Review

Prognostic Value of the Glasgow Prognostic Score or Modified Glasgow Prognostic Score for Patients with Colorectal Cancer Receiving Various Treatments: a Systematic Review and Meta-Analysis

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Key Words

Colorectal cancer • GPS/mGPS • Predictive marker • Prognosis • Meta-analysis

Abstract

Background/Aims: Increasing evidence indicates that the systemic inflammatory response plays a vital role in carcinogenesis. The Glasgow Prognostic Score or modified Glasgow Prognostic Score (GPS/mGPS) is a novel inflammatory indicator which consists of CRP and albumin. Here, we performed a meta-analysis to evaluate the prognostic value of the GPS/mGPS in patients with colorectal cancer (CRC) and to assess its consistency in different CRC therapies. **Methods:** The electronic databases PubMed, Embase, Scopus, Web of Science, and Cochrane Library were searched from inception through December 2017 for the association between the GPS/mGPS and clinical outcomes. Study characteristics and prognostic data were extracted from each relevant study. Overall survival (OS) and cancer-specific survival (CSS) were considered the primary outcomes, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The quality of each study was pooled using the random-effects Mantel-Haenszel model. Finally, subgroup analyses were performed to detect the heterogeneity of

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different CRC treatments. **Results:** Thirty-four studies, with a combined total of 8834 patients, were eligible for this meta-analysis. Data on OS and CSS were available in 23 and 22 studies, respectively. By comparing the prognostic values of different levels of the GPS in CRC patients, the summary HRs for OS and CSS were 2.18 (95% CI 1.83-2.60) and 1.82 (95% CI 1.57-2.11), respectively. According to the different tumor stages, the subgroup analyses were stratified by different treatments, including curative or palliative therapy. The results robustly confirmed the prognostic role of the GPS/mGPS. **Conclusion:** Our results suggest that the GPS/mGPS is a novel and effective prognostic indicator for the OS and CSS of patients with CRC.

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Introduction

According to a recent epidemiological report, colorectal cancer (CRC) is still one of the most impactful diseases worldwide, as the third most diagnosed cancer and the fourth leading cause of cancer-related death [1]. Currently, therapeutic strategies for CRC are determined by the tumor stage and patients' systemic condition. The primary therapy is curative colorectal resection, but immunotherapy, chemotherapy, and targeted therapy are preferred when the CRC is confirmed at an advanced stage [2]. Despite the increasing development of therapeutic strategies and diagnostic techniques, the long-term morbidity and mortality rates for CRC remain high, possibly due to high risk of tumor recurrence and metastasis [1, 2]. In addition to tumor biological characteristics such as size, number, and vascular invasion, other factors also influence CRC progression and patient prognosis [3]. Therefore, it is worth exploring novel indicators that predict the prognosis of CRC patients who have received different therapeutic strategies.

Tumor biological factors, which constitute the tumor-node-metastasis (TNM) stage, were enacted by the American Joint Committee on Cancer (AJCC) and have been validated as indicators to evaluate CRC prognosis before patients undergo treatment [4]. However, the current TNM stage system for CRC lacks information reflecting the inflammatory status in patients. There is now a growing consensus that the systemic inflammatory response is an independent risk factor for the development of malignancy and is associated with worse prognosis in various cancers, such as gastric cancer [5], pancreatic cancer [6], liver cancer [7], breast cancer [8], and esophageal cancer [9]. When cancer generates an inflammatory response, the levels of cytokines are increased and the phenotypes of immune cells are changed, which increase the propensity for tumor growth by promoting angiogenesis and drug therapy resistance, inhibiting apoptosis, and damaging DNA [10-12].

As a consequence of continuous in-depth investigation of the inflammatory response in the tumor microenvironment, more and more inflammatory scores have been proposed for indicating the prognostic and survival outcomes of various cancers in routine clinical practice [13, 14]. These indicators, whose prognostic role has been validated, include the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein (CRP), systematic inflammatory index, and Glasgow Prognostic Score/modified Glasgow Prognostic Score (GPS/mGPS) [15-17]. By combining CRP and albumin [18], the GPS/mGPS reflects both the systematic inflammatory response and nutritional status [19-21]. The GPS score ranges from 0 to 2: patients with both an elevated CRP (>10 mg/l) and decreased albumin (<35 mg/l) are assigned a score of 2, whereas those with either an elevated CRP or decreased albumin alone are assigned a score of 1. Patients with a normal CRP concentration and albumin level are assigned a score of 0. The main difference between the GPS and the mGPS is that the mGPS defines hypoalbuminemic patients without elevated CRP as having low risk (mGPS = 0). A 2003 study by Forrest et al. showed the utility of the GPS as an indicator of prognostic outcomes for non-small-cell lung cancer patients [22]. Subsequently, an increasing number of studies have revealed the predictive values of the GPS/mGPS in other types of cancers, such as pancreatic cancer [23], liver cancer [7], and esophageal cancer [24]. Although

several studies have pointed out the correlation between the GPS/mGPS and prognosis of CRC patients [25], the role of the GPS/mGPS in CRC patients receiving different treatment has not been fully studied.

Therefore, this study aimed to widely explore the prognostic value of the pretreatment GPS/mGPS in CRC patients who undergo different therapeutic strategies by identifying the relevant studies and conducting a meta-analysis. We postulated that the GPS/mGPS might be a readily available and inexpensive objective prognostic index that could be used in daily oncologic clinical practice and could assist in the prognostic stratification of CRC patients.

Materials and Methods

Literature search strategy

A comprehensive search of the PubMed, Scopus, Embase, Web of Science, and Cochrane Library electronic databases was performed to identify possible studies published before January 2018 relevant to the theme of interest with a reported association between CRC prognostic outcomes and the GPS/mGPS. There was no restriction on regions, languages, and publication types. Search terms were limited to combine the following free-text words and Medical Subject Headings (MeSH)/EMTREE terms, as: "C-reactive protein" or "CRP" or "albumin" or "Glasgow Prognostic Score" or "GPS" or "modified Glasgow Prognostic Score" or "mGPS" and "colorectal" or "colon" or "rectum" or "rectal", and "cancer" or "cancers" or "tumor" or "tumors" or "carcinoma" or "carcinomas" or "neoplasm" or "neoplasms". Furthermore, the references in the primary selected studies or reviews were scrutinized for additional potential relevant articles. Two reviewers (L.Y. H. and H.L.) independently completed the electronic search of the above listed databases for titles and abstracts.

Study inclusion and exclusion criteria

Two reviewers (L.C. and J.Y.C.) independently selected the eligible studies based on the prespecified inclusion and exclusion criteria. Any discrepancies between the two reviewers were resolved by the senior reviewer (J.Z.). All authors participated in the final decision on inclusion and exclusion criteria. Studies satisfying the following criteria were included: (1) prospective and retrospective studies analyzing the relationship between the GPS/mGPS and its prognosis prediction efficacy in CRC patients; (2) patients with CRC classified on the basis of the GPS/mGPS scoring system; and (3) articles containing both the hazard ratio (HR) of overall survival (OS) or cancer-specific survival (CSS) and their 95% confidence intervals (CIs) or a *p* value comparing low-level GPS/mGPS with high-level GPS/mGPS in predicting prognostic outcomes. Furthermore, the exclusion criteria were as follows: (1) duplicated articles; (2) experimental studies; (3) case reports; (4) editorial letters, review articles, and meta-analyses; (5) abstracts only; (6) studies with unavailable data and irrelevant articles; and (7) studies without any prognostic outcomes.

Data extraction

Two authors (J.Y.C. and H.L.) independently extracted the data by reading the full text of each article. For each study, the information collected included the full names of the first authors, year of publication, region of study, sample size, age, number of outcome events (OS and CSS), follow-up period, disease stage, survival endpoint, and HRs with 95% CIs, as previously described [26, 27].

Statistical analysis

The main interest was to compare primary outcomes (i.e., OS and CSS) between CRC patients with high and low levels of the GPS/mGPS. For quantitative aggregation of the prognostic outcomes, the HRs with corresponding 95% CIs from the original studies were considered the most appropriate indexes for assessing prognostic outcomes because they were time-to-event data. HRs were collected by means of the following approaches: (1) the HRs could be obtained directly from the publications; if multivariate analysis was performed, the HRs of the multivariate analysis were preferable; and (2) in those studies that only provided survival curves, the HRs and 95% CIs were extracted from the curves. All data were pooled with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). All statistical analyses were two-sided, and *P* < 0.05 was considered statistically significant. The statistical heterogeneity across studies was examined

using the Cochran's Q-test and I^2 statistics [28]. A random-effects Mantel-Haenszel model was used when the $I^2 > 40\%$, considering the P value for substantial heterogeneity [29]. With the $I^2 < 40\%$, a fixed-effects model was used instead. Subgroup analyses were performed to reduce potential sources of heterogeneity. Control-enhanced funnel plots were used to signify publication bias. Funnel plots were used to explore the publication bias. The symmetry of the funnel plot was analyzed using Egger and Begg tests (Stata version 12.0).

Subgroup analysis

With cancer progression, patients undergo different therapeutic strategies, including curative or palliative therapy. Several kinds of therapies are applied to CRC. Patients with early-stage CRC receive surgical resection, whereas chemotherapy or molecular-targeted therapy is performed for advanced CRC. Thus, subgroup analysis was performed to minimize the influence of different therapies on the final outcomes. Patients who underwent surgical resection or chemotherapy were separately analyzed. The overall results were then compared between different groups.

Results

Identification and selection of studies

As shown in the flow chart of Fig. 1, the initial systematic literature search retrieved 2526 eligible citations from the above five major databases. After examination of the title and abstract, 56 potential relevant studies remained after the removal of 2470, including 883 duplicated articles and 1587 unsuitable articles (experimental studies, case reports, letters, review articles, meta-analyses, abstracts only, studies with unavailable data, and irrelevant articles). By scrutinizing the potential full texts, 22 studies were excluded because they contained no data of interest. Thus, 34 studies published between January 2007 and December 2017 met our inclusion criteria and were included in the final analysis [30-56].

Characteristics of the eligible studies

The basic characteristics of all included studies and the quality assessment consequences are summarized in Table S1 (For all supplemental material see www.karger.com/10.1159/000495500/). All trials were performed only using adult patients. Among the 34 studies, 13 were conducted in Japan, 7 in the UK, 4 in China, 4 in Korea, 3 in Australia, 1 in France, 1 in Turkey, and 1 as an international multicenter study. Overall, 8834 patients were included and the sample sizes of the selected studies ranged from 40 to 1000. The GPS score ranged from 0 to 2 based on the CRP and albumin levels, as discussed above. We defined a GPS score of 0 or 1 as the low group and a GPS score of 2 as the high group. Twenty-three studies investigated the association between the level of the GPS/mGPS and OS for CRC patients, whereas 22 reported the CSS. Additionally, 23 studies involved 7385 CRC patients receiving curative therapy, whereas 12 evaluated the prognostic outcomes of 1669 CRC patients treated with chemotherapy. Age at diagnosis,

Fig. 1. PRISMA flow diagram of the study to show the process.

sex, tumor stage, and the value of the GPS/mGPS are commonly investigated covariates that are used in adjusted Cox proportion hazards models when evaluating the role of the GPS/mGPS in predicting prognostic outcomes. In some eligible studies, HRs and 95% CIs were extracted directly from the original literature, whereas we obtained the survival curve from several studies that only provided survival curves.

Fig. 2. Forest plot and subgroup analyses to show the correlation between GPS/mGPS and OS in CRC patients stratified by treatment.

Fig. 3. Forest plot and subgroup analyses to show the correlation between GPS/mGPS and CSS in CRC patients stratified by treatment.

Relationship between the GPS/mGPS and CRC survival

The effect of the GPS/mGPS on OS and CSS in patients with CRC was explored. Twenty-three studies [30-33, 35, 38, 40, 41, 43-46, 48, 49, 51-54, 57-61] including 6218 patients reported OS. After the HRs and 95% CIs were pooled, the results revealed that a high GPS/mGPS was significantly associated with poor outcomes (HR 2.18, 95% CI 1.83-2.60; $P < 0.00001$; Fig. 2) with significant heterogeneity ($I^2=81\%$, $P_{\text{heterogeneity}} < 0.00001$). The analysis of subgroups of patients undergoing resection [30, 32, 33, 38, 40, 43-45, 48, 49, 54, 57-59] or chemotherapy [31, 35, 41, 46, 51-53, 60, 61] showed similar results (HR 2.14, 95% CI 1.71-2.67, $P < 0.0001$; HR 2.35, 95% CI 1.69-3.27, $P < 0.0001$). Data from 22 studies [62] showed the ability of pretreatment GPS/mGPS to predict the CSS of CRC (HR 1.82; 95% CI 1.57-2.11; $P < 0.00001$; Fig. 3) with some heterogeneity ($I^2=62\%$, $P_{\text{heterogeneity}} < 0.00001$). In the resection subgroup [34, 36-38, 40, 42, 44, 47, 49, 50, 55, 57-59, 63, 64], the GPS/mGPS showed a negative association with CSS (HR 1.92, 95% CI 1.60-2.31, $P < 0.0001$). This finding was similar in the subgroup of patients who underwent chemotherapy (HR 1.63, 95% CI 1.24-2.14, $P < 0.0001$).

Clinical features and prognosis of CRC are different between the Eastern and Western countries, which could be attributed to variations in diet, lifestyle or genetics [65]. To minimize the impact of region on the predictive value of GPS/mGPS, studies were further divided into Asian or non-Asian area and subgroup analysis was performed. The predictive value of GPS/mGPS were similar in the region subgroups: the HR was 2.68 (95% CI 2.04-3.52, $P < 0.00001$, $I^2=71\%$, P for heterogeneity < 0.0001 ; Fig. 4) for Asian subgroup [32, 35, 38, 40, 41, 45, 48, 53, 54, 57, 58, 60, 61, 66] and 1.65 for non-Asian subgroup [30, 33, 43, 44, 46, 49, 51, 52, 59] (95% CI 1.37-1.98, $P < 0.00001$, $I^2=65\%$, P for heterogeneity = 0.004). The prognostic effect of GPS/mGPS was also significant in CSS for Asian studies [37-42, 53, 55, 57, 58, 61, 63, 64, 67] was 2.05 (95% CI 1.68-2.51, $P < 0.00001$, $I^2=43\%$, P for heterogeneity = 0.04; Fig. 5), while the HR for non-Asian studies [23, 24, 34, 42, 46, 48, 54, 60] was 1.49 (95% CI 1.27-1.74, $P < 0.00001$, $I^2=37\%$, P for heterogeneity = 0.12).

Fig. 4. Forest plot and subgroup analyses to show the correlation between GPS/mGPS and OS in CRC patients stratified by study region.

Fig. 5. Forest plot and region subgroup analyses to show the correlation between GPS/mGPS and CSS in CRC patients stratified by study region.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by omitting the enrolled articles in sequence to investigate the stability of the synthesized HR concerning OS. Our meta-analysis was considered stable because the pooled HRs were not significantly altered by sequential elimination of the included studies (Fig. 6).

The funnel plot showed a publication bias in the included studies (Fig. 7). Two types of statistical tests were used to evaluate the dissymmetry of the funnel plot: Begg's ($z = 1.85$, $P = 0.064$) and Egger's (bias coefficient 1.846, standard error 0.405, $t = 1.91$, $P = 0.070$).

Fig. 6. Sensitivity analysis of CSS in CRC patients.

Discussion

This meta-analysis examined the results of 34 retrospective studies including 8834 patients to evaluate the prognostic value of the GPS/mGPS in patients with CRC treated with various therapeutic strategies. After we controlled for other individual and clinical variables, the pooled results indicated that patients with a high level of pretreatment GPS/mGPS were more likely to have poor OS and CSS. Furthermore, subgroup analyses revealed the significant relationship between the GPS/mGPS and OS in CRC patients regardless of the treatment received or region of studies. Altogether, the results indicate that the GPS/mGPS can be used as an efficient indicator to predict the prognostic outcomes of CRC patients.

Increasing evidence reveals that the systemic inflammatory response is positively associated with tumor malignancy. Proinflammatory cytokines from the microenvironment affect tumor characteristics, including angiogenesis, tumor growth promotion, and drug resistance [68]. Thus, systemic inflammatory indicators are more widely used for predicting the post-treatment recurrence and survival of CRC patients [7]. Recent studies showed that the GPS/mGPS was a novel inflammatory index, which predict outcomes in various cancers [7, 23, 24]. However, the molecular mechanisms underlying the relationship between the GPS/mGPS and poor CRC prognostic outcomes are still unclear. A plausible explanation is that an elevated GPS/mGPS may reflect an individual's immune and nutritional status. The GPS/mGPS is composed of albumin and CRP, which are both acute-phase proteins synthesized in the liver. Level of CRP is regulated by several proinflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor α , transforming growth factor β , interferon γ and IL-6 [69]. Study has shown that IL-6 is correlated with OS and CSS in CRC, which could be explained by its effect in promoting tumorigenesis and metastasis [70, 71]. Additionally, CRP is associated with the activity of infiltrated immune cells, including dendritic cells, T cells, and natural killer cells [72, 73]. Many studies have shown that CRP is an independent biomarker for predicting prognostic outcome in various cancers [74-76]. The serum albumin level is used as a biomarker to evaluate liver function and nutritional status. Hypoalbuminemia is a common feature of systemic inflammatory response and cancer recurrence and metastasis. Also, it has been shown to be positively correlated with the OS and CSS of patients with various cancers including CRC [24, 77-81].

Since the therapeutic strategy has a strong influence on prognostic outcomes for CRC patients, subgroup analyses were performed to assess the effects of the GPS/mGPS on CRC patients according to treatment stratification. As expected, despite different characteristics, tumor staging, and therapeutic strategies, the pooled consequences in these two subgroups were consistent, which exhibited an important predictive ability of the GPS/mGPS in CRC patients receiving curative or palliative therapy. Taken together, combined with one excluded study that showed the effect of this inflammatory index in CRC patients with targeted therapy [82], the findings demonstrate that the GPS/mGPS is a reliable and inexpensive index for making decisions regarding CRC therapeutic strategies. There is a substantial geographic variations in incidence, prognosis and risk factors of colorectal cancer [83]. Therefore, predictive value of GPS/mGPS of studies from Asian or non-Asian region was explored. The results indicated that high GPS/mGPS showed similar predictive value for prognosis of patients with CRC in spite of their regions and I^2 was reduced for both subgroups.

Fig. 7. Funnel plot of meta-analysis of GPS/mGPS in OS.

There are several limitations to our meta-analyses. The variety of the baseline characteristics of the study population and the follow-up information causes inevitable heterogeneity. Stratified analyses were performed for the various CRC treatments and regions of studies to minimize the heterogeneity. Also, in some included studies, the HRs from the multivariable analyses were not as statistically significant as other systemic inflammatory markers, such as the platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and other systematic inflammatory indexes. These indicators may have affected the role of the GPS/mGPS and thus led to a nonsignificant outcome in a multivariable model. Besides, all of the eligible articles were retrospective studies and the potential effects of unpublished data with negative results may be ignored. Thus, the results may be overestimated due to publication bias.

Conclusion

In conclusion, the current meta-analysis revealed that the GPS/mGPS, calculated from two common laboratory serum parameters, is an independent and promising indicator for predicting the prognostic outcomes of CRC patients regardless of whether they have received a radical or palliative treatment. Clinically, the GPS/mGPS is obtained conveniently and inexpensively before patients undergo their therapy. The pretreatment GPS/mGPS might be considered a biomarker in the management of CRC.

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Disclosure Statement

The authors in the current study have declared no conflicts of interest.

References

- 1 Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683-691.
- 2 DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, Alteri R, Robbins AS, Jemal A: Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252-271.
- 3 van Wyk HC, Park JH, Edwards J, Horgan PG, McMillan DC, Going JJ: The relationship between tumour budding, the tumour microenvironment and survival in patients with primary operable colorectal cancer. *Br J Cancer* 2016;115:156-163.
- 4 Ueno H, Mochizuki H, Akagi Y, Kusumi T, Yamada K, Ikegami M, Kawachi H, Kameoka S, Ohkura Y, Masaki T, Kushima R, Takahashi K, Ajioka Y, Hase K, Ochiai A, Wada R, Iwaya K, Shimazaki H, Nakamura T, Sugihara K: Optimal colorectal cancer staging criteria in TNM classification. *J Clin Oncol* 2012;30:1519-1526.

- 5 Aliustaoglu M, Bilici A, Ustaalioglu BB, Konya V, Gucun M, Seker M, Gumus M: The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. *Med Oncol* 2010;27:1060-1065.
- 6 Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P: Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 2009;197:466-472.
- 7 Yamamura K, Sugimoto H, Kanda M, Yamada S, Nomoto S, Nakayama G, Fujii T, Koike M, Fujiwara M, Kodera Y: Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. *J Hepatobiliary Pancreat Sci* 2014;21:682-688.
- 8 Wariss BR, de Souza Abrahao K, de Aguiar SS, Bergmann A, Thuler LCS: Effectiveness of four inflammatory markers in predicting prognosis in 2374 women with breast cancer. *Maturitas* 2017;101:51-56.
- 9 Altaf K, Xiong JJ, la Iglesia D, Hickey L, Kaul A: Meta-analysis of biomarkers predicting risk of malignant progression in Barrett's oesophagus. *Br J Surg* 2017;104:493-502.
- 10 Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? *Lancet* 2001;357:539-545.
- 11 Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ: Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res* 2000;60:184-190.
- 12 Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD: The codependence of angiogenesis and chronic inflammation. *FASEB J* 1997;11:457-465.
- 13 Coussens LM, Werb Z: Inflammation and cancer. *Nature* 2002;420:860-867.
- 14 Mantovani A: Cancer: Inflaming metastasis. *Nature* 2009;457:36-37.
- 15 Fan H, Shao ZY, Xiao YY, Xie ZH, Chen W, Xie H, Qin GY, Zhao NQ: Comparison of the Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS) in evaluating the prognosis of patients with operable and inoperable non-small cell lung cancer. *J Cancer Res Clin Oncol* 2016;142:1285-1297.
- 16 Chen L, Yan Y, Zhu L, Cong X, Li S, Song S, Song H, Xue Y: Systemic immune-inflammation index as a useful prognostic indicator predicts survival in patients with advanced gastric cancer treated with neoadjuvant chemotherapy. *Cancer Manag Res* 2017;9:849-867.
- 17 Wu Y, Jiang M, Qin Y, Lin F, Lai M: Single and combined use of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and carcinoembryonic antigen in diagnosing gastric cancer. *Clin Chim Acta* 2018;481:20-24.
- 18 Laird BJ, Fallon M, Hjermstad MJ, Tuck S, Kaasa S, Klepstad P, McMillan DC: Quality of Life in Patients With Advanced Cancer: Differential Association With Performance Status and Systemic Inflammatory Response. *J Clin Oncol* 2016;34:2769-2775.
- 19 Pinato DJ, Shiner RJ, Seckl MJ, Stebbing J, Sharma R, Mauri FA: Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. *Br J Cancer* 2014;110:1930-1935.
- 20 Liao C, Yu Z, Guo W, Liu Q, Wu Y, Li Y, Bai L: Prognostic value of circulating inflammatory factors in non-small cell lung cancer: a systematic review and meta-analysis. *Cancer Biomark* 2014;14:469-481.
- 21 Bremnes RM, Al-Shibli K, Donnem T, Sirera R, Al-Saad S, Andersen S, Stenvold H, Camps C, Busund LT: The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. *J Thorac Oncol* 2011;6:824-833.
- 22 Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ: Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2003;89:1028-1030.
- 23 Kurahara H, Maemura K, Mataka Y, Sakoda M, Iino S, Hiwatashi K, Kawasaki Y, Arigami T, Ishigami S, Kijima Y, Shinchu H, Takao S, Natsugoe S: Prognostication by inflammation-based score in patients with locally advanced pancreatic cancer treated with chemoradiotherapy. *Pancreatol* 2015;15:688-693.
- 24 Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC: Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. *Br J Cancer* 2006;94:637-641.
- 25 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;22:881-886.
- 26 Zheng J, Cai J, Li H, Zeng K, He L, Fu H, Zhang J, Chen L, Yao J, Zhang Y, Yang Y: Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Predictors for Hepatocellular Carcinoma Patients with Various Treatments: a Meta-Analysis and Systematic Review. *Cell Physiol Biochem* 2017;44:967-981.

- 27 Li H, Zheng J, Cai JY, Li SH, Zhang JB, Wang XM, Chen GH, Yang Y, Wang GS: Laparoscopic VS open hepatectomy for hepatolithiasis: An updated systematic review and meta-analysis. *World J Gastroenterol* 2017;23:7791-7806.
- 28 Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.
- 29 Higgins JPT, Green S, Cochrane Collaboration.: *Cochrane handbook for systematic reviews of interventions*, Wiley-Blackwell, Chichester, England; Hoboken, NJ, 2008.
- 30 Moug SJ, McColl G, Lloyd SM, Wilson G, Saldanha JD, Diamant RH: Comparison of positive lymph node ratio with an inflammation-based prognostic score in colorectal cancer. *Br J Surg* 2011;98:282-286.
- 31 Lee ASWE: Comparison of selected inflammation-based prognostic markers in relapsed or refractory metastatic colorectal cancer patients. *World J Gastroenterol* 2015;21:12410-12420.
- 32 Adachi T, Hinoi T, Hattori M, Egi H, Shimomura M, Saito Y, Sawada H, Miguchi M, Niitsu H, Mukai S, Yano T, Ohdan H: The modified Glasgow prognostic score for early mortality in patients with synchronous peritoneal carcinomatosis from colorectal cancer. *Surg Today* 2015;45:1396-1403.
- 33 Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, Clarke SJ: The Lymphocyte-to-Monocyte Ratio is a Superior Predictor of Overall Survival in Comparison to Established Biomarkers of Resectable Colorectal Cancer. *Ann Surg* 2017;265:539-546.
- 34 Eren T, Burcu B, Tombalak E, Ozdemir T, Leblebici M, Ozemir IA, Ziyade S, Alimoglu O: Clinical Significance of the Glasgow Prognostic Score for Survival after Colorectal Cancer Surgery. *J Gastrointest Surg* 2016;20:1231-1238.
- 35 Furukawa K, Shiba H, Haruki K, Fujiwara Y, Iida T, Mitsuyama Y, Ogawa M, Ishida Y, Misawa T, Yanaga K: The Glasgow prognostic score is valuable for colorectal cancer with both synchronous and metachronous unresectable liver metastases. *Oncol Lett* 2012;4:324-328.
- 36 Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, Horgan PG, McMillan DC: Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br J Cancer* 2013;109:24-28.
- 37 Hong T, Shen D, Chen X, Cai D, Wu X, Hua D: A novel systematic inflammation related index is prognostic in curatively resected non-metastatic colorectal cancer. *Am J Surg* 2017;10.1016/j.amjsurg.2017.07.021.
- 38 Ide S, Toiyama Y, Okugawa Y, Oki S, Yasuda H, Fujikawa H, Yoshiyama S, Hiro J, Kobayashi M, Ohi M, Araki T, Kusunoki M: Clinical Significance of C-Reactive Protein-to-Albumin Ratio with Rectal Cancer Patient Undergoing Chemoradiotherapy Followed by Surgery. *Anticancer Res* 2017;37:5797-5804.
- 39 Inoue Y, Iwata T, Okugawa Y, Kawamoto A, Hiro J, Toiyama Y, Tanaka K, Uchida K, Mohri Y, Miki C, Kusunoki M: Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. *Oncology* 2013;84:100-107.
- 40 Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K: Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen. *Ann Surg Oncol* 2012;19:3422-3431.
- 41 Kim IH, Lee JE, Yang JH, Jeong JW, Ro S, Lee MA: Clinical significance of changes in systemic inflammatory markers and carcinoembryonic antigen levels in predicting metastatic colorectal cancer prognosis and chemotherapy response. *Asia Pac J Clin Oncol* 2017;10.1111/ajco.12784
- 42 Kishiki T, Masaki T, Matsuoaka H, Kobayashi T, Suzuki Y, Abe N, Mori T, Sugiyama M: Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer. *Am J Surg* 2013;206:234-240.
- 43 Kostner AH, Kersten C, Lowenmark T, Ydsten KA, Peltonen R, Isoniemi H, Haglund C, Gunnarsson U, Isaksson B: The prognostic role of systemic inflammation in patients undergoing resection of colorectal liver metastases: C-reactive protein (CRP) is a strong negative prognostic biomarker. *J Surg Oncol* 2016;114:895-899.
- 44 Leitch EF, Chakrabarti M, Crozier JE, McKee RF, Anderson JH, Horgan PG, McMillan DC: Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. *Br J Cancer* 2007;97:1266-1270.
- 45 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;8:19138-19143.
- 46 Maillet M, Dreanic J, Dhooge M, Mir O, Brezault C, Goldwasser F, Chaussade S, Coriat R: The predictive and prognostic value of the Glasgow Prognostic Score in metastatic colorectal carcinoma patients receiving bevacizumab. *Anticancer Drugs* 2014;25:1215-1219.

- 47 McSorley ST, Khor BY, Tsang K, Colville D, Han S, Horgan PG, McMillan DC: The relationship between 18F FDG-PETCT derived markers of tumour metabolism and systemic inflammation in patients with recurrent disease following surgery for colorectal cancer. *Colorectal Dis* 2017;10.1111/codi.13973.
- 48 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;99:512-517.
- 49 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;263:326-336.
- 50 Powell AG, Wallace R, McKee RF, Anderson JH, Goings JJ, Edwards J, Horgan PG: The relationship between tumour site, clinicopathological characteristics and cancer-specific survival in patients undergoing surgery for colorectal cancer. *Colorectal Dis* 2012;14:1493-1499.
- 51 Read JA, Choy ST, Beale PJ, Clarke SJ: Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. *Nutr Cancer* 2006;55:78-85.
- 52 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;7:331-337.
- 53 Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Yamazoe A, Kimura K, Toyokawa T, Amano R, Kubo N, Tanaka H, Muguruma K, Ohira M, Hirakawa K: Significance of Markers of Systemic Inflammation for Predicting Survival and Chemotherapeutic Outcomes and Monitoring Tumor Progression in Patients with Unresectable Metastatic Colorectal Cancer. *Anticancer Res* 2015;35:5037-5046.
- 54 Shimura T, Toiyama Y, Saigusa S, Imaoka H, Okigami M, Fujikawa H, Hiro J, Kobayashi M, Ohi M, Araki T, Inoue Y, Uchida K, Mohri Y, Kusunoki M: Inflammation-based prognostic scores as indicators to select candidates for primary site resection followed by multimodal therapy among colorectal cancer patients with multiple metastases. *Int J Clin Oncol* 2017;22:758-766.
- 55 Son HJ, Park JW, Chang HJ, Kim DY, Kim BC, Kim SY, Park SC, Choi HS, Oh JH: Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer. *Ann Surg Oncol* 2013;20:2908-2913.
- 56 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;29:503-509.
- 57 Sun ZQ, Han XN, Wang HJ, Tang Y, Zhao ZL, Qu YL, Xu RW, Liu YY, Yu XB: Prognostic significance of preoperative fibrinogen in patients with colon cancer. *World J Gastroenterol* 2014;20:8583-8591.
- 58 Tokunaga R, Sakamoto Y, Nakagawa S, Izumi D, Kosumi K, Taki K, Higashi T, Miyata T, Miyamoto Y, Yoshida N, Baba H: Comparison of systemic inflammatory and nutritional scores in colorectal cancer patients who underwent potentially curative resection. *Int J Clin Oncol* 2017;22:740-748.
- 59 Watt DG, McSorley ST, Park JH, Horgan PG, McMillan DC: A Postoperative Systemic Inflammation Score Predicts Short- and Long-Term Outcomes in Patients Undergoing Surgery for Colorectal Cancer. *Ann Surg Oncol* 2017;24:1100-1109.
- 60 Ni X, Wu P, Wu J, Ji M, Shao Y, Zhou W, Jiang J, Wu C: C-reactive protein/albumin ratio as a predictor of survival of metastatic colorectal cancer patients receiving chemotherapy. *Int J Clin Exp Pathol* 2016;9:5525-5534.
- 61 Toiyama Y, Miki C, Inoue Y, Tanaka K, Mohri Y, Kusunoki M: Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. *Exp Ther Med* 2011;2:95-101.
- 62 Yamamoto M, Yoshinaga K, Matsuyama A, Iwasa T, Osoegawa A, Tsujita E, Yamashita Y, Tsutsui S, Ishida T: Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. *Oncology* 2012;83:10-15.
- 63 Choi KW, Hong SW, Chang YG, Lee WY, Lee B, Paik IW, Lee H: Inflammation-based score (Glasgow prognostic score) as an independent prognostic factor in colorectal cancer patients. *Ann Surg Treat Res* 2014;86:309-313.
- 64 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;29:503-509.
- 65 Pourhoseingholi MA: Increased burden of colorectal cancer in Asia. *World J Gastrointest Oncol* 2012;4:68-70.
- 66 Song A, Eo W, Lee S: Comparison of selected inflammation-based prognostic markers in relapsed or refractory metastatic colorectal cancer patients. *World J Gastroenterol* 2015;21:12410-12420.

- 67 Yamamoto M, Yoshinaga K, Matsuyama A, Iwasa T, Osoegawa A, Tsujita E, Yamashita Y, Tsutsui S, Ishida T: Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. *Oncology* 2012;83:10-15.
- 68 Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:dju124.
- 69 Morris-Stiff G, Gomez D, Prasad KR: C-reactive protein in liver cancer surgery. *Eur J Surg Oncol* 2008;34:727-729.
- 70 Mauer J, Denson JL, Bruning JC: Versatile functions for IL-6 in metabolism and cancer. *Trends Immunol* 2015;36:92-101.
- 71 Lasry A, Zinger A, Ben-Neriah Y: Inflammatory networks underlying colorectal cancer. *Nat Immunol* 2016;17:230-240.
- 72 Inatsu A, Kinoshita M, Nakashima H, Shimizu J, Saitoh D, Tamai S, Seki S: Novel mechanism of C-reactive protein for enhancing mouse liver innate immunity. *Hepatology* 2009;49:2044-2054.
- 73 Van Vre EA, Bult H, Hoymans VY, Van Tendeloo VF, Vrints CJ, Bosmans JM: Human C-reactive protein activates monocyte-derived dendritic cells and induces dendritic cell-mediated T-cell activation. *Arterioscler Thromb Vasc Biol* 2008;28:511-518.
- 74 Rasmussen LJH, Schultz M, Gaardsting A, Ladelund S, Garred P, Iversen K, Eugen-Olsen J, Helms M, David KP, Kjaer A, Lebech AM, Kronborg G: Inflammatory biomarkers and cancer: CRP and suPAR as markers of incident cancer in patients with serious nonspecific symptoms and signs of cancer. *Int J Cancer* 2017;141:191-199.
- 75 Pletnikoff PP, Laukkanen JA, Tuomainen TP, Kauhanen J, Rauramaa R, Ronkainen K, Kurl S: Cardiorespiratory fitness, C-reactive protein and lung cancer risk: A prospective population-based cohort study. *Eur J Cancer* 2015;51:1365-1370.
- 76 Amano K, Maeda I, Morita T, Baba M, Miura T, Hama T, Mori I, Nakajima N, Nishi T, Sakurai H, Shimoyama S, Shinjo T, Shirayama H, Yamada T, Ono S, Ozawa T, Yamamoto R, Yamamoto N, Shishido H, Kinoshita H: C-reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. *J Cachexia Sarcopenia Muscle* 2017;8:457-465.
- 77 Komrokji RS, Corrales-Yepez M, Kharfan-Dabaja MA, Al Ali NH, Padron E, Rollison DE, Pinilla-Ibarz J, Zhang L, Epling-Burnette PK, Lancet JE, List AF: Hypoalbuminemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. *Am J Hematol* 2012;87:1006-1009.
- 78 Ataseven B, du Bois A, Reinthaller A, Traut A, Heitz F, Aust S, Prader S, Polterauer S, Harter P, Grimm C: Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery. *Gynecol Oncol* 2015;138:560-565.
- 79 Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC: Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. *Cancer* 2007;109:205-212.
- 80 Haskins IN, Baginsky M, Amdur RL, Agarwal S: Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients. *Clin Nutr* 2017;36:1333-1338.
- 81 Al-Shaiba R, McMillan DC, Angerson WJ, Leen E, McArdle CS, Horgan P: The relationship between hypoalbuminaemia, tumour volume and the systemic inflammatory response in patients with colorectal liver metastases. *Br J Cancer* 2004;91:205-207.
- 82 Dreanac J, Dhooge M, Barret M, Brezault C, Mir O, Chaussade S, Coriat R: Anti-epidermal or anti-vascular endothelial growth factor as first-line metastatic colorectal cancer in modified Glasgow prognostic score 2' patients. *J Cachexia Sarcopenia Muscle* 2015;6:231-236.
- 83 Hagggar FA, Boushey RP: Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg* 2009;22:191-197.