Journal of Cancer Science and Clinical Oncology
Volume 11 | Issue 1
ISSN: 2394-6520

Research Article Open Access

Dynamic Variations in Peripheral Blood Indices and their Association with Efficacy and Adverse Reactions of PD-1 Inhibitor Combined Chemotherapy in Patients with Advanced Gastric Cancer

Rui Wang[1, 2, *], Huihui Zeng[1, *], Mengting Shi[1], Yue Wu[1], Yang Liu[1] and Tiantian Zhang[1]

[1]Departments of Medical Oncology, The First Affiliated Hospital of Bengbu Medical University, Bengbu 233004, Anhui, People's Republic of China

[2]Anhui Provincial Key Laboratory of Cancer Translational Medicine, Bengbu 233004, Anhui, People's Republic of China

[*]**Corresponding Author:** Tiantian Zhang, Department of Medical Oncology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, People's Republic of China. E-mail: 18355336906@163.com

Citation: Rui Wang, Huihui Zeng, Mengting Shi, Yue Wu, Yang Liu et al. (2024) Dynamic Variations in Peripheral Blood In dices and their Association with Efficacy and Adverse Reactions of PD-1 Inhibitor Combined Chemotherapy in Patients with Advanced Gastric Cancer, J Case Rep Stud Oncl 11(1) : 105

Received Date: October 18, 2024 **Accepted Date:** November 18, 2024 **Published Date:** November 22, 2024

Abstract

Background: Gastric cancer (GC) continues to pose a significant global health challenge, particularly in advanced stages where treatment options are severely constrained. Immunotherapy represents a groundbreaking advancement in cancer treatment, exhibiting promising therapeutic effects in patients diagnosed with gastric cancer. According to the NCCN guidelines, the combination of PD-1 inhibitors and chemotherapy is recommended as a first-line therapeutic approach for patients with metastatic gastric cancer. However, the efficacy of immunotherapy is not universally applicable to all individuals. Revealing precise biomarkers for tumor immunotherapy as targets or indicators for detection and evaluation can facilitate the resolution of this predicament. This study aims to identify serum tumor markers and blood cell ratios as predictive biomarkers to aid in the selection of gastric cancer patients who may benefit from PD-1 inhibitors therapy.

Methods: A retrospective analysis was conducted on the medical records and hematological data of 98 patients with HER2-negative and microsatellite-stable (MSS) metastatic gastric cancer who received first-line treatment with PD-1 inhibitors in combination with chemotherapy at our institution. We investigated peripheral blood parameters, including Neutrophil-to--Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), C-Reactive Protein-to-Albumin Ratio (CAR), AFP, Carcinoembryonic Antigen (CEA), and Sugar antigens 199 (CA199). Logistic regression and Cox regression analyses were employed to assess the correlation of these parameters with treatment response and survival duration. The relationship between these indicators and overall survival was assessed by employing Kaplan-Meier survival curves, in conjunction with an analysis of Overall Response Rate (ORR), Disease Control Rate (DCR), Progression-Free Survival (PFS), Overall Survival (OS), and safety profiles..

Results: Higher pre-treatment levels of NLR, CAR, AFP, and CA199, along with subsequent reductions in NLR, CAR, and CA199 at 12 weeks post-treatment, exhibited a significant associated with extented PFS and OS. Multivariate Cox analysis indicated that pre-treatment levels of AFP, as well as the reduction in NLR and CA199 at 12 weeks post-treatment, independently serve as prognostic factors for PFS and OS in patients with gastric cancer undergoing immunotherapy. Additionally, the reduction in NLR, CAR, and CA199 observed at 12 weeks after treatment exhibited a significant positive correlation with enhanced DCR and ORR. Multivariate logistic regression analysis suggested that the decline in NLR and CA199 levels at 12 weeks post-treatment could sever as independent prognostic factors for DCR, whereas pre-treatment CAR levels and the decrease in CAR after 12 weeks may independently predict ORR in immunotherapy for gastric cancer. Notably, patients with normal AFP levels mPFS of 6.8 months and mOS of 13.2 months, significantly surpassing those with elevated AFP levels, who mPFS of 5.2 months and mOS of 9.4 months, with this difference achieving statistical significance. The AFP level was identified as an independent prognostic factor for both PFS and OS in the context of immunotherapy for gastric cancer.

Conclusion: The combined assessment of NLR, CAR, and CA199 prior to treatment, along with the changes in these indicators post-treatment, serves as critical metrics for evaluating the response to immunotherapy and prognosis in patients with gastric cancer.

Keywords: gastric cancer, PD-1 inhibitor, neutrophil-to-lymphocyte ratio, C-reactive protein-to-albumin ratio, carbohydrate antigen 199

Introduction

Gastric cancer is a highly aggressive malignancy that remains the third leading cause of cancer-related mortality worldwide, despite a recent decline in its incidence and mortality rates [1]. Patients with early-stage gastric cancer frequently exhibit no discernible clinical symptoms, leading to the majority of cases being diagnosed at advanced stages. Due to the scarcity of effective and timely treatment options, individuals with advanced gastric cancer often experience low survival rates, with a median survival time of less than 12 months [2]. Recent advancements in tumor-specific immune checkpoint inhibitors (ICIs) have opened new therapeutic avenues for gastric cancer. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and its ligand, PD-L1, have emerged as promising strategies for cancer treatment, whether used as monotherapy or in combination with chemotherapy [3,4]. Key biomarkers predictive of response to PD-1 inhibitors in gastric cancer patients include PD-L1 expression levels, microsatellite instability (MSI), Epstein-Barr virus (EBV) infection status, and tumor mutational burden (TMB) [5,6]. The broad application of these biomarkers in gastric cancer management, however, is constrained by the diversity in epidemiology, associated costs, and the invasiveness of certain diagnostic tests..Consequently, there is an urgent demand for innovative, accessible, and cost-effective biomarkers that can reliably predict the outcomes of immune checkpoint blockade in advanced gastric cancer.

With the deepening understanding of the tumor microenvironment, a more intricate interplay among inflammation, immunity, and cancer has been increasingly elucidated Inflammation affects nearly every aspect of tumor initiation, promotion, and metastatic progression, while immune surveillance plays a vital role in preventing or suppressing tumor growth [7]. Research has established that inflammatory markers such as NLR, monocyte-to-lymphocyte ratio (MLR), and PLR in peripheral blood can reflect the overall inflammatory status of the body [8, 9]. These markers possess distinctive attrobutes of non-invasiveness, cost-effectiveness, accessibility, and convenience, rendering them valuable tools for evaluting immune and inflammatory responses in various malignancie such as non-small cell lung cancer [10] and malignant melanoma [11]. Clinically, C-reactive protein (CRP), produced by the liver, serves as a non-specific inflammatory marker. While the inflammatory response has traditionally been viewed as having anti-tumor effects, cancer patients often exhibit deficiencies in this response. Serum albumin (Alb), synthesized in the liver, is influenced by factors such as nutritional status, hormonal balance, and plasma osmotic pressure;

low serum albumin levels may indicate poor prognosis in cancer patients. The CRP/albumin ratio (CAR) has emerged as an important inflammatory marker and has been associated with adverse outcomes in gastric cancer [12], pancreatic cancer [13], and other malignancies when elevated prior to treatment. However, current research predominantly focuses on establishing baseline values, with limited exploration of the dynamic changes in peripheral blood indices during treatment and their relationship with therapeutic efficacy. This study aims to integrate inflammatory and tumor markers, thereby reflecting both tumor characteristics and host defenses, which would facilitate the dynamic monitoring of responses to PD-1 inhibitor combined chemotherapy for personalized treatment. To validate this approach, a retrospective analysis was conducted to investigate the relationship between the dynamic changes in peripheral blood markers-including NLR, PLR, CAR, AFP, CEA, and CA19-9 levels and treatment efficacy.

Materials and Methods

Study Design

This study is a retrospective, real-world, single-center investigation that involved no interventions. The subjects included 98 patients with recurrent metastatic gastric cancer who received first-line treatment with PD-1 inhibitors in combination with chemotherapy at the First Affiliated Hospital of Bengbu Medical College from January 1, 2022, to June 30, 2024. The treatment regimens comprised the XELOX protocol (Oxaliplatin+Capecitabine), SOX protocol (Oxaliplatin+Tegio), administered in six cycles (21 days per cycle). Patients concurrently received intravenous injections of either Sintilimab (200 mg), Toripalimab (200 mg), or Camrelizumab (200 mg) every three weeks (21 days per cycle). Following six cycles, patients continued to receive maintenance therapy with the corresponding PD-1 inhibitor combined with single-agent chemotherapy (21 days per cycle) until they experienced intolerability, disease progression, or severe adverse reactions.

Inclusion Criteria

Inclusion criteria comprised an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 and a minimum of four cycles of immunotherapy.

Exclusion Criteria

Exclusion criteria included autoimmune diseases, interstitial lung disease, adrenal insufficiency, systemic immunosuppression, and patients who had experienced inflammation or used corticosteroids within the preceding month.

Data Collection The clinical and pathological characteristics of the patients included age at treatment, sex, Eastern Cooperative Oncology Group (ECOG) performance status score, PD-L1 combined positive score (CPS) expression, sites of distant metastasis, treatment regimen, and best response to treatment. This information was gathered through electronic medical records or telephone follow-ups. Peripheral blood parameters were collected both prior to treatment and at 12 weeks post-treatment (i.e., at baseline and at 12 weeks). These parameters included the Neutrophil-to-Lymphocyte Ratio (NLR; absolute neutrophil count/absolute lymphocyte count), Platelet-to-Lymphocyte Ratio (PLR; absolute platelet count/absolute lymphocyte count), C-Reactive Protein-to-Albumin Ratio (PAR; absolute C-reactive protein count/albumin), AFP, CEA, and CA199.In the analysis, all parameters were treated as binary variables: the first three metrics were dichotomized based on their median values, while the latter three were divided according to clinical significance, either from the upper or lower limits of hematological testing. The reference ranges for tumor markers were established as follows: CEA 0-5 ng/ml; CA199 0-37 IU/ml; AFP 0-20 ng/ml.

Efficacy Assessment

Post-treatment evaluations were conducted every 6 to 8 weeks using systemic Computed Tomography (CT) scans, with treat-

ment responses assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [14]. The final follow-up date was June 30, 2024. Treatment response was evaluated through the Objective Response Rate (ORR) and Disease Control Rate (DCR), while survival outcomes were measured by Progression-Free Survival (PFS) and Overall Survival (OS). Specifically, ORR was defined as the sum of Complete Response (CR) and Partial Response (PR); DCR included CR, PR, and Stable Disease (SD).PFS was defined as the time from the initiation of treatment to clinical or radiographic progression or death, whereas OS was the time from the initiation of treatment to the last follow-up or death, whichever occurred first.In this study, PD-L1 overexpression was expressed as a combined positive score (CPS)> 1. CPS was defined as the percentage of positive tumor live cells (partial or complete membrane staining) and positive lymphocytes and macrophages (the presence of membrane or cytoplasmic staining of any intensity) in all live tumor cells, with results expressed by 0-100 (when calculated over 100, the final result is calculated as 100) [15].Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 provided by the National Cancer Institute. Immune-related adverse events (irAEs) were defined as adverse events associated with immune system dysregulation, including rash, colitis, liver function abnormalities, thyroid disorders, and other conditions. The assessment of irAEs continued for 3 months, as the incidence of these events has been reported to be highest within the initial 12 weeks [16].

Statistical Analysis

Baseline characteristics, peripheral blood parameters, and treatment responses of the patients were reported using the median and interquartile ranges (IQRs) for continuous variables, while categorical variables were presented as frequencies and percentages. For treatment responses, the distribution of clinical factors and peripheral blood parameters between patients with the best response and those without was compared using the Chi-square test. Multivariate logistic regression analysis was employed to explore the relationship between clinical factors, peripheral blood parameters, and optimal treatment response.Progression-Free Survival (PFS) and Overall Survival (OS) curves were computed using the Kaplan-Meier method, with differences between groups assessed by the log-rank test. Cox regression models were utilized to identify independent factors associated with PFS and OS. Factors that demonstrated statistical significance in univariate analysis were included in multivariate analysis. All statistical tests were conducted using SPSS 25.0 andGraphPad Prism 9.0, with a P-value < 0.05 considered to indicate statistical significance.

Ethics Statement: The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (Ethics Approval Number: Lunke Approval [2023] No. 378).The requirement of informed consent was exempted by the IRB due to its retrospective nature. This research involved analyzing data that did not include personal identifying information. Since the data analyzed pertained to patients who had already completed treatment, there was no direct risk or benefit to individuals. Consequently, a waiver of consent was submitted and approval for this study was obtained.

Results

Clinical Characteristics

A total of 98 patients were included in this study. Table 1 displays the detailed baseline clinical and pathological characteristics, as well as treatment responses. The median age of the patients was 65 years, with 74.5% being male. The ECOG PS score was 0 (33.7%) or 1 (66.3%).Out of the 86 patients who underwent peripheral blood Alpha-Fetoprotein (AFP) testing, 69 patients (80.2%) had AFP levels ≤20 ng/ml, while 17 patients (19.8%) had AFP levels >20 ng/ml. PD-L1 CPS expression was detected in 36 patients, with 29 patients (80.6%) CPS ≥1 and 7 patients (19.4%) CPS <1. Among the 98 patients, 92 (93.4%) received immunotherapy combined with oxaliplatin + 5-FU, while 6 (6.1%) received the combination of immunotherapy with cisplatin + docetaxel.As of the follow-up date (June 30, 2024), 58 patients had died, and 40 patients were still receiving treatment. No patients achieved Complete Response (CR), 59 patients (60.2%) achieved Partial Response (PR), 26 patients (26.5%) had Stable

Disease (SD), and 13 patients (13.3%) Progression Disease (PD). The Objective Response Rate (ORR) and Disease Control Rate (DCR) were 560.2% and 86.7%, respectively. Detailed peripheral blood parameters prior to treatment can be found in (Supplementary Table 1), and those at 12 weeks post-treatment are in (Supplementary Table 2).The mPFS and mOS were 6.25 months and 12.6 months, respectively (Supplementary Figure 1). In subgroup analyses, the mPFS for patients with ECOG PS 0 was 7.8 months, and the mOS was 16.2 months; for patients with ECOG PS 1, the mPFS was 6.0 months and the mOS was 11.3 months. Patients with AFP ≤20 ng/ml had a mPFS of 6.8 months, while those with AFP >20 ng/ml had a mPFS of 5.2 months. Patients with PD-L1 CPS ≥1 had a mPFS of 7.6 months, whereas those with PD-L1 CPS <1 had a m PFS of 6.0 months (Supplementary Figure 2).

Table 1: Baseline Characteristics and Treatment Responses of Patients

Characteristics	No. of patients(N = 98)	Percentage(%)
Age(years), median(IQR)	65（29-82）	
<65	49	50
≥65	49	50
Gender		
Female	25	25.5
Male	73	74.5
ECOG PS		
0	33	33.7
1	65	66.3
Liver metastases		
YES	26	26.5
NO	72	73.5
Omental invasion		
YES	35	35.7
NO	63	64.3
Best response		
CR	0	0
PR	51	52
SD	34	34.7
PD	13	13.3
AFP (ng/ml)		
≤20	66	80.2
>20	17	19.8
PD-L1 CPS		
CPS≥1	29	80.6
CPS<1	7	19.4

PR, partial response; SD, stabledisease; PD, progression disease; DCR, disease control rate; ORR, objective response rate; PFS,

progression-free survival; OS:overall survival.

Relationship between Clinical Factors/peripheral blood indicators and Treatment Response

As shown in (Supplementary Table 3), ECOG PS , liver metastasis status, omental invasion status, AFP, PD-L1 CPS, CA199 0w, NLR12w, PLR 12w, CEA12w and CA199 12w were related to DCR or ORR without any adjustments.

We first conducted univariate logistic regression analysis, which revealed that the following factors were significantly associated with DCR: NLR 12w DOWN (OR = 0.111, 95% CI: 0.028 – 0.441), PLR0w >186.15 (OR = 4.123, 95% CI: 1.059 – 16.050), CAR12w UP (OR = 5.253, 95% CI: 1.346 – 20.504), CA1990w (IU/ml) >37 (OR = 4.125, 95% CI: 1.171 – 14.528), CA19912w (IU/ml) >37 (OR = 17.875, 95% CI: 3.653 – 87.462), and CEA12w (ng/ml) >5 (OR = 4.833, 95% CI: 1.367 – 17.094). These results indicate that a decrease in NLR at 12 weeks, lower levels of PLR before treatment, CA19-9 ≤37 (IU/ml) at 0 week or 12 weeks after treatment, and CEA ≤5 (ng/ml) at 12 weeks were associated with a higher DCR (Figure 1).

In contrast, the following factors were significantly associated with ORR: ECOG PS 1 (OR = 8.458, 95% CI: 2.669 – 26.807), AFP (ng/ml) >20 (OR = 3.052, 95% CI: 1.026 – 9.082), PLR0w >186.15 (OR = 3.364, 95% CI: 1.438 – 7.868), CAR0w ≤0.15 (OR = 0.333, 95% CI: 0.144 – 0.772), CAR12w UP (OR = 4.941, 95% CI: 2.066 – 11.820), CA199 0w(ng/ml) >37 (OR = 3.863, 95% CI: 1.638 – 9.113), and CA19-912w (IU/ml) >37 (OR = 15.774, 95% CI: 5.421 – 45.898). The findings suggest that an ECOG PS 0, AFP ≤20 (ng/ml), a decrease in NLR, CAR, and CA19-9 at 12 weeks, as well as lower levels of PLR at baseline and CAR at baseline were associated with a higher ORR (Figure 2).

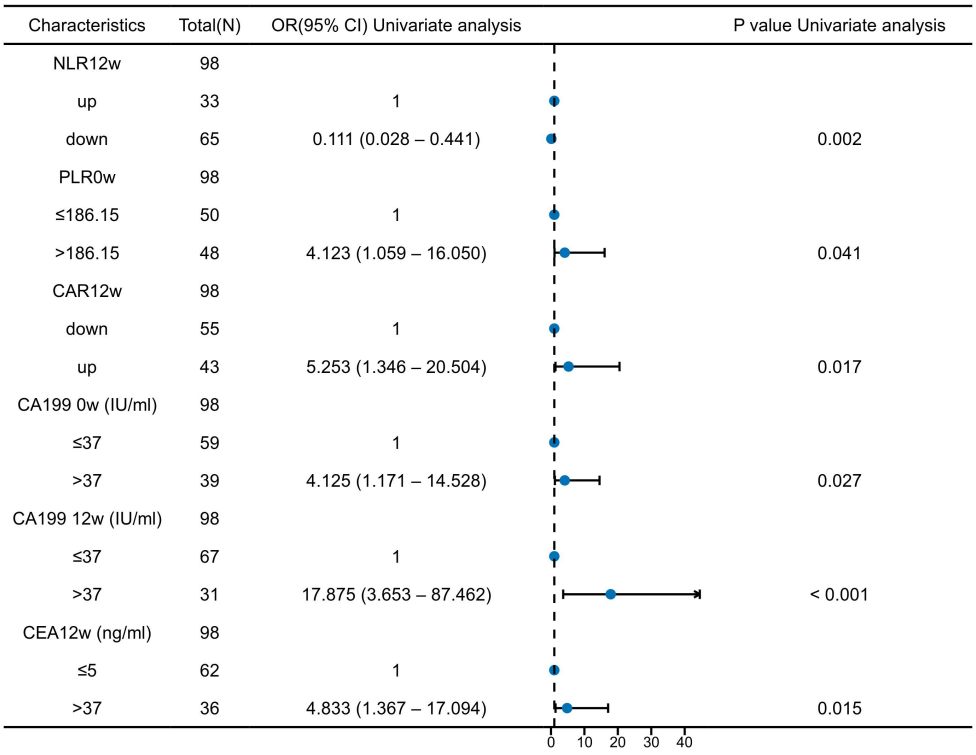

Figure 1: Univariable Logistic regression models for DCR

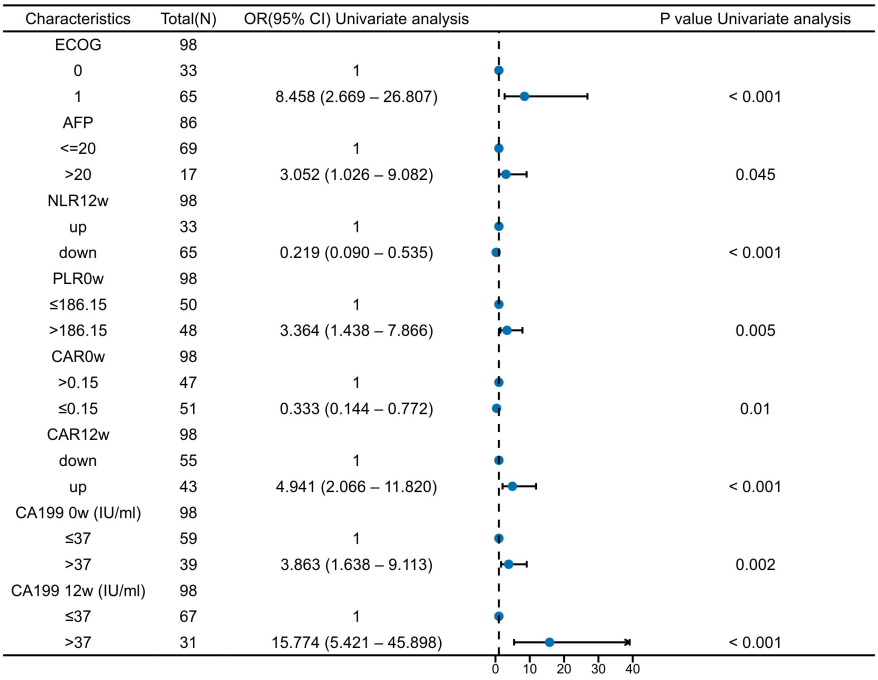

Figure 2: Univariable Logistic regression models for ORR

Subsequently, we conducted a multivariate logistic regression analysis. The results indicated that a decrease in NLR12w(OR = 0.066, 95% CI: 0.007 – 0.639) and CA19912w(IU/ml) >37 (OR = 9.458, 95% CI: 1.167 – 76.674) were independent prognostic factors for DCR. Additionally, CAR0w ≤0.15(OR = 0.248, 95% CI: 0.072 – 0.861), an increase in CAR12w (OR = 5.620, 95% CI: 1.522 – 20.752), and CA19912w(IU/ml) >37 (OR = 10.538, 95% CI: 2.767 – 40.132) were identified as independent prognostic factors for ORR (Supplementary Table 4).

Relationship between Clinical Factors/peripheral blood indicators and Survival Outcomes

Based on the Cox regression analysis (Tables 2,3 only significant variables from univariable analysis are shown), we found that ECOG PS 1 (0 vs. 1: 7.8m vs. 6.0m, HR = 2.013, 95%CI:1.310 - 3.091),AFP(ng/ml) >20(≤20 vs. >20: 6.8m vs.5.2m, HR = 2.400, 95%CI: 1.391 - 4.141),NLR0w >2.72(≤2.72 vs. >2.72: 7.4m vs. 6.0m,HR = 1.697, 95%CI: 1.132 - 2.544), NLR12w DOWN(Down vs. Up: 6.5m vs. 5.2m,HR = 0.417 , 95%CI: 0.267 - 0.652),CAR0w≤0.15(≤0.15 vs. >0.15: 7.4m vs. 5.8m,HR = 0.530, 95%CI: 0.351 - 0.799),CAR12w UP(Down vs. Up: 6.8m vs. 5.4m,HR = 1.878, 95%CI: 1.247 - 2.829),CA1990w(IU/ml)>37(≤37 vs. >37: 7.4m vs. 5.4m, HR =2.181, 95%CI:1.427 - 3.333) ;CA19912w(IU/ml) >37(≤37 vs. >37: 7.4m vs. 5.0m, HR =6.465, 95%CI:3.779 - 11.062) were associated with PFS (Table 2) and(Supplementary Figure 3). And ECOG PS 1 (0 vs. 1: 16.2m vs. 11.3m, HR = 2.903 , 95%CI: 1.548 - 5.442),AFP(ng/ml)>20 (≤20 vs. >20: 13.2m vs.9.4m, HR =3.783, 95%CI: 1.905 - 7.511) ;NLR0w>2.72(≤2.72 vs. >2.72: 13.3m vs. 11.2m,HR = 1.940, 95%CI: 1.133 - 3.322),NLR12w Down (Down vs. Up: 13.4m vs. 10.8m,HR = 0.349 , 95%CI:0.201 - 0.606); CAR0w≤0.15(≤0.15 vs. >0.15: 16m vs. 11.4m,HR = 0.411, 95%CI: 0.242 - 0.701);-CAR12w Up(Down vs. Up: 13.4m vs. 11m,HR = 2.164 , 95%CI: 1.261 - 3.711),CA1990w>37(IU/ml)(≤37 vs. >37: 14.2m vs. 11m, HR =3.071, 95%CI1.766 - 5.342) ,CA19912w>37(IU/ml) (≤37 vs. >37: 14m vs. 10.8m, HR =4.722, 95%CI:2.636 - 8.458) were independently associated with OS (Table 2) and (Supplementary Figure 4).The results of the multivariable Cox regression analysis indicated that AFP (ng/ml) >20 (HR = 2.299, 95% CI: 1.226 - 4.312), a decrease in NLR 12w(HR = 0.357, 95% CI: 0.185 - 0.688), CA19-90w >37 (IU/ml) (HR = 4.539, 95% CI: 2.160 - 9.538), and CEA 0w>5 (ng/ml) (HR = 2.205, 95% CI: 1.080 - 4.506) were identified as independent prognostic factors for Progression-Free Survival (PFS) in gastric cancer immunotherapy. Furthermore, AFP (ng/ml) >20 (HR = 4.644, 95% CI: 2.056 - 10.488), a decrease in NLR 12w(HR = 0.221, 95% CI: 0.102 - 0.477), and CA19-9 12w(IU/ml) >37 (HR = 2.563, 95% CI: 1.046 - 6.280) were found to be independent prognostic factors for Overall Survival (OS) in gastric cancer immunotherapy (Table 3).

Table 2: Univariable Cox regression analysis for PFS and OS

Characteristics	Progression free survival		Characteristics	Overall survival	
	Hazard ratio (95% CI)	P value		Hazard ratio (95% CI)	P value
ECOG			ECOG		
0	Reference		0	1	
1	2.013 (1.310 - 3.091)	**0.001**	1	2.903 (1.548 - 5.442)	< **0.001**
AFP			AFP		
<=20	1		<=20	1	
>20	2.400 (1.391 - 4.141)	**0.002**	>20	3.783 (1.905 - 7.511)	< **0.001**
NLR0w			NLR0w		
≤2.72	1		≤2.72	1	
>2.72	1.697 (1.132 - 2.544)	**0.010**	>2.72	1.940 (1.133 - 3.322)	**0.016**
NLR12w			NLR12w		
up	1		up	1	
down	0.417 (0.267 - 0.652)	< **0.001**	down	0.349 (0.201 - 0.606)	< **0.001**
PLR0w			CAR0w		
≤186.15	1		>0.15	1	
>186.15	1.527 (1.019 - 2.287)	**0.040**	≤0.15	0.411 (0.242 - 0.701)	**0.001**
CAR0w			CAR12w		
>0.15	1		down	1	
≤0.15	0.530 (0.351 - 0.799)	**0.002**	up	2.164 (1.261 - 3.711)	**0.005**
CAR12w			CA199 0w (IU/ml)		
down	1		≤37	1	
up	1.878 (1.247 - 2.829)	**0.003**	>37	3.071 (1.766 - 5.342)	< **0.001**
CA199 0w (IU/ml)			CA199 12w (IU/ml)		
≤37	1		≤37	1	
>37	2.181 (1.427 - 3.333)	< **0.001**	>37	4.722 (2.636 - 8.458)	< **0.001**
CA199 12w (IU/ml)			CEA12w (ng/ml)		
≤37	1		≤5	1	
>37	6.465 (3.779 - 11.062)	< **0.001**	>5	3.072 (1.713 - 5.509)	< **0.001**

CEA0w (ng/ml)					
≤5	1				
>5	1.801 (1.187 - 2.733)	**0.006**			
CEA12w (ng/ml)					
≤5	1				
>5	2.800 (1.786 - 4.391)	**< 0.001**			

Table 3: Multivariable Cox regression analysis for PFS and OS

Characteristics	Progression free survival		Characteristics	Overall survival	
	Hazard ratio (95% CI)	P value		Hazard ratio (95% CI)	P value
AFP			AFP		
<=20	1		<=20	1	
>20	2.299 (1.226 - 4.312)	**0.009**	>20	4.644 (2.056 - 10.488)	**< 0.001**
NLR12w			NLR12w		
up	1		up	1	
down	0.357 (0.185 - 0.688)	**0.002**	down	0.221 (0.102 - 0.477)	**< 0.001**
CA199 12w (IU/ml)			CA199 12w (IU/ml)		
≤37	1		≤37	1	
>37	4.539 (2.160 - 9.538)	**< 0.001**	>37	2.563 (1.046 - 6.280)	**0.040**
CEA0w (ng/ml)					
≤5	1				
>5	2.205 (1.080 - 4.506)	**0.030**			

Based on the baseline and dynamic changes in NLR, CAR, and CA19-9, we grouped the patients and constructed the corresponding survival curves (Figure 3). For patients with low levels of NLR, CAR, and CA19-9 before treatment, themPFS was 8.6 months, significantly longer than those with at least one elevated factor (mPFS: 6.4 months), two elevated factors (mPFS: 5.5 months), and three elevated factors (mPFS: 5 months). Similarly, at 12 weeks post-treatment, patients with decreases in NLR, CAR, and CEA (mPFS: 7.8 months) performed significantly better than those with a single elevated factor (mPFS: 6.2 months), two elevated factors (mPFS: 5.3 months), and three elevated factors (mPFS: 3.8 months).A similar conclusion was reached for Overall Survival (OS): Patients with low levels of all three indicators before treatment had significantly better median OS than the other three groups, while those with reductions in all three indicators at 12 weeks post-treatment also showed markedly improved median OS compared to other groups.Additionally, we regrouped the patients based on the dynamic changes in NLR, CAR, and CA19-9 and constructed the corresponding survival curves (Figure 4). For patients with NLR > 2.72 before treatment, those whose NLR decreased after treatment had an mPFS of 6.3 months, which was significantly higher than that of patients with increased NLR (mPFS: 3.6 months). In patients with NLR ≤ 2.72 before treatment, those with decreased NLR after treatment had an mPFS of 7.8 months, significantly better than the other three groups.

For patients with CAR > 0.16 before treatment, those with decreased CAR after treatment had an mPFS of 6.2 months, significantly higher than those with increased CAR (mPFS: 4 months). Among patients with CAR ≤ 0.16 before treatment, those with

decreased CAR had an mPFS of 8.2 months, significantly better than the other three groups.In patients with CA199 > 37 IU/ml before treatment, those with CA199 ≤ 37 IU/ml after treatment had an mPFS of 6.25 months, significantly higher than those with CA199 > 37 IU/ml (mPFS: 4.8 months). Likewise, among patients with CA199 ≤ 37 IU/ml before treatment, those who maintained CA199 ≤ 37 IU/ml after treatment had an mPFS of 7.6 months, significantly better than the other three groups. Similar conclusions were drawn regarding OS.

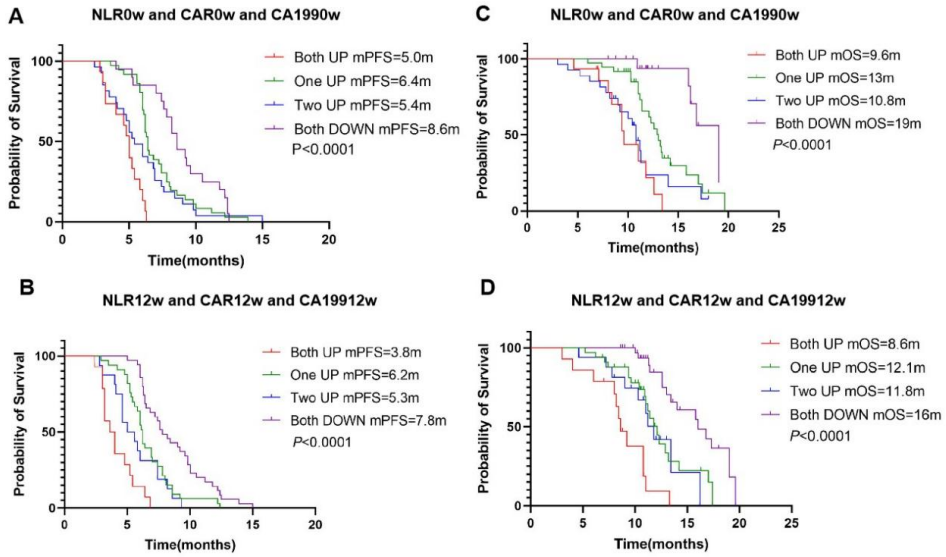

Figure 3: Kaplan–Meier curves for PFS according to "NLR0w and CAR0w and CA199 0w" (A) or "NLR12w and CAR12w and CA199 12w" (B) and for OS according to "NLR0w and CAR0w and CA199 0w" (C) or"NLR12w and CAR12w and CA199 12w" (D) .

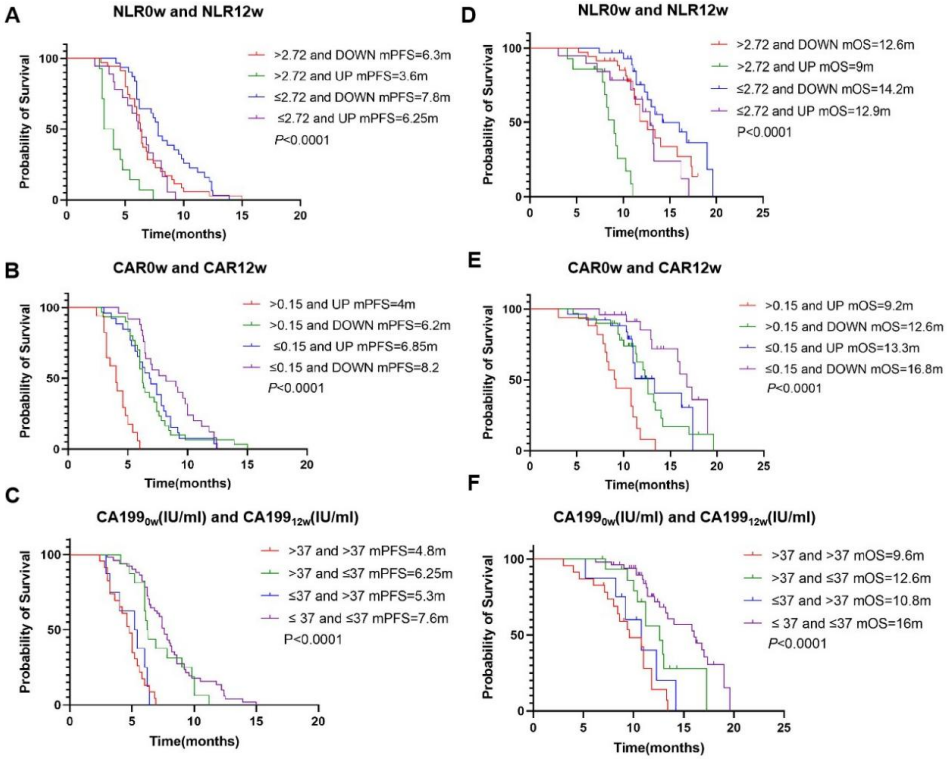

Figure 4: Kaplan–Meier curves for PFS according to "NLR0w and NLR12w" (A) ; "CAR0w and CAR12w" (B) ;"CA199 0w and CA199 12w "(C);and for OS according to "NLR0w and NLR12w" (D) ; "CAR0w and CAR12w" (E) ;"CA199 0w and CA199 12w "(F)

Safety

As of June 30, 2024, among the 98 patients, 70 (70/98) experienced at least one treatment-related adverse event associated with any study medication. The most common drug-related adverse events were gastrointestinal reactions (35 cases), followed by myelosuppression (31 cases) and neurotoxicity (18 cases). Thirteen patients experienced immune-related adverse events, with the most common being immune-related hypothyroidism (4 cases). Among these 13 patients with immune-related adverse events, 6 had elevated baseline NLR (6/9), while 19 patients (19/46) with other types of adverse events also had elevated baseline NLR levels; however, the difference was not statistically significant.

The mPFS for patients with immune-related adverse events was 11.8 months, compared to an mPFS of 7.1 months for those with other adverse events, though this difference was also not statistically significant (Supplementary Figure 5). There were no reported immune-related adverse events of grade 3 or higher. The adverse reactions are listed in Table 5.

Table 5: Summary of Adverse Reactions

Category of irAE	All grades No. (%)
Gastrointestinal adverse reactions(case, %)	35（48.6）
Myelosuppression (case, %)	31（543.1）
Neurovirulence(case, %)	15（20.8）
Hypothyroidism (case, %）	6（8.3）
Dermatotoxicity (case, %)	2（2.8）
immunological liver injury (case, %)	2（3.8）
Adrenocortical hypofunctions(case, %)	2（12.8）
Immune enteritis(case, %)	1（1.4）

Discussion

In the processes of tumor occurrence, progression, and metastasis, patient survival and disease progression are influenced not only by the characteristics of the tumor itself but also by host factors. Obtaining in vivo tumor data through non-invasive and straightforward methods to understand the intrinsic features of tumors has been a focus of research. Our retrospective study explored the prognostic value of dynamic changes in hematological inflammatory markers and tumor markers in patients with advanced gastric cancer undergoing first-line immunotherapy combined with chemotherapy.In our study, we found that lower pre-treatment levels of NLR, CAR, and CA199, as well as the dynamic changes in NLR, CAR, and CA19-9 post-treatment, were strongly correlated with treatment efficacy and prognosis. In summary, lower pre-treatment levels of NLR, CAR, and CA199, along with reductions in NLR, CAR, and CA199 after treatment, were significantly associated with prolonged PFS and OS. A decrease in NLR at 12 weeks post-treatment can serve as an independent prognostic factor for PFS and OS. Furthermore, decreases in NLR, CAR, and CA19-9 at 12 weeks post-treatment were associated with better DCR and ORR, where a reduction in NLR at this time point can also be considered an independent prognostic factor for DCR.

Inflammatory cells and mediators are critical components of the tumor microenvironment, playing significant roles in tumor occurrence, progression, and metastasis. Therefore, inflammatory markers have the potential to serve as predictive and prognostic factors in immunotherapy for advanced gastric cancer. During anti-PD-1/PD-L1 antibody therapy, lymphocyte activation is crucial for re-engaging antitumor immune responses[17]. This activation enhances the immune system's ability to recognize and attack tumor cells, potentially improving patient outcomes.Neutrophils are the predominant white blood cell compo-

nent circulating in peripheral blood and play essential roles in the immune system. These cells not only defend against pathogens but also regulate tissue and tumor microenvironments (TME) through the release of inflammatory mediators, potentially promoting tumor development, angiogenesis, and metastasis[18,19]. Meanwhile, lymphocytes, including T and B cells, are vital parts of the immune system. A reduction in lymphocytes may lead to immune dysregulation, while an increase in CD4+ T lymphocyte concentration at the tumor margin is associated with a reduced risk of recurrence. Conversely, in patients with advanced tumors, decreases in lymphocyte subpopulations (such as CD4+, CD8+, CD3+, and CD56+ T cells) may weaken lymphocyte-driven antitumor immune responses, leading to poorer prognosis[20].Platelets, as crucial factors in thrombosis, play complex roles within the tumor microenvironment. They can shield immune cells from exerting cytotoxic effects on tumor cells and induce epithelial-mesenchymal transition, promoting tumor invasion and migration[21,22]. Current studies indicate that neutrophils significantly contribute to inflammatory responses, lymphocytes participate in immune defense against tumors, and platelets promote malignancy during tumor progression and cancer development[23,24].Thus, inflammatory biomarkers such as the PLR and NLR have been established as prognostic factors across various malignancies. Research shows that NLR and PLR correlate with lymph node metastasis and unfavorable prognosis in gastric cancer patients (NLR ≥ 2.0, PLR ≥ 160)[25]. In gastric cancer, the prognostic value of NLR is superior to that of PLR. An NLR of ≥ 4 preoperatively has been identified as an independent indicator of poor prognosis in surgical patients with gastric cancer[26]. Studies have reported that elevated NLR in early gastric cancer patients correlates with increased cytokine production by activated neutrophils, along with enhanced expression of CD10 and CD35, adversely affecting gastric cancer progression[27].Shaul and Fridlender noted that neutrophils act as critical bridges between circulating tumor cells and metastatic sites[28]. Research by Diema et al. indicated that among 52 non-small cell lung cancer (NSCLC) patients receiving nivolumab treatment, high preoperative NLR and PLR were significantly associated with shorter overall survival (OS) and progression-free survival (PFS)[29]. In summary, NLR represents the relative ratio of inflammation-promoting components (i.e., neutrophils) to anticancer cells (i.e., lymphocytes). High NLR reflects a systemic immunosuppressive state and is linked to a greater likelihood of tumor progression and metastatic development. In our study, patients in the high NLR subgroup also exhibited worse prognoses. Patients with low NLR levels before treatment and reduced NLR at 12 weeks after treatment demonstrated longer PFS and OS compared to those with high NLR, suggesting that these factors can serve as independent prognostic indicators for PFS and OS in gastric cancer patients undergoing immunotherapy.

It is widely acknowledged that inflammatory responses and malnutrition are closely associated with diminished quality of life in cancer patients and adversely impact treatment outcomes. CRP, an acute-phase reactant synthesized by the liver and induced by pro-inflammatory cytokines, is regarded as a predictive marker for infection. During the metastatic progression of tumors, CRP levels may elevate significantly. Albumin (Alb), a protein circulating in plasma, also plays a role in inflammatory responses[30]. Research has indicated that hypoalbuminemia and elevated CRP levels correlate with poor prognosis in cancer patients[31] . The CAR serves as a reflection of the underlying inflammatory state of the body and has been developed as a quantifiable continuous variable. Initially utilized to assess the prognosis of septic patients, CAR has since found widespread application in evaluating the inflammatory and nutritional status of cancer patients throughout the course of treatment. Currently, the CAR has been established as a novel prognostic indicator.Yu et al. discovered that among patients undergoing radical gastrectomy following neoadjuvant chemotherapy, preoperative hypoalbuminemia was identified as a risk factor for postoperative complications ($p = 0.033$). Moreover, research conducted by Migita et al. indicated that a decrease in serum albumin levels post--neoadjuvant therapy is associated with survival outcomes[32,33]. Building upon previous studies, our observations suggest that CAR can be employed to monitor the efficacy of immunotherapy in gastric cancer. Arima et al. conducted a retrospective analysis involving 142 patients who underwent surgical resection for pancreatic cancer and found that the CRP/Albumin ratio on postoperative day 14 correlated with overall survival (OS); a higher CRP/Albumin ratio was associated with the incidence of postoperative complications[34]. Consistent with these findings, we observed that elevated CAR is linked to poor prognosis in gastric cancer. Patients exhibiting a reduction in CAR at twelve weeks post-treatment demonstrated superior disease control rates (DCR) and objective response rates (ORR). Furthermore, patients with low CAR levels prior to treatment and those show-

ing a decrease at twelve weeks post-treatment exhibited longer progression-free survival (PFS) and overall survival (OS) compared to those with higher CAR levels. Collectively, our findings indicate that CAR represents a novel independent risk factor for prognostication in gastric cancer.

In clinical practice, carcinoembryonic antigen (CEA) is commonly utilized as a biomarker to predict treatment outcomes in gastrointestinal tumors. Elevated serum levels of CEA are frequently associated with reduced cancer survival rates[35]. CA199 serves as a tumor marker for malignant gastrointestinal neoplasms and can be detected in various normal epithelial tissues, including those of the gastrointestinal tract, hepatobiliary system, pancreas, and salivary glands. The elevation of CA199 has been widely employed in the screening of gastric cancer, pancreatic cancer, colorectal cancer, and other malignancies of the digestive tract. During the progression of gastric cancer, tumor cells often exist in a hypoxic environment, leading to increased levels of CA199. Therefore, elevated CA199 levels in patients with gastric adenocarcinoma may suggest a more aggressive tumor phenotype. Studies have demonstrated that the preoperative positivity rate of CA199 in gastric cancer correlates positively with the advancing TNM stage, indicating that serum CA199 can serve as a prognostic biomarker for gastric cancer patients[36,37].Our findings suggest that a CA199 level of ≤37 IU/ml at 12 weeks post-treatment may function as an independent prognostic factor for the efficacy and response rate of immunotherapy in gastric cancer. Furthermore, the combined detection of CEA and CA199 enhances predictive accuracy regarding post-immunotherapy prognosis in gastric cancer patients. Patients with normal levels of both CEA and CA199 exhibit longer PFS and OS compared to those with elevated levels of these biomarkers.AFP elevation in gastric cancer (AFPGC) represents a distinct type of gastric cancer. AFP, a plasma glycoprotein predominantly synthesized by the yolk sac and fetal liver during development [38], is notably elevated in gastric cancer, particularly in cases of extrahepatic malignancy[39]. AFPGC is considered a rare tumor, with an incidence ranging from 1.3% to 6.6% in Asian countries, including China[40,41], and approximately 15% in Western countries[42]. Despite the availability of several biological or targeted therapies for gastric cancer in recent years, prognosis for advanced disease remains poor, with five-year survival rates falling below 20%. Reports indicate that the median survival for advanced AFPGC is approximately 9.3 months[43]. In our study, we observed an incidence of AFPGC in gastric cancer of about 19.8%, coupled with significantly reduced PFS and OS; the median PFS was found to be 5.2 months, and the median OS was 9.4 months. Additionally, AFP was identified as an independent prognostic factor for OS and PFS in the context of immunotherapy for gastric cancer.

The combined assessment of inflammatory indicators and tumor markers enables more accurate predictions regarding the outcomes of gastric cancer and its immunotherapy. CA199, CEA, and AFP reflect the hypoxic microenvironment prevalent during the progression of gastric cancer, providing a non-invasive and straightforward method for understanding tumor characteristics. Relying solely on individual inflammatory markers for the prognostication of cancer patients simplifies a complex system; thus, integrating these two categories of biomarkers could yield improved prognostic indicators. While the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and CRP/Albumin Ratio (CAR) relate to host immunity, they primarily reflect the host defense mechanisms against tumor development and do not adequately capture the intrinsic characteristics of the tumor itself. In contrast, CEA, CA199, and AFP directly convey the malignant potential of cancer, addressing this gap in prognostic evaluation.

Immune checkpoint inhibitors (ICIs) represent a groundbreaking advancement in cancer treatment, providing new hope for patients. However, this innovative therapy also presents unique challenges—immune-related adverse events (irAEs). These adverse events arise from the overactivation of the immune system and can affect multiple tissues and organs. Nakaya et al.[44]reported that patients with non-small cell lung cancer (NSCLC) undergoing nivolumab treatment who experienced irAEs had significantly better progression-free survival (PFS) compared to those who did not experience irAEs. The analyses from our study corroborate these findings, indicating that patients suffering from irAEs exhibited improved PFS outcomes; however, due to the small sample size, this difference did not reach statistical significance. Additionally, research by Matsukane et al.[45] found that an elevated neutrophil-to-lymphocyte ratio (NLR) was closely associated with the occurrence and severity of irAEs. These

findings provide new insights into predicting and managing irAEs and may serve as potential biomarkers to enhance the safety and efficacy of ICI therapies. Given the limited sample size of our study, future research should further explore the relationship between inflammatory markers and irAEs.

Limitations

This study has several limitations. Firstly, as a single-center study with a small sample size, it may be subject to selection bias, potentially impacting the reliability of the conclusions drawn. Therefore, larger multi-center prospective cohort studies are needed in future research. Secondly, individual indicators such as leukocytes, platelets, erythrocytes, and neutrophils were not included in the analysis. Moreover, because lactate dehydrogenase (LDH) and other tumor markers were not routinely measured at our institution, these indicators were also excluded from the analysis. Chemotherapy may induce changes in peripheral blood parameters, which could affect the interpretation of the study results. Ideally, a positive control group receiving only chemotherapy should be established; however, due to the rarity of isolated chemotherapy use in current clinical practice, we were unable to recruit a sufficient number of patients. Consequently, we utilized ratio indicators such as NLR, PLR, and CAR to mitigate the potential impact of chemotherapy-induced bone marrow suppression and subsequent white blood cell elevation on the study results.

Conclusions

In summary, for advanced gastric cancer patients receiving first-line treatment with PD-1 inhibitors combined with chemotherapy, lower pretreatment levels of NLR, CAR, and CA199, along with reductions in NLR, CAR, and CA199 post-treatment, serve as predictive factors for response to combined immunotherapy and are associated with better prognoses.

Funding

This work was supported by Bengbu Medical College Natural Science Foundation (no. 2022byzd035); Anhui Provincial Natural Science Foundation (no. 2208085MH248) and The First Affiliated Hospital of Bengbu Medical University Science Found for Distinguished Young Scholars (no. 2019byyfyjq03).

Notes

Disclosure: The authors have no potential conflicts of interest to disclose.

Author Contributions:

Conceptualization:Rui Wang, Tiantian Zhang.

Data curation: Mengting Shi, Yue Wu.

Formal analysis: Huihui Zeng.

Investigation: Yang Liu.

Methodology: Rui Wang.

Software: Mengting Shi.

Validation: Yang Liu.

Writing - original draft: Rui Wang, Huihui Zeng.

Writing - review & editing: Rui Wang, Huihui Zeng,Tiantian Zhang.

References

1. Machlowska J, Baj J, Sitarz M et al. (2020) Gastric cancer: Epidemiology, risk factors, classification, genomic characteristics and treatment strategies. International Journal of Molecular Sciences, 21: 4012.

2. Zhang X, Zhao W, Chen X et al. (2020) Combining the fibrinogen-to-pre-albumin ratio and prognostic nutritional index (F-PR-PNI) predicts survival in elderly gastric cancer patients after gastrectomy. OncoTargets and Therapy, 13: 8845–59.

3. Herbst RS, Baas P, Kim DW et al. (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet, 387: 1540-50.

4. Reck M, Rodríguez-Abreu D, Robinson AG et al. (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small--cell lung cancer. The New England Journal of Medicine, 375: 1823–33.

5. Kim ST, Cristescu R, Bass AJ et al. (2018) Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nature Medicine, 24: 1449–58.

6. Mariathasan S, Turley SJ, Nickles D et al. (2018) TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature, 554: 544–8.

7. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell. 2010; 140(6): 883–899.

8. Cupp MA, Cariolou M, Tzoulaki I et al. (2020) Neutrophil to lymphocyte ratio and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies. BMC Medicine, 18: 360.

9. Gui, W., Wang, X., Luo, Y. et al. Platelet to lymphocyte ratio as a prognostic factor in patients with advanced colorectal cancer undergoing palliative treatment. Annals of Palliative Medicine, 9: 3271–7.

10. Grenader T, Waddell T, Peckitt C et al. (2016) Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago--gastric cancer: Exploratory analysis of the REAL-2 trial. Annals of Oncology, 27: 687–92.

11. Capone M, Giannarelli D, Mallardo D et al. (2019) Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. Journal for ImmunoTherapy of Cancer, 6: 74.

12. Yu Q, Li K Z, Fu YJ et al. (2021) Clinical significance and prognostic value of C-reactive protein/albumin ratio in gastric cancer. Annals of Surgical Treatment and Research, 100: 338–46.

13. Fu YJ, Li KZ, Bai JH et al. (2019) C-reactive protein/albumin ratio is a prognostic indicator in Asians with pancreatic cancers: A meta-analysis. Medicine, 98: e18219.

14. Lathrop K, Kaklamani V (2019) The Response Evaluation Criteria in Solid Tumors (RECIST). In: Badve, S., Kumar, G. L.,

editors. Predictive Biomarkers in Oncology Applications in Precision Medicine. Cham: Springer International Publishing, 501-11.

15. Pathology Quality Control Center, Chinese Society of Pathology, Pathology Committee of Chinese Society of Clinical Oncology. Consensus on the immunohistochemical tests of PD-L1 in solid tumors (2021 version). Chinese Journal of Pathology, 50: 710–8.

16. Haanen J, Carbonnel F, Robert C et al. (2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 28: 119-42.

17. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell, 140: 883–99.

18. Dumitru CA, Lang S, Brandau S (2010) Modulation of neutrophil granulocytes in the tumor microenvironment: mechanisms and consequences for tumor progression. Seminars in Cancer Biology, 23: 141-8.

19. Liang W, Ferrara N (2016) The complex role of neutrophils in tumor angiogenesis and metastasis. Cancer Immunology Research, 4: 83–91.

20. Galon J, Costes A, Sanchez-Cabo F et al. (2006) Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science, 313: 1960-4.

21. Orellana R, Kato S, Erices R, et al. (2015) Platelets enhance tissue factor protein and metastasis initiating cell markers, and act as Chemoattractants increasing the migration of ovarian cancer cells. BMC Cancer, 15: 290.

22. Labelle M, Begum S, Hynes RO (2011) Direct signaling between platelets and cancer cells induces an epithelial-Mesenchymal-like transition and promotes metastasis. Cancer Cell, 20: 576–90.

23. Schnellhardt S, Erber R, Büttner-Herold M et al. (2020) Tumour-infiltrating inflammatory cells in early breast cancer: an underrated prognostic and predictive factor? International Journal of Molecular Sciences, 21: 8238.

24. Tesfamariam B (2016) Involvement of platelets in tumor cell metastasis. Pharmacology & Therapeutics, 157: 112-9.

25. Zhang LX, Wei ZJ, Xu AM et al. (2018) Can the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio be beneficial in predicting lymph node metastasis and promising prognostic markers of gastric cancer patients? International Journal of Surgery, 56: 320–7.

26. Shimada H, Takiguchi N, Kainuma O et al. (2010) High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer, 13: 170–6.

27. Jin H, Zhang G, Liu X et al. (2013) Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy. World Journal of Surgical Oncology, 11: 112.

28. Shaul ME, Fridlender ZG (2017) Neutrophils as active regulators of the immune system in the tumor microenvironment. Journal of Leukocyte Biology, 102: 343–9.

29. Gregory AD, McGarry Houghton A (2011) Tumor-associated neutrophils: new targets for cancer therapy. Cancer Research, 71: 2411–6.

30. Caraceni P, Tufoni M, Bonavita ME (2013) Clinical use of albumin. Blood Transfusion, 11: S18–25.

31. McMillan DC (2009) Systemic inflammation, nutritional status and survival in patients with cancer. Current Opinion in Clinical Nutrition and Metabolic Care, 12: 223-6.

32. Yu H, Xu L, Yin S et al. (2022) Risk factors and prognostic impact of postoperative complications in patients with advanced gastric cancer receiving neoadjuvant chemotherapy. Current Oncology, 29: 6496–507.

33. Migita K, Matsumoto S, Wakatsuki K et al. (2017) A decrease in the prognostic nutritional index is associated with a worse long-term outcome in gastric cancer patients undergoing neoadjuvant chemotherapy. Surgery Today, 47: 1018–26.

34. Arima K, Yamashita YI, Hashimoto D et al. (2018) Clinical usefulness of postoperative C-reactive protein/albumin ratio in pancreatic ductal adenocarcinoma. American Journal of Surgery, 216: 111–5.

35. Chen XK, Gu CL, Fan JQ et al. (2020) P-STAT3 and IL-17 in tumor tissues enhances the prognostic value of CEA and CA125 in patients with lung adenocarcinoma. Biomedical Pharmacotherapy, 125: 109871.

36. Huang ZB, Zhou X, Xu J et al. (2013) Prognostic value of preoperative serum tumor markers in gastric cancer. World Journal of Clinical Oncology, 5: 170-6.

37. Uda H, Kanda M, Tanaka C et al. (2018) Perioperative serum carcinoembryonic antigen levels predict recurrence and survival of patients with pathological T2-4 gastric cancer treated with curative gastrectomy. Digestive Surgery, 35: 55-63.

38. Bergstrand CG, Czar B (1956) Demonstration of a new protein fraction in serum from the human fetus. Scandinavian Journal of Clinical and Laboratory Investigation, 8: 174-9.

39. Metzgeroth G, Strobel P, Baumbusch T et al. (2010) Hepatoid adenocarcinoma - review of the literature illustrated by a rare case originating in the peritoneal cavity. Onkologie, 33: 263–9.

40. Chang YC, Nagasue N, Abe S et al. (1992) Comparison between the clinicopathologic features of AFP-positive and AFP-negative gastric cancers. American Journal of Gastroenterology, 87: 321–5.

41. Li XD, Wu CP, Ji M et al. (2013) Characteristic analysis of α-fetoprotein-producing gastric carcinoma in China. World Journal of Surgical Oncology, 11: 246.

42. KR McIntire, TA Waldmann CG Moertel, et al. (1975) Serum alpha-fetoprotein in patients with neoplasms of the gastrointestinal tract, Cancer Res, 35: 991–6.

43. Bozkaya Y, Demirci NS, Kurtipek A et al. (2017) Clinicopathological and prognostic characteristics in patients with AFP-secreting gastric carcinoma. Molecular and Clinical Oncology, 7: 267-74.

44. Nakaya A, Kurata T, Yoshioka H et al. (2018) Neutrophil-to-lymphocyte ratio as an early marker of outcomes in patients with advanced non-small-cell lung cancer treated with nivolumab. International Journal of Clinical Oncology, 23: 634–40.

45. Matsukane R, Watanabe H, Minami H et al. (2021) Continuous monitoring of neutrophils to lymphocytes ratio for estimating the onset, severity, and subsequent prognosis of immune related adverse events. Scientific Reports, 11: 1324.