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Combining SIRI and AFR to Predict Early Serious Complications and Recurrent or Metastases after Respectable Gastric Cancer

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Abstract

Background: The aim of this study was to assess the clinical importance and prognostic significance of Systemic Inflammatory Response Index (SIRI) and the Albumin Fibrinogen Ratio (AFR) on early postoperative outcomes in patients undergoing radical gastric cancer surgery.

Methods: We conducted a retrospective analysis of the clinicopathological characteristics and relevant laboratory indices of 568 patients with gastric cancer. We examined the diagnostic ability of the combination of SIRI and AFR for early postoperative serious complications. We compared three groups of patients to evaluate the prognostic value of various preoperative SIRI-AFR scores for early postoperative recurrence or metastasis.

Results: The results demonstrated that the SIRI-AFR score was an independent risk factor for early postoperative recurrence or metastasis and had the highest diagnostic power for early serious complications in patients with gastric cancer.

Conclusion: Preoperative SIRI and AFR were significantly associated with early postoperative recurrence or metastasis and the occurrence of severe complications in patients with gastric cancer.

Keywords: Inflammation; Albumin fibrinogen ratio; Gastric cancer; Complications; Prognosis.

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Introduction

Ranking fifth in morbidity and fourth in fatality in all malignancies, gastric cancer is one of the most prominent diseases worldwide [1]. Similarly, gastric cancer has made a great contribution to the cancer burden in China. Gastric cancer is the second highest cancer to be diagnosed and the secondary consideration of cancer-related death in China. As a transitioning country, China bears a massive burden of the morbidity/mortality and five-year prevalence rate for gastric cancer compared to most developed countries [2]. Surgery-based multidisciplinary comprehensive treatment remains the paramount approaches to selection for treating gastric cancer [3]. An essential course of treatment for non-metastatic gastric cancer is gastroplasty with lymph node dissection [4].

Gastrectomy offers a substantial risk of postoperative complications despite significant improvements in surgery and anesthetic procedures, postoperative care, and interventional radiology related to stomach cancer [5]. At the same time, recurrences are common. In actuality, postoperative complications following gastric surgery were reported to be 46% [6]. Undeniably, these complications may reduce quality of life, postpone the start of adjuvant treatment, and impede recovery [7]. Meanwhile, patients with conditions are at greater risk of disease recurrence [8]. Relevant evidence reveals that more than 70% of recurrence and cancer-related mortality develop within two years of surgery, and the recurrence and metastasis of gastric cancer can lead to a significant shortening of the time a patient survives [9].

Chronic and sustained inflammation of the gastric mucosa has been demonstrated to not only act as a stimulant to the occurrence and advancement of gastric cancer [10], furthermore, the inflammatory response stimulates and releases systemic cytokines, which attract the growth of remained cancer cells and promote postoperative recurrence and metastasis [8]. A increasing variety of studies has revealed that several newly established inflammation-based indicators: Neutrophil-To-Lymphocyte Ratio (NLR), Lymphocyte-To-Monocytes Ratio (LMR), Lymphocyte-To-C Reactive Protein Ratio (LCR) [11], including Fibrinogen-To-Albumin Ratio (FAR) [12] and SIRI [13] play an instrumental part in the diagnosis, staging and prediction of gastric cancer. For example, Fibrinogen-NLR (F-NLR) have served to prognostic prediction of patients with esophageal-gastric junction and superior gastric cancer after gastrectomy and have shown favourable predictive effects [14]. Therefore, in order to further explore preoperative indicators that can easily and accurately identify the risk of complication in the early post-operative period and recurrence or metastasis for patients undergoing radical gastrectomy, we propose to combine SIRI and AFR these two biochemical markers with the aim of improving the sensitivity of assessing inflammation, nutritional status and coagulation to improve the accuracy and specificity of predicting postoperative outcomes in short and long-term for patients with gastric carcinoma.

Materials and methods

Patients and follow-up

We conducted retrospective research on patients at the Gansu Provincial Hospital (Lanzhou, China) who had gastric cancer that had been verified by histology from January 2018 to December 2019. The research protocols for the current investigation, which conformed to the principles of the Declaration of Helsinki, and received approval from the ethics board. Ethical consent: 21/10/2022-410, Gansu Provincial Hospital Medical Ethics Committee. From medical records, information was gathered on the sex, age, tumor dimensions, tumor localization metastatic rate of lymph nodes, degree of tumor differentiation, immunohistochemistry results (ki67, P53, Her2), TNM stage (refer to the American Joint Commission on Cancer (AJCC) gastric cancer TNM staging criteria (eighth edition)), ASA score, surgical approach, extent of resection, duration of surgery, blood loss, periprocedural blood transfusion, length of hospitalization, duration of postoperative enteral nutrition. **Inclusive criteria:** (i) Between 18 and 80 years of age with a clinically definite diagnosis of preoperative gastric malignancy; (ii) Patients with postoperative pathological results confirming primary gastric cancer; (iii) Patients undergoing D1/D1+/D2 lymph node dissection with radical R0 resection for the first time for radical gastric cancer. **Exclusion criteria:** (i) Patients with distant tumor metastasis; (ii) Patients with combined hematological diseases, autoimmune diseases, infectious diseases or liver dysfunction that may affect white blood cells; (iii) Preoperative neoadjuvant therapy (radiotherapy or chemotherapy); (iv) Combined with other malignant tumors; (v) Incomplete data. Participants in the included studies were followed up by telephone contact, outpatient review, hospitalization and others. Patients were carefully followed-up every 3 to 6 months after surgery. Annual follow-up was implemented after two years. Follow-up outcomes were recurrence or metastasis within three years of surgery. Postoperative recurrent metastases were defined as the reappearance of malignancy associated with the primary lesion or the presence of abdominal metastases, with or without distant metastases, after radical resection. The last follow-up was processed in December 2022.

Laboratory variables and definition of fibrinogen albumin ratio and SIRI Index (SIRI-AFR)

Relevant indicators levels were assessed in blood samples drawn within a week prior to the surgery. Retrospective analysis and data collection from the electronic medical records included additional parameters. In-hospital or within 30 days occurring were categorized as early postoperative complications, and all complications were graded for severity refer to the Clavien-Dindo complication grading system [15], with Grade I or II complications were categorized into minor complications, whereas Grade III and higher were characterized as major complications. The general post-operative pathology specimen's lengthy diameter was used to calculate the tumor size. Primary tumor locations were classified as upper, middle and lower stomach, accordingly. There were two categories for differentiation level: badly differentiated and moderately/well differentiated.

SIRI and AFR were calculated as the following: SIRI = Neutrophil count × Monocyte count/Lymphocyte count, AFR = Albumin/Fibrinogen. Determined by the SIRI and AFR cut-off values, a scoring system was developed. Patients with a SIRI ≥ 1.007 and a AFR ≤ 9.849 were distributed a SIRI-AFR of 2, patients with a SIRI < 1.007 and a AFR > 9.849 were allocated a SIRI-AFR score of 0, and those with only one of SIRI ≥ 1.007 or AFR ≤ 9.849 were granted a SIRI-AFR of 1.

Statistical analysis

All of the statistically analyzed were completed utilizing the IBM SPSS for Windows, version 26.0 (IBM statistics for Windows, version 26, IBM Corporation, Armonk, New York, United States). Categorize material were indicated as n (number) and percentage (%), for normally distributed measures the information is described as the mean ± standard deviation and the non-normally distributed continuous variables it is expressed as the median (Interquartile Range (IQR)). The paired groups were contrasted using either the Mann Whitney-U test or the Student's t-test, depending on the normality of the data distribution. The Chi-square test was used to evaluate categorical group differences. To identify factors affecting postoperative complications, logistic regression models were employed. Receiver operating characteristic curves with Youden indices were employed to establish the most favorable cut-off values for each outcome. Values of the Area Under the Curve (AUC) were supplied with a 95% Confidence Interval (CI). The Hazard Ratios (HRs) for disease recurrence or metastasis were calculated applying Cox proportional hazards models. P<0.05 was designated as statistical significance.

Results

Patient characteristics

The flowchart for patient screening was displayed in Figure 1. In total, 568 patients fit the inclusion criteria. No chemotherapy or radiotherapy was administered to any of the patients prior to surgery, and there was no perioperative mortality included. This study included 442 men and 126 women. The average age of the population group was 60.29 ± 9.79 (25-87). The average BMI ratio prior surgery for all patients was 22.20 ± 3.37. 31.7% (n = 180) of the patients were operated with open 40.0% (n = 227) with laparoscopic approach and 28.3% (n = 161) with robot-assisted. On the basis of the AJCC staging standards, 119 (21.0%) patients were categorized as stage I, stage II patients accounted for 178 (31.3%), and stage III patients made up 271 (47.7%). No patient was disregarded in the follow-up process. A median follow-up time of 45 months was established for all patients, ranging from 12 to 61 months.

The clinical characterization of the study population was shown in Table 1, along with a comparison of the characteristics and clinical aspects of the two group of patients who had no complications (no) and/or experienced minor complications and those who had major complications. The description of the features and clinicopathological comparison between the group of who did not experience recurrence or metastasis and the group of patients who did recurrence or metastasis were displayed in Table 5.

Postoperative complications

A total of 89 (15.7%) patients in our statistics suffered serious complications. The occurrence of early postoperative complications in individuals experiencing radical gastrectomy was showed in Table 2. Complications included duration of enteral nutrition was longer than 2 weeks in 26 patients, infection-related complications (incision infection, abdominal infection, pulmonary infection) in 234 patients, anastomotic fistula in 6 patients, pyloric or intestinal obstruction in 14 patients, thrombosis or embolism in 15 patients, and seven patients developed postoperative shock, they were all rescued after treatment.

In accordance with Table 1, age (p = 0.046), BMI (p = 0.003), tumour size (<3/≥3 cm/) (p = 0.014), resection range (p = 0.019), perioperative transfusion (p < 0.001), and hospital stay (p < 0.001) were statistical significance between the two groups. For laboratory parameters, lymphocytes (p < 0.001), neutrophils (p < 0.001), platelets (p = 0.013), monocytes (p = 0.032), albumin (p < 0.001), fibrinogen (p < 0.001), CEA (p = 0.011), SIRI (p < 0.001) and AFR (p < 0.001) also differed significantly between groups.

Correlations between SIRI, AFR and the clinicopathological characteristics of gastric cancer

In accordance with the results in Table 3, Preoperative SIRI level was related to the sex (p = 0.002), resection range (p = 0.008) among patients of gastric cancer. AFR had an association with the degree of tumor differentiation (p = 0.002) and duration of enteral nutrition (p = 0.01). Meanwhile, both preoperative conditions were related to age, tumour size (<3/≥3 cm), TNM stage, perioperative transfusion, CA199, CEA, amount of bleeding, relapse or metastasis (p < 0.05).Upon further analysis, among patients under 60 years of age, SIRI levels were lower and AFR levels were higher (SIRI, p = 0.038; AFR, p < 0.001), and SIRI levels were higher and AFR levels were lower in individuals with a maximum tumor diameter >3 cm (SIRI, p < 0.001; AFR, p < 0.001). Furthermore, the level of SIRI in stage III was the highest of the clinical stages, the level of AFR in stage III was the lowest of the clinical stages (SIRI, p < 0.001; AFR, p < 0.001). For the perioperative blood transfusion patients, the level of SIRI was higher and the level of AFR was lower (SIRI, p < 0.001; AFR, p < 0.001). Group of CA199 and CEA positive patients, SIRI levels were higher and AFR levels were lower (SIRI, p = 0.023, p < 0.001; AFR, p = 0.001 p < 0.001). The highest SIRI levels and lowest AFR levels were observed in the group with intraoperative blood loss >400 ml (SIRI, p < 0.001; AFR, p < 0.001). The SIRI level of patients with gastric cancer with relapse or metastasis was noticeably raised (p < 0.001), and the AFR level was prominently reduced (p < 0.001).

Significance of preoperative SIRI and AFR levels for early serious postoperative complications in respectable gastric cancer

Table 4 listed the outcomes of the Univariate regression analysis that was executed to establish the OR values for the complication estimation. The result suggested that high preoperative SIRI was substantially related with early serious postoperative complications (P < 0.001; HR 1.429; 95% CI 1.175-1.738). Meanwhile, elevated preoperative AFR levels was a protective factor against postoperative complications (P < 0.001; HR 0.729; 95% CI 0.665-0.799;). Additionally, age, BMI, tumor size (<3/≥3 cm), resection range, perioperative transfusion and CEA (<5/≥5 ng/mL) were other noteworthy variables revealed by univariate analysis (P < 0.05). Regards to multivariable analyses, preoperative SIRI and AFR remained an independent influencing indicator for postoperative complications. (SIRI: P = 0.02; HR 1.222; 95% CI 1.031-1.446; AFR: P < 0.001; HR 0.771; 95% CI 0.701-0.848). Furthermore, resection range (P=0.044; HR 1.682; 95% CI 1.015-2.787) and perioperative transfusion (P = 0.008; HR 2.028; 95% CI 1.202-3.422) were other contributing factors.

Evaluation of predictive abilities for SIRI and AFR

Since the previous statistical findings concluded that high levels of AFR are a protective parameter for postoperative complica-

tions, in order to facilitate the calculation of the predictive power of SIRI combined with AFR, we take fibrinogen to albumin ratio (the reciprocal of AFR) as the calculation amount. ROC curve generation and AUC calculation were used to determine the prediction capabilities of SIRI and AFR. The AUC values of SIRI, AFR, and SIRI combine AFR levels were summarized in Figure 2. The AUC values computed for the SIRI: AUC 0:765; 95% CI 0.714-0.815), the AFR: AUC 0:743; 95%CI 0.689-0.797, the SIRI-AFR: AUC 0:779; 95% CI 0.737-0.820.

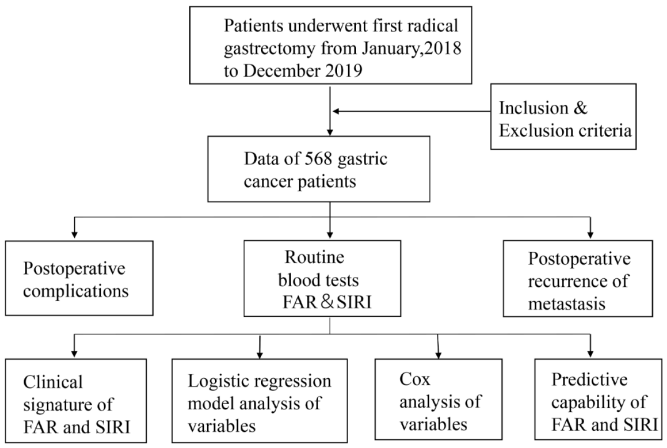

Figure 1: The patient selection flowchart of the present study.

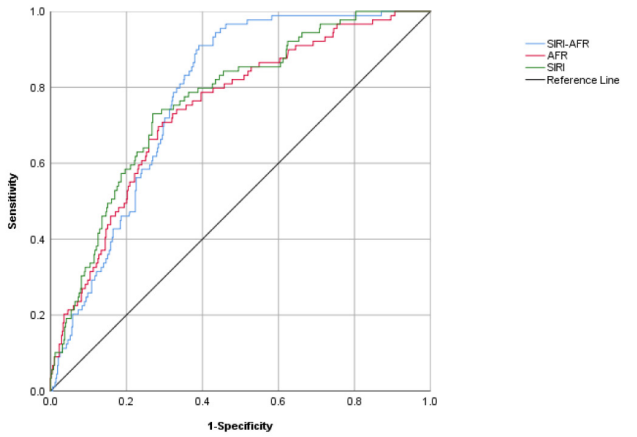

Figure 2: The ROC curve analysis of SIRI, AFR and SIRI-AFR for postoperative early serious complications.

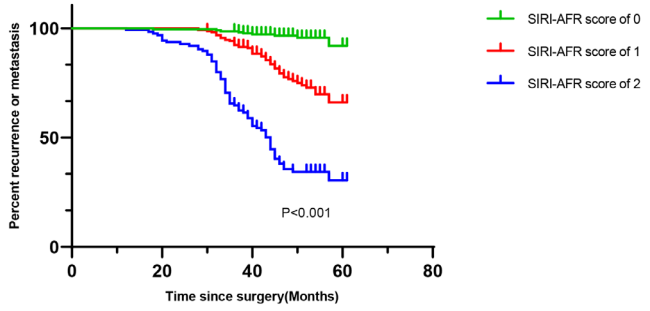

Figure 3: Effect of SIRI-AFR score on recurrence or metastasis rates in patients with gastric cancer. (*P* value was calculated by the log-rank test)

Establishment of the SIRI-AFR Score.

Based on the appropriate cut-off values for each determinant which were established using receiver operating characteristic curves with Youden's index, patients were grouped accordingly. Corresponding to the SIRI-AFR system, 219 (38.6%), 224 (39.4%), and 125 (22.0%) patients had scores of 0, 1, and 2, accordingly.

The correlation between clinicopathological and relapse or metastasis

The relationship between relapse or metastasis and clinicopathological factors was exhibited in Table 5. Recurrence or metastasis within 3 years in patients receiving radical resection of gastric cancer was associated with these factors: Age ($p = 0.019$), tumour location ($p = 0.012$), tumour size (<3/≥3 cm/) ($p < 0.001$), differentiated degree ($p = 0.033$), Her-2 ($p = 0.042$), TNM stage ($p < 0.001$), perioperative transfusion ($p < 0.001$), operation time ($p = 0.001$) , lymph node metastasis rate ($p < 0.001$), lymphocytes ($p < 0.001$), neutrophils ($p < 0.001$), platelets ($p = 0.002$), monocytes ($p < 0.001$), albumin ($p < 0.001$), fibrinogen ($p < 0.001$), SIRI ($p < 0.001$), AFR ($p < 0.001$), SIRI-AFR score ($p < 0.001$), CA199 ($p =0.001$), CEA ($p < 0.001$), postoperative complication ($p < 0.001$) and postoperative adjuvant chemotherapy ($p = 0.012$).

Univariate and multivariate Cox regression analysis for relapse or metastasis

Among patients of stomach carcinoma, univariate analyses identified that the greater risk of relapse or metastasis was profoundly associated with correlated with older age ($p = 0.009$), lower tumour location ($p = 0.006$), large tumor size ($p < 0.001$, later clinical stage ($p < 0.001$), longer operating time ($p = 0.002$), perioperative transfusion ($p < 0.001$), positive CA199 ($p < 0.001$), positive CEA ($p < 0.001$), major postoperative complication ($p < 0.001$), no postoperative adjuvant chemotherapy was performed ($p = 0.006$), high SIRI-AFR score ($p < 0.001$). Multivariate analysis revealed that TNM stage ($p = 0.002$; HR 5.100, 95% CI 1.847-14.086), operation time ($p = 0.029$; HR 1.003, 95.0% CI 1.000-1.005), perioperative transfusion ($p = 0.009$; HR 1.660, 95.0% CI 1.135-2.428), positive CEA ($p = 0.025$; HR 1.528; 95% CI 1.054-2.213), postoperative adjuvant chemotherapy ($p = 0.008$; HR 0.475, 95% CI 0.273-0.826), SIRI-AFR score ($p < 0.001$; HR 4.363, 95% CI 2.170-9.037) were the independently determined prognostic variables for relapse or metastasis (Table 6). Further, as presented in Fig 3, we observed that the SIRI-AFR score could effectively differentiate patients into three distinguishing risk groups for recurrence or metastasis.

Discussion

As a malignancy, gastric cancer seriously endangers public health [16], and the occurrence of serious complications and recurrence and metastasis after surgery were still difficult problems for clinicians. The development of gastric cancer was a multigene, multi-step process and certain key factors may participate in the development of gastric cancer and even infiltration and metastasis at some stage. The systematic inflammatory response and nutritional situation were two considerable contributing factors [17]. SIRI and AFR were valuable novel procedures to evaluate the inflammatory and nutritional condition of patients. To our knowledge, no studies have been done to examine how SIRI and AFR affect patients who received radical gastric cancer surgery in terms

Table 1: Patient baseline characteristics and their correlations with complications after resectable gastric cancer.

Variables		Minor/no complication n = 479 (84.3%)	Major complication n = 89 (15.7%)	*P* values
Gender	Male	378 (78.9%)	64 (71.9%)	0.144[a]
	Female	101 (21.1%)	25 (28.1%)	
Age (y)		59.93 ± 9.66	62.19 ± 10.33	**0.046**[b]
Underlying disease	No	382 (79.7%)	75 (84.3%)	0.323[a]
	Yes	97 (20.3%)	14 (15.7%)	
BMI		22.37 ± 3.36	21.23 ± 3.28	**0.003**[b]
Tumour location	Upper third	56 (11.7%)	15 (16.9%)	0.537[a]
	Middle third	44 (9.2%)	8 (9.0%)	
	Lower third	377 (78.7%)	66 (74.2%)	
Tumor dimensions (cm)	<3	148 (30.9%)	16 (18.0%)	**0.014**[a]
	≥3	331 (69.1%)	73 (82.0%)	
Differentiation	Moderate and poor	460 (96.0%)	86 (96.6%)	1[a]
	Well	19 (4.0%)	3 (3.4%)	
TNM stage	I	106 (22.1%)	13 (14.6%)	0.236[a]
	II	150 (31.3%)	28 (31.5%)	
	III	223 (46.6%)	48 (53.9%)	
Approach	Open	149 (31.1%)	31 (34.8%)	0.539[a]
	Laparoscopic	190 (39.7%)	37 (41.6%)	
	Robot-assisted	140 (29.2%)	21 (23.6%)	
Operation	Subtotal gastrectomy	248 (51.8%)	34 (38.2%)	**0.019**[a]
	Total gastrectomy	231 (48.2%)	55 (61.8%)	
ASA	I-II	433 (90.4%)	76 (85.4%)	0.155[a]
	III-IV	46 (9.6%)	13 (14.6%)	
Blood loss (ml)		100 (100)	150 (200)	0.089[c]
Duration of surgery (minutes)		240 (90)	250 (85)	0.079[c]
Perioperative transfusion	No	389 (81.2%)	50 (56.2%)	**<0.001**[a]
	Yes	90 (18.8%)	39 (43.8%)	
Length of hospitalization (days)		17.00 (5.00)	21.00 (8.00)	**<0.001**[c]
Lymph node metastasis rate (%)		4.02% ± 15.17%	4.52% ± 14.72%	0.264[b]
Lymphocytes ($\times 10^9$/L)		1.44 (0.72)	1.18 (0.59)	**<0.001**[c]
Neutrophils ($\times 10^9$/L)		3.52 (1.76)	5.03 (1.56)	**<0.001**[c]
Platelet ($\times 10^9$/L)		213 (86)	234 (107)	**0.013**[c]
Monocyte ($\times 10^9$/L)		0.39 (0.16)	0.42 (0.17)	**0.032**[c]
Albumin (g/L)		39.40 ± 4.36	36.60 ± 4.50	**<0.001**[b]
Fibrinogen (g/L)		3.39 ± 0.79	4.08 ± 1.04	**<0.001**[b]
SIRI		0.95 (0.82)	1.54 (0.97)	**<0.001**[c]
AFR		12.32 ± 3.46	9.54 ± 2.68	**<0.001**[c]
CA199 (ng/mL)		406 (84.8%)	69 (77.5%)	0.090[a]
		73 (15.2%)	20 (22.5%)	
CEA (ng/mL)		386 (80.6%)	61 (68.5%)	**0.011**[a]
		93 (19.4%)	28 (31.5%)	

The bold numbers in the tables are P-values with statistical significance (<0.05).

[a] Chi-square test, [b] Student's t-test with mean ± standard deviation, [c]Mann-Whitney U test with median (interquartile range), SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, ASA: American society of anesthesiology. SIRI: Systemic Inflammation Response Index; AFR: Albumin Fibrinogen Ratio; CA199: Carbohydrate Antigen 199; CEA: Carcinoembryonic Antigen.

Table 2: Occurrence of short-term postoperative complications in patients undergoing radical gastric cancer resection.

Postoperative complications	N (%)
Enteral nutrition time > 2 weeks	26 (4.58%)
Incision infection	4 (0.70%)
Abdominal infection	160 (28.17%)
Pulmonary infection	70 (12.32%)
Pelvic effusion	6 (1.06%)
Abdominal bleeding	9 (1.58%)
Anastomotic fistula	6 (1.06%)
Pyloric or intestinal obstruction	14 (2.46%)
Deep venous thrombosis	10 (1.76%)
Splenic embolism	1 (0.18%)
Pulmonary embolism	4 (0.70%)
Shock	7 (1.23%)

of early postoperative serious complications, early postoperative recurrence or metastases. We created novel markers in the current study and evaluated their diagnostic and predictive potential to aid in the early identification and therapy of gastric cancer.

Correa sequence, the canonical theory of cancer development in the stomach, indicated the inflammatory response was an indispensable component in the tumor progression [17]. The epidemiological and clinical investigations provided substantial evidences that inflammation is associated with supporting the growth of dissemination tumour cells [18]. Neutrophils, as an essential element of tumor microenvironment, it participated in tumor progression via multiple mechanisms, and activation of neutrophils pathologically may symbolize the beginning of comprehension the procedures behind reactivation of dormant tumor cells [19]. Moreover, neutrophils produced substances, such as chemokines, cytokines, stromal degrading proteases and reactive oxygen species, which can alter tumour growth and invasiveness. Several studies have shown that neutrophils promote tumour progression through stromal degradation and cancer cell prolif-

Table 3: Clinicopathological variables and preoperative SIRI and AFR in gastric cancer patients.

Variables		Preoperative SIRI (Median(IQR))	*P values	Preoperative AFR (mean ± SD)	**P values
Gender	Male	1.11 (0.89)	**0.002**	11.96 ± 3.68	0.252
	Female	0.91 (0.87)		11.62 ± 2.77	
Age (y)	<60	1.03 (0.86)	**0.038**	12.58 ± 3.83	**<0.001**
	≥60	1.14 (0.96)		11.26 ± 3.04	
Underlying disease	No	1.07 (0.90)	0.187	11.88 ± 3.55	0.989
	Yes	1.14 (0.91)		11.89 ± 3.31	
BMI	<24	1.06 (0.89)	0.29	11.82 ± 3.60	0.464
	≥24	1.15 (0.85)		12.06 ± 3.23	
Tumour location	Upper third	1.17 (1.09)	0.164	11.63 ± 3.09	0.695
	Middle third	1.00 (0.80)		12.36 ± 3.14	
	Lower third	1.07 (0.88)		11.88 ± 3.61	
Tumor dimensions (cm)	<3	0.89 (0.69)	**<0.001**	13.44 ± 3.86	**<0.001**
	≥3	1.17 (0.92)		11.26 ± 3.13	
Differentiation	Moderate and poor	1.08 (0.90)	0.235	11.80 ± 3.46	**0.002**
	Well	0.91 (0.71)		14.11 ± 3.90	
TNM stage	I	0.78 (0.58)	**<0.001**	13.70 ± 4.20	**<0.001**
	II	1.08 (0.93)		11.66 ± 3.41	
	III	1.20 (0.92)		11.24 ± 2.90	
Approach	Open	1.16 (0.89)	0.261	12.05 ± 3.97	0.617
	Laparoscopic	1.05 (0.87)		11.90 ± 3.29	
	Robot-assisted	1.08 (0.97)		11.68 ± 3.22	
Operation	Subtotal gastrectomy	0.97 (0.84)	**0.008**	12.10 ± 3.41	0.169
	Total gastrectomy	1.15 (0.94)		11.67 ± 3.58	
ASA	I-II	1.07 (0.90)	0.458	11.89 ± 3.53	0.906
	III-IV	1.23 (0.85)		11.83 ± 3.24	
Perioperative transfusion	No	1.02 (0.81)	**<0.001**	12.37 ± 3.50	**<0.001**
	Yes	1.44 (1.20)		10.25 ± 3.00	

CA199 (ng/mL)	Negative	1.06 (0.86)	**0.023**	12.14 ± 3.16	**0.001**
	Postive	1.23 (1.17)		10.57 ± 2.83	
CEA (ng/mL)	Negative	1.03 (0.83)	**<0.001**	12.24 ± 3.59	**<0.001**
	Postive	1.29 (1.30)		10.58 ± 2.81	
Blood loss (ml)	<200	1.02 (0.77)	**0.011**	12.24 ± 3.63	**0.013**
	200≤ X ≤400	1.16 (1.02)		11.49 ± 3.32	
	>400	1.25 (0.95)		11.00 ± 3.00	
Relapse or metastasis	No	0.93 (0.82)	**<0.001**	12.65 ± 3.35	**<0.001**
	Yes	1.48 (1.07)		9.40 ± 2.77	
P53	Wild	1.14 (0.94)	0.372	11.89 ± 3.40	0.997
	Mutant	1.06 (0.82)		11.89 ± 3.56	
Ki-67	0%-49%	0.92 (0.79)	0.183	12.58 ± 3.16	0.249
	50%-74%	1.14 (0.79)		11.87 ± 3.30	
	75%-100%	1.07 (0.95)		11.76 ± 3.66	
Her-2	Negative	1.08 (0.91)	0.795	11.88 ± 3.53	0.891
	Postive	0.98 (0.75)		11.95 ± 3.19	
Lymph node metastasis rate (%)	<4.60%	1.07 (0.90)	0.471	11.95 ± 3.55	0.112
	≥4.60%	1.20 (0.83)		11.10 ± 2.81	
Enteral nutrition time	≤7 days	1.06 (0.91)	0.087	12.18 ± 3.62	**0.01**
	>days	1.15 (0.88)		11.40 ± 3.23	

The bold numbers in the tables are P-values with statistical significance (<0.05).
*p-value using Mann-Whitney U test with median (IQR), **p-value using Student's t-test with mean ± standard deviation. SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, ASA: American society of anesthesiology, CA199: Carbohydrate antigen 199, CEA: carcinoembryonic antigen SIRI: Systemic inflammation response index; AFR: Albumin fibrinogen ratio.

Table 4: Univariate and multivariate analyses of the logistic regression model for postoperative complications in patients.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (y)	**1.025**	**(1.000 - 1.049)**	**0.046**	**1.003**	**(0.977 - 1.030)**	**0.819**
BMI	0.896	(0.832 - 0.964)	**0.003**	0.928	(0.857 - 1.005)	0.068
Tumor dimensions (cm)	2.04	(1.148 - 3.624)	**0.015**	1.003	(0.523 - 1.926)	0.992
Operation	1.737	(1.092 - 2.761)	**0.02**	1.682	(1.015 - 2.787)	**0.044**
Perioperative transfusion	3.371	(2.091 - 5.434)	**<0.001**	2.028	(1.202 - 3.422)	**0.008**
CEA (ng/mL)	1.905	(1.154 - 3.146)	**0.012**	1.213	(0.696 - 2.112)	0.496
SIRI	1.429	(1.175 - 1.738)	**<0.001**	1.222	(1.031 - 1.446)	**0.02**
AFR	0.729	(0.665 - 0.799)	**<0.001**	0.771	(0.701 - 0.848)	**<0.001**

The bold numbers in the tables are P-values with statistical significance (<0.05).
BMI: Body mass index, SIRI: Systemic inflammation response index; AFR: Albumin fibrinogen ratio.

Table 5: Patient baseline characteristics and their correlations with relapse or metastasis in 3 years after surgery.

Variables		No relapse or metastasis n = 435 (76.6%)	Relapse or metastasis n = 133 (23.4%)	*P* values
Gender	Male	333 (76.6%)	109 (82.0%)	0.189[a]
	Female	102 (23.4%)	24 (18.0%)	
Age (y)		59.75 ± 9.51	62.02 ± 10.51	**0.019**[b]
Underlying disease	No	350 (80.5%)	107 (80.5%)	0.998[a]
	Yes	85 (19.5%)	26 (19.5%)	
BMI		22.24 ± 3.39	22.03 ± 3.30	0.524[b]

Tumour location	Upper third	48 (11.0%)	23 (17.3%)	**0.012**[a]
	Middle third	48 (11.0%)	4 (3.0%)	
	Lower third	337 (77.5%)	106 (79.7%)	
Tumor dimensions (cm)	<3	145 (33.3%)	19 (14.3%)	<**0.001**[a]
	≥3	290 (66.7%)	114 (85.7%)	
Differentiation	Moderate and poor	414 (95.2%)	132 (99.2%)	**0.033**[a]
	Well	21 (4.8%)	1 (0.8%)	
P53	Wild	157 (36.1%)	48 (36.1%)	1[a]
	Mutant	278 (63.9%)	85 (63.9%)	
Ki-67	0%-49%	49 (11.3%)	11 (8.3%)	0.513[a]
	50%-74%	134 (30.8%)	46 (34.6%)	
	75%-100%	140 (29.2%)	21 (23.6%)	
Her-2	Negative	395 (90.8%)	128 (96.2%)	**0.042**[a]
	Postive	40 (9.2%)	5 (3.8%)	
TNM stage	I	112 (25.7%)	7 (5.3%)	**<0.001**[a]
	II	145 (33.3%)	33 (24.8%)	
	III	178 (40.9%)	93 (69.9%)	
Approach	Open	135 (31.0%)	45 (33.8%)	0.099[a]
	Laparoscopic	190 (39.7%)	37 (41.6%)	
	Robot-assisted	116 (26.7%)	45 (33.8%)	
Operation	Subtotal gastrectomy	223 (51.3%)	59 (44.4%)	0.163[a]
	Total gastrectomy	212 (48.7%)	74 (55.6%)	
ASA	I-II	394 (90.6%)	115 (86.5%)	0.174[a]
	III-IV	41 (9.4%)	18 (13.5%)	
Blood loss (ml)	<200	258 (59.3%)	72 (54.1%)	0.485[a]
	200≤ X ≤400	145 (33.3%)	48 (36.1%)	
	>400	32 (7.4%)	13 (59.8%)	
Perioperative transfusion	No	359 (82.5%)	80 (60.2%)	**<0.001**[a]
	Yes	76 (17.5%)	53 (39.8%)	
Enteral nutrition time (days)		7.00 (4.00)	7.00 (3.00)	0.149[c]
Duration of surgery (minutes)		240 (80)	260 (95)	**0.001**[c]
Length of hospitalization (days)		17.00 (6.00)	18.00 (7.00)	0.157[c]
Lymph node metastasis rate (%)		0.06% (0.33%)	0.27% (0.70%)	**<0.001**[c]
Lymphocytes ($\times10^9$/L)		1.44 (0.71)	1.20 (0.56)	**<0.001**[c]
Neutrophils ($\times10^9$/L)		3.52 (1.90)	4.32 (1.54)	**<0.001**[c]
Platelet ($\times10^9$/L)		209 (86)	228 (93)	**0.002**[c]
Monocyte ($\times10^9$/L)		0.38 (0.17)	0.44 (0.17)	**<0.001**[c]
Albumin (g/L)		39.68 ± 3.99	36.59 ± 6.18	**<0.001**[b]
Fibrinogen (g/L)		3.30 ± 0.71	4.14 ± 1.01	**<0.001**[b]
SIRI		0.93 (0.82)	1.48 (1.07)	**<0.001**[c]
AFR		12.65 ± 3.35	9.40 ± 2.76	**<0.001**[b]
SIRI-ARF score	0	210 (48.3%)	9 (6.8%)	**<0.001**[a]
	1	175 (40.2%)	49 (36.8%)	
	2	50 (11.5%)	75 (56.4%)	
CA199 (ng/mL)	Negative	376 (86.4%)	99 (74.4%)	**0.001**[a]
	Postive	59 (13.6%)	34 (25.6%)	

CEA (ng/mL)	Negative	361 (83.0%)	86 (64.7%)	**<0.001**[a]
	Postive	74 (17.0%)	47 (35.3%)	
Postoperative complication	Minor/no	390 (89.7%)	89 (66.9%)	**<0.001**[a]
	Major	45 (10.3%)	44 (33.1%)	
Postoperative chemotherapy	No	130 (29.9%)	25 (18.8%)	**0.012**[a]
	Yes	305 (70.1%)	108 (81.2%)	

The bold numbers in the tables are P-values with statistical significance (<0.05).

[a] Chi-square test, [b] Student's t-test with mean ± standard deviation, [c] Mann-Whitney U test with median (interquartile range), SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, ASA: American society of anesthesiology. SIRI: Systemic inflammation response index; AFR: Albumin fibrinogen ratio, CA199: Carbohydrate antigen 199, CEA: Carcinoembryonic antigen.

Table 6: Univariate and multivariate Cox regression analyses for relapse or metastasis in patients with gastric cancer.

Variables		Univariate analysis			Multivariate analysis		
		OR	95% CI	P	OR	95% CI	P
Age (y)		1.025	(1.006 - 1.044)	**0.009**	1.008	(0.990 - 1.027)	0.381
Tumour location				0.053			0.231
	Upper 1/3	0.224	(0.077 - 0.647)	**0.006**	0.451	(0.153 - 1.336)	0.151
	Middle 1/3	0.843	(0.537 - 1.323)	0.391	1.239	(0.774 - 1.985)	0.372
	Low 1/3	Ref			Ref		
Tumor dimensions (cm)							
	<3/≥3	3.002	(1.845 - 4.884)	**<0.001**	1.428	(0.835 - 2.444)	0.193
Differentiation							
	Moderate and poor/ Well	0.159	(0.022 - 1.134)	0.067	0.667	(0.081 - 5.491)	0.707
Her - 2							
	Negative/Positive	2.151	(0.880 - 5.258)	0.093	0.520	(0.209 - 1.295)	0.160
TNM stage							**<0.001**
	I	Ref			Ref		
	II	3.533	(1.563 - 7.989)	**0.002**	1.704	(0.634 - 4.576)	0.291
	III	7.427	(3.443 - 16.022)	**<0.001**	5.100	(1.847 - 14.086)	**0.002**
Operation time (minutes)		1.004	(1.001 - 1.006)	**0.002**	1.003	(1.000 - 1.005)	**0.029**
Perioperative transfusion							
	No/Yes	2.65	(1.872 - 3.752)	**<0.001**	1.660	(1.135 - 2.428)	**0.009**
CA199 (ng/mL)							
	Negative/Positive	2.039	(1.380 - 3.013)	**<0.001**	1.417	(0.942 - 2.130)	0.094
CEA (ng/mL)							
	Negative/Positive	2.198	(1.540 - 3.137)	**<0.001**	1.528	(1.054 - 2.213)	**0.025**
Lymph node metastasis rate (%)		1.001	(0.991 - 1.012)	0.790	0.997	(0.986 - 1.009)	0.666
Postoperative complication							
	No or Minor/Major	3.35	(2.331 - 4.813)	**<0.001**	1.220	(0.820 - 1.815)	0.327
Postoperative chemotherapy							
	No/Yes	1.850	(1.197 - 2.859)	**0.006**	0.475	(0.273 - 0.826)	**0.008**
SIRI - AFR score							
	0	Ref			Ref		
	1	6.057	(2.975 - 12.334)	**<0.001**	4.363	(2.107 - 9.037)	**<0.001**
	2	22.705	(11.354 - 45.402)	**<0.001**	12.554	(5.995 - 26.291)	**<0.001**

The bold numbers in the tables are P-values with statistical significance (<0.05).

CA199: Carbohydrate Antigen 199; CEA: Carcinoembryonic Antigen; SIRI: Systemic Inflammation Response Index; AFR: Albumin Fibrinogen Ratio.

eration [20]. Largely, neutrophil physiology at the cellular and molecular levels seems to determine that their primary function is to facilitate transferential seeding. Neutrophil extracellular traps, shaped by molecularly released DNA intended to capture tumor cells in the circulation. Such an entanglement of circulating tumor cells may be beneficial to intraluminal survival, adhesion to endothelium, and extravasation [21].

Monocytes serve as cells bridging the innate and adaptive immunity, they can promote cancer immune escape by differentiation into immunomodulatory cells [22]. Factually, certain mutual interactions between circulation of carcinoma cells and circulating monocytes can effectively accelerate their dissemination and extravasation at distant sites [23]. They can have an immediate involvement in promotion, support and maintenance of tumour growth by affecting the tumor microenvironment through multiple mechanisms that produce tolerance, angiogenesis and accelerated tumor cell proliferation [24].

Lymphocytes played a part in immunologic surveillance and were contributory to identification and destruction [25]. Importantly, a biochemical alteration of T cells can modulate cellular activities and promote tumor progression [26]. With evidence that the magnitude and composition of tumour infiltrating lymphocytes can affect survival of oesophageal adenocarcinoma [27].

The abnormal fibrinogen levels can lead to disturbances in the control of normal homeostasis during coagulation. And quite possibly, sedimentation of fibrinogen on cancer cells can form a physical shield to protect cancer cells from recognition and lysis by NK cells [28].

The level of albumin is influenced by nutritional status and metabolism. Hypoalbuminemia can generate immunodeficiency in tumour patients, which reduces the effectiveness of treatment and increases mortality [29]. As such, albumin levels were a recognized prognostic factor for a number of malignancies [30,31]. Similarly, some research suggested that albumin levels affect the likelihood of postoperative complications and cancer recurrence [32,33].

Furthermore, mounting data pointed to the usefulness of SIRI as a predictor of adverse survival in patients with a range of malignancies, including gastric cancer [34-36]. According to our findings, SIRI constituted an independently attributable risk for severe postoperative complications in patients with radical gastrectomy. Recently, Mario and his colleagues confirmed that SIRI can be considered to potentially predict anastomotic fistula after total gastrectomy [37]. Similarly, related research has also demonstrated that AFR can predict patients with pancreatic cancer [30], gallbladder cancer [38], and colorectal cancer [39] prognosis. Our findings suggested that AFR was also a worthwhile parameter for predicting serious complications and recurrent metastases in patients receiving radical gastrectomy in the early postoperative period. The predictive value of combining SIRI and AFR for early postoperative serious complications and recurrent metastases in patients undergoing radical gastrectomy was first identified through our study, and it was an encouraging tool for cancer treatment strategy decisions.

In particular, the surgical resection range was also discovered in our study to be a risk factor for early complications following radical gastric cancer resection. Total gastrectomy significantly damaged the digestive system and had systemic repercussions, which warned us of the importance and necessity of early discovery, diagnosis and treatment of gastric cancer. Interestingly, we observed perioperative blood transfusion to be a contributing factor for early recurrence metastases as well as postoperative problems. A growing body of research suggested that transfusions of allogeneic blood may have immunomodulatory impact that lowered the threshold for periprosthetic infections through a number of mechanisms, including decreased natural killer cell activity, an imbalance in the normal distribution of helper and/or suppressor T cells and improper antigen presentation by host cells [40]. In fact, there were also studies have shown that perioperative blood transfusion can increase the chance of postoperative infection [41], and was associated with complications after gastrectomy [42]. Our results were consistent with those observed by Stephen T McSorley [43] and Xiaowen Liu [44], who noted perioperative blood transfusion is linked to worse survival following surgery for colorectal cancer and gastric cancer. Furthermore, postoperative adjuvant chemotherapy was also a noteworthy factor affecting recurrent metastasis. However, when assessing the risks and advantages of treatment, adverse effects of chemotherapy may be a crucial consideration. During our follow-up, we learned that many patients did not complete the regular chemotherapy cycle due to adverse reactions such as nausea and vomiting after chemotherapy, which is a question worth pondering.

A few limitations applied to this investigation. Firstly, the retrospective nature of the study at a single institution restricts its statistical power. Subsequently, we lacked evaluation of postoperative SIRI and AFR dynamic changes in a relatively large cohort of GC patients, larger multicenter prospective randomized controlled trials are needed to verify our conclusion. Finally, despite the fact that SIRI and AFR are worthwhile and easily obtainable routine blood parameters, the underlying biological and molecular mechanisms that account for their prognostic and predictive nature remain unclear.

Conclusion

Overall, the findings of this investigation indicate a significant association between preoperative SIRI and AFR in individuals with gastric cancer and the occurrence of severe complications, as well as early postoperative recurrence or metastasis. These results may aid surgeons and oncologists in conducting more effective preoperative evaluations and management, and developing postoperative monitoring plans for patients with gastric cancer.

Abbreviations

SIRI: Systemic Inflammatory Response Index; AFR: Albumin Fibrinogen Ratio; NLR: Neutrophil-To-Lymphocyte Ratio; LMR: Lymphocyte-To-Monocytes Ratio; LCR: Lymphocyte-To-C Reactive Protein Ratio; FAR: Fibrinogen-To-Albumin Ratio; F-NLR: Fibrinogen- Neutrophil-To-Lymphocyte Ratio; AJCC: American Joint Commission On Cancer; IQR: Interquartile Range; CA199: Carbohydrate Antigen 199; CEA: Carcinoembryonic Antigen; AUC: Area Under The Curve; CI: Confidence Interval; HR: Hazard Ratio.

Declarations

Ethical approval: The research protocols for the current investigation, which conformed to the principles of the Declaration of Helsinki, and received approval from the ethics board. Ethical consent: 21/10/2022-410, Gansu Provincial Hospital Medical Ethics Committee.

Data availability statement: The datasets used and/or analyzed during the current study are available from the correspondingauthor on reasonable request.

Conflict of interest: The authors declared no conflict of interest in the publication of this paper.

Contributors: JR conceived and designed the study and revised the manuscript. JR, DW, LZ, SL, and MY conducted all data collection and analysis and compiled charts. All authors read and approved the final manuscript.

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