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Dysregulation of systemic immunity and its clinical application in gastric cancer

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Immunotherapy has profoundly changed the treatment of gastric cancer, but only a minority of patients benefit from immunotherapy. Therefore, numerous studies have been devoted to clarifying the mechanisms underlying resistance to immunotherapy or developing biomarkers for patient stratification. However, previous studies have focused mainly on the tumor microenvironment. Systemic immune perturbations have long been observed in patients with gastric cancer, and the involvement of the peripheral immune system in effective anticancer responses has attracted much attention in recent years. Therefore, understanding the distinct types of systemic immune organization in gastric cancer will aid personalized treatment designed to pair with traditional therapies to alleviate their detrimental effects on systemic immunity or to directly activate the anticancer response of systemic immunity. Herein, this review aims to comprehensively summarize systemic immunity in gastric cancer, including perturbations in systemic immunity induced by cancer and traditional therapies, and the potential clinical applications of systemic immunity in the detection, prediction, prognosis and therapy of gastric cancer.

KEYWORDS

gastric cancer, systemic immunity, detection, prognosis, cancer therapy

1 Introduction

Although its incidence has decreased in recent decades, gastric cancer (GC) remains the most common cause of cancer-related death worldwide, especially in regions with high *Helicobacter pylori* infection, such as East Asia, South America and the Middle East (1). In 2022, both the number of new cases of GC worldwide and the number of GC-related deaths ranked fifth, with estimated values of 968350 and 659853, respectively (2). Except in some countries and regions with well-established screening programs, such as Japan, Korea and some areas in China, the majority of GC patients are diagnosed at late stages, leading to dismal long-term survival (3).

Traditionally, the main strategy for curing GC is radical gastrectomy, and in some cases, chemotherapy and/or radiotherapy are needed to reduce recurrence. However, in unresectable advanced patients, systemic chemotherapy combined with targeted therapy is the standard treatment, aiming to prolong survival and improve quality of life (3). The participation of the immune system in tumorigenesis has long been heavily investigated, resulting in the impressive success of immunotherapy in the past decade. Immunotherapy, including immune checkpoint inhibitors (ICIs), cell-based therapy and vaccines, has revolutionized cancer therapy, and several recently published phase 3 clinical trials have proven the encouraging effects of immunotherapy in patients with GC in first- or late-line settings (4–7). Nevertheless, patients who achieve a durable response are limited, while the majority of patients with GC are primarily or secondarily resistant to immunotherapy. Therefore, numerous efforts have been devoted to elucidating the mechanisms underlying the responsiveness of GC to immunotherapy. However, most of these studies are limited to the tumor microenvironment (TME), such as programmed cell death-ligand 1 (PD-L1) expression, the tumor neoantigen load and the profile of infiltrating immune cells (8, 9).

Although perturbations in systemic immunity have long been observed in cancer patients, how they influence the progression of tumors and the effects of cancer therapies, especially immunotherapy, have not received much attention until recently (10). Inspired by these findings, this review aimed to focus on systemic immunity in GC. We first summarize the perturbations of systemic immunity induced by GCs and then outline the effects of traditional therapies, including radical gastrectomy and chemotherapy, on systemic immunity. Finally, we address the potential clinical applications of systemic immunity in the detection, prediction, prognosis and therapy of GC.

2 Perturbations in systemic immunity induced by GC

Through the disruption of hematopoiesis or direct effects on peripheral immune cells, both human cancers and animal tumor models have been shown to induce extensive perturbations in systemic immunity, manifesting as alterations in circulating cytokines, the expansion of immunosuppressive myeloid populations and a decrease in immune cells with antitumor ability (11, 12). Progenitors with myeloid differentiation potential have been found to increase in the bone marrow of mouse models, leading to elevated frequencies of neutrophils and monocytes, along with reductions in dendritic cell (DC) and lymphocyte populations, which can be reversed by resection of cancer or cytokine blockage, suggesting that circulating cytokines secreted by cancer cells drive the remodeling of systemic immunity (12). Currently, no studies have investigated the changes in hematopoiesis in bone marrow induced by GCs; however, numerous studies have reported perturbations in cytokines and major immune lineages in peripheral blood (Figure 1; Supplementary Table S1).

2.1 Circulating cytokines

Cytokines are a collection of molecules that participate in almost every step of tumorigenesis and immunology (13). Numerous studies have investigated the perturbations of circulating cytokines in GC patients (14). In general, the concentrations of cytokines, including interleukin-1β (IL-1β), IL-6, IL-10, IL-17, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), in the peripheral blood of GC patients are commonly

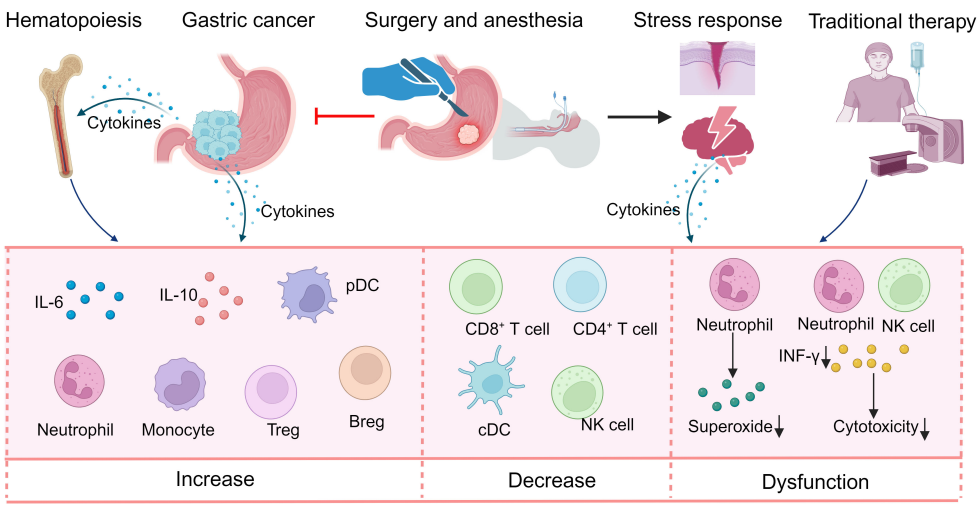

FIGURE 1
Perturbations in systemic immunity in gastric cancer. Gastric cancer itself and traditional therapy can induce reorganization of systemic immunity, manifesting most prominently in alterations in circulating cytokines, expansion of immunosuppressive myeloid populations and a decrease in immune cells with antitumor ability. Breg, regular B cell; cDC, classical dendritic cell; INF, interferon; NK, natural killer; pDC, plasmacytoid dendritic cell; Treg, regular T cell.

greater than those in healthy subjects, whereas the concentration of macrophage chemotactic protein (MCP)-1 has been found to be lower in several studies (15–19). However, cytokines in the circulation can be secreted by nearly all cells, including immune cells and GC cells themselves, and their levels are strongly affected by various factors, such as age, sex, lifestyle and genetic background (20–23). Therefore, inconsistent findings are common across studies, and accurately interpreting the perturbations in circulating cytokines induced by GCs is difficult. For individual cytokines, the peripheral changes in GC patients may be context dependent rather than a regular phenomenon. For example, although IL-6 is one of the most common cytokines whose peripheral levels are increased in GC patients, several studies have not shown significant differences between GC patients and controls (16, 24–26). Furthermore, the serum levels of several cytokines are associated with clinicopathological features. For example, IL-6 levels are elevated only in intestinal GC patients, whereas MCP-1 levels are lower only in diffuse GC patients (16). Nevertheless, a general finding is that the degree of alterations in peripheral cytokines increases with disease progression (21, 27, 28).

2.2 Myeloid lineages

Several cancers have been demonstrated to promote hematopoiesis toward monocytic and granulocytic lineages through cancer-derived factors (10). Although such hematopoietic alterations have not been validated in GC, many studies have reported that both neutrophils and monocytes are extensively perturbed in GC patients. However, these perturbations are commonly represented by ratios between different immune cells, while studies on their functions are limited. In general, patients with GC have a greater percentage of neutrophils in the peripheral blood than healthy donors do, and with increasing tumor burden, the percentage of neutrophils in the periphery significantly increases (29, 30). Although disparities in phenotype and function have been found between neutrophils obtained from cancer tissues and peripheral blood, these differences between neutrophils from GC patients and those from healthy subjects have not been addressed (29). In terms of function, peripheral neutrophils from GC patients exhibit normal phagocytic activity but reduced superoxide generation (31). Furthermore, a subset of myeloid-derived suppressor cells (MDSCs), which highly express neutrophil markers, is dramatically increased in the circulation of GC patients and has the ability to suppress the activity of CD8+ T cells (32). In addition, neutrophil extracellular traps (NETs), one of the main contributors to the cancer-promoting ability of neutrophils, were found to be more abundant in the blood of GC patients, especially those with late-stage disease (33, 34). Another cell type of myeloid origin, monocytes, was also found to be increased in the peripheral blood of GC patients with decreased chemotactic responsiveness and upregulated T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) expression, which may be an important mechanism in GC progression (35, 36). In addition to these findings, few studies have investigated GC-induced dysfunction of neutrophils and monocytes. As both neutrophils and monocytes are composed of heterogeneous cell populations with pro- and anticancer abilities, determining their alterations is important for clinical applications.

Dendritic cells, which participate in antigen presentation and T-cell priming and proliferation, are critical orchestrators of innate and adaptive immunity in cancer (37). Therefore, perturbation of DCs from the peripheral circulation has long been observed in many cancers, including GC (10). Compared with healthy individuals, patients with GC have lower circulating DC counts and percentages, with reduced cytotoxicity and TNF-α, IL-2 and CD40 expression, indicating impaired function and immature status (38, 39). However, similar to other immune cells, DCs are composed of various heterogeneous subsets, including plasmacytoid DCs (pDCs), classical DCs (cDCs) and inflammatory DCs, which play different roles in human diseases (40). Therefore, despite the overall decrease in peripheral DCs, subsets with tumor-promoting effects, such as pDCs and DC-10 cells, were found to be elevated in the periphery of GC patients (41–43). In patients with GC, the frequency and mean fluorescence intensity of DC-10 in the peripheral blood are dramatically increased and strongly associated with tumor grade (41). The levels of other tolerogenic DCs, pDCs, are also significantly increased in the blood of GC patients, and these pDCs are proposed to be recruited to the TME through chemokine receptor 9 (CCR9) and C-C motif chemokine (CCL25) interactions, leading to an immunosuppressive microenvironment in GC (42). Therefore, subsets and functional states should be taken into consideration when peripheral DCs are utilized for clinical application.

2.3 Lymphoid lineage

As the main participants in antitumor immunity, lymphocytes have long been the focus of cancer immunology. In terms of peripheral immune cells in GC, substantially more studies have investigated alterations in lymphocytes. Despite a few inconsistent findings, lymphopenia is common in GC patients (15, 44). However, circulating lymphocytes are composed of complicated subsets with both cancer-promoting and cancer-inhibiting activities. Therefore, in addition to the total lymphocyte population, individual subsets have also been extensively studied. CD8+ T cells are the main effector cells involved in tumor cell killing, and their functions are strongly impaired in the peripheral blood of GC patients (45, 46). Under some conditions, CD8+ T cells can be induced by GCs to express IL-10, PD-1 and TIM-3, which inhibit the effector function of CD8+ T cells (46, 47). In contrast, the levels of suppressive lymphocytes, such as regulatory T (Treg) cells, regulatory B (Breg) cells and IL-17-producing T cells, are typically greater in GC patients than in normal controls (48–52). These cell types synergize with each other to establish an immunosuppressive environment in GC patients. For example, increased Breg cells in the blood of GC patients inhibited the production of T-cell cytokines and converted T cells to Treg cells, leading to immune escape in GC (52).

Natural killer (NK) cells are a type of innate immune cell that differentiates from common lymphoid progenitors and participates

in cancer immunosurveillance through direct cancer cell killing and orchestrates the functions of other players in the immune system (53). The phenotype of circulating NK cells from GC patients differed from that from healthy controls, characterized by a decrease in the number of NK cells expressing activating molecules, including NKp30, NKp46, NKG2D and DNAM-1, and an increase in the number of NK cells expressing the inhibitory molecules KIR3DL1 and TIM-3; these perturbations are significantly associated with cancer progression (54–56). Additionally, the anticancer capacity of these NK cells has been shown to be impaired in GC patients, manifesting as decreased IFN-γ production and cytotoxic function (21, 57, 58).

2.4 Indices derived from multiple immune components

The human immune system is an intricate network with complex synergistic and/or antagonistic interactions among individual immune components. Therefore, various indices derived from multiple immune components have been established to reflect the peripheral immune state more precisely. Owing to their low cost and noninvasive accessibility, numerous studies have investigated alterations in these indices in patients with GC. In general, compared with healthy individuals, patients with cancer present with a greater neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), and lower lymphocyte-to-monocyte ratio (LMR), and the severity of perturbations increases with disease progression (15, 59–61).

Overall, these findings strongly indicate that systemic immunity, which results from the effects of cancer cells and participates in the progression of cancer, is reduced in GC patients. Further efforts are warranted to fully clarify the systemic immune landscape of patients with GC and its associations with disease stage and patient demographics. The mechanisms underlying these perturbations are also largely unknown in GC, and elucidating these mechanisms is critical for therapeutic development.

3 Changes in systemic immunity during traditional therapy for GC

Traditional therapies for GC, including surgery, chemotherapy, and radiotherapy, have long been known to positively or negatively affect systemic immunity, which may determine the efficacy of treatment and oncological outcomes (Supplementary Table S2). In contrast, although targeted therapy has been developed as a standardized treatment for GC in various settings and research on its combination with immunotherapy has been increasing, few studies have been conducted to investigate the effects of targeted therapy on systemic immunity in patients with GC. Elucidating the changes in systemic immunity during traditional GC therapy is critical for optimizing these strategies to strengthen rather than impair anticancer immunity.

3.1 Radical gastrectomy and perioperative events

Radical gastrectomy is the main method for achieving complete disease control and long-term disease-free survival in GC patients. As mentioned above, systemic immune perturbations are induced mainly by various factors derived from the primary tumor; therefore, radical gastrectomy can eliminate these factors and restore normal peripheral immunity, which has been demonstrated in breast and colon cancer (12). However, wound healing and the stress response following gastrectomy also have detrimental effects on systemic immunity.

After radical gastrectomy, wound healing programs remodel systemic immunity, characterized by elevated circulating IL-2, IL-6, IL-10, TNF-α and IFN-γ, ultimately driving peripheral immune cells to immunosuppressive states (62–64). In addition to gastrectomy, perioperative events, including anesthesia, analgesia, postoperative complications, intraoperative blood loss and blood transfusion, all activate or prolong the surgical stress response, leading to the activation of neural signaling and systemic inflammation (65). More extended surgery and an eventful postoperative course are associated with elevated serum catecholamines, which have been shown to suppress anticancer immunity (66). Therefore, the peripheral IL-6 concentration is greater in GC patients who have undergone longer operations (62). In patients who underwent gastrectomy in combination with splenectomy, the T-cell subsets were decreased, and their functions were significantly suppressed (64). The number and cancer cell-killing potential of NK cells are also decreased by abdominal laparotomy, which leads to lung metastasis (67). In addition to the direct suppression of anticancer effector immune cells, surgical stress also increases the levels of immune inhibitory molecules and cells in the periphery. For example, in mouse models, gastrectomy can induce the accumulation of γδT cells in mesenteric lymph nodes, which suppresses the cell-mediated response by transforming growth factor-β (TGF-β) (68). Although some studies have shown that increased proinflammatory cytokines return to normal levels immediately after gastrectomy, long-term functional suppression of immune cells in the blood has been demonstrated in breast cancer models (62, 63, 69). Collectively, these findings suggest that gastrectomy and perioperative events can induce systemic immune perturbations.

3.2 Cytotoxic therapy

The majority of chemotherapeutics and radiation kill cancer cells through direct damage and induction of apoptosis. Although the latter mechanism may cause immunogenic death, which enhances anticancer immunity, acute cancer cell death and the stress response of cells within the TME release various proinflammatory molecules into the circulation to modulate the function of peripheral immune cells (70). Currently, although chemotherapy and radiotherapy are known to cause granulopenia and lymphopenia in clinical practice, studies investigating the effects of cytotoxic therapy on systemic immunity in GC patients

are scarce. Few studies have suggested that following chemotherapy, the levels of immune-enhancing cytokines, including IL-2, IL-4, IL-10, and IFN-γ, decrease in the serum of GC patients (15, 71). Nevertheless, the most commonly used cytotoxic drugs in GC, such as oxaliplatin and 5-fluorouracil (5-FU), were found to reorganize systemic immunity in patients with cancer. For example, oxaliplatin induces the systemic release of ectoenzyme-expressing extracellular vesicles (EVs) from B cells and ATP from cancer cells, leading to the production of adenosine, which contributes to CD8+ T cell dysfunction (72). In addition, in response to 5-FU, circulating proinflammatory factors secreted by myeloid and CD4+ T cells promote tumor progression (73, 74). Whether these impairments also occur in patients with GC needs further clinical study.

4 Potential for clinical application

4.1 Roles of systemic immunity in cancer progression

Multiple decades of research have demonstrated that the immune system has both cancer-promoting and cancer-inhibiting functions, the process of which is referred to as cancer immunoediting and comprises three phases: elimination, equilibrium and escape (75). However, the conceptual development has been based mainly on the TME, whereas the role of systemic immunity has been less considered. For successful cancer cell elimination by natural and therapeutically induced anticancer immunity, intact peripheral immunity is a critical determinant, as the majority of steps of the tumor-immune cycle, including tumor antigen presentation, effector cell priming, proliferation and trafficking, occur outside the TME (76). Therefore, when the progression of effector cells is blocked or cancer drainage lymph nodes are resected, immunotherapeutic efficacy is abrogated (77, 78). On the other hand, through various secreted factors, many cancers can disrupt hematopoiesis extensively and drive circulating immune cells toward accomplices to facilitate tumor progression (10). In addition to preresident cells, the majority of cancer-infiltrated immune components circulate from the periphery and participate in the development of an immunosuppressive TME. For example, a strong association was observed between the levels of peripheral and intratumoral neutrophils, indicating that the expanded immature neutrophils in the peripheral blood of GC patients also infiltrate cancer tissues, resulting from the high expression of molecules involved in neutrophil recruitment and plasticity modulation (79). Furthermore, perturbed systemic immunity is involved in many steps of the cancer invasion-metastasis cascade. For example, cancer-edited immune cells induce the formation of premetastatic niches that are conducive to the survival and proliferation of cancers before their arrival (80). During trafficking in the circulation, cancer cells are protected and supported by many immune components, including neutrophils and platelets (81, 82) (Figure 2).

Because of its critical roles and extensive perturbations that occur during cancer progression, the potential of systemic immunity for GC detection, efficacy prediction, prognosis and therapy has been extensively investigated (Figure 3).

4.2 Detection

As mentioned above, compared with healthy subjects, GC patients exhibit extensive alterations in peripheral immune components. Owing to their low cost and noninvasive

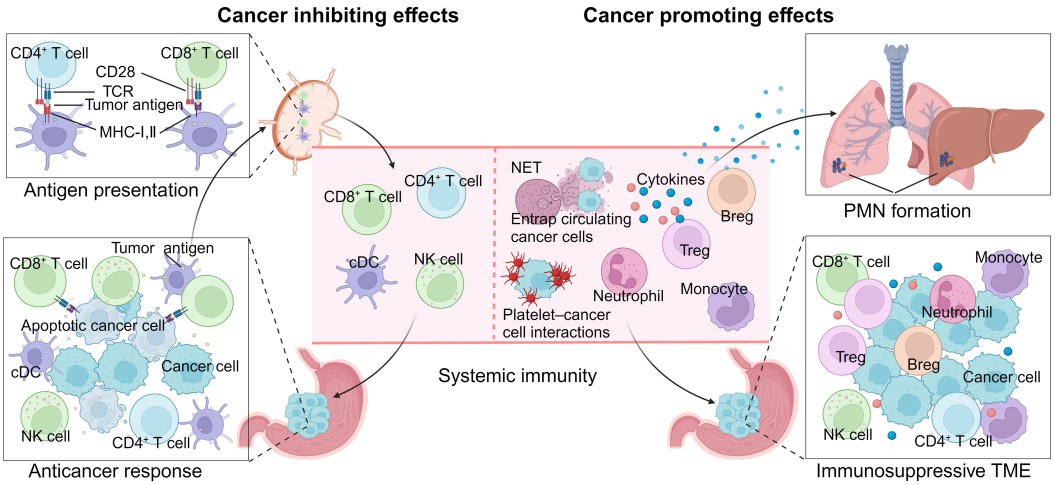

FIGURE 2
Roles of systemic immunity in gastric cancer progression. On the one hand, intact peripheral immunity is essential for the anticancer immune response, as the majority of steps of the tumor-immune cycle occur outside the tumor microenvironment (TME). On the other hand, dysregulated systemic immunity promotes cancer progression through immunosuppressive TME development, premetastatic niche (PMN) formation and circulating tumor cell protection. Breg, regular B cell; cDC, classical dendritic cell; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; NK, natural killer; PMN, premetastatic niche; TME, tumor microenvironment; TCR, T-cell receptor; Treg, regular T cell.

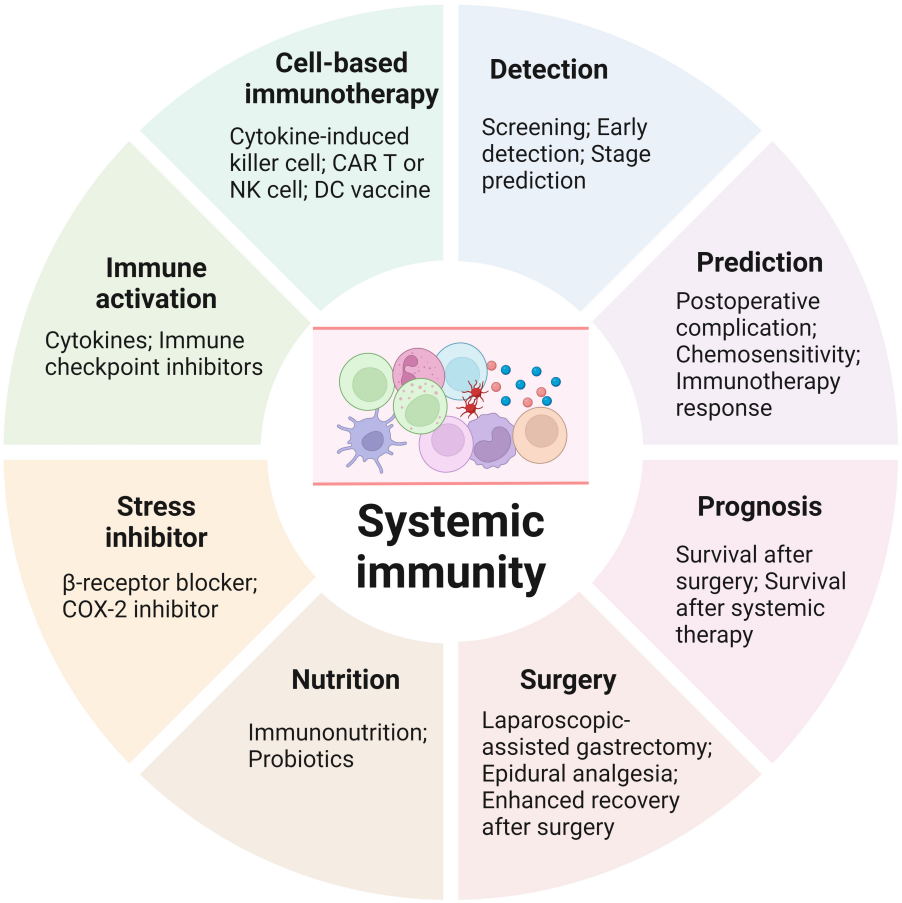

FIGURE 3
Clinical applications of systemic immunity in gastric cancer. Biomarkers based on systemic immunity can be utilized for gastric cancer detection, therapy response prediction and prognosis. Various strategies have been shown to preserve or activate systemic immunity in patients with gastric cancer. Furthermore, cells from systemic immunity are the main sources of cell-based immunotherapies. CAR, chimeric antigen receptor; COX-2, cyclooxygenase; DC, dendritic cell; NK, natural killer.

accessibility, the potential of these alterations as biomarkers for GC detection has been explored. For example, the serum MIC-1 is significantly elevated in early GC, and the performance of early GC detection was 72.9% (83). A diagnostic model including CEA, CA724, IL-6, IL-8, and TNF-α showed the potential to screen for GC, including patients with early-stage disease (84). Peripheral immune cells and indices derived from them also have diagnostic value for GC (41, 59, 85). In addition, the preoperative NLR is significantly correlated with the presence of peritoneal metastasis, especially for type 4 or diffuse type 3 cancers, which may have potential in decision-making regarding staging laparoscopy (86). Despite these promising findings, the application of these biomarkers for the screening and identification of high-risk populations for GC is still lacking. First, all the data were obtained from retrospective cohorts, the majority of which had small sample sizes and were not validated prospectively or externally. Second, the cut-offs used to define high or low levels varied across studies, impeding the development of an optimal method for generalization. Third, peripheral immune components are widely affected by various factors, leading to low specificity for the detection of GC. Therefore, systemic immunity-related biomarkers may be utilized as supplements rather than methods to screen for GC independently.

4.3 Efficacy prediction

Treatment for GC, including surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, puts patients at risk for complications and adverse effects. Therefore, exactly predicting the efficacy and possible adverse effects has long been a goal in the management of GC. Postoperative complications following radical gastrectomy, especially infections, including anastomotic leakage, pneumonia and intraabdominal infections, are significantly associated with oncological outcomes (65, 87). Therefore, various prediction models, including indices based on components of systemic immunity, have been established to assess the risk of postoperative complications. For example, preoperative peripheral T cells, B cells, NK cells, the NLR, the PLR and the LMR are predictive of prolonged hospital stays and infectious complications (88, 89). Furthermore, the postoperative systemic immune state is also a predictor of infectious complications (90). Nevertheless, whether

preoperative strategies based on these prediction models will improve the short-term outcomes of GC patients has not been investigated. In terms of chemotherapy and immunotherapy alone or in combination, which are used to reduce recurrence following radical gastrectomy or to prolong the survival of patients with advanced disease, the predictive value of biomarkers based on peripheral immune components has also been suggested. The PLR obtained prior to chemotherapy might be a useful indicator for predicting chemosensitivity, whereas the baseline IL-6 concentration and progressive decrease in the PLR during treatment can predict the therapeutic benefits of immunochemotherapy (91–94). Furthermore, baseline circulating Treg cell levels can predict the probability of the occurrence of immunotherapy-related adverse events (95). In the future, if these predictive biomarkers can be regularly and dynamically monitored, personalized therapy for GC can optimize therapeutic effects while reducing adverse events.

4.4 Prognosis

A precise prognosis is critical in the management of GC patients, as more intensive therapy may be needed for patients with negative prognostic factors. Therefore, numerous host and cancer features, including biomarkers based on systemic immunity, have been explored as prognostic factors. In general, higher levels of peripheral immune components involved in anticancer responses indicate better survival. For example, IL-2 and INF-γ levels are positively associated with overall survival (OS), whereas IL-6, IL-10 and IL-17A levels are negatively associated with OS (15, 24, 96). C-reactive protein (CRP), an indicator of ongoing proinflammatory response, was negatively associated with OS in a meta-analysis (97). In addition, ICOS+Foxp3+ Treg cells and pDCs in the peripheral blood could predict poor clinical outcomes in GC patients (98). In the literature, the most studied systemic immune biomarkers with prognostic value in GC are indices derived from multiple immune components, such as the NLR, PLR, LMR and prognostic nutritional index (PNI). Table 1 summarizes the results of the meta-analyses on the prognostic value of these indices in patients with GC receiving different treatment strategies. These meta-analyses consistently suggest that higher levels of neutrophils, monocytes and platelets and lower levels of lymphocytes are significantly associated with poor OS (Table 2) (91, 97, 99–122).

Nevertheless, despite tremendous interest in the development of predictive and prognostic biomarkers derived from peripheral immunity, no such biomarkers have shown sufficient ability to guide bedside decision-making. First, because of the wide range of cutoff values used across studies, the optimal values of these indices as prognostic factors are unknown and need to be standardized through multicenter and international studies. Second, systemic immunity is continuously influenced by various factors, including cancer treatment. Although changes in some indices during therapy have shown better prognostic value, studies dedicated to monitoring the dynamics of systemic immune biomarkers in GC are limited (15, 24). Finally, the predictive and prognostic values of systemic immune biomarkers may be context dependent. For example, the prognostic value of circulating cytokines was exclusive to patients receiving immunotherapy in combination with chemotherapy but not to patients receiving chemotherapy alone (15). Therefore, further studies are needed to fully understand why the prognostic value of systemic immune components in GC patients is inconsistent across different contexts.

4.5 Harnessing systemic immunity for GC therapy

Although the exact mechanisms underlying the contribution of systemic immunity to GC progression remain unknown, its distinct perturbations during carcinogenesis and prognostic value suggest that systemic immunity has the potential to be harnessed for GC therapy. As surgery and anesthesia are two of the strongest inducers of the stress response, studies have focused on exploring strategies to alleviate their effects on systemic immune function and inflammation (123). Compared with open gastrectomy, laparoscopic-assisted gastrectomy (LAG) has a weaker inflammatory response and less impact on the immune system. Furthermore, in recent years, the noninferiority of LAG in long-term survival has been strongly established for both early and locally advanced GC patients (124–127). Therefore, LAG is recommended for GC patients without contraindications to reduce the detrimental effects of surgery on systemic immunity. In terms of anesthesia and analgesia, the available evidence supports the combination of epidural analgesia and general anesthesia, which has the potential to improve systemic immunity while inhibiting the inflammatory response. As discussed above, activation of the sympathetic nervous system contributes the most to postoperative immune suppression; therefore, intraoperative administration of esmolol, a β-receptor blocker, decreases the inflammatory response and CRP production in a dose-dependent manner. In addition to these examples, various other perioperative strategies, including analgesics, anesthesia at low depths, goal-directed fluid therapy, enhanced recovery after surgery (ERAS), probiotics and enteral immunonutrition, have also shown beneficial effects on systemic immunity, and their regular administration is worthy of further exploration (Table 2) (128–147).

In addition to these strategies aimed at preserving systemic immunity through a reduction in the stress response and inflammation following radical gastrectomy, another means to harness systemic immunity for GC therapy is to directly enhance the anticancer response. One unsophisticated strategy involves the use of recombinant cytokines, such as IL-2, type I IFNs and granulocyte-macrophage colony-stimulating factor (GM-CSF), which can activate peripheral lymphocytes and improve survival (148–151). However, cytokine therapy has been discontinued in recent years, largely owing to severe systemic adverse events. Cell-based immunotherapies, such as cytokine-induced killer cell (CIK) therapy, dendritic cell-based vaccines, and chimeric antigen receptor (CAR) T or NK cell therapy, mainly involve obtaining therapeutic cells from the periphery and have shown promising results in both preclinical and clinical trials in GC (152–157). Another class of immunotherapy, ICIs, has revolutionized the field of oncology in the past decade. Many clinical trials have demonstrated the efficacy of ICIs in patients with GC (4–7). Although many studies have focused

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TABLE 1 Meta-analyses investigating the prognostic value of systemic immune biomarkers in gastric cancer.

Author	Year	Treatment	Index	Cutoff	OS			Reference
					No. of comparison	HR (95% CI)	I^2	
Szor DJ	2018	Surgery	NLR	1.40-4.02	7	2.89 (2.41-3.47)	85%	(99)
Mellor KL	2018	Surgery	NLR	1.44-5.5	5	2.31 (1.40-3.83)	84%	(100)
Li LL	2023	Immunotherapy	NLR	2.5-5.0	10	2.13 (1.70-2.66)	13%	(101)
Zhang S	2023	Immunotherapy	NLR	2.5-5.0	9	1.98 (1.67-2.35)	19%	(102)
Matsas S	2024	Immunotherapy	NLR	2.5-5.0	10	2.11 (1.70-2.62)	45%	(103)
Du S	2021	Systemic therapy	NLR	2.5-5.0	36	1.78 (1.59-1.99)	80%	(104)
Sun J	2016	Not specific	NLR	1.44-5	19	1.98 (1.75-2.24)	53%	(105)
Kim MR	2020	Not specific	NLR	1.44-5.0	24	1.61 (1.45-1.78)	51%	(91)
Xu Z	2016	Surgery	PLR	126-184	7	0.99 (0.89-1.10)	12%	(106)
Matsas S	2024	Immunotherapy	PLR	139.41-267.00	5	1.77 (1.44-2.17)	25%	(103)
Chen J	2015	Chemotherapy	PLR	2.15-5.0	9	2.16 (1.86-2.51)	65%	(107)
Hu G	2022	Chemotherapy	PLR	107.7-284	11	1.60 (1.41-1.82)	39%	(108)
Peng X	2022	Chemotherapy	PLR	107.7-284	16	1.43 (1.25-1.64)	54%	(97)
Zhang X	2014	Not specific	PLR	NR	10	1.83 (1.62-2.07)	30%	(109)
Zhang X	2020	Not specific	PLR	10.1-350	44	1.37 (1.26-1.49)	80%	(110)
Cao W	2020	Not specific	PLR	108-350	28	1.37 (1.24-1.51)	68%	(111)
Gu X	2016	Not specific	PLR	126-235	14	1.30 (1.10-1.52)	69%	(112)
Ma JY	2018	Surgery	LMR	3.15-5.15	6	0.66 (0.54-0.82	75%	(113)
Mei P	2023	Immunotherapy	LMR	2.8-5.0	7	0.51 (0.33-0.79)	55%	(114)
Yang Y	2016	Surgery	PNI	45-49.7	10	1.89 (1.67-2.13)	7.40%	(115)
Li J	2019	Surgery	PNI	40-52	15	1.81 (1.56-2.09	49%	(116)
Yang X	2024	Not specific	SII	315-1185.2	27	1.53 (1.34-1.75)	72.40%	(117)
Fu S	2021	Not specific	SII	320-802	12	1.53 (1.27-1.83)	77%	(118)
Qiu Y	2021	Not specific	SII	320-802	8	1.40 (1.08-1.81)	88%	(119)
Yin J	2023	Surgery	CONUT	1-5	14	1.75 (1.55-1.96)	12%	(120)
Takagi K	2019	Surgery	CONUT	1-5	4	1.85 (1.38-2.48)	54%	(121)
Pang H	2024	Surgery	ALI	24.81-40.50	4	1.45 (1.02-1.73)	0%	(122)
Kim MR	2020	Not specific	CRP	0.3-13.9	11	1.65 (1.27-2.15)	86%	(91)

ALI, advanced lung cancer inflammation index; CONUT, controlling nutritional status; CRP, C-reactive protein; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

on the TME to investigate the mechanisms underlying the anticancer effects of ICIs, the involvement of systemic immunity has also been noted in recent years. As persistence in the TME rapidly drives dysfunctional differentiation of T cells, effective immunotherapies need continuous new effector T-cell infiltration. Several studies have shown that the *de novo* immune response mainly occurs in the periphery (158–160). In GC patients, ICIs have been shown to increase the levels of circulating IL-2 and IFN-γ and enhance the activation of central/effector memory and effector subsets of CD4+/CD8+ T cells (15, 161). As discussed above, traditional therapies for GC have detrimental effects on systemic immunity; therefore, pairing chemotherapy with ICIs significantly improved the oncological outcomes of GC patients with GC (4–7). In contrast, the application of immunotherapy during the perioperative timeframe has been limited by the established and theoretical risks pertinent around the time of surgery. However, as perioperative immune preservation or stimulation have various advantages, further investigations are needed to develop potential strategies.

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TABLE 2 Randomized controlled studies and meta-analyses investigating strategies to preserve or enhance systemic immunity following radical gastrectomy.

Author	Years	Design	Intervention	Control	Findings	Reference
Ma Z	2016	RCT	LAG, 129	OG, 107	Higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ cell ratios and lower IL-6, TNF and CRP in LAG group	(128)
Aoyama T	2014	RCT	LAG, 13	OG, 13	No significant difference between two groups in WBC count, IL-6 and CRP	(129)
Fujii K	2003	RCT	LAG, 10	OG, 10	Higher TNF-γ production, lower IL-4 production in LAG group	(130)
Shu ZB	2015	Meta-analysis	LAG, 427	OG, 240	LAG is associated with significantly lower serum IL-6 levels	(131)
Lv AQ	2022	RCT	Low anesthetic depth, 40	High anesthetic depth, 40	The perioperative release of inflammatory factors (IL-6, IL-10) is less in patients with low anesthetic depth	(132)
Liu W	2019	RCT	Epidural and general anesthesia, 54	General anesthesia, 53	Lower IL-1, IL-8, hs-CRP and TNF-α, while higher $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ cell ratio in the epidural and general anesthesia group	(133)
Wang L	2019	RCT	Epidural and general anesthesia, 20	General anesthesia, 20	$CD3^+$ T cells decreased less, while IL-4 and IL-6 increased less in the epidural and general anesthesia group	(134)
Kun L	2014	RCT	Epidural and general anesthesia	General anesthesia	Less suppression of NK cell activity, higher IL-2 and IL-10, and lower IL-1β and IL-6 in the epidural and general anesthesia group	(135)
Konstantis G	2023	Meta-analysis	Epidural and general anesthesia, 54	General anesthesia, 53	Higher NK cells and $CD4^+$ T cells in the epidural and general anesthesia group	(136)
Liu R	2019	RCT	Transversus abdominis plane, 30	General anesthesia, 31	IL-6 and IL-10 were significantly lower in the transversus abdominis plane group	(137)
Moon J	2023	RCT	Dexmedetomidine, 42	Control, 42	The IL-6 levels at the end of the surgery was significantly lower in the dexmedetomidine group	(138)
Zhu M	2021	RCT	Quadratus lumborum block, 32	Control, 32	HMGB1, TNF-α, and IL-6 were significantly decreased after surgery in the quadratus lumborum block group	(139)
Lao WL	2021	RCT	Oxycodone, 30	Sufentanil, 30	Lower postoperative IL-6 while higher IL-10 in the oxycodone group	(140)
Kim Y	2015	RCT	Esmolol, 26	Control, 32	Esmolol decreased postoperative IL-6, IL-10, IL-4 and CRP	(141)
Zang YF	2018	RCT	ERAS, 20	Control, 20	Lower WBC, CRP, IL-6 in the ERAS group	(142)
Tang A	2021	RCT	Goal-directed fluid therapy, 37	Conventional fluids, 37	Lower CPR, IL-6 and PCT in the goal-directed fluid therapy group	(143)
Miyachi T	2013	Surgery	Cystine and theanine, 15	Placebo, 18	Significantly lower IL-6, CRP, and neutrophils in the intervention group	(144)
Cao W	2022	RCT	Clostridium butyricum, 47	Placebo, 45	Significantly reduced leucocytes, neutrophils, IL-1β, IL-6, and TNF-α, markedly enhanced immunoglobulin and lymphocytes in the intervention group	(145)
Fu H	2022	Meta-analysis	Enteral immunonutrition, 505	Standard enteral nutrition, 551	Higher proalbumin, IgM, and IgG in the enteral immunonutrition group	(146)
Cheng Y	2018	Meta-analysis	Enteral immunonutrition, 297	Standard enteral nutrition, 286	Higher $CD4^+$, $CD4^+/CD8^+$, IgM, IgG, and lymphocytes in the enteral immunonutrition group	(147)

CRP, C-reactive protein; ERAS, enhanced recovery after surgery; HMGB1, high mobility group box 1 protein; IL, interleukin; LAG, laparoscopic-assisted gastrectomy; NK, natural killer; OG, open gastrectomy; PCT, procalcitonin; RCT, randomized controlled study; TNF, tumor necrosis factor; WBC, white blood cell.

5 Conclusions and future perspectives

With the progression of GC, not only the local but also the systemic immune landscape are strongly perturbed by cancer. In addition, traditional treatments for GC, including radical gastrectomy and chemotherapy, also have detrimental effects on systemic immunity. Although effector immune cells in the TME are the key executors, the localized anticancer immune response cannot persist without continuous communication with the periphery. As systemic immunity closely participates in the progression of GC and is a critical determinant of the efficacy of other therapeutic methods, systemic immunity can be widely applied as a biomarker for GC detection, prediction and prognosis and can be harnessed for GC treatment.

Nevertheless, the majority of currently available data are limited to exploring the perturbations and their associations with therapeutic efficacy and oncological outcomes, and few studies have elucidated the underlying mechanisms involved. Although some critical progress has been made in other cancer types, because systemic immune alterations vary across cancer tissue origins, disease stages and patient characteristics, more studies are needed to clarify the distinct immune states and critical mechanisms involved in directing treatment development to restore an anticancer immune macroenvironment. In recent years, the progress of single-cell technologies has provided many impressive transcriptomic, epigenomic and proteomic data on the immune microenvironment, which can also be applied to assess alterations in systemic immunity. In addition to traditional measurement methods, such as peripheral blood cell counts, circulating molecule detection and flow cytometry, these single-cell technologies can inform the distinct types of systemic immune organization in GC, which will aid personalized treatment designed to pair with traditional therapies to alleviate their detrimental effects on systemic immunity or to directly activate the anticancer response of systemic immunity. Although various strategies have been shown to improve the function of systemic immunity in GC patients during traditional therapy, the translation of these effects into survival benefits is limited, and further studies are needed to determine the underlying mechanisms involved. On the other hand, immunotherapy has achieved impressive success in patients with GC; however, the majority of patients obtained no benefit from this therapeutic strategy. Previous studies on the mechanisms underlying resistance to immunotherapy or biomarkers for patient stratification have focused mainly on the TME. Owing to the close associations with effective anticancer immune responses, strategies harnessing systemic immunity to improve the oncological outcomes of patients with GC warrant further research.

Author contributions

YZ: Data curation, Formal analysis, Writing – original draft. JFL: Writing – original draft. JL: Conceptualization, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing. JW: Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1450128/full#supplementary-material

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