD-L1-positive gastric adenocarcinoma (GAC) using CT imaging characteristics, thereby providing a non-invasive and objective basis for clinical treatment strategies in GAC.

Materials and Methods

General Information

The study retrospectively examined 231 patients with GAC who were treated at Shanxi Cancer Hospital between September 2017 and July 2022. The patients were randomly assigned to a training set (n = 161) and a validation set (n = 70) in a 7:3 ratio. Within the training set, patients were further categorized into a PD-L1 positive group (CPS ≥ 5) and a PD-L1 negative group (CPS < 5) based on their CPS.

Inclusion criteria: (1) Patients with GAC confirmed through pathological histology or cytology; (2) Availability of PD-L1 immunohistochemical testing results; (3) Initial abdominal CT examination conducted prior to biopsy or surgery; (4) Availability of complete abdominal CT data, including both plain scan and triphasic enhanced scan; (5) Complete clinical baseline characteristics and test data required for the initial diagnosis. Exclusion Criteria: (1) Insufficient gastric distension or poor quality of CT images; (2) History of anti-tumor therapy prior to CT examination and immunohistochemistry; (3) Presence of other concurrent tumor diseases; (4) Unclear histological results; (5) Significant missing of pathological, clinical, laboratory and CT imaging data. This study was reviewed and approved by the ethics committee of Shanxi Province Cancer Hospital (NO. 2022007).

Methods

Data Collection

Clinical data collected from patients included age, sex, family history. Additionally, complete blood count (CBC) parameters were recorded, including red blood cells (RBC), white blood cells (WBC), hemoglobin (HGB), platelets (PLT), neutrophils (NEUT), lymphocytes (LYMPH), eosinophils (EOS), and lactate dehydrogenase (LDH). The neutrophil-to-lymphocyte ratio (NLR) and tumor markers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and alpha-fetoprotein (AFP), were also assessed. Complete blood counts were performed using the automated hematology analyzer XP-100 (Sysmex, Japan), while tumor marker assays were conducted with the ADVIA Centaur XP instrument (Siemens, Germany).

CT Image Examination

The examination was performed using an energy spectral CT scanner (Discovery CT750 hD, GE Healthcare, USA). Patients were instructed to fast (avoid food and drink) the night before the scan and to consume 800 to 1000 mL of water to ensure adequate stomach distension 5 to 10 minutes prior to the scan. The patient was positioned supine, and the scan range extended from the lower edge of the T11 vertebral body to the lower edge of the L2 vertebral body. The CT imaging parameters included a slice thickness and inter-slice spacing of 5 mm, a tube voltage of 120 kV, and a tube current of 240 mA. The contrast agent Iohexol (300 mg/100 mL; 1.5 mL/kg, GE Pharmaceuticals) was administered through the cubital vein via a high-pressure syringe at a flow rate of 3.0 mL/s. Scans were conducted in the arterial phase, venous phase, and delayed phase at 30 seconds, 60 seconds, and 120 seconds post-injection, respectively, with images reconstructed in the coronal and sagittal planes. CT images were independently and blindly analyzed by two radiologists with over 10 years of diagnostic experience. The final results were determined through mutual consultation and consensus between the radiologists. The criteria for CT evaluation included: (1) The location of the lesion was categorized as cardia, gastric corpus, or antrum; (2) The thickness of the lesion was defined as the diameter of the thickest part of the lesion measured on the axial CT image; (3) CT Value of Lesion: A region of interest (ROI) was manually outlined on the slice showing the maximum diameter of the gastric cancer lesion, excluding the lesion edge. The CT value was measured in this area, with at least three measurements taken to determine the average value. The tumor attenuation value was calculated as the difference between the arterial/venous phase CT value and

the non-enhanced CT value. (4) cTNM staging (Table 1): Assessed according to the Chinese 2021 Clinical Guidelines for the Diagnosis and Treatment of Gastric Cancer.[6] (5) Extramural venous invasion (EMVI) of gastric tumors (Table 2): evaluated using the CT-EMVI scoring criteria, with scores of 0–2 indicating EMVI negative and scores of 3–4 indicating EMVI positive.[11,12] (6) Short diameter of LNs. (7) With or without ascites. (8) With or without peritoneal metastasis.

Immunohistochemical Staining

Immunohistochemistry was conducted on biopsy specimens obtained through surgery or gastroscopy, utilizing the Roche Ventana BenchMark ULTRA series automated immunohistochemistry detection platform.

The detection reagent for PD-L1 was a mouse monoclonal anti-PD-L1 antibody (clone 22C3, prediluted, Roche, Switzerland). The CPS was used to assess the level of PD-L1 expression, calculated as CPS = (total number of PD-L1 positive tumor cells, lymphocytes, and macrophages) / (total number of live tumor cells) × 100%. PD-L1 expression is classified as positive when CPS ≥ 5 and negative when CPS < 5.

Statistical Analysis

Statistical analysis was performed using R software version 3.6.3. Non-normally distributed quantitative data were summarized as median and interquartile range (M [Q1, Q3]), with group comparisons made using the rank-sum test. Categorical data were reported as case counts, and comparisons between groups were assessed using the chi-square test. A univariate analysis was conducted on CT imaging features and clinical pathological data. Variables that demonstrated statistically significant differences in the univariate analysis were further analyzed using multivariate logistic regression to identify independent predictors of PD-L1 positivity. A nomogram was developed based on the results of the multivariate logistic regression. The predictive efficacy of the model was evaluated through receiver operating characteristic (ROC) curve analysis, calibration curve analysis, and decision curve analysis (DCA), followed by further comparison with other prediction model. A p-value < 0.05 was considered statistically significant.

Table 1 T-Staging Criteria for Gastric Cancer Based on CT Imaging

T Staging	CT Staging Criteria
T1	Mild thickening of the stomach wall with an intact low-density submucosal layer
T2	Localized thickening of the stomach wall with disruption or absence of the low-density submucosal layer
T3	Prominent enhancement and thickening of the entire stomach wall with a well-defined and smooth outer margin around the lesion
T4	Marked enhancement and thickening of the entire stomach wall with the lesion extending throughout the wall displaying an irregular margin, or evidence of invasion into adjacent tissues and organs

Table 2 Typical CT Imaging Features Indicative of EMVI in Gastric Cancer

CT-EMVI Score	Typical Image Features
0	The lesion does not infiltrate the gastric wall, and no extramural blood vessels are present in the vicinity of the tumor
1	Slight extramural nodular extension is present, with no evidence of invasion into the vascular structures beyond the tumor region
2	The mass infiltrates the gastric wall, with extramural blood vessels present near the tumor area. However, there is no evidence of tumor density within the vascular lumen, and the vessels maintain a normal caliber
3	The mass invades the gastric wall and extends in a linear fashion into the extramural vascular lumen, with the caliber of the affected vessels showing only minor enlargement
4	Significant tubular or nodular soft tissue extends irregularly into the extramural vascular lumen, causing noticeable distention of the vessel

Results

Univariate Analysis of Clinical and CT Imaging Features in GAC Patients With Different PD-L1 Expression Levels

In the training set, there were 120 patients in the PD-L1 positive group and 41 patients in the PD-L1 negative group. Univariate analysis results indicated that, compared to the PD-L1 negative group, the PD-L1 positive group had a higher incidence of lymph nodes (LNs) with a short diameter ≥ 1, with rates of 75.6% versus 53.3% (p = 0.012). The CT attenuation values in both the venous phase and delayed phase were lower in the PD-L1 positive group compared to the PD-L1 negative group, with values of 37.00 [24.00, 53.00] versus 46.00 [33.50, 60.25] (p = 0.034) and 40.00 [31.00, 52.00] versus 49.50 [35.00, 64.50] (p = 0.005), respectively. No other differences between the groups were statistically significant (all $p > 0.05$) (Tables 3 and 4).

Multivariate Logistic Regression Analysis

Indicators that showed statistical significance in the univariate analysis were included in the multivariate logistic regression analysis. The results indicated that short diameter of LNs on CT images, and CT attenuation values in the delayed phase were independent predictors of PD-L1 positivity (Table 5).

Table 3 Univariate Analysis of Clinical Characteristics of Patients With GAC With Varying PD-L1 Expression Statuses in the Training Set

Items	PD-L1 Negative Group (CPS < 5, n=120)	PD-L1 Positive Group (CPS≥5, n=41)	P
Age [y, M (Q1,Q3)]	62.00 [53.00, 70.00]	63.00 [58.00, 68.00]	0.636
Gender [n(%)]			0.95
Male	99 (82.5)	34 (82.9)	
Female	21 (17.5)	7 (17.1)	
Family history [n(%)]			0.248
Yes	11(9.2)	7(17.1)	
No	109 (90.8))	34 (82.9)	
Metastasis [n(%)]			0.856
M0	95 (79.2)	33 (80.5)	
M1	25 (20.8)	8 (19.5)	
WBC [x10^9/L, M (Q1,Q3)]	6.21 [5.02, 8.06]	7.04 [5.46, 8.32]	0.37
RBC [x10^9/L, M (Q1,Q3)]	4.44 [4.02, 4.77]	4.28 [3.85, 4.76]	0.339
HBG [x10^9/L, M (Q1,Q3)]	135.00 [111.75,147.25]	126.00 [104.00,143.00]	0.135
PLT [x10^9/L, M (Q1,Q3)]	272.50 [211.00,353.00]	277.00 [230.00,366.00]	0.473
NEUT [x10^9/L, M (Q1,Q3)]	3.85 [3.02, 5.12]	4.01 [3.00, 5.40]	0.535
LYMPH [x10^9/L, M (Q1,Q3)]	1.73 [1.37, 2.29]	1.78 [1.32, 2.33]	0.775
EOS [x10^9/L, M (Q1,Q3)]	0.10 [0.06, 0.17]	0.11 [0.07, 0.18]	0.395
LDH [U/L, M (Q1,Q3)]			0.564
Normal	106 (88.3)	38 (92.7)	
High	14 (11.7)	3 (7.3)	
NLR [n(%)]			1
≥5	112 (93.3)	38 (92.7)	
<5	8 (6.7)	3 (7.3)	
CEA [ug/L, M (Q1,Q3)]	1.68 [0.68, 5.38]	2.82 [0.84, 10.91]	0.541
CA19-9 [U/mL, M (Q1,Q3)]	15.54 [8.11, 43.93]	14.65 [7.88, 22.87]	0.992
AFP [n(%)]			0.149
Normal	114 (95.0)	36 (87.8)	
High	6 (5.0)	5 (12.2)	

Table 4 Univariate Analysis of CT Imaging Features in Patients With GAC With Varying PD-L1 Expression Statuses in the Training Set

Items	PD-L1 Negative Group (CPS < 5, n=120)	PD-L1 Positive Group (CPS≥5, n=41)	P
Location [n(%)]			0.327
Cardia	41 (34.2)	17 (41.5)	
Body	38 (31.7)	8 (19.5)	
Antrum	41 (34.2)	16 (39.0)	
Thickness	1.60 [1.40, 2.10]	1.80 [1.30, 2.30]	0.589
Tumor attenuation in arterial phase [HU, M (Q1,Q3)]	26.00 [17.75, 39.00]	28.00 [19.00, 35.00]	0.583
Tumor attenuation in venous phase [HU, M (Q1,Q3)]	46.00 [33.50, 60.25]	37.00 [24.00, 53.00]	0.034
Tumor attenuation in delayed phase [HU, M (Q1,Q3)]	49.50 [35.00, 64.50]	40.00 [31.00, 52.00]	0.005
cT stage [n(%)]			0.186
T1	1 (0.8)	1 (2.4)	
T2	11 (9.2)	2 (4.9)	
T3	28 (23.3)	6 (14.6)	
T4a	58 (48.3)	18 (43.9)	
T4b	22 (18.3)	14 (34.1)	
cN stage [n(%)]			0.096
N0	56 (46.7)	10 (24.4)	
N1	30 (25.0)	15 (36.6)	
N2	18 (15.0)	9 (22.0)	
N3	16 (13.3)	7 (17.1)	
EMVI [n(%)]			0.241
Yes	10 (8.3)	6 (14.6)	
No	110 (91.7)	35 (85.4)	
LNs with SD >1 [n(%)]			0.012
Presence	64 (53.3)	31 (75.6)	
Absence	56 (46.7)	10 (24.4)	
Ascites [n(%)]			0.752
Yes	18 (15.0)	7 (17.1)	
No	102 (85.0)	34 (82.9)	
Peritoneal metastasis [n(%)]	106 (88.3)	38 (92.7)	0.694
Yes	6 (5.0)	3 (7.3)	
No	114 (95.0)	38 (92.7)	

Table 5 Multivariate Logistic Regression Analysis of Patients With GAC With Varying PD-L1 Expression Statuses in the Training Set

Items	β	SE	OR (95% CI)	P
Presence of LNs with SD >1cm	1.148	0.069	1.160 (1.013–1.327)	0.033
Tumor attenuation in delayed phase	−0.004	0.002	0.996 (0.993–0.999)	0.023

Construction of the Nomogram Model

Based on the logistic regression results for the variables under consideration, a nomogram model was developed using the nomogram function in the R language rms package for visualizing the equation. The equation is F= −0.5573 +0.8469*short diameter of LNs-0.0231*CT attenuation values in the delayed phase. This model indicated that CT attenuation values in the delayed phase were the most significant predictors of PD-L1 positivity, followed by the short diameter of LNs (Figure 1).

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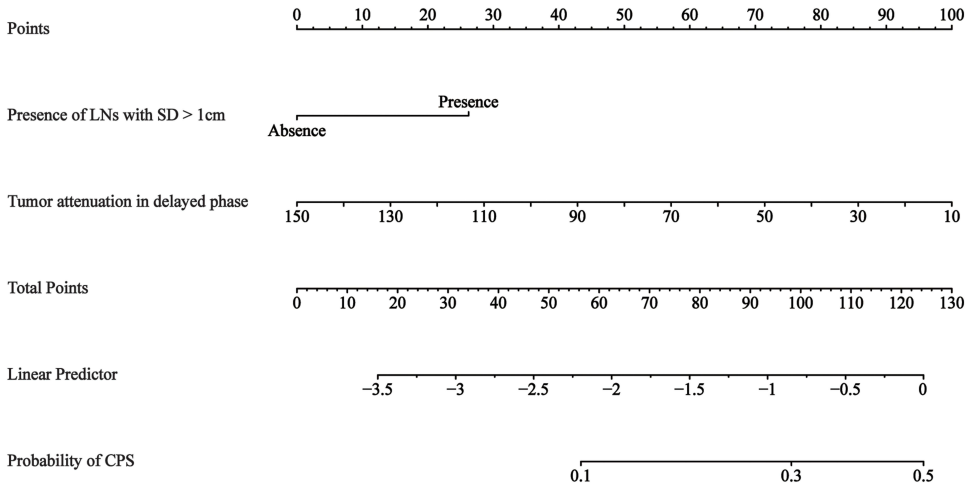

Figure 1 Nomogram predicting the expression of PD-L1 in GC patients. For an individual patient, points for each of the 2 risk factors are summed to give a total points. The horizontal axis representing the total points which was used to calculate the corresponding probability of the expression of PD-L1.
Abbreviations: SD, short diameter; LNs, lymph nodes.

Evaluation of the Nomogram

ROC curves were plotted, indicating areas under the curve (AUC) of 0.679 for the training set (Figure 2A) and 0.670 for the validation set (Figure 2B). These values indicate that the model possesses satisfactory discriminative capability (Figure 2).

The predictive performance of the model was validated using the Bootstrap self-sampling method. Patients in both the training and validation sets were resampled 1,000 times and calibration curves were generated post-validation. The dashed line represents the ideal scenario where predicted probabilities perfectly matched actual probabilities, while the dotted line depicts the actual performance of the model. The solid line represents the bootstrapped corrected performance of the model, with B = 1000 repetitions. The bias-corrected curve approached the ideal curve, indicating that the model's

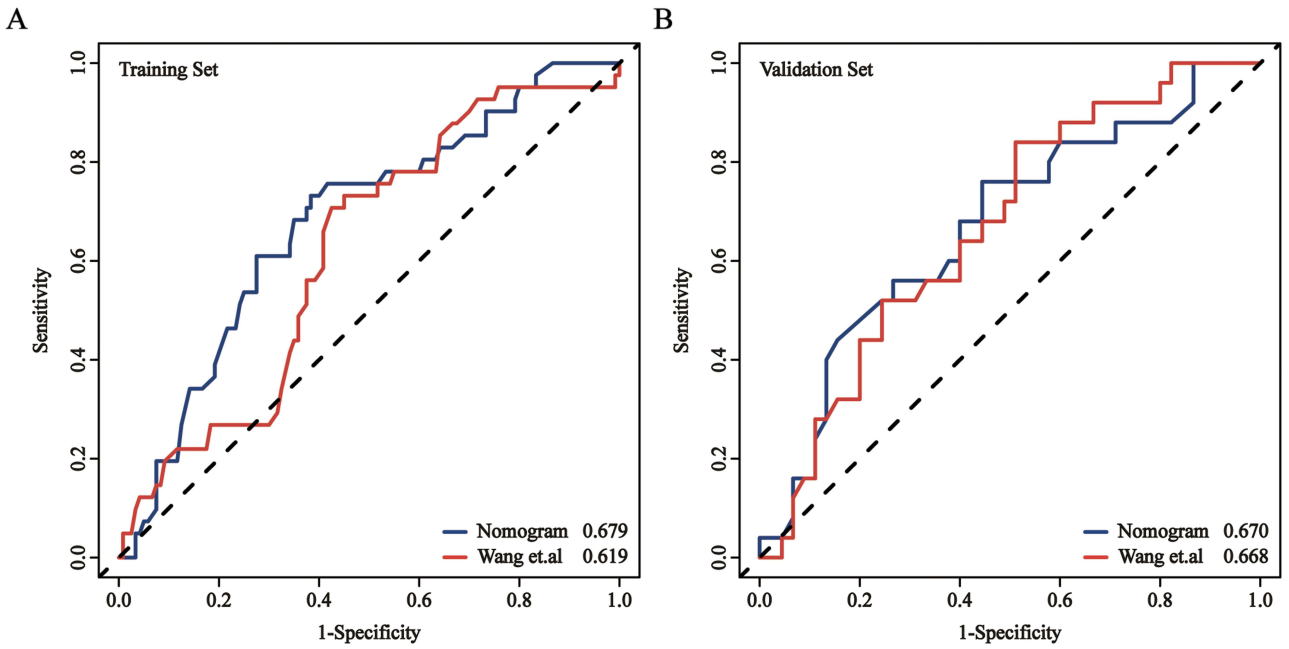

Figure 2 The ROC curves of the training set (**A**) and validation set (**B**). The discrimination of the training set and the validation set of this study (blue line) were both better than that of Wang et al's model (red line).

predictions closely align with the actual observations. The mean absolute error (MAE) was 0.024 in the training set (Figure 3A) and 0.015 in the validation set (Figure 3B).

DCA demonstrated a high net benefit in both raining set (Figure 4A) and validation set (Figure 4B), affirming the model's satisfactory clinical applicability for predicting PD-L1 expression levels in GAC (Figure 4).

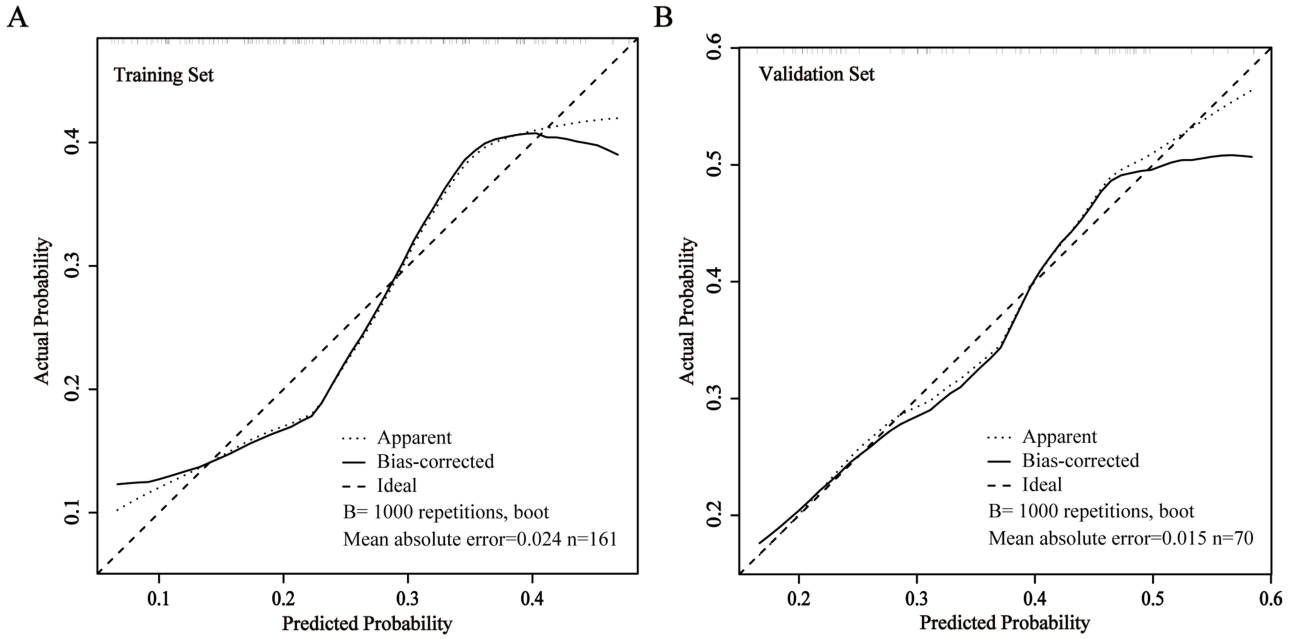

Figure 3 Calibration curve of the training set (**A**) and validation set (**B**). The dashed line indicates the ideal nomogram in which the predicted and actual probabilities are exactly the same. The dotted line represents the actual nomogram performance. The solid line shows the bootstrap corrected performance of our nomogram in this study (B = 1000 repetitions). The calibration curve illustrates good predictive accuracy in the training set (**A**) and validation set (**B**).

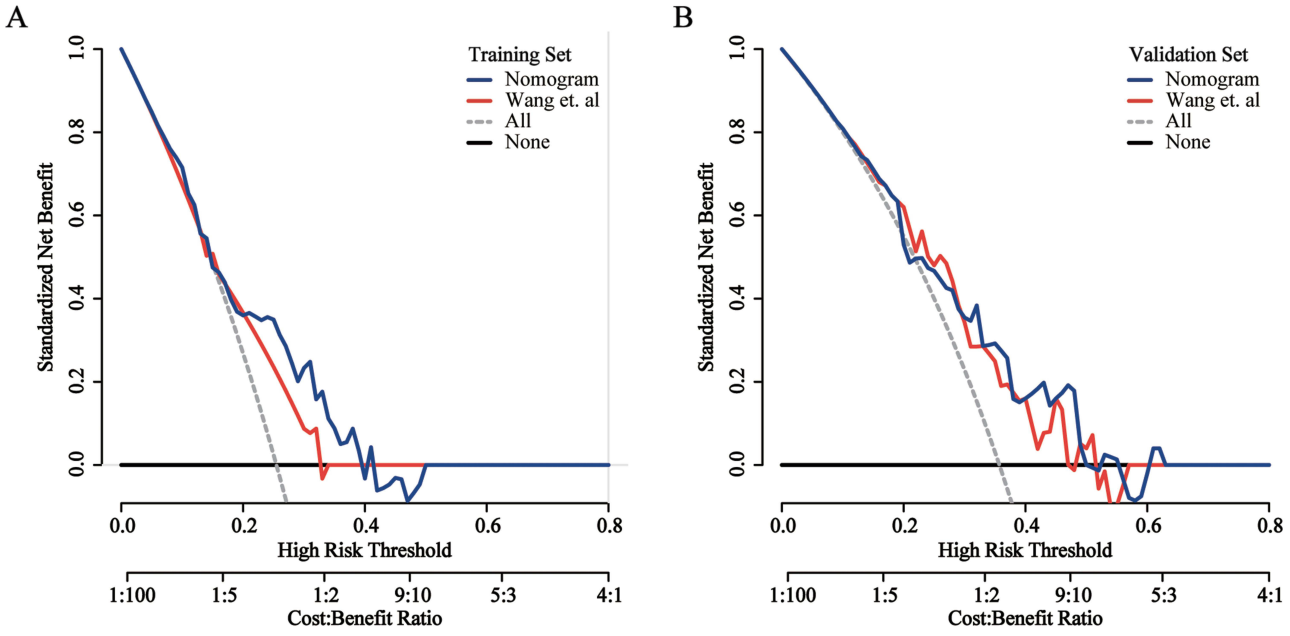

Figure 4 DCA for the the training set (**A**) and validation set (**B**). The Y-axis and the x-axis represent the net benefit and the threshold probability respectively. "All" refers to the assumption that all patients express PD-L1 and "None" to the assumption that no patient express PD-L1. The clinical net benefit of the training set and validation set of this study (blue line) were higher than that of Wang et al (red line).

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Comparison With Other Models

Wang et al recently proposed a prediction model that correlates CT imaging features with PD-L1 expression levels, evaluated by CPS in patients with gastric cancer.[10] However, this model has yet to be further validated. Using the data from this study, we compared the proposed nomogram model with the model developed by Wang et al by plotting ROC curves and DCA curves. The ROC curves revealed superior discriminative performance of the current model compared to Wang's model, with AUC of 0.679 versus 0.619 in the training set and 0.670 versus 0.668 in the validation set. Additionally, the DCA curve showed that for the training set, the clinical net benefit of the model is higher than that of Wang et al at threshold probabilities ranging from 0.21 to 0.39, and for the validation set, the clinical net benefit of the model is higher than that of Wang et al at threshold probabilities ranging from 0.30 to 0.48 (Figure 4A and B).

Discussion

Clinically, assessing PD-L1 expression levels is crucial for evaluating the potential efficacy of immunotherapy. Elevated PD-L1 expression is frequently associated with a more favorable response to immunotherapy. Evaluation of PD-L1 expression is conducted using criteria such as the CPS, tumor positive score (TPS), and immune cell proportion score (IPS), with the choice of criterion dependent on the cancer type. Previous research has demonstrated that CPS is more effective than TPS in predicting the prognosis of advanced gastric cancer and is recognized as a prognostic biomarker.[13] A higher CPS score typically indicates greater tumor sensitivity to immunotherapy. The Checkmate 649 trial, a randomized, open-label Phase 3 study, found that patients with gastric cancer and a PD-L1 CPS ≥ 5 benefit from the combination of PD-L1 inhibitors and chemotherapy.[14] Accordingly, this study utilized CPS to evaluate PD-L1 expression, designating a CPS value ≥ 5 as indicative of PD-L1 positivity. In this study, 28.6% (66/231) of patients exhibited positive PD-L1 expression, a rate lower than previously reported proportions ranging from 37.3% to 59.8%.[15,16] This discrepancy may be attributed to variations in detection antibodies, thresholds for defining PD-L1 positivity, tissue processing methods, and evaluation systems used to determine PD-L1 status.

Patients' clinical information and laboratory findings were incorporated into this study. Notably, patient age, gender, and family history showed no significant correlation with PD-L1 expression in GAC patients, which aligns with previous research.[8,10] The laboratory results encompassed a range of tests including CBC (RBC, WBC, HGB, PLT, NEUT, LYMPH, EOS), LDH, NLR, CEA, CA19-9, and AFP. CBC, a standard part of clinical examinations, and the tumor markers CEA, CA19-9, and AFP, which are readily accessible through blood tests, were also assessed. Wang et al's research on "Peripheral blood nutrient indices as biomarkers for anti-PD-1 therapy efficacy and prognosis in patients with advanced gastric cancer" demonstrated that the prognostic nutritional index (PNI), derived from CBC data, plays a crucial role in predicting gastric cancer prognosis and is an independent predictor of the short-term efficacy of immunotherapy for advanced gastric cancer.[17] Additionally, CEA, CA19-9, and AFP have been implicated in the effectiveness of immunotherapy for gastric cancer patients. Their study indicated that patients responsive to immunotherapy exhibited lower CEA and CA19-9 levels post-treatment, with low PNI associated with increased CEA levels and low advanced lung cancer inflammation index (ALI) associated with elevated AFP levels and PD-L1 negativity.[17] These findings suggest a potential correlation between CBC and tumor markers with PD-L1 expression in GAC (Table 3). Based on these findings, our study included these indicators but did not find a significant correlation between CBC, CEA, CA19-9, AFP, and PD-L1 expression in GAC, possibly due to insufficient sample size or the correlation not being strong enough to achieve statistical significance. Prior studies have indicated differences in NLR and LDH among patients receiving or not receiving PD-1/PD-L1 inhibitor therapy.[17,18] Wang et al's research identified NLR as a potential predictor of immune-related adverse events (irAEs) in cancer patients treated with immune checkpoint inhibitors, with post-treatment LDH potentially predicting the severity of irAEs.[17] Mezquita et al suggested that LDH is independently associated with overall survival and disease control rate in non-small cell lung cancer patients treated with immune checkpoint inhibitors.[18] Our study found there were no significant statistical differences in NLR and LDH between the two groups (Table 3), leading us to conclude that NLR and LDH cannot serve as independent predictors of PD-L1 expression in gastric cancer. Further studies with larger sample sizes or multicenter studies may be necessary to obtain more definitive results.

In this study, it was observed that PD-L1 expression was more frequently associated with CT-positive LNs with a short diameter of ≥ 1 cm, aligning with the findings of Wang et al[10] (Table 4, Figures 5 and 6). This association was identified as an independent predictor of PD-L1 positivity (Table 5). PD-L1 is expressed on tumor cells as well as on immune cells associated with the tumor. Wang et al have posited that PD-L1 may correlate with a more extensive inflammatory response, which in turn can lead to lymph node enlargement.[10] Furthermore, we conjecture that PD-L1 may be implicated in lymphatic infiltration and metastasis. A meta-analysis of 1,901 gastric cancer patients indicated a significantly reduced survival time for PD-L1 positive individuals (HR = 1.64, 95% CI: 1.11–2.43, P = 0.01), suggesting a correlation between high PD-L1 expression and adverse outcomes, which supported our speculation.

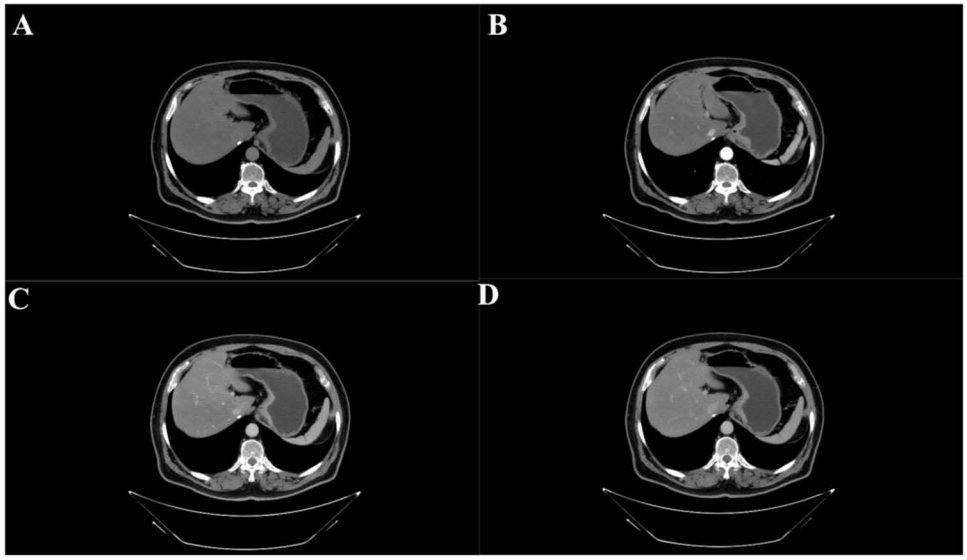

Figure 5 A 56-year-old man with PD-L1-negative. The gastric wall was thickened at the cardia, the CT values of the lesion on plain scan (**A**) and in the arterial phase (**B**), venous phase (**C**), delayed phase (**D**) were 27HU, 57HU, 76HU and 79HU, respectively. No enlarged lymph nodes, ascites and peritoneal metastasis were found in the abdominal cavity. EMVI was negative, and the CT stage was cT2N0.
Abbreviation: EMVI, Extramural venous invasion.

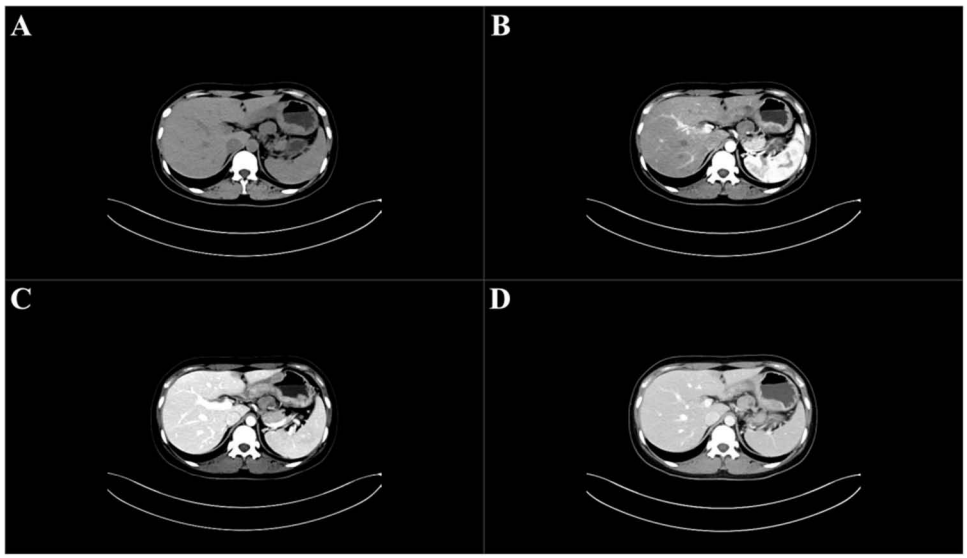

Figure 6 A 64-year-old man with PD-L1-positive. The body of the gastric wall was thickened significantly, the CT values of the lesion on plain scan (**A**) and in the arterial phase (**B**), venous phase (**C**), delayed phase (**D**) were 53HU, 104HU, 141HU and 120HU, respectively. There were a lot of enlarged lymph nodes around, and ascites and peritoneal metastasis were not exist. EMVI was positive, and the CT stage was cT4N2.
Abbreviation: EMVI, Extramural venous invasion.

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Notably, 90% of the studies in this meta-analysis were conducted in Asian populations.[19] Conversely, research from Germany has suggested that elevated PD-L1 expression may be associated with improved prognosis.[20] These discrepancies may be due to racial differences. Additionally, while it was hypothesized that PD-L1 expression might correlate with poorer prognosis, this study found no significant relationship between PD-L1 expression and cT, cN, or M stages (Table 3), which is consistent with the findings of Chen et al.[21] However, several studies have reported that PD-L1 expression is prevalent in gastric cancer patients with advanced T stages and lymph node metastasis.[22,23] Therefore, the relationship between gastric cancer staging and PD-L1 expression remains controversial and warrants further investigation with a larger study population. Furthermore, research indicates that patients with heightened PD-L1 expression on immune cells face an elevated risk of disease recurrence and progression, and the utilization of PD-1/PD-L1 immune checkpoint inhibitors has been shown to decrease the recurrence rates in a range of tumors, including gastric cancer.[24,25] Based on these findings, it is reasonable to hypothesize that PD-L1 may also be correlated with the recurrence of diseases.

In the study conducted by Wang et al, patients were categorized based on CPS cut-off values of 5 and 10.[10] The findings indicated no significant difference in CT enhancement between the groups with CPS $\geq$ 5 and CPS < 5. However, patients with CPS $\geq$ 10 exhibited greater arterial phase tumor enhancement compared to those with CPS < 10, which was hypothesized to correlate with a higher presence of immune cells at the lesion site. In contrast, our study, found that CT attenuation values during the venous and delayed phases were significantly associated with PD-L1 expression (Table 4), while no such association was observed in the arterial phase (Table 4, Figures 5 and 6). The CT attenuation values in the delayed phase emerged as an independent predictor for positive PD-L1 expression (Table 5). In theoretical terms, arterial phase hemodynamics mirror the tumor's arterial blood supply, which is largely contingent upon the density of intratumoral neo vasculature. Conversely, venous phase hemodynamics depict the tumor's microcirculatory conditions and the diffusion of contrast media in the interstitial spaces, primarily signifying the permeability of the tumor's neo vasculature.[26] Tumor enhancement on CT scans is often linked to tumor vascular density, with vascular endothelial growth factor (VEGF) playing a crucial role in angiogenesis and potentially influencing PD-L1 expression. Previous research has established a positive correlation between PD-L1 expression and VEGF in patients with clear cell renal cell carcinoma and glioma.[24,25] Additionally, M2 macrophages have been shown to produce VEGF autocrine signals that upregulate PD-L1 expression.[27] Hence, PD-L1 may be correlated with the generation of new blood vessels within tumors. The study by Yin et al demonstrates that gastric cancers with intratumoral microvascular invasion exhibit a significantly higher arterial phase contrast enhancement ratio (CER) compared to those without such invasion, potentially linking to neovascularization. In gastric cancers with intratumoral microvascular invasion, the CER during the arterial phase is notably lower than in non-invasive cases, which could be attributed to the permeability of the blood vessels.[28] In gastric cancers with microvascular invasion, PD-L1-driven immunosuppression in the tumor microenvironment might facilitate microvascular aggression, and the incomplete neovascular walls of the tumor are more permeable than healthy blood vessels, further augmenting the tumor's blood supply.[8,28] Our study reveals that the CT enhancement values during the venous and delayed phases are lower in the PD-L1-positive group than in the PD-L1-negative group. It is hypothesized that PD-L1 expression enhances tumor aggressiveness, increases the density of intratumoral micro vessels, and raises their permeability, consequently leading to a quicker drainage of the contrast agent and reduced CT enhancement values in the venous and delayed phases. However, additional multicenter studies are required to validate these findings and elucidate the underlying pathophysiological mechanisms.

Current research indicates that a positive CT-EMVI status serves as an independent predictor for local tumor recurrence, metachronous lymph node and distant metastasis, and increased overall mortality.[29,30] This status is often observed in patients with stage T4 gastric cancer and those with lymph node metastasis.[12,16,31] Despite the common occurrence of PD-L1 expression in patients with advanced gastric cancer (Figure 6), this study did not find a correlation between CT-EMVI and PD-L1 expression (Table 4). Peritoneal metastasis, a frequent site of metastasis in gastric cancer and a marker of poor prognosis, typically shows less frequent PD-L1 expression.[32,33] In another study, peritoneal metastases showed PD-L1 expression less frequently.[34] This study also found no significant correlation between ascites and PD-L1 expression (Table 4).

The nomogram model developed in this study, which incorporates the short diameter of LNs observed in CT scans, and CT attenuation values in the delayed phase, demonstrated high efficacy in differentiating PD-L1 expression in both the training and validation datasets. The delayed phase CT enhancement value contributes the most to predicting PD-L1 positivity, indicating that CT features have significant importance for predicting the expression of PD-L1 in gastric cancer (Figure 2). The calibration curve further validated the model's performance, revealing a strong agreement between the predicted and actual probabilities of PD-L1 positivity, indicating its practical utility and significant clinical benefit (Figure 3). This model not only offers valuable insights for clinical decision-making but also translates complex regression equations into visual graphs, thus enhancing its practical application and usability. Compared with the model proposed by Wang et al, this model was superior in terms of discriminatory power and clinical benefit, as evidenced by the comparative analyses in the training and validation sets (Figures 2 and 4). This reinforces the nomogram's effectiveness in predicting PD-L1 expression in gastric adenocarcinoma and highlights its clinical relevance.

This study has several limitations. First, the inclusion of both resectable early-stage gastric adenocarcinoma and unresectable advanced gastric adenocarcinoma may introduce confounding variables. Second, the use of a CPS threshold of 5 for grouping may contribute to inconsistencies in the results. Third, the relatively small sample size limits the robustness of the data model, indicating a need for larger samples to improve model stability. Fourth, the CT features analyzed were influenced by physician-dependent factors, including the delineation of the ROI and the measurement of lymph node diameters. Additionally, the study did not include radiomics analysis, which could impact the objectivity and reproducibility of the data. Future research should integrate radiomics to enhance diagnostic accuracy and efficiency.

Conclusion

CT imaging can be an effective clinical approach for predicting PD-L1 expression. In this study, PD-L1 positive (CPS $\geq$ 5) was frequently observed in patients having GAC with a short diameter of LNs $\geq$ 1 cm, and no notable CT enhancement in the delayed phase. Furthermore, the nomogram model established based on CT imaging features demonstrated strong predictive capability for PD-L1 expression and showed significant clinical utility. Most hospitals can obtain the relevant data on lymph nodes short diameter, and delayed phase CT attenuation values from CT imaging assessments. Further research is needed to explore the potential of these indicators as biomarkers for anti-PD-L1 therapy, which could aid in differentiating tumor subtypes and developing personalized immunotherapies based on molecular profiles.

Abbreviations

GAC, gastric adenocarcinoma; CT, computed tomography; PD-L1, programmed death ligand 1; CPS, combined positive score; ROC, receiver operating characteristic curve; DCA, decision curve analysis; PD-1, programmed cell death protein 1; RBC, red blood cell; WBC, white blood cell; HBG, hemoglobin; PLT, platelet; NEUT, neutrophile granulocyte; LYMPH, lymphocyte; EOS, eosinophilic granulocyte; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AFP, alpha fetoprotein; EMVI, extramural venous invasion; LNs, lymph nodes; SD, short diameter; AUC, area under the curve; MAE, mean absolute error; TPS, tumor positive score; IPS, immune cell proportion score; VEGF, vascular endothelial growth factor; ROI, region of interest.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Shanxi Province Cancer Hospital (NO.2022007). This study was conducted in accordance with the declaration of Helsinki. Consent was not required and waived by the ethics committee because it's a retrospectively study and data analysis was conducted for the article only with good confidentiality.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33. doi:10.3322/caac.21708
2. Lupu J, Hamann P, Routier É, Robert C. Traitement du mélanome par les inhibiteurs du contrôle immunitaire [Treatment of melanoma with immune checkpoints inhibitors]. *Rev Prat*. 2021;71(4):380–383. French.
3. Tu E, McGlinchey K, Wang J, et al. Anti-PD-L1 and anti-CD73 combination therapy promotes T cell response to EGFR-mutated NSCLC. *JCI Insight*. 2022;7(3):e142843. doi:10.1172/jci.insight.142843
4. Chen F, Chen N, Gao Y, Jia L, Lyu Z, Cui J. Clinical progress of PD-1/L1 inhibitors in breast cancer immunotherapy. *Front Oncol*. 2022;11:724424. doi:10.3389/fonc.2021.724424
5. Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. *Acta Histochem*. 2006;108(1):19–24. doi:10.1016/j.acthis.2006.01.003
6. Wang FH, Zhang XT, Li YF, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun*. 2021;41(8):747–795. doi:10.1002/cac2.12193
7. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. *J Hematol Oncol*. 2023;16(1):57. doi:10.1186/s13045-023-01451-3
8. Xu M, Ren T, Deng J, et al. Correlation of CT parameters and PD-L1 expression status in gastric cancer. *Abdom Radiol*. 2024;49(4):1320–1329. doi:10.1007/s00261-024-04200-3
9. Gu X, Yu X, Shi G, Li Y, Yang L. Can PD-L1 expression be predicted by contrast-enhanced CT in patients with gastric adenocarcinoma? A preliminary retrospective study. *Abdom Radiol*. 2023;48(1):220–228. doi:10.1007/s00261-022-03709-9
10. Wang Z, Wang Y, Li X, et al. Correlation between imaging features on computed tomography and combined positive score of PD-L1 expression in patients with gastric cancer. *Chin J Cancer Res*. 2022;34(5):510–518. doi:10.21147/j.issn.1000-9604.2022.05.10
11. Tan CH, Vikram R, Boonsirikamchai P, et al. Extramural venous invasion by gastrointestinal malignancies: CT appearances. *Abdom Imaging*. 2011;36(5):491–502. doi:10.1007/s00261-010-9667-8
12. Yang YT, Dong SY, Zhao J, Wang WT, Zeng MS, Rao SX. CT-detected extramural venous invasion is corelated with presence of lymph node metastasis and progression-free survival in gastric cancer. *Br J Radiol*. 2020;93(1116):20200673. doi:10.1259/bjr.20200673
13. Yamashita K, Iwatsuki M, Harada K, et al. Prognostic impacts of the combined positive score and the tumor proportion score for programmed death ligand-1 expression by double immunohistochemical staining in patients with advanced gastric cancer. *Gastric Cancer*. 2020;23(1):95–104. doi:10.1007/s10120-019-00999-9
14. 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. doi:10.1016/S0140-6736(21)00797-2
15. Zhang L, Qiu M, Jin Y, et al. Programmed cell death ligand 1 (PD-L1) expression on gastric cancer and its relationship with clinicopathologic factors. *Int J Clin Exp Pathol*. 2015;8(9):11084–11091.
16. Wang L, Zhang Q, Ni S, et al. Programmed death-ligand 1 expression in gastric cancer: correlation with mismatch repair deficiency and HER2-negative status. *Cancer Med*. 2018;7(6):2612–2620. doi:10.1002/cam4.1502
17. Wang J, Ma Y, Lin H, Wang J, Cao B. Predictive biomarkers for immune-related adverse events in cancer patients treated with immune-checkpoint inhibitors. *BMC Immunol*. 2024;25(1):8. doi:10.1186/s12865-024-00599-y
18. Mezquita L, Auclin E, Ferrara R, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *JAMA Oncol*. 2018;4(3):351–357. doi:10.1001/jamaoncol.2017.4771
19. Zhang M, Dong Y, Liu H, et al. The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: a meta-analysis of 10 studies with 1,901 patients. *Sci Rep*. 2016;6:37933. doi:10.1038/srep37933
20. 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. doi:10.18632/oncotarget.8169
21. Chen X, Zhang H, Wang M, et al. Relationship between programmed death ligand 1 expression and other clinicopathological features in a large cohort of gastric cancer patients. *Front Immunol*. 2022;13:783695. doi:10.3389/fimmu.2022.783695
22. Lv H, Zhang J, Sun K, et al. Expression of human epidermal growth factor receptor-2 status and programmed cell death protein-1 ligand is associated with prognosis in gastric cancer. *Front Oncol*. 2021;10:580045. doi:10.3389/fonc.2020.580045
23. Yun T, Wang S, Jiang B, et al. Significance of detection of the HER2 gene and PD-1/PD-L1 in gastric cancer. *J Oncol*. 2020;2020:8678945. doi:10.1155/2020/8678945
24. Toren P, Brisson H, Simonyan D, et al. Androgen receptor and immune cell PD-L1 expression in bladder tumors predicts disease recurrence and survival. *World J Urol*. 2021;39(5):1549–1558. doi:10.1007/s00345-020-03358-x
25. Dedecker H, Teuwen LA, Vandamme T, Domen A, Prenen H. The role of immunotherapy in esophageal and gastric cancer. *Clin Colorectal Cancer*. 2023;22(2):175–182. doi:10.1016/j.clcc.2023.03.001

26. Ren T, Zhang W, Li S, et al. Combination of clinical and spectral-CT parameters for predicting lymphovascular and perineural invasion in gastric cancer. *Diagn Interv Imaging*. 2022;103(12):584–593. doi:10.1016/j.diii.2022.07.004
27. Oki E, Okano S, Saeki H, et al. Protein expression of programmed death 1 ligand 1 and HER2 in gastric carcinoma. *Oncology*. 2017;93(6):387–394. doi:10.1159/000479231
28. Yin XD, Huang WB, Lü CY, Zhang L, Wang LW, Xie GH. A preliminary study on correlations of triple-phase multi-slice CT scan with histological differentiation and intratumoral microvascular/lymphatic invasion in gastric cancer. *Chin Med J*. 2011;124(3):347–351.
29. McClelland D, Murray GI. A comprehensive study of extramural venous invasion in colorectal cancer. *PLoS One*. 2015;10(12):e0144987. doi:10.1371/journal.pone.0144987
30. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229–236. doi:10.1002/bjs.5917
31. Cheng J, Wu J, Ye Y, Zhang C, Zhang Y, Wang Y. Extramural venous invasion detected by MDCT as an adverse imaging feature for predicting synchronous metastases in T4 gastric cancer. *Acta Radiol*. 2017;58(4):387–393. doi:10.1177/0284185116658323
32. Bernards N, Creemers GJ, Nieuwenhuijzen GA, Bosscha K, Pruijt JF, Lemmens VE. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. *Ann Oncol*. 2013;24(12):3056–3060. doi:10.1093/annonc/mdt401
33. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. Metastatic spread in patients with gastric cancer. *Oncotarget*. 2016;7(32):52307–52316. doi:10.18632/oncotarget.10740
34. Kawazoe A, Shitara K, Kuboki Y, et al. Clinicopathological features of 22C3 PD-L1 expression with mismatch repair, Epstein-Barr virus status, and cancer genome alterations in metastatic gastric cancer. *Gastric Cancer*. 2019;22(1):69–76. doi:10.1007/s10120-018-0843-9