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Review Article

Biomarkers for Evaluating the Inflammation Status in Patients with Cancer

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ABSTRACT

Inflammation can be a causative factor for carcinogenesis or can result from a consequence of cancer progression. Moreover, cancer therapeutic interventions can also induce an inflammatory response. Various inflammatory parameters are used to assess the inflammatory status during cancer treatment. It is important to select the most optimal biomarker among these parameters. Additionally, suitable biomarkers must be examined if there are no known parameters. We briefly reviewed the published literature for the use of inflammatory parameters in the treatment of patients with cancer. Most studies on inflammation evaluated the correlation between host characteristics, effect of interventions, and clinical outcomes. Additionally, the levels of C-reactive protein, albumin, lymphocytes, and platelets were the most commonly used laboratory parameters, either independently or in combination with other laboratory parameters and clinical characteristics. Furthermore, the immune parameters are classically examined using flow cytometry, immunohistochemical staining, and enzyme-linked immunosorbent assay techniques. However, gene expression profiling can aid in assessing the overall peri-interventional immune status. The checklists of guidelines, such as STAndards for Reporting of Diagnostic accuracy and REporting recommendations for tumor MARKer prognostic studies should be considered when designing studies to investigate the inflammatory parameters. Finally, the data should be interpreted after adjusting for clinically important variables, such as age and cancer stage.

Keywords: Inflammation; Cancer; Biomarkers; Immune system; Outcome assessment

INTRODUCTION

Inflammatory response, which promotes the healing of injured tissues, is a physiological defense mechanism against foreign substances. Inflammation can be a causative factor in cancer development or can result from a consequence of cancer progression. Additionally, inflammation can be induced by cancer interventions and/or by the cancer-associated complications and subsequently affect the tumor recurrence, progression, and metastasis [1]. It is important to determine the molecular players involved in the inflammatory response against cancer cells to assess the inflammation status and to devise the best therapeutic strategy [2].

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Surgery is an invasive intervention for cancer treatment. Clinicians gather routine clinical and laboratory information perioperatively to predict the surgical outcomes. However, the clinical and laboratory information is sometimes insufficient to assess the inflammation status in patients. Hence, novel parameters must be investigated for a more reliable prediction of surgical outcomes. Currently, various inflammatory and nutritional parameters as well as the body weight-related data are used to evaluate the inflammatory response associated with therapeutic interventions. In a recent study, we compared multiple parameters and demonstrated that simple biomarkers, such as albumin level, body mass index (BMI), and neutrophil count were more effective in predicting surgical outcomes than sophisticated biomarkers, such as the prognostic nutritional index (PNI), nutritional risk index (NRI), and neutrophil-to-lymphocyte ratio (NLR) [3]. The results of the study suggested that low albumin level, high BMI, high neutrophil count are predictors of major complications, operative mortality and unfavorable recurrence-free survival, and unfavorable overall and recurrence-free survival, respectively. These observations indicated that we must reconsider the parameters currently used for determining the surgical outcome of patients. We reviewed the published literature for parameters used to determine inflammatory response in patients with cancer. Further, the parameters were classified to guide researchers to systematically evaluate the inflammatory response in patients.

FACTORS ASSOCIATED WITH INFLAMMATION IN PATIENTS WITH CANCER

We grouped the published studies into three groups (**Table 1**) [3-81]. The first group included studies that identified the characteristics of hosts exhibiting inflammation, the second group included studies that measured the effect of treatment interventions, and the third group included studies that predicted the outcomes of interventions.

Host factors

Among the various factors that affect inflammatory response, the inherent factors, such as sex, age, and obesity are well-known and are the most important host factors. Men and women exhibit differential immune response due to the difference in the number of X

Table 1. Studies on inflammatory response parameters in cancer

Host			Intervention		Outcomes	
Inherence	Behavior	Disease	Surgical	Medical	Prediction	Prognosis
Sex [4-6]	Immunosuppressive medication [12]	Chronic disease [16]	Open surgery vs MIS [21-24]	Anesthesia, analgesia [30-32]	Morbidity and mortality [56-63]	Recurrence [68-72]
Age [7,8]	Nutritional status [13]	Cancer progression [17]	Major vs minor surgery [1,25]	Fast track protocol [33-35]	Infection [64,65]	Survival [12,26,73-81]
Obesity [3,9-11]	Smoking [14]	Psychiatric disease [18]	Emergency surgery [26,27]	Transfusion [36,37]	Prediction of neoadjuvant response [66,67]	
	Exercise [15]	Ischemia [19]	Surgical stress [28,29]	Nutritional support* [38-44]		
		Sepsis [20]		Steroid and other immune modulators [25,45-50]		
				Adjuvant/neoadjuvant treatment [51-53]		
				NSAID [54]		
				Statin [55]		

MIS = minimally invasive surgery; NSAID = non-steroid anti-inflammatory drug.
*Includes enteral, parenteral, and immune-enhancing nutrition.

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chromosomes and variations in sex hormones [4]. Estrogen promotes T helper cell type 2 (Th2) and suppresses T helper cell type 1 (Th1) immune responses, whereas testosterone suppresses the Th2 immune response [5]. The Th1 immune responses are cell-mediated responses that target the intracellular pathogen, whereas Th2 responses are antibody-mediated responses that target the extra-cellular pathogen. The analysis of differential immune response between the genders revealed that women have a lower risk of microbial infections and higher prevalence of autoimmune disease, whereas men have a higher susceptibility to systemic inflammatory response syndrome or infectious complications after surgery [6]. Age is also an important clinical parameter. The body's ability to distinguish between self and non-self cells decreases with age. Hence, decreased number of immune cells and weakened immune function associated with aging increase the susceptibility to malignancies and reactivation of chronic infections among aged individuals. Thus, several studies have evaluated the postoperative outcomes for elderly patients [7,8]. Obesity, which is generally measured by BMI, is associated with impaired immune function [9], inflammation [10], and complications following treatment interventions [11].

Other factors that may affect the inflammatory response and clinical outcomes include behavior- and disease-related characteristics, such as immunosuppressive medication usage [12], nutritional status [13], smoking status [14], exercise habits [15], presence of chronic disease [16], cancer stage [17], psychiatric condition [18], and presence of ischemia [19] or sepsis [20].

Intervention factors

Among the various therapeutic interventions, surgery is the most invasive intervention. The incision size or resection extent is directly correlated with the degree of surgical trauma. Hence, several studies are focused on developing novel surgical techniques that are associated with less surgical trauma and exhibit similar therapeutic efficacy. In the last few decades, comparative efficacy of open and laparoscopic surgery has been well studied [21]. The advantages of laparoscopic surgery include decreased surgical trauma and attenuated inflammatory response. The Th1/Th2 ratio is modulated to favor a decreased inflammatory response and decreased concentration of acute phase markers [22,23]. Recently, minimally invasive surgical procedures, such as reduced port laparoscopy and robotic surgery have been used to reduce the inflammatory response associated with open surgery [23,24].

The inflammatory response resulting from surgical intervention correlates with surgical trauma and is easy to predict. However, inflammatory responses resulting from other medical interventions are diverse and difficult to predict. Anesthetic techniques affect not only postoperative recovery but can also potentially impair the survival outcomes due to the suppression of inflammation [30,82,83]. Regional or epidural anesthesia is reported to be a factor that mitigates surgery-induced immunosuppression [31,32]. Moreover, peri-operative management [33-35], transfusion strategy [36,37], and pain management [32] are reported to considerably influence the inflammatory response.

Nutritional supplements, such as glutamine and arginine are used to enhance the immune response (referred to as immunonutrition) [38,39], while probiotics are used for perioperative modulation of the gut microbiome [40,41]. Nutrional supplements and probiotics have been extensively studied to determine their effect on the immune response and clinical outcomes. However, it is difficult to evaluate the effect of nutritional interventions on well-nourished patients. The nutritional interventions are most effective in patients exhibiting malnourishment [84,85].

https://doi.org/10.5230/jgc.2019.19.e29

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Finally, steroids are one of the most well studied drugs that are used to attenuate the immune response. Preoperative steroid administration is reported to markedly decrease systemic inflammatory cytokine release and improve the postoperative clinical course of patients, without adverse effects on immunity [45,46]. The immune modulators, such as dendritic cell-activated cytokine-induced killer cells [47], interleukin (IL)-2 [48], neutrophil elastase inhibitors [49], protease inhibitors [50], and recombinant human granulocyte colony-stimulating factor [25] have been studied to determine their effectiveness during the peri-intervention period.

Outcomes

The most classical clinical outcomes measured following therapeutic interventions, such as surgery, chemotherapy, or radiotherapy are complication rates and recovery time in short-term [61], and survival without unfavorable events in long-term [71]. Additionally, some inflammation parameters including tumor-infiltrating lymphocytes or composite scores can be used for predicting the inflammation response following neoadjuvant chemo-radiation therapy [64,65] or for anticipating an infection [66] following an intervention.

APPROACHES FOR EVALUATING INFLAMMATORY PARAMETERS

Laboratory parameters

Historically, laboratory values are used to assess the inflammatory status of the patients (**Table 2**) [3,17,23,26,34,35,38,39,42,44,50,59,62,66,69,71,73-79,84,86-89,90-106]. Laboratory

Table 2. Laboratory parameters

Parameters	
Single value	Combined values
Positive APPs	
CRP [34,39,71,86]	NRS-2002 [3,44,84]
High sensitivity CRP [87,88]	MUST [3]
Erythrocyte sedimentation rate [89]	Skeletal muscle index [90]
Alpha 1-acid glycoprotein levels [91]	NRI [3]
Serum amyloid A levels [92,93]	SIRS criteria [50,94]
Alpha-1-antitrypsin levels [95]	CRP/Albumin ratio [17,75]
Procalcitonin levels [23,62,96]	GPS, modified GPS, hepatic GPS [17,26,66,79]
Fibrinogen levels [88,97]	PNI [69,98]
Complement-C3 and C4 levels [35,44]	Prognostic index [98]
	APRI [99]
Negative APPs	CONUT [78]
Albumin levels [3,100]	Naples prognostic score [73]
Prealbumin levels [38,42]	Canton score [101]
Retinol-binding protein levels [38,95]	PLR [74,102]
Transferrin levels [39,95]	NLR [59,74,77,102]
	COP-NLR [76]
	NMLR [103]
	GLR [104]
	LMR [105]
	SII [106]

APP = acute phase protein; CRP = C-reactive protein; NRS = nutritional risk screening; MUST = malnutrition universal screening tool; NRI = nutritional risk index; SIRS = systemic inflammatory response syndrome; GPS = Glasgow prognostic score; PNI = prognostic nutritional index; APRI = aspartate aminotransferase/platelet count ratio index; CONUT = controlling nutritional status; PLR = platelet-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; COP-NLR = combination of platelet count and neutrophil-to-lymphocyte ratio; NMLR = neutrophil-monocyte-to-lymphocyte ratio; GLR = granulocyte-to-lymphocyte ratio; LMR = lymphocyte-to-monocyte ratio; SII = systemic immune-inflammation index.

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parameters are economical to evaluate, easily measurable, repeatable, and ready to use in daily clinical practice. Among the various laboratory parameters, acute phase protein levels are the most relevant to determine the inflammatory status of patients. The levels of positive acute phase proteins increase, whereas those of negative acute phase proteins decrease during inflammation [107]. C-reactive protein (CRP) and albumin are the most commonly used positive and negative acute phase proteins, respectively. CRP is secreted from the liver and the CRP levels increase upon secretion of IL-6 by macrophages and T-cells. Although meta-analyses have revealed limited diagnostic value of CRP for diagnosing postoperative complications [108,109], CRP level is useful during follow-up as it has a short half-life.

The predominant protein in the blood serum is albumin. Albumin carries water-insoluble molecules necessary for various metabolic processes. Although albumin is reported to be a negative acute phase protein, hypoalbuminemia does not represent an increased inflammatory status in patients [110]. Hence, albumin level is used independently or in combination with other laboratory values to assess the nutritional status in patients [100].

The combination of CRP and albumin has been extensively studied for the prediction of survival [106,111], tumor recurrence [70,71], peri-operative mortality [58], and specific outcomes, such as central venous catheter-related bloodstream infection [66]. The predictive value of CRP and albumin combination is not conclusive due to the heterogeneity in results reported by different studies. However, the CRP and albumin levels are the most sensitive and reliable biomarkers among the various inflammation-based scores [98,111-113].

Currently, CRP, albumin, lymphocytes, or platelets are used in combination to predict the surgical outcomes. **Fig. 1** shows the relationship among these parameters. However, the use of combinations of these four parameters without accounting for the clinical parameters can be misleading as these 4 parameters are not independent but associated with patient characteristics, such as age and cancer stage. Thus, combined parameters based on albumin may lose their predictive value after adjustment with patient characteristics [3,114]. As shown in **Fig. 2**, there is a correlation between albumin level, age, and cancer stage [115].

Immune parameters

Immune cells

Assessment of immune cells and cytokines is necessary to evaluate the immune response in patients (**Table 3**) [1,3,13,14,18,20,22,25,27,29,30,31,34,35,39,42-44,47,50-54,60,63,67,72,79,80,81,85-88,90,91,93,95,97,103,116-132]. The innate immune response is rapid and does not require prior exposure to an antigen. This general, non-specific, and first-line defense system against foreign substances is mediated by the natural killer (NK) cells. In response to injury, macrophages and mast cells are the first host tissue cells that are activated, which subsequently coordinate the immune response. The adaptive immune cells mainly consist of B and T lymphocytes. The analysis of complete blood count (CBC) provides the crude numbers of neutrophils, granulocytes, lymphocytes, and platelets. However, evaluating the lymphocyte subpopulations of dendritic cells and T-cells is more complicated and requires flow cytometric analysis. The T-cells comprise cytotoxic T-cell and helper T-cell subpopulations, which can be further classified as Th1, Th2, Th17, and regulatory T cells. Cancer recurrence can be predicted by phenotyping and functional assay of lymphocytes from the peripheral blood and tumor lysate [68]. If fresh blood is not available, the immune status of tumor tissues can be evaluated by immunohistochemical staining. The advantage of using paraffin-embedded tissue blocks is that the long-term outcome of the treated patients

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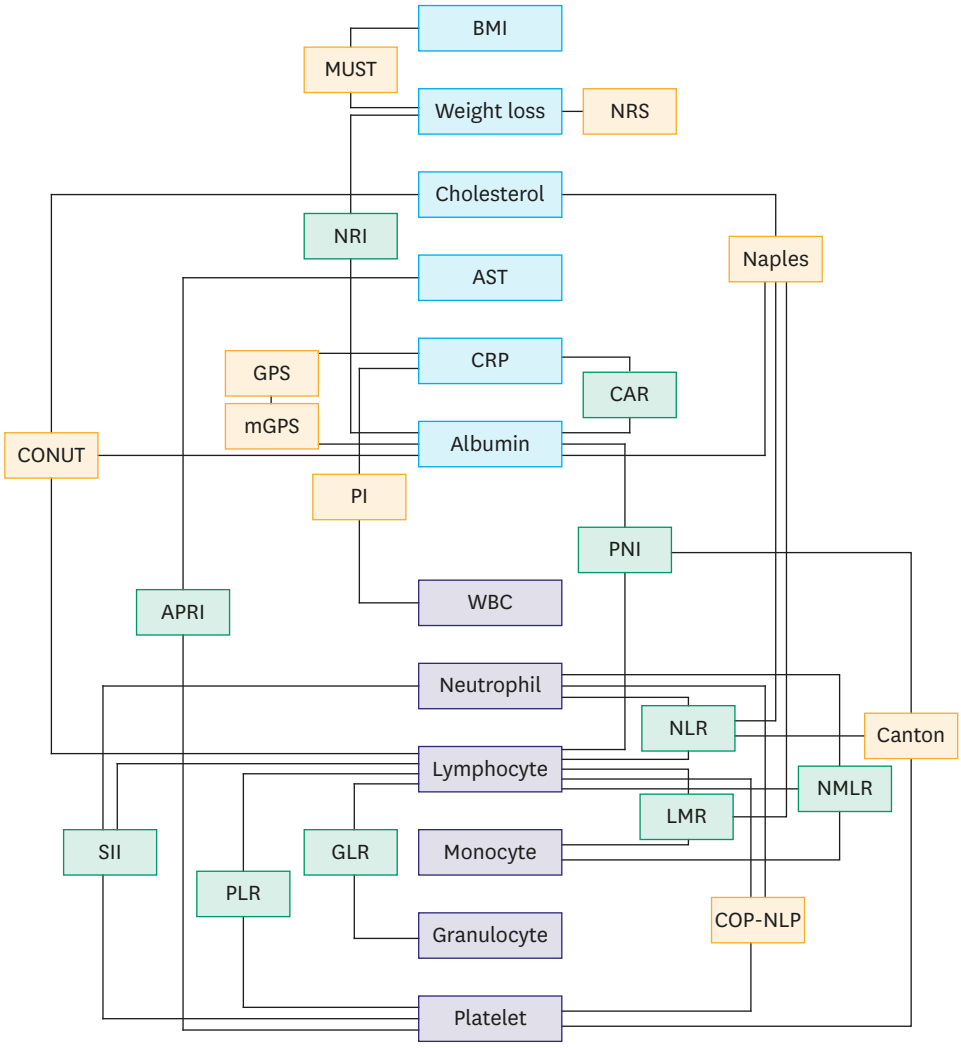

Fig. 1. Relationship among parameters. Parameters with continuous values (Green boxes) and with categorical values (Orange boxes). Detail of values are presented in **Appendix 1**.
BMI = body mass index; MUST = malnutrition universal screening tool; NRS = nutritional risk screening; NRI = nutritional risk index; AST = aspartate transaminase; CRP = C-reactive protein; GPS = Glasgow prognostic score; CAR = C-reactive protein-to-albumin ratio; CONUT = controlling nutritional status; PI = prognostic index; PNI = prognostic nutritional index; WBC = white blood cell; APRI = aspartate aminotransferase/platelet count ratio index; NLR = neutrophil-to-lymphocyte ratio; NMLR = neutrophil-monocyte-to-lymphocyte ratio; LMR = lymphocyte-to-monocyte ratio; SII = systemic immune-inflammation index; GLR = granulocyte-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; COP-NLR = combination of platelet count and neutrophil-to-lymphocyte ratio.

is already known. The tumor microenvironment is assessed by evaluating the lymphocytes [133-135], tumor-associated macrophages [72], and myeloid-derived suppressor cells [136].

Cytokines

The immune cells communicate with each other through signaling molecules or cell-to-cell communication, which involve toll-like receptors, B and T cell receptors and the complement system [137,138]. However, majority of the immune cells communicate through the secretion of cytokines. Cytokines are a category of cell-signaling proteins that regulate various immunological functions. Various proteins, such as lymphokines (produced by lymphocytes), monokines (produced by monocytes), chemokines (regulate chemotactic activities between cells), interferons (involved in the antiviral activity), and interleukins function as cytokines. Several cytokine classifications were proposed based on the Th1/2 axis [139,140]: receptor

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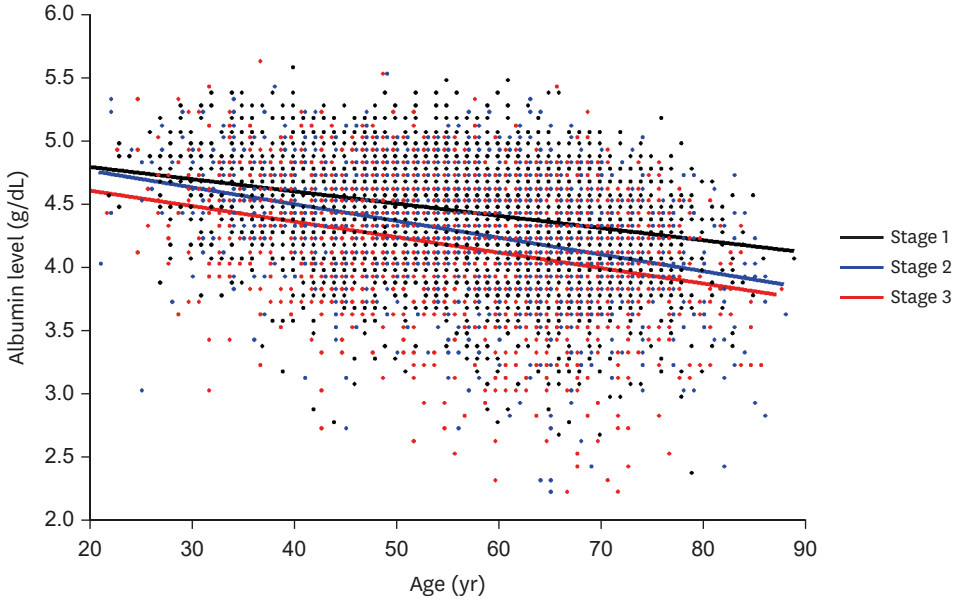

Fig. 2. Relationship of albumin level with age according to stage. Each point represents age and albumin level of a patient. Linear regression of each stage group shows that mean albumin level at same age decrease as the disease progresses. Dataset from Lee et al. [115].

and cytokine structures [141], the position of cysteine residues [142], and pro-inflammatory or anti-inflammatory parameters [143].

Among these classifications, the functional classifications (Th1/2) and receptor structures is the most relevant grouping method (**Table 4**) [144]. The functional classification is widely used in clinical and experimental practice and categorize the cytokines based on their involvement in cellular immune responses (Th1) and antibody-mediated responses (Th2). The Th1 response is the principal immune mechanism underlying cellular immunity. Cell-mediated immune response includes activation of monocytes and cytotoxic T lymphocytes against virus-infected cells, intracellular parasites, intracellular bacteria, and tumors [145]. The critical cytokines involved in type I response are interferon-gamma (IFN-γ) and IL-12. The mechanism underlying humoral immunity involves type II response. Humoral immune response includes the activation of eosinophils, mast cells, and B lymphocyte proliferation

Table 3. Immune parameters

	Parameter
Immune cells	Peripheral blood
	Lymphocyte counts [22,85]
	Neutrophil counts [3,51,79,116]
	Monocyte counts [103]
	Dendritic cell counts [54,80]
	NK cell counts [117,118]
	T lymphocyte subpopulation counts [42,44,53,81]
	B lymphocyte counts [53,117,118]
	Tissue
	Tumor-infiltrating lymphocyte levels [52,81]
	Tumor-associated macrophage levels [72]
	Mast cell density positive to tryptase [119]
	Other fluid
	Peritoneal fluid: Lymphocyte subsets and HLA-DR expression [120]

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https://doi.org/10.5230/jgc.2019.19.e29

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Table 3. (Continued) Immune parameters

	Parameter
Cytokines	Peripheral blood
	TNF-α levels [22,39,50]
	IFN-γ levels [22,53,54]
	Th1/Th2 ratio [30,31,121,122]
	IL-1 levels [1]
	IL-2 levels [53,123]
	IL-4 levels [1,53,123]
	IL-5 levels [123]
	IL-6 levels [22,34,43,50]
	IL-8 levels [18,116]
	IL-9 levels [124]
	IL-10 levels [29,63]
	IL-12 levels [20,63]
	IL-13 levels [53]
	IL-15 levels [27]
	IL-17 levels [30,54]
	IL-18 levels [13]
	Levels of multiple cytokines [47,124]
	TNF-R levels [25,125]
	TNF-R inhibitor levels [125,126]
	IL-2 receptor levels [42]
	IL-1 receptor antagonist levels [25,60,95]
	IL-6 soluble receptor levels [127]
	Adipocytokine leptin levels [93]
	Immunosuppressive acidic protein levels [127]
	Neopterin levels [39]
	Levels of globulins including IgG, IgA, and IgM [35,44,86]
	Proapoptotic protein-soluble Fas levels [126]
	MCP-1 levels [97]
	Calprotectin levels [90]
	Levels of DAMPs (HSP-S100A-HMGB) [128]
	Neutrophil elastase levels [67,88,116]
	Other fluid
	Alveolar lavage: levels of multiple cytokines [129]
	Peritoneal lavage: levels of multiple cytokines [120]
Gene expression	Peripheral blood
	HLA-DR expression on monocytes [1,25,29,34]
	mRNA expression of TLR2-TLR4 [91]
	Expression of histamine receptors [130]
	Other fluid
	Alveolar lavage: RT-PCR for proinflammatory cytokines [14]
Others	NK activity [13,15,36,43]
	Lymphocyte oxidative activity [131]
	Lymphocyte proliferation [25,43]
	Phagocytic capacity [132]
	Skin-prick tests [130]
	Oxidative stress-antioxidant capacity [87]

NK = natural killer; HLA-DR = human leukocyte antigen-DR isotype; TNF = tumor necrosis factor; INF, interferon; Th = T helper; IL = interleukin; Ig = immunoglobulin; MCP-1 = monocyte chemoattractant protein-1; DAMP = damage-associated molecular patterns; TLR = Toll-like receptors; RT-PCR = real-time polymerase chain reaction.

and differentiation. The key cytokines involved in mediating type II response are IL-4 and IL-10. Type II response is immunosuppressive and is observed after extensive injury in patients with cancer undergoing surgery. IL-4 and IL-10 inhibit type I response, whereas IFN-γ inhibits type II response. As these 2 response mechanisms may inhibit each other, the ratio of the major molecular players involved in type I and type II responses (the ratio of IFN-γ or IL-12/IL-4 or IL-10) can be useful biomarkers [30,31,121,122,143,145].

https://doi.org/10.5230/jgc.2019.19.e29

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Table 4. Representative cytokines of each classification

Representative cytokine	Th1/2	Receptor structure	Example*
IL-2†	Th1	Type 1, common r-chain†	IL-7,9,15,21
IL-6	Th1	Type 1, IL-6 like cytokines	IL-11,30
IL-12	Th1	Type 1, IL-12 subfamilies	IL-23, 27, 35
IL-17	Th1	Type 1, IL-17R	
TNF-α	Th1	Type 1, TNF	TNF-β
IFN-γ	Th1	Type 2, IFN	
IL-8	Th1	Chemokine R	
IL-3	Th1 & Th2	Type 1, common-b-chain	IL-5, GM-CSF
IL-4†	Th2	Type 1, common r-chain†	IL-13
IL-1	Th2	Type 1, IG	IL-18, 33, 36, 37, 38
IL-10	Th2	Type 2, IL-10 subfamily	IL-19, 20, 22, 24, 26
MCP-1	Th2	Chemokine R	
TGF-β	Th2	TGF receptor family	

IL = interleukin; Th = T helper; TNF = tumor necrosis factor-alpha; IFN, interferon; GM-CSF = granulocyte-macrophage colony-stimulating factor; MCP-1 = monocyte chemoattractant protein-1; TGF = transforming growth factor.
*Examples according to receptor structure; may not show the same Th1/2 balance as representative cytokines;
†IL-2 and IL-4 share the same receptor structure but show opposite Th1/2 balance.

Gene expression

Flow cytometry and enzyme-linked immunosorbent assay are used for classical hypothesis-driven studies. These are confirmatory techniques that are specific for the selected parameters (**Fig. 3**) [23,24,33,45-47,86,122,123,125,146-152]. However, measuring only selected immune responses does not provide information on the global changes associated with complex immune response. The inflammatory response status can be evaluated using gene expression. A study on patients with colon cancer undergoing surgery demonstrated that the genes associated with antigen presentation, general T-cell receptor signaling, and granzyme-B encoding for NK and $CD8^+$ T-cells are downregulated [153]. Additionally, the study revealed that the genes encoding cytokines (IL-1B, IL-6, tumor necrosis factor [TNF], and IL-10), CRP, growth factor, and matrix metalloproteinase were upregulated [153]. This indicated downregulation of T-cell receptor signaling, antigen presentation, and NK cell activity and promotion of metastases, growth, and angiogenesis. The strength of this high-throughput study enables us to assess the "genomic storm" of peri-operative changes in gene expression. The gene expression changes indicate not only immune system activation but also the inability to maintain homeostasis. Another study demonstrated the downregulation of differentiation/clonal expansion of T cytotoxic cell and T-cell surface markers and up-regulation of IL-18 and IL-10 signaling pathways [154].

It is intriguing that transcriptomic data from a bulk tumor can be used to predict the status of immune cell infiltration. **Fig. 4** illustrates a heatmap of 22 types of immune cell infiltration inferred from The Cancer Genome Atlas stomach adenocarcinoma gene expression cohort [155]. Cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) is a deconvolution algorithm that uses a set of reference gene expression values to support the vector regression inference immune cell types in data from mixed cell types of bulk tumor samples [156].

Guidelines

Effective data collection is necessary to identify the relevant parameters associated with the inflammatory response. REporting recommendations for tumor MARKer prognostic studies (REMARK) and STAndards for Reporting of Diagnostic accuracy studies (STARD) provide suggested guidelines as checklists to supply relevant information necessary for the design and reporting of prognostic markers and diagnostic accuracy [157,158]. STARD guidelines are

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Intervention	First author	Year	Patient group	Intervention	Cytokines: Th1 response: IFN-γ	Cytokines: Th1 response: IL-2	Cytokines: Th1 response: IL-6	Cytokines: Th1 response: IL-12	Cytokines: IFN-γ/IL-10 (4) ratio	Cytokines: TNF-α	Cytokines: Th2 response: IL-4	Cytokines: Th2 response: IL-5	Cytokines: Th2 response: IL-10	Immune cells: CD3	Immune cells: CD4	Immune cells: CD8	Immune cells: CD4/CD8 ratio	Immune cells: B-cell	Immune cells: NK cell	Immune cells: HLA-DR expression	Conclusion of the study
Minimally invasive surgery	Kvarnström [146]	2013	Rectal cancer	Laparoscopy																	Leads to a lower degree of inflammatory response
	Wu [147]	2003	Colon cancer	Laparoscopy																	No differences in cellular response between groups
	Leung [148]	2000	Rectosigmoid cancer	Laparoscopy																	Less systemic cytokine response after laparoscopy
	Zawadzki [23]	2017	Colorectal cancer	Robotic surgery																	Less inflammatory response and more anti-inflammatory action after robotic surgery
	Pilka [24]	2016	Endometrial cancer	Robotic surgery																	Differential response to surgical trauma in patients with endometrial carcinoma
Perioperative	Ahlers [149]	2008	Major abdominal surgery	Epidural anesthesia																	Reduces stress response
	Sun [150]	2016	Hepatocellular cancer	Epidural anesthesia																	Hastens the recovery of immunologic suppression after surgery
	Martínez [33]	2017	Colorectal cancer	ERAS plus laparoscopy																	Tendency to reduce the alteration in the immune system with laparoscopy
	Chen [86]	2016	Esophageal cancer	Fast track surgery																	Improves postoperative clinical recovery and effectively inhibites release of inflammatory factors
Nutrition	Yeh [151]	2008	Gastrointestinal surgery	Parenteral glutamine																	Attenuates post-operative inflammation and ameliorates postoperative immunodepression
	Spittler [125]	2001	Major abdominal surgery	Glycyl-glutamine																	Induces preservation of HLA-DR
	Chen [152]	2005	Gastric cancer	Enteral immunonutrition																	Restores immunity and modulates inflammatory reaction
	Matsuda [122]	2006	Colorectal cancer	Immune-enhancing nutrition																	Corrects impaired Th1/Th2 balance
Drugs	Pratschke [46]	2014	Major abdominal surgery	Dehydroepiandrosterone																	Controls Th1/Th2 balance
	Li [47]	2009	Lung cancer	DC-activated CIK cell																	Up-regulation of the production of cytokines involved in the anti-tumor effect
	Kirman [123]	2007	Colon cancer	Recombinant human GM-CSF																	Not associated with an immune function benefit
	Schmidt [45]	2007	Liver surgery	Preoperative steroid																	Reduces systemic inflammatory cytokine release

□ No change ■ Increased ■ Decreased

Fig. 3. Associations of interventions with response patterns.
INF = interferon; IL = interleukin; TNF = tumor necrosis factor; NK = natural killer; HLA-DR = human leukocyte antigen-DR isotype; ERAS = enhanced recovery after surgery; Th = T helper; DC = dendritic cell; CIK = cytokine-induced killer; GM-CSF = granulocyte-macrophage colony-stimulating factor.

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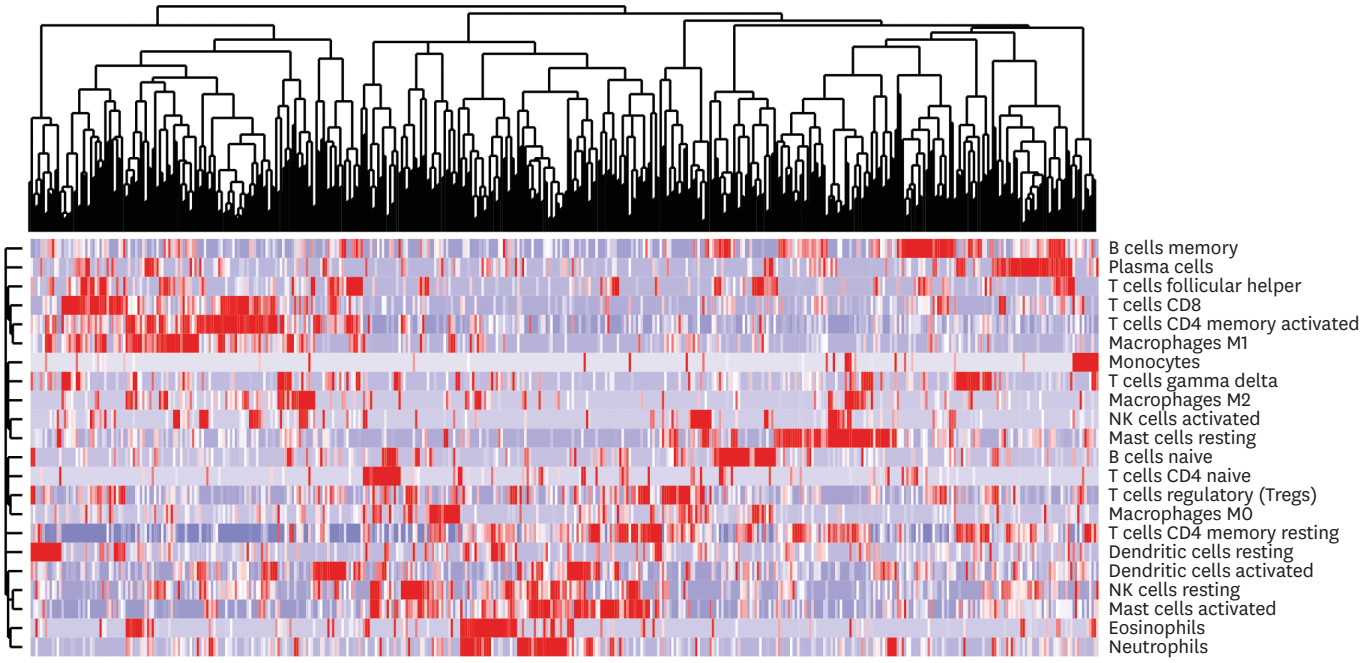

Fig. 4. Unsupervised clustering of inferred immune fraction using leukocyte signature matrix in the cancer genome atlas stomach adenocarcinoma (TCGA-STAD) transcriptomic dataset (n=450). Integrative transcriptomic analysis enables the identification of distinct immune landscapes associated clinical phenotypes using the fraction of infiltrated immune subsets in each sample as well as the evaluation of oncogenic pathway specific to each sample.

focused on the preciseness of a parameter compared to the gold-standard. The prediction of complications based on preoperative or immediate postoperative laboratory values provides a good example of STARD guidelines [108,159]. REMARK guidelines are used to predict the survival of patients undergoing a test or treatment. A preoperative neutrophil-to-lymphocyte ratio predicting long term survival would be an example of application of REMARK guidelines [77]. As REMARK guidelines are related to survival, it is important to assess time-to-event and associated clinical factors such as age, sex, and disease status. These two guidelines share the essential factors of describing a good study and defining other unique requirements. We compared the checklists of STARD and REMARK guidelines to guide good study design and data analysis (**Table 5**).

Interpretation of data

A prerequisite for the identification of a novel biomarker is the valid interpretation of data. We suggest that three issues must be elaborated during the data interpretation. First, inherent characteristics of patients, such as age, sex, and disease status, should be adjusted using a multivariate analysis for assessing the value of inflammatory parameters. This is to prevent the misinterpretation of data. The level of albumin, which is required for calculation of PNI, is highly correlated with age and cancer stage, such that the diagnostic value of PNI decreases after adjustment [3,115]. Second, most of the inflammatory parameters exhibit continuous variation. For any regression analysis, it is always preferable to treat continuous parameters as continuous. However, these parameters are converted to categorical values to enter into regression models in most studies. An arbitrary decision for the cut-off values may result in a misinterpretation of data and hinders their routine use in clinical practice. Third, a value could be interpreted differently in the context of the inflammatory response. Skewing Th1/Th2 immune function, proportion of regulatory T-cells among helper T-cells, and a sequential change of parameters following surgery are good examples.

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Table 5. Guidelines for biomarker studies

Structure	Common guidelines	STARD-specific guidelines	REMARK-specific guidelines
Introduction	Background, objective, and hypothesis		
Methods	· Eligibility criteria · Participants chosen for the study · Detailed protocol sufficient to replicate · Study performer, readers, or assessors blinded to identifying information · Data collection methods (retrospective vs prospective) · Sample size determination · Missing data handling · Rationale for cut-offs	· Participant identification methods · Rationale for reference standard	· Description of biological material used · Clinical endpoints examined · List of all candidate variables initially examined
Results	· Study flow · Characteristics of patients · Relation of index test (marker) and reference standard (prognosis) · Estimation of accuracy and precision (STARD) or confidence intervals (REMARK)	· Time interval between index test and reference standard · Adverse events due to the index test or the reference standard	· Univariable analyses revealing the correlation between the marker and outcome · Confidence intervals from an analysis in which the marker and standard prognostic variables are included · Results of further investigations
Discussion	· Limitations, implications for practice, and future research		· Interpret the results in the context of the pre-specified hypotheses

STARD = STAndards for Reporting of Diagnostic accuracy studies; REMARK = REporting recommendations for tumor MARKer prognostic studies.

INFLAMMATION AND GASTRIC CANCER

Various aspects of the relationship between inflammation and gastric cancer treatment have also been studied. Microenvironment generated by unresolved inflammation is involved in the pathogenesis of non-cardia gastric cancer [160]. The host factors, such as age, obesity, and nutritional status are reported to be associated with the outcome of gastric cancer treatment [161,162]. Minimally invasive surgery has been widely used and several studies, including randomized trials have demonstrated the higher efficacy of laparoscopic and robot-assisted surgeries compared to open surgery [163,164]. Anesthesia techniques and perioperative nutritional support have enhanced postoperative recovery after the guidelines for gastric cancer surgery were published [165,166]. Laboratory and immune parameters are reported to be a predictor of outcomes in several studies, including our earlier studies [3,101,115].

Inflammation is the common condition that was evaluated in all these studies. The purpose of cancer research should not only include killing cancer cells but also patient care. However, there are limited studies that have comprehensively evaluated the correlation between high-quality clinical parameters, immune cells, and cytokines. We believe that sharing insights of inflammation during the disease process and biomedical literacy of clinicians in molecular, genetic, and immune mechanisms will change the way of providing care to patients with gastric cancer in the future [153,155].

CONCLUSIONS

There has been an increased interest in predicting short- and long-term treatment outcomes. To show a significant difference during the hypothesis test, study aim, selection of parameters, and interpretation of results should be carefully performed, as recommended in this review. Although not discussed here, issues associated with the sources of examined material (peripheral blood, tumor lysate, or tumor draining vein) and timing of examination

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(pre- or immediate post-interventional) are also important. Selection of when, how, and what to measure during the intervention may critically affect the decisions and clinical outcomes. Thus, peri-interventional inflammatory responses in patients with cancer require further exploration by a clinical oncologist.

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APPENDIX 1

Parameters with continuous values (Green boxes in Fig. 1)

NRI (nutritional risk index): 15.19 × albumin level (g/dL) + 41.7 × (present weight/usual weight)
CAR (C-reactive protein [CRP]-to-albumin ratio): serum CRP level (mg/dL)/serum albumin level (g/dL)
PNI (prognostic nutritional index): 10 × albumin level (g/dL) + (0.005 × lymphocyte count [number/mm^3])
SII (systemic immune-inflammation index): (platelet count × neutrophil count)/lymphocyte count
NLR (neutrophil-to-lymphocyte ratio): neutrophil count/lymphocyte count
PLR (platelet-to-lymphocyte ratio): platelet count/lymphocyte count
GLR (granulocyte-to-lymphocyte ratio): granulocyte count/lymphocyte count
LMR (lymphocyte-to-monocyte ratio): lymphocyte count/monocyte count
NMLR (neutrophil-monocyte-to-lymphocyte ratio): (neutrophil count × monocyte count)/lymphocyte count
APRI (aspartate aminotransferase-to-platelet count ratio): Aspartate aminotransferase level (units/L)/platelet count

Parameters with categorical values (Orange boxes in Fig. 1)

NRS (nutritional risk screening 2002):
Summation of points for (1) nutritional status (0, weight loss ≤5% in 3 months; 1, >5% in 3 months; 2, >5% in 2 months; 3, >5% in 1 month), (2) severity of disease (0, normal; 1, hip fracture; 2, major abdominal surgery; 3, head injury and APACHE score ≥10), and (3) age (0, <70 years; 1, ≥70 years)
MUST (malnutrition universal screening tool):
Summation of points for (1) body mass index (BMI) score (0, BMI ≥20 kg/m^2; 1, BMI=18.5–20 kg/m^2; 2, BMI ≤18.5 kg/m^2), (2) weight loss in 3 months (0, ≥5%; 1, 5%–10%; 2, ≥10%), and (3) acute disease effect score (0, normal; 2: no nutritional intake >5 days)
COP-NLR (combination of platelet count and neutrophil-to-lymphocyte ratio): Composite score of platelet count and NLR (Score 0/1/2)
COP-NLR 0: normal platelet count (<300 × 10^3/mL) or a normal NLR (<3)
COP-NLR 1: elevated platelet count (>300 × 10^3/mL) or an elevated NLR (>3)
COP-NLR 2: elevated platelet count (>300 × 10^3/mL) and an elevated NLR (>3)
PI (prognostic index): Composite score of serum CRP and white blood cell (WBC) count (Score 0/1/2)
PI 0: normal CRP levels (<1.0 mg/dL) and normal WBC count (<11 × 10^9/L)
PI 1: elevated CRP levels (>1.0 mg/dL) or elevated WBC count (>11 × 10^9/L)
PI 2: elevated CRP levels (>1.0 mg/dL) and elevated WBC count (>11 × 10^9/L)
GPS (Glasgow prognostic score): Composite score of serum CRP and albumin levels (Score 0/1/2)
GPS 0: Normal albumin (>3.5 g/dL) and normal CRP (<1.0 mg/dL) levels
GPS 1: Low albumin (<3.5 g/dL) or elevated CRP (>1.0 mg/dL) levels
GPS 2: Both low albumin (<3.5 g/dL) and elevated CRP (>1.0 mg/dL) levels
mGPS (modified Glasgow prognostic score): Composite score of serum CRP and albumin levels (Score 0/1/2)
mGPS 0: Normal CRP levels (≤1.0 mg/dL) regardless of albumin levels
mGPS 1: Normal albumin (≥3.5 g/dL) and elevated CRP (>1.0 mg/dL) levels
mGPS 2: Low albumin (<3.5 g/dL) and elevated CRP (>1.0 mg/dL) levels
Canton score: Composite score of PNI, NLR, and platelet count (Score 0/1/2/3)
Canton 0: elevated PNI (≥48), low NLR (≤1.83), and normal platelet count (≤300 × 10^3/mL)
Canton 1: presence of one among the predictors of poor outcome: low PNI (<48), elevated NLR (>1.83), and elevated platelet count (>300 × 10^3/mL)
Canton 2: presence of two among the predictors of poor outcome: low PNI (<48), elevated NLR (>1.83), and elevated platelet count (>300 × 10^3/mL)
Canton 3: low PNI (< 48), elevated NLR (> 1.83), and elevated platelet count (> 300 × 10^3/mL)

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Naples prognostic score: Composite score of the serum albumin level, total cholesterol level, NLR, and LMR (Score 0/1/2)

Summation of points for (1) serum albumin level (0, ≥4 g/dL; 1, <4 g/dL), (2) Total cholesterol level (0, >180 mg/dL; 1, ≤180 mg/dL), (3) NLR (0, ≤2.96; 1, >2.9), and (4) LMR (0, >4.44; 1, ≤4.44). The sum of all four points: 0, Naples group 0; 1 or 2, Naples group 1; 3 or 4, Naples group 2

CONUT (controlling nutritional status): Composite score of the serum albumin level, lymphocyte count, and total cholesterol value

Sum of the albumin score (scores 1, 2, 4, and 6 for 3.5–4.5, 3–3.49, 2.5–2.9, and < 2.5 g/dL, respectively), lymphocyte score (scores 0, 1, 2, and 3 for ≥ 1600, 1200–1599, 800–1199, and < 800/mm^3, respectively), and total cholesterol score (scores 0, 1, 2, and 3 for >180, 140–180, 100–139, and < 100 mg/dL, respectively). The summation of all three scores: 0–1, Normal; 2–4, Light; 5–8, Moderate; 9–12, Severe

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