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Review Article

Advanced Lung Cancer Inflammation Index: A Novel Comprehensive Biomarker of Host Status for Patients with Metastatic Colorectal Cancer

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Abstract

Numerous biomarkers that reflect host status have been identified for patients with metastatic colorectal cancer (mCRC). However, there has been a paucity of biomarker studies that comprehensively indicate body composition, nutritional assessment, and systemic inflammation status. The advanced lung cancer inflammation index (ALI), initially introduced as a screening tool for patients with non-small-cell lung cancer in 2013, emerges as a holistic marker encompassing all body composition, nutritional status, and systemic inflammation status. The index is calculated by the simple formula: body mass index × albumin value / neutrophil-to-lymphocyte ratio. Given its accessibility in routine clinical practice, the ALI has exhibited promising clinical utility in prognosticating outcomes for patients with multiple types of cancer. In this review, we focus on the significance of host status and the clinical applicability of the ALI in the treatment and management of patients with malignancies, including mCRC. We also suggest its potential in guiding the formulation of treatment strategies against mCRC and outline future perspectives.

Keywords

advanced lung cancer inflammation index, metastatic colorectal cancer, host factor, body composition, nutrition, systemic inflammation

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Introduction

Host factors, such as weight loss, malnutrition, and systemic inflammation, are strongly associated with cancer progression and patient outcomes[1,2]. In colorectal cancer (CRC), indicators such as low body mass index (BMI), hypoalbuminemia, and high inflammation have emerged as predictive markers for postoperative complications, recurrence, and a poor prognosis[3,4]. Given their impact on tumor progression and treatment resistance through various mechanisms, it becomes imperative to develop appropriate tailored cancer treatment strategies by effectively focusing on pre-treatment host conditions. However, there have been few reports on predictive indices that comprehensively encompass body composition, nutritional status, and systemic inflammation status in cancer patients. There exists a need for a comprehensive marker, that simply reflects host status.

The advanced lung cancer inflammation index (ALI) initially introduced by Jafari et al. in 2013, originated as a screening tool to clarify the degree of systemic inflammation during the diagnosis of non-small-cell lung cancer (NSCLC)[5]. This index is formulated based on the patient's BMI, serum albumin level, and neutrophil-to-lymphocyte ratio (NLR), calculated as the ALI = BMI × albumin value / NLR[5].

The BMI, which concept was first reported in the 19th century[6], is a conveniently available tool to estimate body composition based only on physical measures: height and weight. Although the BMI has some limitations including less correlation with body fat or not showing the distribution

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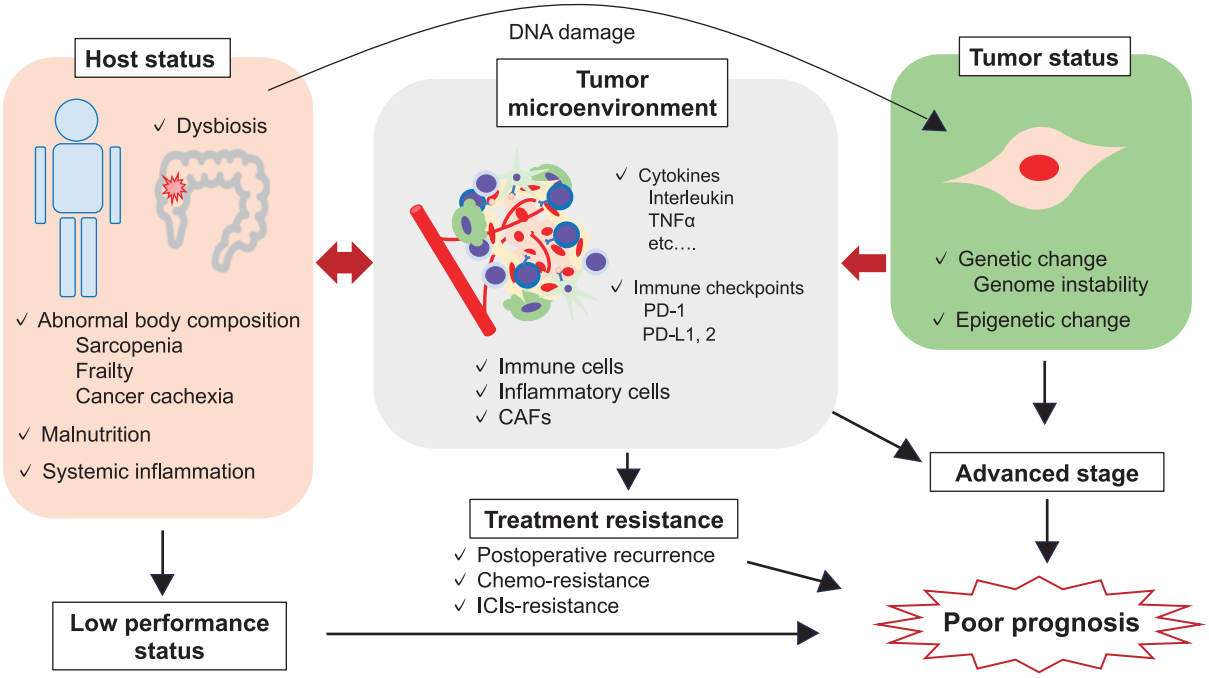

Figure 1. The relationship between host status and cancer progression. Systemic inflammation, abnormal body composition, and malnutrition are all closely and complexly associated with tumor microenvironment. Both host factors and tumor status affect tumor microenvironment in complicated manner, which result in cancer progression and poor prognosis. CAF, cancer associated fibroblasts; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L, programmed death-ligand; TNF α; tumor necrosis factor α

of body fat[6], it is widely recognized as a useful marker of body composition. It reflects the status of cancer cachexia, and low BMI (< 18 kg/m^2) correlating with shorter survival in cancer patients[7].

Albumin is a circulating protein which is the most abundant in human plasma, and is easily measurable by laboratory testing[8]. Only a little albumin can be stored in the liver. Albumin is a significant modulator of plasma oncotic pressure, thus hypoalbuminemia reflects malnutrition or increased capillary permeability suggesting systemic inflammation[8,9]. An independent association of hypoalbuminemia with poor overall survival (OS) and cancer-specific survival (CSS) in patients with cancer has been already known[10].

In systemic inflammation, the individual component of white cell counts has prognostic utility in patients with cancers[11]. Especially, the combination of neutrophil and lymphocyte: NLR, is reported to be an indicator of systemic inflammation and decreased immune status[11]. The NLR, which is calculated by the neutrophil count/ the lymphocyte counts of a full blood count, also functions as a prognostic biomarker for patients with cancer[12].

The ALI is used as a comprehensive assessment of these useful markers. Recently, the ALI has been widely reported as a prognostic marker across diverse cancer types and even non-malignant diseases. We also previously reported that a low pre-treatment ALI status is an independent predictor of poor survival in patients with CRC who have undergone curative resection and received first-line chemotherapy[13,14].

Herein, we review and discuss the clinical significance of host factors and the usefulness of the ALI for the management and treatment of patients with malignancies, especially metastatic CRC (mCRC).

Host Factors Strongly Associated with Cancer Progression

Host factors exert a notable influence on tumor progression and resistance to cancer treatment through various mechanisms, such as metabolism, systemic inflammation, immune system, and microbiota interactions. The reported relationship between host status and cancer progression is depicted in Figure 1.

Abnormal body composition in conditions such as sarcopenia, frailty, and cancer cachexia, is closely linked to prognostic severity because it generally activates the host metabolism and induces malnutrition, inflammation, and fluid retention issues including ascites, pleural effusion, and peripheral edema[15]. Sarcopenia denotes the progressive and generalised loss of skeletal muscle mass and strength, leading to lower performance status that contributes to more

postoperative complications and poor overall survival[16]. Frailty, characterised by a decline in physiological function due to age-related disability, is associated with poor treatment tolerance and unfavorable prognosis in patients with cancer[17]. Moreover, cancer cachexia, a more severe condition than sarcopenia, involves weight loss via skeletal muscle and adipose tissue atrophy, catabolic activity, and systemic inflammation. Cancer cachexia is reported to be associated with tumor microenvironment (TME) cells, including macrophages, neutrophils, T cells, B cells, and fibroblasts[18]. Pro-inflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1, IL-6, and IL-8 play pivotal roles in mediating this interaction[18]. In addition, treatment type also influences the risk of nutritional issues. For instance, postoperative malnutrition after gastrointestinal surgery can diminish the feasibility of systemic treatments such as chemotherapy[19]. Therefore, evaluating pre-treatment nutritional status through easy-to-use markers is important for comprehensively developing treatment strategies.

Systemic inflammation exerts a significant influence impact on TME. Persistent exposure of TME cells, such as cancer-associated fibroblasts and tumor-associated macrophages, to pro-inflammatory cytokines, such as IL-1, IL-6, and IL17, leads to tumor growth through sustained activation of pro-inflammatory signalling pathways[20]. Furthermore, immune cells such as T cells, B cells, and tumor-associated macrophages also have signalling interactions during cancer progression and are important components of TME through systemic inflammation[21]. Conversely, a highly inflammatory state can lead the tumor towards acquiring a more malignant phenotype, which induces metastasis[22]. Based on such mechanisms, systemic inflammation is a critical indicator of tumor progression, with numerous studies underscoring its association with increased postoperative complications and a more unfavorable prognosis[4,23,24]. Moreover, postoperative complications can cause a severe inflammatory response, which results in immune suppression and activation of invasion capacities of cancer cells. Relationships between postoperative complications and higher recurrence or poor survival have been reported in patients with gastrointestinal cancer after surgical resection[25].

The host's immune status assumes importance in the era of immunotherapy. Tumors evolve several mechanisms to suppress anti-tumor immune responses. At first, tumor antigen presentation to T cells occurs by antigen-presenting cells or tumor cells, followed by T cell activation against tumor cells. In the TME, tumors employ checkpoint pathways, including the programmed cell death protein 1 (PD-1) along with its ligands, programmed death-ligand 1 (PD-L1), and PD-L2, to establish resistance against this immune response. The interaction between tumor PD-L1 and PD-L2 and the PD-1 has been recognized as a major mechanism of tumor immune evasion, rendering this interaction the main target for immunotherapy[26,27]. Although immunotherapy presents a promising therapeutic strategy against cancer, its efficacy is limited to certain patients, while a substantial portion of patients demonstrate an initial lack of response to treatment[28]. The clinical efficacy of immunotherapy is also shown in the patients with CRC. The utility of immune checkpoint inhibitors in microsatellite instability-high (MSI-H) patients has been clarified in the clinical trials, thus the guideline recommends a PD-1 inhibitor: pembrolizumab, as first-line therapy for those patients[29-31]. Similarly, nivolumab, another PD-1 inhibitor, is regarded as the second-line treatment of patients with MSI-H CRC[32]. Moreover, some preclinical data suggest the clinical efficacy of other immunotherapeutic approaches against solid tumors including a combination of mitogen-activated protein kinase inhibitor with the PD-L1 inhibitor[33], bispecific antibody therapy, or a combination with antiangiogenic therapy[34].

Furthermore, the emergence of acquired resistance can complicate the treatment of patients with a positive initial response. Acquired resistance can be attributed to multidimensional interactions between the tumor itself, host immune system, and other systemic host-related factors. For example, robust systemic immune responses are reported as an essential factor of cancer immunotherapies[27,35]. The secretion of inflammatory cytokines, including IL-1α or IL-12, and anti-cancer T-cell responses via antigen presentation and upregulation of activation markers play essential roles in shaping treatment responses[35]. Besides, intrinsic host factors such as Human Leukocyte Antigen (HLA) heterozygosity, obesity, gut microbiota, and endocrine status have all been implicated in immunotherapy response[27]. Extrinsic factors such as chronic stress or drug use, can lead to immunosuppression, thereby impairing the anti-tumor immune response[36,37]. In line with this evidence, the role of host factors gains prominence in shaping effective treatment strategies.

Microbiota is also closely linked to host status. Host factors, including diet, exercise, smoking, and antibiotics, significantly impact gut microbial composition. Conditions such as obesity, diabetes, and malignancies can cause dysbiosis[38,39]. Dysbiosis in turn exerts a direct influence on TME. Some bacterial species can directly trigger proliferative signals and modulate the growth-inhibitory mechanisms of tumors[40]. For example, genotoxic *pks*$^{+}$ *Escherichia coli* induces mutagenesis in colonic epithelial cells, consequently producing bacterial toxins and other molecules that directly damage DNA, thus disrupting genomic integrity[41]. Moreover, certain butyrate-producing bacterial strains promote innate immune inflammation[42]. Although host-microbiota interactions has the potential to instigate and influence cancer development, there remains a need for further understanding of host-microbiota interactions and their effect on

TME[43].

As host factors influence tumor progression and treatment resistance through various mechanisms, the development of appropriate cancer treatment strategies by focusing on properly pre-treatment host status is important.

Biomarkers Reflecting Body Composition, Nutrition, Inflammation, and Survival Outcomes in Patients with CRC

Multiple prognostic biomarkers associated with host status, such as body composition, nutritional state, and inflammation, have been identified for the evaluation of the pre-treatment status of patients with CRC. Table 1 summarises such prognostic factors.

Regarding body composition, low BMI is well known as a poor prognostic factor for patients with CRC[3,7,44]. In a clinical trial involving 25,291 patients with stage II-III CRC, Sinicrope et al. demonstrated that low BMI independently correlated with poor OS (hazard ratio [HR] = 1.21, 95% confidence interval [CI] = 1.11-1.32, $p < 0.001$)[44]. Moreover, skeletal muscle index, derived from the volume of the psoas major muscle in the L3 level CT scanning, is a prognostic factor of cancer patients. In a meta-analysis of 2,377 patients with all-stage rectal cancer, Zhu et al. revealed that low skeletal muscle mass index was independently associated with poor OS (HR = 2.37, 95% CI = 1.13-4.98, $p = 0.02$)[45]. Furthermore, a decrease in skeletal muscle mass (SMM) by >5% after chemotherapy has also been linked to poorer outcomes[46,47]. However, conflicting reports exist; some studies have found no association between changes in SMM and survival in patients with mCRC[48], despite SMM itself being an independent prognostic indicator[49]. The distribution of visceral and subcutaneous fat also affects host status. Visceral fat contributes to the production of pro-inflammatory cytokines, thereby influencing cancer progression[50], while subcutaneous fat is linked to a more favorable metabolic status[51]. Fleming et al. reported that a high visceral-to-total fat ratio was associated with increased 5-year disease-free survival (DFS) mortality (HR = 5.92, 95% CI = 4.04-8.00, $p = 0.02$), while Kim et al. reported that high subcutaneous fat area independently predicted longer DFS (HR = 0.505, 95% CI = 0.266-0.957, $p = 0.036$)[52,53]. Moreover, cancer often leads to conditions involving fluid retention, including ascites, pleural effusion, and peripheral edema, closely linking cancer and extracellular water levels[15]. Recent research has demonstrated that a higher preoperative extracellular water-to-total body water ratio, measured via multifrequency bioelectrical impedance analysis, significantly correlates with poor relapse-free survival (RFS) and OS mortality in patients with CRC who have undergone curative resection[54]. However, despite the wealth of literature on the prognostic efficacy of body composition markers, a lack of methodological consistency in measuring body composition among patients with CRC exists. Various methodologies, including CT-based calculations, multifrequency bioelectrical impedance, and dual-energy X-ray absorptiometry, are widely used. Standardised protocols and definitions for measuring body composition are required[55].

Nutritional status plays a pivotal role in reflecting the host's overall condition. Hypoalbuminemia, indicative of the pre-cachexia/cachexia status, is related to cancer progression and metastasis[10]. The Glasgow prognostic score (GPS) includes serum C-reactive protein (CRP) levels and albumin levels, and high GPS reflects both systemic inflammation and low nutritional status. In a meta-analysis involving 5,421 patients with all-stage CRC, Lu et al. found that a high GPS was independently associated with poor OS (HR = 2.23, 95% CI = 1.79-2.78, $p < 0.00001$)[56]. The prognostic nutritional index (PNI), calculated as 'Albumin value + 0.005 × lymphocyte count', provides insights into nutritional status, with decreased PNI correlating with poor nutritional status. Yang et al. performed meta-analysis on survival outcomes of 3,788 patients with CRC who underwent surgery and found that PNI < 45 was associated with poor OS (HR = 1.972, 95% CI = 1.536-2.532, $p < 0.001$)[57]. The Controlling Nutritional Status (CONUT), calculated from serum albumin value, total cholesterol levels, and total lymphocyte count, offers a scoring system to assess nutritional status. Takagi et al. performed a meta-analysis of survival data of 2,601 patients with CRC who underwent surgery and found that high CONUT score was associated with poor OS (HR = 1.97, 95% CI = 1.40-2.77, $p < 0.001$)[58].

Systemic inflammation is also important for regulating tumor angiogenesis and metastasis[21,59]. It often correlates with an increase in circulating neutrophil counts. In CRC patients, reduced circulating lymphocyte counts negatively impacted prognosis[4,12]. Therefore, the NLR, an integral constituent of the ALI, is a robust biomarker for patients with various types of cancer[4]. In a large-scale meta-analysis involving 32,788 patients with all-stage CRC, Nasazi et al. found that high NLR was independently associated with poor OS (HR = 1.57, 95% CI = 1.39-1.78, $p < 0.0001$)[23]. Moreover, monocytes, which differentiate into tumor-associated macrophages and contribute to tumor progression and metastasis, augment the activation of TME[4]. In a meta-analysis of 14,205 patients with all-stage rectal cancer who underwent surgery, Portale et al. revealed that low lymphocyte-to-monocyte ratio (LMR) was independently associated with improved OS (HR = 0.67, 95% CI = 0.49-0.91, $p = 0.01$)[24].

As mentioned above, numerous markers are suggested to reflect host status and can evaluate nutritional and inflammation status. Although previous reports show the clinical utility of these biomarkers, there remains a scarcity of re-

Table 1. Biomarkers Reflecting Body Composition, Nutrition, and Systemic Inflammation and Survival Outcomes in Patients with Colorectal Cancer.

Markers	Type of CRC	Study	Region	Design	Sample size	Male/Female	Treatment	Cut-off	Endpoint	OS results*	Ref.
Body composition											
BMI	mCRC	Renfro et al. 2016	US	R	21149	13061/8088	1st line chemotherapy	BMI < 18.5	OS PFS	$P < 0.001$	[3]
BMI	Stage II-III CRC	Sinicrope et al. 2014	US	R	25291	-	Adjuvant chemotherapy	BMI < 20	OS DFS	$P < 0.001$ HR 1.21	[44]
SMI	All stage rectal cancer	Zhu et al. 2022	China	M	2377	-	Varied	Low SMI Varied cut-off	OS	$P = 0.02$ HR 2.37	[45]
ΔSMI	mCRC	Miyamoto et al. 2015	Japan	R	182	112/70	1st line chemotherapy	> 5% skeletal muscle loss	OS PFS	$P = 0.01$ HR 2.08	[47]
SFA	Stage I-III CRC	Kim et al. 2021	South Korea	R	987	583/404	Surgery	Male: > 142 Female: > 169	DFS	$P = 0.036$ HR 0.51	[53]
ECW/TBW	Stage I-III CRC	Horino et al. 2023	Japan	R	320	198/122	Surgery	> 0.389	OS RFS	$P = 0.016$ HR 3.23	[54]
Nutrition											
GPS	All stage CRC	Lu et al. 2019	China	M	2293	-	Surgery Chemotherapy	GPS > 0	OS CSS	$P < 0.001$ HR 2.08	[56]
mGPS	All stage CRC	Lu et al. 2019	China	M	5421	-	Surgery Chemotherapy	mGPS > 0	OS CSS	$P < 0.001$ HR 2.23	[56]
PNI	All Stage CRC	Yang et al. 2016	China	M	3788	-	Surgery	PNI < 45	OS CSS	$P < 0.001$ HR 1.97	[57]
CONUT	All stage CRC	Takagi et al. 2020	Japan	M	2601	-	Surgery	CONUT High	OS	$P < 0.001$ HR 1.97	[58]
Systemic inflammation											
NLR	All Stage CRC	Naszai et al. 2021	UK	M	32788	15244/11333	Varied	High NLR Varied Cut-off	OS	$P < 0.001$ HR 1.57	[23]
LMR	All stage rectal cancer	Portale et al. 2023	Italy	M	14205	-	Surgery Chemotherapy	Low LMR Varied Cut-off	OS DFS	$P = 0.01$ HR 0.67	[24]

*Using multivariate analysis.

BMI, body mass index; CI, confidence interval; CONUT, Controlling Nutritional Status; CRC, colorectal cancer; CSS, cancer-specific survival; CT, computed tomography; DFS; disease-free survival; DLT, dose-limiting toxicities; ECW/TBW, extracellular water to total body water ratio; GPS, Glasgow-prognostic scale; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; mCRC, metastatic colorectal cancer; mGPS, modified Glasgow-prognostic scale; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression free survival; PNI, prognostic nutritional index; RFS, relapse-free survival; SFA, subcutaneous fat area; SMI, skeletal muscle index; SMM, skeletal muscle mass.

M, meta-analysis; P, prospective study; R, retrospective study

ports comprehensively encapsulating body composition, nutritional status, and systemic inflammation status.

Previous Reports of the ALI as a Useful Prognostic or Predictive Tool for Patients with Cancer or Non-cancerous Diseases

Jafari et al. aimed to elucidate whether the extent of systemic inflammation at the time of diagnosis in patients with advanced NSCLC could serve as a prognostic indicator for survival outcomes. In 2013, they introduced a simple marker, the ALI, calculated using the patient's BMI, serum albumin level, and NLR (ALI = BMI × albumin value / NLR)[5]. The ALI stands as an inclusive marker that encapsulates body composition, nutritional status, and inflammation. Over the course of a decade, various studies have been conducted to assess its clinical significance as a prognostic indicator, spanning from benign cardiovascular conditions to cancer.

Table 2 provides an overview of previous reports of the ALI as a prognostic marker. The efficacy of the ALI has been reported in patients with lung cancer, including both small cell lung cancer (SCLC) and NSCLC[5,60-66].

Additionally, Andersen et al. revealed that the depressive symptom score was significantly associated with low ALI in patients with depression and NSCLC[67]. Mountzios et al. reported that high ALI values were significantly associated with more prolonged OS for patients with advanced NSCLC receiving immunotherapy[62].

Furthermore, there are numerous reports of prognostic significance in patients with gastrointestinal cancer, hepato-pancreato-biliary cancer, hematologic malignancies, head and neck squamous cell carcinoma, neuroblastoma, melanoma, oral cavity squamous cell carcinoma, and nasopharyngeal carcinoma[68-80]. Li et al. reported pre-treatment ALI as an independent prognostic factor of OS in patients with advanced hepatocellular carcinoma treated with immunotherapy[73]. In a meta-analysis, Hua et al. reported that low ALI was associated with poor OS (HR = 1.70, 95% CI = 1.41-1.99, $p < 0.001$) in various cancer types, including lung cancer, CRC, lymphoma, and head and neck squamous cell carcinoma[81]. Zhang et al. showed that low ALI before treatments indicates poor prognosis (HR = 1.64, 95% CI = 1.34-1.93, $p < 0.001$) in lung cancer patients[82]. Recently, two meta-analysis showed the prognostic significance of the ALI in patients with gastrointestinal cancer[83,84], with both demonstrating the correlation of low ALI with poor OS (HR = 2.09, 95% CI = 1.53-2.85, $p < 0.01$ and HR = 1.914, 95% CI = 1.514-2.419, $p < 0.001$, respectively.).

Due to its capacity to reflect host status comprehensively, the ALI has demonstrated its utility in managing certain benign conditions as well. In this regard, Inoue et al. elucidated that the pre-treatment ALI correlated with the clinical severity of coronavirus disease 2019[85]. Zhang et al. explored the correlation between the ALI and long-term mortality among patients with hypertension[86]. Clinical efficacy of the ALI to develop treatment strategies for patients with coronary arterial disease or heart failure is also known[87]. Moreover, Kusunoki et al. evaluated the predictive value of the ALI for postoperative surgical relapse in patients with Crohn's disease[88].

On the other hand, there are some negative reports regarding the prognostic efficacy of the ALI. Chantharakhit et al. reported that low ALI referred to a non-significant prognostic factor in their multivariate analysis[89]. Similarly, Barth et al. showed that the ALI failed to independently predict CSS in multivariate models among patients with histologically confirmed pancreatic cancer[90]. Moreover, Cheng et al. reported that while the ALI is an independent predictive factor for evaluating the efficiency of induction chemotherapy against multiple myeloma, it did not exhibit the same independent predictive value in terms of patient survival[91].

Furthermore, determining the certain cut-off value of the ALI is equivocal. In the first report by Jafri et al., the optimal cut-off point for the ALI was identified as 18.4, yielding a sensitivity of 77.3% and specificity of 63.9%. This selection was based on the minimum distance approach, which identifies the point on the receiver operating characteristic (ROC) curve[5]. Similarly, in most studies, the cut-off value of the ALI was determined by ROC curves, which ranged from 18 to 30, as shown in Table 2.

Nevertheless, more evidence shown above suggests the solid prognostic value of the ALI in patients with various malignancies and benign diseases.

Additionally, other novel biomarkers combined with the ALI have been reported. Tomita et al. reported the utility of the ALI_CRP score, a combination of the ALI and serum CRP[92]. Kim et al. introduced the modified ALI (mALI), calculated from L3 skeletal muscle index × ALB/NLR. This was based on the idea that skeletal muscle mass offers a more accurate representation of body composition than BMI. However, their study did not reveal the additional prognostic value beyond the original ALI in patients with SCLC[93]. Interestingly, the modified ALI emerged as an independent risk factor for OS in patients with renal cell carcinoma undergoing nephrectomy, unlike the original ALI, which was not significantly associated[94]. Xie et al. reported that mALI served an independent prognostic factor of OS (HR = 0.531, 95% CI = 0.402-0.700, $p < 0.001$) in overweight or obese patients with lung cancer[95].

Previous Reports of the ALI in Patients with CRC

Six previous reports demonstrate the prognostic efficacy of the ALI in patients with CRC (Table 3). Four studies

Table 2. Previous Reports of the ALI as a Useful Prognostic Tool for Patients with Cancer.

Type of cancer	Study	Region	Design	Sample size	Male/Female	Treatment	Cut-off (method)	End-point	OS results*	Ref.
Lung cancer										
Stage IV NSCLC	Jafri et al. 2013	US	R	173	116/57	Chemotherapy BSC	<18 (ROC)	OS PFS	$P = 0.047$ HR 1.42	[5]
SCLC	He et al. 2015	China	R	365	310/55	Chemotherapy Radiotherapy	<19.5 (ROC)	OS	$P = 0.005$ HR 1.62	[60]
Stage I-III NSCLC	Tomita et al. 2018	Japan	R	343	175/168	Surgery	>37.66 (Cut-off finder)	OS	$P < 0.001$ HR 0.44	[61]
Stage IV NSCLC	Mountzious et al. 2021	Greece	R	460	324/116	PD-L1 inhibitor	>18	OS	$P < 0.001$ HR 0.40	[62]
Stage I-IV lung cancer	Song et al. 2022	China	P	1772	1132/638	Surgery Chemotherapy Radiotherapy	<34.19 (ROC)	OS	$P < 0.001$ HR 1.30	[63]
Upper gastrointestinal cancer										
Esophageal SCC	Feng et al. 2014	China	R	293	259/34	Surgery	>18	CSS	(CSS) $P = 0.024$ HR 1.43	[68]
Stage I-IV gastric cancer	Yin et al. 2021	Japan	R	620	424/196	Surgery	<30 (ROC)	OS DFS	$P = 0.006$ HR 1.59	[69]
Stage I-III gastric cancer	Chen et al.2023	China	R	949	615/334	Surgery	<24.81 (X-tile)	OS CSS	$P = 0.010$ HR 1.55	[70]
Hepato-pancreato-biliary cancer										
LAPC	Topkan et al. 2019	Turkey	R	141	111/30	Chemotherapy+ Radiotherapy	<25.3 (ROC)	OS PFS	$P < 0.001$ HR 2.65	[71]
Cholangiocarcinoma	Wu et al. 2022	China	R	97	58/39	Surgery	>31.8 (ROC)	OS DFS	$P = 0.037$ HR 0.97	[72]
Advanced HCC	Li et al. 2023	China	R	98	66/32	PD-1 inhibitors	>36.5 (ROC)	OS	$P < 0.001$ HR 0.41	[73]
Hematologic malignancies										
DLBCL	Liu et al. 2021	China	R	117	62/55	Chemotherapy	>31.26 (ROC)	OS	$P = 0.038$ HR 0.45	[74]
Other malignancies										
HNSCC	Jank et al. 2019	Austria	R	93	72/21	Surger + Radiotherapy	>37.6 (median)	OS DFS	$P = 0.022$ HR 0.45	[75]
HPV-negative HNSCC	Gaudioso et al. 2020	Italy	R	223	151/72	Surgery± Radiotherapy	<20.4 (Harell's C-index)	OS	HR 3.41	[76]
LA-NPC	Topkan et al. 2020	Turkey	R	164	129/35	Chemotherapy Radiotherapy	<24.2 (ROC)	OS PFS	$P < 0.001$ HR 2.32	[77]
Melanoma	Cheng et al. 2021	China	R	43	19/24	Second-line immunotherapy	>50.98 (ROC)	OS PFS	$P = 0.033$ HR 0.41	[78]
Oral cavity SCC	Tsai et al. 2021	Taiwan	R	372	336/36	Surgery	<33.6 (ROC)	OS DFS	$P < 0.001$ HR 2.52	[79]
Neuroblastoma	Qi et al. 2022	China	R	72	33/39	Surgery Chemotherapy	>49.17 (ROC)	OS	$P = 0.015$ HR 0.44	[80]

*Using multivariate analysis.

BSC; best supportive care, CI; confidence interval, CSS; cancer-specific survival, DFS; disease-free survival, DLBCL, diffuse large B cell lymphoma, ESCC; esophageal squamous cell carcinoma, HCC; hepatocellular carcinoma, HNSCC; head and neck squamous cell carcinoma, HPV; human papillomavirus, HR; hazard ratio, LA-NPC; locally advanced nasopharyngeal carcinoma, LAPC; locally advanced pancreatic cancer, NSCLC; non-small cell lung cancer, OS; overall survival, PD-L1; programmed cell death protein 1, PFS; progression free survival, ROC; receiver operating characteristic, SCC; squamous cell carcinoma, SCLC; small cell lung cancer, VATS; video-assisted thoracoscopic surgery

R; retrospective study

Table 3. Previous Reports of the ALI in Patients with Colorectal Cancer.

Type of CRC	Study	Region	Design	Sample size	Male/ Female	Treatment	Cut-off (method)	Endpoint	OS results*	Ref.
Surgical resection of the primary tumor										
Stage I-IV CRC	Kusunoki et al. 2020	Japan	R	298	171/127	Surgery	The lowest quartile	OS DFS	$P < 0.001$ HR 3.21	[96]
Stage I-IV CRC	Xie et al. 2020	China	R	662	408/254	Surgery	M <31.6 F <24.4 (X-tile)	OS PFS	$P = 0.006$ HR 1.45	[97]
Stage I-III CRC	Horino et al. 2022	Japan	R	813	464/349	Surgery	M <43.1 F <13.2 (CART analysis)	OS RFS	$P < 0.001$ HR 2.30	[13]
Stage I-III right-sided CRC	Deng et al. 2022	China	R	441	234/207	Surgery	<36.3 (X-tile)	OS DFS	$P < 0.001$ HR 3.31	[98]
Systemic chemotherapy										
Unresectable mCRC	Shibutani et al. 2019	Japan	R	159	87/72	Chemo-therapy	<28.9 (ROC)	OS	$P < 0.001$ HR 2.77	[99]
Unresectable mCRC	Horino et al. 2023	Japan	R	356	196/160	Chemo-therapy	M <17.0 F <23.3 (CART analysis)	OS	$P = 0.001$ HR 1.78	[14]
Surgical resection of liver metastasis										
mCRC (Liver)	Pian et al. 2022	South Korea	R	132	88/44	Surgery (Hepatec-tomy)	<70.40 (X-tile)	OS DFS	$P = 0.009$ HR 0.34	[100]

CART; classification and regression tree, CI; confidence interval, CME; complete mesocolic excision, CRC; colorectal cancer, DFS; disease-free survival, HR; hazard ratio, OS; overall survival, PFS; progression-free survival, ROC; receiver operating characteristic
R; retrospective study

evaluated patients who underwent resection of the primary tumor. Kusunoki et al. and Xie et al. evaluated patients with all-stage CRC following surgical resection of the primary tumor and concluded that low ALI is an independent prognostic factor for survival[96,97]. In addition, we demonstrated that both postoperative complications and severe complications occurred more frequently in the ALI-low group than in the ALI-high group ($p < 0.001$ and $p < 0.001$, respectively), especially postoperative complications in stage III CRC patients ($p < 0.001$) and severe complications in stages II and III CRC patients ($p = 0.024$ and $p = 0.004$, respectively)[13]. Deng et al. focused on patients with right-sided tumors who underwent complete mesocolic resection and showed that ALI was independently correlated with OS[98].

The initial exploration into the clinical utility of the ALI in patients with metastatic colorectal cancer (mCRC) was undertaken by Shibutani et al. in 2019[99]. Their retrospective analysis encompassed 159 patients with unresectable mCRC who underwent combination chemotherapy within a single centre. Within this cohort, the group with a low ALI exhibited a significantly worse OS rate ($p < 0.0001$). Remarkably, the pre-treatment ALI emerged as an independent prognostic factor for OS (HR = 2.773, 95% CI: 1.773-4.335, $p < 0.001$). We also showed the pre-treatment ALI as a robust independent prognostic indicator for survival in mCRC patients. Additionally, the ALI-low status was notably associated with a higher incidence of synchronous metastases and multiple metastatic sites ($p < 0.001$ and $p = 0.016$, respectively). Remarkably, the type of first-line chemotherapy did not substantially impact the association between prognosis and the ALI status[14].

Pian et al. contributed further evidence regarding the prognostic importance of the preoperative ALI in individuals with colorectal cancer liver metastasis (CRLM)[100]. Their investigation encompassed a cohort of 132 patients afflicted with CRLM, specifically excluding cases with extrahepatic metastasis. Within this cohort, patients characterised by a low preoperative ALI exhibited significantly poorer OS outcomes ($p = 0.010$). Intriguingly, through multivariate analysis, it was unveiled that a high ALI was independently associated with superior OS (HR = 0.336, 95% CI: 0.149-0.760, $p = 0.009$).

Future Perspective of the ALI as a Predictive Biomarker of Patients with mCRC

According to the latest guidelines, unresectable mCRC should be initially treated by a doublet or triplet backbone

systemic chemotherapy with molecularly targeted drugs, which should be based on tumor *RAS* and *BRAF* status. Resection should be considered if both primary tumor and liver metastases are resectable, alongside perioperative chemotherapy[31,101,102].

Based on previous studies, the ALI may be a beneficial prognostic factor for patients with mCRC undergoing both systemic chemotherapy and resection of metastatic sites. In cases of resectable mCRC following chemotherapy, where patients exhibit compromised host status, the choice between continuing systemic chemotherapy and proceeding with hepatectomy becomes a nuanced consideration. The latter option poses the potential for physical and immune function deterioration, thereby heightening the risk of recurrence. We have suggested keeping chemotherapy with consideration of the ALI status in cases with poor host status rather than performing hepatectomy[14]. The ALI could make it possible to formulate a treatment plan that comprehensively takes host status into account and allow us to provide 'tailored' treatment for patients with mCRC.

Recently, immunotherapy, including immune checkpoint inhibitors, has become widely recognized as a new standard treatment for multiple types of cancer[103]. In terms of mCRC, some clinical trials have evaluated the efficacy of immune checkpoint inhibitors in microsatellite MSI-H CRC[29,30,32]. According to the latest guideline, pembrolizumab should be offered as first-line therapy to patients with MSI-H or deficient mismatch repair mCRC[31]. Moreover, nivolumab, another PD-1 inhibitor, is recommended for the second-line treatment of patients with MSI-H status[32]. Although several studies showed the prognostic value of the ALI for patients with lung cancer, hepatocellular carcinoma, and melanoma who were treated by immunotherapy, the clinical efficacy of the ALI for patients with mCRC who underwent immunotherapy remains unclear[62,65,73,78]. Because the ALI is simple and readily available for evaluating pre-treatment host status, further investigation is required to evaluate its efficacy for patients with mCRC who underwent immunotherapy.

There are still some remaining issues as for the ALI which should be further elucidated in the future. First, the optimal cut-off value of the ALI remains controversial. Those in previous reports varied depending on cancer type, tumor stage, and sex. Also, as shown in Table 2, 3, various calculation methods were applied, including separate calculations for male and female patients and those calculated by the ROC curve or X-tile program. Naturally, cut-off values differ depending on the type and clinical stage of cancer because of differing host status. However, even if limited to studies for mCRC, the cut-off value varied[14,99,100]. Further large-scale validation studies in clinical settings are essential to evaluate the optimal cut-off value of the ALI for mCRC patients.

Second, no studies have evaluated pre-treatment interventions targeting the ALI. Several pieces of evidence showed the clinical efficacy of pre-treatment interventions such as prehabilitation or preoperative nutritional guidance to ameliorate intrinsic host status. Multimodal prehabilitation is known to enhance functional capacity and reduce postoperative complications, and similarly, nutritional prehabilitation is known to decrease the length of hospital stay significantly, both for patients with CRC who underwent resection[104-106]. Moreover, there is a study of an intervention targeted LMR before the initiation of chemotherapy against mCRC. It showed that normalisation of LMR before treatment exhibited a better OS[107]. According to these studies, pre-treatment intervention may improve prognosis for patients with mCRC. Because the ALI can reflect host status comprehensively, it may be an appropriate pre-treatment intervention target for improving prognosis.

Third, no association between the ALI and microbiota or TME that affects the prognosis of cancer patients has been reported. Microbiota is closely linked to host factors, and dysbiosis could occur under malignancies[26,27]. Hence, an association between the ALI and bacterial composition may exist, which also could become the target of pre-treatment interventions. Similarly, we should consider the status of immune cells in TME and tumor factors when we attempt to understand detailed host circumstances.

Further evaluation might clarify the answers to those questions, and clinicians could draw on the prognostic efficacy of the ALI when we develop treatment strategies for patients with mCRC.

Conclusions

The ALI can comprehensively evaluate host status so that it might serve as a reliable prognostic biomarker for patients with cancer, including mCRC. Calculating the pre-treatment ALI could be a simple and robust tool for constructing treatment strategies for patients with mCRC.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

T.H. described and designed the article. R.T. edited the article. Y.M. and H.B. supervised the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

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