


Modified Neutrophil Platelet Scores (MNPs): A Novel Prognostic Marker in Colorectal Cancer

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Background: Inflammation can influence how tumors develop and is linked to patient outcomes. We studied a new marker called the Modified Neutrophil Platelet Score (MNPs), which uses blood neutrophil and platelet counts. This research aimed to verify if MNPs and other clinical markers help doctors better predict disease severity after surgery for people with colorectal cancer.

Methods: We reviewed records from 503 patients with colorectal cancer. All patients had curative surgery at the Second Affiliated Hospital of Harbin Medical University (2016–2018). We collected their blood test results one week before surgery, including neutrophil, platelet, lymphocyte, and monocyte counts, plus CEA and CA199 levels. Using Kaplan–Meier analysis, we examined how MNPs relates to patients' overall survival (OS) and recurrence-free survival (RFS). We performed univariate and multivariate Cox regression analyses. To compare MNPs with other inflammation markers, we calculated time-dependent ROC curves, C-index, and Brier scores.

Results: Overall Survival (OS): Patients with lower MNPs (score 0) lived longer. Compared to score 0 patients, those with score 1 had shorter survival (HR = 3.180, 95% CI 2.028–4.988, $p < 0.001$), and score 2 patients lived significantly shorter lives (HR = 7.430, 95% CI 4.672–11.816, $p < 0.001$). Recurrence-Free Survival (RFS): Patients with lower MNPs (score 0) stayed cancer-free longer. Score 1 patients had higher recurrence risk than score 0 patients (HR = 3.790, 95% CI 2.065–6.954, $p < 0.001$), while score 2 patients faced the highest recurrence risk (HR = 10.023, 95% CI 5.428–18.510, $p < 0.001$). Multivariate analysis confirmed MNPs independently predicts OS and RFS outcomes. Time-dependent ROC curves, C-index, and Brier scores showed MNPs predicts patient outcomes more accurately than other inflammation markers.

Conclusion: MNPs can help doctors predict outcomes for people with colorectal cancer. Patients with lower MNPs tend to live longer and stay cancer-free longer after surgery.

Keywords: modified neutrophil platelet score, colorectal cancer, platelet-lymphocyte ratio, neutrophil-to-lymphocyte ratio, systemic inflammation response index, systemic immune-inflammation index, prognosis

Introduction

The occurrence, development, and prognosis of various malignant tumors are all significantly affected by the inflammatory response.¹ Proinflammatory cytokines, chemokines, and growth factors are released by inflammatory cells (such as neutrophils, macrophages, etc.) to form a tumor-promoting microenvironment (TME). Tumor cell survival, proliferation, metastasis, angiogenesis, and immune evasion can all be facilitated by persistent inflammation in the TME. Chronic inflammation also causes genomic instability and DNA damage, and it can further accelerate the development of cancer by destroying normal tissues' ability to heal.² In conclusion, inflammation plays a significant role in the onset and spread of cancer. A number of investigations have demonstrated that the prognosis of a variety of malignant tumors can be predicted using peripheral serum indicators of inflammatory response.³ Therefore, an increasing number of researchers are committed to studying the clinical value of new biomarkers in the diagnosis and prognosis of malignant tumors.⁴ Numerous serological markers, including C-reactive protein (CRP), SIRI, SII, NLR, PLR, albumin, neutrophils and platelets, have been crucial in the systemic inflammatory response (SIR) in predicting malignant tumors.^{5–9}

In 2015, the British scholar Watt suggested that the survival rate of several common malignancies may be predicted using the neutrophil platelet score (NPs).¹⁰ In order to compensate for the limitations brought about by the ethnic variations in the traditional NPs score, Okugawa proposed the modified neutrophil platelet score (MNPs) in 2019. This study selected 621 patients with gastric cancer, confirmed the significant value of preoperative MNPs in the prediction of various common malignant tumors, and also proved that MNPs was significantly correlated with the clinicopathological characteristics of common diseases.¹¹ Through a retrospective cohort study, Otani found 168 patients who had radical surgery for gastric cancer in 2024, and used the chi-square test to determine the significance of the difference between MNPs and clinicopathological factors. The risk factors for overall survival (OS) and recurrence-free survival (RFS) were assessed using Kaplan–Meier analysis, and univariate and multivariate survival analyses were conducted using the Cox regression model. The results demonstrated that MNPs was a significant independent prognostic factor for OS and RFS.¹² This implies that MNPs can serve as a reference index for individualized therapy of gastric cancer, but the clinical evidence of MNPs in other malignant tumors remains to be discussed, and its prognostic value needs to be further verified.

The third most prevalent malignant tumor worldwide, colorectal cancer (CRC) poses a major threat to human life and health.¹³ Young adults, particularly those under 55, have seen a roughly 50% increase in the incidence of colorectal cancer (CRC) in recent years.¹⁴ Despite ongoing advancements in preoperative neoadjuvant chemotherapy, surgical resection, postoperative adjuvant therapy, targeted drug therapy, immunotherapy, and palliative care, the mortality rate for colorectal cancer remains elevated,¹⁵ particularly for patients who experience distant metastases and recurrence following CRC surgery. With the continuous development of CRC screening, researchers are dedicated to developing biomarkers that can be used to predict cancer recurrence and poor prognosis. Most patients are more willing to serological testing.¹⁶ These markers can be obtained from regular blood tests without expensive equipment and setups.⁴ For instance, NLR and PLR can be employed for the early detection and prognosis of CRC and are associated with the extent and stage of the cancer.¹⁷ Neutrophils can induce a rapid rise in platelets during the early stages of the systemic inflammatory response (SIR). Additionally, the interaction between platelets and neutrophils can further amplify the inflammatory response and protumor effects.^{18–20} MNPs directly reflect the SIR status. This status heralds stronger pro-tumor inflammation, angiogenesis, invasion and metastasis potential, and immunosuppression, which is associated with a worse prognosis in patients with malignant tumors. Effectively predicting the prognosis of patients with colorectal cancer prior to surgery may help clinicians detect tumor recurrence and metastasis risks early, follow up with high-risk patients more closely, administer more extensive chemotherapy, and improve patient quality of life.

Therefore, we propose a novel biomarker based on neutrophils and platelets to study whether it can predict the long-term survival rate of patients with resectable colorectal cancer. Our goals also include evaluating the clinical prognostic usefulness of MNPs in CRC patients and providing fresh research evidence for personalized treatment.

Materials and Methods

Study Populations

This study retrospectively selected 503 patients who underwent radical surgery for colorectal cancer in the Department of general surgery, the Second Affiliated Hospital of Harbin Medical University from 2016 to 2018. Inclusion criteria: (1) participants who were older than 18; (2) postoperative pathology verified primary colorectal cancer; (3) blood test indexes were accessible within a week before to surgery; (4) comprehensive clinical and follow-up data. Exclusion criteria: (1) non-primary colorectal cancer; (2) complicated by a major infection, immune system disease, or malignant tumor; (3) distant metastases of the lesions that were impossible to remove; (4) afflicted with autoimmune diseases or blood system disorders; (5) experiencing severe pathological alterations of the liver, kidney, heart, and other organs. Results of the data came from the hospital electronic medical record system or family contacts. Death, loss of follow-up, or December 2024 marked the end of the follow-up period. The primary end points were OS and RFS. OS was defined as the time between surgery and death from any cause. RFS is defined as the time between surgery and recurrence or death, whichever occurs first. We conducted this retrospective study in compliance with the Declaration of Helsinki, obtained

informed consent from all patients, and received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (YJSKY2024-267).

Date Collection

Clinical information such as sex, age, height, and weight are included in the baseline data. Hematological parameters one week prior to surgery include the following: neutrophil, platelet, CEA, CA199, lymphocyte, and monocyte. Postoperative pathology includes the following: Maximum tumor diameter, tumor location, Tumor differentiation, Specimen type, TNM stage, Number of lymphatic invasion, whether nerve invasion is present, vascular tumor thrombus, lymphatic tumor thrombus, and survival time. MNPs was calculated as 0 for patients with neutrophil count $\leq 4170/\mu\text{L}$ and platelet count $\leq 26.6 \times 10^4/\mu\text{L}$, 1 for patients with neutrophil count $>4170/\mu\text{L}$ or platelet count $>26.6 \times 10^4/\mu\text{L}$, and 2 for patients with neutrophil count $>4170/\mu\text{L}$ and platelet count $>26.6 \times 10^4/\mu\text{L}$; NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; SII = platelet count \times neutrophil count/lymphocyte count; SIRI = monocyte count \times neutrophil count/lymphocyte count.

Statistical Analysis

The mean \pm standard deviation is used to describe continuous quantitative data that follows the normal distribution, while one-way ANOVA is used to compare groups. The rank sum test is used to compare groups if it does not fit the normal distribution, and the median [p25, p75] is used for statistical description. The chi-square test or Fisher exact probability method was used to compare groups, and the number of cases (%) was utilized to describe the counting data. A KM curve was created for study of the OS/RFs differences across groups, and the logrank test was employed to compare the group differences. To investigate the relationship between MNPs and OS/RFs, univariate and multivariate Cox regression were employed. We conducted the proportional hazards assumption for all variables in the Cox model and the model passed. Then, the time-dependent ROC curve was used to analyze the predictive value of MNPs relative to other different indicators, draw the time-dependent ROC curve, and calculate the C index. The degree of calibration of several indicators was compared using the Brier score.

All statistical analysis and related charts were drawn in R language (version 4.4.1), and bilateral $p < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

This study retrospectively analyzed 503 patients with colorectal cancer, including 319 males (63.4%) with a median age of 61 years. The median follow-up time was 75.5 months (95% CI: 75.2 to 77.1). TNM1 accounted for 15.7%, TNM2 for 45.5%, and TNM3 for 38.8%. About 26 instances (5.2%) had good differentiation, 76 cases (15.1%) had poor differentiation, and 401 cases (79.7%) had moderate differentiation. For further baseline data, see [Table 1](#). According to the MNPs score, they were split into three groups (0 point: $n = 275$; 1 point: $n = 156$; 2 point: $n = 72$). [Table 1](#) shows that there were no appreciable variations between the three groups in terms of sex, age, BMI, or Tumor location.

Correlation Between MNPs and OS/RFS

OS KM curve study under various MNPs groups revealed a correlation between MNPs and OS, with the greater the MNPs, the worse the OS (logrank test $p < 0.001$). As seen in [Figure 1](#), there was a substantial difference between the survival curves of the three groups (0, 1, 2).

[Figure 2](#) illustrates the correlation between MNPs and RFS KM curve analysis of RFS under various MNPs groups. The results indicated that the RFS were worse the higher the MNPs (logrank test $p < 0.001$), and the three groups' survival curves (0, 1, 2) were more clearly separated.

OS and RFS with distinct risk classifications for rectal and colon cancer Colorectal cancer overall survival (OS): The low-risk group's survival rate is 12.7%, the moderate-risk group's is 30.7%, and the high-risk group's is 51.1%. Survival

Table 1 Association Between Preoperative Modified Neutrophil Platelet Score and Systemic Inflammatory Response Index and Clinicopathological Characteristics in Patients with Colorectal Cancer, n (%)

Variables	Total (n = 503)	0 (n = 275)	1 (n = 156)	2 (n = 72)	p
CEA, Median (Q1,Q3)	3.30 (2.00, 7.62)	3.15 (1.92, 5.99)	3.43 (2.01, 8.08)	4.56 (2.42, 10.03)	0.021
CA199, Median (Q1,Q3)	7.45 (3.74, 17.83)	6.72 (3.86, 14.79)	9.03 (3.58, 25.75)	8.70 (3.23, 25.59)	0.285
PLR, Median (Q1,Q3)	132.82 (100.97, 176.39)	117.70 (91.65, 148.02)	150.48 (113.38, 208.08)	191.49 (139.74, 225.44)	<0.001
NLR, Median (Q1,Q3)	1.86 (1.45, 2.64)	1.73 (1.39, 2.26)	1.87 (1.44, 2.64)	3.08 (2.40, 4.32)	<0.001
SIRI, Median (Q1,Q3)	0.67 (0.47, 1.01)	0.57 (0.43, 0.83)	0.68 (0.45, 1.03)	1.24 (0.93, 2.24)	<0.001
SII, Median (Q1,Q3)	249.85 (154.01, 446.61)	198.31 (132.60, 313.92)	269.21 (185.53, 473.09)	585.82 (351.11, 901.23)	<0.001
Neu, Median (Q1,Q3)	3.51 (3.04, 4.14)	3.31 (2.88, 3.64)	3.66 (3.02, 4.72)	5.62 (4.83, 7.04)	<0.001
PLT, Median (Q1,Q3)	245.00 (207.00, 288.50)	218.00 (191.00, 241.00)	286.00 (257.00, 319.25)	325.00 (287.25, 394.25)	<0.001
Lym, Median (Q1,Q3)	1.86 (1.46, 2.33)	1.79 (1.42, 2.27)	1.91 (1.49, 2.37)	1.92 (1.55, 2.42)	0.240
Mon, Median (Q1,Q3)	0.35 (0.28, 0.45)	0.33 (0.26, 0.43)	0.35 (0.28, 0.43)	0.44 (0.34, 0.54)	<0.001
Sex, n (%)					0.124
Female	184 (36.6)	91 (33.1)	67 (42.9)	26 (36.1)	
Male	319 (63.4)	184 (66.9)	89 (57.1)	46 (63.9)	
Age, Median (Q1,Q3)	61.00 (53.50, 67.00)	61.00 (54.00, 67.00)	62.00 (54.00, 67.00)	60.00 (49.75, 66.00)	0.378
BMI, Median (Q1,Q3)	23.23 (21.22, 25.41)	23.39 (21.30, 25.71)	23.12 (20.98, 25.44)	22.67 (20.80, 24.79)	0.303
Tumor location, n (%)					0.088
Colon	254 (50.5)	134 (48.7)	75 (48.1)	45 (62.5)	
Rectal	249 (49.5)	141 (51.3)	81 (51.9)	27 (37.5)	
Maximum tumor diameter, Median (Q1,Q3)	4.50 (3.50, 5.90)	4.00 (3.50, 5.25)	5.00 (3.50, 6.00)	5.00 (3.50, 6.12)	0.004
Specimen type n (%)					0.501
Ulcer type	365 (72.6)	195 (70.9)	114 (73.1)	56 (77.8)	
Raised type	138 (27.4)	80 (29.1)	42 (26.9)	16 (22.2)	
Tumor differentiation, n (%)					0.059
Poor	76 (15.1)	34 (12.4)	26 (16.7)	16 (22.2)	
Moderate	401 (79.7)	228 (82.9)	118 (75.6)	55 (76.4)	
Well	26 (5.2)	13 (4.7)	12 (7.7)	1 (1.4)	
T, n (%)					0.004
1	20 (4)	10 (3.6)	10 (6.4)	0 (0)	
2	79 (15.7)	52 (18.9)	22 (14.1)	5 (6.9)	
3	403 (80.1)	213 (77.5)	124 (79.5)	66 (91.7)	
4	1 (0.2)	0 (0)	0 (0)	1 (1.4)	
N, n (%)					0.007
0	309 (61.4)	175 (63.6)	95 (60.9)	39 (54.2)	
1	130 (25.8)	78 (28.4)	32 (20.5)	20 (27.8)	
2	64 (12.7)	22 (8)	29 (18.6)	13 (18.1)	

(Continued)

Table I (Continued).

Variables	Total (n = 503)	0 (n = 275)	1 (n = 156)	2 (n = 72)	P
M, n (%)					1.000
0	503 (100)	275 (100)	156 (100)	72 (100)	
Tumor stage, n (%)					0.106
I	79 (15.7)	47 (17.1)	28 (17.9)	4 (5.6)	
II	229 (45.5)	128 (46.5)	67 (42.9)	34 (47.2)	
III	195 (38.8)	100 (36.4)	61 (39.1)	34 (47.2)	
Number of lymphatic invasion, Median (Q1,Q3)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	0.283
Nerve invasion, n (%)					0.425
0	196 (39)	106 (38.5)	66 (42.3)	24 (33.3)	
I	307 (61)	169 (61.5)	90 (57.7)	48 (66.7)	
Vascular invasion, n (%)					0.960
0	341 (67.8)	185 (67.3)	107 (68.6)	49 (68.1)	
I	162 (32.2)	90 (32.7)	49 (31.4)	23 (31.9)	
Lymphatic invasion, n (%)					0.964
0	381 (75.7)	209 (76)	117 (75)	55 (76.4)	
I	122 (24.3)	66 (24)	39 (25)	17 (23.6)	

rates sharply decline with increasing risk. The survival rate for rectal cancer is 74.1% for the high-risk group, 32.1% for the moderate-risk group, and 9.9% for the low-risk group. Likewise, [Figure 3](#) shows that survival rates fall with increasing danger.

Colorectal cancer recurrence-free survival (RFS): The RFS rate was 6.7% for the low-risk group, 16.0% for the moderate-risk group, and 35.6% for the high-risk group. A lower RFS rate is the result of increased risk. The RFS rate was 48.1% for the high-risk group, 22.2% for the moderate-risk group, and 5.0% for the low-risk group for rectal cancer. As risk rises, the RFS likewise falls, as [Figure 3](#) illustrates.

As seen in [Figure 3](#), the predictive ability of MNPs does not significantly alter depending on the location of the tumor (colon or rectum), despite the fact that survival rates for colon and rectal cancer differed among risk categories.

Univariate and Multivariate Cox Regression Analysis of MNPs and OS/RFS

Univariate and multivariate Cox regression analysis of MNPs and OS: Univariate Cox regression analysis showed that MNPs (1 point vs 0 point: HR = 3.180, 95% CI 2.028–4.988, $p < 0.001$; 2 vs 0: HR = 7.430, 95% CI 4.672–11.816, $p < 0.001$) was linked to OS. The higher the MNPs, the higher the risk of death. [Table 2](#) shows that MNPs remained an independent predictor of OS after controlling for confounding factors (variables with $p < 0.05$ in a single component) (1 point vs 0 point: HR = 3.494, 95% CI 2.220–5.499; 2 vs 0: HR = 6.641, 95% CI 4.161–10.601, all $p < 0.001$).

Univariate and multivariate Cox regression analysis of MNPs and RFS: Cox regression analysis of MNPs and other variables and OS showed that MNPs (1 point vs 0 point: HR = 3.790, 95% CI 2.065–6.954, $p < 0.001$; HR = 3.790, 95% CI 2.065–6.954, $P < 0.001$; HR = 0.090; 2 point vs 0 point: HR = 10.023, 95% CI 5.428–18.510, $p < 0.001$) correlated with RFS. The higher the MNPs, the higher the risk of recurrence. As shown in [Table 3](#), the MNPs remained an independent predictor of RFS even after controlling for confounding variables (1 point vs 0 point: HR = 4.120, 95% CI 2.236–7.590; 2 point vs 0 point: HR = 9.350, 95% CI 5.040–17.348, All $p < 0.001$).

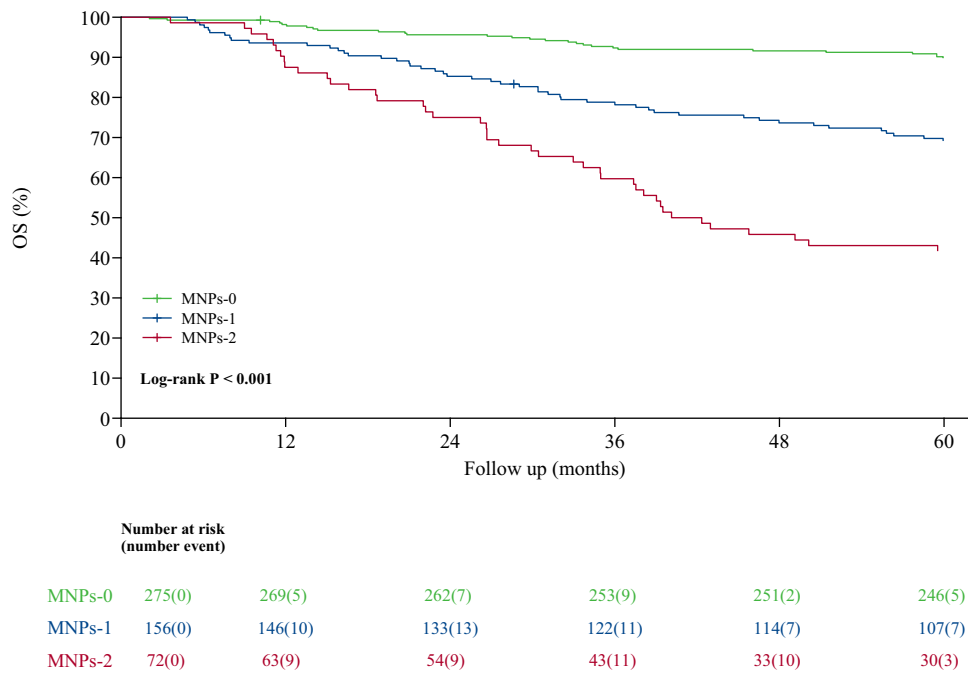


Figure 1 Relationship between preoperative modified neutrophil platelet score and OS in patients with colorectal cancer.

Comparison of C-Index of OS/RFS Predicted by MNPs and Other Indicators

Comparison of C-index of OS predicted by MNPs and other indicators: The MNPs and the C-index of CEA, CA199, PLR, NLR, SIRI and SII predicted OS were evaluated. As seen in **Figure 4**, the results indicate that MNPs have superior discrimination capacity because the C-index is 0.699, which is much higher than other indicators.

As shown in **Figure 5**, the results indicate that MNPs have a superior ability to differentiate RFS, as seen by the C-index of MNPs of 0.727, which is noticeably better than other indicators.

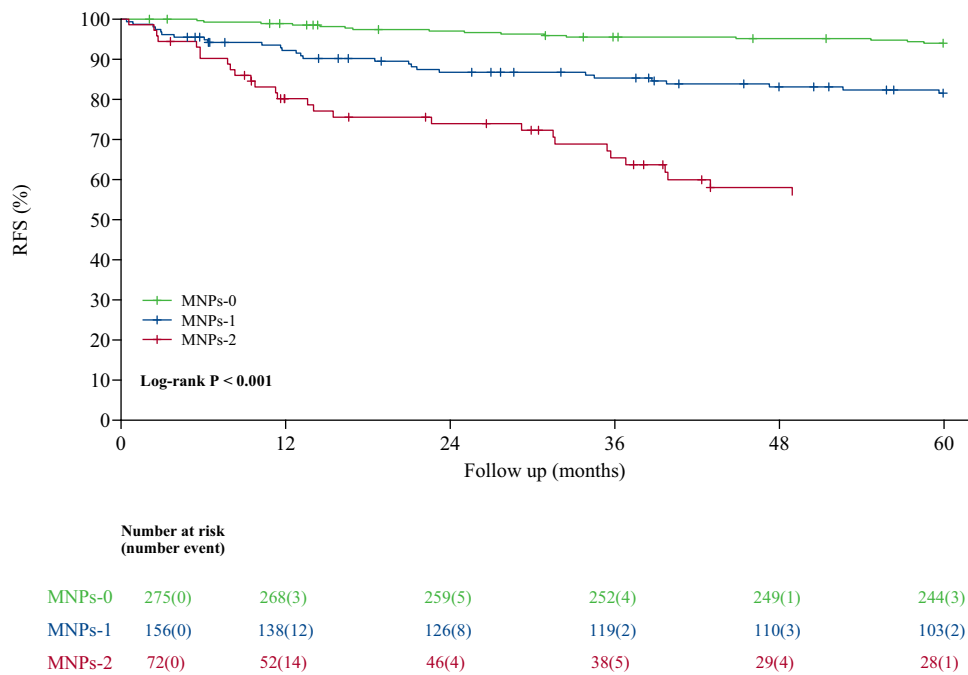


Figure 2 Relationship between preoperative modified neutrophil platelet score and RFS in patients with colorectal cancer.

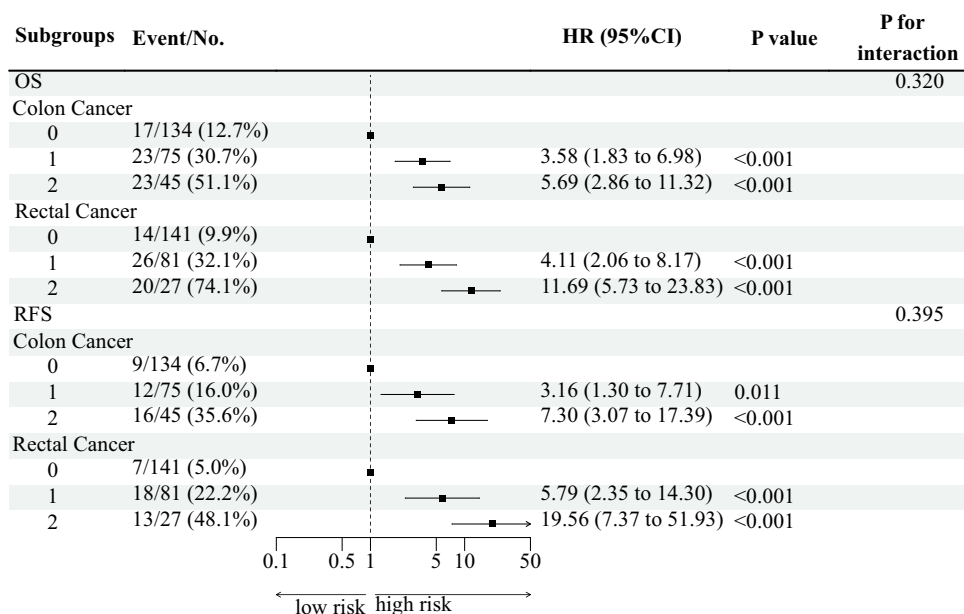


Figure 3 OS and RFS with distinct risk classifications for rectal and colon cancer.

Time-Dependent ROC Curve Analysis for OS/RFS Prediction Using MNPs and Additional Indicators

Time dependent ROC curve analysis of MNPs and other indicators in predicting OS: We assessed how well MNPs, CEA, CA199, PLR, NLR, SIRI, and SII predicted patients’ OS based on the time-dependent ROS curve. According to the findings, MNPs were better than other markers in predicting OS in three and five years, with area under the ROC curves of 0.708 (95% CI: 0.650–0.765) and 0.736 (95% CI: 0.687–0.785), respectively. The time-dependent C-index variations of different indicators at each time point were displayed in Figures 6–8. It was also demonstrated that the MNPs had the highest value in predicting OS after 24 months.

Table 2 Uni and Multivariate Cox Proportional Hazards Analysis of Clinicopathological Factors for OS

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
MNPs				
0	reference		reference	
1	3.180 (2.028, 4.988)	<0.001	3.494 (2.220, 5.499)	<0.001
2	7.430 (4.672, 11.816)	<0.001	6.641 (4.161, 10.601)	<0.001
Age	1.008 (0.992, 1.025)	0.337		
BMI	0.991 (0.939, 1.046)	0.74		
Tumor location				
Colon	Reference			
Rectal	0.962 (0.675, 1.370)	0.83		

(Continued)

Table 2 (Continued).

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Maximum tumor diameter	1.011 (0.921, 1.108)	0.823		
Specimen type				
Ulcer type	Reference		Reference	
Raised type	0.410 (0.248, 0.675)	<0.001	0.762 (0.452, 1.287)	0.31
Tumor differentiation				
Poor	Reference		Reference	
Moderate	0.422 (0.283, 0.631)	<0.001	0.670 (0.442, 1.014)	0.058
Well	0.212 (0.065, 0.693)	0.01	0.373 (0.113, 1.237)	0.107
Tumor stage				
I	Reference		Reference	
II	5.101 (1.580, 16.473)	0.006	3.440 (1.035, 11.429)	0.044
III	13.496 (4.260, 42.756)	<0.001	6.475 (1.923, 21.803)	0.003
Number of lymphatic invasion	1.169 (1.120, 1.220)	<0.001	1.075 (1.004, 1.151)	0.039
Nerve invasion				
0	Reference			
I	1.381 (0.947, 2.014)	0.094		
Vascular invasion				
0	Reference		Reference	
I	1.708 (1.195, 2.441)	0.003	1.270 (0.870, 1.854)	0.215
Lymphatic invasion				
0	Reference		Reference	
I	1.805 (1.243, 2.620)	0.002	1.085 (0.719, 1.637)	0.698

Analysis of MNPs and other indicators using time-dependent ROC curves to predict RFS. Based on the time-dependent ROC curve, we evaluated the accuracy of MNPs, CEA, CA199, PLR, NLR, SIRI and SII in predicting RFS of patients. In comparison to other indicators, the results demonstrated that the area under the ROC curve of MNPs predicting RFS in three and five years was 0.742 (95% CI: 0.676–0.809) and 0.751 (95% CI: 0.690–0.812). The change in the time-dependent C-index of RFS predicted by several indicators at each time point is displayed in [Figures 9–11](#). The findings indicate that the MNPs has the ability to predict RFS because the C-index of RFS predicted by the score is higher than that of other indicators at all time points.

Brier Score Analysis of MNPs and Other Indicators Predicting OS/RFS

Brier score comparison of OS predicted by MNPs and other indicators: [Figure 12](#) illustrates that the calibration degree of MNPs was superior to that of other indicators, as the Brier score comparison of OS predicted by MNPs and other indicators revealed that the Brier score of OS predicted by MNPs was lower than that predicted by other indicators.

Table 3 Uni and Multivariate Cox Proportional Hazards Analysis of Clinicopathological Factors for RFS

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
MNPs				
0	Reference		Reference	
I	3.790 (2.065, 6.954)	<0.001	4.120 (2.236, 7.590)	<0.001
2	10.023 (5.428, 18.510)	<0.001	9.350 (5.040, 17.348)	<0.001
Age	0.995 (0.974, 1.016)	0.61		
BMI	0.981 (0.916, 1.052)	0.595		
Tumor location				
Colon	Reference			
Rectal	1.047 (0.665, 1.646)	0.844		
Maximum tumor diameter	0.997 (0.885, 1.124)	0.966		
Specimen type				
Ulcer type	Reference		Reference	
Raised type	0.503 (0.277, 0.915)	0.024	0.837 (0.436, 1.608)	0.593
Tumor differentiation				
Poor	Reference		Reference	
Moderate	0.495 (0.290, 0.843)	0.01	0.745 (0.432, 1.286)	0.29
Well	0.264 (0.061, 1.140)	0.074	0.395 (0.090, 1.735)	0.219
Tumor stage				
I	Reference		Reference	
II	1.928 (0.740, 5.020)	0.179	1.214 (0.439, 3.359)	0.708
III	4.356 (1.726, 10.993)	0.002	2.358 (0.816, 6.808)	0.113
Number of lymphatic invasion	1.125 (1.056, 1.198)	<0.001	1.017 (0.921, 1.123)	0.737
Nerve invasion				
0	Reference			
I	1.515 (0.927, 2.475)	0.097		
Vascular invasion				
0	Reference		Reference	
I	2.211 (1.406, 3.477)	0.001	1.964 (1.222, 3.157)	0.005
Lymphatic invasion				
0	Reference		Reference	
I	1.230 (0.737, 2.052)	0.428	1.085 (0.719, 1.637)	0.698

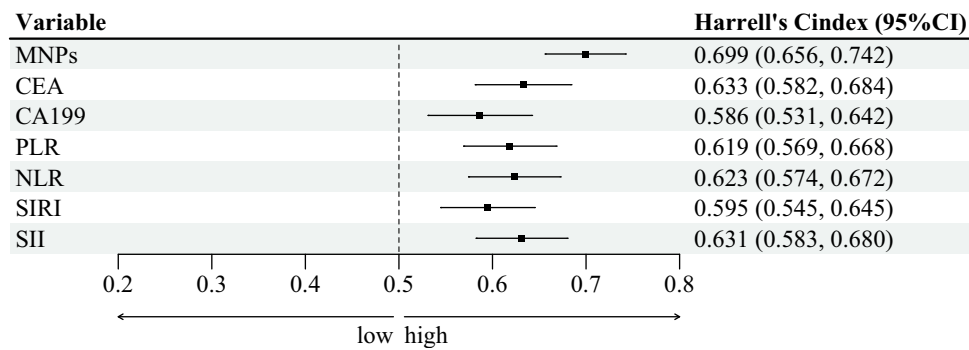


Figure 4 Comparison of c-index of OS predicted by MNPs and other indicators.

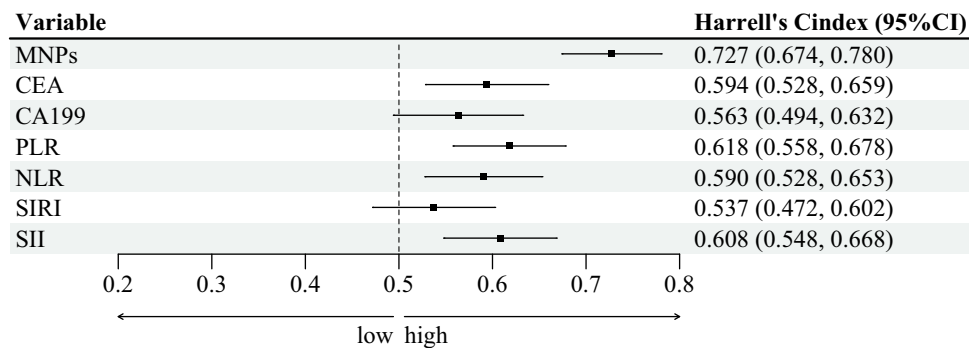


Figure 5 Comparison of c-index of RFS predicted by MNPs and other indicators.

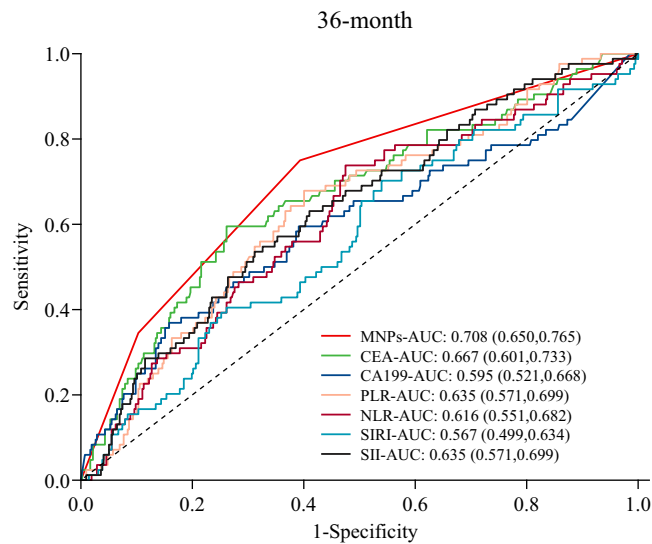


Figure 6 ROC curve of MNPs predicting 3-year OS.

Brier score analysis of RFS predicted by MNPs and other indicators: As illustrated in Figure 13, the Brier score analysis of RFS predicted by MNPs and other indicators revealed that the Brier score of RFS predicted by MNPs was likewise lower than that of other indicators, indicating that the calibration degree of RFS predicted by MNPs was superior to that of other indicators.

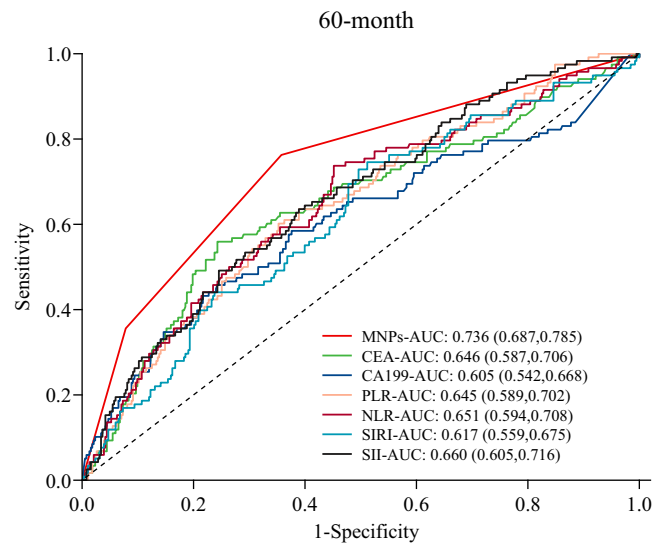


Figure 7 ROC curve of MNPs predicting 5-year OS.

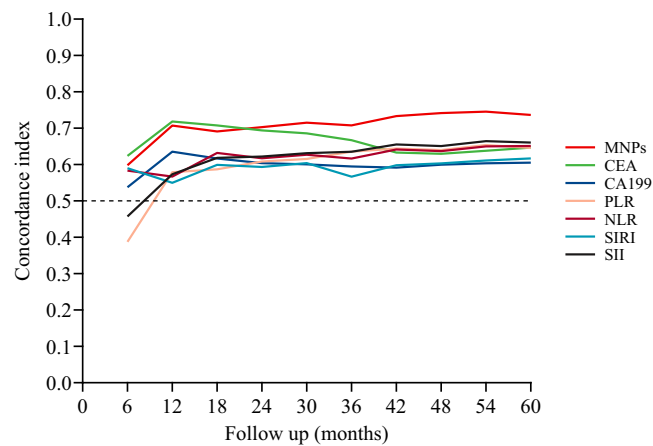


Figure 8 Time dependent C-index of OS predicted by different indicators at each time point.

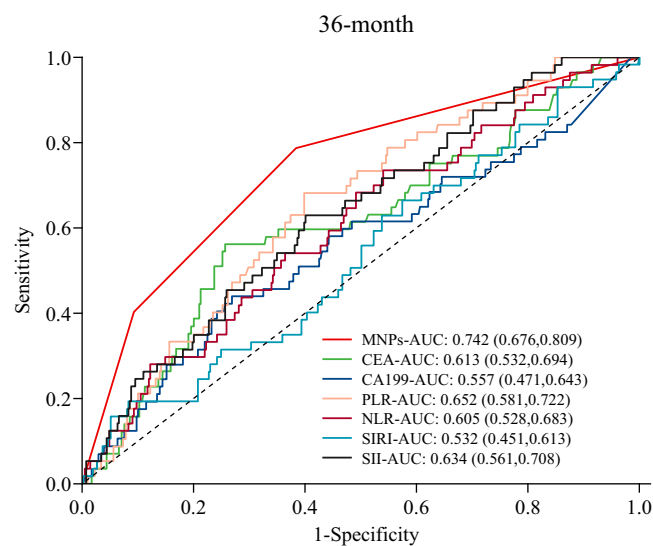


Figure 9 ROC curve of MNPs predicting 3-year RFS.

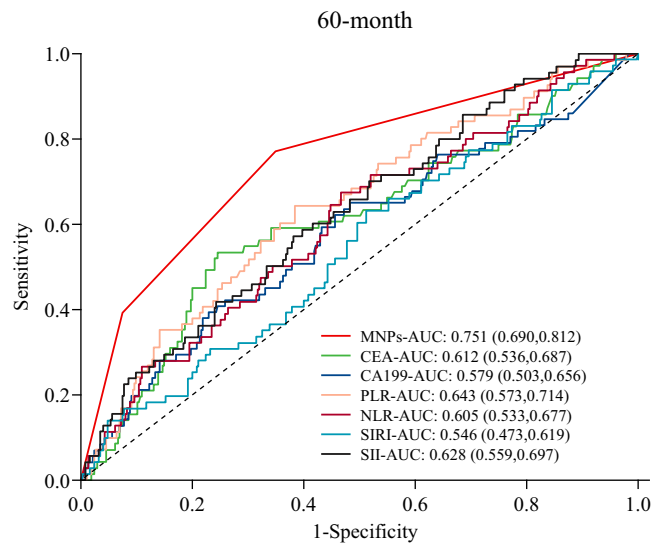


Figure 10 ROC curve of MNPs predicting 5-year RFS.

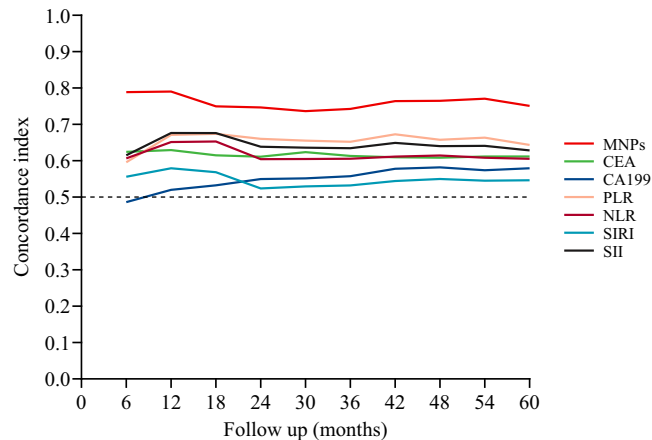


Figure 11 Time dependent C-index of RFS predicted by different indicators at each time point.

Discussion

Researchers have become increasingly interested in the connection between inflammation and cancer.^{21–23} Both infectious and non infectious inflammation can lead to cancer. However, it is typically challenging to identify cancer micrometastases. To enhance the quality of life and assist physicians in predicting the prognosis of cancer patients, we require more sensitive biomarkers.²⁴ In recent years, systemic inflammatory markers have been shown to have clinical significance in the prognosis of CRC patients, such as SII, NLR and PLR, which are linked to a poor prognosis for CRC patients.²⁵ Our research verified that preoperative high MNPs was associated with low OS and low RFS in CRC patients. Additionally, we proved that MNPs was better at predicting clinical prognosis than CEA, CA199, PLR, NLR, SIRI, and SII. This study is the first to explore the prognostic value of preoperative MNPs in patients with resectable colorectal cancer.

Inflammation plays a significant function in the tumor microenvironment, according to numerous studies conducted recently. Immune cells in the tumor microenvironment interact with tumor cells, thereby inducing biological behaviors such as angiogenesis and immunosuppression.²⁶ Notably, Vinatha Sreeramkumar discovered that the dynamic recombination of neutrophils interacts with the vascular wall and activated platelets during the early stages of inflammation.²⁷ Neutrophils and platelets promote the proliferation and diffusion of malignant tumors through various ways.^{28,29} In 2024, Yingcheng found that neutrophils have 10 different states, including inflammation, angiogenesis and antigen

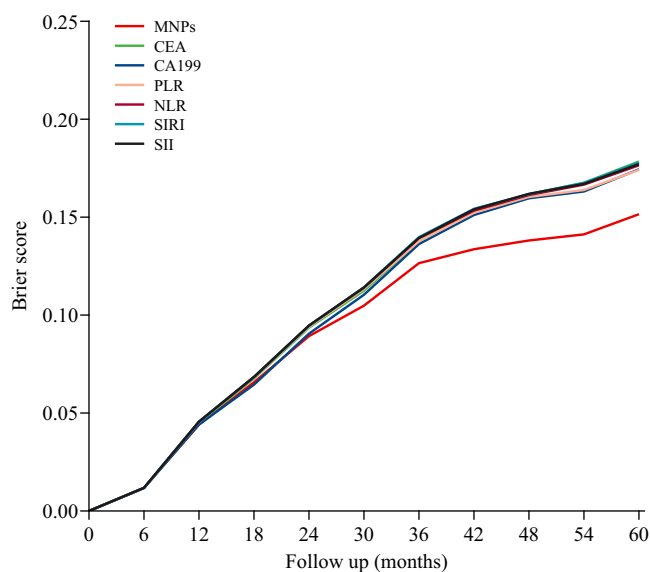


Figure 12 Brier score of OS predicted by MNPs and other indicators.

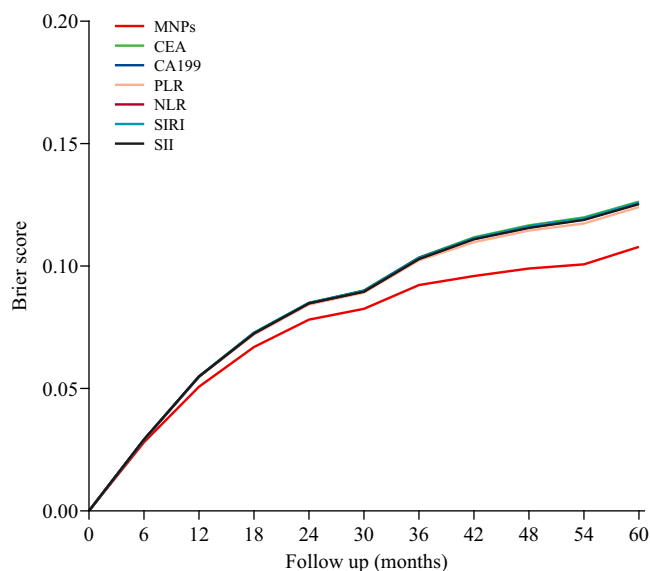


Figure 13 Brier score of RFs predicted by MNPs and other indicators.

presentation. Antigen presentation is frequently linked to better prognosis of most malignant tumors.³⁰ Platelets are closely associated with the risk of thrombosis. Malignant tumors will spread more quickly if platelet counts rise, and cancer cells have the ability to activate platelets, leading to further activation of platelets.⁴ Chronic damage and infection can raise the risk of cancer, cause a variety of inflammations and illnesses, and hasten the development of cancer from precancerous lesions.³¹ In 2020, Angelika copija selected 247 patients with CRC confirmed by histology. The study found that patients with high NPs were more common in metastatic diseases.³² In 2018, Yoshinaga okugawa discovered that sarcopenia in CRC patients was significantly correlated with the increase of CRP, SII and NPs, and the decrease of lymphocyte monocyte ratio, prognostic nutritional index and serum albumin level.³³ In 2021, Aktan observed a correlation between overall survival and disease-free survival and indicators of systemic inflammatory response in patients receiving neoadjuvant chemotherapy (NCRT).³⁴ Meiyuan Huang found the clinical diagnostic value of the

methylated SEPT9 combined with NLR, PLR and LMR in colorectal cancer. The accuracy of CRC diagnosis was further enhanced by the combined use of these biomarkers.³⁵ Liang Yu discovered that for GC patients, the NLR-CA19-9 score (NCS) offered a more precise prognostic prediction. Its predictive value is noticeably higher than that of conventional tumor or inflammatory markers.³⁶

Moreover, MNPs as an indicator that comprehensively reflects the count of neutrophils and platelets, its elevation may imply the existence of specific, persistently activated pro-tumor inflammatory pathways in the body. Elevated MNPs (high neutrophil count) suggest enhanced neutrophil activation, which may involve the activation of the neutrophil extracellular traps (NETosis) pathway. Researchers have verified that NETs play a critical role in immunosuppression and CRC metastasis.^{37–39} Activated neutrophils also release large amounts of pro-inflammatory cytokines, which promote tumor cell proliferation, survival, and angiogenesis.⁴⁰ In the meantime, the reactive oxygen species and matrix metalloproteinases produced by neutrophils can lead to tissue damage and microenvironment remodeling, which is conducive to tumor invasion.⁴¹ High platelet counts are often associated with hypercoagulable state, and activated platelets can release a variety of angiogenic and growth factors. These can directly stimulate tumor growth and angiogenesis and epithelial-mesenchymal transition, and participate in the formation of immunosuppressive microenvironment.^{42,43} Platelets can directly interact with circulating tumor cells by physically engulfing tumor cells, releasing cytokines, etc., forming platelet-tumor cell aggregates, enhancing the metastatic colonization ability of tumor cells.⁴⁴ Notably, there is a complex bidirectional action between neutrophils and platelets. Activated platelets can bind and activate neutrophils through molecules such as P-selectin and vice versa. This interaction can amplify inflammatory responses and protumor effects.^{18–20} All in all, the elevation of MNPs is the hematological manifestation of a sustained amplified state of the neutrophil-platelet axis activation and systemic load in the body. The elevation of MNPs indirectly and comprehensively reflects a pro-tumor inflammatory state with enhanced activities of neutrophils and platelets. This condition is linked to a worse prognosis for individuals with malignant tumors because it generates higher pro-tumor inflammation, angiogenesis, invasion and metastatic potential, and immunosuppression.

This study retrospectively analyzed 503 patients who underwent radical surgery for colorectal cancer in the Department of General Surgery, the Second Affiliated Hospital of Harbin Medical University from 2016 to 2018. In patients with colorectal cancer, we first examined the association between the preoperative modified neutrophil platelet score, the systemic inflammatory response index, and clinicopathological features. The MNPs was used to separate them into three groups (0 points: $n = 275$; 1 point: $n = 156$; 2 points: $n = 72$). The three groups did not differ significantly in terms of gender, age, BMI, or tumor site. The survival curves of the three groups (0, 1, 2) were considerably separated, and survival analysis revealed that the OS/RFS decreased with increasing MNPs (logrank test $p < 0.001$). Analysis of several risk groups revealed that both OS and RFS tended to shorten dramatically as the risk group increased, no matter whether the cancer was rectal or colon. However, the prognostic potential of MNPs was not significantly affected by the location of the tumor. MNPs (1 point vs 0 point: HR = 3.180, 95% CI 2.028–4.988, $p < 0.001$; 2 point vs 0 point: HR = 7.430, 95% CI 4.672–11.816, $p < 0.001$) was linked to OS, according to univariate Cox regression analysis. The higher the MNPs, the higher the risk of death. MNPs remained an independent predictor of OS after controlling for confounding variables (variables with $p < 0.05$ in a single component) (1 point vs 0 point: HR = 3.494, 95% CI 2.220–5.499; 2 point vs 0 point: HR = 6.641, 95% CI 4.161–10.601, all $p < 0.001$). There was a correlation between MNPs and RFS (1 point vs 0 point: HR = 3.790, 95% CI 2.065–6.954, $p < 0.001$; 2 point vs 0 point: HR = 10.023, 95% CI 5.428–18.510, $p < 0.001$). The higher the MNPs, the higher the risk of recurrence. MNPs remained an independent predictor of RFS after controlling for confounding variables (1 point vs 0 point: HR = 4.120, 95% CI 2.236–7.590; 2 point vs 0 point: HR = 9.350, 95% CI 5.040–17.348, all $p < 0.001$). When assessing clinical prognosis, MNPs outperformed other inflammatory indicators, according to the C-index, time-dependent ROC curves, and Brier scores. It demonstrated the clinical predictive utility of MNPs in assessing CRC patients' overall and recurrence-free survival. Patients with a higher risk of an early malignant tumor, recurrence, and metastasis can receive more individualized and precise treatment as a result, which eventually increases patient survival.

Despite certain limitations, this work offers fresh perspectives on the predictive potential of novel inflammatory markers, such as MNPs, in colorectal cancer surgery. First of all, this is a single center retrospective study. Every patient is from our hospital and has no outside validation. There is potential for bias in patient selection and patient information.

We have attempted to ensure data quality by strict inclusion and exclusion criteria, but potential missing data (eg, certain laboratory measures or detailed comorbidity information) may still affect the completeness of the results. Second, there was no precise date; all the data came from the blood test one week before the procedure. Third, all clinical data come from different pathologists and surgeons, which may lack consistency. This study was conducted primarily in patients who received curative resection and had no distant metastases (M0), and its extrapolation needs to be done with. It should be further validated in future prospective or external validation studies or in studies that include a more extensive spectrum of staging patients. In addition, this study did not account for potential influence of comorbidities such as hypertension on inflammatory markers, which might affect the robustness of the conclusions. Future studies should prospectively collect corresponding data to refine the model. Therefore, in order to dynamically detect inflammatory signs and maximize prognosis evaluation, multicenter prospective studies in the future will need to use large samples and external validation. Given the sensitivity of MNPs to systemic inflammation, combining MNPs with other biomarkers is an important direction for future improvements in precision in prognostic models. It is promising to achieve more accurate individualized prognostic stratification.

Conclusion

In summary, research has shown that the preoperative modified neutrophil platelet score (MNPs) is a predictor of OS and RFS on its own and is linked to a poor prognosis in colorectal patients. Preoperative detection of MNPs can early identify patients with high risk, recurrence and metastasis of colorectal cancer and provide individualized intervention and treatment. Clinicians could incorporate the MNPs score into existing prognostic assessment tools. For patients with high MNPs, more intensive follow-up, higher postoperative treatment regimens could be considered, even if conventional staging is low. However, this study was a single-center retrospective analysis, and external validation in a multi-prospective setting is needed before it can be used in the clinic. Additionally, platelets activate neutrophils, which in turn feedback to activate platelets, forming a positive feedback loop. This interaction can rapidly amplify inflammatory responses protumor effects. MNPs integrate these two key components, offering reliable evidence to guide prognosis in patients with malignant neoplasms.

Date Accessibility

Data can be obtained from the corresponding author on a reasonable request.

Ethics Approval and Informed Consent

The study was carried out according to the guidelines of Helsinki Declaration and was approved by the medical ethics committee of the Second Affiliated Hospital of Harbin Medical University.

We conducted this retrospective study in compliance with the Declaration of Helsinki, obtained verbal informed consent from all patients and received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (YJSKY2024-267). Given the retrospective nature of the study and the need to protect patient privacy, the Ethics Committee approved the use of verbal informed consent to obtain consent from patients or their legal representatives. All patient information was strictly anonymized.

Funding

This work was supported by grants from Postdoctoral Scientific Research Developmental Fund of Heilongjiang Province (LBH-Q21026); Heilongjiang Provincial Traditional Chinese Medicine Administration Research Project (zhy 2020-169).

Disclosure

The authors report no conflicts of interest in this work.

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