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Original Article

Baseline Inflammatory Burden Index Predicts Primary Resistance to Combinations of ICIs With Chemotherapy in Patients With HER-2-Negative Advanced Gastric Cancer

Tingting Wang *, **Huihui Zeng** *, **Ting Hu**, **Junhao Zhang**, **Zishu Wang**

Department of Oncology, the First Affiliated Hospital of Bengbu Medical University, Bengbu, China

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Correspondence to
Zishu Wang
Department of Oncology, The First Affiliated Hospital of Bengbu Medical University, No. 287 Changhuai Road, Bengbu 233000, China.
Email: wzsh51103@bbmc.edu.cn

*Tingting Wang and Huihui Zeng contributed equally to this work.

ORCID iDs
Tingting Wang
https://orcid.org/0009-0006-6982-9185
Huihui Zeng
https://orcid.org/0000-0003-4638-2238
Ting Hu
https://orcid.org/0009-0001-7079-0672
Junhao Zhang
https://orcid.org/0009-0000-4146-5750
Zishu Wang
https://orcid.org/0009-0008-8079-7457

ABSTRACT

Purpose: Combinations of immune checkpoint inhibitors (ICIs) and chemotherapy have become the standard first-line treatment for human epidermal growth factor receptor 2 (HER-2)-negative advanced gastric cancer. However, primary resistance remains a challenge, with no effective biomarkers available for its prediction. This retrospective study explores the relationship between the baseline inflammatory burden index (IBI) and primary resistance in such context.

Materials and Methods: We analyzed 62 patients with HER-2-negative advanced gastric cancer who received ICIs and chemotherapy as their first-line treatment. The IBI was calculated as follows: C-reactive protein (mg/L) × neutrophil count (10^3/mm^3)/lymphocyte count (10^3/mm^3). Based on disease progression within 6 months, patients were categorized into the primary resistant or the control group. We compared baseline characteristics and IBI scores between the groups and assessed the predictive value of the IBI using the receiver operating characteristic curve. Both univariate and multivariate binary logistic regression analyses were conducted to identify factors influencing primary resistance.

Results: Nineteen patients were included in the primary resistance group, and forty-three patients were included in the control group. The IBI was significantly higher in the resistant group compared to the control group (P<0.01). The area under the curve for the IBI was 0.82, indicating a strong predictive value. Multivariate analysis identified the IBI as an independent predictor of primary resistance (P=0.014).

Conclusions: The baseline IBI holds promise as a predictor of primary resistance to combined ICIs and chemotherapy in patients with HER-2-negative advanced gastric cancer.

Keywords: Gastric cancer; Inflammation; Immune checkpoint inhibitors; Chemotherapy; Drug resistance

INTRODUCTION

Gastric cancer ranks among the most prevalent malignancies and is the fourth leading cause of cancer-related death worldwide [1]. Systemic chemotherapy remains the primary

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Conflict of Interest
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Author Contributions
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treatment for advanced gastric cancer. However, the median overall survival (OS) for patients undergoing conventional chemotherapy is only approximately 12 months [2]. Recent advancements in immunotherapy, particularly immune checkpoint inhibitors (ICIs), have made breakthroughs in the treatment of advanced gastric cancer. In first-line treatments for human epidermal growth factor receptor 2 (HER-2)-negative advanced gastric cancer, pembrolizumab combined with chemotherapy has demonstrated a survival advantage over chemotherapy alone [3]. Similarly, the CheckMate-649 study showed that nivolumab plus chemotherapy improved OS and progression-free survival (PFS) compared to chemotherapy alone [4]. The ORIENT-16 and RATIONALE-305 clinical trials further confirmed that ICIs with chemotherapy significantly improved clinical outcomes for all patients [5,6]. Based on these findings, ICIs combined with chemotherapy have been established as the standard first-line treatment for HER-2-negative advanced gastric cancer. Nevertheless, some patients exhibit primary resistance to this combination. The Society for Immunotherapy of Cancer defines primary resistance to ICIs with chemotherapy as disease progression within 6 months of treatment initiation, following a minimum of 6 weeks of drug exposure [7]. The underlying mechanisms of primary resistance remain largely unknown, and few studies have investigated this resistance in the context of combined immunotherapy and chemotherapy for gastric cancer. Identifying biomarkers to predict primary resistance is crucial for developing personalized treatment strategies and further exploring the molecular mechanisms behind primary resistance in gastric cancer.

At present, biomarkers such as programmed death ligand-1 (PD-L1) expression, tumor mutation burden (TMB), mismatch repair status, and Epstein–Barr virus (EBV) infection have demonstrated some predictive value for the efficacy of immunotherapy in patients with gastric cancer. However, each biomarker has inherent limitations. The role of PD-L1 expression in predicting the success of immunotherapy for gastric cancer remains contentious. A meta-analysis showed that ICIs combined with first-line chemotherapy benefited patients with gastric or gastroesophageal junction cancer, in terms of both OS and PFS, and irrespective of their combined positive score (CPS) status [8]. Another meta-analysis found a survival benefit for patients with a CPS of ≥1 who were treated with ICI monotherapy [9]. In the analysis of the KEYNOTE-062 clinical trial, TMB levels were associated with the effectiveness of first-line pembrolizumab combined with chemotherapy among gastric cancer patients [10]. Nevertheless, TMB is influenced by numerous factors including tumor type, genetic variations, external carcinogens, and detection methods, and its high cost, time demands, and requirement for fresh samples pose significant clinical challenges [11]. Studies have indicated that patients with high microsatellite instability (MSI-H) or defective mismatch repair (dMMR) are more responsive to ICI-based treatments [12,13], although MSI status is considered a less reliable biomarker due to its low prevalence and variability [14,15]. Notably, about 50% of MSI-H tumor patients show primary resistance to PD-1 inhibitors [16]. In one observational study, 3 out of 9 patients with EBV-associated gastric cancer achieved a partial response to ICIs, while 5 others maintained stable disease (SD) [17]. Conversely, another study involving 6 patients with EBV-associated gastric cancer treated with camrelizumab reported no objective responses [18]. Thus, the predictive value of EBV infection for ICI response in gastric cancer remains uncertain. Given these limitations, it is crucial to identify new biomarkers that can more accurately predict the clinical outcomes of ICIs combined with chemotherapy.

Systemic inflammation, which reflects the interaction between a tumor and its host, is closely linked to disease progression and prognosis in cancer patients [19]. C-reactive protein

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(CRP), an acute-phase protein synthesized by liver cells in response to inflammation, is the most commonly used marker of inflammation in clinical settings. CRP not only affects the function of activated immune cells but also influences the cytotoxic immune response and promotes the immune escape of tumor cells [20]. Neutrophils and lymphocytes, critical components of humoral immunity, play significant roles as well. Increased neutrophil levels can suppress the activity of T-cells and natural killer cells, while a decrease in lymphocytes indicates a compromised immune response to tumors [21,22]. Among patients with advanced colorectal cancer who received ICIs, those with a lower baseline neutrophil-to-lymphocyte ratio (NLR) had longer survival [23]. A similar association between a lower NLR and improved outcomes was observed in patients with non-small cell lung carcinoma treated with Nivolumab [24]. Additionally, a higher pan-immune-inflammation value—which includes neutrophil, platelet, monocyte, and lymphocyte counts—has been linked to primary resistance in patients with advanced malignant melanoma [25].

The inflammatory burden index (IBI), developed by Shi Hanping's team, integrates CRP, neutrophils, and lymphocytes. It has proven to be a more accurate predictor of survival compared to other systemic inflammatory biomarkers. A high IBI correlates with poorer survival outcomes [26]. However, the relationship between IBI and primary resistance to ICI and chemotherapy combinations has not yet been explored. Thus, this retrospective study aims to investigate the correlation between baseline IBI and primary resistance in patients with HER-2-negative advanced gastric cancer treated with these combinations.

MATERIALS AND METHODS

Study population

A total of 62 patients with HER-2-negative advanced gastric cancer were enrolled in this study at the First Affiliated Hospital of Bengbu Medical University. These patients received first-line treatment with ICIs combined with chemotherapy from August 1, 2020, to May 20, 2024. The inclusion criteria were as follows: patients must be 18 years of age or older with a cytologically or histologically confirmed diagnosis of HER-2-negative gastric cancer; have unresectable or metastatic disease; possess an Eastern Cooperative Oncology Group performance status of 0 or 1; demonstrate adequate organ function; and have received a minimum drug exposure of 6 weeks. Patients were excluded if they had an acute infection, had undergone surgery or experienced trauma within one week prior to enrollment, or had active autoimmune or cardiovascular diseases.

Determination of the NLR, IBI, and efficacy

Blood parameters were analyzed within 7 days before initiating treatment with ICIs and chemotherapy. The NLR was calculated as the neutrophil count (10^3/mm^3) divided by the lymphocyte count (10^3/mm^3). The IBI was calculated as [CRP (mg/L) × neutrophil count (10^3/mm^3)]/lymphocyte count (10^3/mm^3). The efficacy of the treatments was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1, which categorizes responses as progressive disease, SD, partial remission, and complete remission. Based on whether disease progression occurred within 6 months, patients were assigned to either the primary resistant group or the control group.

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Statistical analyses

Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test, as appropriate. Numerical variables were evaluated with the t-test. The values of the NLR and IBI for primary resistance were assessed using receiver operating characteristic curves, which included calculations of the area under the curve (AUC) and the Youden index. The Youden index was calculated as follows: Sensitivity + Specificity − 1. Optimal cutoff values were determined by the maximum Youden index. Based on these values, patients were categorized into high-IBI and low-IBI groups. Univariate and multivariate binary logistic regression analyses were performed to identify factors influencing primary resistance. In the multivariate analysis, any variable with a P-value less than 0.1 in the univariate analysis was included. Multicollinearity between independent variables was checked and excluded via collinearity diagnosis. All analyses were conducted using SPSS version 22.0, and a P-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the included patients

Nineteen patients who experienced disease progression within 6 months were assigned to the resistant group, while forty-three patients were placed in the control group. There were no significant differences in age, sex, liver metastasis, peritoneal metastasis, or chemotherapy regimens between the 2 groups. However, the IBI and NLR were significantly higher in the resistant group compared to the control group (P<0.01). The baseline characteristics of the 2 groups are shown in **Table 1**.

The values of the NLR and IBI in predicting primary resistance

The optimal cutoff value for the NLR in predicting primary resistance to combinations of ICIs with chemotherapy was 2.21, exhibiting a sensitivity of 0.84, a specificity of 0.58, and AUC of 0.74 (95% confidence interval [CI], 0.605–0.880; P=0.003). For the IBI, the optimal cutoff value was 7.91, with a sensitivity of 0.81, a specificity of 0.78, and an AUC of 0.82 (95% CI, 0.709–0.932; P<0.001), as illustrated in **Fig. 1**. The IBI demonstrated greater efficacy than the

Table 1. Baseline characteristics of the 2 groups

Characteristics	Resistant group (n=19)	Control group (n=43)	P-value
Age (yr)	58.79±12.36	59.63±11.06	0.792
Sex			0.368
Male	12 (63.16)	32 (74.42)	
Female	7 (36.84)	11 (25.58)	
IBI	44.20±48.83	5.43±7.04	0.003
NLR	3.22±1.22	2.18±0.87	<0.001
Liver metastasis			0.742
Yes	7 (36.84)	14 (32.56)	
No	12 (63.16)	29 (67.44)	
Peritoneal metastasis			0.173
Yes	5 (26.32)	4 (9.30)	
No	14 (73.68)	39 (90.70)	
Chemotherapy regimens			0.825
Oxaliplatin + fluorouracil	11 (57.89)	25 (58.14)	
Docetaxel + cisplatin	3 (15.79)	4 (9.30)	
Paclitaxel + S-1	1 (5.26)	5 (11.63)	
Others	4 (21.05)	9 (20.93)	

Values are presented as mean ± standard deviation or number (%).
IBI = inflammatory burden index; NLR = neutrophil-to-lymphocyte ratio.

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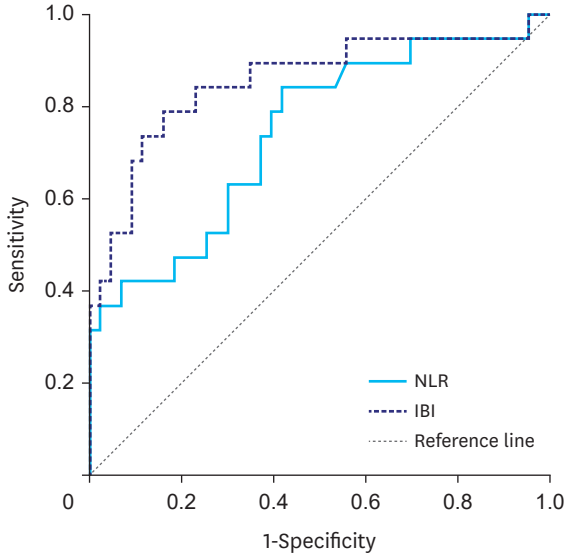

Fig. 1. The AUC of NLR for predicting primary resistance to combinations of ICIs with chemotherapy was 0.74 (95% CI, 0.605–0.880; P=0.003). The AUC of IBI for predicting primary resistance to combinations of ICIs with chemotherapy was 0.82 (95% CI, 0.709–0.932; P<0.001).
NLR = neutrophil-to-lymphocyte ratio; IBI = inflammatory burden index; AUC = area under the curve; CI = confidence interval; ICI = immune checkpoint inhibitor.

Table 2. Primary resistance in the different IBI groups

Variable	High IBI-group (n=27)	Low IBI-group (n=35)	P-value
Primary resistance			<0.001
Yes	16 (59.26)	3 (8.57)	
No	11 (40.74)	32 (91.43)	

Values are presented as number (%).
IBI = inflammatory burden index.

NLR in predicting primary resistance to the treatment combination. Based on the IBI cutoff value, patients were divided into 2 groups: 27 in the high IBI group (IBI >7.91) and 35 in the low IBI group (IBI ≤7.91). The incidence of primary resistance was significantly higher in the high IBI group at 59.26% (16/27) compared to 8.57% (3/35) in the low IBI group (P<0.001). The distribution of primary resistance across the different IBI groups is shown in **Table 2**.

Univariate and multivariate binary logistic regression analyses of factors affecting primary resistance

In the univariate analysis, variables included were age (≤50 years), sex, liver metastasis, peritoneal metastasis, chemotherapy regimens, the NLR and the IBI. The results indicated that the IBI, NLR, and the incidence of peritoneal metastasis were significantly associated with primary resistance (P=0.006, P=0.002, P=0.092, respectively) as shown in **Table 3**. These variables were subsequently included in the multivariate analysis. Collinearity diagnosis confirmed that there was no multicollinearity among the independent variables. The multivariate analysis revealed that the IBI was significantly related to primary resistance to combinations of ICIs with chemotherapy (odds ratio [OR], 1.138; 95% CI, 1.027–1.262; P=0.014). This suggests that the IBI serves as an independent predictive factor for primary resistance to these treatments, as detailed in **Table 4**.

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Table 3. Univariate binary logistic regression analysis of factors affecting primary resistance

Variables	β	SE	Wald	P-value	OR	95% CI
IBI	0.106	0.039	7.478	0.006	1.112	1.030–1.199
NLR	1.007	0.326	9.548	0.002	2.736	1.445–5.182
Peritoneal metastasis	−1.248	0.740	2.845	0.092	0.287	0.067–1.224
Liver metastasis	−0.189	0.576	0.108	0.743	0.828	0.267–2.561
Age ≤50 yr	−0.145	0.768	0.036	0.850	0.865	0.192–3.895
Sex	−0.529	0.590	0.803	0.370	0.589	0.185–1.874
Chemotherapy regimens						
Others			1.000	0.801		
Oxaliplatin + fluorouracil	−0.010	0.701	0.000	0.989	0.990	0.250–3.915
Docetaxel + cisplatin	0.523	0.972	0.290	0.590	1.688	0.251–11.336
Paclitaxel + S-1	−0.811	1.249	0.408	0.523	0.450	0.039–5.209

SE = standard error; OR = odds ratio; CI = confidence interval; IBI = inflammatory burden index; NLR = neutrophil-to-lymphocyte ratio.

Table 4. Multivariable binary logistic regression analysis of factors affecting primary resistance

Variables	β	SE	Wald	P-value	OR	95% CI
IBI	0.130	0.053	6.054	0.014	1.138	1.027–1.262
NLR	−0.426	0.565	0.568	0.451	0.653	0.216–1.977
Peritoneal metastasis	−1.343	0.903	2.214	0.137	0.261	0.044–1.531

SE = standard error; OR = odds ratio; CI = confidence interval; IBI = inflammatory burden index; NLR = neutrophil-to-lymphocyte ratio.

DISCUSSION

At present, the mechanisms underlying resistance to ICIs in gastric cancer are complex and not fully understood. The potential mechanisms of resistance can be categorized into tumor-intrinsic, tumor-extrinsic, and other mechanisms. Tumor-intrinsic mechanisms include reduced expression of co-inhibitory receptors, abnormalities in key signaling pathways, loss or mutation of antigens, and deficiencies in tumor antigen presentation. Tumor-extrinsic mechanisms encompass T-cell rejection, the presence of immunosuppressive cells within the tumor microenvironment (TME), and inhibitory factors in both the TME and microbiota. Other possible mechanisms could involve metabolic and epigenetic changes. However, some of these resistance mechanisms have yet to be confirmed in gastric cancer [27]. Therefore, the identification of effective biomarkers to predict primary resistance is crucial for further elucidation of the molecular mechanisms driving primary resistance to immunotherapy in gastric cancer.

Gastric cancer commonly spreads to the peritoneum and liver. The peritoneum, the largest of the 3 serous cavities in the human body, is separated from systemic circulation by the peritoneal plasma barrier, which may reduce the effectiveness of ICIs [28]. Factors such as immunosuppression, inflammation, and angiogenesis contribute to the development of peritoneal metastasis [29]. A multicenter study focusing on dMMR/MSI-H metastatic colorectal and gastric cancer patients found that those with peritoneal metastases and ascites had poorer survival compared to those with peritoneal metastases without ascites or those with other non-peritoneal metastases [30]. In preclinical models, liver metastases have been shown to create a systemic immune desert. Clinically, patients with liver metastasis exhibit reduced peripheral T-cell counts and diminished tumoral T-cell diversity and function [31]. A real-world study analyzing the efficacy of ICIs in patients with dMMR/MSI-H metastatic gastrointestinal cancers revealed that 25.1% of patients exhibited primary resistance to ICIs. Multivariate analysis indicated that primary resistance was associated with peritoneal (OR, 2.00) and liver metastases (OR, 2.19) [32]. Age is also a critical factor influencing immunotherapy response. Studies on melanoma have shown that younger patients tend

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to have higher levels of regulatory T-cells and fewer CD8+ effector T-cells [33], and clinical studies have observed that younger patients with solid tumors receiving ICIs generally show lower clinical response rates [34,35]. In the context of primary resistance, individuals aged 50 years or younger were found to be at increased risk (OR, 1.76) [32]. Our study further explores the clinical relevance of liver metastasis, peritoneal metastasis, and age in predicting primary resistance to combined ICIs and chemotherapy in patients with gastric cancer. The results indicated no significant differences in the prevalence of liver metastasis, peritoneal metastasis, or age ≤50 years between the resistant and control groups. However, the inflammatory index showed a statistically significant difference.

Chronic inflammation is pivotal in the onset and progression of cancer. In the TME, inflammatory stimulation can lead to CD8+ T cell dysfunction and hinder antigen presentation by dendritic cells, thereby contributing to immunotherapy resistance [36]. In MSI-H colorectal cancer patients, local tumor inflammation is linked with resistance to ICIs. Single-cell RNA sequencing has suggested that neutrophils may suppress the immune environment via the CD80/CD86-CTLA4 signaling pathway [37]. A previous study indicated that a high pre-treatment NLR was associated with poor PFS and OS in patients with gastric cancer treated with ICIs [38]. Our research supports these findings, showing that a higher baseline NLR correlates with primary resistance to ICIs and chemotherapy in patients with HER-2-negative advanced gastric cancer. We identified an optimal NLR cutoff value of 2.21, with a sensitivity of 0.84, specificity of 0.58, and an AUC of 0.74 for predicting primary resistance. Furthermore, the IBI, which integrates CRP levels and the NLR, was significantly linked to primary resistance. The IBI proved more predictive than the NLR alone, with a sensitivity of 0.81, specificity of 0.78, and AUC of 0.82. Multivariable binary logistic regression analysis confirmed the IBI as an independent risk factor for primary resistance to ICIs and chemotherapy in this patient group. Inflammatory cells within the TME can activate factors like interleukins and tumor necrosis factor, promoting tumor progression and enhancing the synthesis and secretion of CRP and neutrophils. These elements further produce vascular endothelial growth factor and interleukin-10, fostering tumor cell growth [39]. Neutrophils also release tumor-related proteases that induce extracellular stromal remodeling, creating a conducive environment for cancer invasion and migration [40]. Overall, the tumor-associated microenvironment is immunosuppressive, generally characterized by reduced lymphocyte counts in response to nonspecific tumor-induced inflammation [41]. These findings underscore that the IBI effectively reflects the interplay between the tumor and the host immune system, establishing it as a promising biomarker for predicting primary resistance to ICIs and chemotherapy in HER-2-negative advanced gastric cancer. For patients with a high baseline IBI, reducing the IBI may provide a strategy to overcome primary resistance, although further research and validation are required.

To the best of our knowledge, this is the first study to investigate the relationship between the IBI and primary resistance to combinations of ICIs with chemotherapy in patients with HER-2-negative advanced gastric cancer. Additionally, the IBI is easily measurable through the analysis of peripheral blood samples, which allows for convenient and repeatable assessments. Our findings enhance the understanding of the link between systemic inflammation and primary resistance to ICIs and chemotherapy combinations. However, our study does have some limitations. Firstly, it was retrospective in nature, which could introduce bias. Secondly, the sample size was relatively small.

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Our study demonstrated that the baseline IBI is significantly associated with primary resistance to combinations of ICIs with chemotherapy in HER-2-negative advanced gastric cancer patients. The baseline IBI may be used as a promising predictor of primary resistance to combinations of ICIs with chemotherapy in patients with HER-2-negative advanced gastric cancer. Future research should include a prospective study with a larger sample size to validate these findings. Additionally, further investigation into the relationship between inflammation and primary resistance from cellular and molecular perspectives is warranted.

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