Nutritional C-Reactive Protein Ratio as a Prognostic Biomarker in Metastatic Colorectal Cancer: A Comprehensive Review

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Abstract

Background: Metastatic colorectal cancer (mCRC) remains a major global health burden, ranking among the leading causes of cancer-related deaths worldwide. Despite significant advances in systemic therapy, including cytotoxic chemotherapy, targeted agents, and immunotherapy, overall survival in advanced disease remains suboptimal. This unmet clinical need has intensified the search for reliable, inexpensive, and widely applicable biomarkers that can guide prognostication and treatment stratification. Among such emerging tools, the nutritional C-reactive protein ratio (NCR) has garnered increasing attention as a composite marker that integrates both systemic inflammation and nutritional status—two key determinants of cancer outcomes. C-reactive protein (CRP), an acute-phase reactant, reflects systemic inflammation and tumor-promoting processes, while nutritional parameters such as albumin, prognostic nutritional index, and other related indices capture host immune-nutritional reserve. By combining these dimensions, the NCR offers a more comprehensive representation of the tumor–host interaction. Several recent studies have suggested that a high NCR is associated with unfavorable clinicopathological features, including larger tumor burden, presence of liver metastasis, poor performance status, and reduced responsiveness to systemic therapies. Furthermore, elevated NCR have consistently correlated with inferior overall survival (OS) and progression-free survival (PFS) in mCRC patients, underscoring their prognostic relevance. When compared to established inflammatory and nutritional scores such as neutrophil-to-lymphocyte ratio (NLR), Glasgow Prognostic Score (GPS), and prognostic nutritional index (PNI), the NCR appears to provide additive prognostic information and may better stratify patients in terms of treatment outcomes. Importantly, the simplicity and accessibility of CRP and nutritional marker measurements in routine clinical practice make this ratio highly feasible as a clinical biomarker. Nevertheless, heterogeneity in cutoff definitions, limited prospective validation, and the lack of standardized methodology remain barriers to widespread adoption. The aim of this review is to provide a comprehensive synthesis of the prognostic and clinicopathological significance of the NCR in metastatic colorectal cancer. We summarize current evidence, explore mechanistic underpinnings, and critically compare this ratio to other inflammation- and nutrition-based prognostic models. Furthermore, we highlight limitations in the existing literature and outline future research directions to establish NCR as a robust biomarker in the personalized management of metastatic colorectal cancer.

Keywords: *Nutritional C-Reactive Protein Ratio , Metastatic Colorectal Cancer*

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy and the second leading cause of cancer-related mortality worldwide. Approximately 20–25% of patients present with metastatic disease at initial diagnosis, while nearly 50% eventually develop distant metastases during the course of their illness [1]. Despite substantial advances in systemic chemotherapy, targeted biological agents, and more recently immunotherapeutics, the prognosis of metastatic colorectal cancer (mCRC) remains poor, with five-year overall survival rates rarely exceeding 15% in unselected populations [2]. This clinical challenge highlights the urgent need for reliable, cost-effective, and universally accessible biomarkers that can guide prognosis and help optimize individualized therapeutic strategies.

Systemic inflammation and nutritional status are now recognized as pivotal determinants of cancer progression and patient outcomes. Chronic inflammation promotes tumor growth, angiogenesis, and metastasis, while malnutrition weakens host immunity and impairs tolerance to oncologic treatments [3]. Traditionally, separate markers such as C-reactive protein (CRP), albumin, neutrophil-to-lymphocyte ratio (NLR), and prognostic nutritional index (PNI) have been studied as independent prognostic indicators. However, none of these indices alone fully encapsulates the dynamic interplay between inflammation and nutrition in shaping clinical outcomes in mCRC [4].

The nutritional C-reactive protein ratio (NCR) has emerged as a promising composite biomarker that integrates both systemic inflammation and host nutritional reserve. By combining these biologically linked domains, the NCR offers a more comprehensive picture of tumor–host interactions than isolated indicators. Early evidence suggests that elevated NCRs are strongly associated with aggressive tumor biology, adverse clinicopathological features, and poorer survival outcomes in patients with mCRC [5].

The primary aim of this review is to comprehensively evaluate the clinicopathological and prognostic significance of the NCR in metastatic colorectal cancer. In addition, this article seeks to compare its predictive performance with established inflammation–nutrition-based indices and to explore mechanistic explanations for its clinical associations. Finally, we will highlight existing knowledge gaps and outline directions for future research to establish NCR as a clinically actionable biomarker.

Epidemiology and Burden of Metastatic Colorectal Cancer

Colorectal cancer (CRC) represents a major global health concern, with more than 1.9 million new cases and approximately 935,000 deaths reported worldwide in 2020, according to the GLOBOCAN database [6]. It accounts for nearly 10% of all cancer diagnoses and deaths, ranking as the third most common malignancy and the second most frequent cause of cancer-related mortality [7]. The incidence of CRC shows striking geographic variability, with the highest rates observed in high-income countries, including those in Europe, North America, and Oceania. However, rising incidence and mortality are increasingly reported in transitioning economies, largely attributable to lifestyle changes, obesity, smoking, and dietary factors [8].

At initial presentation, nearly 20–25% of CRC patients already harbor distant metastases, most frequently to the liver, lungs, and peritoneum. Additionally, among those diagnosed at earlier stages, up to 50% eventually develop metastatic disease during the course of their illness [9]. These statistics underscore the high clinical burden of metastatic colorectal cancer (mCRC), which significantly contributes to global cancer mortality. Despite therapeutic advances, the median overall survival for patients with mCRC remains approximately 30 months in selected trial populations but is considerably shorter in real-world cohorts [10].

The burden of mCRC extends beyond survival outcomes, encompassing quality of life, economic impact, and healthcare resource utilization. Patients often endure treatment-related toxicities, cumulative organ dysfunction from disease progression, and significant psychosocial distress. From a societal perspective, mCRC generates substantial direct healthcare costs related to systemic therapies, hospitalizations, and palliative care, in addition to indirect costs arising from loss of productivity and caregiver burden [11]. These multifaceted challenges reinforce the urgency of identifying cost-effective

biomarkers that can refine prognostication, optimize treatment selection, and reduce unnecessary healthcare expenditure.

In this context, prognostic indicators that integrate both tumor-related and host-related factors, such as systemic inflammation and nutritional reserve, have become an area of intensive research. Traditional staging systems like TNM classification, while essential, do not fully account for host biology or systemic response to the tumor. Hence, biomarkers like the nutritional C-reactive protein ratio (NCR) hold significant promise in complementing conventional clinicopathological parameters to better stratify patient outcomes in mCRC [12].

Systemic Inflammation and Nutritional Status in Cancer Prognosis

Systemic inflammation has emerged as a central hallmark of cancer biology, influencing multiple steps of tumor initiation, progression, and metastasis. Chronic inflammatory responses create a pro-tumorigenic microenvironment by promoting angiogenesis, DNA damage, immune evasion, and epithelial–mesenchymal transition [13]. In colorectal cancer, elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) have been directly linked to tumor aggressiveness and worse clinical outcomes [14]. These cytokines drive hepatic synthesis of acute-phase reactants, including C-reactive protein (CRP), which serves as a robust surrogate marker of systemic inflammation in oncology patients.

Parallel to inflammation, host nutritional status plays an equally important role in determining cancer prognosis. Malnutrition, frequently observed in patients with advanced malignancies, weakens cell-mediated immunity, impairs wound healing, and reduces tolerance to systemic therapies [15]. In colorectal cancer, protein-calorie malnutrition is particularly common due to tumor-induced cachexia, treatment-related gastrointestinal toxicity, and metabolic dysregulation [16]. Poor nutritional reserves not only compromise functional status but are also independently associated with increased postoperative complications, treatment delays, and inferior survival outcomes.

To better quantify the prognostic value of host immunity and nutrition, several composite scores have been proposed. These include the prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the Glasgow Prognostic Score (GPS), all of which incorporate inflammation and/or nutrition-related variables [17]. While these indices have demonstrated prognostic relevance across multiple cancers, including colorectal cancer, their predictive accuracy remains inconsistent, partly due to variability in cutoff definitions and lack of integration of both inflammation and nutritional domains into a single unified metric.

The nutritional C-reactive protein ratio (NCR) was therefore conceptualized as an integrative biomarker that reflects both systemic inflammation and nutritional status. Unlike traditional markers, it offers a simplified yet comprehensive measure of the tumor–host interaction, which may better capture the biological complexity underlying cancer progression. Growing evidence suggests that elevated NCR predict unfavorable outcomes in metastatic colorectal cancer, highlighting the interplay between inflammation-driven tumorigenesis and host nutritional decline [18].

C-Reactive Protein: Biology and Clinical Relevance

C-reactive protein (CRP) is one of the most extensively studied acute-phase proteins, produced primarily by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and interleukin-1β (IL-1β) [19]. It plays a fundamental role in the innate immune response, binding to phosphocholine expressed on the surface of dead or dying cells and certain bacteria, thereby activating the classical complement pathway. Beyond its physiological function, CRP has emerged as a clinically relevant biomarker of systemic inflammation, with elevated levels correlating with disease severity in infections, autoimmune disorders, and malignancies [20].

In oncology, CRP has consistently been associated with tumor-promoting processes such as angiogenesis, immune evasion, and resistance to apoptosis. Elevated CRP concentrations in serum are thought to reflect both tumor-induced cytokine release and systemic host inflammatory responses [21].

In colorectal cancer specifically, high pre-treatment CRP levels have been correlated with advanced tumor stage, poor differentiation, larger tumor burden, and presence of distant metastases [22]. Moreover, persistently elevated CRP levels during therapy have been linked with early disease progression and worse survival outcomes, underscoring its role as a dynamic prognostic indicator.

From a clinical perspective, CRP measurement offers several advantages. It is widely available, inexpensive, reproducible, and routinely used in clinical practice across the world. Unlike more complex molecular markers, CRP assays require no specialized technology and can be easily integrated into patient monitoring protocols [23]. However, CRP is not cancer-specific, as it can be elevated in a variety of non-malignant conditions including infections, cardiovascular disease, and autoimmune disorders. This lack of specificity limits its utility as a stand-alone biomarker for cancer prognosis.

To overcome these limitations, researchers have increasingly explored composite indices that incorporate CRP with other clinical or laboratory variables to improve predictive accuracy. Examples include the Glasgow Prognostic Score (GPS), which combines CRP and albumin, and the CRP-to-lymphocyte ratio (CLR). Within this framework, the nutritional C-reactive protein ratio (NCR) represents a novel evolution of CRP-based biomarkers, offering a more balanced reflection of both inflammation and host nutritional reserves in metastatic colorectal cancer [24].

Nutritional Markers and Their Prognostic Role

Nutritional status has long been recognized as a key determinant of outcomes in oncology, particularly in gastrointestinal malignancies such as colorectal cancer. Malnutrition not only weakens immune competence but also impairs tolerance to systemic therapies, increases susceptibility to infections, and reduces physical resilience [25]. In advanced colorectal cancer, malnutrition is highly prevalent due to tumor-related cachexia, anorexia, and treatment-induced gastrointestinal toxicity. Consequently, accurate and reliable assessment of nutritional status is essential for prognostication and clinical decision-making [26].

Several nutritional markers and indices have been developed to quantify host nutritional reserve. Serum albumin remains one of the most widely used markers, reflecting both nutritional status and systemic inflammatory response. Hypoalbuminemia in cancer patients has consistently been associated with poor survival, higher rates of treatment-related complications, and worse postoperative outcomes [27]. Similarly, body mass index (BMI) and weight loss trajectories provide useful insights, although they may not fully capture the complex metabolic disturbances seen in cancer-associated cachexia [28].

Among composite indices, the Prognostic Nutritional Index (PNI), which incorporates serum albumin and lymphocyte counts, has shown robust prognostic value in colorectal cancer. Low PNI scores are associated with reduced overall survival (OS), increased postoperative complications, and poorer tolerance to chemotherapy [29]. Other nutritional assessments, such as the Controlling Nutritional Status (CONUT) score and Subjective Global Assessment (SGA), have also demonstrated utility, though they are more complex and less frequently used in routine oncology practice [30].

Despite their relevance, most traditional nutritional markers have limitations when used in isolation. Albumin levels, for instance, may be influenced not only by nutrition but also by systemic inflammation, liver function, and hydration status. This has fueled interest in composite biomarkers that integrate nutritional indicators with inflammatory markers to achieve more accurate prognostication. In this context, the development of the nutritional C-reactive protein ratio (NCR) represents a significant advancement, as it combines the prognostic dimensions of both nutrition and inflammation into a single, clinically practical measure [31].

Concept and Calculation of Nutritional C-Reactive Protein Ratio (NCR)

The nutritional C-reactive protein ratio (NCR) is a recently proposed composite biomarker designed to reflect the interplay between systemic inflammation and host nutritional status in cancer patients. It is generally calculated as the ratio of serum C-reactive protein (CRP, mg/L) to a selected nutritional parameter, most frequently serum albumin (g/dL) or prognostic nutritional index (PNI). The most

commonly adopted formula is:

NCR = BMI × Albumin (g/L) / C-reactive protein (CRP) (mg/L) [32].

The rationale behind this calculation is straightforward yet biologically meaningful. Elevated CRP reflects systemic inflammation driven by tumor-promoting cytokines such as IL-6 and TNF-α, while reduced albumin levels serve as a surrogate for impaired nutritional reserve and cancer cachexia. By combining these two parameters into a ratio, the NCR provides a balanced reflection of the tumor–host interaction, capturing the dual prognostic impact of inflammation and malnutrition [33].

Several studies have examined the prognostic significance of the NCR in patients with gastrointestinal malignancies, particularly colorectal cancer. Ishizuka et al. first reported that an elevated CRP-to-albumin ratio was strongly associated with worse overall survival (OS) following colorectal cancer surgery [34]. Subsequent investigations expanded its utility to metastatic colorectal cancer (mCRC), where the ratio was shown to correlate with disease burden, resistance to systemic therapy, and poor survival outcomes [35].

A key advantage of the NCR lies in its simplicity and universal availability. Both CRP and albumin are routinely measured in standard oncology practice, making the ratio easily applicable across diverse healthcare settings without requiring additional costs or specialized assays [36]. Furthermore, unlike more complex multivariable prognostic models, the NCR can be quickly calculated and interpreted at the bedside, facilitating real-time clinical decision-making.

However, challenges remain in the standardization of cutoff values. Different studies have applied various thresholds, ranging from 0.05 to 0.5, leading to heterogeneity in prognostic results and limiting comparability across cohorts [37]. Prospective studies are needed to establish uniform cutoffs and validate the ratio's prognostic power in broader populations before widespread clinical adoption can be recommended.

Clinicopathological Correlations of NCR

Emerging evidence suggests that the nutritional C-reactive protein ratio (NCR) is strongly correlated with adverse clinicopathological features in colorectal cancer, particularly in patients with metastatic disease. Low NCR have been associated with larger primary tumor size, poor histological differentiation, advanced T stage, and higher tumor-node-metastasis (TNM) stage at diagnosis [38]. These associations highlight the capacity of the NCR to reflect not only systemic host status but also aggressive tumor biology.

In metastatic colorectal cancer (mCRC), low NCR have been consistently linked with increased tumor burden, including liver and peritoneal metastases. Patients with low ratios are more likely to present with multiple metastatic sites and higher tumor volumes, suggesting that the NCR may serve as a surrogate for disease extent [39]. Additionally, patients with poor Eastern Cooperative Oncology Group (ECOG) performance status, weight loss, and cancer cachexia often demonstrate lower NCR values, reinforcing its relationship with host frailty and nutritional decline [40].

The prognostic implications of NCR extend to treatment responsiveness. Studies have reported that patients with low NCR exhibit reduced sensitivity to first-line chemotherapy and targeted agents, including bevacizumab and cetuximab [41]. This may be attributable to the pro-inflammatory tumor microenvironment reflected by high CRP levels, coupled with impaired nutritional reserve, which reduces tolerance and compliance with systemic therapy. Conversely, patients with higher NCR tend to achieve higher objective response rates and longer progression-free survival.

Another important clinicopathological correlation is the association between the NCR and postoperative outcomes. In surgical candidates, lower ratios have been linked with increased postoperative complications, including infections, delayed wound healing, and prolonged hospital stay [42]. This underscores the potential utility of the NCR in perioperative risk stratification and optimization of supportive care measures.

Collectively, these findings indicate that the NCR serves as a valuable reflection of both tumor

aggressiveness and host vulnerability. Its integration into routine assessment could help clinicians identify high-risk patients who may require intensified monitoring, supportive interventions, or modified therapeutic strategies to improve outcomes.

NCR and Survival Outcomes in Metastatic CRC

The prognostic impact of the nutritional C-reactive protein ratio (NCR) in metastatic colorectal cancer (mCRC) has been investigated in several retrospective and prospective studies, consistently demonstrating its strong association with survival outcomes. Low NCR have been shown to predict both shorter overall survival (OS) and progression-free survival (PFS), regardless of treatment modality or disease stage at diagnosis [43].

In a large multicenter cohort study, patients with low pre-treatment NCR experienced significantly worse median OS compared to those with higher ratios, independent of tumor stage, performance status, and treatment type [44]. These findings were corroborated by subgroup analyses demonstrating that NCR retained its prognostic power across different lines of therapy, including patients receiving cytotoxic chemotherapy, targeted biologics, and palliative regimens [45]. Importantly, this suggests that the NCR is not merely a reflection of tumor burden, but rather an independent indicator of host–tumor interaction dynamics that directly affect survival.

The NCR has also shown value in stratifying patients within clinically homogeneous groups. For instance, among patients with liver-limited metastases treated with resection, those with lower NCR had significantly worse postoperative survival, highlighting its role in refining prognostic stratification beyond conventional clinicopathological variables [46]. Similarly, in patients undergoing palliative chemotherapy, a low NCR was associated with reduced objective response rates, earlier disease progression, and diminished treatment benefit, underscoring its utility in predicting therapeutic efficacy [47].

Meta-analyses further strengthen the evidence for NCR as a prognostic biomarker. A systematic review encompassing colorectal cancer populations reported that low NCR were consistently associated with poor OS and PFS, with hazard ratios ranging from 1.5 to 3.0 across studies [48]. These results position NCR as a clinically relevant biomarker capable of refining survival predictions beyond standard TNM staging and commonly used inflammatory scores.

Collectively, these findings highlight the prognostic robustness of the NCR in mCRC, supporting its potential incorporation into risk stratification models. By identifying patients at higher risk of poor outcomes, clinicians may tailor surveillance, intensify supportive care, or consider alternative therapeutic strategies to improve clinical management.

Comparison with Other Inflammation–Nutrition Based Prognostic Scores (PNI, NLR, GPS)

The search for reliable prognostic markers in metastatic colorectal cancer (mCRC) has led to the development of several inflammation- and nutrition-based indices, including the Prognostic Nutritional Index (PNI), Neutrophil-to-Lymphocyte Ratio (NLR), and Glasgow Prognostic Score (GPS). While these markers have shown clinical utility, the nutritional C-reactive protein ratio (NCR) may provide superior prognostic accuracy due to its integration of both inflammatory and nutritional domains.

The **Prognostic Nutritional Index (PNI)**, derived from serum albumin and lymphocyte counts, has been widely studied in colorectal cancer. Low PNI scores indicate poor immune-nutritional status and are associated with inferior survival outcomes. However, PNI is more heavily influenced by nutritional reserve than inflammation, potentially limiting its ability to fully capture the systemic tumor–host interaction [49]. In contrast, the NCR balances both dimensions, enhancing its predictive performance in mCRC.

The **Neutrophil-to-Lymphocyte Ratio (NLR)** reflects the relative balance between pro-tumor inflammatory neutrophils and anti-tumor lymphocytes. Elevated NLR values have been linked to poor OS and PFS in colorectal cancer, with some studies suggesting its role in predicting chemotherapy resistance [50]. Nevertheless, NLR may be influenced by transient factors such as infections or steroid

use, reducing its specificity as a cancer biomarker. The NCR, by incorporating CRP and albumin, offers greater stability and may more accurately reflect chronic systemic inflammation rather than transient changes [51].

The **Glasgow Prognostic Score (GPS)** is among the most validated inflammation-based prognostic tools, combining CRP and albumin into categorical scores (0–2). GPS has demonstrated prognostic significance across multiple cancers, including colorectal cancer, but its categorical nature may oversimplify continuous biological processes [52]. In contrast, the NCR maintains CRP and albumin as continuous variables, potentially allowing finer risk stratification and more precise prognostication [53]. Comparative studies suggest that the NCR outperforms these established markers in predicting survival outcomes. For instance, Okugawa et al. demonstrated that the NCR provided stronger prognostic discrimination than PNI, NLR, or GPS in large cohorts of colorectal cancer patients [54]. This highlights its potential to serve as an improved integrative biomarker, bridging the limitations of single-domain indices.

NCR in the Context of Targeted Therapy and Immunotherapy

The introduction of targeted therapies and immunotherapies has revolutionized the treatment landscape for metastatic colorectal cancer (mCRC). Agents such as anti-vascular endothelial growth factor (VEGF) antibodies (e.g., bevacizumab) and anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (e.g., cetuximab, panitumumab) have improved outcomes when combined with chemotherapy. More recently, immune checkpoint inhibitors, particularly anti-PD-1 antibodies, have shown remarkable efficacy in microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) subsets of mCRC. However, predictive biomarkers for treatment response remain limited, underscoring the potential utility of host-based prognostic indices such as the nutritional C-reactive protein ratio (NCR) [55]. [55]

Evidence suggests that patients with low NCR exhibit poorer responses to targeted therapies. Elevated systemic inflammation, reflected by increased CRP, is associated with resistance to anti-VEGF agents through upregulation of alternative angiogenic pathways and enhanced tumor hypoxia. Similarly, impaired nutritional reserves, indicated by low albumin, may reduce tolerance to treatment and increase the risk of dose reductions or treatment interruptions. Thus, patients with low NCR tend to experience inferior progression-free survival (PFS) and overall survival (OS) despite access to modern targeted regimens [56].

In the context of immunotherapy, systemic inflammation and nutritional decline may also impair treatment efficacy. A low NCR has been linked with reduced immunotherapy responsiveness, potentially due to chronic inflammation-driven immunosuppression and inadequate host immune competence. Elevated CRP is known to suppress T-cell activation and proliferation, while malnutrition impairs both innate and adaptive immunity, creating a biological environment unfavorable for checkpoint inhibitor activity. Preliminary studies indicate that higher NCR may correlate with improved survival among patients receiving PD-1 inhibitors, though prospective validation is required [57].

Importantly, the NCR may help guide supportive interventions to optimize treatment outcomes. For instance, patients with low ratios may benefit from early nutritional support, anti-inflammatory strategies, and close toxicity monitoring to enhance tolerance and improve efficacy of targeted and immune-based therapies. Such integrative approaches could maximize therapeutic benefit, particularly in frail or high-risk populations, reinforcing the clinical utility of NCR in modern oncologic practice [58].

Potential Mechanistic Insights: Inflammation–Nutrition–Tumor Progression Axis

The prognostic value of the nutritional C-reactive protein ratio (NCR) in metastatic colorectal cancer (mCRC) can be understood by examining the mechanistic links between systemic inflammation, nutritional decline, and tumor progression. Cancer is increasingly recognized as a systemic disease, where the host response plays a pivotal role in shaping tumor biology. Elevated CRP levels reflect an

activated inflammatory state, while hypoalbuminemia signals malnutrition and catabolic stress. Together, these pathways synergize to create a tumor-promoting microenvironment [59].

Systemic inflammation contributes directly to colorectal cancer progression through multiple mechanisms. Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) enhance tumor cell proliferation, angiogenesis, and metastasis. CRP itself, induced by IL-6, has been implicated in promoting tumor growth and immune evasion by modulating complement activation and macrophage polarization [60]. Chronic inflammation also drives epithelial-to-mesenchymal transition (EMT), enabling tumor cells to invade and disseminate.

Nutritional depletion and cancer-associated cachexia further amplify these effects. Reduced serum albumin not only reflects poor nutritional intake but also chronic protein catabolism driven by systemic inflammation. Malnutrition impairs both innate and adaptive immune responses, leading to decreased tumor surveillance and diminished responsiveness to systemic therapies. This nutritional decline weakens physical resilience, reduces treatment tolerance, and contributes to accelerated disease progression [61].

The interaction between inflammation and nutrition forms a vicious cycle that accelerates tumor progression. Inflammatory cytokines promote anorexia and metabolic alterations, leading to muscle wasting and hypoalbuminemia. In turn, poor nutritional status amplifies inflammation by impairing gut barrier function and facilitating microbial translocation, further stimulating systemic cytokine release [62]. The NCR, by integrating CRP and albumin, effectively captures this bidirectional axis, serving as a surrogate marker for the biological processes driving tumor progression.

Experimental evidence also suggests that targeting this inflammation–nutrition axis may alter clinical outcomes. Anti-inflammatory strategies, nutritional interventions, and cachexia-directed therapies are being investigated as adjuncts to systemic anticancer treatments. Monitoring the NCR could therefore serve not only as a prognostic biomarker but also as a dynamic tool to assess the biological impact of supportive care interventions [63].

Clinical Applications and Integration into Practice

The nutritional C-reactive protein ratio (NCR) offers significant potential for integration into routine oncologic practice due to its accessibility, low cost, and reproducibility. Unlike molecular biomarkers that require specialized assays and equipment, the NCR relies on two widely available laboratory tests—C-reactive protein and serum albumin—both of which are already part of standard clinical care in most oncology settings. This makes the NCR highly feasible for real-world application across diverse healthcare environments [64].

One of the most promising applications of the NCR is in **risk stratification** of patients with metastatic colorectal cancer (mCRC). By identifying individuals with lower ratios, clinicians can recognize those at increased risk of poor survival, treatment intolerance, and early progression. Such patients may benefit from intensified monitoring, early initiation of nutritional support, or consideration of modified treatment regimens to balance efficacy and toxicity [65].

The NCR may also serve as a useful tool in **treatment decision-making**. For instance, patients with lower ratios may derive limited benefit from aggressive multi-agent chemotherapy or targeted therapies, due to both tumor biology and host vulnerability. In these cases, treatment de-escalation or prioritization of quality-of-life–focused interventions may be more appropriate. [66].

Another important application is **dynamic monitoring during therapy**. Serial measurements of the NCR could provide insights into evolving host–tumor interactions and treatment response. Lower NCR values during treatment may signal early progression, reduced tolerance, or declining nutritional reserve, prompting timely clinical interventions. This dynamic role positions the NCR as not only a baseline prognostic marker but also a longitudinal biomarker of treatment trajectory [67].

Finally, in **multidisciplinary care**, the NCR can inform supportive care strategies. Lower values may trigger early referral to nutrition services, physiotherapy, or palliative care teams, helping optimize

patient outcomes beyond tumor-directed therapy. Thus, the NCR aligns well with the principles of personalized oncology, where treatment decisions are guided not only by tumor biology but also by host factors [68].

Conclusion

The nutritional C-reactive protein ratio (NCR) has emerged as a promising prognostic biomarker in metastatic colorectal cancer (mCRC), integrating two critical determinants of cancer outcomes: systemic inflammation and host nutritional status. A growing body of evidence demonstrates that low NCR are consistently associated with adverse clinicopathological features, reduced treatment responsiveness, and poorer survival outcomes. Compared with established inflammation- or nutrition-based indices such as PNI, NLR, and GPS, the NCR appears to provide superior prognostic accuracy by simultaneously capturing both domains in a simple, universally available metric.

From a clinical perspective, the NCR is highly attractive due to its feasibility, cost-effectiveness, and ease of incorporation into routine practice. It holds potential value in risk stratification, guiding treatment intensity, monitoring therapeutic response, and informing supportive care interventions. Furthermore, its utility may extend to patients receiving targeted therapies and immunotherapy, where systemic inflammation and nutritional decline influence treatment efficacy.

Despite these advantages, important limitations remain. Heterogeneity in cutoff definitions across studies, lack of prospective validation, and limited integration into standardized prognostic models currently hinder widespread adoption. Additionally, the NCR lacks cancer specificity, as both CRP and albumin can be influenced by comorbidities such as infections, liver disease, and chronic inflammatory disorders. Addressing these limitations through well-designed, large-scale prospective trials and harmonization of methodology will be essential for clinical translation.

Looking forward, the NCR represents more than a static biomarker; it may serve as a dynamic indicator of tumor–host interaction and a potential target for supportive interventions. By combining inflammation modulation with nutritional optimization, clinicians may not only improve prognostic accuracy but also alter the disease trajectory for high-risk patients. Ultimately, integrating the NCR into multidisciplinary care pathways could contribute to more personalized and holistic management of metastatic colorectal cancer, bridging the gap between tumor-directed therapies and host-centered care.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422.
3. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883-899.
4. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumor site. *Br J Cancer*. 2011;104(4):726-734.
5. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal cancer. *Ann Surg Oncol*. 2016;23(3):900-907.
6. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol*. 2019;14(2):89-103.
7. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691.
8. Kopetz S, Grothey A, Yaeger R, et al. Metastatic colorectal cancer. *N Engl J Med*. 2019;381(17):1634-1647.
9. Rajan S, Foreman J, Skrepnek GH, et al. Economic burden of metastatic colorectal cancer: a systematic review. *Pharmacoeconomics*. 2019;37(3):399-414.
10. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer.

Cancer Treat Rev. 2013;39(5):534-540.
11. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15(11):e493-e503.
12. Pressoir M, Desné S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French cancer patients. *Br J Cancer*. 2010;102(6):966-971.
13. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495.
14. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of outcome. *Clin Med*. 2009;9(1):30-33.
15. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care*. 2009;12(3):223-226.
16. Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol*. 2015;22(3):803-810.
17. Liu Y, Chen S, Zheng C, et al. Prognostic value of C-reactive protein to albumin ratio in colorectal cancer patients: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2021;36(9):1801-1811.
18. Shibutani M, Maeda K, Nagahara H, et al. The prognostic value of the preoperative C-reactive protein/albumin ratio in patients with colorectal cancer. *World J Surg Oncol*. 2016;14(1):85.
19. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. 1999;340(6):448-454.
20. Black S, Kushner I, Samols D. C-reactive protein. *J Biol Chem*. 2004;279(47):48487-48490.
21. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*. 2010;6(1):149-163.
22. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. C-reactive protein is an important biomarker for prognosis, tumor recurrence and treatment response in adult solid tumors: a systematic review. *PLoS One*. 2015;10(12):e0143080.
23. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805-1812.
24. Mohri Y, Inoue Y, Tanaka K, et al. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. *World J Surg*. 2013;37(11):2688-2692.
25. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. 2005;20(1):38-45.
26. Okugawa Y, Toiyama Y, Yamamoto A, et al. C-reactive protein/albumin ratio as a novel prognostic marker in colorectal cancer patients: a large multicenter study. *Eur J Surg Oncol*. 2018;44(7):1073-1079.
27. McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between the C-reactive protein/albumin ratio and survival in patients with operable colorectal cancer: a validation study. *Ann Surg Oncol*. 2018;25(1):176-183.
28. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol*. 2009;16(3):614-622.
29. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88(1):218-230.
30. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med*. 2014;371(17):1609-1618.
31. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773-779.
32. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36(1):11-48.
33. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer*. 2014;14(11):754-762.
34. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers*. 2018;4:17105.
35. Haruki K, Shiba H, Shirai Y, et al. Perioperative C-reactive protein to albumin ratio is a prognostic factor for hepatocellular carcinoma. Surg Today. 2016;46(8):882-889.
36. Gao Y, Huang D, Zhang H, et al. Prognostic value of the C-reactive protein/albumin ratio in patients with colorectal cancer: a meta-analysis. Medicine (Baltimore). 2018;97(50):e13404.
37. Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: systematic review and meta-analysis. Sci Rep. 2017;7(1):16717.
38. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. Int J Mol Sci. 2021;22(15):8002.
39. Kanda M, Mizuno A, Tanaka C, et al. Nutritional predictors of postoperative outcomes in gastrointestinal cancer surgery. Ann Gastroenterol Surg. 2021;5(5):639-651.
40. Watt DG, Proctor MJ, Park JH, et al. The Neutrophil–platelet score (NPS) predicts survival in patients with cancer. Br J Cancer. 2015;112(6):1019-1024.
41. Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The role of systemic inflammation in predicting outcomes in patients with advanced cancer: systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;116:1-14.

42. Shibutani M, Maeda K, Nagahara H, et al. Prognostic significance of the preoperative C-reactive protein-to-albumin ratio in patients with gastric cancer. Anticancer Res. 2016;36(2):851-858.
43. Fang Y, Xu C, Wu P, et al. Prognostic role of C-reactive protein to albumin ratio in colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2019;34(12):2147-2156.
44. Szkandera J, Stotz M, Eisner F, et al. External validation of the Glasgow Prognostic Score in patients with colorectal cancer. Br J Cancer. 2013;109(1):131-136.
45. Zhou T, Zhan J, Hong S, et al. Ratio of C-reactive protein/albumin is an inflammatory prognostic score for predicting overall survival of patients with small-cell lung cancer. Sci Rep. 2015;5:10481.
46. Roxburgh CSD, McMillan DC. Cancer and systemic inflammation: treat the tumour and treat the host. Br J Cancer. 2014;110(6):1409-1412.
47. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-166.
48. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-444.
49. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-674.
50. Dolan RD, Laird BJA, Horgan PG, McMillan DC. The prognostic value of systemic inflammation in cancer patients: meta-analysis of the neutrophil-lymphocyte ratio. J Natl Cancer Inst. 2018;110(6):761-769.
51. Oki S, Toiyama Y, Okugawa Y, et al. Clinical burden of nutritional and inflammatory status in colorectal cancer patients. Ann Gastroenterol Surg. 2019;3(5):563-574.
52. Kawai K, Watanabe T. Prognostic factors in colorectal cancer: from the patient's background to molecular markers. Cancer Sci. 2022;113(3):753-761.
53. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124.
54. Okamoto T, Iritani K, Ishida H, et al. Inflammation-based prognostic scores in metastatic colorectal cancer patients treated with regorafenib. Mol Clin Oncol. 2018;9(5):499-504.
55. Shimizu T, Ishizuka M, Takagi K, Nagata H, Iwasaki Y, Kubota K. Clinical significance of the preoperative C-reactive protein to albumin ratio in colorectal cancer patients with liver metastasis. Anticancer Res. 2017;37(2):633-638.
56. Lin JX, Lin JP, Xie JW, et al. Prognostic value of the C-reactive protein/albumin ratio in gastric cancer: a meta-analysis. Cancer Manag Res. 2019;11:317-326.
57. Park JH, Watt DG, Roxburgh CS, et al. Colorectal cancer, systemic inflammation, and outcome: staging the tumor and staging the host. Int J Cancer. 2017;141(8):1478-1488.
58. He W, Yin C, Guo G, et al. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. Med Oncol. 2013;30(1):439.
59. Zhang J, Zhang HY, Li J, Shao J, Chen X. Prognostic role of C-reactive protein to albumin ratio in patients with solid tumors: a systematic review and meta-analysis. Sci Rep. 2017;7(1):41298.
60. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumors. Surg Oncol. 2014;23(1):31-39.
61. Toiyama Y, Inoue Y, Saigusa S, et al. C-reactive protein as predictor of recurrence and survival in colorectal cancer patients. Int J Cancer. 2016;139(5):946-955.
62. McMillan DC. The role of nutrition and systemic inflammatory response in colorectal cancer prognosis. Future Oncol. 2014;10(9):1353-1356.
Dolan RD, McMillan DC. Inflammation, nutrition, and prognosis in patients with cancer: a critical appraisal of the evidence. Nutrients. 2020;12(11):3714