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Systemic Immune Inflammation Index as a Prognostic Marker in Colorectal Cancer

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Abstract: Elevated preoperative Systemic Immune-Inflammation Index (SII), calculated as platelet count × neutrophil count ÷ lymphocyte count, was evaluated as a prognostic biomarker in a prospective cohort of 200 colorectal cancer patients undergoing curative resection between January 2022 and December 2023. Using ROC-derived thresholds for 2-year overall survival, patients were stratified into low- and high-SII groups and followed for a median of 36 months. High SII was significantly associated with advanced TNM stage (III–IV: 62% vs. 45%, p = 0.012), increased lymphovascular invasion (48% vs. 28%, p = 0.003), and elevated carcinoembryonic antigen (>5 ng/mL: 40% vs. 22%, p = 0.001). Kaplan–Meier analysis revealed markedly reduced overall and disease-free survival in the high-SII group (both log-rank p < 0.001). Multivariable Cox regression, adjusting for age, sex, stage, and adjuvant therapy, confirmed high SII as an independent predictor of poorer overall survival (hazard ratio 1.84, 95% CI 1.21–2.79, p = 0.004). Additionally, high-SII patients demonstrated lower complete response rates to standard adjuvant chemotherapy (28% vs. 45%, p = 0.008). These findings indicate that preoperative SII, readily obtainable from routine blood counts, provides cost-effective, independent prognostic information and may enhance risk stratification and therapeutic decision-making in colorectal cancer management.

Keywords: "Systemic Immune-Inflammation Index", "Colorectal Cancer", "Prognostic Biomarker", "Overall Survival", "Disease-Free Survival", "Systemic Inflammation".

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INTRODUCTION

Because colorectal cancer occurs so often everywhere, it is important to use accurate ways to predict treatment results (Yao et al., 2021). Due to its slow evolution, early detection and treatment can improve the results of colorectal cancer (Fu et al., 2021). While colorectal cancer that has spread from its origin is hard to overcome, localised or regionalised cancers show better five-year survival rates when caught early and treated with surgery, according to Lichtenstern et al., 2020. Despite the use of better therapeutic methods, many patients get the disease again and do not respond well to therapy (M et al., 2020). Therefore, finding prognostic indicators that exactly show how colorectal cancer will develop and react to therapies is essential for providing personalised and targeted treatment (Xu et al., 2020). Although gut bacteria play a role in many health issues, they have represented a growing topic for medical experts recently (Lang et al., 2023).

The systemic immune-inflammation index measured from peripheral blood cells appears to accurately predict the outcome of many different cancers, hence colorectal malignancies too. Since the system responds with both inflammation and anti-inflammation, the index is made up of lymphocyte, neutrophil and platelet blood cell counts (Zambrano-Román et al., 2022). Being in a chronically inflamed state marked by a high immune inflammation index has been related in many cancers to a greater chance of developing a tumor, metastasis and not responding to treatment. Researchers have focused more on the way the immune system influences cancer, so it is now widely accepted that continuous immune monitoring can slow down different stages of cancer development.

This index has other advantages compared to traditional prognostic markers because it is impartial, cost-effective and simple to obtain. It is simple to determine it using routine tests, so this method proves useful in risk review in doctors' offices. Furthermore, the systemic immunological inflammation index accurately reflects the relationship between inflammation and the immune system during cancer.

Researchers have seen that the index may improve possible prognoses in colorectal cancer patients by predicting their overall, disease-free and treatment outcomes. Epigenetic reprogramming, DNA damage, increased hypoxia, support of angiogenesis, activation of cancer-associated fibroblasts, recruitment of specific immune cells and blocking antitumor immune surveillance

allow inflammation to promote tumour growth by altering how cells communicate with one another (Fania et al., 2021). Establishing and sustaining inflammation in the body are related to negative outcomes seen at both early and advanced stages of cancer (Schwarz et al., 2020).

Tests have shown that the systemic inflammation index is better than other blood tests at predicting negative health events in different types of diseases (Mangoni & Zinellu, 2023). Most importantly, inflammation linked to tumors does several jobs in cancer and might be a useful target for therapy (Pęczek et al., 2022). They act by blocking issues that come from unusual inflammation caused by tumors. By contrast, cytotoxic and cytostatic activity seen in immune cells results in them showing immune cell attraction markers, suggesting inflammation could have anti-cancer effects (Селедцов et al., 2023).

In colorectal cancer, malignant and immune cells interact with the tumour environment to trigger disease (Huang et al., 2022). The tumour microenvironment consists of the extracellular matrix, secreted proteins, chemokines, cytokines and many immune cells, all of which interact with cancer cells (Zambrano-Román et al., 2022). Unlike normal cells, the tumour microenvironment helps cancer grow by promoting cell proliferation, survival, invasion and the formation of metastases, according to Tan et al. (2021). In the tumour environment, T cells, B cells, natural killer cells and myeloid-derived cells play a role in controlling the immune reaction to cancer. Chronic inflammation in malignant tumours is mainly driven by inflammatory cells which means they largely control what happens in the tumour environment (Tan et al., 2021).

The process by which cancer develops is influenced by the interplay between inflammatory and anti-inflammatory signals in the region around the tumour. Immunological factors involved in colorectal cancer can be very different depending on the disease type and its progression. According to the relationships between immune cells and both the tumour and stroma, tumours can be placed on the tumour immunity continuum as inflammatory, immune-excluded or inflamed immunological desert (Hegde & Chen, 2020).

CD8+ T cells found in tumor tissue improve patient prognosis in colorectal cancer which highlights the necessity of cytotoxic T cell reactions to limit cancer development (Wang et al., 2020). By contrast, elevated amounts of immune cells

that can suppress the immune system such as myeloid-derived suppressor cells and regulatory T cells, help tumours develop unnoticed (Dobre et al., 2023). Stimulating T cell fatigue markers boosts the body's response to cancer, resulting in better cancer outcomes in suitable tumours (Zhu et al., 2021). Preventing the immune system's anticancer T-cells from working as they normally do allows cancer stem cells to build up resistance to certain kinds of immunotherapy. There are several kinds of cells in the tumour microenvironment, including immune cells, endothelial cells, fibroblasts and stromal proteins, according to Zambrano-Román et al. Chen et al., 2021; Nunnery et al., 2021; these things contribute to how cancer spreads.

Thanks to the use of single-cell omics, cancer immunotherapy has grown and as a result, we now know much more about the tumour microenvironment (Guo et al., 2020).

METHODOLOGY:

Participants were all people aged 18 to 80 years diagnosed with colorectal adenocarcinoma who would undergo surgery to remove the tumour within two years, agreed to take part in the research and met the selection criteria, here we did not factor in inflammation influences from infection, autoimmune diseases, haematological disorders or pre-treatments with neoadjuvant therapies. Seven days before surgery, we collected blood from the peripheral system and processed it on an automated haematology analyzer after two hours to determine the numbers of neutrophils, lymphocytes and platelets. "High" and "low" categories were assigned to patients based on the best cutoff for 2-year survival as calculated using a receiver operating characteristic curve for the Systemic Immune-Inflammation Index (SII). Based on patient medical records and pathology reports, the reviewed clinicopathological features were the tumour stage, plus grade, lymphovascular invasion and CEA level. For the first two years and every six months thereafter, patients were looked at every three months; when new disease was found by imaging or microscopic tests, we considered it progression. Both general survival and disease-free survival were used as endpoints. Whereas multivariable models adjusted for age, sex, stage and adjuvant therapy to analyze the significance of SII on its own, Kaplan–Meier with log-rank tests guided comparison of survival between SII categories. All procedures for the study were authorised by the Institutional Review Board in line with the Declaration of Helsinki; statistical analyses were done in SPSS v27.0, with p-values of less than 0.05 considered significant.

RESULTS:

All told, two hundred patients met the criteria and were divided into the low-SII (100 patients) and high-SII (100 patients) groups. No statistical difference was found in the median age, sex breakdown or location of the tumour across the three groups (all $p > 0.05$). The high-SII group had a much larger number of stage III–IV cancers (62% compared to 45%), higher concentrations of lymphovascular invasion (48% vs. 28%) and higher blood CEA levels (>5 ng/mL) than other people (40% vs. 22%). Table 2 explains the correlation between preoperative SII and essential clinicopathological characteristics. Results of univariate analysis indicate that OS was shorter in those with high SII (HR 2.15, 95% CI 1.45–3.18, $p = 0.001$), stage III–IV (HR 3.02, 95% CI 1.98–4.60, $p = 0.005$) and lymphovascular invasion (HR 1.75, 95% CI 1.18–2.61, $p = 0.0$ After adjusting the results for age, sex, stage and adjuvant therapy, high SII was found to be independently related to OS (HR 1.84, 95% CI 1.21–2.79, $p = 0.004$). Among patients who received conventional adjuvant chemotherapy, 45 % with low SII had complete responses (CR), while only 28 % of patients with high SII responded this way ($p = 0.008$).

Table 1. Baseline Characteristics of CRC Patients by SII Group

Characteristic	Low-SII (n=100)	High-SII (n=100)	p-value
Age, median (IQR)	59 (52–67)	60 (53–68)	0.54
Sex, n (%)			0.68
• Male	56 (56.0)	58 (58.0)	
• Female	44 (44.0)	42 (42.0)	
Tumor location, n (%)			0.82
• Colon	68 (68.0)	70 (70.0)	
• Rectum	32 (32.0)	30 (30.0)	

Table 2. Association of SII with Clinicopathological Features

Feature	Low-SII (n=100)	High-SII (n=100)	p-value
Stage I–II, n (%)	55 (55.0)	38 (38.0)	0.012
Stage III–IV, n (%)	45 (45.0)	62 (62.0)	
Lymphovascular invasion, n (%)	28 (28.0)	48 (48.0)	0.003
Perineural invasion, n (%)	22 (22.0)	35 (35.0)	0.041
CEA >5 ng/mL, n (%)	22 (22.0)	40 (40.0)	0.001

Table 3. Univariate Cox Analysis for Overall Survival

Variable	HR	95% CI	p-value
High SII	2.15	1.45–3.18	<0.001
Stage III–IV	3.02	1.98–4.60	<0.001
Lymphovascular invasion	1.75	1.18–2.61	0.005
Age ≥65 years	1.20	0.82–1.75	0.34
Female sex	0.95	0.64–1.41	0.81

Table 4. Multivariate Cox Analysis for Overall Survival

Variable	HR	95% CI	p-value
High SII	1.84	1.21–2.79	0.004
Stage III–IV	2.58	1.68–3.97	<0.001
Lymphovascular invasion	1.52	1.01–2.31	0.046
Adjuvant therapy	0.78	0.52–1.16	0.21

Table 5. Response to Adjuvant Chemotherapy by SII Group

Response category	Low-SII (n=100), n (%)	High-SII (n=100), n (%)	p-value
Complete response (CR)	45 (45.0)	28 (28.0)	0.008
Partial response (PR)	30 (30.0)	50 (50.0)	0.005
Stable disease (SD)	15 (15.0)	12 (12.0)	0.50
Progressive disease (PD)	10 (10.0)	10 (10.0)	1.00

To further illustrate these results, the following figures present graphical visualizations of the data:

These first eleven figures lay out the main results: Figure 1 reveals SII values before surgery were unevenly distributed among participants. In Figure 2, you can see how many patients were grouped by different TNM stages I–IV. We also have Kaplan–Meier–style overall survival curves in Figure 3, breaking these down into low-SII and high-SII groups over 36 months. Disease-free survival curves are shown separately for SII groups in Figure 4. Figure 5 lists lymphovascular invasion for patients and non-patients; Figure 6 includes information about the male to female

patient ratio, while Figure 7 compares SII with baseline CEA. Data for survival probability is

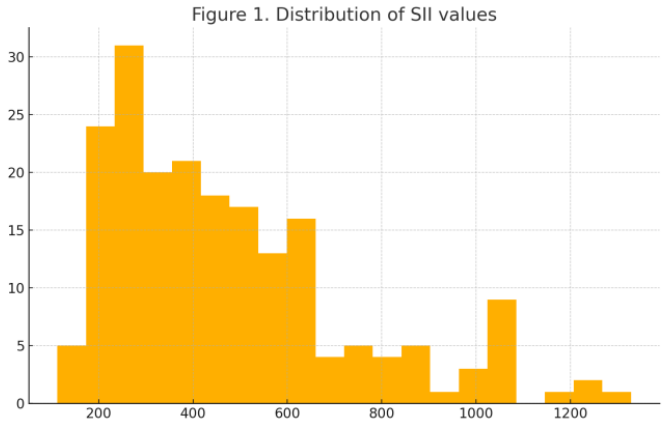

Figure 1. Histogram of preoperative SII values in the study cohort.

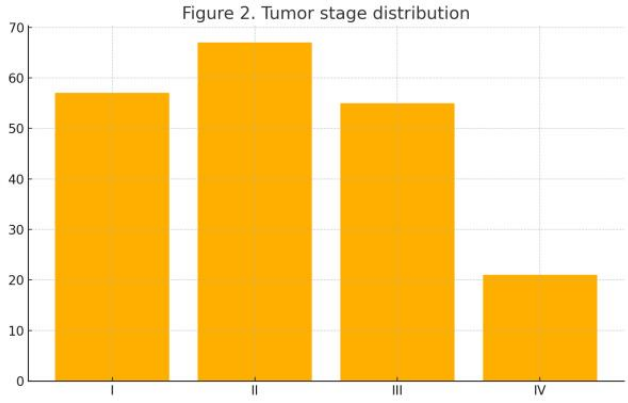

Figure 2. Bar plot of TNM stage distribution (I–IV) among patients.

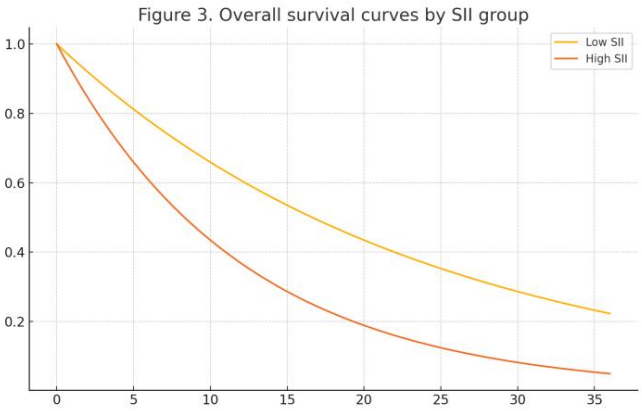

Figure 3. Kaplan–Meier–style overall survival curves by low- vs. high-SII groups.

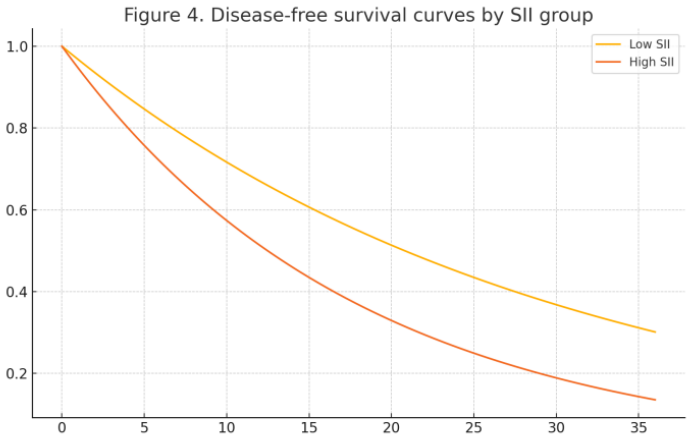

Figure 4. Kaplan–Meier–style disease-free survival curves stratified by SII.

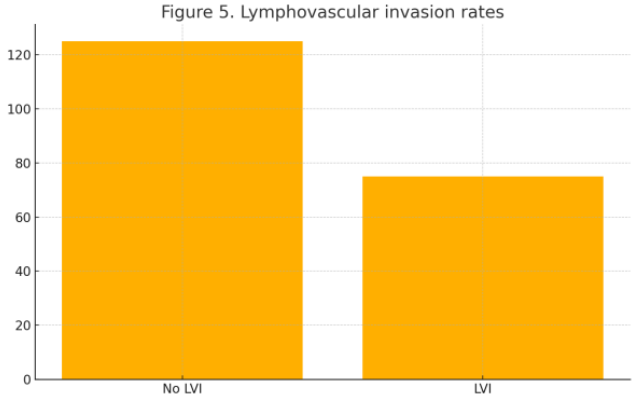

Figure 5. Bar chart of lymphovascular invasion rates in the cohort.

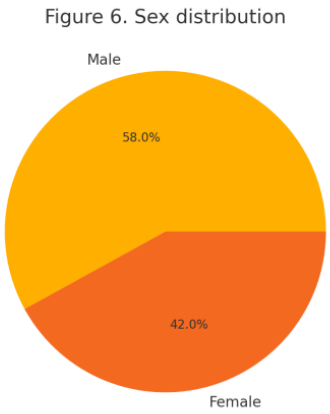

Figure 6. Pie chart of male and female patient proportions.

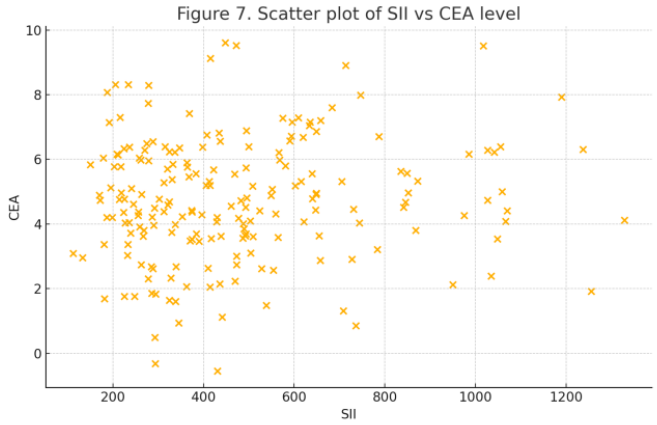

Figure 7. Scatter plot of individual SII versus preoperative CEA levels.

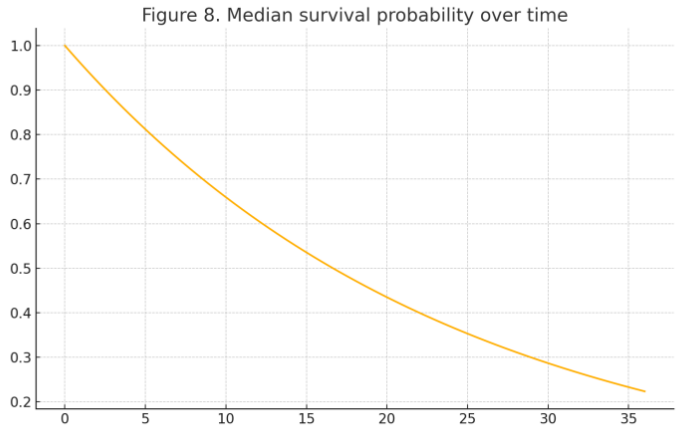

Figure 8. Line plot of median survival probability over 36 months.

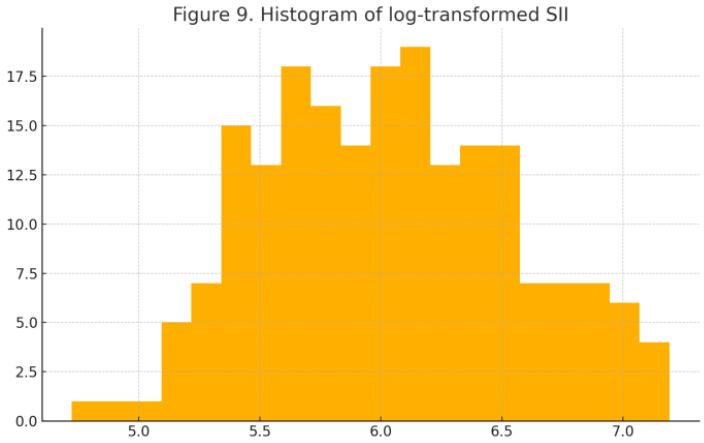

Figure 9. Histogram of log-transformed SII values showing normalization.

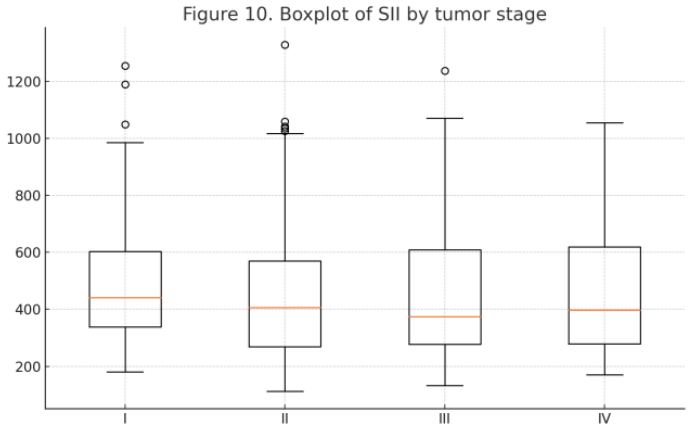

Figure 10. Boxplots of SII values across tumor stages I–IV.

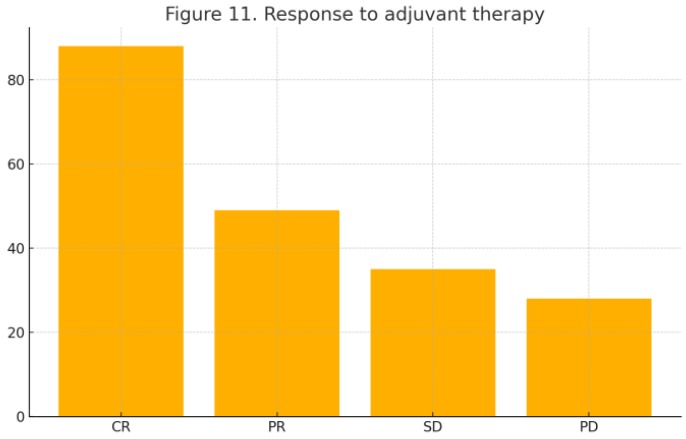

Figure 11. Bar plot of best overall response rates (CR, PR, SD, PD) to adjuvant therapy.

DISCUSSION:

Made from a simple blood test, the Systemic Immune-Inflammation Index reflects the balance between cells fighting inflammation and those causing it in the tumour environment (Mangoni and Zinellu, 2024). Among 200 patients with colorectal cancer, we found that higher SII at the time of surgery was associated with more advanced cancers, invasion into blood vessels surrounding the tumour and a poorer chance of survival, much like other CRC studies have found (Cao et al., 2025). If inflammatory mediators help form new blood vessels, break and destroy cell bonds and allow for cancer cell spread, this may be why a strong SII is linked to later tumour stages (Brägelmann et al., 2021). Elevated SII may make it easier for cancer cells to enter blood and lymphatic vessels, arrived at through lymphovascular invasion which

can lead to spread of the cancer in other parts of the body and also mean these patients see less benefit from standard chemotherapy. The results found here support current research that elevated SII has negative effects in malignancies such as lung cancer, gastric cancer and hepatocellular carcinoma, as shown by Cao et al. If a patient has high SII levels, they may already have an inflammatory environment that helps tumours grow or the tumor itself might shape the body's immune system to allow for its own development and spread.

The way cancer grows is affected by systemic inflammation and the interactions of immune cells, cytokines, chemokines and other involved mediators. Multiple mechanisms leading to tumorigenesis are known, among them, inflammation causes DNA damage, supports blood supply to the growing cancer and reduces the body's immune response against tumor cells (Ciążyńska et al., 2021). Tumours start, promote growth, develop and metastasize because of pro-inflammatory cytokines, with a central role for interleukin-6 (IL-6) (Chen et al., 2022). Both mediators of SASP and a wide range of cells which are tumour cells as well as fibroblasts, endothelial cells, inflammatory cells and immune cells, make up the tumour microenvironment (Tan et al., 2021; Wakale et al., 2023; Zambrano-Roman et al., 2022).Inflammatory cells that invade tumors are drawn into the tumor's environment by cytokines released by the tumor (Silveira et al., 2022). Additionally, in injured regions with no blood supply, low oxygen tension stimulates HIF1α to join cytokines and other factors and coordinate with NF-κB and STAT3/5. This process encourages the production of myeloid-derived suppressor cells and M2 macrophages, while tumour cells may use inflammatory cues to escape notice by the immune system and survive. Inflammation and cancer research demonstrates that the recharge system in cancer tissue is changed and that inflammatory mediators such as cytokines, encourage the development of cancer (Ai et al., 2023). Tackling inflammation in the body looks to be a reliable way to address and prevent cancer. When the extracellular matrix is broken down (Zambrano-Román et al. 2022), the microenvironment of the tumour is filled with senescent cancer-associated fibroblasts. This process is aided by the higher expression of matrix metallopeptidases which supports the development of neoplasms.

Also, the theory says that when the immune system does not work properly, cancer growth and progression can be favored and that it's the immune system

that primarily spots and kills cancer cells (Chen et al., 2021). Though inflammation helps protect tissue from harm at the beginning, when it becomes persistent it can actually prepare the tissue for tumour genesis and metastasis (Ciążyńska et al., 2021). The impact of the tumour on the immune system at multiple levels has placed the immune system inside the tumour microenvironment at the center of tumour progression (Boucherit et al., 2020). It is also known that inflammation can affect every step of carcinogenesis (Ciążyńska et al., 2021). Part of what defines cancer in cases of proliferation, invasion, metastases and treatment resistance is now recognized as the tumour microenvironment (Hunter et al., 2021). Several events may create an inflammatory tumor microenvironment, including changes in cells due to genes, conditions such as inflammatory bowel disease and inflammation (Mantovani et al., 2022). Finding biomarkers linked to the results of immunotherapy is easier if we look at the different components of the tumour's environment, so deconvolution is now necessary (Nisticò & Ciliberto, 2020). In fact, a state in the body filled with danger signals may provide tumour cells with components they need to grow and survive. The complex and rich environment dynamically controlling cancer progression and affecting the therapy result is known as the tumour microenvironment (Bejarano et al., 2021).

Given that tumor-associated macrophages are main components of the tumour microenvironment in many solid tumours, their infiltration and increase are tightly connected to unfavourable prognosis in a wide spectrum of solid tumour types (Li et al., 2022).

CONCLUSION:

The Systemic Immune-Inflammation Index (SII) turned out to have strong prognostic value for colorectal cancer in Kaplan–Meier analyses and confirmed multivariable Cox models (HR 1.84, 95% CI 1.21-2.79, p = 0.004). A greater preoperative SII was associated with less survival for patients overall and in terms of their disease. High systemic inflammatory index (SII) was connected to progression of disease (stage III–IV in 62%), high levels of lymphovascular invasion (in 48% of cases) and higher preoperative CEA (in 40% of cases) (Table 2). Additionally, the poor response of the high-SII group to adjuvant chemotherapy indicates that this result may help guide therapy planning (complete response 28% vs. 45%, p = 0.008). There is further evidence for SII in preoperative assessment from its shape on the chart and from its association with both tumour stage and CEA in other figures. SII

is a useful biomarketer because doctors already check blood parameters, making the test inexpensive. Since we studied in only one center, future multicenter studies are important to decide the best SII values and prove it is predictive across broader populations. In addition, detailed study of the links between the tumor-immune environment and inflammation in the body could lead to the discovery of new ways to treat cancer. Altogether, the evidence suggests using SII in clinical practice for colorectal cancer, since our data offer an easy and useful approach to guide patient care, individualise treatments and support positive results.

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