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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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EDITORIAL

Is nutritional status a new indicator to use in clinical practice for colorectal cancer patients?

Rossana Berardi, Rebecca Chiariotti, Giulia Mentrasti

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Abstract

In this editorial we comment on the interesting article by Liu *et al*. The topic of discussion is the need for a cost-effective and easy-to-use scoring system for predicting the prognosis of colorectal cancer patients. In this context, nutritional assessment plays a crucial role in the multimodal evaluation of patients. In particular, the controlling nutritional status score was found to be an effective tool in the clinical decision-making process, in order to customize treatment strategies and to improve patient outcomes.

Key Words: Controlling nutritional status score; Colorectal cancer; Nutritional status; Clinical outcome; Nutritional biomarkers; Tailored-medicine; Personalized therapies

Core Tip: The controlling nutritional status (CONUT) score is significantly associated with the prognosis of colorectal cancer patients, as supported by a large body of literature. Compared with other nutritional scores, the CONUT score may be introduced in clinical practice as an optimal prognostic nutritional index to predict patient outcome.

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INTRODUCTION

Colorectal cancer (CRC) represents a significant global health and financial burden, and is currently ranked the third most common cancer in the world and the second leading cause of cancer-related death[1] in both sexes. Over a million new cases of CRC have been diagnosed globally every year in the past decade[2].

Cancer patients usually experience malnutrition and weight loss, especially those with gastrointestinal tumors. Previous studies have shown that malnutrition and cachexia are responsible for 20% of cancer-related deaths, rather than cancer itself[3].

Malnutrition is linked to an increased risk of postoperative complications and to prolonged hospitalization, with a considerable burden in terms of health care costs[4]. Besides, a compromised nutritional status reduces patient's tolerance to radiation and chemotherapy, resulting in a poor response to treatment and worse prognosis[5]. Thus, nutritional assessment of CRC patients should become a part of routine clinical practice to determine its impact on treatment efficacy and survival[6,7].

Patients with good nutritional status at diagnosis and during treatments are expected to have a better quality of life and longer survival[8], but it has also been postulated that nutritional status may impact the activity of immune cells against cancer in patients receiving treatments with chemotherapy, targeted therapy or immune checkpoint inhibitors (ICIs)[4]. The matter of discussion is how systemic inflammation and body composition (BC) influence prognosis, and the identification of nutritional and immunological signatures able to predict clinical outcome and response to therapies, with the aim of better stratification of patients and personalized treatments.

Systemic inflammation status

Tumor growth has been essentially linked to cancer-associated systemic inflammatory response. A consistent body of literature has identified several circulating inflammatory indicators as potentially helpful for prognosis prediction. Serum markers associated with inflammation can be divided into two categories: Upregulated in disease progression (neutrophils, platelets, monocytes, and C-reactive protein), and downregulated in disease progression (lymphocytes and albumin). Their combination can be used as inflammation-related markers.

In this regard, Yamamoto *et al*[9] reviewed the prognostic impact of inflammation-related markers in CRC and their use in clinical practice.

They divided the markers into five groups: Neutrophil-related markers, albumin-related markers, monocyte-related markers, C-reactive protein-related markers[10] and platelet-related markers. The most relevant in CRC are reported in the Table 1.

Nutritional status and body composition

In the issue of the *World Journal of Gastrointestinal Oncology* Liu *et al*[6], published a valuable paper. This case control study highlights the role of preoperative nutritional status as an independent prognostic factor to predict the outcome of CRC patients who underwent potentially curative resection. In particular, the study addresses the role of the Controlling Nutritional Status (CONUT) score, an immune-nutritional screening tool based on serum albumin, total cholesterol, and lymphocyte count, in predicting CRC patients' prognosis[11]. According to the study, a pre-operative CONUT score ≥ 5, characterizing patients with moderate or severe malnutrition, was independently associated with poorer overall survival (OS) and relapse-free survival (RFS) compared to those with a CONUT score ≤ 4, who showed significantly longer RFS and OS (Table 2).

Recent studies have confirmed that the CONUT score is an easy-to-use parameter to prognosticate cancer response during treatment[12-14]. A review published by Chen *et al*[7] including 62 studies involving a total of 25224 patients showed the value of the CONUT score, assessed before surgical or medical treatment. A high CONUT was correlated with shorter OS, cancer-specific survival, progression and recurrence-free survival, disease-free survival and a higher incidence of postoperative complications and mortality.

WHAT IS INNOVATIVE ABOUT CONUT COMPARED TO OTHER SCORES?

The CONUT score is a cost-effective immuno-metabolic tool evaluated from three peripheral blood parameters routinely assessed in clinical practice. Compared to the abovementioned biomarkers, derived from a maximum of two serum markers, the CONUT score provides a more comprehensive representation of both the nutritional and immunological status of patients[14].

Albumin, the main component of serum proteins, is highly correlated with body cell mass and inflammation. The presence of an ongoing inflammatory response contributes to sarcopenia, with repercussions on patients' prognosis[15]. The albumin level reflects nutritional and metabolic status in cancer patients.

Lymphopenia is independently associated with poorer survival outcomes in cancer patients, as the lymphocyte count suggests the grade of immunological and systemic inflammatory response in these patients[16,17].

The neutrophil-to-lymphocyte ratio (NLR) describes tumor inflammation. According to many studies, a high NLR is linked to poor survival in different solid tumors, including colon cancer[18,19].

Lymphocytes and the NLR play a crucial role in cancer immune evasion and surveillance, in addition to the tumor microenvironment, and this seems to be related to response to immunotherapy[20].

Table 1 Most frequently reported inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients as shown in previous reports[9]

Inflammation-related biomarkers	
Neutrophil-related markers	NLR: Low NLR was related to better CSS and DFS, with different cut-off values depending on the study: The smallest was 2, while the largest was 5
Albumin-related markers	GPS that includes serum CRP levels and serum albumin levels: High GPS indicated systemic inflammation (elevated CRP) and low nutritional state (hypoalbuminemia), that was associated with lower CSS and DFS
Monocyte-related markers	Monocyte count: Elevated monocyte count was significantly associated with poor OS and DFS, with variable cut off values depending on the study. LMR: Low LMR was independently associated with worse OS and DFS. The cutoff value depended on the study
C-reactive protein-related markers	CAR: Elevated CAR was significantly associated with worse OS and RFS in patients who underwent curative resection. The cutoff value varied between 0.025 and 0.22 according to the study. LCR: Low LCR (cut off between 12980 and 6000 depending on the study) was most significantly and independently correlated with worse OS and DFS. CLR: Was reported as an independent and significant indicator of poor long-term outcomes in patients with CRCm after hepatic resection, with a cutoff level of 62.8×10^{-6}[10]
Platelet-related markers	PLR: High PLT reflects both an increase in PLT count and a decrease in lymphocyte count and was negatively related to OS in previous reports on colorectal cancer. The cutoff value varied among studies from 150 to 246.36

CSS: Cancer-specific survival; DFS: Disease-free survival; GPS: Glasgow prognostic score; CRP: C-reactive protein; OS: Overall survival; LMR: Lymphocyte–monocyte ratio; CAR: C-reactive protein–albumin ratio; LCR: Lymphocyte–C-reactive protein ratio; CLR: C-reactive protein–lymphocyte ratio; CRCm: Metastatic colorectal cancer; PLR: Platelet–lymphocyte ratio; PLT: Platelet.

Table 2 Definition of controlling nutritional status score

Variable	Normal	Light	Moderate	Severe
Albumin (g/dL)	3.5-4.5	3.0-3.49	2.5-2.9	< 2.5
Albumin score	0	2	4	6
Total lymphocyte count (mm^3)	≥ 1600	1200-1599	800-1199	< 800
Total lymphocyte count score	0	1	2	3
Total cholesterol (mg/dL)	< 180	140-180	100-139	< 100
Total cholesterol score	0	1	2	3
CONUT score	0-1	2-4	5-8	9-12
Assessment	Normal	Light	Moderate	Severe

Low controlling nutritional status (CONUT) score includes: Normal (0-1) and light (2-4) subgroups. High CONUT score includes: Moderate (5-8) and severe (9-12) subgroups[6]. CONUT: Controlling nutritional status.

With regard to the CONUT score, high serum cholesterol levels have been shown to enhance the anticancer activity of natural killer cells in mice[21], and in solid cancers treated with ICIs, high cholesterol has been demonstrated to correlate with better clinical outcomes[22].

Another element worth mentioning is the relationship between the CONUT score and BC.

In the study of Liu *et al*[6], no significant association was observed between body mass index (BMI) and the CONUT score. BMI is a crude measure, does not adequately discriminate the percentage of fat-free mass and does not rule out sarcopenia in cancer patients.

By contrast, in their study an inverse correlation between the CONUT score and skeletal muscle mass index (SMI) was shown (Liu *et al*[6], Figure 4C). The incidence of sarcopenia was higher in the high CONUT group. Moreover, comparing the time-dependent curves of CONUT + tumor-node-metastasis (TNM) stage and SMI + TNM stage, they showed concordance in both 3-year OS (Liu *et al*[6], Figure 4A) and 3-year RFS (Liu *et al*[6], Figure 4B), suggesting that the CONUT score is as reliable as SMI in predicting the postoperative prognosis of CRC. This association likely relies on both the CONUT score and SMI reflecting the body protein reserves.

KEY POINTS

The SMI was obtained by dividing the skeletal muscle area (SMA) (cm^2) by the square of height (m). The SMA was evaluated in a cross-section of the third lumbar vertebrae on CT, by measuring the areas of psoas major, paraspinal

muscles, transverse abdominis, external oblique, internal oblique, and rectus abdominis muscles. Sarcopenia was defined as SMI < 40.8 (cm^2/m^2) in men and SMI < 34.9 (cm^2/m^2) in women.

Sarcopenia is a multifactorial condition that is frequently seen in cancer patients. It is characterized by a degenerative and systemic loss of skeletal muscle mass (SMM) and function[23].

Previous studies have demonstrated that a decreased SMM in cancer patients, as well as proven sarcopenia/cachexia, have negative effects on response to treatments, both in surgical and oncological treatments[24,25].

In addition, a SMM assessed by CT seems to be associated with increased chemotherapy and radiotherapy toxicity[26].

Several studies in advanced tumors treated with ICIs have confirmed the key prognostic role of SMM and the importance of patients' assessment, at baseline and during treatment, to actively assess the efficacy and tolerance of immunotherapy[27].

One of the potential limitations of the paper written by Liu *et al*[6] is that the authors focused on the CONUT score, neglecting other nutritional markers, such as the NLR, Glasgow prognostic score (GPS/modified GPS, (mGPS)) and prognostic nutritional index, which have been largely validated in previous studies[9]. However, their choice to focus on the CONUT score could be justified considering that it represents a more comprehensive prognostic indicator, as it combines nutritional parameters (albumin, and cholesterol) with immunologic status (including lymphocyte count), whose interplay validated by a body of literature, is significant in prognosis[7].

Nutritional assessment has an essential role in gastrointestinal tumors, particularly in CRC, that has generally a low survival rate due to its high prevalence, delayed diagnosis and elevated rate of local recurrence or metastasis, despite continuous therapeutic progress.

A multidisciplinary team-based approach has improved clinical outcomes, but substantial disparities between patients are still often observed in terms of disease presentation, response to treatments and prognosis. Therefore, it is necessary to identify new biological indicators to improve the accuracy of prognostic prediction and patient outcome[25,28].

In this context, nutritional evaluation could have a key role, representing a cost-effective and modifiable chance of therapeutic intervention for clinicians. In fact, various effective nutritional assessment tools have already been described, especially in the pre-operative setting, but there is no gold standard and they have not been routinely implemented in clinical practice[29,30].

Shan *et al*[25] suggested a prognostic model based on multiple parameters such as psoas muscle index in stage II-III CRC patients, highlighting how the presence of sarcopenia before adjuvant chemotherapy affects RFS and OS[25].

A recent study by Wang *et al*[31] including 5014 CRC patients indicated white blood cells, neutrophils, monocytes, eosinophils, alkaline phosphatase, and lactate dehydrogenase levels as additional indicators to be included in the CONUT scoring system, to provide a more accurate assessment of the clinical prognosis for patients with CRC.

Considering the concordance between the CONUT score and SMI, both resonating with TNM staging in CRC patients undergoing surgery, the two indicators could be combined in an innovative prognostic index to better stratify patients before and during treatments. In this regard, in the pre- and post-operative setting it could help in selecting patients with an increased risk of relapse, who would benefit from a more intensive adjuvant and neo-adjuvant treatment, from those who do not require oncological therapy after curative resection. The role of the CONUT score together with TNM stage in predicting the risk of relapse in the study by Liu *et al*[6], suggests that the data recently observed on circulating tumor DNA in the adjuvant setting of CRC could be replicated with nutritional and metabolic tools in the future[32].

Therefore, in the era of immuno-oncology a new body of research is attempting to clarify the mechanism of resistance to immunotherapy in proficient mismatch repair CRC patients to enhance sensitivity to ICIs[8]. Ongoing clinical trials are focusing on this matter especially in the peri-operative setting[32]. Given its immune-metabolic dimension and the relationship to immunotherapy outcome[33], the CONUT score could also be considered in this setting as a stratification factor to evaluate patients.

CONCLUSION

The role of the CONUT score, as an independent prognostic factor in patients undergoing surgery for CRC and in advanced disease, is well established. Based on the abovementioned evidence and the valuable findings of Liu *et al*[6], use of the CONUT score should also be encouraged and considered in clinical practice due to its affordability[34]. Further studies are needed to validate the relevance of this promising score in the clinical decision-making process, and to suggest when early nutritional interventions are indicated; thus, implementing personalized oncology from a supportive care perspective[8].

FOOTNOTES

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