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Inflammatory Biomarkers as Prognostic Factors in Short-Term Postoperative Complications in Operable Gastric Cancer

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Rezumat

Biomarkeri inflamatori ca factori prognostici în complicațiile postoperatorii pe termen scurt în cancerul gastric operabil

Studiul a avut ca scop evaluarea efectului markerilor inflamatori sanguini asupra rezultatelor postoperatorii la pacienții cu cancer gastric. Am căutat să evaluăm valoarea prognostică a biomarkerilor şi scorurile prognostice privind rezultatele postoperatorii precoce.
Materiale şi metode: A fost realizat un studiu retrospectiv nerandomizat, incluzând pacienți cu cancer gastric propuşi pentru gastrectomie cu intenție curativă între 2012-2024 în secția de chirurgie generală a Spitalului Județean Mureş. Am măsurat inflamația sistemică prin determinarea raportului neutrofile-limfocite, a raportului neutrofile-trombocite şi a raportului trombocite-limfocite, a indicelui nutrițional prognostic (PNI), a scorului Glasgow modificat (mGS) şi a indicelui inflamator sistemic (SII).
Rezultate: numărul de leucocite (p<0,0001), numărul de neutrofile (p<0,0001), numărul de limfocite (p=0,001), numărul de trombocite (p=0,01), nivelurile proteinei C reactive (p<0,0001), nivelurile de albumină (p<0,0001), raportul neutrofile-trombocite (p=0,01), indicele nutrițional prognostic (p<0,0001), scorul Glasgow modificat (p<0,0001) şi indicele inflamator sistemic (p<0,0001) au fost puternic asociate cu rezultatul postoperator. În analiza multivariată, nivelurile CRP şi scorul Glasgow au fost semnificativ asociate cu rezultatul postoperator.
Concluzie: Markerii inflamatori sistemici joacă un rol semnificativ în prezicerea complicațiilor postoperatorii în cancerul gastric. Interacțiunea dintre markerii inflamatori, tehnicile chirurgicale, suportul nutrițional şi gestionarea complicațiilor formează o abordare complexă pentru prezicerea rezultatelor postoperatorii.

Cuvinte cheie: markeri inflamatori, prognostic pe termen scurt, cancer gastric

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Abstract

The study aimed to evaluate the effect of inflammatory blood markers on the postoperative outcomes of gastric cancer patients. We sought to assess the prognostic value of biomarkers and prognostic scores concerning short-term postoperative results.

Material and methods: A non-randomized retrospective study was conducted, including gastric cancer patients proposed for curative-intent gastrectomy between 2012-2024 in the general surgery department of Mures County Hospital. We measured systemic inflammation by determining the neutrophile-to-lymphocyte ratio, neutrophile-to-platelet ratio, and platelet-to-lymphocyte ratio, prognostic nutritional index (PNI), modified Glasgow score (mGS), and Systemic Inflammatory Index (SII).

Results: the white blood cell count ($p<0.0001$), the neutrophile count ($p<0.0001$), the lymphocyte count ($p=0.001$), the platelet count ($p=0,01$), the C-reactive protein levels ($p<0.0001$), the albumin levels ($p<0.0001$), the neutrophil-to- platelet ratio ($p=0.01$), the prognostic nutritional index ($p<0.0001$), the modified Glasgow score ($p<0.0001$) and the Systemic inflammatory index ($p<0.0001$) were strongly associated with the postoperative outcome. In the multivariate analysis, CRP levels and modified Glasgow score were significantly associated with postoperative outcome.

Conclusion: Systemic inflammatory markers play a significant role in predicting postoperative complications in gastric cancer. The interplay between inflammatory markers, surgical techniques, nutritional support, and complication management forms a multifaceted approach to predict postoperative outcomes.

Keywords: inflammatory markers, short-term outcome, gastric cancer

Background

Gastric cancer (GC) is a major health concern worldwide, characterized by significant variability in its incidence and postoperative outcomes. Globally, gastric cancer ranks as the fifth most common malignancy and the third leading cause of cancer-related deaths, with incidence rates notably high in East Asia, particularly Japan and Korea (1). The surgical management of gastric cancer, typically involving gastrectomy, aims for curative treatment. However, it is associated with a considerable risk of postoperative complications, which can adversely affect both short- and long-term outcomes (2,3).

Postoperative complications following gastric cancer surgery occur at varying rates, reportedly between 10% and 46% across multiple studies (3,4).

The most common complications include anastomotic leaks, surgical site infections, and abdominal abscesses, with rates of anastomotic leakage reported as high as 34% in specific contexts (2,5). Research indicates that patients who experience complications, such as intra-abdominal infections or inflammatory responses, face a notably increased risk of cancer recurrence and worse overall outcomes, highlighting the importance of minimizing postoperative complications (5,6).

Several factors have been identified as contributors to the risk of postoperative complications. These include nutritional status, inflammatory markers, and specific surgical techniques. For instance, preoperative serum albumin levels and the C-reactive protein/albumin (CRP/Alb) ratio have emerged as significant prognostic indicators, with lower values correlating with higher complication rates and poorer outcomes (7,8).

Additionally, older age and the extent of surgical resection - such as total gastrectomy - are associated with an increased risk of complications (9,10).

The study aimed to evaluate the effect of inflammatory blood markers on the postoperative outcome of gastric cancer patients. We wanted to assess the prognostic value of biomarkers and prognostic scores in patients submitted to curative resectional surgery.

Material and Methods

A single-cohort non-randomized retrospective study was conducted, including patients with stage I-III gastric cancer proposed for curative-intent gastrectomy between 2012-2024 in the general surgery department of Mures County Hospital. Preoperative staging was based on endoscopy, biopsy, and CT scan of the abdomen, thorax, and pelvis.

The type of surgery for gastric cancer was decided based on the location of the tumor. Subtotal gastrectomy was performed for tumors of the antrum, while total gastrectomy was the

treatment of choice in tumors of the cardia, body of the stomach, or linitis plastica. In addition to the resection, D2 lymphadenectomy was performed. In all cases, an open approach was performed.

The routine blood test was taken 1-3 days before surgery. In the study, the values of white blood cells, neutrophils, lymphocytes, platelets, CRP (C-reactive protein) and albumin levels were measured.

We measured the systemic inflammation by determining the neutrophile-to-lymphocyte ratio, neutrophile-to-platelet ratio, and platelet-to-lymphocyte ratio. In addition we determined the prognostic nutritional index (PNI), modified Glasgow score (mGS), and Systemic Inflammatory Index (SII) to evaluate them as predictive factors for postoperative outcome.

Normal values:

White Blood Cell Count (WBC);

Normal Range: 4,000 to 11,000 cells per microliter (4.0–11.0 × 10^9/L).

Neutrophils (Neu)

Normal Range: 40% to 60% of total WBC;

Absolute Neutrophil Count (ANC): 1,500 to 8,000 cells per microliter (1.5–8.0 × 10^9/L).

Lymphocytes (LYM)

Normal Range: 20% to 40% of total WBC;

Absolute Lymphocyte Count: 1,000 to 4,800 cells per microliter (1.0–4.8 × 10^9/L).

Platelet Count (PLT)

Normal Range: 150,000 to 450,000 platelets per microliter (150–450 × 10^9/L).

C-reactive Protein (CRP)

Normal Range: Less than 1.0 mg/dL (or < 10 mg/L).

Albumin

Normal Range: 3.5 to 5.0 grams per deciliter (g/dL).

PNI (Prognostic Nutritional Index) - evaluates nutritional status.

Calculation:

PNI = (Serum Albumin in g/dL) + 0.005 × (Total Lymphocyte Count per mm^3);

The cut-off value for PNI was set to 45, as in most studies found in the literature, and to have two similar groups for comparison.

Interpretation:

- PNI ≥ 45: Generally considered indicative of good nutritional status;
- PNI < 45: Suggests malnutrition and worse prognosis.

SII (Systemic inflammatory index): reflects systemic inflammatory response

SII = (Neutrophil count × Platelet count) / Lymphocyte count;

The cut-off value of SII was set to 450.

Interpretation:

SII>450 High systemic inflammation and poorer outcome;

SII </=450 Low level of inflammation and better prognosis.

Modified Glasgow Score: Based on serum C-reactive protein (CRP) and serum Albumin:

Score 0: CRP ≤ 1.0 mg/dL and Albumin ≥ 3.5 g/dL;

Score 1: CRP > 1.0 mg/dL or Albumin < 3.5 g/dL;

Score 2: CRP > 1.0 mg/dL and Albumin < 3.5 g/dL;

Interpretation:

A score of 0 suggests low systemic inflammation and better prognosis.

A score of 1 indicates mild to moderate inflammation or nutritional impairment.

A score of 2 correlates with high systemic inflammation and poorer outcomes.

Statistical Analysis

Statistical analysis was performed using the Data tab software. Univariate analysis was performed using Fisher's exact test and Chi2 test, while for multivariate analysis, a logistic regression model was created. We considered statistically significant the value of p<0,05.

Results

A total of 230 patients were included in this study. The mean age of patients was 61.55 years with a 11.12 standard deviation. In our study group, there were 169 (73,48%) male and 61 (26,52%) female patients. Regarding BMI groups, there were 15 (6,52%) underweight patients (BMI< 18,5 %), 113 (49,13%) normal weight patients (BMI 18,5-24,9), 59 (25,65%) overweight patients (BMI 25-29,9), and 43 (18,7 %) obese patients (BMI >30).

In 131 (56.96%) cases, total gastrectomy was performed, while in 99 (43,04%) subtotal gastrectomy.

Postoperative outcome was favorable in 202 cases (87,82%), and 28 patients (12,17%) developed complications, which needed reinterventions, categorizing them in Clavien Dindo Index 3-5. Out of these complicated cases there were 12 cases of anastomotic fistulas, 8 cases of duodenal stump fistulas, 3 eviscerations, 3 intraabdominal abscesses and 2 pancreatic fistulas. 16 patients (6,95%) died in the early postoperative period.

In the univariate analysis, the patients' sex (p=0.82), age (p=0.06), BMI (p=0.99), the tumor location (p=0.97), the staging (p=0.7), type of gastrectomy performed (p=0.42), and the platelet-to-lymphocyte ratio (p=0.8) were not statistically associated with the postoperative outcome *(Table 1)*.

Table 1. Univariate analysis

Variables	N	%	Major complications	Uncoplicated	p
Sex					0.82
Female	61	26.52	8	53	
Male	169	73.48	20	149	
Age					0.06
<65	106	46.09	8	98	
>65	124	53.91	20	104	
BMI					0.99
Underweight	15	6.52	2	13	
Normalweight	113	49.13	14	99	
Overweight	59	25.65	7	52	
Obese	43	18.70	5	38	
Tumor location					0.97
Proximal	74	32.17	9	65	
Body	30	13.04	4	26	
Distal	126	54.78	15	111	
Stage					0.7
I	12	5.22	4	8	
II	73	31.74	8	65	
III	145	63.04	16	129	
Gastrectomy					p=0.42
Total	131	56.96	18	113	
Subtotal	99	43.04	10	89	
WBC					p<0.00001
Normal	179	77.83	3	176	
High	52	22.61	25	27	
NEU					p<0.00001
Normal	179	77.83	1	178	
High	52	22.61	27	25	
LY					0.001
Normal	189	82.17	16	173	
High	42	18.26	12	30	
TC					0.01
Normal	119	51.74	8	111	
High	112	48.70	20	92	
PCR					p<0.00001
Normal	203	88.26	2	201	
High	28	12.17	26	2	
NEU-LY Ratio					0.32
<3	181	78.70	20	161	
>3	49	21.30	8	41	
NEU-PLT Ratio					0.01
Normal	146	63.48	12	134	
High	84	36.52	16	68	
PLT-LY RAtio					0.8
Normal	73	31.74	8	65	
High	158	68.70	20	138	
PNI					p<0.00001
≥ 45	117	50.87	3	114	
<45	114	49.57	25	89	
Glasgow score					p<0.00001
0	200	86.96	0	200	
1	13	5.65	12	1	
2	17	7.39	16	1	
Albumin					p<0.00001
≤ 3.5	24	10.43	19	5	
>3.5	207	90.00	9	198	
SII					p<0.00001
≤ 450	115	50.00	2	113	
>450	116	50.43	26	90	

In our series the white blood cell count (p<0.0001), the neutrophile count (p<0.0001), the lymphocyte count (p=0.001), the platelet count (p=0,01), the C-reactive protein levels (p<0.0001), the albumin levels (p<0.0001), the neutrophil- to-platelet ratio (p=0.01), the prognostic nutritional index (p<0.0001), the modified Glasgow score (p<0.0001) and the Systemic inflammatory index (p<0.0001) were strongly associated with the post-operative outcome. Higher levels of these values indicate a higher grade of inflammation and a worse prognosis.

For multivariate analysis, a multiple linear regression model was created to examine the influence of the variables on the postoperative complications (*Table 2*).

The model shows a very high positive relationship between the observed values and the prediction, explains 92.44% of the variance in the dependent variable (*Table 3*).

ANOVA results indicate that your regression model is statistically significant, suggesting a good fit compared to a model without any predictors.

With a p-value of <.001, the results are highly statistically significant. This suggests you can reject the null hypothesis with a high degree of confidence. It's improbable that the observed results are due to chance, indicating that the independent variables (predictors) in the model have a statistically significant effect on the dependent variable, the postoperative complications. In the multivariate analysis, CRP levels and modified Glasgow score were significantly associated with postoperative outcome. Higher levels of these markers were associated with more postoperative complications and poorer outcomes (*Table 4*).

Table 2. Multivariate analisys model summary (R- correlation coeficcient), R^2 - the proportion of the variance in the dependent variable)

R	R^2	Adjusted R^2	Standard error of the estimate
0.96	0.92	0.92	0.09

Table 3. ANOVA (dF - degrees of freedom; F-F Statistic)

Model	df	F	p
Regression	16	161.94	<.001

Discussions

We examined the capacity of various inflammatory and nutritional markers to forecast short-term postoperative outcomes in patients who underwent curative gastrectomy. Our assessment included laboratory values, related parameters, body weight data, and associated indicators. While several parameters appeared to be strong predictors in univariate analysis, only a few remained statistically significant independent risk factors after adjusting for clinical variables such as age,

Table 4. Result of the multivariate analysis

	Unstandardized Coefficients	Standardized Coefficients	95% confidence interval for B				
Model	B	Beta	Standard error	t	p	lower bound	upper bound
Constant	-0.05		0.08	-0.61	.54	-0.21	0.11
WBC	-0	-0.03	0.01	-0.68	.498	-0.02	0.01
NEU	0.01	0.09	0.01	1.46	.146	-0	0.03
LYM	0.01	0.03	0.01	1	.317	-0.01	0.02
CRP	0.02	0.33	0	7.73	<.001	0.02	0.03
ALB	-0	-0	0	-1.32	.187	-0	0
Glasgow 2	0.56	0.44	0.05	10.57	<.001	0.46	0.67
Glasgow 1	0.51	0.39	0.05	11.12	<.001	0.42	0.61
PNI	-0	-0.03	0	-1.1	.273	-0	0
Sex B	-0	-0.01	0.01	-0.32	.75	-0.03	0.02
Age	0	0.01	0	0.28	.78	-0	0
SII	0	0.05	0	1.3	.195	-0	0
NEU-LY	-0.01	-0.05	0.01	-1.21	.228	-0.02	0
NEU-PLT	-0.04	-0	0.52	-0.08	.938	-1.07	0.99
PLT-LY	0	0.03	0	0.76	.447	-0	0
BMI	0	0.03	0	1.74	.084	-0	0
PLT	0	0.01	0	0.41	.686	-0	0

sex, extent of gastrectomy, and disease stage. The results indicated that low albumin levels, elevated lymphocyte counts, and a PNI of less than 45 were significant predictors of major complications.

The management of gastric cancer requires a meticulous understanding of prognostic factors influencing postoperative outcomes. Among the variables assessed, blood values such as White Blood Cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), lymphocytes, C-reactive protein (CRP), albumin levels, and platelet counts have been identified as significant indicators of both short-term and long-term postoperative outcomes in patients undergoing gastric cancer resection.

Multiple studies have demonstrated the utility of inflammatory markers such as the NLR in predicting outcomes following gastrectomy. Research indicates that both preoperative and postoperative NLRs are closely associated with the prognostic outcomes in gastric cancer patients. Elevated NLR is linked to a higher risk of post-operative complications and poorer overall survival, making it a potent prognostic marker (11,12). Specifically, a high preoperative NLR may indicate a more aggressive tumor biology and systemic inflammatory response, affecting the postoperative healing process and patient recovery (13).

In our study, the preoperative high neutrophil levels were significantly associated with post-operative complications; interestingly, the neutrophil to lymphocyte ratio was not associated with a poorer postoperative outcome.

CRP levels and their elevation postoperatively are equally significant. Studies suggest that elevated postoperative CRP levels correlate with unfavorable outcomes, including increased morbidity and mortality (14,15). They indicate a heightened inflammatory state and potential complications, leading researchers to advocate for its routine measurement as a prognostic factor during follow-ups (7).

In our series, high CRP levels were strongly associated with postoperative complications in the univariate and multivariate analyses as well.

Albumin levels, another critical parameter, are indicative of nutritional status and inflammatory response. Low serum albumin is a known predictor of postoperative complications and is commonly associated with poor nutritional status and systemic inflammation (16). A low albumin level at the time of surgery can correlate with a higher likelihood of both short-term surgical complications and long-term survival detriments, affirming its significance as a prognostic marker (17).

In our study, low albumin levels were significantly associated with poor postoperative outcome in univariate analysis.

The impact of leukocyte counts, specifically lymphocyte counts, holds significant prognostic implications. Lower lymphocyte counts have been associated with a higher incidence of infectious complications and poorer overall outcomes post-surgery (18).

In our study, the postoperative outcome was influenced by the white blood cell count, although in the multivariate analysis it wasn't a prognostic factor for postoperative complications.

Hence, a thorough assessment of these hematological parameters can furnish clinicians with invaluable insight into a patient's preoperative condition and potential recovery trajectory.

The role of platelets in postoperative outcomes has garnered attention as well, with elevated platelet counts suggesting a hypercoagulable state associated with inflammation or malignancy (19). Studies have illustrated that platelet counts can serve as a significant prognostic factor, impacting both short-term complications and long-term survival (20). The combined assessment of platelets with other inflammatory markers produces a more comprehensive understanding of the inflammatory and nutritional status of gastric cancer patients.

The Glasgow Prognostic Score (GPS) is a clinical tool that integrates serum CRP levels and albumin concentration to evaluate systemic inflammation and malnutrition, both of which are critical for determining prognosis in gastric cancer patients. Hsueh et al. have illustrated that the GPS, which combines the elevation of CRP levels and hypoalbuminemia, is a valid independent prognostic marker for worse outcomes in patients with advanced gastric cancer (7). Studies have shown that elevated GPS scores correlate with poorer surgical outcomes and lower overall survival rates postoperatively (7,21).

In our study, high GPS was significantly associated with postoperative complications in univariate analysis and multivariate analysis as well.

Conclusion

In conclusion, systemic inflammatory markers play a significant role in predicting postoperative complications in gastric cancer. In our study, inflammatory markers, albuminemia, PNI, GPS, and SII were strongly associated with the post-

operative outcome. The interplay between inflammatory markers, surgical techniques, nutritional support, and complication management forms a multifaceted approach to predicting postoperative outcomes in gastric cancer surgeries. Continued research into these elements is crucial for enhancing both recovery and long-term survival rates in affected patients.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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