



Immune-Nutritional Biomarkers in Resectable Gastric Cancer: From Host–Tumor Interactions to Prognostic Stratification

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Abstract

Background: Gastric cancer remains a major cause of cancer-related mortality despite improvements in staging, surgery, perioperative chemotherapy, and molecularly directed treatment. In patients with resectable disease, conventional prognostication depends mainly on tumor-related variables such as depth of invasion, nodal involvement, histological subtype, and pathological response. However, patients with apparently comparable tumor characteristics can experience markedly different treatment tolerance, pathological response, recurrence risk, and survival, indicating that host-related determinants are clinically important. Cancer-associated systemic inflammation, malnutrition, anemia, lymphocyte depletion, thrombocytosis, sarcopenia, and altered acute-phase responses interact with tumor biology and influence therapeutic outcomes. Consequently, readily available immune-nutritional biomarkers have emerged as potential tools for refining risk stratification. Among these, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score integrates four biologically relevant parameters into a single index reflecting oxygen-carrying capacity, nutritional and inflammatory status, antitumor immunity, and platelet-associated tumor progression. Retrospective gastric cancer studies and broader meta-analyses have associated low HALP values with adverse clinicopathological characteristics and poorer survival, although considerable heterogeneity exists in cutoff values, study populations, timing of assessment, and treatment strategies. Other indices, including the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein-based scores, and nutritional measures, provide complementary prognostic information. This review examines the biological foundation, available clinical evidence, limitations, and future role of immune-nutritional biomarkers in resectable gastric cancer. Their greatest potential may lie not as isolated prognostic tests but as components of integrated models incorporating tumor stage, pathological response, molecular subtype, and longitudinal host assessment.

Keywords: gastric cancer, HALP score, immune-nutritional biomarkers, prognosis



Introduction

Gastric cancer remains among the most clinically important gastrointestinal malignancies, with a substantial worldwide burden and pronounced geographical variation. Although earlier detection has improved outcomes in screening-intensive countries, many patients outside these settings present with locally advanced disease requiring multimodality therapy. For resectable cT2 or node-positive gastric and gastroesophageal junction adenocarcinoma, perioperative systemic treatment has become fundamental, with the FLOT regimen establishing a major therapeutic benchmark. However, recurrence after apparently curative therapy remains common, demonstrating that anatomic staging alone incompletely captures the biological heterogeneity of the disease. [1, 2]

The FLOT4 trial demonstrated that perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel improved survival compared with epirubicin-based perioperative chemotherapy and increased the probability of achieving favorable pathological outcomes. Yet the benefits of treatment are heterogeneous: some tumors undergo major regression whereas others remain resistant, and some patients are unable to complete postoperative therapy because of postoperative morbidity, nutritional deterioration, toxicity, or declining performance status. Such variation shows that clinical outcome results from an interaction between tumor characteristics, treatment efficacy, surgical quality, and the physiological reserve of the patient. [2]

Traditional prognostication in gastric cancer relies principally on TNM stage, histopathology, resection margins, lymphovascular invasion, and increasingly molecular features. However, patients within the same pathological stage frequently demonstrate substantially different survival. A major research gap is therefore the absence of inexpensive, standardized, clinically applicable methods for quantifying the host component of cancer prognosis before multimodality treatment. The present review aims to critically evaluate immune-inflammatory and nutritional biomarkers, with particular emphasis on HALP, and to define how these variables could complement contemporary clinicopathological and molecular risk assessment.

Review Methods

This narrative review examines the biological rationale and clinical evidence for immune-inflammatory and nutritional biomarkers in resectable gastric cancer, with particular emphasis on HALP. The literature assessment was restricted to publications available through December 2024. Relevant sources were identified through targeted online searches of PubMed-indexed publications and journal websites, supplemented by examination of the reference lists of relevant articles. Search concepts combined gastric or gastroesophageal junction cancer with HALP, hemoglobin, albumin, lymphocytes, platelets, systemic inflammation, nutritional status, sarcopenia, prognosis, and perioperative treatment. Gastric cancer cohorts, systematic reviews, and meta-analyses were prioritized for clinical associations, while mechanistic studies and broader oncology reviews were used to explain host–tumor interactions. Studies were considered according to their population, treatment setting, timing of biomarker measurement, endpoint definition, adjustment for confounding, and validation approach. Bibliographic details and the correspondence between individual citations and the statements they support were checked. The evidence was synthesized qualitatively, distinguishing prognostic associations from evidence of differential treatment benefit. No registered systematic-review protocol, formal pooled reanalysis, or exhaustive study-selection process was undertaken.

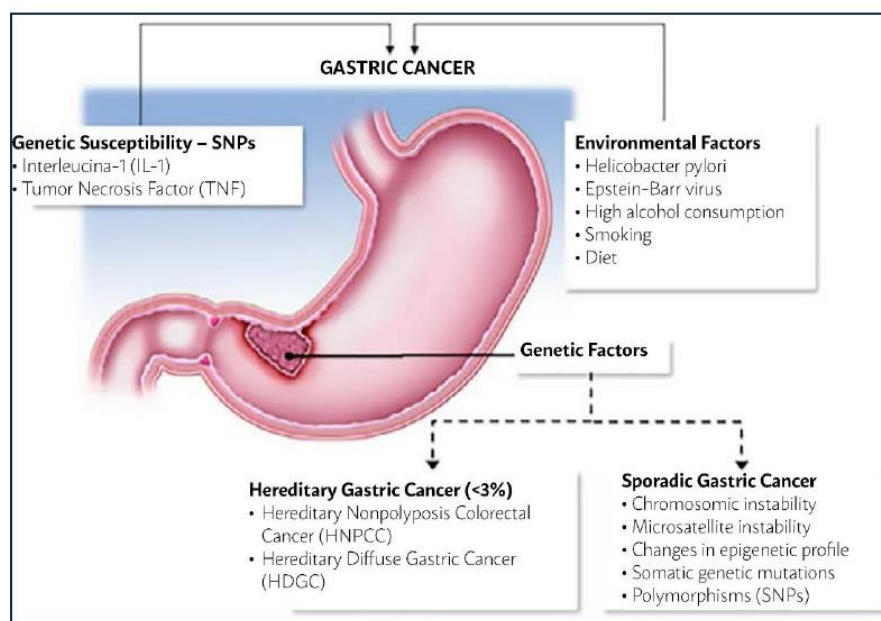


Figure (1): Gastric cancer risk factors (Ramos et al., 2018).

Source for Figure 1: Ramos et al. [3]

The Host-Tumor Interface in Gastric Cancer

Cancer-associated inflammation is not simply a consequence of malignant disease. It participates in tumor initiation, proliferation, angiogenesis, invasion, immune evasion, and metastatic dissemination. Pro-inflammatory cytokines can alter hematopoiesis, hepatic protein synthesis, vascular permeability, energy metabolism, and immune-cell distribution. These systemic effects are particularly relevant in gastric cancer because the primary tumor may simultaneously impair oral intake, cause occult bleeding, generate chronic inflammation, and contribute to progressive nutritional depletion. [4]

The nutritional consequences of gastric cancer are equally complex. Reduced dietary intake, early satiety, gastric outlet symptoms, systemic catabolism, and inflammatory cytokines can lead to weight loss and depletion of skeletal muscle even before definitive therapy. Cytotoxic chemotherapy can subsequently worsen anorexia, mucositis, nausea, diarrhea, or myelosuppression, while gastrectomy alters gastrointestinal anatomy and nutrient absorption. Nutritional status should therefore be conceptualized as a dynamic biological variable rather than a simple measure of body weight. [5]

The interaction between systemic inflammation and nutritional deterioration generates a clinically important feedback loop. Inflammatory signaling promotes protein catabolism and reduces serum albumin, whereas malnutrition impairs tissue repair, immune competence, chemotherapy tolerance, and postoperative recovery. Consequently, host-related laboratory parameters may indirectly capture multiple biological processes that are not represented by conventional anatomical staging. [4, 5]

Biological Components of the HALP Score

The HALP score combines hemoglobin, albumin, lymphocyte count, and platelet count according to the formula:

$$\text{HALP} = \text{hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocyte count (/L)} / \text{platelet count (/L)}.$$

The index was initially investigated in gastric carcinoma because each component has an independently plausible relationship with malignant progression and treatment tolerance. In the original 1,332-patient gastric cancer study, a higher preoperative HALP score was associated with more favorable clinicopathological characteristics and better survival, and a HALP-based prognostic model improved discrimination compared with TNM staging alone. [6]

Hemoglobin and albumin should be expressed in g/L, with lymphocyte and platelet counts reported on the same numerical scale. Unit consistency is essential because alternative conventions change the calculated score and make published cutoffs difficult to compare. [6]



Hemoglobin and Tumor Hypoxia

Anemia in gastric cancer can result from chronic blood loss, inadequate nutritional intake, systemic inflammation, marrow suppression, renal dysfunction, or chemotherapy. Reduction in oxygen-carrying capacity contributes to tissue hypoxia, while intratumoral hypoxia activates molecular programs related to angiogenesis, altered metabolism, survival signaling, invasion, and treatment resistance. Hemoglobin is therefore not only a measure of hematological reserve but potentially an indirect marker of biologically unfavorable conditions within the tumor-host system. [7]

Clinically, anemia may also reduce tolerance of intensive perioperative chemotherapy and major gastric surgery. However, hemoglobin is influenced by numerous non-cancer variables, including iron deficiency, transfusion, hydration, bleeding, chronic kidney disease, and treatment-related marrow suppression. Its prognostic interpretation requires recognition of these potential confounders; the strength of HALP lies partly in combining hemoglobin with markers representing other host domains rather than depending on anemia alone. [7]

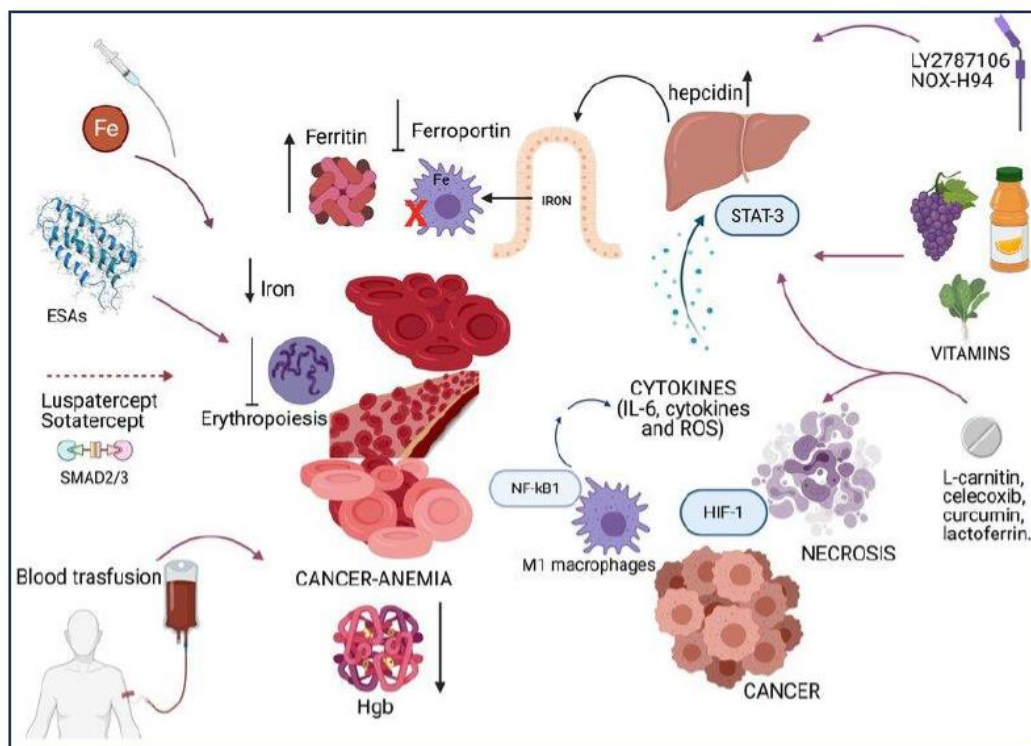


Figure 2. Pathogenetic mechanisms and potential therapeutic targets in cancer-related anemia.

Reproduced from Madeddu et al. [7]

Albumin: Nutrition, Inflammation, and Physiological Reserve

Serum albumin has traditionally been considered a nutritional biomarker, but this interpretation is incomplete. Albumin behaves as a negative acute-phase protein; systemic inflammation alters vascular permeability, distribution, degradation, and hepatic protein metabolism. Consequently, hypoalbuminemia can reflect both nutritional depletion and the intensity of the inflammatory response. Albumin also has antioxidant, transport, and oncotic functions, making low concentrations a broad marker of impaired physiological reserve. [8]

This distinction is clinically important because low albumin should not automatically be interpreted as an isolated protein deficiency that can be corrected simply through albumin administration. Rather, hypoalbuminemia often identifies a patient with systemic inflammation, catabolic stress, comorbidity, or advanced cancer-related nutritional compromise. In gastric oncology, this information is particularly relevant before perioperative chemotherapy and gastrectomy. [8]



Lymphocytes and Antitumor Immunity

Circulating lymphocytes provide a readily measurable, though nonspecific, representation of cellular immune competence. Cytotoxic T lymphocytes and other lymphocyte subsets contribute to immunosurveillance and tumor-cell killing, while persistent lymphopenia may characterize systemic immune dysfunction, severe inflammation, advanced disease, malnutrition, or treatment-induced marrow suppression. A reduced lymphocyte count therefore lowers HALP but increases NLR and PLR when neutrophil and platelet counts remain unchanged. [9]

The biological interpretation must remain cautious because routine complete blood counts do not distinguish functionally different lymphocyte subsets. However, persistent lymphopenia before or during treatment may identify patients with reduced immunological and nutritional reserve. This may become increasingly relevant as immune checkpoint inhibition moves into curative-intent gastric cancer treatment. [9]

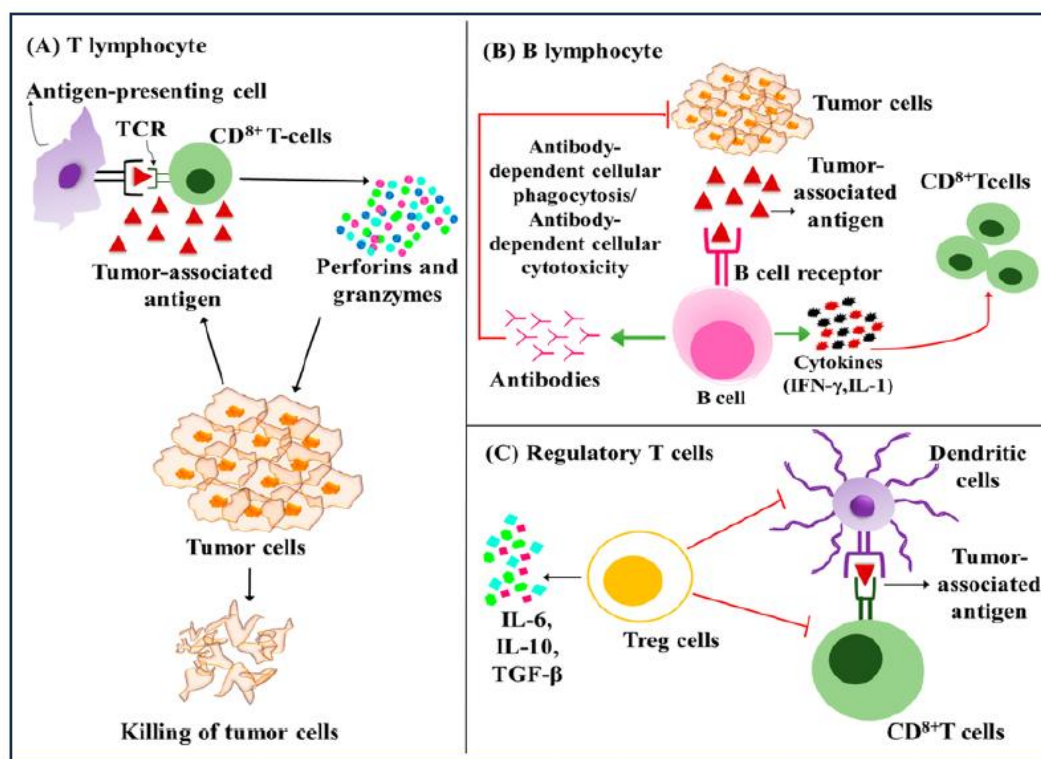


Figure 3. Roles of T lymphocytes, B lymphocytes, and regulatory T cells in cancer. Reproduced from Devan et al. [10]

Platelets and Tumor Progression

Platelets participate actively in malignant progression. Activated platelets can protect circulating tumor cells from immune destruction, facilitate interactions with vascular endothelium, and release mediators that support angiogenesis and metastatic colonization. Platelet count is therefore positioned in the denominator of HALP, so thrombocytosis contributes to a lower—and theoretically less favorable—score. [11]

Beyond circulating counts, platelets contain angiogenic mediators and can influence vascular remodeling within tumors. Their relationship with cancer is bidirectional: tumor-derived inflammatory mediators may stimulate thrombopoiesis, while platelets can subsequently facilitate dissemination. This



biological link provides a rationale for the repeatedly observed association between thrombocytosis or elevated platelet-based inflammatory indices and poor outcomes across malignancies. [12]

Other Systemic Inflammatory and Nutritional Biomarkers

Neutrophil-to-Lymphocyte Ratio

The neutrophil-to-lymphocyte ratio is one of the most extensively studied systemic inflammatory biomarkers in gastric cancer. Elevated NLR represents a combination of neutrophilia—potentially reflecting tumor-promoting inflammation—and relative lymphopenia, representing reduced antitumor immune competence. Meta-analytic evidence has consistently linked elevated NLR with adverse outcomes in gastric cancer, although cutoff values differ substantially among studies. [13]

NLR is attractive because it is inexpensive and universally available, but it is highly sensitive to infection, corticosteroids, smoking, acute physiological stress, and hematological disorders. Its role is consequently prognostic rather than cancer-specific, and single measurements should not be interpreted independently of clinical context. [14]

Platelet-to-Lymphocyte Ratio

PLR similarly combines platelet-mediated tumor biology with lymphocyte-dependent immune status. An updated meta-analysis demonstrated an association between elevated PLR and unfavorable clinicopathological characteristics and survival in gastric cancer. Like NLR, however, PLR suffers from threshold heterogeneity and confounding by inflammatory, hematological, and treatment-related conditions. [15]

The shared dependence of NLR and PLR on lymphocyte count also means these indices are statistically and biologically correlated. Multivariable prognostic models therefore require careful assessment of collinearity before incorporating multiple inflammatory ratios simultaneously. [15]

C-Reactive Protein and Glasgow-Type Scores

C-reactive protein directly reflects hepatic acute-phase activation driven principally by inflammatory cytokines. Composite systems such as the Glasgow Prognostic Score combine CRP with albumin, thereby integrating inflammatory activation and physiological reserve. A meta-analysis involving more than 5,000 gastric cancer patients found that an elevated pretreatment Glasgow Prognostic Score was associated with worse overall and disease-free survival as well as more advanced pathological characteristics. [16]

CRP-based indices have conceptual advantages because they directly incorporate acute-phase activity, but CRP may increase abruptly due to infection, invasive procedures, or other inflammatory disorders. Timing relative to endoscopy, biliary events, acute infection, surgery, and chemotherapy is therefore essential when interpreting values. [16]

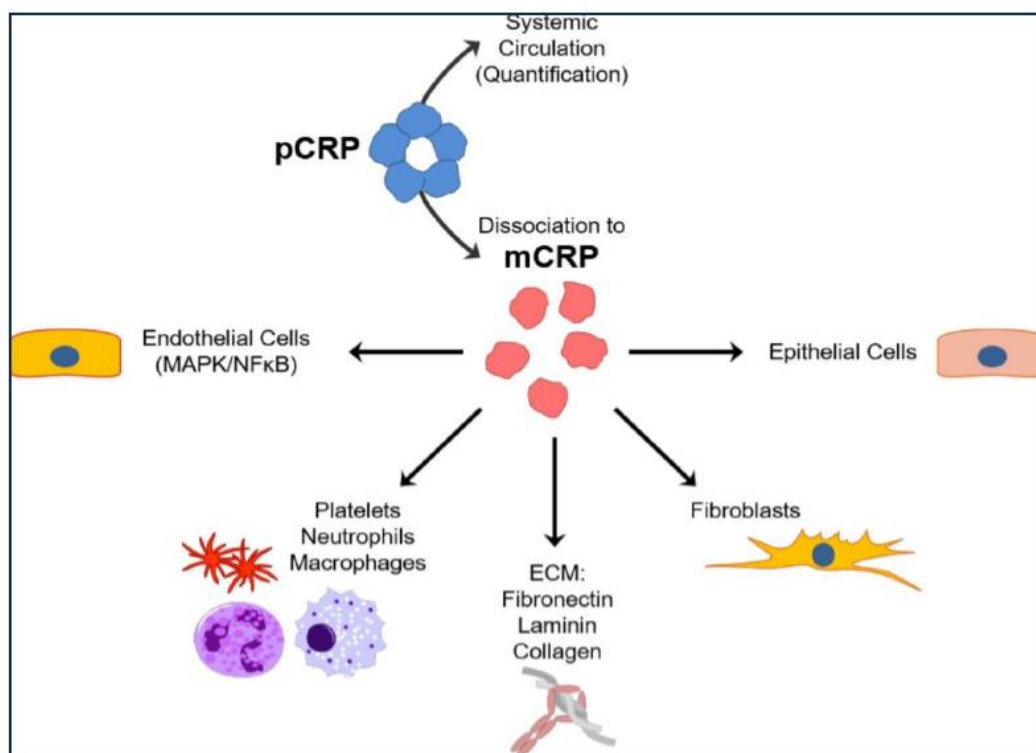


Figure 4. Interactions of pentameric and monomeric C-reactive protein in the inflammatory microenvironment. Reproduced from Hart et al. [17]

HALP as an Integrated Immune-Nutritional Biomarker

The biological appeal of HALP lies in its attempt to summarize several nonredundant dimensions of host status. Hemoglobin represents oxygen-carrying and hematological reserve; albumin integrates inflammation and nutrition; lymphocytes provide a surrogate for immune competence; and platelets reflect inflammation, thrombosis, and tumor-associated angiogenic activity. Because these variables are routinely measured before systemic therapy, HALP requires no specialized molecular assay or additional blood collection. [18]

In the seminal gastric carcinoma cohort, Chen and colleagues analyzed 1,332 patients undergoing gastrectomy. A cutoff of 56.8 was derived, and patients with higher HALP had significantly superior survival in both training and validation populations. HALP remained prognostically relevant after adjustment for established factors, and models incorporating HALP achieved better prognostic discrimination than TNM stage alone. However, this was a retrospective surgical cohort rather than a contemporary perioperative FLOT-treated population. [6]

Wang and colleagues subsequently evaluated HALP in a preoperative nomogram for lymph-node metastasis. Lower HALP values were associated with nodal disease, and combining HALP with clinical and tumor-related parameters produced substantially better discrimination than HALP alone. This finding illustrates an important principle: the most realistic clinical role for HALP is probably integration into multiparametric prediction models rather than use as an isolated binary classifier. [19]

A 2023 systematic review and meta-analysis across solid malignancies reinforced the broader prognostic signal of HALP. Low HALP was associated with poorer overall survival and adverse recurrence-related outcomes across more than 13,000 patients, although heterogeneity was substantial and tumor stage explained part of the variation. These findings support biological plausibility but do not establish treatment-specific predictive utility in gastric cancer. [18]

More recent gastric-specific evidence has continued to demonstrate associations between HALP and outcomes after curative treatment. Aoyama and colleagues reported clinically relevant prognostic associations in patients receiving curative therapy, adding contemporary evidence that the index remains



potentially useful. However, such studies are predominantly retrospective, and their populations, disease stages, cutoff derivation methods, surgical approaches, and systemic therapies differ. [20]

Body Composition and the Limits of BMI

Body mass index is easily obtained and remains part of routine nutritional assessment, but it cannot distinguish skeletal muscle from adipose tissue or identify clinically important sarcopenia. Some gastric cancer cohorts have demonstrated inferior outcomes in patients with low BMI, whereas normal and overweight groups may show comparable survival, contributing to discussion of an “obesity paradox.” Such observations should not be interpreted as evidence that adiposity is protective because BMI is heavily confounded by disease-related weight loss and body composition. [21]

CT-based assessment of skeletal muscle provides a more direct measure of muscle depletion. Sarcopenia is common among patients with gastric cancer and may coexist with normal or elevated BMI. It has been associated with postoperative morbidity, reduced treatment tolerance, and adverse survival in multiple cohorts. Host assessment based solely on serum indices may therefore miss important structural manifestations of cancer-associated catabolism. [22]

Immune-Nutritional Status During Perioperative Chemotherapy

Perioperative therapy creates a particularly compelling setting for host biomarkers. Baseline inflammatory and nutritional status may influence chemotherapy tolerance, dose intensity, the probability of reaching surgery, postoperative recovery, and completion of adjuvant treatment. Conversely, chemotherapy itself changes hemoglobin, lymphocyte count, platelet count, albumin, body weight, and skeletal muscle. A single pretreatment HALP measurement therefore represents only one point in a dynamic biological process. [2, 5]

Longitudinal assessment may ultimately be more informative than a baseline cutoff. For example, persistently low HALP despite treatment could indicate continuing systemic inflammation, inadequate nutritional reserve, occult progression, or treatment toxicity, whereas recovery after tumor reduction might reflect biological response. Such hypotheses require prospective validation because postoperative and chemotherapy-related hematological changes can themselves generate apparent biomarker associations. [20]

Integration With TNM and Molecular Classification

TNM remains the dominant clinicopathological prognostic framework because depth of invasion and nodal burden strongly determine recurrence risk. HALP should therefore complement rather than replace anatomical staging. The most clinically useful models are likely to incorporate cTNM stage, pathological stage, tumor regression, histological subtype, performance status, body composition, and host biomarkers. [23]

Molecular classification further complicates this landscape. The Cancer Genome Atlas divided gastric adenocarcinoma into Epstein-Barr virus-associated, microsatellite unstable, genomically stable, and chromosomal-instability subtypes, each characterized by distinct biological alterations. Molecular features increasingly affect therapeutic decision-making and may also modify the prognostic meaning of systemic inflammatory markers. [24]

MSI-high/dMMR disease is particularly important. Individual-patient meta-analysis suggested that MSI-high resectable gastric cancer has a favorable natural prognosis and may derive less benefit from conventional perioperative/adjuvant cytotoxic chemotherapy than microsatellite-stable disease. Therefore, a patient with favorable molecular biology but an unfavorable immune-nutritional index represents a biologically distinct risk state that cannot be interpreted accurately using either tumor or host factors alone. [25]

This principle is likely to become more important with perioperative immunotherapy. The NEONIPIGA study demonstrated striking pathological complete responses using nivolumab plus ipilimumab in localized MSI-high/dMMR gastric and gastroesophageal junction cancer. As immunotherapy becomes incorporated into curative strategies, the relationship between systemic immune competence, nutritional status, molecular subtype, and therapeutic response warrants prospective investigation. Early MATTERHORN findings also reported a higher pathological complete response rate with durvalumab



plus FLOT than with FLOT alone, supporting investigation of the interaction between host status and perioperative immunotherapy. These pathological findings do not by themselves establish survival benefit or validate HALP as a treatment-selection marker. [26, 27]

Methodological Challenges Preventing Routine HALP Adoption

The major limitation of HALP is not lack of biological rationale but lack of standardization. Published studies have derived markedly different cutoff values, often using receiver-operating-characteristic analysis or data-driven approaches within individual cohorts. A threshold optimized for one population cannot automatically be transported to another population with different ethnicity, disease stage, laboratory reference ranges, treatment strategy, or endpoint. [9]

HALP is also sensitive to common clinical confounders. Gastrointestinal bleeding alters hemoglobin; infection influences lymphocytes and platelets; hydration affects albumin; corticosteroids alter leukocyte distributions; transfusion changes hemoglobin; anticoagulation or inflammatory disorders may accompany thrombocytosis; and chemotherapy modifies all four components. Prospective studies should predefine blood-sampling windows and systematically document such factors. [9]

Another methodological distinction is that prognostic and predictive biomarkers are not interchangeable. A low HALP score may identify patients with poor outcomes regardless of therapy, establishing prognostic value. Demonstrating that HALP predicts differential benefit from FLOT, immunotherapy, or nutritional intervention requires an interaction between biomarker status and treatment effect. Existing evidence is insufficient for this stronger predictive claim. [18]

The next generation of studies should prospectively validate HALP as both a continuous and categorical variable, avoid arbitrary threshold selection, and compare its incremental discrimination against validated baseline models. Multicenter cohorts should include standardized timing before chemotherapy, before surgery, and after surgery to determine whether dynamic HALP trajectories outperform single measurements.

Integrated models should combine HALP with NLR or CRP only when each provides independent information and should incorporate CT-defined skeletal muscle, clinical stage, pathological regression, MSI/MMR, HER2, PD-L1 where relevant, and postoperative molecular residual disease. Such approaches could transform immune-nutritional markers from descriptive variables into components of clinically actionable risk stratification.

Finally, intervention studies are required. If low HALP simply reflects aggressive cancer biology, modifying the score may not improve survival. Conversely, if components of the score identify correctable anemia, malnutrition, inflammatory complications, or inadequate physiological reserve, structured nutritional care, prehabilitation, treatment optimization, and supportive oncology interventions may improve treatment delivery even if they do not directly alter tumor biology.

Limitations

Several limitations should be considered when interpreting this review. The narrative approach permits integration of biological and clinical evidence but remains vulnerable to selective retrieval and interpretation because it did not use an exhaustive search or a prespecified systematic-review protocol. Most gastric cancer studies of HALP are retrospective, and many derive their cutoffs from the same dataset in which prognostic performance is evaluated. Differences in laboratory units, sampling times, disease stages, treatment regimens, and outcome definitions limit direct comparison and the transferability of proposed thresholds. Residual confounding by bleeding, infection, comorbidity, corticosteroid exposure, transfusion, and treatment-related hematological changes may partly explain reported associations. Broader meta-analyses across malignancies support the general prognostic signal but cannot establish gastric cancer-specific predictive utility. Evidence from surgical cohorts also does not necessarily apply to patients receiving contemporary perioperative therapy. Finally, an association between low HALP and poor outcome does not demonstrate that correcting the score, or changing anticancer treatment according to it, improves survival. These limitations support standardized prospective validation, external assessment of integrated models, and intervention studies before routine treatment-selection use.



Conclusion

Immune-nutritional biomarkers provide an important host-centered dimension of prognostication in resectable gastric cancer. HALP is particularly attractive because it combines four inexpensive and routinely available parameters reflecting hematological reserve, nutrition, inflammation, immunity, and platelet-associated tumor biology. Existing evidence generally links low HALP with adverse outcomes, but heterogeneity in thresholds, populations, timing, and treatments currently prevents its use as an independent treatment-selection biomarker. Its most promising future role is within prospectively validated, longitudinal models that integrate host status with TNM stage, pathological response, body composition, and molecular tumor biology.

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