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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Are preoperative inflammatory and nutritional markers important for the prognosis of patients with peritoneal metastasis of colorectal cancer?

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Abstract

Colorectal cancer (CRC) is a type of cancer that grows from polypoid lesions developing over the years. It has a high incidence of about 1.8 million new cases annually. While screening and lifestyle modifications have stabilized the rate of CRC in high-income countries, the incidence of early-onset CRC is increasing globally. The worst prognosis for this cancer is linked to recurrence and metastasis, with peritoneal metastasis occurring in 8% to 20% of cases. In these cases, treatment with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is indicated. However, this approach is risky and requires careful selection of patients who will truly benefit from it. This article will discuss the correlation between nutrition and inflammation in patients with peritoneal metastasis and advanced CRC, emphasizing the importance of nutritional and inflammatory markers for assessing disease status. Finally, we will highlight the main biomarkers in the field.

Key Words: Colorectal cancer; Peritoneal metastasis; Inflammation; Nutrition; Biomarkers; Prognosis

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Core Tip: In this study, the clinical data of patients with colorectal cancer (CRC) from a single center were retrospectively analyzed. A high neutrophil-to-lymphocyte ratio and low hemoglobin levels were independent predictive risk factors for poor prognosis in patients with peritoneal metastasis (PM) of CRC. The established nomogram including CA 19-9 levels and patient age accurately predicted the overall survival of patients having PM, indicating its usefulness as a valuable prognostic tool for this patient cohort.

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TO THE EDITOR

In this letter, we comment on the interesting article published by Wu *et al*[1] addressing the association between preoperative inflammatory biomarkers and prognosis in patients with colorectal cancer (CRC) with peritoneal metastasis (PM). CRC accounts for approximately 10% of diagnosed cancers[2], with about 1.8 million new cases annually[3]. Its risk factors include increasing age, a positive family history of the disease, hereditary diseases such as Lynch Syndrome, and long-standing inflammatory bowel disease among others[2]. Adherence to screening and disease tracking as well as lifestyle changes have helped stabilize the incidence of CRC in high-income countries[4]. However, over the last several decades, the incidence of early-onset CRC (*i.e.* in patients under the age of 50 years) has increased worldwide[3]. CRC develops from polypoid lesions with malignant potential over 10 years to 15 years. These lesions can occur *via* distinct pathways: the adenoma-carcinoma sequence (70%-90% of cases) and the serrated neoplasia pathway (10%-20% of cases) [3]. CRC can be classified into four consensus molecular subtypes (CMS), which offer a feasible prognostic framework: immune (CMS1), canonical (CMS2), metabolic (CMS3), and mesenchymal (CMS4), although these have not yet been validated as predictive biomarkers. Right-sided CRC is often associated with poorer survival outcomes[2]. Approximately half of the patients with CRC are diagnosed at an advanced stage, with distant metastases already present. The liver and lungs are the most common metastatic sites[3,5]. PM is a common site of recurrence and is associated with worse survival outcomes[6]. For a long time, CRC with PM was considered a terminal stage of the disease. However, the introduction of Sugarbaker's treatment, combining peritonectomy and hyperthermal intraperitoneal chemotherapy (HIPEC), has offered a treatment option for PM, considering systemic chemotherapy is often ineffective for these cases[3, 6]. Although PM can be asymptomatic, severe symptoms such as ascites and intestinal obstruction can occur[6]. Therefore, timely disease staging at diagnosis is critical to assess tumor burden and disease severity, enabling early implementation of therapies such as peritonectomy and HIPEC that can improve the patient's prognosis. At this stage, preoperative assessments, including scores and markers of inflammatory and nutritional status through blood tests, can help identify patients who are most likely to benefit from these treatment strategies[3].

Case series

The article by Wu *et al*[1] describes a retrospective study evaluating 133 patients (66.9% male) from the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) diagnosed with CRC with PM. Each patient underwent assessment for combined treatment with cytoreductive surgery (CRS) followed by HIPEC. This treatment has been reported to offer improved survival outcomes. However, its complexity is associated with high morbidity. Therefore, careful patient selection is crucial for optimizing the success of this procedure (Table 1). Although there are prognostic scoring systems for patients with PM, they rely on intraoperative or postoperative data (Table 2). Therefore, preoperative clinical assessment may also help identify subgroups of more vulnerable patients[1]. In this context, Wu *et al*[1] aimed to evaluate inflammatory and nutritional markers as prognostic factors in preoperative assessments. Among the markers they examined were the neutrophil-to-lymphocyte ratio (NLR) and hemoglobin (Hb). Neutrophils were evaluated because they are a crucial part of white blood cells that contribute to remodeling the cellular matrix to promote tumor growth. Previous data have shown that elevated NLR is associated with poorer overall survival in various cancer types[7]. In this study, about 40% of patients exhibited a high NLR and had an inferior median overall survival (mOS) of 7.9 months. In contrast, those with a low NLR had an average mOS of 17.5 months. Additionally, patients with normal Hb levels had an mOS that was 12.2 months longer compared to those with low Hb levels[1]. These markers were also significantly associated with the success of CRS and albumin levels. Therefore, this study concluded that high NLR and low Hb are independent prognostic risk factors. Furthermore, a nomogram with these biomarkers, along with patient age, CA 19-9 levels, and the peritoneal cancer index was validated to predict 1-year and 2-year survival probabilities[1].

For the discussion, in July 2024, we searched PubMed for pertinent articles, using various combinations of the search terms "peritoneal carcinomatosis," "colorectal cancer," "inflammatory markers," "nutritional markers," "cytoreductive surgery," "anemia," and "albumin." The articles most relevant to the purpose of this study have been reviewed and discussed below.

Discussion

Despite advances in various approaches, including surgery, chemotherapy, and radiotherapy, mortality rates for CRC

Table 1 Summary of the results found in the original article

Parameter	<i>n</i> among 133 patients	Most common age in years	Most common sex	Normal albumin, \geq 35 g/L	Tumor most prevalent location	Most common histology	Number of patients with CC 0/1 ¹	Number of patients treated with HIPEC ²
High NLR	54 (40.6)	\geq 60 (54.1)	Men	46 (85.1)	Left side of the colon	Adenocarcinoma	30 (55.6)	16 (29.6)
Low NLR	79 (59.4)			53 (67.1)			27 (34.1)	19 (24.1)
Normal Hb	94 (70.7)	< 60 (58.5)		78 (82.9)			49 (52.1)	29 (30.8)
Low Hb	39 (29.3)	\geq 60 (64.1)		21 (53.9)			8 (20.5)	6 (15.3)

Data are *n* (%).

¹Patients with cytoreduction scores of 0 or 1 were considered eligible for hyperthermal intraperitoneal chemotherapy.

²Among the patients pre-selected for hyperthermal intraperitoneal chemotherapy, only those deemed capable of tolerating the procedure received the treatment.

CC: Cytoreduction; Hb: Hemoglobin; HIPEC: Hyperthermal intraperitoneal chemotherapy; NLR: Neutrophil-to-lymphocyte ratio.

Table 2 Clinical relevance of the association between neutrophil-to-lymphocyte ratio, hemoglobin, and colorectal cancer prognosis

Parameter	High NLR	Low Hb
Clinical associated factors	Higher secretion of chemokines and inflammatory cytokines	Anemia and iron losses (bleeding, ingestion and absorption deficiency)
Clinical outcomes	Suppression of apoptosis, increased proliferation, migration, and invasion of tumor cells, and organ dysfunction	Reduced erythropoiesis, low iron release, cachexia
Number of patients admitted with CRC-PM (poor prognosis)	40.6% (54/133)	70.6% (94/133)

CRC: Colorectal cancer; Hb: Hemoglobin; NLR: Neutrophil-to-lymphocyte ratio.

with PM remain high[1]. Therefore, carefully selecting patients who may benefit from intensive treatments is necessary [5]. In this group, screening patients eligible for CRS and HIPEC is important to weigh the risks of the treatment against potential survival benefits. Therefore, the decision to proceed should be based on biomarkers capable of predicting unfavorable prognoses[8,9]. The evaluation of patients who may be candidates for CRS and HIPEC includes scores like the PCI and Peritoneal Surface Disease Severity Score, the latter of which also incorporates clinical factors. Considering that cancer-related systemic inflammatory and nutritional responses are often linked to tumor progression, measuring these biological markers could be important for predicting negative outcomes that influence patient survival after treatment[3,5]. Patients with metastatic disease have a significantly higher likelihood of dying compared to those with non-metastatic cancer. Nonetheless, the factors determining cancer mortality are complex and involve the dysfunction of various interconnected systems in the body[1]. Metastatic cancer is associated with the dysfunction of multiple organ systems. This occurs due to the intense activation of local and systemic inflammatory pathways, as well as tissue repair and immunosuppressive mechanisms[10]. Chronic inflammation leads to a persistent leukocyte infiltrate that causes pathological inflammation, resulting in tissue damage and an increase in mutagenic agents. This creates an environment conducive to dysplasia and tumor proliferation[11]. In this context, inflammation markers detectable through blood tests can assess the prognosis of patients[5,7]. Neutrophils secrete chemokines and inflammatory cytokines that contribute to cancer development and organ dysfunction[5]. As a result, there is suppression of apoptosis and increased proliferation, migration, and invasion of tumor cells[11]. In contrast, lymphocytes are involved in the cytotoxic immune response to cancer through cell-mediated immunity[5,8,12]. In summary, serum inflammation markers can be divided into upregulators (neutrophils, platelets, and C-reactive protein [CRP]) and downregulators (lymphocytes). The comparative relationship between their values enables the assessment of the patient's inflammatory prognosis. Commonly used ratios include the NLR, lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and lymphocyte-CRP ratio. Other scores that are evaluated include the Glasgow prognostic score (GPS), which evaluates serum levels of CRP and albumin, the Systemic Inflammation Score (SIS), which correlates serum albumin levels with LMR, and the Prognostic Nutritional Index (PNI)[5,7,8]. These biomarkers provide a general assessment of the patient and are potential predictive tools for inflammation indices and deterioration in the performance of patients with cancer. NLR and PLR are markers of systemic inflammation related to toxicity and thrombocytosis, respectively, and their prognostic value for various types of cancer, along with their ease of calculation, make them useful measures for assessing inflammatory status in clinical practice. Similarly, markers related to the measurement of monocyte quantities (such as the LMR) also reflect inflammatory activity. Additionally, GPS, SIS, and PNI scores propose a combination of these defense cell indices with other established laboratory markers of inflammation and nutrition (such as CRP and albumin). Therefore, they allow for clinical comparison of predictive performance for patient prognosis. Since these immune status coefficients are known to be correlated with prognostic outcomes, they can be explored as possibly associated with patient risk stratification.

Owing to the differing roles of neutrophils and lymphocytes in tumor development, the NLR has become a robust prognostic marker. A high NLR is associated with poorer overall survival and recurrence-free survival. Monocytes differentiate into tumor-associated macrophages, creating a favorable tumor microenvironment. Therefore, a low LMR, due to increased monocyte count relative to lymphocytes, is linked to poorer prognosis[5,7,8]. Since CRP is an inflammation marker, a low lymphocyte-CRP ratio can also be a sensitive biomarker for adverse outcomes. Finally, platelet release factors (such as vascular endothelial growth factor, transforming growth factor beta, and platelet-derived growth factor) contribute to inflammation and tumorigenesis[7]. A high platelet count (high PLR) also suggests a poorer prognosis[5,7,12].

Two other markers have been proposed for the concurrent evaluation of different immune cells: the systemic immune-inflammation index (SII) and, more recently, the systemic inflammation response index (SIRI). Both scores assess neutrophils and lymphocytes, but the SII also considers platelet count, while the SIRI includes monocyte count. A high SII value indicates neutrophilia and thrombocytosis (pro-tumor cells) along with lymphopenia (anti-tumor cells), indicating a pro-tumor inflammatory state and a weakened immune surveillance. Therefore, high systemic inflammation measured by the SII is a marker of poor outcome[9]. This index has been proposed as having better prognostic performance compared to NLR and PLR[5]. Conversely, a high SIRI value driven by monocytosis allows for the assessment of a favorable tumor microenvironment. However, it remains a less extensively studied marker in CRC. In summary, these markers indicate a decreased immune response against the tumor or an increased likelihood of tumor dissemination or recurrence[9].

A meta-analysis published in 2024 gathered data from studies aiming to validate the prognostic significance of both scores in CRC. Elevated levels of both SII and SIRI were associated with worse overall survival. However, the validation of these scores as prognostic predictors may still be inconsistent and vary for metastatic CRC, primarily depending on the location of the metastasis (especially considering the inflammatory characteristics of peritoneal carcinomatosis), patient heterogeneity, and the different treatments used, including decisions related to CRS and HIPEC[9].

The presence of metastatic disease is related to increased metabolic demands on the body. The combination of increased catabolism and energy expenditure, along with decreased caloric intake in patients with metastatic cancer, culminates in cachexia and sarcopenia, which are complex nutrient loss syndromes[10]. Caloric deficits induced by oncological treatments may also contribute to nutritional and immunological impairment. Therefore, this nutritional deficiency is multifactorial. In addition to being associated with the propensity of the metastatic tumor environment, elevated levels of cytokines, such as tumor necrosis factor and interleukins 1 and 6, also influence this nutritional loss. Conversely, altered metabolism also contributes to the immune dysfunction observed in some cancer patients[10]. The association between immune and inflammatory markers is widely studied. The Hb, albumin, lymphocyte, and platelet score has emerged as a biomarker that integrates routinely collected indicators for various types of cancer, including CRC [12]. Although it is still largely theoretical and research-focused, it is worth noting that it proposes the combined use of markers known to be related to cancer prognosis. This suggests that these markers should indeed be incorporated into the prognosis of overall survival, progression-free survival, and disease recurrence[12]. Albumin, a protein that decreases in both malnutrition and cases of exacerbated inflammation secondary to cancer, is particularly significant. Therefore, hypoalbuminemia is associated with a poor prognosis in patients with cancer[5].

As previously mentioned, the GPS, SIS, and PNI scores associate inflammatory markers with albumin to predict outcomes in patients with CRC with PM. A high GPS reflects both systemic inflammation (elevated CRP) and poor nutritional status (hypoalbuminemia)[5,12]. A high SIS indicates a worse prognosis as it corresponds to low albumin levels. Finally, in advanced tumors, a decreased PNI may predict poor patient status and the occurrence of postoperative complications[5]. Chronic disease-associated anemia is a well-recognized condition in patients with cancer. The release of inflammatory cytokines affects erythropoiesis, increases hepcidin secretion, and reduces iron release. In gastrointestinal cancers (including CRC), deficiencies in intake, absorption, and blood loss can also lead to anemia. Therefore, anemia is often present in both acute and advanced stages of cancer and serves as an important marker in patients with advanced CRC[12,13]. Additionally, anemia and hypoalbuminemia, commonly seen in cancer-related malnutrition, often accompany cachexia. Therefore, Hb becomes an important marker of the patient's nutritional status, crucial for clinical assessment. Several studies have evaluated the Hb, albumin, lymphocyte, and platelet score in patients with CRC. These assessments were both prospective and retrospective, aiming to predict patient survival after curative surgery. The results indicated that a higher Hb, albumin, lymphocyte, and platelet score was a statistically significant predictor of better survival outcomes[12]. Although this marker requires further investigation before being incorporated into clinical practice, these findings suggest the importance of integrating nutritional and immunological biomarkers into the preoperative assessment of patients with CRC, especially those with metastatic disease. However, the exact association between these markers and their cutoff values still needs to be better established[3]. Considering the high incidence of CRC, the selection of patients who will benefit from surgical intervention must be meticulous. Therefore, incorporating biological biomarkers (such as NLR and Hb) into disease status assessment scores is of great importance and aligns with the current understanding of their prognostic value.

Conclusion

The study presented by Wu *et al*[1] is relevant as it reiterates the importance of using nutritional and inflammatory markers as predictors of prognosis in patients with CRC and PM who undergo CRS and HIPEC.

Future directions

Despite the various biomarkers mentioned, solid clinical evidence to establish their use as robust prognostic markers for CRC remains limited. Randomized clinical trials are still needed to more conclusively test and validate these markers in the literature. At present, most studies rely on retrospective assessments of patients with CRC and PM and are therefore

subject to biases related to the progression of the disease and the impact of external factors, such as chronic inflammation and organ failure. Recent studies have focused on elucidating ctDNA, which are fragments of DNA released by tumor cells, as a promising prognostic biomarker for CRC, particularly in cases with PM. Peritoneal fluid biopsy shows a strong resemblance to tissue biopsies and generally has a high mutation detection rate. Moreover, there is a well-known significant association between the detection of ctDNA, and disease recurrence and poorer prognosis. Therefore, detecting ctDNA in primary or metastatic sites of peritoneal disease could serve as a complementary prognostic surveillance tool to clinical markers. It could also assist in predicting responses to immunotherapy, detecting recurrence, or uncovering associated systemic disease[14]. However, detecting ctDNA in primary or metastatic sites of peritoneal disease remains complex and has variable sensitivity. It is also crucial to determine whether this biomarker, along with other biomarkers, has robust evidence to predict poor outcomes and guide early interventions. Considering the ongoing efforts to improve treatments for disease progression, address residual disease, and enhance oncological outcomes, there is a strong rationale to focus on establishing reliable prognostic markers[14].

FOOTNOTES

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