Review Article

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Inflammatory Response Markers as Predictors of Colorectal Cancer Prognosis

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Colorectal cancer (CRC) is a globally prevalent and challenging malignancy. Accurate prognosis prediction is essential for optimizing patient care. This comprehensive review discusses the intricate relationships between inflammatory response markers and CRC prognosis. Inflammatory response markers have gained prominence as a prognostic tool. Elevations in the preoperative neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and C-reactive protein-albumin ratio predict a poor prognosis for patients with CRC. A decreased lymphocyte-monocyte ratio is also a poor prognostic factor. A high Glasgow prognostic score and a high modified Glasgow prognostic score are associated with adverse outcomes, including reduced survival. While significant progress has been made, challenges remain in standardizing the clinical application of these inflammatory response markers. Prospective research and further investigations are warranted to refine the prognostic models. Enhanced understanding and utilization of these inflammatory response markers will help advance personalized treatment strategies, refine surveillance protocols, and improve the management of CRC.

Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies and a leading cause of cancer-related death worldwide [1,2]. Advances in screening and treatment modalities have improved the survival of patients with CRC; however, the mortality rate remains high in cases of metastasis or recurrence [1,3]. The complexity of tumor progression—including, for instance, tumor heterogeneity, resistance mechanisms, genetic alterations, and micromolecular biology—contributes to the difficulty of achieving improvements in prognosis; therefore, more sophisticated and tailored treatment strategies are needed [4–7]. It is thus important to identify factors associated with a poor prognosis in patients with CRC. The conventional prognostic model for CRC is the TNM staging system, which was proposed by the American Joint Committee on Cancer. Clinical characteristics and additional pathologic features are also used to predict the patient's prognosis [5,6,8,9]. However, patients with a similar clinicopathologic status and staging may have different prognoses.

Biomarkers are quantifiable and measurable indicators that reflect normal biological processes, pathological conditions, or responses to therapeutic interventions. Biomarkers serve as diagnostic tools that provide early disease detection and act as prognostic markers to offer insights into disease progression and potential outcomes [9–12]. Inflammatory response markers, which are among the most easily measurable biomarkers, reflect the body's immune response and provide

insights into the tumor microenvironment and its impact on the prognosis of CRC. Numerous previous studies have reported that inflammatory response markers, such as the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), can be useful for predicting the CRC prognosis [3,10,13,14]. The purpose of this study was to review inflammatory response markers that, according to current research, exhibit potential for predicting the prognosis of patients with CRC. This review summarizes the inflammatory response markers that can be obtained from routinely performed blood tests before CRC treatment, with the aim of offering an understanding of how inflammatory response markers may predict the prognosis of CRC and contribute to advances in the field of precision medicine in CRC [7].

Inflammatory Response Markers

1. Inflammation and cancer

Chronic inflammation has been recognized as an important factor in cancer initiation and progression [15]. It induces tissue damage, in response to which cell proliferation is activated as a part of the healing process. When chronic inflammation persists, there is a repeated cycle of tissue damage and regeneration, leading to the occurrence of genetic mutations. Inflammatory cells, such as macrophages and T cells, secrete cytokines and chemokines in response to tissue damage [16]. These signaling molecules (such as tumor necrosis factor-alpha and CXCL8) can affect tumor biology, including growth, migration, and differentiation, by releasing growth factors, promoting angiogenesis, and causing DNA damage [17]. Table 1 summarizes the inflammatory response markers and the prognosis of CRC.

2. Neutrophil-lymphocyte ratio

The NLR is a widely used biomarker to predict prognosis in CRC; it is defined as the absolute neutrophil count divided by the absolute lymphocyte count. Several studies have shown that a high preoperative NLR is associated with a poor prognosis in patients with stage I–III CRC who underwent curative resection. The cutoff values were different depending on the study and ranged from 2.05–5.00 [18–23]. Chiang et al. analyzed 3,857 patients with stage I–III CRC who underwent curative resection and found that a preoperative NLR>3 was a significant predictor of disease-free survival (DFS) [18]. Li et al. reported that a preoperative NLR>2.72 was associated with significantly lower DFS and overall survival (OS) rates in 5,336 patients with stage I–III CRC who underwent curative resection [21]. Some studies have concluded that a high preoperative NLR predicted a poor prognosis in patients with CRC who underwent curative-intent resection, including stage IV patients [23,24]. Song et al. reported that a preoperative NLR>2 was associated with lower cancer-specific survival (CSS) and OS rates in patients with stage I–IV CRC who underwent resection [23]. Several studies have focused on high NLR values and the prognosis of rectal cancer [25–28]. Zhang et al. analyzed 472 patients with advanced rectal cancer who underwent preoperative chemoradiotherapy followed by curative resection. A high NLR before chemoradiotherapy was significantly associated with worse DFS and OS [26]. Yosida et al. reported that a preoperative NLR>2.58 was associated with a lower DFS in patients with stage I–II rectal cancer who underwent curative resection [27]. Other studies have focused on high NLR values and the prognosis of colon cancer [28,29]. Hung et al. analyzed 1,040 patients with stage II colon cancer who underwent curative resection and found that a preoperative NLR>5 was associated with a lower OS rate [29].

Several studies have investigated the role of pretreatment NLR in colon cancer with distant

metastasis [30–33]. A study by Halazun et al. demonstrated that a preoperative NLR>5 had a poor prognostic impact in patients with concurrent CRC liver metastasis who underwent curative-intent resection [30]. Mao et al. analyzed 183 patients who were diagnosed with CRC with liver metastasis and performed neoadjuvant chemotherapy followed by surgery. An NLR>2.3 before chemotherapy was associated with poor recurrence-free survival and OS [31]. Casadei-Gardini et al. performed a randomized-controlled trial in patients with Stage IV CRC who underwent chemotherapy and reported that a pretreatment NLR>3 was associated with poor progression-free survival and OS [33] .

Table 1. Inflammatory response markers associated with the prognosis of CRC

Author	Year	Population	Patients (n)	Main outcome	HR (95% CI)	P-value	Cut-off
Neutrophil–lymphocyte ratio							
Halazun [30]	2008	CRLM following curative-intent resection	440	DFS	2.26 (1.65–3.13)	<0.001	5
Ding [28]	2010	CC following curative resection (stage IIA)	141	RFS	4.88 (1.73–13.75)	0.003	4
Hung [29]	2011	CC following curative resection (stage II)	1,040	OS	1.29 (1.07–1.80)	0.012	5
Chiang [18]	2012	CRC following curative resection (stage I-III)	3,857	DFS	1.31 (1.09–1.57) (especially CC)	0.013	3
Guthrie [19]	2013	CRC following curative resection (stage I-III)	206	CSS	3.07 (1.23–7.63)	<0.05	5
Malietzis [20]	2014	CRC following curative resection (stage I-III)	506	DFS	2.41 (1.12–5.15)	0.024	3
Nagasaki [25]	2015	RC following nCRT and curative resection (stage I-III)	201	OS	3.38	0.012	3
Li [21]	2016	CRC following curative resection (stage I-III)	5,336	DFS OS	1.20 (1.05–1.37) 1.23 (1.01–1.50)	0.009 0.047	2.72
Song [23]	2017	CRC following resection (stage I-IV)	1,744	CSS OS	0.74 (0.57–0.95) 0.76 (0.60–0.96) (reference: NLR≥2)	0.018 0.021	2
Pedrazzani [24]	2017	CRC following curative resection (stage I-IV)	603	CSS OS	1.22 (0.77–1.93) 1.15 (0.86–1.54)	0.40 0.003	3.5
Mao [31]	2019	CRLM following nCT and resection	183	RFS OS	1.53 (1.08–2.18) 2.43 (1.49–3.94)	0.017 <0.001	2.3
Casadei-Gardini [33]	2019	CRC following CT (stage IV)	276	PFS OS	2.27 (1.59–3.23) 14.4 (11.4–17.1)	<0.001 <0.001	3
Inamoto [22]	2019	CRC following curative resection (stage I-III)	448	DFS CSS OS	1.71 (1.12–2.66) 2.11 (0.96–5.05) 2.04 (1.11–3.96)	0.01 0.06 0.02	2.05
Erstad [32]	2020	CRLM following curative-intent resection	151	OS	2.46 (1.08–5.60)	0.032	5
Yosida [27]	2020	RC following curative resection (T1-2)	151	DFS	5.11 (1.84–16.4)	0.002	2.58
Zhang [26]	2020	RC following nCRT and curative resection (stage II-III)	472	DFS OS	1.71 (1.02–2.87) 1.80 (1.01–3.20)	0.044 0.046	2.3

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Table 1. Continued

Author	Year	Population	Patients (n)	Main outcome	HR (95% CI)	P-value	Cut-off
Platelet–lymphocyte ratio							
Pedrazzani [24]	2017	CRC following curative resection (stage I-IV)	603	CSS OS	1.64 (0.74–3.62) 1.86 (1.05–3.32)	0.22 0.034	350
Erstad [32]	2020	CRLM following curative-intent resection	151	OS	2.10 (1.04–4.23)	0.037	220
An [14]	2022	RC following nCRT and curative resection (stage I-III)	168	OS	1.79 (1.01–3.17)	0.047	170
Lymphocyte–monocyte ratio							
Li [21]	2016	CRC following curative resection (stage I-III)	5,336	DFS OS	0.77 (0.67–0.88) 0.76 (0.62–0.93)	<0.001 0.008	2.83
Chan [35]	2017	CRC following curative resection (stage I-III)	1,623	OS	0.57 (0.48–0.68)	<0.001	2.38
Chen [37]	2019	Obstructive CRC with stent insertion following resection	128	DFS OS	0.42 (0.17–1.07) 0.40 (0.18–0.92)	0.068 0.031	1.67
Glasgow prognostic score							
Choi [39]	2014	CRC following resection (stage I-IV)	105	CSS	5.17 (1.76–15.18)	0.003	
Inamoto [22]	2019	CRC following curative resection (stage I-III)	448	DFS CSS OS	1.68 (1.03–2.67) 2.17 (1.03–4.49) 1.73 (0.97–3.02)	0.04 0.04 0.06	
Lee [40]	2020	CRC following curative-intent resection (stage I-IV)	1,590	DFS OS	1.71 (1.23–2.38) 2.34 (1.62–3.39)	0.001 0.001	
Modified Glasgow prognostic score							
Leitch [43]	2007	CRC following curative-intent resection (stage I-IV)	149	CSS	1.44 (1.01–2.04)	0.043	
Roxburgh [41]	2009	CRC following curative resection (stage I-III)	287	CSS	2.65 (1.66–4.25)	<0.001	
Park [44]	2016	CRC following curative-intent resection (stage I-IV)	1,000	CSS OS	1.28 (1.09–1.52) 1.28 (1.13–1.45)	0.003 <0.001	
Tokunaga [42]	2017	CRC following curative resection (stage I-III)	468	RFS OS	2.14 (1.40–3.24) 2.45 (1.53–3.88)	<0.001 <0.001	
Suzuki [45]	2018	CRC following curative-intent resection (stage I-IV)	727	OS	2.01	0.005	

CRC, colorectal cancer; HR, hazard ratio; CRLM, colorectal cancer with liver metastasis; DFS, disease-free survival; CC, colon cancer; RFS, recurrence-free survival; OS, overall survival; CSS, cancer-specific survival; RC, rectal cancer; nCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-lymphocyte ratio; PFS, progression-free survival.

3. Platelet-lymphocyte ratio

The PLR, which is defined as the ratio of the platelet count to the lymphocyte count, has also been suggested as a prognostic marker for CRC. Several studies have reported that a high preoperative PLR was associated with a poor prognosis in patients with CRC [24,32,34]. Pedrazzani et al. analyzed 603 patients with CRC who underwent curative resection and found that a preoperative PLR>350 was a significant predictor of CSS and OS [24]. Erstad et al. reported that a preoperative PLR>220 in patients with concurrent CRC liver metastasis who underwent curative-intent resection was associated with a worse OS [32].

4. Lymphocyte-monocyte ratio

The lymphocyte-monocyte ratio (LMR), which is defined as the ratio of the lymphocyte count to the monocyte count, can predict the prognosis of CRC. Several studies have shown that a high preoperative LMR is associated with a poor prognosis in patients with CRC who underwent curative resection [21,35,36]. Chan et al. analyzed 1,623 patients with stage I–III CRC and the prognostic impact of LMR. A preoperative LMR<2.38 was an independent prognostic factor and was superior to other biomarkers, such as the NLR and PLR [35]. Li et al. also reported that a preoperative LMR<2.83 was associated with lower DFS and OS in patients with stage I–III CRC who underwent curative resection [21]. A study by Chen et al. focused on obstructive CRC and the prognostic impact of the pretreatment LMR. An LMR<1.67 before endoscopic stenting was associated with poor DFS and OS [37].

5. Glasgow prognostic score and modified Glasgow prognostic score

The combination of a higher CRP value and hypoalbuminemia can be a sensitive biomarker for prognosis of CRC. The Glasgow prognostic score (GPS) is a useful scoring system for predicting the prognosis of patients with CRC, as well as other malignant tumors [38]. The GPS is based on the combination of hypoalbuminemia (<3.5 g/dL) and elevated CRP (>10 mg/L); if both are abnormal, the score is 2; if one or the other is abnormal, the score is 1; if neither is abnormal, the score is 0. Multiple studies have shown that a high GPS before surgery was associated with a poor prognosis for patients with stage I–III CRC who have undergone curative resection [22,38]. Choi et al. reported that a preoperative GPS of 2 was associated with a worse CSS in patients with stage I–IV CRC who underwent resection [39]. A study by Lee et al. evaluated 1,590 patients with CRC, including stage IV, who underwent curative-intent resection and revealed that a GPS of 1 or 2 was associated with DFS and OS rates [40]. The modified GPS (mGPS) is defined as follows: patients with a CRP level ≤10 mg/L and an albumin level ≥3.5 g/dL are scored as 0; those with a CRP level >10 mg/L are scored as 1; and those with a CRP level >10 mg/L and an albumin level <3.5 g/dL are scored as 2. Several studies have demonstrated that the preoperative mGPS was associated with the prognosis in patients with stage I–III CRC who underwent curative resection [41,42]. Roxburgh et al. reported that a preoperative mGPS of 1 or 2 was associated with lower CSS rates in patients with stage I–III CRC who underwent curative resection [41]. Other studies have evaluated the association between the prognosis of patients with CRC (including stage IV) who underwent curative-intent resection and had a preoperative mGPS [43–45]. Leitch et al. reported that a preoperative mGPS of 1 or 2 was associated with lower CSS rates in patients with stage I–IV CRC who underwent curative-intent resection [43]. A study by Park et al. analyzed 1,000 patients with stage I–IV CRC who underwent curative-intent resection and reported that a preoperative GPS of 1 or 2 was associated with poor CSS and OS [44]. A study by Suzuki et al. evaluated 737 patients with stage I–IV CRC who underwent curative-intent resection and concluded that a preoperative mGPS of 1 or 2 was associated with poor CSS [45].

Conclusion

In summary, our comprehensive review has shed light on the complex interplay between the prognosis of CRC and the roles of inflammatory response markers. These non-invasive biomarkers are easily accessible both before and after surgery. The findings discussed herein collectively highlight the critical significance of considering these inflammatory response

markers when assessing the clinical prognosis of patients with CRC.

The evidence presented suggests that elevated levels of inflammatory response markers are associated with a poor prognosis in patients with CRC. These markers reflect the systemic inflammation that often accompanies malignancies, as well as the intricate relationship between the tumor microenvironment and the host immune response. Incorporating these markers into clinical practice could enhance the precision of prognosis prediction and inform treatment decisions. When used in combination with clinical assessments, these markers offer valuable insight into the management of patients with CRC.

Despite significant progress in understanding the relationship between these inflammatory response markers and the prognosis of CRC, challenges remain. The heterogeneity of CRC and the influence of various factors on inflammatory response marker levels underscore the need for continued research. Prospective studies, multi-center trials, and the exploration of emerging inflammatory response markers hold promise for refining prognostic models and improving patient outcomes. Ultimately, the integration of these inflammatory response markers into the clinical evaluation of patients with CRC is a promising way to improve personalized treatment strategies, optimize surveillance protocols, and advance the field of CRC management. As our understanding of these inflammatory response markers continues to evolve, so will our ability to predict, prevent, and effectively treat malignancies.

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Conflict of Interest

Bo Young Oh serves as the editorial board members of the *Ewha Medical Journal*, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article was reported.

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