Clinical Case Reports International

Review Article
Published: 27 May, 2023

Role of Systemic Inflammation Markers in Colorectal Cancer Prognosis - A Narrative Review

Iaciu CI[1,2], Emilescu RA[3,4], Cotan HT[1], Orlov C[1,2], Popa AC[1,2] and Nitipir C[1,2]*

[1]Department of Oncology, Elias Emergency University Hospital, Romania

[2]Department of Medical Oncology, Carol Davila University of Medicine and Pharmacy, Romania

[3]Department of Endocrinology, C.I. Parhon National Institute of Endocrinology, Romania

[4]Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Romania

Abstract

Introduction: Systemic inflammation plays an essential role in cancer promotion, progression, and metastasis. The scope of this review is to establish the role of various inflammation-based markers as prognostic tools in Colorectal Cancer (CRC).

Methods: A literature search was performed for articles that reported on the prognostic and predictive value of the Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), Lymphocyte-Monocyte Ratio (LMR), and Glasgow Prognostic Score as well as the modified Glasgow Prognostic Score (GPS/mGPS) in relation to CRC.

Conclusion: Further prospective studies may result in better risk stratification in patients eligible for curative surgery, limiting the administration of neo-adjuvant and adjuvant therapy to high-risk candidates. In patients with unresectable metastatic disease, inflammation markers can be used as a tool for predicting chemotherapeutic outcomes and monitoring tumor progression.

Introduction and Background

Colorectal Cancer (CRC) is a significant public health issue; currently, it is the third most prevalent cancer with 1,931,590 cases diagnosed in 2020 behind breast and lung cancer. In 2020 colorectal cancer accounted for 9.4% of the total cancer-related deaths with 935,173 deaths. These numbers are predicted to increase to 3.2 million new cases and 1.6 million deaths per year by 2040 [1,2]. Despite advancements in surgical methods, adjuvant and neoadjuvant therapy dose, and scheduling, the 5-year survival rate for patients with CRC ranges from 90% to 10% with tumor [3]. Currently, the International Union Against Cancer (UICC-TNM) [4] and American Joint Committee on Cancer (AJCC) [5] staging categories are used to predict the prognosis of newly diagnosed CRC patients. Several parameters for predicting survival in CRC patients have been identified, including patient characteristics (performance status, age, gender) and tumor characteristics (TNM stage, biomarkers, gene mutations), but it is well known that survival time can vary even among patients with the same characteristics and disease stage at diagnosis. The host inflammatory response to tumors is currently one of the most intriguing areas of clinical investigation. In many cancer forms, systemic inflammation has been shown to be significantly related to the risk and amount of metastatic involvement [6,7]. A series of studies have shown that inflammation may play an important role in cancer growth and metastasis because inflammatory mediators enhance vascular permeability, allowing cancer cells to infiltrate lymphatic and blood arteries. Additionally, these cytokines contribute to tumor angiogenesis and protumoral immune cell recruitment [8,9].

Although several cytokines are involved in the systemic inflammatory response, Interleukin-6 (IL-6) plays a critical role due to its capacity to boost the synthesis of acute phase proteins, notably C-Reactive Protein (CRP), while decreasing albumin production in the liver. It also accelerates the development of megakaryocytes into platelets, is implicated in neutrophil recruitment, and can boost thrombopoietin synthesis, resulting in increased platelet numbers [10-12]. Another important cytokine in the antitumoral systemic inflammatory response is TGF-β which polarizes antitumoral neutrophils into protumoral neutrophils. This polarization creates a tumor immune microenvironment conducive to tumoral growth and invasion [13,14]. Numerous studies have evaluated the role of inflammatory response in the tumor microenvironment and as a result, an increasing number of inflammatory scores have been proposed for predicting survival in several

OPEN ACCESS

Correspondence:
Horia-Teodor Cotan, Department of Oncology, Elias Emergency University Hospital, Bucharest, ROU, Romania, E-mail: horia-teodor.cotan@rez.umfcd.ro

Received Date: *10 May 2023*
Accepted Date: *23 May 2023*
Published Date: *27 May 2023*

Citation:
Iaciu CI, Emilescu RA, Cotan HT, Orlov C, Popa AC, Nitipir C. Role of Systemic Inflammation Markers in Colorectal Cancer Prognosis - A Narrative Review. Clin Case Rep Int. 2023; 7: 1551.

tumor types. Several of these inflammatory biomarkers have been included in colorectal prognostication models such as Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS), others biomarkers such as Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR) and Lymphocyte-to-Monocyte Ratio (LMR) have been extensively researched as independent prognostic factors for survival in patients with colorectal cancer [15-17].

The aim of the current review is to provide an overview of the role of inflammatory biomarkers in colorectal cancer prognosis.

Methods

A literature search evaluating the prognostic role of Glasgow Prognosis Score (GPS), modified GPS (mGPS), Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and Lymphocyte-Monocyte Ratio (LMR) was conducted in the National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE), and the Cochrane Database of Systematic Reviews (CDSR). The inclusion criteria consisted of only English-language research articles that reported on the prognostic value of the aforementioned biomarkers. We examined the title and abstract of each identified study, and the full text of the study was obtained for relevant studies.

Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS)

The Glasgow Prognosis Score (GPS), an inflammation-based cancer-prognostic marker constituted of serum CRP elevation and albumin concentration decrease, is considered to reflect the host systemic inflammatory response as well as his metabolic stress, and has been demonstrated to be a helpful prognostic factor in the survival of patients with colorectal cancer [18]. According to the GPS individuals with both increased CRP (>10 mg/l) and hypoalbuminemia (3.5 g/dL receive a score of 2; individuals with just one parameter or none of these biochemical abnormalities receive a score of 1 or 0, respectively. Since hypoalbuminemia alone does not have prognostic value the GPS has been modified as follows: The mGPS score can have a value of 0 for patients with low CRP ≤ 10 mg/L and any value of albumin, 1 for patients with CRP>10 mg/L and albumin ≥ 3.5 g/dL, and 2 for patients with CRP>10 mg/L and albumin <3.5 g/dL [19,20].

Numerous studies have suggested that GPS/mGPS is an important prognostic factor for survival in patients diagnosed with CRC. A retrospective study that included 105 patients diagnosed with stage I-IV CRC showed that patients with elevated GPS/mGPS had a lower rate of survival independently from other common factors that influence survival such as TNM stage and tumor differentiation [18]. Another similar retrospective study which included 271 patients with stage I-IV CRC showed that an elevated mGPS had a lower 5-year survival rate (mGPS 2 *vs.* mGPS 1 *vs.* mGPS 0; 35.2% *vs.* 74.9% *vs.* 92.6%, p=0.0001) [21].

A high GPS score has been shown to reflect metabolic stress, more precisely malnutrition in patients with CRC [22]. Richards et al. assessed 174 patients with CRC from stage I to III and discovered a tight connection between high mGPS and sarcopenia (p=0.001). However, there was no link between CRP and the total fat index, subcutaneous fat index, or visceral fat index. Albumin had no relationship with the total fat index or the subcutaneous fat index, but it did have a significant positive link with the visceral fat index (p=0.02) and the skeletal muscle index (p=0.001) [23]. Mauricio et al. reported in a prospective study that all patients with a GPS 2 were malnourished according to the Subjective Global Assessment (SGA), while 80.9% of patients with GPS 0 had no signs of malnutrition. There was a significant correlation between the three SGA categories (A-well nourished, B-moderately malnourished, C-severely malnourished) and GPS/mGPS score, suggesting inflammation's role in cancer-induced cachexia [22].

Several studies have shown that GPS/mGPS is a useful prognostic model in resectable early-stage CRC, in terms of both postoperative complications as well as survival [23-26]. Moyes et al. reported an association between postoperative complications such as infectious complications, pulmonary embolism, cardiac complications, and a higher GPS [27]. Similarly, Park et al. conducted a comprehensive retrospective analysis to assess the predictive impact of mGPS and its association with other prognostic markers in 1,000 patients with early-stage CRC (stage I to III) undergoing possibly curative surgery. A high mGPS level was linked with aging and emergency presentation (both p<0.001), primary site, increasing T and TNM stage, poor tumor differentiation, surgical margin involvement, peritoneal involvement, and tumor perforation (all p=0.001). Cancer-Specific Survival (CSS) ranged from 80% in patients with mGPS=0 to 61% in people with mGPS =2. Overall Survival (OS) was also reduced with a 5-year OS of 70% for patients with a mGPS=0 to 46% in patients with mGPS=2 [28].

The role of adjuvant chemotherapy is uncertain in stage II CRC, so newly validated prognostic models can be useful for better patient selection. A retrospective study done on 99 patients with stage II CRC who underwent curative surgery has shown that patients with a mGPS of 0 had a 5-year OS of 83.6%, while patients with a mGPS of 1 and 2 had a 5-year OS of 75.9% and 33.3%, respectively [29]. A retrospective study by Sugimoto et al. reported that after multivariate analysis mGPS was the strongest prognostic factor for CSS in patients with stage II CRC, in stage III CRC therre was no significant correlation between CSS and mGPS [30]. Some studies have reported that a higher GPS score is associated with a higher risk of distant metastasis [31].

Palliative surgical resections are advised in some patients with metastatic CRC (mCRC) to ease symptoms such as blockage, perforation, or bleeding. Kishiki et al. investigated the predictive value of mGPS in 79 mCRC patients who underwent palliative surgical procedures (resection of a main lesion alone, bypass surgery, or colostomy). The presence of lung metastases, peritoneal spread, distant metastases, low hemoglobin, elevated CRP levels, decreased albumin, and prior chemotherapy were all associated with lower overall survival. Tumor excision, adjuvant chemotherapy, and mGPS were all used. When the population was separated into three groups based on mGPS score, significant differences in mean survival time were found: with mGPS=0/1/2, CSS was 24, 18, and 8 months, respectively (95% CI of 19 to 37 months, 7 to 41 months, and 1 to 9 months, respectively) [32].

A retrospective study by Adachi et al. with a cohort of 65 patients with mCRC who received surgical intervention and systemic chemotherapy showed that mGPS is an independent predictor of fatality rate. A greater 3-month death rate was associated with a higher mGPS score (p=0.00001) and multivariate analysis demonstrated that mGPS (0/1, 2) was an independent risk factor [33]. Furukawa et al. investigated the role of GPS in 40 patients with unresectable

synchronous and metachronous liver metastases from CRC [34]. The absence of initial tumor resection and systemic treatment, blood CEA>100 ng/ml, serum CA19-9 100 U/ml, and GPS=2 (p=0.0362) were significant predictors of inferior outcome. Recent research has revealed that mGPS can predict outcomes in mCRC patients who have undergone chemotherapy. Ishizuka et al. conducted a retrospective study of a cohort of 112 patients who were taking chemotherapy for advanced or recurrent CRC with regimens such as FOLFIRI (5-Fluorouracil/Leucovorin/Irinotecan hydrochloride) or FOLFOX (5-Fluorouracil/l-Leucovorin/Oxaliplatin) and found that a mGPS=2 predicted a greater risk of mortality than mGPS=0 or 1 (p<0.001). Only mGPS was found to be an independent risk factor of death in multivariate analyses that included neutrophil ratio, CA 19-9, CRP, albumin, and mGPS.

Dréanic et al. investigated the predictive effect of GPS in 49 patients with mCRC who were receiving 5-fluorouracil with cetuximab and oxaliplatin (60%) or irinotecan (30%) [35]. 55%, 29%, and 16% of patients had GPS values of 0, 1, and 2, respectively, at the time of diagnosis. In the first group, median Progression-Free Survival (PFS) and median Overall Survival (OS) were considerably longer (p=0.0084 and 0.0093, respectively). GPS was also tested in a group of 80 patients with mCRC who were taking bevacizumab and 5-fluorouracil plus oxaliplatin (51%) or irinotecan (34%). At diagnosis, 56%, 31%, and 13% of patients had GPS values of 0, 1, and 2, respectively. The median PFS in these groups was 10.1, 6.5, and 5.6 months, respectively (p=0.16). The median OS was 20.1, 11.4, and 6.5 months (p=0.004), respectively. Sharma et al. investigated 55 patients with mCRC undertaking first-line oral capecitabine mono chemotherapy. GPS (p=0.016), colonic primary (p=0.022), high CEA (p=0.027), and hypoalbuminemia (p=0.008) were significant predictors of CSS on univariate analysis; patients with GPS scores equal to 2 had a lower OS compared to those with GPS scores of 0 or 1 [36].

Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor in CRC

The antitumoral inflammatory response is distinguished by an increase in circulating neutrophil levels and a decrease in circulating lymphocyte levels. Because a high concentration of neutrophils is known to promote tumor progression and to suppress the antitumor effect of lymphocytes, the Neutrophil-Lymphocyte Ratio (NLR) may be regarded as the balance between pro-tumor inflammatory status and antitumor immune status. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Several studies suggested that an imbalance of neutrophils and lymphocytes in peripheral blood is correlated with the imbalance of the same cells in the tumor microenvironment and that this imbalance can be associated with tumor development [37-39]. Although the NLR is associated with survival, the GPS/mGPS appears to be a better predictor of survival. In a large cohort study (Glasgow Inflammation Outcome Study), mGPS outperformed the NLR. Although an advantage of NLR is that it can distinguish between good and bad prognostic groups in a range of tumor types, including CRC [40]. A retrospective study by Inamoto et al. showed that the combination of the NLR and GPS/mGPS into a novel prognostic model for CRC survival was superior to the NLR and GPS/mGPS alone [41]. Because of its ease of calculation, the preoperative NLR is gaining popularity as a prognostic marker; its relevance in predicting disease recurrence and postoperative problems has been explored at length in the literature. Interestingly, several studies have revealed that assessing local lymphocyte response, which is defined as a prominent lymphocytic reaction near the invasive boundary, is related to a lower NLR and thus a better prognosis [39]. Cook et al. discovered that a high NLR value on the first postoperative day is a good predictor of postoperative complications. In this study, the NLR cut-off was high with a cut-off value of 9.3, one argument for this high cut-off value is its proximity to the surgery [42].

In a retrospective investigation of 524 patients with stage II-III CRC who underwent curative laparotomic resection, Kubo et al. developed a novel NLR score based on both preoperative and postoperative neutrophil and lymphocyte counts. Adjuvant chemotherapy was administered according to their risk class, 156 individuals with stage III CRC and 38 patients with stage II received the treatment. Patients with R1 and R2 resections and those undergoing emergency intervention, laparoscopic surgery, multiple carcinomas, inflammatory bowel disease, preoperative clinical evidence of infection, or other inflammatory conditions were excluded. Neutrophil and lymphocyte counts were performed as follows: Before surgery, on the first postoperative day, and on the third or fourth postoperative day. Patients were categorized into two groups: Those with a low perioperative NLR (score of 0 or 1) and those with a high perioperative NLR (score of 2 or 3). NLR score was found to be an independent risk factor for both DFS (HR=1.53, 95% CI 1.01-2.37; p=0.02) and CSS (HR=1.71, 95% CI 1.03-2.88; p=0.04) in multivariate analyses [43].

In a retrospective study performed by Yasui et al. on 568 stage I-III CRC patients, patients were stratified by inflammation status: Preoperative low NLR (normal group), preoperatively high NLR but normalized after surgery (normalized group), and persistently high NLR (elevated group). They reported an OS time superior for the normal and normalized group compared to the elevated group [44].

The function of NLR in resectable CRC liver metastases was explored in a retrospective study of 169 patients who had liver resection after neoadjuvant chemotherapy. The previously established NLR cut-off number was 2.5. Higher NLR was linked with both lower OS (HR=1.17; 95% CI, 1.03-132; p=0.011) and increased probability of extrahepatic/multifocal recurrence (p=0.007), implying a decreased post-recurrence survival (HR=1.24, 95% CI, 1.02-1.52; p=0.032) [45]. Similarly in another retrospective study of 289 patients with resectable liver metastases, patients with high NLR had significantly lower 5-year survival than patients with lower NLR (22% *vs.* 43%, p<0.001). On both univariate and multivariate analysis, high NLR was associated with a poorer survival outcome (p <0.001) [46].

Ganhim et al. conducted a prospective study on 52 patients who were candidates for the first excision of CRC pulmonary metastases. Neutrophil and lymphocyte counts were measured upon admission to the hospital, prior to surgery or any other procedure. The NLR cut-off value was determined to be 4. Patients were divided into two groups, an inflammatory phenotype group (high NLR and mGPS value), and a non-inflammatory phenotype group (no signs of systemic inflammation). The inflammatory phenotype group had a shorter median OS time as well as a shorter time to recurrence [47].

A series of retrospective studies reported that NLR could have predictive value for liver recurrence after metastasectomy. Giakoustidis et al. reported that patients with an elevated NLR had a higher risk of hepatic recurrence [45]. Verter et al. showed that a high

NLR value after metastasectomy was associated with a higher rate of extrahepatic recurrence [48].

Elevated NLR appears to be a strong predictor of poor response to palliative chemotherapy in individuals with unresectable mCRC, regardless of treatment. A retrospective by Chua et al. evaluated the prognostic role of NLR in a study that included 349 patients with unresectable mCRC who were receiving first-line palliative care chemotherapy [49].

Another retrospective study performed by Kaneko et al. included 50 patients with metastatic CRC treated with oxaliplatin-based chemotherapy. After ROC curve analysis the NLR cut-off value was set to 4. In univariate analysis, a higher NLR value, hypoalbuminemia, and worse performance status was correlated with a shorter OS and PFS. In multivariate analysis, NLR (HR=4.39, 95% CI 1.82-10.7, p=0.0013) and thrombocytosis (HR=5.02, 95% CI 1.69-13.4; p=0.0066) were the only variables that were significantly associated with OS [50].

A retrospective analysis of 104 patients with CRC with unresectable liver metastases who were treated with liver radioembolization after failing first and second-line chemotherapy found that NLR could be a valuable biomarker for predicting outcome in these patients. A cutoff value of 5 was determined using ROC analysis. The median survival time for patients with elevated NLR was 5.6 *vs.* 10.6 months. A high NLR value, a lack of radiographic response after radioembolization, and the presence of extrahepatic illness were all independently correlated with an increased risk of death in a multivariate analysis [51].

Platelet-to-Lymphocyte Ratio (PLR)

Similar to neutrophils platelets are a common blood component with a significant role in the antitumoral inflammatory response. Thrombocytosis is frequently detected in solid tumor patients with persistent inflammation [52,53]. Platelets can stimulate tumor growth by secreting a variety of cytokines and growth factors in the tumor microenvironment that are conducive to tumor growth and invasion. The main cytokines are proangiogenic factors such as Vascular Epidermal Growth Factor (VEGF) and Transforming Growth Factor-Beta (TGF-β). PLR is a well-known prognostic factor for CRC, an increase in platelet count is usually associated with a decrease in lymphocyte count.

Most studies assessed or compared the Platelet-Lymphocyte Ratio (PLR) to the NLR. In a retrospective study conducted by Emir et al., PLR was assessed in three groups of patients: The first with only colorectal polyps (n=100; Group A), the second with CRC (n=113; Group B), and the third with solely healthy people (n=124; Group C). Patients in group B had a higher median NLR and PLR value compared to patients in groups A and C. There was no significant difference between groups A and C regarding NLR and PLR [54].

Ishizuka et al. assessed the predictive value of an inflammation-based prognostic score which includes platelet count and the NLR in retrospective research on 490 patients with resectable CRC. The COP-NLR (Combination of Platelet count and Neutrophil to Lymphocyte Ratio), was calculated as follows: Patients with elevated NLR (>3) and elevated platelet count (>30 × 10^4 mm^{-3}) were allocated 2 points, and patients with only one parameter elevated parameter had a score of 1. Patients with no elevated parameters had a score of 0. In both univariate and multivariate analyses, the COP-NLR score showed a significant correlation with CSS [55].

Patients with stage II CRC and low preoperative PLR who have undergone curative surgery had no high risk of recurrence and did not benefit from adjuvant chemotherapy exhibited significantly better CSS and PFS compared to patients with high preoperative PLR [56].

He et al. looked at the prognostic and predictive value of NLR and PLR in 243 patients with newly diagnosed mCRC, excluding those with infection, hematological illness, hyperpyrexia, or intestinal obstruction. While only the NLR was verified as an independent predictive factor for OS in multivariate analysis, elevated levels of both the NLR and PLR were related to a shorter OS time in univariate analysis, showing that the NLR is preferable to the PLR as a prognostic factor for survival in CRC patients [57].

In a retrospective study by Erstad et al., 151 patients with Colorectal Liver Metastases (CRLM) who underwent liver resection a PLR>220 and an NLR>5 were independent variables that decreased OS in both univariate as well as multivariate analysis [58].

The role of PLR as a predictive factor for patients with resected CRLM was evaluated in a retrospective study by Neofytou et al.; preoperative NLR was high (>2.4) in 53 patients while preoperative PLR was high (>150) in 58 patients. Elevated NLR and PLR were associated with decreased OS and PFS in univariate analysis, while only PLR remained significantly associated with PFS and OS in multivariate analysis [59].

Lymphocyte-to-Monocyte Ratio (LMR)

Monocytes play a vital role in tumor growth in the tumor microenvironment. Tumor-Associated Macrophages (TAMs) are formed when monocytes differentiate into protumoral macrophages as a result of the tumor microenvironment. TAMs can contribute to tumor infiltration and metastasis. Circulating lymphocytes, on the other hand, can transform into Tumor-Infiltrating Lymphocytes (TILs) by migrating into the tumor microenvironment; it has been established that stage III CRC patients with a high number of TILs had a better prognosis [60,61].

Zhang et al. reported in a study done on 270 patients with resected T3N0M0 CRC that an elevated monocyte count (>595/mm^3) was correlated with poor OS and DFS [62]. Similarly, Sasaki et al. reported that an elevated monocyte count (>300/mm^3) was associated with poor CSS in CRC patients with liver metastases who underwent metastasectomy [63].

A study of 372 patients with stage II and III colon cancer found that patients with preoperative LMR>2.83 had significantly better time-to-recurrence and OS than patients with LMR ≤ 2.83 and that the benefit of adjuvant 5-FU-based chemotherapy was limited to patients with LMR>2.83. Increased preoperative LMR was associated with longer time-to-recurrence (HR=0.47, 95% CI: 0.29-0.76, p=0.002) and OS (HR=0.48, 95% CI: 0.29-0.78, p=0.003) in univariate analysis and remained significant in multivariate analysis for both time-to-recurrence and OS [64].

Chang et al. were the first to use SIS as a predictive factor in patients with renal cell carcinoma. SIS is a novel prognostic model that uses the serum albumin level and LMR. Patients with albumin >4.0 g/dL and LMR>4.44 were assigned a score of 0, patients with albumin >4.0 g/dL and LMR>4.44 were assigned a score of 2, and everyone else was assigned a score of 1 [65]. Suzuki et al. examined 727 stages

I-IV CRC patients who underwent curative resection and found that higher SIS and higher mGPS scores were both independently related to a worse prognosis [66]. By using a time-dependent ROC curve to assess the prediction abilities of SIS and mGPS, they discovered that SIS was a better prognostic model for OS than mGPS.

CRP-Related Markers

CRP is an excellent biomarker to evaluate the inflammation status of cancer patients. As a prognostic factor in CRC Koike et al. evaluated 300 patients with CRC and showed that a high preoperative value of CRP (>0.5 mg/dL) was an independent predictor of prognosis [67]. Another CRP-related prognostic marker is the Lymphocyte-C-Reactive protein ratio (LCR). In a large retrospective study by Suzuki et al., they evaluated the prognostic value of 16 inflammation-related markers such as NLR, LMR, PLR, Neutrophil-to-Albumin Ratio (NAR), Monocyte–Albumin (MAR), Platelet–Albumin Ratio (PAR) and LCR in 1303 patients with stage II-III CRC. The study reported that a low LCR value (≤ 12,980) was associated with a lower OS and DFS median time [68].

A similar prognostic marker to LCR for CRC survival is CAR (C-reactive protein-to-albumin ratio). Several studies have evaluated the role of CAR in postoperative CRC survival, the main consensus is that a higher value is significantly correlated to a shorter OS and CSS [69-71].

Discussion

One of the most important indications of tumor development is the cancer-associated systemic inflammatory response. The relationship between hematological indicators of the systemic inflammatory response and survival outcomes in cancer patients has been an intensely studied subject. One of the most important indications of tumor development is the cancer-associated systemic inflammatory response. Numerous previous studies have identified serum systemic inflammatory markers that can be used to predict prognoses, such as the Glasgow Prognostic Score and the modified Glasgow Prognostic (GPS/mGPS), Neutrophil-Lymphocyte Ratio (NLR), Lymphocyte-Monocyte Ratio (LMR), Platelet-Lymphocyte Ratio (PLR), LCR (Lymphocyte-C-Reactive protein ratio), SIS (Systemic Inflammation Score). One of the biggest advantages of these markers is their availability by use of routine blood examinations.

Despite these advantages, the majority of studies that evaluated potential inflammatory prognostic markers are retrospective in nature and do not have a shared platform of exclusion criteria regarding patient pathologies or treatments that could skew the blood cell count. Also, the best cut-off value can vary between patient groups and cancer types, which makes any conclusion regarding the clinical utility of these scores difficult. However, the results of the studies presented in this review suggest that inflammatory biomarkers of prognosis have value in patients treated with curative intent, in patients with advanced CRC that receive palliative chemotherapy where inflammation scores have been associated with PFS, and in patients with resectable liver or lung metastases where inflammation scores seem to be associated with a poor DFS.

In this review, we have analyzed the main inflammatory biomarkers that have been developed and validated, and accumulating evidence suggests that inflammation-based biomarkers appear to be independent powerful prognostic indicators; thus, combining these criteria with traditional clinicopathological markers may be beneficial. Further prospective research is needed to find the optimal cut-off values.

References

1. WHO. Colorectal cancer. International Agency for Research on Cancer. 2020.
2. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, et al. Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. Gut. 2023;72:338-44.
3. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004;96:1420-5.
4. Sobin L, Wittekind C, editors. TNM classification of malignant tumors. New York: Wiley-Liss, 2002.
5. AJCC. Cancer staging manual, 6th Ed. New York: Springer, 2002.
6. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-6.
7. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and tumor progression: Signaling pathways and targeted intervention. Sig Transduct Target Ther. 2021;6:263.
8. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860-7.
9. Guadagni F, Ferroni P, Palmirotta R, Portarena I, Formica V, Roselli M. Review: TNF/VEGF cross-talk in chronic inflammation- related cancer initiation and progression: An early target in anticancer therapeutic strategy. *In Vivo*. 2007;21:147-61.
10. Ohsugi Y. Recent advances in immunopathophysiology of interleukin-6: An innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biol Pharm Bull. 2007;30:2001-6.
11. Imai T, Koike K, Kubo T, Kikuchi T, Amano Y, Takagi M, et al. Interleukin-6 supports human megakaryocytic proliferation and differentiation *in vitro*. Blood 1991;78:1969-74.
12. Klinger MH, Jelkmann W. Role of blood platelets in infection and inflammation. J Interferon Cytokine Res. 2002;22:913-22.
13. Sagiv JY, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, et al. Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Rep. 2015;10(4):562-73.
14. Chraa D, Naim A, Olive D, Badou A. T lymphocyte subsets in cancer immunity: Friends or foes. J Leukoc Biol. 2019;105(2):243-55.
15. Mazaki J, Katsumata K, Kasahara K, Tago T, Wada T, Kuwabara H, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: A propensity score analysis. BMC Cancer. 2020;20(1):922.
16. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, et al. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who did not receive adjuvant chemotherapy. Int J Colorectal Dis. 2011;26:1059-65.
17. Wu Y, Li C, Zhao J, Yang L, Liu F, Zheng H, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis. World J Surg Oncol. 2016;14(1):289.
18. Choi KW, Hong SW, Chang YG, Lee WY, Lee B, Paik IW, et al. Inflammation-based score (Glasgow prognostic score) as an independent prognostic factor in colorectal cancer patients. Ann Surg Treat Res. 2014;86(6):309-13.
19. McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis. 2007;22(8):881-6.

20. Hirahara N, Matsubara T, Kaji S, Kawabata Y, Hyakudomi R, Yamamoto T, et al. Glasgow prognostic score is a better predictor of the long-term survival in patients with gastric cancer, compared to the modified Glasgow prognostic score or high-sensitivity modified Glasgow prognostic score. Oncotarget. 2020;11:4169-77.

21. Nozoe T, Matono R, Ijichi H, Ohga T, Ezaki T. Glasgow Prognostic Score (GPS) can be a useful indicator to determine prognosis of patients with colorectal carcinoma. Int Surg. 2014;99(5):512-7.

22. Maurício SF, da Silva JB, Bering T, Correia MI. Relationship between nutritional status and the Glasgow Prognostic Score in patients with colorectal cancer. Nutrition. 2013;29(4):625-9.

23. Richards CH, Roxburgh CS, MacMillan MT, Isswiasi S, Robertson EG, Guthrie GK, et al. The relationships between body composition and the systemic inflammatory response in patients with primary operable colorectal cancer. PLoS One. 2012;7(8):e41883.

24. Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. Ann Surg. 2007;246(6):1047-51.

25. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with anormal preoperative serum level of carcinoembryonic antigen. Ann Surg Oncol. 2012;19(11):3422-31.

26. Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC. Comparison of the prognostic value of inflammation based pathologic and biochemical criteria in patients undergoing potentially curative resection for colorectal cancer. Ann Surg. 2009;249(5):788-93.

27. Moyes LH, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC, et al. Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer. Br J Cancer. 2009;100(8):1236-9.

28. Park JH, Watt DG, Roxburgh CS, Horgan PG, McMillan DC. Colorectal cancer, systemic inflammation, and outcome: Staging the tumor and staging the host. Ann Surg. 2016;263(2):326-36.

29. Lin MS, Huang JX, Yu H. Prognostic significance of Glasgow prognostic score in patients with stage II colorectal cancer. Int J Clin Exp Med. 2015;8(10):19138-43.

30. Sugimoto K, Komiyama H, Kojima Y, Goto M, Tomiki Y, Sakamoto K. Glasgow prognostic score as a prognostic factor in patients undergoing curative surgery for colorectal cancer. Dig Surg. 2012;29(6):503-9.

31. Ishizuka M, Nagata H, Takagi K, Kubota K. Systemic inflammatory response associated with distant metastasis of T1 or T2 colorectal cancer. Dig Dis Sci. 2010;55(11):3181-7.

32. Kishiki T, Masaki T, Matsuoka H, Kobayashi T, Suzuki Y, Abe N, et al. Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer. Am J Surg. 2013;206(2):234-40.

33. Adachi T, Hinoi T, Hattori M, Egi H, Shimomura M, Saito Y, et al. The modified Glasgow prognostic score for early mortality in patients with synchronous peritoneal carcinomatosis from colorectal cancer. Surg Today. 2015;45(11):1396-403.

34. Furukawa K, Shiba H, Haruki K, Fujiwara Y, Iida T, Mitsuyama Y, et al. The Glasgow prognostic score is valuable for colorectal cancer with both synchronous and metachronous unresectable liver metastases. Oncol Lett. 2012;4(2):324-8.

35. Dréanic J, Maillet M, Dhooge M, Mir O, Brezault C, Goldwasser F, et al. Prognostic value of the Glasgow Prognostic Score in metastatic colorectal cancer in the era of anti-EGFR therapies. Med Oncol. 2013;30(3):656.

36. Sharma R, Zucknick M, London R, Kacevska M, Liddle C, Clarke SJ. Systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. Clin Colorectal Cancer. 2008;7(5):331-7.

37. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer. 2012;107(4):695-9.

38. Zahorec R. Ratio of neutrophil to lymphocyte counts e rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(1):5-14.

39. Pine JK, Morris E, Hutchins GG, West NP, Jayne DG, Quirke P, et al. Systemic neutrophil-to-lymphocyte ratio in colorectal cancer: the relationship to patient survival, tumor biology and local lymphocytic response to tumour. Br J Cancer. 2015;113(2):204-11.

40. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow inflammation outcome study. Eur J Cancer 2011;47(17):2633-41.

41. Inamoto S, Kawada K, Okamura R, Hida K, Sakai Y. Prognostic impact of the combination of neutrophil-to-lymphocyte ratio and Glasgow prognostic score in colorectal cancer: A retrospective cohort study. Int J Colorectal Dis. 2019;34(7):1303-15.

42. Cook EJ, Walsh SR, Farooq N, Alberts JC, Justin TA, Keeling NJ. Post-operative neutrophil-lymphocyte ratio predicts complications following colorectal surgery. Int J Surg. 2007;5(1):27-30.

43. Kubo T, Ono S, Ueno H, Shinto E, Yamamoto J, Hase K. Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma. Int J Colorectal Dis. 2014;29(9):1091-9.

44. Yasui K, Shida D, Nakamura Y, Ahiko Y, Tsukamoto S, Kanemitsu Y. Postoperative, but not preoperative, inflammation based prognostic markers are prognostic factors in stage III colorectal cancer patients. Br J Cancer. 2021;124:933-41.

45. Giakoustidis A, Neofytou K, Khan AZ, Mudan S. Neutrophil to lymphocyte ratio predicts pattern of recurrence in patients undergoing liver resection for colorectal liver metastasis and thus the overall survival. J Surg Oncol. 2015;111(4):445-50.

46. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol. 2008;34(1):55-60.

47. Ghanim B, Schweiger T, Jedamzik J, Glueck O, Glogner C, Lang G, et al. Elevated inflammatory parameters and inflammation scores are associated with poor prognosis in patients undergoing pulmonary metastasectomy for colorectal cancer. Interact Cardiovasc Thorac Surg. 2015;21(5):616-23.

48. Verter E, Berger Y, Perl G, Peretz I, Tovar A, Morgenstern S, et al. Neutrophil-to lymphocyte ratio predicts recurrence pattern in patients with resectable colorectal liver metastases. Ann Surg Oncol. 2021;28(8):4320-29.

49. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104(8):1288-95.

50. Kaneko M, Nozawa H, Sasaki K, Hongo K, Hiyoshi M, Tada N, et al. Elevated neutrophil to lymphocyte ratio predicts poor prognosis in advanced colorectal cancer patients receiving oxaliplatin-based chemotherapy. Oncology. 2012;82(5):261-8.

51. Tohme S, Sukato D, Chalhoub D, McDonald KACA, Zajko A, Amesur N, et al. Neutrophil-lymphocyte ratio is a simple and novel biomarker for prediction of survival after radioembolization for metastatic colorectal cancer. Ann Surg Oncol. 2015;22(5):1701-7.

52. Wagner DD. New links between inflammation and thrombosis. Arterioscler Thromb Vasc Biol. 2005:25;1321-4.

53. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, et al. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med. 2012;366:610-18.

54. Emir S, Aydin M, Can G, Bali I, Yildirim O, Öznur M, et al. Comparison of colorectal neoplastic polyps and adenocarcinoma with regard to NLR and PLR. Eur Rev Med Pharmacol Sci. 2015;19(19):3613-8.

55. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: Neutrophil-lymphocyte versus platelet lymphocyte ratio. Am J Surg. 2010;200:197-203.

56. Ozawa T, Ishihara S, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, et al. The preoperative platelet to lymphocyte ratio is a prognostic marker in patients with stage II colorectal cancer. Int J Colorectal Dis. 2015;30(9):1165-71.

57. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H, 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;30:439.

58. Erstad DJ, Taylor MS, Qadan M, Axtell AL, Fuchs BC, Berger DL, et al. Platelet and neutrophil to lymphocyte ratios predict survival in patients with resectable colorectal liver metastases. Am J Surg. 2020;220:1579-85.

59. Neofytou K, Smyth EC, Giakoustidis A, Khan AZ, Cunningham D, Mudan S. Elevated platelet to lymphocyte ratio predicts poor prognosis after hepatectomy for liver-only colorectal metastases, and it is superior to neutrophil to lymphocyte ratio as an adverse prognostic factor. Med Oncol. 2014;31(10):239.

60. Condeelis J, Pollard JW. Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006;124:263-6.

61. Huh JW, Lee JH, Kim HR. Prognostic significance of tumor-infiltrating lymphocytes for patients with colorectal cancer. Arch Surg. 2012;147:366-72.

62. Zhang LN, Xiao W, OuYang PY, You K, Zeng ZF, Ding PR, et al. The prognostic impact of preoperative blood monocyte count in pathological T3N0M0 rectal cancer without neoadjuvant chemoradiotherapy. Tumour Biol. 2015;36:8213-9.

63. Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Tominaga M, et al. Prognostic value of preoperative peripheral blood monocyte count in patients with colorectal liver metastasis after liver resection. J Gastrointest Surg. 2007;11:596-602.

64. Stotz M, Pichler M, Absenger G, Szkandera J, Arminger F, Schaberl-Moser R, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer. 2014;110:435-40.

65. Chang Y, An H, Xu L, Zhu Y, Yang Y, Lin Z, et al. Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma. Br J Cancer. 2015;113:626-33.

66. Suzuki Y, Okabayashi K, Hasegawa H, Tsuruta M, Shigeta K, Kondo T, et al. Comparison of preoperative inflammation-based prognostic scores in patients with colorectal cancer. Ann Surg. 2018;267:527-31.

67. Koike Y, Miki C, Okugawa Y, Yokoe T, Toiyama Y, Tanaka K, et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. J Surg Oncol. 2008;98:540-44.

68. Suzuki S, Akiyoshi T, Oba K, Otsuka F, Tominaga T, Nagasaki T, et al. Comprehensive comparative analysis of prognostic value of systemic inflammatory biomarkers for patients with stage II/III colon cancer. Ann Surg Oncol. 2020;27:844-52.

69. Ide S, Toiyama Y, Okugawa Y, Oki S, Yasuda H, Fujikawa H, et al. Clinical significance of C-reactive protein-to-albumin ratio with rectal cancer patient undergoing chemoradiotherapy followed by surgery. Anticancer Res. 2017;37:5797-804.

70. Matsuoka H, Ando K, Hu Q, Zaitsu Y, Tsuda Y, Hisamatsu Y, et al. Postoperative C-reactive protein/albumin ratio is a biomarker of risk of recurrence and need for adjuvant chemotherapy for stage III colorectal cancer. Int J Clin Oncol. 2020;25:1318-26.

71. Dolan RD, McSorley ST, Park JH, Watt DG, Roxburgh CS, Horgan PG, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: Comparison of composite ratios and cumulative scores. Br J Cancer. 2018;119:40-51.