A propensity-matched analysis of the prognostic value of advanced lung cancer inflammation index in patients with gastric cancer after curative resection

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Abstract. The prognostic significance of inflammation, immune response and nutritional status in patients with cancer is well-documented. The advanced lung cancer inflammation index (ALI) has emerged as a novel prognostic indicator, reflecting both inflammation and nutritional status. This study aimed to assess the prognostic relevance of preoperative ALI in patients with gastric cancer (GC). Data of 459 patients who underwent curative gastrectomy for GC between December 2013 and November 2017 at the Kanagawa Cancer Center (Yokohama, Japan) were retrospectively analyzed. Preoperative ALI was calculated from blood tests. Patients were divided into the high- and low-ALI groups. This study investigated the association between preoperative ALI, clinicopathological features, overall survival (OS) and relapse-free survival (RFS) after propensity-matched analysis. Comparative analysis revealed that patients in the low-ALI group tended to be older, were predominantly female, had lower body mass index and had a higher incidence of lymphatic invasion compared with those in the high-ALI group before propensity-matched analysis. Notably, the low-ALI group exhibited significantly reduced OS and RFS post-gastrectomy (85.5% vs. 93.8%, P=0.01; and 82.1% vs. 91.8%, P=0.02, respectively). Multivariate analysis identified low ALI as an independent prognostic factor for both OS and RFS. In conclusion, preoperative ALI could provide a valuable prognostic tool for patients with GC undergoing curative resection, offering insights into patient survival outcomes based on their inflammatory and nutritional status.

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Abbreviations: ALI, advanced lung cancer inflammation index; BMI, body mass index; CI, confidence interval; HR, hazard ratio; pStage, pathological stage; TG, total gastrectomy; OS, overall survival; RFS, relapse-free survival; GC, gastric cancer; NLR/Alb, neutrophil-to-lymphocyte ratio/albumin; CSS, cancer-specific survival

Key words: gastric cancer, advanced lung cancer inflammation index, prognostic tool, overall survival, relapse-free survival

Introduction

Gastric cancer (GC) is the third leading cause of cancer-related mortality globally and is identified as the fifth most prevalent malignancy in the world (1). Despite significant advancements in GC management encompassing endoscopy, surgical interventions, and chemotherapy, treatment outcomes remain to be significantly improved (2). In recent years, the perioperative inflammatory and nutritional status of patients has garnered increased attention for its potential impact on the treatment outcomes and overall prognosis of cancer (3-9). Several methodologies have been developed for the assessment of inflammation and nutritional status in patients with GC (10-12). Nonetheless, further research to refine and develop more effective indices for the assessment of patients with GC is warranted.

The Advanced Lung Cancer Inflammation Index (ALI), conceptualized by Jafri *et al*, is a novel prognostic predictor for patients with metastatic non-small cell lung cancer (13). ALI combines the Neutrophil-to-Lymphocyte Ratio/Albumin (NLR/Alb) ratio (14), which reflects inflammation, nutritional, and immune status, with the body mass index (BMI) (15), a straightforward metric of obesity. The prognostic value of ALI has been documented across various cancer types (16-18). However, the applicability of ALI as a prognostic tool specifically for patients with GC has been sporadically reported (19-23) and remains insufficiently explored. Consequently, in this study, we aimed to evaluate the clinical significance of preoperative ALI measurement in patients with GC undergoing curative resection.

Materials and methods

Patients. A total of 459 patients with GC were enrolled in this study at the Kanagawa Cancer Center between December 2013

and November 2017. The inclusion criteria were as follows: i) GC confirmed by pathological diagnosis; ii) gastrectomy achieving R0 resection with radical lymph node resection as the initial treatment for GC; iii) age over 20 years, and iv) Eastern Cooperative Oncology Group performance status of 0-2. In principle, pathological stage (pStage) II patients received S-1 mono-therapy, and pStage III patients received S-1 therapy plus docetaxel or capecitabine plus oxaliplatin therapy for one year. All study protocols were approved by the Ethics Committee of the Kanagawa Cancer Center (approval number: 25Research-20), and all procedures were conducted following the Declaration of Helsinki in 1996. In this study, informed consent was obtained from all patients by completing an informed consent form.

Measurement of ALI. We calculated ALI based on preoperative blood test data as follows: ALI=BMI (kg/m^2) * albumin (g/dl)/[Neutrophil (/μl)/Lymphocyte (/μl)]. The cutoff value was defined as 56.8 based on a receiver operating characteristic analysis of survival and death (area under the curve 0.61, 95% confidence interval 0.54-0.68). According to the cutoff value, the patients were categorized into high- and low-ALI groups.

Analyzed parameters. Prognostic factors were examined using the following variables: patient age, sex, BMI, operation, tumor size, histological type, lymphatic invasion, venous invasion, pathological Stage (pStage), and postoperative complications.

Statistical analyses. Categorical variables were examined using the $\chi 2$ test or Fisher exact test, as appropriate. Propensity matched analysis was performed for ALI. The matched variables included age, sex, and lymphatic invasion. Overall survival (OS) and relapse-free survival (RFS) were assessed using the Kaplan-Meier method and log-rank test. Variables identified as significant (P<0.05) in the univariate analysis were considered candidates for the multivariate COX regression analysis, and results were presented as hazard ratios (HRs) with a 95% confidence interval (CI). A P-value <0.05 was considered significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Relationship between ALI and clinicopathological factors. Table I shows the relationship between preoperative ALI and clinicopathological factors in patients with GC. A total of 459 patients were categorized into the high-ALI (n=150) and low-ALI (n=309) groups based on their preoperative ALI (Table I). In the low-ALI group, patients were older (P=0.017), more likely to be female (P=0.007), had lower BMI (P<0.001), and had a higher incidence of lymphatic invasion (P=0.03) by comparison with the high-ALI group before propensity matched analysis.

Relationship between ALI and OS and RFS. The OS of the low-ALI group was significantly poorer than that of the high-ALI group (85.5% vs. 93.8%, P=0.01) (Fig. 1). The RFS

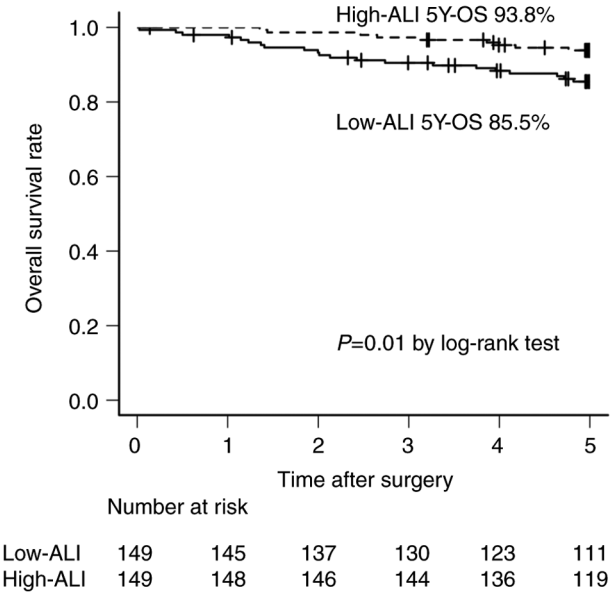

Figure 1. Kaplan-Meier 5-year overall survival curve according to ALI after propensity matched analysis. The OS of the low-ALI group was significantly poorer compared with that of the high-ALI group. ALI, advanced lung cancer inflammation index; OS, overall survival.

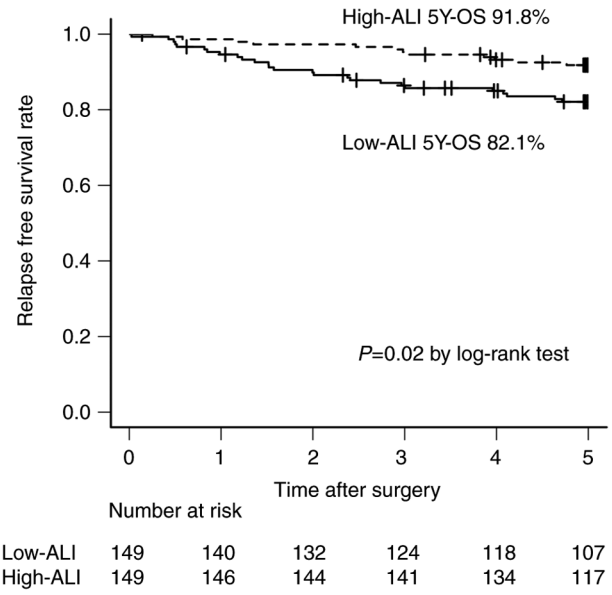

Figure 2. Kaplan-Meier 5-year RFS curve according to ALI after propensity matched analysis. The RFS of the low-ALI group was significantly poorer compared with that of the high-ALI group. ALI, advanced lung cancer inflammation index; RFS, relapse-free survival.

of the low-ALI group was significantly poorer than that of the high-ALI group (82.1% vs. 91.8%, P=0.02) (Fig. 2).

Univariate and multivariate analyses for OS and RFS. Tables II and III show the results of the univariate and multivariate analyses of OS and RFS in patients with GC, who underwent gastrectomy according to ALI. Multivariate analyses for OS demonstrated that low ALI (Hazard Ratio [HR]: 2.26; 95% CI: 1.11-4.59; P=0.03) was an independent prognostic factor (Table II). Moreover, multivariate analyses

Table I. Clinicopathological data between low-ALI vs. high-ALI groups.

	ALI of the original dataset			ALI of the 1:1 matched dataset		
Variables	Low (n=309)	High (n=150)	P-value	Low (n=149)	High (n=149)	P-value
Age						
<65	83 (26.9)	57 (38.0)	0.017	56 (37.6)	56 (37.6)	1.000
≥65	226 (73.1)	93 (62.0)		93 (62.4)	93 (62.4)	
Sex						
Male	189 (61.2)	111 (74.0)	0.007	110 (73.8)	110 (73.8)	1.000
Female	120 (38.8)	39 (26.0)		39 (26.2)	39 (26.2)	
BMI						
<18.5	44 (14.2)	3 (2.0)	<0.001	14 (9.4)	3 (2.0)	<0.001
≥18.5, <25.0	217 (70.2)	94 (62.7)		111 (74.5)	94 (63.1)	
≥ 25	48 (15.5)	53 (35.3)		24 (16.1)	52 (34.9)	
Operation						
Not TG	229 (74.1)	120 (80.0)	0.200	115 (77.2)	119 (79.9)	0.672
TG	80 (25.9)	30 (20.0)		34 (22.8)	30 (20.1)	
Histological type						
Well/moderately differentiated	156 (50.5)	70 (46.7)	0.486	84 (56.4)	70 (47.0)	0.132
Poorly differentiated	153 (49.5)	80 (53.3)		65 (43.6)	79 (53.0)	
Lymphatic invasion						
-	205 (66.3)	115 (76.7)	0.030	115 (77.2)	115 (77.2)	1.000
+	104 (33.7)	35 (23.3)		34 (22.8)	34 (22.8)	
Venous invasion						
-	178 (57.6)	93 (62.0)	0.418	91 (61.1)	93 (62.4)	0.905
+	131 (42.4)	57 (38.0)		58 (38.9)	56 (37.6)	
pStage						
I	205 (66.3)	111 (74.0)	0.107	106 (71.1)	111 (74.5)	0.603
II/III	104 (33.7)	39 (26.0)		43 (28.9)	38 (25.5)	
Surgical complications						
-	265 (85.8)	123 (82.0)	0.336	129 (86.6)	122 (81.9)	0.266
+	44 (14.2)	27 (18.0)		20 (13.4)	27 (18.1)	

Results are presented as n (%). ALI, advanced lung cancer inflammation index; BMI, body mass index; pStage, pathological Stage; TG, total gastrectomy.

for RFS demonstrated that age≥65 years (HR: 2.35; 95% CI: 1.15-4.80; P=0.03), lymphatic invasion (HR: 2.08; 95% CI: 1.03-4.18; P=0.04), pStage II/III (HR: 2.13; 95% CI: 1.03-4.41; P=0.04), and low ALI (HR: 1.97; 95% CI: 1.06-3.69; P=0.03) were independent prognostic factors (Table III).

Discussion

This research focused on ALI as a marker of inflammation and nutritional status in patients with GC undergoing curative resection. We examined its clinical utility by analyzing the association between preoperative ALI and survival. Our findings revealed a significantly poorer prognosis in terms of OS and RFS in the low-ALI group compared with that in the high-ALI group. Multivariate analysis further confirmed that low ALI was an independent poor prognostic indicator for both OS and RFS.

Initially, ALI was reported as a prognostic factor in patients with lung cancer, although recent studies have highlighted the prognostic value of ALI in various gastrointestinal malignancies postoperatively. In esophageal squamous cell carcinoma, retrospective studies demonstrated that lower ALI correlated with worse cancer-specific survival (CSS) and OS (24,25). Similarly, in colorectal cancer, patients with lower ALI exhibited poorer PFS and OS, with ALI identified as an independent prognostic factor in multivariate analyses (26,27). For GC, our results align with those of previous research, underscoring the potential of ALI as a significant prognostic marker postoperatively.

Several investigations have examined the prognostic significance of ALI in patients with GC after surgery, and these results are generally consistent with those of the present study. A retrospective study of 620 patients with GC

Table II. Univariate and multivariate analyses of clinicopathological factors and preoperative ALI for overall survival after propensity matched analysis.

		Univariate			Multivariate		
Factors	Groups	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	<65	1					
	≥65	2.21	1.01-4.85	0.05			
Sex	Male	1					
	Female	0.46	0.18-1.17	0.10			
Surgery	Not TG	1					
	TG	1.36	0.65-2.82	0.41			
Histological type	Well/Moderately differentiated	1					
	Poorly differentiated	0.66	0.34-1.29	0.23			
Lymphatic invasion	-	1			1		
	+	2.76	1.41-5.39	0.003	1.60	0.74-3.49	0.23
Venous invasion	-	1			1		
	+	2.92	1.48-5.78	0.002	1.86	0.83-4.18	0.13
pStage	I	1			1		
	II/III	3.03	1.57-5.84	<0.001	1.75	0.77-3.97	0.18
Surgical complications	-	1					
	+	0.66	0.23-1.86	0.43			
Preoperative ALI	High	1			1		
	Low	2.33	1.15-4.74	0.02	2.26	1.11-4.59	0.03

ALI, advanced lung cancer inflammation index; BMI, body mass index; CI, Confidence interval; HR, Hazard Ratio; pStage, pathological Stage; TG, total gastrectomy; OS, overall survival.

Table III. Univariate and multivariate analyses of clinicopathological factors and preoperative ALI for relapse-free survival after propensity matched analysis.

		Univariate			Multivariate		
Factors	Groups	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	<65	1			1		
	≥65	2.13	1.05-4.31	0.04	2.35	1.15-4.80	0.03
Sex	Male	1					
	Female	0.53	0.23-1.18	0.12			
Surgery	Not TG	1					
	TG	1.33	0.68-2.58	0.40			
Histological type	Well/moderately differentiated	1					
	Poorly differentiated	0.80	0.44-1.45	0.45			
Lymphatic invasion	-	1			1		
	+	2.81	1.53-5.16	<0.001	2.08	1.03-4.18	0.04
Venous invasion	-	1			1		
	+	2.23	1.23-4.05	0.009	1.20	0.58-2.45	0.62
pStage	I	1			1		
	II/III	3.13	1.73-5.67	<0.001	2.13	1.03-4.41	0.04
Surgical complications	-	1					
	+	0.82	0.35-1.95	0.66			
Preoperative ALI	High	1			1		
	Low	2.01	1.08-3.75	0.03	1.97	1.06-3.69	0.03

ALI, advanced lung cancer inflammation index; BMI, body mass index; CI, Confidence interval; HR, Hazard Ratio; pStage, pathological Stage; TG, total gastrectomy; RFS, relapse-free survival.

after surgery showed that patients with low ALI had significantly poorer OS and DFS than that of those with high ALI (P<0.001 and P<0.001, respectively) (19). In multivariate analysis, ALI was an independent prognostic indicator for OS (P=0.006). A retrospective study of 615 patients with GC after surgery showed that patients with high ALI had significantly longer OS and DFS than that of those with low ALI (P<0.001 and P<0.001, respectively) (20). In multivariate analysis, ALI was an independent prognostic factor for OS and DFS (P=0.001 and P=0.009, respectively). A retrospective study of 1657 patients with GC after surgery showed that patients with low ALI had significantly worse OS and CSS than that of those with low ALI (P<0.001 and P=0.001, respectively) (21). In multivariate analysis, ALI was an independent prognostic factor for OS and DFS (P=0.01 and P=0.04, respectively). In light of these findings, this study is one of the few novel studies to identify ALI as a useful prognostic factor for patients with GC using propensity score matching analysis. Furthermore, our results support the robustness of ALI as a prognostic predictor and may lead to further large-scale prospective studies in the future.

The effectiveness of ALI as a prognostic tool likely stems from its incorporation of both BMI and NLR/Alb, reflecting a patient's inflammatory immune function and nutritional status. In GC, low BMI has been established as a prognostic factor for DFS, and a positive correlation exists between preoperative BMI and prognostic nutritional indices (28), thereby emphasizing the importance of nutritional and immune status in patient outcomes. Recently, NLR/Alb has also been reported to be an important prognostic factor in patients with GC (29,30). Therefore, interventions such as aggressive nutritional therapy and rehabilitation (31) may be possible in patients with low ALI, which may contribute to improved prognosis.

However, this study had some limitations. First, is its single-center and retrospective design. Second, the paucity of literature on ALI in GC left the optimal cutoff value undetermined. Further multicenter, prospective studies are required to validate the utility of ALI and establish a clinically relevant cutoff value. Third, the data set used was that of Japanese people only, thus no comparisons could be made between races.

In conclusion, preoperative ALI emerges as a potentially valuable prognostic tool in patients with GC undergoing radical surgery. Our study supports the notion that lower ALI levels are indicative of poorer survival outcomes, highlighting the need for further research to effectively integrate this marker into clinical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

IH and TOs conceived and designed the study. IH, MT, SO, JM, SN, YM, KK, TA, TY, TOg, NY, AS, YR and TOs analyzed and interpreted the data. IH and TOs confirm the authenticity of all the raw data. IH and TOs prepared the draft manuscript and figures. IH, MT, SO, JO, SN, YM, KK, TA, TY, TOg, NY, AS, YR and TOs collected the data and performed the literature search. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Kanagawa Cancer Center (approval no. 25Research-20), and all procedures were conducted following the Declaration of Helsinki in 1996. Written informed consent was obtained from all patients in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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