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ORIGINAL RESEARCH

Pan-Immune-Inflammation Value (PIV) and Prognostic Nutritional Index (PNI) are Associated with Distant Metastasis in Colorectal Cancer with *KRAS* Mutation but Not in Those with *KRAS* Wild-Type

Yunlin Li, Yuwen Zeng

Department of Gastrointestinal Surgery, Meizhou People's Hospital, Meizhou, People's Republic of China

Correspondence: Yuwen Zeng, Department of Gastrointestinal Surgery, Meizhou People's Hospital, Meizhou, People's Republic of China, Email 14754938521@163.com

Background: Pan-immune-inflammation value (PIV) and prognostic nutritional index (PNI) have values in the prognosis assessment of tumors. However, their relationship with the distant metastasis risk of colorectal cancer (CRC) remains unclear. The aim of our study was to explore the relationship between PIV and PNI and the risk of distant metastasis in CRC patients with and without *KRAS* mutation.

Methods: The clinical data (age, gender, body mass index (BMI), cigarette smoking, alcoholism, and diabetes mellitus, family history of tumor, tumor stage, and *KRAS/NRAS* mutation status) of 2408 CRC patients were retrospectively collected and analyzed. The optimal thresholds of PIV and PNI were evaluated by receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used to reveal the relationship of PIV and PNI and distant metastasis in CRC with and without *KRAS* mutation, respectively.

Results: The average levels of PIV and PNI was 327.62 (183.19, 590.36) and 46.70 (43.10, 50.90). There were 825 (34.3%) patients with distant metastasis and 1583 (65.7%) without. The optimal threshold of PIV and PNI was 339.50 and 45.53 by ROC analysis. Logistic regression analysis showed that stage T3-T4 (odds ratio (OR): 2.967, 95% confidence interval (CI): 1.804–4.880, $p<0.001$), and stage N2-N3 (OR: 5.109, 95% CI: 3.886–6.717, $p<0.001$) were associated with distant metastasis in CRC with *KRAS* wild-type; while stage T3-T4 (OR: 5.963, 95% CI: 2.897–12.273, $p<0.001$), and stage N2-N3 (OR: 7.094, 95% CI: 5.070–9.926, $p<0.001$), high PIV (OR: 2.867, 95% CI: 2.119–3.879, $p<0.001$), and low PNI (OR: 1.620, 95% CI: 1.184–2.215, $p=0.003$) were associated with distant metastasis in CRC with *KRAS* mutation.

Conclusion: Stages T3-T4 and N2-N3 were associated with distant metastasis in CRC with and without *KRAS* mutation. High PIV and low PNI were associated with distant metastasis in CRC patients with *KRAS* mutation, but not in patients without *KRAS* mutation.

Keywords: colorectal cancer, distant metastasis, *KRAS*, pan-immune-inflammation value, prognostic nutritional index

Introduction

Colorectal Cancer (CRC) is a malignant tumor that originates from the mucosal epithelial cells of the colorectal tract, including colon cancer and rectal cancer.[1] The pathological type of CRC is most commonly adenocarcinoma, which is mainly caused by the combined effect of genetic and environmental factors.[2,3] The lesion often gradually develops from adenomatous polyps of the colorectal mucosal epithelium. At present, globally, the incidence rate of colorectal cancer ranks third and the mortality rate ranks second.[4] The incidence and mortality rates of CRC in developing countries are both on a rapid upward trend, CRC is the second most common type of cancer in China.[5,6]

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Distant metastasis of CRC refers to the process in which cancer cells break through the local tissue barrier of the colon and rectum, spread to distant organs of the body through the blood circulation, lymphatic system or directly, and form new tumor lesions.[7] The common distant metastasis sites of CRC include organs such as the liver, lungs, bones, and brain.[8,9] Distant metastasis of CRC means that tumor cells establish a new growth environment in distant organs, which greatly increases the difficulty and complexity of treatment.[10,11] Distant metastasis has a significant adverse effect on the prognosis of CRC. Studies have shown that the survival rate of CRC patients with distant metastasis is significantly lower than that of patients without distant metastasis.[12,13] In addition, distant metastasis not only directly affects the survival of CRC patients, but also triggers a series of serious clinical symptoms.[13,14]

Distant metastasis of CRC is jointly affected by multiple risk factors. Distant metastasis of CRC is influenced by the pathological characteristics of the tumor and molecular biological factors.[15,16] In addition, factors such as the patient's age and physical condition can also affect the risk of distant metastasis.[17,18] Elderly patients and those with underlying diseases are more prone to distant metastasis due to their weakened immune systems.[19] Meanwhile, unhealthy lifestyles such as smoking, excessive drinking, as well as obesity, which can cause metabolic abnormalities, also promote the occurrence and development of distant metastasis of CRC to a certain extent.[20] Clarifying the risk factors of distant metastasis of CRC is of great significance for the early identification of high-risk populations and the formulation of individualized prevention and treatment strategies.

In the research field of risk factors for distant metastasis of CRC, the inflammatory state and nutritional level of the body have attracted much attention in recent years. The inflammatory environment can have a significant impact on the occurrence and development of tumors.[21] Studies have found that chronic inflammation can promote the proliferation, survival, invasion, and metastasis of tumor cells by activating key signaling pathways such as nuclear factor κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3).[22,23] In addition, chronic inflammation can also reshape the tumor microenvironment, promote angiogenesis, and create conditions for tumor cells to enter the bloodstream and colonize at a distance.[21] Nutritional status also plays an important role in the process of distant metastasis of CRC. On the one hand, malnutrition can weaken the immune function of the body, reducing the immune system's ability to monitor and kill tumor cells, and providing conditions for the distant metastasis of tumor cells.[24] On the other hand, abnormal metabolism of nutrients may affect the proliferation, apoptosis and metastasis-related signaling pathways of tumor cells, promoting the occurrence of distant metastasis of CRC.[25]

Pan-immune inflammation value (PIV), as an emerging biomarker, can comprehensively and intuitively assess the systemic inflammatory and immune status by integrating the counts of neutrophils, monocytes, lymphocytes, and platelets in the circulating blood (monocyte×neutrophil×platelet/lymphocyte).[26] PIV is a comprehensive immunoinflammatory biomarker associated with the clinical stage,[27,28] and prognosis[26] of CRC. Prognostic nutritional index (PNI) is calculated by the formula: serum albumin + 5 × lymphocyte count. It combines the serum albumin level, which reflects the nutritional status, and the lymphocyte count, which reflects the immune function, and can better represent the overall nutritional and immune status of patients.[29] PNI is often used to predict the incidence and prognosis of malignant tumors.[30] Are PIV and PNI levels associated with the risk of distant metastasis of CRC? Kirsten rat sarcoma viral oncogene homologue (KRAS) is a key molecule in the EGFR-dependent RAS/RAF/MAPK pathway, *KRAS* mutations can lead to the continuous activation of this signaling pathway and induce the progression of CRC.[31] Are there any differences in the relationship between PIV and PNI and the risk of distant metastasis in CRC patients with *KRAS* mutations and those without *KRAS* mutations? To solve this problem, this study was carried out.

Materials and Methods

Study Cohort

This study retrospectively analyzed 2408 patients with CRC who were treated at Meizhou People's Hospital from December 2018 to March 2025. This study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital. Patients who met the following conditions were included in this study: (1) patients confirmed as CRC by pathological examination; (2) CRC patients without other malignant tumors; (3) no anti-tumor treatment was received before admission; and (4) the test records of

laboratory indicators are complete. Patients with the following conditions were excluded from this study: (1) patients with a previous history of other malignant tumors; (2) patients with severe systemic underlying diseases and incomplete or failed functions of important organs; (3) CRC patients with other malignant tumors; and (4) clinical records incomplete.

Data Collection

The clinical data were collected, such as age, gender, body mass index (BMI), personal living habits (history of cigarette smoking and alcoholism), disease history (hypertension, diabetes mellitus, viral hepatitis), tumor stage (T stage and N stage), and the pathological and imaging examination results. The results of count of monocyte, neutrophil, platelet, and lymphocyte, and albumin were collected during the first hospital examination. The degree of obesity or emaciation is classified into three grades based on BMI: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to 23.9 kg/m^2), and overweight (BMI 24.0 to 28.0 kg/m^2).[32]

Calculation of PIV and PNI and Statistics Analysis

PIV and PNI were calculated according to the following formula:

- PIV = monocyte count (10^9/L) × neutrophil count (10^9/L) × platelet count (10^9/L) / lymphocyte count (10^9/L)
- PNI=serum albumin (g/L) + 5 × lymphocyte count (10^9/L)

In our study, we aimed to determine a moderate effect size with a significance level (α) set at 0.05 and a power (1-β) set at 0.80. The sample size required was approximately 500 patients as calculated using the G*Power software. Data analysis was performed using SPSS statistical software version 26.0 (IBM Inc., USA). Continuous variables are expressed as median and interquartile range (IQR) (25th to 75th percentiles), and are compared by Mann–Whitney *U*-test. Categorical variables are expressed as n (%), and analyzed using χ^2 test. The optimal thresholds of PIV and PNI were evaluated by receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used to reveal the relationship of PIV and PNI and distant metastasis in CRC with and without *KRAS* mutation, respectively, adjusting for some influencing factors, such as age, gender, BMI, cigarette smoking, alcoholism, diabetes mellitus, family history of tumor, T stage, and N stage. $p<0.05$.

Results

The Clinical Features of the Patients with CRC

In this study cohort, there were 1502 (62.4%) male, 906 (37.6%) female, 783 (32.5%) <60 years old and 1625 (67.5%) aged ≥60, respectively. There were 294 (12.2%) cases with underweight and 729 (30.3%) cases with overweight respectively. The number of patients with a history of cigarette smoking, alcoholism, diabetes mellitus, and family history of tumor was 211 (8.8%), 95 (3.9%), 361 (15.0%), and 33 (1.4%), respectively. There were 308 (12.8%) and 2100 (87.2%) cases with T1-T2, and T3-T4 stage; 1813 (75.3%) and 595 (24.7%) cases with N0-N1 and N2-N3 stage, respectively. The number of patients with *KRAS* mutation and *NRAS* mutation was 1085 (45.1%) and 86 (3.6%), respectively. The average levels of PIV and PNI was 327.62 (183.19, 590.36) and 46.70 (43.10, 50.90), respectively. There were 825 (34.3%) patients with distant metastasis and 1583 (65.7%) without (Table 1).

Comparison of the Clinical Features Between Patients with and Without Distant Metastasis in CRC

The proportions of patients with stage T3-T4 (χ^2=96.795, $p<0.001$), stage N2-N3 (χ^2=377.441, $p<0.001$), and *KRAS* mutation (χ^2=4.033, p=0.047) in CRC patients with distant metastasis were higher than those in patients without distant metastasis. There were no significant differences in other clinical features between the two groups (Table 2).

The average levels of PIV and PNI was 296.25 (171.62, 500.02) and 47.20 (43.60, 51.15) in patients without distant metastasis, 405.94 (214.04, 852.33) and 46.00 (42.08, 50.05) in patients without distant metastasis, respectively. The differences in PIV and PNI levels between the two groups were statistically significant ($p<0.001$) (Table 2).

Table 1 The Clinical Features of the Patients with CRC

Clinical Characteristics	Colorectal Cancer (n=2408)
Age (years)	
<60, n(%)	783 (32.5%)
≥60, n(%)	1625 (67.5%)
Gender	
Male, n(%)	1502 (62.4%)
Female, n(%)	906 (37.6%)
BMI (kg/m^2)	
Underweight, n (%)	294 (12.2%)
Normal weight, n (%)	1385 (57.5%)
Overweight, n (%)	729 (30.3%)
Cigarette smoking	
No, n(%)	2197 (91.2%)
Yes, n(%)	211 (8.8%)
Alcoholism	
No, n(%)	2313 (96.1%)
Yes, n(%)	95 (3.9%)
Diabetes mellitus	
No, n(%)	2047 (85.0%)
Yes, n(%)	361 (15.0%)
Family history of tumor	
No, n(%)	2375 (98.6%)
Yes, n(%)	33 (1.4%)
T stage	
T1-T2, n (%)	308 (12.8%)
T3-T4, n (%)	2100 (87.2%)
N stage	
N0-N1, n (%)	1813 (75.3%)
N2-N3, n (%)	595 (24.7%)
KRAS mutation	
No, n (%)	1323 (54.9%)
Yes, n (%)	1085 (45.1%)
NRAS mutation	
No, n (%)	2322 (96.4%)
Yes, n (%)	86 (3.6%)
Distant metastasis	
No, n (%)	1583 (65.7%)
Yes, n (%)	825 (34.3%)
PIV, median (IQR)	327.62 (183.19, 590.36)
PNI, median (IQR)	46.70 (43.10, 50.90)

Abbreviations: BMI, body mass index; *KRAS, Kirsten rat sarcoma viral oncogene homologue* gene; *NRAS, neuroblastoma RAS viral oncogene homolog* gene; PIV, pan-immune-inflammation value; PNI, prognostic nutritional index; IQR, interquartile range.

When distant metastasis was set as the endpoint of PIV and PNI in ROC analysis, the cutoff value of PIV was 339.50 (sensitivity 58.9%, specificity 62.5%, area under the ROC curve (AUC): 0.627), and the PNI cutoff value was 45.53 (sensitivity 47.3%, specificity 66.4%, AUC: 0.590) (Figure 1).

Table 2 Comparison of the Clinical Features Between Patients with and Without Without Distant Metastasis in CRC Patients

Clinical Characteristics	Without Distant Metastasis (n=1583)	With Distant Metastasis (n=825)	*p* (χ^2/Z)
Age (years)			
<60, n(%)	500 (31.6%)	283 (34.3%)	0.184
≥60, n(%)	1083 (68.4%)	542 (65.7%)	(χ^2=1.825)
Gender			
Male, n(%)	981 (62.0%)	521 (63.2%)	0.595
Female, n(%)	602 (38.0%)	304 (36.8%)	(χ^2=0.322)
BMI (kg/m^2)			
Underweight, n (%)	190 (12.0%)	104 (12.6%)	0.741
Normal weight, n (%)	906 (57.2%)	479 (58.1%)	(χ^2=0.593)
Overweight, n (%)	487 (30.8%)	242 (29.3%)	
Cigarette smoking			
No, n(%)	1436 (90.7%)	761 (92.2%)	0.225
Yes, n(%)	147 (9.3%)	64 (7.8%)	(χ^2=1.585)
Alcoholism			
No, n(%)	1514 (95.6%)	799 (96.8%)	0.154
Yes, n(%)	69 (4.4%)	26 (3.2%)	(χ^2=2.086)
Diabetes mellitus			
No, n(%)	1330 (84.0%)	717 (86.9%)	0.062
Yes, n(%)	253 (16.0%)	108 (13.1%)	(χ^2=3.558)
Family history of tumor			
No, n(%)	1558 (98.4%)	817 (99.0%)	0.270
Yes, n(%)	25 (1.6%)	8 (1.0%)	(χ^2=1.491)
Tstage			
T1-T2, n (%)	279 (17.6%)	29 (3.5%)	<0.001
T3-T4, n (%)	1304 (82.4%)	796 (96.5%)	(χ^2=96.795)
N stage			
N0-N1, n (%)	1387 (87.6%)	426 (51.6%)	<0.001
N2-N3, n (%)	196 (12.4%)	399 (48.4%)	(χ^2=377.441)
KRAS mutation			
No, n (%)	893 (56.4%)	430 (52.1%)	0.047
Yes, n (%)	690 (43.6%)	395 (47.9%)	(χ^2=4.033)
NRAS mutation			
No, n (%)	1530 (96.7%)	792 (96.0%)	0.419
Yes, n (%)	53 (3.3%)	33 (4.0%)	(χ^2=0.669)
PIV, median (IQR)	296.25 (171.62, 500.02)	405.94 (214.04, 852.33)	<0.001 (Z=−8.146)
PNI, median (IQR)	47.20 (43.60, 51.15)	46.00 (42.08, 50.05)	<0.001 (Z=−4.960)

Abbreviations: BMI, body mass index; *KRAS, Kirsten rat sarcoma viral oncogene homologue* gene; *NRAS, neuroblastoma RAS viral oncogene homolog* gene; PIV, pan-immune-inflammation value; PNI, prognostic nutritional index; IQR, interquartile range.

Comparison of the Clinical Features Between Distant Metastasis Patients and No Distant Metastasis Patients in CRC Patients Without and with KRAS Mutation, Respectively

In CRC patients without *KRAS* mutation, the proportions of patients with stage T3-T4 (χ^2=39.267, p<0.001), and stage N2-N3 (χ^2=176.372, p<0.001) in CRC patients with distant metastasis were higher than those in patients without distant metastasis. In CRC patients with *KRAS* mutation, the proportions of patients with stage T3-T4 (χ^2=59.593, p<0.001), stage N2-N3 (χ^2=205.034, p<0.001), high PIV (≥339.50) (χ^2=97.343, p<0.001), and low PNI (<45.53) (χ^2=29.400, p<0.001) in CRC patients with distant metastasis were higher than those in patients without distant metastasis (Table 3).

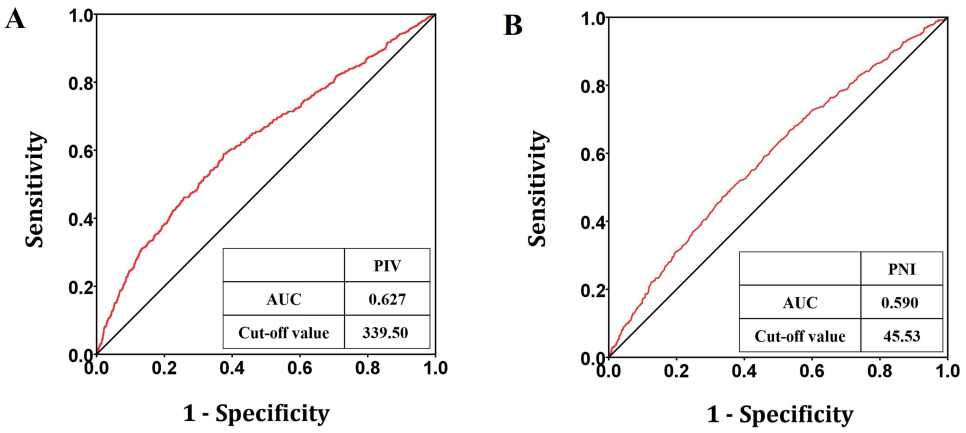

Figure 1 The ROC curve analysis of PIV (**A**) and PNI (**B**) to distinguish distant metastasis.
Abbreviations: PIV, pan-immune-inflammation value; PNI, prognostic nutritional index.

Logistic Regression Analysis of Risk Factors Associated with Distant Metastasis in CRC

Univariate analysis showed that stage T3-T4 (odds ratio (OR): 5.873, 95% confidence interval (CI): 3.967–8.695, $p<0.001$), and stage N2-N3 (OR: 6.628, 95% CI: 5.413–8.116, $p<0.001$), *KRAS* mutation (OR: 1.189, 95% CI: 1.004–1.408, $p=0.045$), high PIV (OR: 1.938, 95% CI: 1.634–2.299, $p<0.001$), and low PNI (OR: 1.457, 95% CI: 1.229–1.727, $p<0.001$) were significantly associated with distant metastasis in CRC (Table 4).

Multivariate logistic regression analysis showed that stage T3-T4 (OR: 3.827, 95% CI: 2.549–5.746, $p<0.001$), and stage N2-N3 (OR: 5.797, 95% CI: 4.705–7.144, $p<0.001$), *KRAS* mutation (OR: 1.400, 95% CI: 1.151–1.702, $p=0.001$), high PIV (OR: 1.713, 95% CI: 1.407–2.086, $p<0.001$), and low PNI (OR: 1.236, 95% CI: 1.013–1.50, $p=0.037$) were independently associated with distant metastasis in CRC (Table 4).

Logistic Regression Analysis of Risk Factors Associated with Distant Metastasis in CRC Without and with KRAS Mutation, Respectively

In CRC without *KRAS* mutation, multivariate regression analysis showed that stage T3-T4 (OR: 2.967, 95% CI: 1.804–4.880, $p<0.001$), and stage N2-N3 (OR: 5.109, 95% CI: 3.886–6.717, $p<0.001$) were associated with distant metastasis (Table 5).

In CRC with *KRAS* mutation, multivariate regression analysis showed that stage T3-T4 (OR: 5.963, 95% CI: 2.897–12.273, $p<0.001$), and stage N2-N3 (OR: 7.094, 95% CI: 5.070–9.926, $p<0.001$), high PIV (OR: 2.867, 95% CI: 2.119–3.879, $p<0.001$), and low PNI (OR: 1.620, 95% CI: 1.184–2.215, $p=0.003$) were associated with distant metastasis (Table 5).

Discussion

Accurate prediction of distant metastasis of CRC can effectively assist clinical decision-making, create space for early intervention, and improve the survival rate and quality of life of patients. In this study, stage T3-T4 and stage N2-N3 were associated with distant metastasis in CRC with and without *KRAS* mutation. High PIV and low PNI were associated with distant metastasis in CRC patients with *KRAS* mutation, but not in patients without *KRAS* mutation.

The results of this study shows that the detection rate of *KRAS* gene mutations in CRC patients with distant metastasis is significantly higher than that in patients without distant metastasis, which is consistent with the conclusions of some previous studies.[33–36] It indicates that *KRAS* gene mutation may be an important molecular event promoting distant metastasis of CRC. *KRAS* gene is a key node of the RAS-mitogen activated protein kinase (MAPK) signaling pathway, its mutation will lead to the continuous activation of this pathway.[37,38] The continuously activated RAS-MAPK signaling pathway can enhance the proliferation ability of tumor cells, enabling tumor cells to gain a stronger survival advantage and thereby laying the cell

Table 3 Comparison of the Clinical Features Between Distant Metastasis Patients and No Distant Metastasis Patients in CRC Patients Without and with KRAS Mutation, Respectively

Clinical Characteristics	Without *KRAS* Mutation (n=1323)			With *KRAS* Mutation (n=1085)		
	No Distant Metastasis (n=893)	Distant Metastasis (n=430)	*p* (χ^2)	No Distant Metastasis (n=690)	Distant Metastasis (n=395)	*p* (χ^2)
Age (years)						
<60, n(%)	263 (29.5%)	128 (29.8%)	0.949	237 (34.3%)	155 (39.2%)	0.115
≥60, n(%)	630 (70.5%)	302 (70.2%)	(χ^2=0.014)	453 (65.7%)	240 (60.8%)	(χ^2=2.606)
Gender						
Male, n(%)	601 (67.3%)	281 (65.3%)	0.494	380 (55.1%)	240 (60.8%)	0.074
Female, n(%)	292 (32.7%)	149 (34.7%)	(χ^2=0.498)	310 (44.9%)	155 (39.2%)	(χ^2=3.317)
BMI (kg/m^2)						
Underweight, n (%)	116 (13.0%)	53 (12.3%)	0.393	74 (10.7%)	51 (12.9%)	0.529
Normal weight, n (%)	514 (57.6%)	264 (61.4%)	(χ^2=1.854)	392 (56.8%)	215 (54.4%)	(χ^2=1.300)
Overweight, n (%)	263 (29.5%)	113 (26.3%)		224 (32.5%)	129 (32.7%)	
Cigarette smoking						
No, n(%)	800 (89.6%)	393 (91.4%)	0.325	636 (92.2%)	368 (93.2%)	0.631
Yes, n(%)	93 (10.4%)	37 (8.6%)	(χ^2=1.073)	54 (7.8%)	27 (6.8%)	(χ^2=0.357)
Alcoholism						
No, n(%)	850 (95.2%)	414 (96.3%)	0.397	664 (96.2%)	385 (97.5%)	0.297
Yes, n(%)	43 (4.8%)	16 (3.7%)	(χ^2=0.816)	26 (3.8%)	10 (2.5%)	(χ^2=1.197)
Diabetes mellitus						
No, n(%)	734 (82.2%)	370 (86.0%)	0.082	596 (86.4%)	347 (87.8%)	0.514
Yes, n(%)	159 (17.8%)	60 (14.0%)	(χ^2=3.117)	94 (13.6%)	48 (12.2%)	(χ^2=0.478)
Family history of tumor						
No, n(%)	882 (98.8%)	427 (99.3%)	0.415	676 (98.0%)	390 (98.7%)	0.473
Yes, n(%)	11 (1.2%)	3 (0.7%)	(χ^2=0.791)	14 (2.0%)	5 (1.3%)	(χ^2=0.850)
T stage						
T1-T2, n (%)	152 (17.0%)	20 (4.7%)	<0.001	127 (18.4%)	9 (2.3%)	<0.001
T3-T4, n (%)	741 (83.0%)	410 (95.3%)	(χ^2=39.267)	563 (81.6%)	386 (97.7%)	(χ^2=59.593)
N stage						
N0-N1, n (%)	767 (85.9%)	224 (52.1%)	<0.001	620 (89.9%)	202 (51.1%)	<0.001
N2-N3, n (%)	126 (14.1%)	206 (47.9%)	(χ^2=176.372)	70 (10.1%)	193 (48.9%)	(χ^2=205.034)
PIV						
<339.50	420 (47.0%)	179 (41.6%)	0.068	490 (71.0%)	160 (40.5%)	<0.001
≥339.50	473 (53.0%)	251 (58.4%)	(χ^2=3.422)	200 (29.0%)	235 (59.5%)	(χ^2=97.343)
PNI						
≥45.53	487 (54.5%)	217 (50.5%)	0.176	493 (71.4%)	218 (55.2%)	<0.001
<45.53	406 (45.5%)	213 (49.5%)	(χ^2=1.931)	197 (28.6%)	177 (44.8%)	(χ^2=29.400)

Abbreviations: BMI, body mass index; *KRAS*, *Kirsten rat sarcoma viral oncogene homologue* gene; *NRAS*, *neuroblastoma RAS viral oncogene homolog* gene; PIV, pan-immune-inflammation value; PNI, prognostic nutritional index.

quantity basis for distant metastasis.[39] Meanwhile, the abnormal activation of this pathway can also affect the epithelial-mesenchymal transition (EMT) process of tumor cells, promoting the loss of polarity of epithelial cells, the acquisition of mesenchymal cell characteristics, changes in cell morphology, significantly enhanced invasion ability, and thus making it easier to break through the basement membrane, enter the blood circulation or lymphatic circulation, and undergo distant metastasis.[40,41] In CRC without *KRAS* mutation, the RAS-MAPK signaling pathway is in a relatively normal regulatory state, and the invasion and metastasis ability of tumor cells is somewhat limited.

In addition, the influence of the tumor microenvironment on the difference in distant metastasis risk between patients with and without *KRAS* mutation cannot be ignored either.[42] Mutations in the *KRAS* gene may alter the pattern of cytokine secretion by tumor cells, promoting the activation of tumor-associated fibroblasts (CAFs) and tumor

Table 4 Logistic Regression Analysis of Risk Factors Associated with Distant Metastasis in CRC

Variables	Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age (≥60 vs <60, years)	0.884(0.740–1.057)	0.177	1.004(0.817–1.233)	0.972
Gender (male vs female)	0.951(0.799–1.132)	0.570	0.978(0.798–1.198)	0.829
BMI (kg/m^2)				
Normal weight	1.000 (reference)	–	1.000 (reference)	–
Underweight	1.035(0.796–1.347)	0.796	0.982(0.730–1.321)	0.904
Overweight	0.940(0.777–1.136)	0.522	0.973(0.786–1.204)	0.800
Cigarette smoking (yes vs no)	0.822(0.605–1.116)	0.209	0.899(0.597–1.354)	0.612
Alcoholism (yes vs no)	0.714(0.451–1.130)	0.150	0.715(0.391–1.306)	0.275
Diabetes mellitus (yes vs no)	0.792(0.621–1.010)	0.060	0.825(0.628–1.083)	0.165
Family history of tumor (yes vs no)	0.610(0.274–1.359)	0.227	0.688(0.274–1.731)	0.427
T stage (T3-T4 vs T1-T2)	5.873(3.967–8.695)	<0.001	3.827(2.549–5.746)	<0.001
N stage (N2-N3 vs N0-N1)	6.628(5.413–8.116)	<0.001	5.797(4.705–7.144)	<0.001
KRAS mutation (yes vs no)	1.189(1.004–1.408)	0.045	1.400(1.151–1.702)	0.001
NRAS mutation (yes vs no)	1.203(0.772–1.873)	0.414	1.281(0.775–2.116)	0.334
PIV (≥339.50 vs <339.50)	1.938(1.634–2.299)	<0.001	1.713(1.407–2.086)	<0.001
PNI (<45.53 vs ≥45.53)	1.457(1.229–1.727)	<0.001	1.236(1.013–1.507)	0.037

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; *KRAS, Kirsten rat sarcoma viral oncogene homologue* gene; *NRAS, neuroblastoma RAS viral oncogene homolog* gene; PIV, pan-immune-inflammation value; PNI, prognostic nutritional index.

angiogenesis.[43,44] Activated CAFs can secrete transforming growth factor -β (TGF-β), inducing epithelial-mesenchymal transition (EMT) in tumor cells, enabling tumor cells to acquire the characteristics of mesenchymal cells, enhancing their motility and making them more prone to distant metastasis.[45] Meanwhile, the abnormally generated tumor blood vessels provide a convenient channel for tumor cells to enter the bloodstream.[46] In contrast, in the tumor microenvironment where the *KRAS* gene has not mutated, the interaction patterns between tumor cells and surrounding cells and the matrix are different, which is not conducive to the migration and distant colonization of tumor cells.

In terms of inflammation, *KRAS* mutations activate inflammatory signaling pathways such as nuclear factor-kappaB (NF-κB), and the persistent inflammatory microenvironment further intensifies this activation effect.[47] Inflammatory cells such as macrophages and neutrophils accumulate in tumor tissues and secrete pro-inflammatory factors such as tumor necrosis factor -α (TNF-α) and interleukin-6 (IL-6).[48] TNF-α can enhance the epithelial-mesenchymal transition (EMT) process of cells with *KRAS* mutation, enabling tumor cells to acquire stronger invasive ability.[49] At the same time, TNF-α promotes angiogenesis, providing convenient conditions for tumor cells to enter the circulatory system and undergo distant metastasis.[50] IL-6 can collaborate with the RAS-MAPK pathway activated by *KRAS* mutations through the JAK-STAT3 signaling pathway, enhancing the proliferation and survival ability of tumor cells and increasing the risk of distant metastasis.[51] In addition, reactive oxygen species (ROS) produced under chronic inflammatory conditions may also induce mutations in other genes, forming a "secondary blow" with *KRAS* mutations, further intensifying the malignancy and metastasis potential of tumors.[52] Liang et al found that the PIV level of CRC patients with *KRAS* mutations was significantly higher than that of patients without *KRAS* mutations.[53] Xiong et al found that the PIV level of breast cancer patients with lymph node metastasis was significantly higher than that of patients without lymph node metastasis.[54] Furthermore, some studies suggested that PIV was a promising biomarker to predict the prognosis of some tumors.[55–57] In this study, high PIV is associated with distant metastasis in CRC patients with *KRAS* mutation, it enriches the data on the value of PIV in the assessment of tumor progression and prognosis.

Nutritional factors also have profound impacts on distant metastasis of CRC with *KRAS* mutations. Tumor cells have abnormal metabolism, especially in the context of *KRAS* mutation, and have a more vigorous demand for nutrients. Cells with *KRAS* mutation up-regulate glucose transporters to take up more glucose and perform aerobic glycolysis (Warburg effect), providing energy and biosynthetic raw materials for cell proliferation and metastasis.[58,59] Meanwhile, abnormal fatty acid metabolism is also associated with *KRAS* mutation.[60] Tumor cells can utilize fatty acid β-oxidation to generate

Table 5 Logistic Regression Analysis of Risk Factors Associated with Distant Metastasis in CRC Without and with KRAS Mutation, Respectively

Variables	Without *KRAS* Mutation				With *KRAS* Mutation			
	Unadjusted Values		Adjusted Values		Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age (≥60 vs <60, years)	0.985(0.766–1.267)	0.906	1.168(0.879–1.552)	0.284	0.810(0.627–1.046)	0.107	0.855(0.629–1.162)	0.317
Gender (male vs female)	1.091(0.856–1.391)	0.480	1.058(0.803–1.393)	0.689	0.792(0.616–1.018)	0.069	0.907(0.666–1.235)	0.535
BMI (kg/m^2)								
Normal weight	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–
Underweight	0.890(0.622–1.272)	0.521	0.858(0.580–1.269)	0.444	1.257(0.848–1.863)	0.255	1.217(0.762–1.944)	0.412
Overweight	0.837(0.641–1.091)	0.188	0.897(0.671–1.199)	0.463	1.050(0.799–1.380)	0.726	1.059(0.767–1.461)	0.728
Cigarette smoking (yes vs no)	0.810(0.543–1.208)	0.301	0.961(0.579–1.596)	0.879	0.864(0.535–1.396)	0.551	0.762(0.374–1.554)	0.455
Alcoholism (yes vs no)	0.764(0.425–1.372)	0.368	0.733(0.350–1.534)	0.410	0.663(0.316–1.390)	0.277	0.662(0.229–1.917)	0.447
Diabetes mellitus (yes vs no)	0.749(0.542–1.033)	0.078	0.728(0.513–1.035)	0.077	0.877(0.605–1.272)	0.490	1.060(0.679–1.654)	0.798
Family history of tumor (yes vs no)	0.563(0.156–2.030)	0.380	0.874(0.231–3.306)	0.842	0.619(0.221–1.732)	0.361	0.454(0.124–1.664)	0.234
T stage (T3-T4 vs T1-T2)	4.205(2.598–6.806)	<0.001	2.967(1.804–4.880)	<0.001	9.675(4.861–19.257)	<0.001	5.963(2.897–12.273)	<0.001
N stage (N2-N3 vs N0-N1)	5.598(4.286–7.311)	<0.001	5.109(3.886–6.717)	<0.001	8.463(6.168–11.610)	<0.001	7.094(5.070–9.926)	<0.001
PIV (≥339.50 vs <339.50)	1.245(0.987–1.571)	0.065	1.133(0.873–1.471)	0.347	3.598(2.776–4.665)	<0.001	2.867(2.119–3.879)	<0.001
PNI (<45.53 vs ≥45.53)	1.177(0.935–1.482)	0.165	1.027(0.792–1.332)	0.840	2.032(1.570–2.630)	<0.001	1.620(1.184–2.215)	0.003

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; *KRAS, Kirsten rat sarcoma viral oncogene homologue* gene; *NRAS, neuroblastoma RAS viral oncogene homolog* gene; PIV, pan-immune-inflammation value; PNI, prognostic nutritional index.

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energy or de novo synthesize fatty acids for cell membrane construction and signal transduction.[61] When the body is malnourished, tumor cells may reshape their own metabolic patterns by plundering the nutrients of the host's normal tissues, thereby enhancing their ability to colonize and survive at a distance.[62] Some studies have suggested that PNI was associated with distant metastasis,[25,63] recurrence,[64] and long-term outcome[30] in patients with CRC. In this study, low PNI is associated with distant metastasis in CRC patients with *KRAS* mutation, this result enriches the information of PNI in related fields.

The clinical significance of this study lies in providing new biomarkers for the prognosis assessment of CRC patients with *KRAS* mutation. By detecting the levels of PIV and PNI, clinicians can more accurately determine the risk of distant metastasis in patients, thereby formulating more individualized treatment plans. For *KRAS*-mutated CRC patients with elevated PIV and decreased PNI, it may be necessary to strengthen anti-inflammatory treatment and nutritional support to improve the immune-inflammatory state and nutritional status of the patients, and reduce the risk of distant metastasis. Moreover, this discovery also provides a direction for the development of new therapeutic targets. By targeting the immune-inflammatory and nutritional metabolic abnormalities reflected by PIV and PNI, corresponding therapeutic drugs may be developed to improve the efficacy and survival rate of CRC patients with *KRAS* mutation.

Although this study has obtained some valuable information, there are still some deficiencies. First, as a single-center retrospective study, the subjects of this research all came from the same medical institution. The representativeness of the sample was to some extent limited, which might lead to potential selection bias. Therefore, the results of this study require more research findings to be verified. Second, the cutoff values of PIV and PNI in this study were determined through ROC analysis. Currently, there is no widely accepted and unified cutoff value, and the cutoff values may vary among different studies. The AUC of PIV and PNI (0.627 and 0.590, respectively) for predicting distant metastasis of CRC is relatively low in this study, suggesting that these two indicators have limited discriminatory power. It might be related to the complexity of tumor metastasis and the high heterogeneity of CRC patients, therefore, more studies are needed to verify this result in the future. Third, this study was limited to analyzing PIV and PNI before treatment, but failed to consider the relationship between the changes of PIV and PNI before and after chemotherapy and distant metastasis. Finally, this study did not combine the indicators of inflammation and nutritional statuses with imaging variables to assess the risk of distant metastasis of CRC. Despite the above limitations, since the indicators related to PIV and PNI indices can be easily obtained from laboratory tests. The levels of PIV and PNI have certain clinical application value in predicting distant metastasis in CRC patients, especially for CRC patients with *KRAS* mutation.

Conclusion

Stage T3-T4 and stage N2-N3 were associated with distant metastasis in CRC with and without *KRAS* mutation. High PIV and low PNI were associated with distant metastasis in CRC patients with *KRAS* mutation, but not in patients without *KRAS* mutation. Inflammation and nutritional status are closely related to distant metastasis of CRC. PIV and PNI can effectively predict the risk of distant metastasis of CRC, and the detection method has the advantages of simplicity, economy, and convenience. Of course, since this single-center retrospective study may introduce bias in the results, the findings of this study require further researches to be validated.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Abedizadeh R, Majidi F, Khorasani HR, Abedi H, Sabour D. Colorectal cancer: a comprehensive review of carcinogenesis, diagnosis, and novel strategies for classified treatments. *Cancer Metastasis Rev*. 2024;43(2):729–753. doi:10.1007/s10555-023-10158-3
2. Ionescu VA, Gheorghe G, Bacalbasa N, Chiotoroiu AL, Diaconu C. Colorectal cancer: from risk factors to oncogenesis. *Medicina*. 2023;59(9):1646. doi:10.3390/medicina59091646
3. Li Q, Geng S, Luo H, et al. Signaling pathways involved in colorectal cancer: pathogenesis and targeted therapy. *Signal Transduct Target Ther*. 2024;9(1):266. doi:10.1038/s41392-024-01953-7
4. Bray F, Laversanne M, Sung H. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
5. He S, Xia C, Li H, et al. Cancer profiles in China and comparisons with the USA: a comprehensive analysis in the incidence, mortality, survival, staging, and attribution to risk factors. *Sci China Life Sci*. 2024;67(1):122–131. doi:10.1007/s11427-023-2423-1
6. Wu Y, He S, Cao M, et al. Comparative analysis of cancer statistics in China and the United States in 2024. *Chin Med J*. 2024;137(24):3093–3100. doi:10.1097/CM9.0000000000003442
7. Lord AC, Knijn N, Brown G, Nagtegaal ID. Pathways of spread in rectal cancer: a reappraisal of the true routes to distant metastatic disease. *Eur J Cancer*. 2020;128:1–6. doi:10.1016/j.ejca.2019.12.025
8. Liu Z, Xu Y, Xu G, et al. Nomogram for predicting overall survival in colorectal cancer with distant metastasis. *BMC Gastroenterol*. 2021;21(1):103. doi:10.1186/s12876-021-01692-x
9. Lan X, Wang Z, Zeng Z, Yao H, Xu W, Zhang Y. Association of different combinations of ALDH2 rs671, APOE rs429358, rs7412 polymorphisms with hypertension in middle-aged and elderly people: a case-control study. *Int J Gen Med*. 2023;16:915–927.
10. He K, Wang Z, Luo M, et al. Metastasis organotropism in colorectal cancer: advancing toward innovative therapies. *J Transl Med*. 2023;21(1):612. doi:10.1186/s12967-023-04460-5
11. Shin AE, Giancotti FG, Rustgi AK. Metastatic colorectal cancer: mechanisms and emerging therapeutics. *Trends Pharmacol Sci*. 2023;44(4):222–236. doi:10.1016/j.tips.2023.01.003
12. Poturnajova M, Furielova T, Balintova S, Schmidtova S, Kucerova L, Matuskova M. Molecular features and gene expression signature of metastatic colorectal cancer (Review). *Oncol Rep*. 2021;45(4):10. doi:10.3892/or.2021.7961
13. Hsiao CH, Li YL, Kiu KT, Yen MH, Chang TC. Clinical characteristics and prognostic impact of direct distant organ metastasis in colorectal cancer. *Surg Oncol*. 2024;53:102063. doi:10.1016/j.suronc.2024.102063
14. Sastre J, Orden V, Martínez A, et al. Association between baseline circulating tumor cells, molecular tumor profiling, and clinical characteristics in a large cohort of chemo-naïve metastatic colorectal cancer patients prospectively collected. *Clin Colorectal Cancer*. 2020;19(3):e110–e116. doi:10.1016/j.clcc.2020.02.014
15. Filip S, Vymetalkova V. Distant metastasis in colorectal cancer patients-do we have new predicting clinicopathological and molecular biomarkers? A comprehensive review. *Int J Mol Sci*. 2020;21(15):5255. doi:10.3390/ijms21155255
16. Wang Y, Jia J, Wang F, et al. Pre-metastatic niche: formation, characteristics and therapeutic implication. *Signal Transduct Target Ther*. 2024;9(1):236. doi:10.1038/s41392-024-01937-7
17. Kusunoki K, Toiyama Y, Okugawa Y, et al. Advanced lung cancer inflammation index predicts outcomes of patients with colorectal cancer after surgical resection. *Dis Colon Rectum*. 2020;63(9):1242–1250. doi:10.1097/DCR.0000000000001658
18. Huang L, Liu J, Huang X, et al. Serum C-reactive protein-to-body mass index ratio predicts overall survival in patients with resected colorectal cancer. *Technol Cancer Res Treat*. 2021;20:15330338211037418. doi:10.1177/15330338211037418
19. Zhu Z, Li J, Fa Z, et al. Functional gene signature offers a powerful tool for characterizing clinicopathological features and depicting tumor immune microenvironment of colorectal cancer. *BMC Cancer*. 2024;24(1):1199. doi:10.1186/s12885-024-12996-y
20. Islam MR, Akash S, Rahman MM, et al. Colon cancer and colorectal cancer: prevention and treatment by potential natural products. *Chem Biol Interact*. 2022;368:110170. doi:10.1016/j.cbi.2022.110170
21. Bhat AA, Nisar S, Singh M, et al. Cytokine- and chemokine-induced inflammatory colorectal tumor microenvironment: emerging avenue for targeted therapy. *Cancer Commun*. 2022;42(8):689–715. doi:10.1002/cac2.12295
22. Liu B, Zheng X, Li J, et al. Atovaquone inhibits colorectal cancer metastasis by regulating PDGFRβ/NF-κB signaling pathway. *BMC Cancer*. 2023;23(1):1070. doi:10.1186/s12885-023-11585-9

23. Yu J, Yang H, Zhang L, et al. Effect and potential mechanism of oncometabolite succinate promotes distant metastasis of colorectal cancer by activating STAT3. *BMC Gastroenterol*. 2024;24(1):106. doi:10.1186/s12876-024-03195-x
24. Yuan J, Zhang Y, Wu S, Zheng L. The intestinal flora and nutritional status and immune function characteristics of obese colon cancer patients. *BMC Gastroenterol*. 2024;24(1):237. doi:10.1186/s12876-024-03304-w
25. Tokunaga R, Sakamoto Y, Nakagawa S, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. *Dis Colon Rectum*. 2015;58(11):1048–1057. doi:10.1097/DCR.0000000000000458
26. Yang XC, Liu H, Liu DC, Tong C, Liang XW, Chen RH. Prognostic value of pan-immune-inflammation value in colorectal cancer patients: a systematic review and meta-analysis. *Front Oncol*. 2022;12:1036890. doi:10.3389/fonc.2022.1036890
27. Zhao H, Chen X, Zhang W, et al. Pan-immune-inflammation value is associated with the clinical stage of colorectal cancer. *Front Surg*. 2022;9:996844. doi:10.3389/fsurg.2022.996844
28. Fucà G, Guarini V, Antoniotti C, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the valentino and TRIBE first-line trials. *Br J Cancer*. 2020;123(3):403–409. doi:10.1038/s41416-020-0894-7
29. Sun G, Li Y, Peng Y, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2019;34(4):681–689. doi:10.1007/s00384-019-03241-1
30. Noh GT, Han J, Cho MS, et al. Impact of the prognostic nutritional index on the recovery and long-term oncologic outcome of patients with colorectal cancer. *J Cancer Res Clin Oncol*. 2017;143(7):1235–1242. doi:10.1007/s00432-017-2366-x
31. Ta TV, Nguyen QN, Chu HH, Truong VL, Vuong LD. RAS/RAF mutations and their associations with epigenetic alterations for distinct pathways in vietnamese colorectal cancer. *Pathol Res Pract*. 2020;216(4):152898. doi:10.1016/j.prp.2020.152898
32. Shi J, Liu T, Ge Y, et al. Cholesterol-modified prognostic nutritional index (CPNI) as an effective tool for assessing the nutrition status and predicting survival in patients with breast cancer. *BMC Med*. 2023;21(1):512. doi:10.1186/s12916-023-03225-7
33. Zhu K, Yan H, Wang R, et al. Mutations of KRAS and PIK3CA as independent predictors of distant metastases in colorectal cancer. *Med Oncol*. 2014;31(7):16. doi:10.1007/s12032-014-0016-6
34. Huang D, Sun W, Zhou Y, et al. Mutations of key driver genes in colorectal cancer progression and metastasis. *Cancer Metastasis Rev*. 2018;37(1):173–187. doi:10.1007/s10555-017-9726-5
35. Zeng J, Fan W, Li J, Wu G, Wu H. KRAS/NRAS mutations associated with distant metastasis and BRAF/PIK3CA mutations associated with poor tumor differentiation in colorectal cancer. *Int J Gen Med*. 2023;16:4109–4120. doi:10.2147/IJGM.S428580
36. Cheng B, Xu L, Zhang Y, et al. Correlation between NGS panel-based mutation results and clinical information in colorectal cancer patients. *Heliyon*. 2024;10(7):e29299. doi:10.1016/j.heliyon.2024.e29299
37. Vitiello PP, Cardone C, Martini G, et al. Receptor tyrosine kinase-dependent PI3K activation is an escape mechanism to vertical suppression of the EGFR/RAS/MAPK pathway in KRAS-mutated human colorectal cancer cell lines. *J Exp Clin Cancer Res*. 2019;38(1):41. doi:10.1186/s13046-019-1035-0
38. Bteich F, Mohammadi M, Li T, Bhat MA, Sofianidi A. Targeting KRAS in colorectal cancer: a bench to bedside review. *Int J Mol Sci*. 2023;24(15):12030. doi:10.3390/ijms241512030
39. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. *Signal Transduct Target Ther*. 2023;8(1):455. doi:10.1038/s41392-023-01705-z
40. Ma J, Shi Y, Lu Q, Huang D. F2RL3 regulates epithelial-mesenchymal transition and angiogenesis in gastric cancer through the Rap1/MAPK signaling pathway. *Front Biosci*. 2024;29(5):177. doi:10.31083/j.fbl2905177
41. Yoshimura A, Horinaka M. Epithelial-mesenchymal transition status is a remarkable biomarker for the combination treatment with avutometinib and defactinib in KRAS-mutated non-small cell lung cancer. *Br J Cancer*. 2024;131(2):361–371. doi:10.1038/s41416-024-02727-2
42. Xu M, Zhao X, Wen T, Qu X. Unveiling the role of KRAS in tumor immune microenvironment. *Biomed Pharmacother*. 2024;171:116058. doi:10.1016/j.biopha.2023.116058
43. Kim JK, Marco MR, Choi SH, et al. KRAS mutant rectal cancer cells interact with surrounding fibroblasts to deplete the extracellular matrix. *Mol Oncol*. 2021;15(10):2766–2781. doi:10.1002/1878-0261.12960
44. Müller S, Krishnamurty AT. One mutation to rule them all: mutant KRAS controls tumor intrinsic and microenvironment signaling. *Cancer Res*. 2024;84(1):6–8. doi:10.1158/0008-5472.CAN-23-3682
45. Yang M, Li D. TGF-β-induced FLRT3 attenuation is essential for cancer-associated fibroblast-mediated epithelial-mesenchymal transition in colorectal cancer. *Mol Cancer Res*. 2022;20(8):1247–1259. doi:10.1158/1541-7786.MCR-21-0924
46. Hsu WH, LaBella KA. Oncogenic KRAS drives lipofibrogenesis to promote angiogenesis and colon cancer progression. *Cancer Discov*. 2023;13(12):2652–2673. doi:10.1158/2159-8290.CD-22-1467
47. Lin G, Zheng XW, Li C, Chen Q, Ye YB. KRAS mutation and NF-κB activation indicates tolerance of chemotherapy and poor prognosis in colorectal cancer. *Dig Dis Sci*. 2012;57(9):2325–2333. doi:10.1007/s10620-012-2172-x
48. Kasprzak A. The role of tumor microenvironment cells in colorectal cancer (CRC) cachexia. *Int J Mol Sci*. 2021;22(4):1565. doi:10.3390/ijms22041565
49. Jo SY, Hong N, Lee S, et al. Genomic and transcriptomic profiling reveal molecular characteristics of parathyroid carcinoma. *Exp Mol Med*. 2023;55(5):886–897. doi:10.1038/s12276-023-00968-4
50. Emamalipour M, Shamdani S. The implications of the TNFα-TNFR2 immune checkpoint signaling pathway in cancer treatment: from immunoregulation to angiogenesis. *Int J Cancer*. 2025;156(1):7–19. doi:10.1002/ijc.35130
51. Tokumaru Y, Oshi M, Katsuta E, et al. KRAS signaling enriched triple negative breast cancer is associated with favorable tumor immune microenvironment and better survival. *Am J Cancer Res*. 2020;10(3):897–907. PMID: 32266098.
52. Checa J, Aran JM. Reactive oxygen species: drivers of physiological and pathological processes. *J Inflamm Res*. 2020;13:1057–1073. doi:10.2147/JIR.S275595
53. Liang L, Guo X, Ye W, Liu Y. KRAS gene mutation associated with grade of tumor budding and peripheral immunoinflammatory indices in patients with colorectal cancer. *Int J Gen Med*. 2024;17:4769–4780. doi:10.2147/IJGM.S487525
54. Xiong N, Han W, Yu Z. ABO blood type and pretreatment systemic inflammatory response index associated with lymph node metastasis in patients with breast cancer. *Int J Gen Med*. 2024;17:4823–4833. doi:10.2147/IJGM.S486873

55. Yeh CC, Kao HK. Discovering the clinical and prognostic role of pan-immune-inflammation values on oral cavity squamous cell carcinoma. *Cancers*. 2023;15(1):322. doi:10.3390/cancers15010322
56. Topkan E, Selek U, Ozturk D, Şenyürek Ş, Kılıç Durankuş N. Prognostic value of pre-chemoradiotherapy pan-immune-inflammation value (PIV) in locally advanced nasopharyngeal cancers. *Cancer Control*. 2024;31:10732748241290746. doi:10.1177/10732748241290746
57. Zhang N, Hou T, Zhang S, et al. Prognostic significance of pan-immune-inflammation value (PIV) in nasopharyngeal carcinoma patients. *Heliyon*. 2024;10(2):e24804. doi:10.1016/j.heliyon.2024.e24804
58. Liang C, Qin Y, Zhang B, et al. ARF6, induced by mutant Kras, promotes proliferation and Warburg effect in pancreatic cancer. *Cancer Lett*. 2017;388:303–311. doi:10.1016/j.canlet.2016.12.014
59. Wang F, Qi XM, Wertz R, Mortensen M. p38γ MAPK is essential for aerobic glycolysis and pancreatic tumorigenesis. *Cancer Res*. 2020;80 (16):3251–3264. doi:10.1158/0008-5472.CAN-19-3281
60. Bartolacci C, Andreani C. Targeting de novo lipogenesis and the Lands cycle induces ferroptosis in KRAS-mutant lung cancer. *Nat Commun*. 2022;13(1):4327. doi:10.1038/s41467-022-31963-4
61. Padanad MS, Konstantinidou G, Venkateswaran N, et al. Fatty acid oxidation mediated by Acyl-CoA synthetase long chain 3 is required for mutant KRAS lung tumorigenesis. *Cell Rep*. 2016;16(6):1614–1628. doi:10.1016/j.celrep.2016.07.009
62. Cortellino S, D'Angelo M, Quintiliani M, Giordano A. Cancer knocks you out by fasting: cachexia as a consequence of metabolic alterations in cancer. *J Cell Physiol*. 2025;240(1):e31417. doi:10.1002/jcp.31417
63. Shen X, Xiang M, Tang J, et al. Evaluation of peripheral blood inflammation indexes as prognostic markers for colorectal cancer metastasis. *Sci Rep*. 2024;14(1):20489. doi:10.1038/s41598-024-68150-y
64. Qiu J, Yu Y. Developing individualized follow-up strategies based on high-risk recurrence factors and dynamic risk assessment for locally advanced rectal cancer. *Cancer Med*. 2024;13(20):e70323. doi:10.1002/cam4.70323