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Original Article

Albumin-Bilirubin Score Predicts Tolerability to Adjuvant S-1 Monotherapy after Curative Gastrectomy

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ABSTRACT

Purpose: Due to adverse events, dose reduction or withdrawal of adjuvant chemotherapy is required for some patients. To identify the predictive factors for tolerability to postoperative adjuvant S-1 monotherapy in gastric cancer (GC) patients, we evaluated the predictive values of blood indicators.

Materials and Methods: We analyzed 98 patients with pStage II/III GC who underwent postoperative adjuvant S-1 monotherapy. We retrospectively analyzed correlations between 14 parameters obtained from perioperative routine blood tests to assess their influence on the withdrawal of postoperative adjuvant S-1 monotherapy, within 6 months after discontinuation.

Results: Postoperative adjuvant chemotherapy was discontinued in 21 patients (21.4%) within 6 months. Univariable analysis revealed that high preoperative albumin-bilirubin (ALBI) scores had the highest odds ratio (OR) for predicting the failure of adjuvant S-1 chemotherapy (OR, 6.47; 95% confidence interval [CI], 2.08–20.1; cutoff value, –2.696). The high ALBI group had a significantly shorter time to failure of postoperative adjuvant S-1monotherapy (hazard ratio, 3.48; 95% CI, 1.69–7.25; P=0.001). Multivariable analysis identified high preoperative ALBI score as an independent prognostic factor for tolerability (OR, 10.3; 95% CI, 2.33–45.8; P=0.002).

Conclusions: Preoperative ALBI shows promise as an indicator associated with the tolerability of adjuvant S-1 monotherapy in patients with pStage II/III GC.

Keywords: Gastric cancer; S-1; Adjuvant chemotherapy; Biomarker; Albumin-bilirubin score

INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related deaths worldwide [1]. Multimodality treatment is mandatory to improve treatment outcomes of patients with advanced GC, and postoperative adjuvant chemotherapy is the standard of care in East Asia. Adjuvant chemotherapy with S-1 (an oral fluoropyrimidine) after curative gastrectomy has been a standard regimen based on the Adjuvant Chemotherapy Trial of TS-1 for GC [2]. It

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Author Contributions

Conceptualization: M.K.; Data curation: M.H.; Formal analysis: S.Y.; Investigation: C.T.; Methodology: G.N.; Project administration: M.K.; Resources: D.K.; Software: T.M.; Supervision: Y.K.; Visualization: T.M.; Writing - original draft: T.M.; Writing - review & editing: T.M.

Conflict of Interest

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

has to be administered for 12 months, in contrast to adjuvant chemotherapy for other cancer types, which are delivered for 6 months [3,4].

Inadequately shortened duration or suboptimal dosages of adjuvant chemotherapy may adversely affect long term outcomes in patients with cancer [5]. However, dose reduction or even termination of drug administration is inevitable in some patients because of severe adverse events, especially in GC, in which consequences of the surgery could render patients vulnerable to toxicity. Predicting the likelihood of such adverse events could be useful in planning the treatment schedule and deciding the initial dose and may even encourage a shift to neoadjuvant therapy if an accurate prediction is made preoperatively. JCOG1104 was a phase III trial designed to investigate the non-inferiority of adjuvant S-1 chemotherapy for 6 months compared with that for 12 months in patients with stage II GC. This study failed to demonstrate the non-inferiority of adjuvant S-1 chemotherapy for 6 months, suggesting the importance of continuation of the treatment for more than 6 months [6]. This motivated us to identify the predictive factors for its withdrawal within 6 months. Aoyama et al. reported that creatinine clearance (CCr) and body-weight loss were the risk factors for early termination of postoperative adjuvant S-1 chemotherapy [7,8]. Other risk factors could be identified by analyzing preoperative data.

The aim of the present study was to identify the risk factors for adverse events associated with the withdrawal of postoperative adjuvant S-1 monotherapy within 6 months, using laboratory data acquired preoperatively through cross-sectional and temporal analyses. We identified preoperative albumin-bilirubin (ALBI) score to be the most predictive factor. The ALBI score was initially developed to identify objective measures of liver dysfunction in patients with hepatocellular carcinoma (HCC) [9]. In this study, we demonstrate the clinical significance of ALBI score for predicting tolerability to adjuvant S-1 monotherapy in patients with advanced GC.

MATERIALS AND METHODS

Ethics

This study fully conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects (2013). Written informed consent for the use of clinical data was obtained from all patients as required by the Institutional Review Board (IRB) of our University (IRB No. 2018-0424).

Inclusion eligibility and treatment

Patients inclusion criteria were as follows: 1) underwent total or partial gastrectomy and systemic lymphadenectomy between January 2005 and July 2017 at our hospital, 2) had previously untreated stage II/III GC, and 3) received postoperative S-1 adjuvant monotherapy, excluding patients who experienced disease recurrence within 6 months and required another chemotherapy to treat recurrent lesions. Eventually, 98 patients were included in the analysis. These patients were started on S-1 adjuvant monotherapy within 6 weeks after surgery at a dose corresponding to the body surface area as follows: <1.25 m^2 (40 mg twice daily), 1.25–1.50 m^2 (50 mg twice daily), and ≥1.50 m^2 (60 mg twice daily). S-1 was given for 4 weeks followed by 2 weeks' rest and the treatment was to be continued for 12 months unless rendered impossible due to severe adverse events, patient's refusal or recurrent disease. Treatment-related adverse events were graded according to the criteria of the Common

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Terminology Criteria for Adverse Events [10]. Changing the schedule to deliver S-1 for 2 weeks followed by 1 weeks' rest was recommended when patients experienced adverse effects of ≥grade 2 within the first 2 weeks of treatment, and the dose was reduced from 120 mg to 100 mg, 100 mg to 80 mg, or 80 mg to 50 mg in case of other circumstances at the discretion of the physicians. Postoperative follow-up, which was conducted according to the Japanese Gastric Cancer Treatment Guidelines, included physical examinations, laboratory tests, and diagnostic imaging. Patients underwent computed tomography at 6-month intervals and endoscopy at 12-month intervals until 5 years after surgery. Clinical recurrences required confirmation using imaging modalities [11].

Study parameters

Blood tests were routinely performed 2 days before surgery and on the day of postoperative adjuvant chemotherapy initiation. A total of 14 parameters were investigated as candidate predictive factors for early discontinuation of adjuvant S-1 monotherapy due to adverse effects. These parameters can be determined by preoperative routine blood test at any hospital and were potentially correlated to nutritional status and functions of the liver, kidney and bone marrow. The following data were retrospectively retrieved from the medical records: white blood cell count, neutrophil count, total lymphocyte count (TLC), platelet count (Plt), total protein, albumin (Alb), cholinesterase, total bilirubin (T-Bil), aspartate aminotransferase, alanine aminotransferase, indices as candidate predictors: CCr (Cockroft-Gault method), ALBI score [ALBI=log10 T-Bil (μmol/L)×0.66+Alb (g/L)×−0.0852], platelet-lymphocyte ratio (PLR) (PLR=TLC/Plt×100), Onodera's prognostic nutritional index (PNI) (PNI=10×Alb g/dL+0.005×TLC) [12,13].

Statistical analysis

The significance of the differences between the values of qualitative variables between groups was compared using the χ^2 test. The cutoff values for predicting the failure of adjuvant S-1 monotherapy within 6 months were determined using receiver operating characteristic (ROC) curve analysis. Univariable and multivariable regression analyses to detect prognostic factors were performed using logistic regression analysis. The Kaplan–Meier method was used to assess overall, disease-free and time-to-treatment failure rates, and the differences between survival curves were analyzed using the log-rank test. The $P<0.05$ indicated a significant difference. These analyses were performed using R software (The R Foundation for Statistical Computing, Vienna, Austria) with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

RESULTS

Patients' characteristics

The baseline characteristics of the patients are shown in **Table 1**. We analyzed 98 patients (male, 73.5%; median age, 67 years; total gastrectomy, 39.8%). Postoperative adjuvant S-1 monotherapy was withdrawn within 6 months from initiation of the treatment in 21 patients (21.4%), because of adverse events as follows; fatigue (n=5), diarrhea (n=4), anorexia (n=4), oral mucositis (n=2), leukopenia (n=1), dacryorrhea (n=1), and others (n=4), all adverse events were grade 3. These patients were considered as the main target population to identify risk factors for early discontinuation of adjuvant S-1 monotherapy, and hence were included in all analyses. The median duration of S-1 administration was 10.2 months and 1.6 months in the patient subgroup with S-withdrawal within 6 months.

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Table 1. Clinical characteristics of 98 patients

Variables	No. of patients (n=98)
Age (yr)	67 (20–88)
Sex (male/female)	72/26
Preoperative BMI (kg/m^2)	22.6±3.7
Diabetes mellitus	
Absent	81
Present	17
Cardiopulmonary comorbidities	
Absent	64
Present	34
Type of gastrectomy	
Total	39
Partial	59
Tumor depth (UICC 8th)	
pT1	5
pT2	11
pT3	37
pT4	45
UICC N factor	
pN0	16
pN1	23
pN2	26
pN3	33
Pathological stage (UICC 8th)	
IIA	15
IIB	24
IIIA	17
IIIB	23
IIIC	19
Follow-up (median, mo)	55.2 (2.2–137.3)
S-1 withdrawal (median, mo)	10.2
<6	21 (1.6)
≥6	77 (11.2)

Values are presented as mean±standard deviation, number (%) or number (range).
BMI = body mass index; UICC = Union for International Cancer Control.

Association of the compliance to the chemotherapy with the outcome

Patients who withdrew from adjuvant chemotherapy within 6 months were inclined to have poor long-term survival (**Fig. 1A**).

Comparison of parameters affecting tolerability

We analyzed 14 parameters at 3 time points as indicated in the materials and methods section. The highest odds ratio (OR) associated with predicting the failure of adjuvant S-1 monotherapy within 6 months was the preoperative ALBI score (OR, 6.47; 95% confidence interval [CI], 2.08–20.1) (**Fig. 1B**). The optimal cutoff value of ALBI to predict discontinuation of S-1 adjuvant was determined at −2.696 by the ROC analysis (**Supplementary Fig. 1A**). The ORs of the ALBI score, Alb, and T-Bil at each time point are shown in **Fig. 2A**.

Predictive significance of the preoperative ALBI score

The median preoperative ALBI score was −3.000 (range, −3.620, −1.529). We evaluated the clinical significance of the preoperative ALBI score by dividing the 98 patients into high ALBI (ALBI >−2.696, n=17) and low ALBI (ALBI ≤−2.696, n=81) groups according to the cutoff value determined through the ROC analysis. The relationships between the ALBI scores and various clinicopathological parameters are shown in **Table 2**. High ALBI scores were significantly associated with the age and the Union for International Cancer Control

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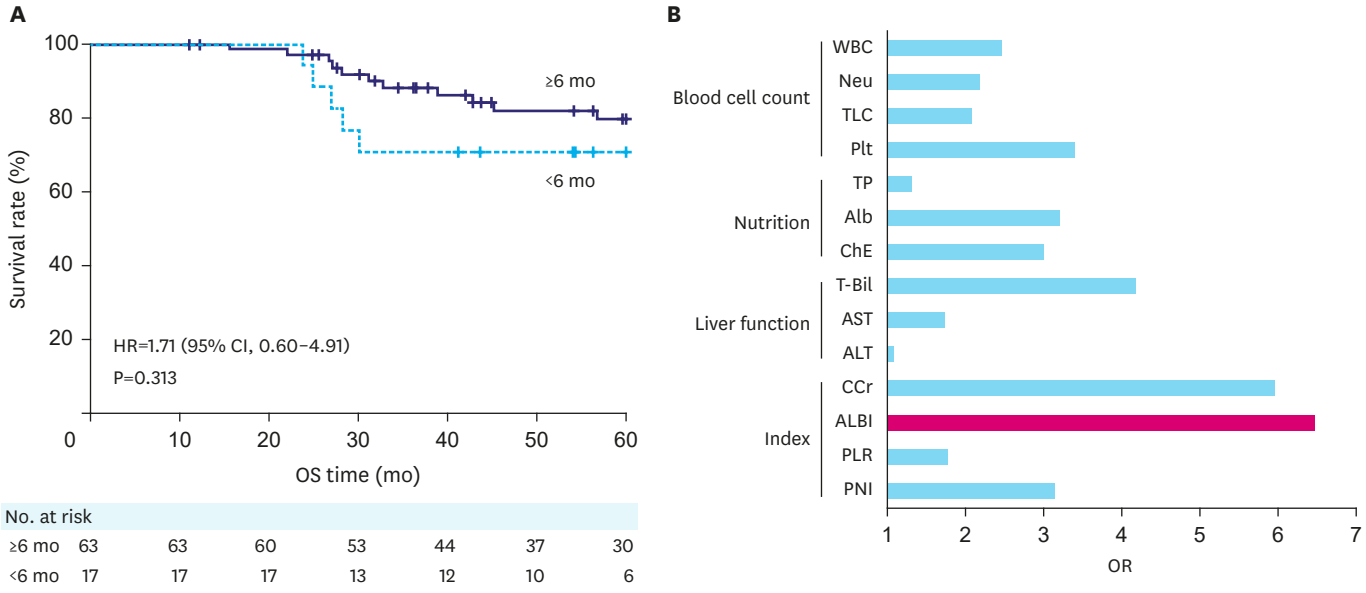

Fig. 1. (A) OS of patients with pStage II/III gastric cancer with or without 6 months of S-1 postoperative adjuvant monotherapy. (B) Preoperative study parameters and ORs.
OS = overall survival; OR = odds ratio; HR = hazard ratio; CI = confidence interval; WBC = white blood cell; Neu = neutrophil count; TLC = total lymphocyte count; Plt = platelet count; TP = total protein; Alb = albumin; ChE = cholinesterase; T-Bil = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CCr = creatinine clearance; ALBI = albumin-bilirubin; PLR = platelet-lymphocyte ratio; PNI = prognostic nutritional index.

stage. The high ALBI group was shown to suffer from significantly shorter time to failure of postoperative adjuvant S-1 monotherapy (hazard ratio [HR], 3.48; 95% CI, 1.69–7.25; P=0.001) (**Fig. 2B**). Multivariable analysis identified preoperative high ALBI score and preoperative CCr<60 mL/min as independent predictive factors for tolerability of 6 months of postoperative adjuvant S-1 monotherapy (ALBI: OR, 10.3; 95% CI, 2.33–45.8; P=0.002 and CCr: OR, 7.28; 95% CI, 1.76–30.1; P=0.006) (**Table 3**). Disease-free survival (DFS) after

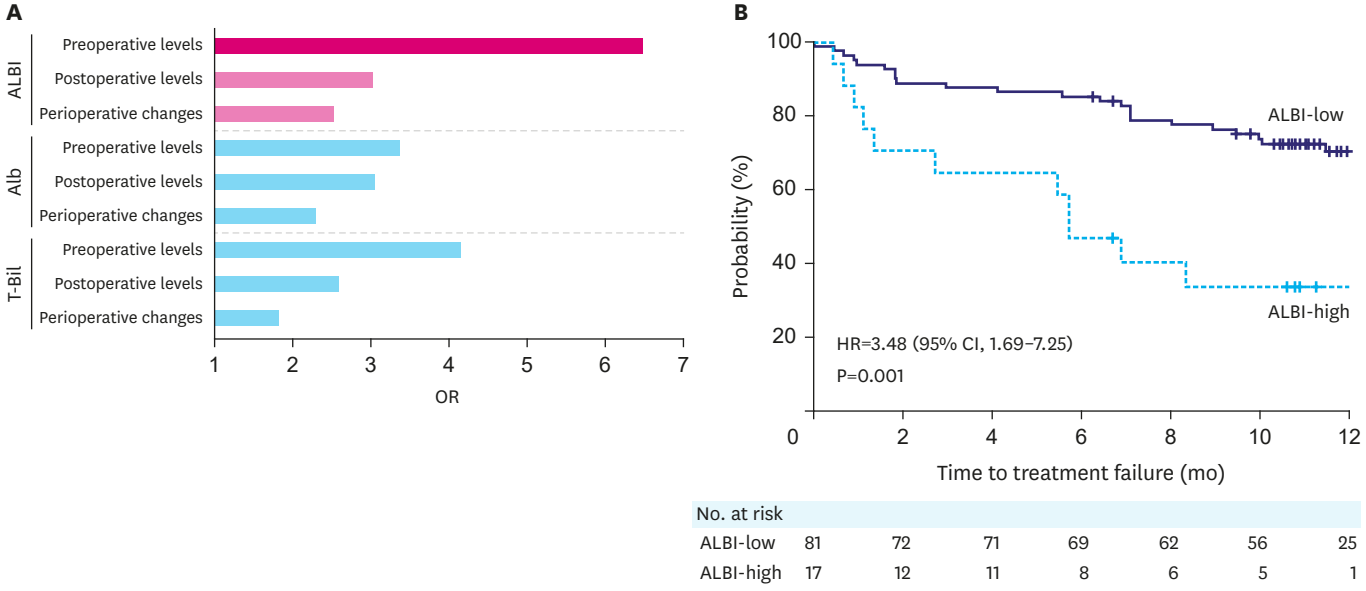

Fig. 2. (A) ORs of ALBI scores and its variables before surgery and postoperative adjuvant chemotherapy initiation and perioperative changes. (B) Time-to-treatment failure of postoperative adjuvant S-1 monotherapy with high and low ALBI scores.
OR = odds ratio; ALBI = albumin-bilirubin; HR = hazard ratio; CI = confidence interval; Alb = albumin; T-Bil = total bilirubin.

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Table 2. Association between ALBI scores and clinicopathological parameters of 98 patients with gastric cancer

Variables	Low ALBI	High ALBI	P-value
Age (yr)			0.010
<70	58 (72)	6 (35)	
≥70	23 (28)	11 (65)	
Sex			0.589
Male	59 (73)	13 (76)	
Female	22 (27)	4 (24)	
BMI (kg/m^2)			1.000
<22	50 (62)	10 (59)	
≥22	31 (38)	7 (41)	
Diabetes mellitus			0.487
Absent	68 (84)	13 (76)	
Present	13 (16)	4 (24)	
Cardiopulmonary comorbidities			0.270
Absent	55 (68)	9 (53)	
Present	26 (32)	8 (47)	
Type of gastrectomy			0.589
Total	31 (38)	8 (47)	
Partial	50 (62)	9 (53)	
Tumor depth (UICC 8th)			0.624
pT1	5 (6)	0 (0)	
pT2	9 (11)	2 (12)	
pT3	32 (40)	5 (29)	
pT4	35 (43)	10 (59)	
Differentiation			0.098
Differentiated	33 (41)	3 (18)	
Undifferentiated	48 (59)	14 (82)	
Lymphatic involvement			1.000
Absent	4 (5)	1 (6)	
Present	77 (95)	16 (94)	
Vessel invasion			1.000
Absent	26 (32)	5 (29)	
Present	55 (68)	12 (71)	
Lymph node metastasis (UICC 8th)			0.329
pN0	13 (16)	4 (23)	
pN1	20 (24)	3 (18)	
pN2	24 (30)	2 (12)	
pN3	24 (30)	8 (47)	
Pathological stage (UICC 8th)			0.009
IIA	11 (13)	4 (23)	
IIB	23 (28)	1 (6)	
IIIA	16 (19)	1 (6)	
IIIB	20 (24)	3 (18)	
IIIC	11 (16)	8 (47)	

Values are presented as number (%).
ALBI = albumin-bilirubin; BMI = body mass index; UICC = Union for International Cancer Control.

curative gastrectomy was significantly shorter in the high ALBI group (HR, 4.33; 95% CI, 1.61–11.7; P=0.003) (**Supplementary Fig. 1B**). The recurrence rate in the high ALBI group was 50.0% (7 out of 14 patients) and that in the low ALBI group was 13.6% (9 out of 66 patients), within 5 years after curative gastrectomy.

DISCUSSION

The ALBI score is calculated from the serum Alb and bilirubin concentrations. Assessment of subjective variables such as ascites and encephalopathy are necessary for the conventional Child-Pugh grade to assess liver function. The ALBI score was developed initially to eliminate

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Table 3. Predictive factors for the discontinuation of S-1 monotherapy within 6 months

Variables	Univariate			Multivariable		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (≥70 yr)	3.33	1.23–9.02	0.018	2.35	0.81–6.86	0.118
Sex (male)	1.70	0.51–5.62	0.385	-	-	-
Preoperative BMI (<22, kg/m^2)	2.22	0.82–6.02	0.118	-	-	-
Perioperative body weight loss (≥10%)	1.47	0.50–4.31	0.479	-	-	-
Preoperative CCr (<60 mL/min)	5.94	1.99–17.8	0.001	7.28	1.76–30.1	0.006
Diabetes mellitus	1.69	0.52–5.50	0.381	-	-	-
Cardiopulmonary comorbidities	1.21	0.44–3.28	0.712	-	-	-
Surgical approach (open)	2.11	0.44–10.1	0.350	-	-	-
Type of gastrectomy (total)	0.70	0.26–1.94	0.496	-	-	-
Intraoperative bleeding (≥200 mL)	1.43	0.50–4.10	0.507	-	-	-
Intraoperative transfusion	1.33	0.33–5.46	0.689	-	-	-
Operative time (≥240 min)	1.57	0.55–4.54	0.402	-	-	-
Splenectomy	1.19	0.38–3.74	0.764	-	-	-
Reconstruction method (Billroth I)	0.71	0.14–3.50	0.669	-	-	-
Tumor location (lower third)	1.44	0.53–3.95	0.474	-	-	-
Multifocal lesions	1.23	0.12–12.5	0.859	-	-	-
Tumor size (≥50 mm)	1.03	0.39–2.78	0.946	-	-	-
Tumor differentiation (undifferentiated)	3.02	0.93–9.38	0.661	-	-	-
Pathological stage (stage III)	1.10	0.41–2.95	0.857	-	-	-
Postoperative complication	1.66	0.62–4.46	0.318	-	-	-
Preoperative ALBI (high)	6.47	2.08–20.1	0.001	10.3	2.33–45.8	0.002

BMI = body mass index; CI = confidence interval; OR = odds ratio; CCr = creatinine clearance; ALBI = albumin-bilirubin.

the need for subjective variables and to identify objective measures of liver dysfunction, which independently influence the survival of patients with HCC [9]. This score was also reported to be related to postoperative complications and liver failure [14]. In the present study, we analyzed 14 parameters obtained before surgery and before the initiation of postoperative adjuvant chemotherapy and evaluated the perioperative changes of these parameters.

The CCr was already recognized as a significant predictor of non-compliance to adjuvant S-1 monotherapy [7]. We found a closer correlation between the preoperative ALBI score and tolerability after 6 months of S-1 adjuvant monotherapy. The preoperative ALBI score had the highest OR for the incidence of withdrawal of postoperative adjuvant S-1monotherapy within 6 months. Furthermore, multivariable analysis identified preoperative high ALBI scores and preoperative CCr as 2 independent predictive factors in this aspect.

Alb and bilirubin concentrations to determine the ALBI score are easily measured using standard laboratory tests in most hospitals. Moreover, the ALBI score can serve as a prognostic factor for certain malignancies [9,13,15]. This study revealed that high ALBI scores are associated with shorter time to failure of postoperative adjuvant S-1 monotherapy and caused shorter DFS. Furthermore, the type of gastrectomy was not correlated with the ALBI score, and total gastrectomy was not an independent prognostic factor for discontinuation of S-1 monotherapy within 6 months. These results suggest irrespective of the gastrectomy type, the ALBI score acts as a prognostic factor. However, the reason that the ALBI score predicted patient compliance to adjuvant S-1 chemotherapy remains unclear. S-1 comprises tegafur, gimeracil, and oteracil potassium. Tegafur is a prodrug of the active metabolite fluorouracil (5-FU). Gimeracil inhibits the degradation of 5-FU by reversibly inhibiting dihydropyrimidine dehydrogenase (DPD). Oteracil mainly remains in the gut and reduces the production of 5-FU. 5-FU is metabolized by DPD, and lower 5-FU levels in the gut cause less gastrointestinal toxicity. The degradation of 5-FU occurs in all tissues, including tumor tissues, but mainly in the liver [16,17]. 5-FU is mainly bound to

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Alb in the blood, and the free drug is pharmacologically active. Hypoalbuminemia leads to increased blood concentrations of the free drug, which induces profound toxicity [18]. The liver produces Alb, and hypoalbuminemia is defined as malnutrition and liver dysfunction, and hyperbilirubinemia indicates liver dysfunction as well. We hypothesize that, for these reasons, hypoalbuminemia and liver dysfunction are associated with the tolerability of chemotherapy in patients with other cancers [19,20].

High ALBI scores were significantly associated with advanced disease stages. Preoperative high ALBI scores were partially attributed to malnutrition caused by advanced disease [21,22]. Adjuvant chemotherapy is necessary to improve the prognosis of patients in advanced stages, although the high ALBI group had significantly shorter times-to-treatment failure of postoperative S-1 adjuvant monotherapy. To address this paradox, for patients with high preoperative ALBI, first, dose modification or measures against adverse effects can be considered before implementation of S-1 adjuvant to prevent early discontinuation of the S-1 adjuvant. Second, comprehensive perioperative nutrition improvement programs have been attempted to enhance nutritional status, of which postoperative preservation of body weight is a parameter [23]. Such attempts may increase the compliance to evidence-based adjuvant chemotherapy, ultimately leading to improvements in survival [8]. Lastly, intensive follow-up after initiation of S-1 adjuvant should be provided for patients with high preoperative ALBI for early detection of symptoms from adverse effects. For patients with low ALBI, decision has to be made to dose S-1 appropriately.

Interestingly, preoperative ALBI score was the most predicting value of the failure of postoperative adjuvant S-1 monotherapy. Postoperative ALBI can be influenced by hypoalbuminemia from surgical stress, hemodilution, acute inflammation, and elevated T-Bil due to blood transfusion and drug-induced liver dysfunction. These complications might weaken the correlation between postoperative ALBI and times-to-treatment failure of S-1. In contrast, preoperative ALBI reflects innate nutrition status and liver functions. Therefore, preoperative ALBI score may reflect the tolerability of postoperative S-1 adjuvant monotherapy.

We acknowledge the limitations of our study. The evaluation of dose intensities, which were not available at this time, will possibly provide valuable insights into the understanding of the significance of the ALBI score and its relation to the tolerability of chemotherapy. Second, we did not evaluate adverse drug reactions. Various adverse effects were manifested, but we could not assess ALBI score linked to the adverse effect type. A rigid and comprehensive program performed by a multidisciplinary team to detect and promptly deal with adverse drug reactions, unachievable in the current study, may be able to improve the continuation of chemotherapy. Finally, we conducted a retrospective analysis of data acquired from a relatively small number of patients in single institution. Thus, our findings require validation by further large-scale prospective studies.

In conclusion, the preoperative ALBI score may serve as a significant prognostic biomarker associated with the tolerability of adjuvant S-1 monotherapy in patients with pStage II/III GC.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Receiver operating characteristic curve analysis of the association of ALBI score with 6 months continuation of S-1 monotherapy. (B) DFS after curative gastrectomy of patients with high and low ALBI scores.

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