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Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate?

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Abstract

Albumin is the single most abundant protein in the human serum. Its roles in physiology and pathology are diverse. Serum albumin levels have been classically thought to reflect the nutritional status of patients. This concept has been challenged in the last two decades as multiple factors, such as inflammation, appeared to affect albumin levels independent of nutrition. In general, cancer patients have a high prevalence of hypoalbuminemia. As such, the role of hypoalbuminemia in patients with colorectal cancer has received significant interest. We reviewed the English literature on the prognostic value of pretreatment albumin levels in colorectal cancer. We also consolidated the evidence that led to the current understanding of hypoalbuminemia as an inflammatory marker rather than as a nutritional one among patients with colorectal cancer.

Key words: Hypoalbuminemia; Albumin; Colorectal cancer; Albumin-to-globulin ratio; Cancer survival; Systemic inflammatory response; Glasgow prognostic score

Core tip: Early studies had shown a prognostic value of hypoalbuminemia in colorectal cancer. The relationship between albumin levels and survival was more consistent when the former was coupled to C-reactive protein, a classic inflammatory marker, in the modified Glasgow prognostic score (mGPS). This relationship also appeared to be independent of nutrition on multivariate analyses. The superiority of mGPS in predicting survival supports inflammation as the major culprit of poorer outcomes. A number of studies showing an association of lower albumin-to-globulin ratios with poorer survival are also in favor of a tilt towards proinflammatory states as the cause of morbidity and mortality. Cancer cachexia is a downstream consequence of the systemic inflammation brought in by colorectal cancer. In this view, albumin is a negative acute phase reactant rather than a nutritional marker. Interventions aimed to halt cancer cachexia should therefore target inflammation.

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BACKGROUND

Albumin is the most abundant protein in the human serum. This monomeric macromolecule constitutes about 60% of the serum proteins by weight, the rest being globulins. It is also present in the interstitial space and body fluids. Albumin is produced by the liver at a rate of 9 to 12 g/d. Its hepatic synthesis is primarily affected by osmotic colloid pressure and inflammatory states, but also, and to a lesser degree, by nutritional status and hormones. The catabolism of this protein is still not completely understood but is postulated to take place in the vascular endothelium[1,2].

Albumin is the most important contributor to the osmotic colloid pressure. In fact, given its negative charge at normal pH, it retains sodium cations, and therefore water, in the intravascular compartment. It also plays central roles in cellular physiology, including intravascular transport of molecules (like hormones) and lipid metabolism[1]. A dye-binding method is used to measure serum albumin. Once bound to bromocresol, the complex absorbs light at a different wavelength than unbound bromocresol[3]. Bromocresol can also bind to other proteins and thus can lead to an overestimation of albumin levels.

Historically, the nutritional status of patients has been evaluated through two approaches: Anthropometric methods and laboratory markers. The former includes physical parameters, such as triceps skin fold to assess fat composition, mid-arm circumference to assess muscle composition, or body mass index[4]. The latter approach relies on hepatic proteins like albumin, prealbumin and transferrin, which have been believed to be reflective of nutritional status[5]. Deficiencies in these hepatic proteins were an indicator of malnutrition and prompted at times the use of aggressive nutritional support.

Despite the persistence of the perception among clinicians that albumin is a nutritional marker, the literature in the last two decades has challenged this concept as additional factors were found to impact the serum albumin level[6]. While reduced food intake can result in hypoalbuminemia, these effects are generally mild. In fact, experimental starvation demonstrated that albumin concentrations may not change for several weeks[7]. Additionally, inflammation was found to reduce albumin concentration regardless of malnutrition[8,9].

Among cancer patients, the prevalence of both hypoalbuminemia and malnutrition is common. Those with a malignancy of the gastrointestinal tract also face the risk of physical interference of the tumor with their feeding, such as a mechanical obstruction. As a result, the role of hypoalbuminemia in patients with colorectal cancer has received significant interest. In this work, we review the English literature on the role of serum albumin levels as a prognostic tool in colorectal cancer. We also present the body of evidence that led to the current understanding of hypoalbuminemia as an inflammatory surrogate rather than nutritional marker among these patients.

ALBUMIN AND CANCER

For the host body, cancer represents a state of high physiological stress, with tumor hypoxia/necrosis and local tissue damage. In an attempt to counteract these changes, the body responds with a systemic release of proinflammatory cytokines and growth factors[10]. When faced with these stimuli, isolated hepatocytes increase their production of acute-phase proteins, such as C-reactive protein (CRP), and decrease their production of albumin[11]. This response is often accompanied by a nutritional and functional decline of patients, especially among those with advanced cancer[12-14].

Babson *et al*[15] first described a potential association between cancer and plasma proteins in 1954. The authors demonstrated that tumors act as a trap for plasma proteins and use their degradation products for tumor growth. Their findings were later confirmed by several studies: When serum albumin was either radiolabeled or conjugated with dyes, up to 25% of the dose was accumulated in solid tumors[16,17]. Albumin therefore appeared to be a possible nutritional source for tumor growth[17]. Interestingly, evidence points to a physiological anticancer effect of albumin through its antioxidant properties and demonstrated roles in stabilizing DNA replication (among other functions)[18]. Such characteristics highlight complicated interconnections between albumin and cancer.

The main reason for low albumin levels in patients with cancer remains unclear, yet various mechanisms have been proposed. For instance, cancer cells can produce cytokines, such as interleukin-6 (IL-6), that modulates the production of albumin[14]. In addition, the presence of hepatic micrometastases may stimulate Kupffer cells to produce cytokines (such as IL-1β, IL-6 and tumor necrosis factor), which may also affect albumin synthesis. However, the fractional rate of albumin synthesis in cachectic hypoalbuminemic patients with advanced pancreatic cancer was found to be no different compared to healthy controls[19]. Alternatively, it has also been shown that, in patients with cancer, there is an increase in vascular permeability and hence increase in the albumin flux across the capillary wall towards the extravascular compartment[20]. This is due to the release of tumor necrosis factor, which may increase microvascular permeability, leading to hypoalbuminemia[21]. Nonetheless, only small changes in transcapillary escape rates were founds among patients

with advanced cancer who had hypoalbuminemia. These rates had little correlation with serum albumin concentrations[22]. Lastly, a disproportionate increase in albumin degradation without a corresponding increase in synthesis can contribute to hypoalbuminemia. This is evidenced by albumin degradation in sarcoma-bearing mice models compared to controls[23]. However, using ^{131}I-labeled albumin, Steinfeld[24] reported an opposite finding; a reduced albumin degradation in patients with advanced cancer.

In patients with cancer, serum albumin continues to be clinically central to assessing the nutritional status, severity of the disease, disease progression, and prognosis. Moreover, serum albumin level has been found to be an independent prognostic factor for survival in various cancers such as melanoma[25], colorectal[7,26], pancreatic[27], lung[28], gastric[29], and breast cancer[30].

ALBUMIN IN COLORECTAL CANCER

Colorectal cancer is the third most common cancer affecting males and females in the United States, and is the second leading cause in terms of cancer-related deaths[31]. According to the American Cancer Society, the disease is expected to result in 49700 deaths nationally in 2015[32]. Most early stage disease is detected on screening colonoscopy. However, patients found to have colorectal cancer after symptoms onset tend to have an advanced disease. For localized disease, tumor resection is the only curative modality. Adjuvant chemotherapy regimens based on oxaliplatin have a demonstrated role in increasing cure rates and reducing chances of recurrence among patients with stage Ⅲ disease[33]. For patients with stage Ⅳ disease, the 5-year survival continues to be poor (13%) despite advances in therapeutic options[34].

The prognosis of affected patients is currently best predicted by surgical resection and pathological analysis of specimens. The depth of tumor invasion into the bowel wall, the involvement of regional lymph nodes and the presence of distant metastases are the cornerstone of the tumor node metastasis staging system used in this cancer[33]. A growing body of literature has investigated laboratory markers as prognostic factors adjunct to pathological staging.

The role of pretreatment serum albumin as a prognostic tool was demonstrated by many studies. Heys *et al*[7] provided the first documentation of such role. Among 431 patients with localized colorectal cancer, serum albumin was an independent prognostic factor for survival. A remarkable 25% increase in the risk of death was seen for each 0.5 g/dL reduction of serum albumin. While the authors did not investigate the effect of the nutritional status on albumin in the study population, their eloquent discussion on the role of inflammation in hypoalbuminemia was an early sign of a paradigm shift[7].

As surgery is the mainstay of treatment for localized colon cancer, preoperative hypoalbuminemia later received considerable attention (Table 1). In a Taiwanese study of 3849 colon cancer patients who underwent curative surgery, hypoalbuminemia predicted higher rates of postoperative mortality for both localized (stage Ⅰ and Ⅱ) and regionally advanced cancer. The impact was significant 30 d and 5 years after surgery, and remained significant on multivariate analysis. Further, preoperative hypoalbuminemia was associated with more common wound-healing and anastomotic complications, as well as postoperative pulmonary and urinary morbidities. Interestingly, the study found no statistically significant excess of gastrointestinal or cardiovascular surgery-related morbidity in patients with lower albumin levels[35]. In another study, albumin levels among patients with preoperative metastatic disease appeared to be lower compared to those who are metastasis-free. Such observation is in favor of a systemic inflammatory response as an etiology of hypoalbuminemia, a response that entails a poorer prognosis. Among patients with advanced disease, albumin levels were more reflective of the tumor size rather than the specific tumor stage, with larger tumors having lower serum albumin levels. The authors suggest that the larger volume of tumor cells translates into a higher production of proinflammatory cytokines, which in turn suppress albumin's hepatic production[36].

Similar results were found among 260 patients with rectal cancer where hypoalbuminemia was an independent risk factor for poor survival following surgery. In the first thirty postoperative days, however, albumin level had no statistically significant impact on survival[37]. Of note, we found no studies that assessed whether the impact of preoperative albumin level is essentially equal in the surgical treatment of colon and rectal cancer.

The predictive effect of albumin on survival is also seen in cancers across the gastrointestinal tract. In their systematic review, Gupta *et al*[38] found that, in an overwhelming majority of 26 out of 29 studies, high levels of albumin were associated with better survival among patients with gastrointestinal cancers. A limitation of such review is the heterogeneity in the way albumin was analyzed along with differences in selection criteria (such as tumor stage). In some studies, the serum level as a predictor of outcomes was treated as a continuous variable, while the majority looked at cutoff values that show differences in survival. In most cases, the cutoff was 3.5 g/dL, the lower limit of serum albumin's normal range. Furthermore, the studies were retrospective, which may have led to patient and treatment selection biases. The outcomes of interest and their measurement were also different across the studies.

Hypoalbuminemia was not consistently a prognostic factor in colorectal cancer. Boonpipattanapong *et al*[26] showed that hypoalbuminemia, when taken alone, has no statistically significant effect on survival among patients who underwent curative surgery. If combined with the level of carcinogen embryonic antigen, a tumor marker that correlates with tumor size, the resulting

Table 1 Pretreatment serum albumin and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Heys *et al*[7]	Retrospective cohort study	ALB's prognostic value in localized and metastatic CRC	431 patients	On multivariate analysis, reduced OS with lower ALB	First report of ALB's prognostic value in CRC
Boonpipattanapong *et al*[26]	Retrospective cohort study	Preoperative CEA and ALB's prognostic value in CRC following curative surgery	384 patients	Combination of CEA ⩾ 5 ng/dL and ALB ⩽ 3.5 g/dL predicts lower 5-yr OS. No statistically significant association of either alone with survival	Linking a tumor marker (CEA) to a host marker (ALB) can have a prognostic significance
Lai *et al*[35]	Retrospective cohort study	Preoperative ALB's value in predicting postoperative outcomes in CRC	3849 patients	Short-term: More complications related to wounds, anastomosis, lungs and urinary system in low ALB group Long-term: Lower 5-yr OS (60% *vs* 78%) and 5-yr RFS (73.5% *vs* 78.9%) in low compared to normal ALB group	No difference in short-term postoperative GI and cardiovascular complications
Cengiz *et al*[36]	Retrospective cohort study	Pretreatment ALB and cholesterol's prognostic value in CRC following curative surgery	99 patients	2.8 RR of death in low compared to normal ALB group. No survival effect for cholesterol on multivariate analysis	No difference in CRC recurrence between low and normal ALB groups
Chandrasinghe *et al*[37]	Retrospective cohort study	Pretreatment ALB's prognostic value in rectal cancer following curative surgery	226 patients	Lower 5-yr OS (47% *vs* 69%) and RFS (69.7% *vs* 83%) in low compared to normal ALB group. No differences in 30-d postoperative mortality/ complications	First report on ALB's long-term prognostic value in rectal cancer
Gupta *et al*[38]	Systematic review	Relationship between pretreatment ALB and cancer survival	59 studies in total; 29 on GI cancers including 12 on CRC	26 of 29 studies on GI cancers had higher OS with higher ALB on multivariate analysis	Inter-study differences in definition of low ALB (continuous variable *vs* cut-off points)

ALB: Serum albumin; CRC: Colorectal cancer; OS: Overall survival; RR: Relative risk; CEA: Serum carcinoembryonic antigen; RFS: Recurrence-free survival; GI: Gastrointestinal.

score becomes significant in predicting the 5-year survival in all disease stages[25]. Their finding, however, had a low power (22%). In other studies, it also was noted that albumin levels were normal among patients with early stages of cancer (stages Ⅰ and Ⅱ), which would limit its use in prognostication[8,14]. These results also indicated that more upstream factors potentially precede changes in albumin levels. As such, studies started to look at albumin's relation to other serum proteins, *i.e.*, globulins.

GLOBULIN

The globulin portion of serum is composed of carrier proteins, immunoglobulins, complement factors and enzymes, almost exclusively synthesized by the liver and plasma cells. The myriad of globulin proteins can be classified into four distinct groups by electrophoresis: α1, α2, β, and γ[2].

Changes in the individual or overall globulin fractions have been clinically used to identify several pathologic states, irrespective of changes in albumin. Generally speaking, increases in overall globulins denoted increases in immunoglobulins such as polyclonal gammopathy, and decreases point to reduced synthesis, *via* malnutrition and congenital immune deficiency, or protein loss due to nephrotic syndrome.

Albumin-to-globulin ratio

As aforementioned, albumin and globulin, individually, can be prognostic indicators for a variety of medical states and conditions. However, it has been hypothesized that the albumin-to-globulin ratio (AGR) has greater clinical significance. This ratio has previously been used as a marker for immunoproliferative diseases and multiple myeloma[1]. It is a marker of chronic inflammation and it is believed that AGR can be used to predict those at risk for malignancy since carcinogenesis is associated with chronic inflammation[39,40]. As previously mentioned, a systemic cytokine release in cancer leads to hypoalbuminemia, which in turn results in a low AGR. In a sense, a lower AGR would represent a tilt towards proinflammatory states and therefore involves worse outcomes. Indeed, several studies have demonstrated that a low ratio is associated with increased long-term mortality in cancer patients, including those with gastric[28], breast[41], and pancreatic cancer[26].

The AGR has greater predictive value in patients with gastrointestinal cancer, including colorectal cancer (Table 2). In addition to inflammation, this may be a function of the disease processes causing malabsorption and malnutrition[42]. A study conducted by Azab *et al*[43] demonstrated that in colorectal cancer, a low ratio is an independent risk factor for 4-year mortality. Previous studies had shown that low pretreatment albumin was

Table 2 Pretreatment albumin-to-globulin ratio and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Azab *et al*[43]	Retrospective cohort study	AGR's prognostic value in CRC-related mortality	534 patients	75% lower 4-yr mortality in high AGR (> 1.32) compared to low AGR tertile (< 1.03), independent of ALB	Study excluded patients who received preoperative chemotherapy
Shibutani *et al*[44]	Retrospective cohort study	AGR's prognostic value in unresectable metastatic CRC treated with palliative chemotherapy	66 patients	High AGR group had higher OS (HR = 2.25, P = 0.03) and PFS (HR = 2.66, P = 0.03) than low AGR group on multivariate analysis	No statistically significant difference in ORR between high and low AGR groups
Suh *et al*[45]	Retrospective cohort study	Relationship between AGR and cancer incidence among healthy adults	26974 adults (30 ⩽ age ⩽ 80)	Low AGR (< 1.1) had higher cancer incidence, an OR = 3.28 for CRC development and higher cancer mortality compared to AGR > 1.1	First report on association of low AGR with the risk of cancer incidence and mortality in healthy adults

AGR: Serum albumin-to-globulin ratio; ALB: Serum albumin; CRC: Colorectal cancer; OS: Overall survival; PFS: Progression-free survival; OR: Odds ratio; ORR: Overall response rate.

related to poor outcomes[7,20,36]. However, Azab *et al*[43] established that the negative impact of a low ratio was maintained in patients with a normal albumin. It was also found that colorectal cancer patients with high globulins had worse outcomes and this was preserved in patients with normal albumin. Overall, patients with low albumin and high globulins were associated with worse 4-year survival, and the AGR was an independent predictor of long-term mortality in colorectal cancer.

Another study of 66 patients with unresectable metastatic colorectal cancer receiving palliative chemotherapy showed that higher pretreatment AGR was associated with improved disease control rates. Patients with higher AGR also had more favorable progression free survival, a finding that was independent of clinicopathological features on multivariate analysis. The objective response rate in the high-AGR group (44.1%) was higher than the low-AGR one (28.1%) but the difference did not reach statistical significance (P = 0.208). However, taken as a whole, the study suggests that palliative chemotherapy is less effective with low pretreatment AGR, a marker of underlying inflammatory conditions[44].

Interestingly, Suh *et al*[45] set out to determine if the ratio could identify those at increased risk for the development of malignancy in a large sample of healthy adults (n = 28292)[44]. Not only was a low AGR associated with an increased risk for cancer incidence and cancer mortality, but also higher all-cause mortality[45]. Given the fact that the authors excluded individuals with major chronic diseases or acute illnesses and those with albumin levels less than 3.2 g/dL, one can infer that a malnutrition leading to hypoalbuminemia was not a determinative factor in a causal pathway to the observed worse outcome. Of interest, the higher incidence of colorectal cancer in the low AGR group was statistically significant. Further, a large genome-wide study of 290659 South Korean individuals demonstrated a strong association between a low AGR phenotype and a single nucleotide polymorphism (SNP) in the gene locus of tumor necrosis factor receptor superfamily member 13 (TNFRSF13B). As this receptor regulates multiple components of the inflammatory response, the SNP is indicative of a genetic susceptibility to inflammatory states[46]. The broader implication of both previous studies is that the ratio can identify healthy individuals with inflammation and therefore those at risk for developing cancer. More importantly, the findings suggest that there may in fact be a common inflammatory pathway for carcinogenesis.

Glasgow prognostic score

Besides the relation of albumin to total globulin, a parallel interest arose in individual globulins, specifically those that are classical inflammatory markers such as CRP. Similar to albumin, many articles had demonstrated an association of higher CRP with poorer outcomes. In advanced cancer patients, including patients with colorectal cancer, elevated CRP levels were correlated with poorer cancer and non-cancer survival[47]. Results, however, are inconsistent as a number of studies showed no survival effect of CRP on multivariate analysis[48]. Earlier data had also suggested that in many malignancies a rise in CRP was accompanied by a fall in albumin[47]. These observations led McMillan *et al*[47] to combine both CRP and albumin into one score, the glasgow prognostic score (GPS).

The original GPS assigned a score of 0 to patients with CRP < 10 mg/dL and albumin > 3.5 g/dL, and a score of 2 for those with both CRP > 10 mg/dL and albumin < 3.5 g/dL. Patients with either abnormality received a score of 1. The authors, however, observed that hypoalbuminemia with a normal CRP was rare and had an excellent prognosis. In a sense, hypoalbuminemia alone once again had no effect on survival. This gave rise to the modified GPS (mGPS) where a score of 1 was reserved for patients with CRP > 10 mg/dL. Regardless of albumin levels, patients with CRP < 10 mg/dL had a score of 0, and those with CRP > 10 mg/dL and albumin < 3.5 g/dL were assigned a score of 2. Both the cancer-specific and overall survival significantly correlated with mGPS[49]. The implication of such correlation is the idea that a systemic inflammatory responses occurs before hypoalbuminemia. The deve-

Table 3 Glasgow prognostic score and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Petrelli *et al*[50]	Systematic review and meta-analysis	Quantification of impact of mGPS on OS in CRC	2227 patients from 9 studies	High mGPS was associated with worse OS (HR = 1.69) and CSS (HR = 1.84)	Studies in meta-analysis did not control for concurrent conditions that may affect mGPS, such as sepsis or medications
McMillan *et al*[51]	Systematic review	Relationship between mGPS and cancer outcome	60 studies with 18 on CRC	Higher mGPS in CRC predicted numerous worse outcomes (*e.g.*, postoperative infections, toxicity, survival, *etc.*)	Study looked at all cancer patients. CRC studies were geographically restricted to the United Kingdom and Japan
Richards *et al*[52]	Prospective cohort study	Correlation between parameters of body composition and systemic inflammatory response in operable CRC	174 patients	Elevated mGPS was associated with low skeletal muscle index (P = 0.001)	No association seen between skeletal mass index and tumor-related variables such as tumor stage
Read *et al*[55]	Prospective cohort study	Relationship between inflammatory/nutritional prognostic factors and outcomes in advanced CRC	51 patients	High GPS was associated with worse OS (HR = 2.27), while the nutritional status as measured by validated scores was not on multivariate analysis	Small and heterogeneous study population

GPS: Glasgow prognostic score; mGPS: Modified glasgow prognostic score; CRC: Colorectal cancer; OS: Overall survival; CSS: Cancer-specific survival.

lopment of the latter would mark a more advanced inflammatory status and therefore worse outcomes.

The mGPS has been remarkably consistent in predicting survival (Table 3). A recent pooled analysis of nine studies with a total of 2227 colorectal cancer patients showed an association between higher scores and both poorer overall survival and cancer-specific survival across various disease stages[50]. Another systematic review of GPS/mGPS and cancer-related outcomes demonstrates that the scores are independent prognostic factors among patients with operable disease, inoperable disease and those receiving chemoradiation, not only in colorectal cancer but also across other malignancies. The review listed 18 colorectal studies that outlined widespread prognostic implications independent of a variety of clinical factors, such as tumor stage and emergency presentation. The studies were geographically restricted to the United Kingdom and Japan, with no reports from the United States. The reliability of the GPS/mGPS led the authors to suggest that it should be part of the routine assessment of cancer patients, in conjunction with the currently recommended staging[51].

Many colorectal cancer patients experience cancer cachexia, an involuntary weight loss that is accompanied by a worsening quality of life and mortality. In a study of 174 patients who underwent surgery for primary colorectal cancer, a systemic inflammatory response as measured by mGPS was a major predictor of cancer cachexia. This association was not seen with the white cell count and the neutrophil-to-lymphocyte ratio, two well-established inflammatory scores[52]. Such findings are in line with previous data indicating that scores that are based on CRP as a specific marker of inflammation are superior in predicting poorer outcomes among cancer patients[53]. Despite its multifactorial nature and the multitude of available definitions, cancer cachexia is well predicted by mGPS, suggesting that mGPS can be used as a simple tool to investigate and treat cancer cachexia[54].

Read *et al*[55] compared the impact of nutritional and inflammatory factors on survival among 51 colorectal cancer patients followed over 30 mo. The patient-generated subjective global assessment (PG-SGA) is a validated nutritional assessment tool extensively used in cancer patients. The multivariate analysis revealed that mGPS was a strong predictor of poor prognosis, while the nutritional status as assessed by PG-SGA was not[55]. Despite its small sample size, the study offers additional evidence that the systemic inflammatory response essentially mediates the observed relationship between the nutritional status and the decline in survival in colorectal cancer.

CONCLUSION

We highlighted how pretreatment serum albumin levels, AGR and mGPS have prognostic values among colorectal cancer patients. Their measurement is relatively cheap, reproducible and widely available, which led many to call for their incorporation into the routine assessment of these patients. The potential of a publication bias to positive associations with survival, although a concern, is less likely given the diversity of study designs and their institutions of origin. Another possible limitation of the listed studies is the combination of colon and rectal cancer into one entity. Evidence exists that the two malignancies have biological distinctions that give rise to differences in their behaviors[56].

Basic and clinical research results suggest that hypoalbuminemia, malnutrition and cancer cachexia are all consequences of the body's systemic inflammatory response to the malignancy. The superiority and consistency of mGPS in predicting poorer outcomes greatly support such pathophysiology. Also in favor are the studies on AGR, although limited in number. Recent years have seen this literature shift in our understanding

of hypoalbuminemia. Albumin is now seen as the main negative acute phase reactant in humans. We found no studies that investigated clinicians' perceptions of hypoalbuminemia, yet we believe that the view of hypoalbuminemia as a nutritional marker among cancer patients remains to be a common one.

Despite the multitude of studies supporting the prognostic role of mGPS in colorectal cancer prognosis, its use remains at the research level. In the absence of validated controlled trials, the score is yet to be incorporated into clinical treatment algorithms. Future research should clarify its role in patient stratification and thus clinical decisions. Work is also needed to come up with interventions aimed at moderating the inflammatory response in order to halt the slow, yet fatal, progression of cancer cachexia.

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