

## Inflammation-based factors and prognosis in patients with colorectal cancer

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**Author contributions:** All authors contributed to this manuscript.

**Conflict-of-interest statement:** There is no financial support or relationships that may pose any conflict of interest.

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Received: January 14, 2015  
Peer-review started: January 16, 2015  
First decision: April 24, 2015  
Revised: April 30, 2015  
Accepted: July 7, 2015  
Article in press: July 8, 2015  
Published online: August 15, 2015

### Abstract

Several parameters for predicting survival in patients with colorectal cancer have been identified, including the performance status, age, gender and tumor-node-

metastasis (TNM) stage. Although the TNM stage is important and useful for predicting the prognosis and determining the appropriate treatment, it is well known that the survival time varies widely, even in patients with the same stage of disease. Therefore, the identification of new parameters capable of more precisely predicting patient survival is needed to help select the optimal treatment, especially in patients in the advanced stage of disease. Although the TNM stage reflects the tumor characteristics, cancer progression and survival are not determined solely based on the local characteristics of the tumor, but also the host systemic immune/inflammatory response. Therefore, using a combination of parameters that reflect both tumor characteristics and the host systemic inflammatory status is thought to be important for accurately predicting patient survival.

**Key words:** Colorectal cancer; Platelet-to-lymphocyte ratio; Prognosis; Glasgow Prognostic Score; C-reactive protein; Neutrophil-to-lymphocyte ratio; Inflammation-based factor; Nutritional Prognostic Index

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**Core tip:** Recently, it has become clear that an elevated systemic inflammatory response is consistently associated with a poor outcome, independent of the tumor stage. The inflammatory response is represented by the levels of serum neutrophils, lymphocytes and platelet s as well as acute-phase proteins and their combinations. These parameters are simple and easy to measure using widely available standardized assays. In this review, we discuss the prognostic value of various inflammation-based factors in patients with colorectal cancer.

Maeda K, Shibutani M, Otani H, Nagahara H, Ikeya T, Iseki Y, Tanaka H, Muguruma K, Hirakawa K. Inflammation-based factors and prognosis in patients with colorectal cancer. *World*

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related death worldwide<sup>[1]</sup>. Approximately 20% of patients with CRC present with distant metastasis at the time of diagnosis<sup>[1]</sup>, and the survival of patients with unresectable stage IV CRC is very poor, with a median survival time (MST) of approximately six to eight months among those who receive the best supportive care without chemotherapy<sup>[2]</sup>. However, due to the development of chemotherapeutic and molecular targeting agents, the survival time has improved dramatically within the last decade, with an MST of 24-30 mo<sup>[3-6]</sup>.

Several parameters for predicting survival in patients with CRC have been identified, including patient characteristics, such as the performance status (PS), age and gender, and tumor characteristics, such as clinicopathological factors and the TNM stage. Although the stage determined according to the Union for International Cancer Control (UICC) TNM classification<sup>[7]</sup> is important and useful for predicting the prognosis and determining the appropriate treatment, it is well known that the survival time varies widely, even in patients with the same stage of disease. Therefore, the development of a new parameter able to more precisely predict the patient survival required to help select the optimal treatment, especially in patients with advanced disease. It has been reported that many molecular parameters (such as proteins involved in cell cycle regulation, apoptosis and angiogenesis or RAS/RAF mutations) are associated with survival<sup>[8-14]</sup>. However, measuring these molecular parameters requires sophisticated and expensive laboratory techniques.

It is now recognized that disease progression in cancer patients is determined not only by tumor characteristics, but also the host inflammatory response<sup>[15]</sup>. Moreover, it has become clear that an elevated systemic inflammatory response is consistently associated with a poor outcome independent of the tumor stage<sup>[16-18]</sup>. The inflammatory response is represented by the levels of serum white blood cells, neutrophils, lymphocytes and platelets and acute-phase proteins, such as C-reactive protein (CRP) and albumin. These parameters are simple and easy to measure using widely available standardized assays.

Recently, several combinations of these factors, including Glasgow Prognostic Score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have also been reported to be useful prognostic factors in various malignant solid tumors, including CRC (Table 1)<sup>[19-32]</sup>.

The aim of this review was to examine the value of various inflammation-based factors as useful prognostic factors in patients with CRC.

## CRP LEVEL

CRP is an acute-phase protein synthesized in hepatocytes whose serum level increases in response to inflammatory disease<sup>[33,34]</sup>. Cancer growth also induces a tissue inflammatory response, and thus increases the serum CRP level. Elevation of the serum CRP concentration reflects a state of hyper-cytokemia, as the CRP level is upregulated by proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)<sup>[33,34]</sup>. These cytokines have the ability to promote tumor growth and metastasis and play a role in tumor progression.

Many investigators have reported that a high level of serum CRP significantly correlates with poor survival in patients with CRC treated with curative surgery<sup>[19-21]</sup>. Nozoe *et al*<sup>[19]</sup> reported that the preoperative elevation of CRP was related to recurrence after curative resection for CRC. Toiyama *et al*<sup>[20]</sup> reported a correlation between elevated CRP and recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. We investigated the correlation between serum CRP levels and the prognosis of patients with stage IV CRC who underwent the palliative resection of their primary tumor<sup>[20]</sup>. We found that a high preoperative serum CRP level was a convenient marker for identifying the stage IV CRC patients with a poor prognosis.

## GPS

GPS, which is also an inflammation-based factor, is defined according to the presence of an elevated serum CRP level and hypoalbuminemia. Briefly, patients with both an elevated CRP level (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) are allocated a score of 2. Patients in whom only one of these biochemical abnormalities is present are allocated a score of 1 and those in whom neither of these abnormalities are present are allocated a score of 0<sup>[17,18]</sup>. This score has been shown to be a prognostic indicator, independent of the tumor stage, in a variety of gastrointestinal cancers<sup>[22-24,35,36]</sup>. Sugimoto *et al*<sup>[22]</sup> examined patients with stage II CRC who underwent a curative resection and reported that the cancer specific survival was significantly worse in the patients with a GPS of 2 than in those with a GPS of 1 or 0. Proctor *et al*<sup>[35]</sup> also reported that a raised GPS was associated with reduced overall survival and cancer specific survival in CRC patients, independent of age, gender and Dukes' stage. Moreover, GPS of 2 has been reported to be an independent significant prognostic factor, even in patients with unresectable stage IV CRC<sup>[23,24]</sup>. Ishizuka *et al*<sup>[24]</sup> reported a correlation between GPS and chemotherapy tolerance and noted that it would be useful for deciding

**Table 1** Previously reported correlations between various inflammation-based factors and the prognosis

Inflammation-based factors	Ref.	Year	Timing of measurement	n	TNM staging	Treatment	Survival analysis	Summary results
CRP	Nozoe <i>et al.</i> <sup>[19]</sup>	1998	Preoperation	120	I -IV	Resection	OS	Positive
	Toiyama <i>et al.</i> <sup>[20]</sup>	2013	Preoperation	84	I -III	Resection and CRT	DFS, OS	Positive
GPS	Shibutani <i>et al.</i> <sup>[21]</sup>	2014	Preoperation	144	IV	Resection and CT	PFS, OS	Positive
	Sugimoto <i>et al.</i> <sup>[22]</sup>	2012	Preoperation	166	II	Resection	OS	Positive
	Kishiki <i>et al.</i> <sup>[23]</sup>	2013	Pretreatment	79	IV	CT	OS	Positive
NLR	Ishizuka <i>et al.</i> <sup>[24]</sup>	2013	Preoperation	108	IV	Resection	OS	Positive
	Chua <i>et al.</i> <sup>[26]</sup>	2011	Pre and post treatment	171	IV	CT	OS	Positive
	Chua <i>et al.</i> <sup>[26]</sup>	2011	Preoperation	674	I -IV	Resection	OS	Positive
OPNI	Li <i>et al.</i> <sup>[27]</sup>	2014	-	-	Meta-analysis	-	DFS, OS	Positive
	Nozoe <i>et al.</i> <sup>[28]</sup>	2012	Preoperation	219	I -IV	Resection	OS	Positive
	Maeda <i>et al.</i> <sup>[29]</sup>	2014	Preoperation	100	IV	Resection and CT	OS	Positive
PLR, NLR	Ikeya <i>et al.</i> <sup>[30]</sup>	2014	Pre and post treatment	80	IV	CT	OS	Positive
	Kwon <i>et al.</i> <sup>[31]</sup>	2012	Preoperation	200	I -III	Resection	OS	Positive
GPS, NLR	Maeda <i>et al.</i> <sup>[32]</sup>	2013	Preoperation	94	IV	resection and CT	OS	Positive

CRP: C-reactive protein; GPS: Glasgow Prognostic Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CT: Chemotherapy; CRT: Chemoradiotherapy; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

the indications for palliative surgery or preoperative chemotherapy.

### Neutrophil-to-lymphocyte ratio

The neutrophil-to-lymphocyte ratio (NLR), calculated as the neutrophil count divided by the lymphocyte count, is suggested to be a marker of general immune response to various stress stimuli. Initially, the NLR was described to be correlated with the severity of the clinical course of severely ill patients in the intensive care unit by Zahorec *et al.*<sup>[37]</sup>.

Neutrophils play a key role in tumor proliferation, producing a number of ligands that induce tumor cell proliferation and invasion and promoting tumor vascularization by releasing proangiogenic chemokines and other factors<sup>[38,39]</sup>. Therefore, increased neutrophils may promote tumor growth and metastasis. On the other hand, lymphocytes play a key role in tumor suppression<sup>[40]</sup>. The function of lymphocytes is to induce cytotoxic cell death and the production of cytokines in cancer cells<sup>[40]</sup>. A decrease in the number of lymphocytes impairs the host's antitumor immune response and confers a poor prognosis<sup>[25]</sup>. NLR can therefore be considered as a balance between the pro-tumor inflammation status and the anti-tumor immune status. Although the cut-off values varied between 2.5 to 5 in the previous reports<sup>[25-27]</sup>, emerging evidence shows that an elevated NLR is significantly associated with poor prognosis in patients with CRC. We analyzed 674 CRC patients who underwent surgery and used a receiver operating characteristic curve to determine an appropriate cut-off value<sup>[25]</sup>. As a result, an NLR > 2.5 was a significant independent predictive factor for cancer-specific survival. With respect to patients with unresectable stage IV CRC, Chua *et al.*<sup>[26]</sup> examined 349 patients with unresectable CRC who received first-line palliative chemotherapy and reported that the prognosis of patients with an NLR of > 5 was significantly worse than the prognosis of the patients with an NLR of < 5.

They also reported that a high NLR resulted in a reduced response to chemotherapy and that the reduction of NLR after one cycle of chemotherapy in a subset of patients resulted in improved survival. Li *et al.*<sup>[27]</sup> performed a meta-analysis of CRC patients and concluded that the NLR is an inexpensive, widely available and reproducible index that is closely associated with survival. Because a peripheral blood cell count is a quick and easy assay to perform, NLR is a useful marker for identifying patients with a poor prognosis and allows for the planning of more frequent surveillance and intensive therapy in patients with unresectable stage IV CRC.

### Platelet-to-lymphocyte ratio

Malignant solid tumors commonly induce a hypercoagulable state, resulting in a predisposition to thromboembolic events<sup>[41,42]</sup>. Reactive thrombocytosis is induced against a background of hypercytokinemia *via* tumor vs host interactions<sup>[43]</sup>. Among several inflammatory cytokines, IL-6 has an important role in the onset of reactive thrombocytosis, as it is a multifunctional cytokine with a number of physiological actions, stimulating not only CRP up-regulation but also albumin down-regulation in the liver, as well as protein synthesis<sup>[44]</sup>. Similarly, IL-6 has a cell-proliferative effect, triggering the differentiation of megakaryocytes to platelets in the bone marrow<sup>[44]</sup>. Hence, it is reasonable that reactive thrombocytosis would be associated with the survival of patients with malignant tumors.

As previously described, lymphocytopenia has shown to be associated with poor survival. Therefore, the platelet-to-lymphocyte ratio (PLR) is also thought to be a powerful prognostic factor in patients with malignant tumors. Indeed, PLR is an independent prognostic factor, in addition to other inflammation-based factors, for pancreatic ductal adenocarcinoma according to Smith *et al.*<sup>[45]</sup>, ovarian cancer according to Raungkaewmanee *et al.*<sup>[46]</sup>, and CRC according to Kwon *et al.*<sup>[31]</sup>.

### Nutritional Prognostic Index

The inflammatory response has been proposed to be pathogenic with respect to the development of cancer-associated malnutrition<sup>[47]</sup>. Several studies have reported that patients with advanced gastrointestinal malignancies are often malnourished, and that the preoperative nutritional status is associated with postoperative complications, tumor progression and a poor clinical outcome<sup>[48,49]</sup>. There are several assessment tools for evaluating the nutritional status, including the malnutrition universal screening tool (MUST), nutritional risk scoring 2002 (NRS2002) and mini nutritional assessment<sup>[50,51]</sup>. These tools are simple, well-validated and cost-effective and are widely utilized to assess the nutritional status of cancer patients. Onodera's Prognostic Nutritional Index (OPNI) is another such tool and a simple index that can be calculated using only two parameters, the serum albumin level and total lymphocyte count (TLC)<sup>[52]</sup>. The OPNI is calculated using the following formula:  $10 \times \text{serum albumin concentration (g/dL)} + 0.005 \times \text{lymphocyte count (number/mm}^2\text{)}$  in the peripheral blood. Albumin is a main component of plasma proteins that preserves the colloid osmotic pressure, and its level reflects the nutritional status. The TLC has also been proposed to be a useful indicator of the nutritional, as well as host inflammatory status. Both albumin and TLC levels are routinely examined in daily clinical practice. Therefore, the OPNI, which reflects the immunonutritional status, is thought to be a useful and convenient index for predicting tumor progression and survival in patients with malignancy.

Regarding the prognosis, Nozoe *et al.*<sup>[28]</sup> reported that the OPNI is significantly correlated with the prognosis of patients with CRC. The above study examined patients who underwent curative surgery. Therefore, we thought to clarify the prognostic value of the OPNI in patients with unresectable stage IV CRC<sup>[29]</sup>. Initially, we examined patients who underwent palliative resection of the primary tumor. The result revealed that a low-OPNI is an independent predictor of a worse prognosis, even in patients limited to stage IV CRC disease. In particular, the MST of the patients with a low-OPNI was 9.5 mo, which was shorter than that reported for patients with stage IV CRC treated with chemotherapy alone. Therefore, although the necessity of palliative resection in patients with asymptomatic primary tumors and unresectable stage IV CRC remains controversial, measuring the OPNI may be useful for selecting patients expected to receive a survival benefit associated with palliative resection.

It has been reported that malnutrition results in the loss of lean body mass, an impaired immune function, a reduced rate of response to chemotherapy and poor survival<sup>[53]</sup>. Therefore, we evaluated the clinical significance of the OPNI among patients with unresectable stage IV CRC treated with chemotherapy<sup>[30]</sup>. We collected data from blood tests conducted within one week prior to the start of the first-line chemotherapy and

at eight weeks after the first day of chemotherapy. As a result, the overall survival of the patients with a high pretreatment OPNI was significantly ( $P = 0.005$ ) better than that of the patients with a low pretreatment OPNI; the MST was 37 and 22.8 mo, respectively. Moreover, when we categorized the patients into four groups according to the combination of the pre- and post-treatment OPNI values, only the group who maintained a high OPNI had a better prognosis than the other groups, and a decrease in the OPNI after chemotherapy was associated with a worse survival, even in the patients with a high pretreatment OPNI value. Therefore, it is important to maintain a good nutritional and immune status before and during treatment in patients receiving chemotherapy. It has also been reported that nutritional interventions may improve the immunonutritional system, response to chemotherapy and patient survival<sup>[54-56]</sup>. Such nutritional interventions should be implemented in order to improve the survival of patients with a low-OPNI.

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## COMBINATION OF CLINICOPATHOLOGICAL AND INFLAMMATION-BASED FACTORS

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The current report of inflammation-based factors is by no means exhaustive, although we wish to provide an overview of the topic in order to help guide the management of CRC patients. Both clinicopathological and inflammation-based parameters are independent powerful prognostic factors; therefore, the user of a combination of these factors may have more precise clinical, prognostic and therapeutic value compared to a single factor.

From the above point of view, Laird *et al.*<sup>[17]</sup> reported that the GPS is similar to the PS in terms of prognostic power and that the combination of these factors may have a potential role in effectively predicting survival.

We investigated the correlation between clinicopathological factors, the GPS, NLR and prognosis in order to identify parameters useful for selecting stage IV CRC patients with a poor prognosis. As a result, the GPS, NLR, performance status (PS) and extent of distant metastasis were found to be independent predictors of survival<sup>[32]</sup>. We classified the patients, using a combination of four prognostic factors, into three risk groups: patients without any prognostic factors (the low-risk group), patients with one or two prognostic factors (the intermediate-risk group) and patients with three or four prognostic factors (the high-risk group). There were significant ( $P < 0.0001$ ) differences in the postoperative cancer specific survival rates among the three groups. The median survival time (MST) was only five months in the high-risk group, compared to 21.5 mo in the intermediate-risk group and 37 mo in the low-risk group. The MST of the high-risk group was five months, which was very short and similar

to that reported for patients with stage IV CRC who received the best supportive care without surgery or chemotherapy. Therefore, there may be no survival benefit associated with palliative resection in the high-risk group. On the other hand, relatively better survival is expected in the low-risk group. This risk classification is simple and easy to use and may be helpful for determining the optimal treatment for patients with stage IV CRC.

## CONCLUSION

Conventional clinicopathological factors are currently widely- used and important prognostic factors for patients with CRC. However, these factors are not universally helpful for predicting the prognosis in patients within the same stage of disease. Inflammation-based factors are determined based on laboratory data that are routinely recorded in the clinical setting and can be easily estimated prior to treatment.

Although clinicopathological factors reflect the tumor characteristics, cancer progression and survival are not determined solely according to the local characteristics of the tumor, but also the host systemic immune/ inflammatory response. Therefore, the application of a combination of these parameters reflecting both the tumor characteristics and host systemic inflammatory status is important for predicting patient survival more precisely and selecting the optimal treatment in patients with CRC.

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