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ORIGINAL SCIENTIFIC REPORT

Proposal of a Scoring Scale to Estimate Risk of the Discontinuation of S-1 Adjuvant Monotherapy in Patients with Stage II to III Gastric Cancer: A Multi-Institutional Dataset Analysis

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Abstract

Background Discontinuation of postoperative S-1 adjuvant monotherapy is a frequent problem in the management of patients with gastric cancer.

Methods A total of 355 stage II/III gastric cancer patients who underwent gastrectomy and adjuvant S-1 were retrospectively analyzed using a multicenter dataset. We randomly assigned patients into either discovery or validation cohort in a 2:1 ratio. In the discovery cohort, 29 parameters were assessed as candidate factors to predict discontinuation of S-1 adjuvant within 6 months. A scoring system was designed using independent risk factors identified by the multivariate analysis. Reproducibility was tested in the validation cohort.

Results Overall, 92 patients (25.9%) discontinued the treatment within 6 months because of adverse effects. Age, preoperative urea nitrogen (UN) and the preoperative albumin-to-bilirubin index (ALBI) showed the highest area under the curve (AUC) for the discontinuation of S-1 adjuvant within 6 months in each category: body status, blood tests and indices. In the multivariate analysis, age $\geq$ 64 years, preoperative UN $\geq$ 15.2 mg/dl and preoperative ALBI ≥ -0.265 were identified as independent risk factors. A scoring scale consisting of these three factors was developed for the prediction of drug discontinuation and demonstrated a greater AUC (0.728) than that of each of the three constituents. The time to treatment discontinuation decreased incrementally as the risk score increased. The reproducible findings were confirmed in the validation cohort.

Conclusions We identified risk factors and developed a scoring scale to predict S-1 adjuvant monotherapy discontinuation in patients with stage II/III gastric cancer.

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Introduction

For patients with early gastric cancer, an excellent prognosis can be achieved by endoscopic or surgical resection [1]. In contrast, stage II to III disease frequently recurs even after radical gastrectomy due to microscopic residual disease [2, 3]. Adjuvant chemotherapy has been recognized as an effective method for eradicating micrometastatic tumor cells in order to enhance the chance of cure [4, 5].

According to a previous pivotal clinical trial, the ACTS-GC (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer) trial, 12 months of postoperative adjuvant S-1 monotherapy has been positioned as the standard treatment for patients with stage II to III gastric cancer who have undergone radical resection [6, 7]. As an attempt to shorten the duration of treatment for patients with stage II gastric cancer, a phase III randomized trial to compare four and eight courses of adjuvant S-1 monotherapy (JCOG 1104, OPAS-1 trial) was carried out. However, the study was stopped prematurely at an interim analysis since it was deemed unlikely that non-inferiority of the shorter duration could be proved. Thus, to prescribe S-1 for 12 months remains to be the standard for all patients with stage II to III gastric cancer [8]. However, the continuation of S-1 is not easy for every patient because of adverse effects, such as general fatigue and diarrhea [9, 10]. To make the matters worse, the tolerability is decreased by the negative influence of gastric resection [3, 11]. From the data of the ACTS-GC trial, 34.2% of patients discontinued S-1 while on treatment [7]. Patient management, including controlling adverse effects and the medical examination interval, can be optimized if compliance with S-1 monotherapy is accurately predicted before treatment initiation. Previous reports indicated that creatinine clearance (CCr), body weight loss and side effects of nausea were risk factors for the treatment failure of adjuvant S-1 monotherapy [12, 13]. However, a limited number of patients were included in those studies from a single institute and analyzed each individual factor mainly measured only before surgery [12, 13]. Thus, further investigation for development of a risk estimation system for accurate patient stratification is warranted.

Herein, we designed a multicenter integrated database and conducted a cross-sectional analysis of correlations between the perioperative values of candidate factors and tolerability of S-1 adjuvant monotherapy. We aimed here to propose a scoring system to estimate the risk of discontinuation of S-1 adjuvant monotherapy for patients with stage II to III gastric cancer.

Materials and methods

Patient inclusion

Data from 3484 patients who underwent gastrectomy for gastric cancer between January 2010 and December 2014 were retrospectively collected at nine institutions [14]. Of these, we included 355 patients in the analysis who met the following inclusion criteria: no preoperative treatment, pathological stage II/III gastric cancer according to the TNM Classification of Malignant Tumors, 8th Edition [15], R0 gastrectomy with systematic lymphadenectomy performed according to the Japanese Gastric Cancer Treatment Guidelines [16], administration of S-1 adjuvant monotherapy and sufficient data for analysis. Patients pathologically diagnosed as T1N2/3 and T3N0 were included. Patients who were treated with a regimen other than S-1 monotherapy and those who experienced disease recurrence within 6 months were excluded. We assigned 355 patients into the discovery (n = 237) and validation cohorts (n = 118) in a 2:1 ratio using a table of random numbers (Fig. 1).

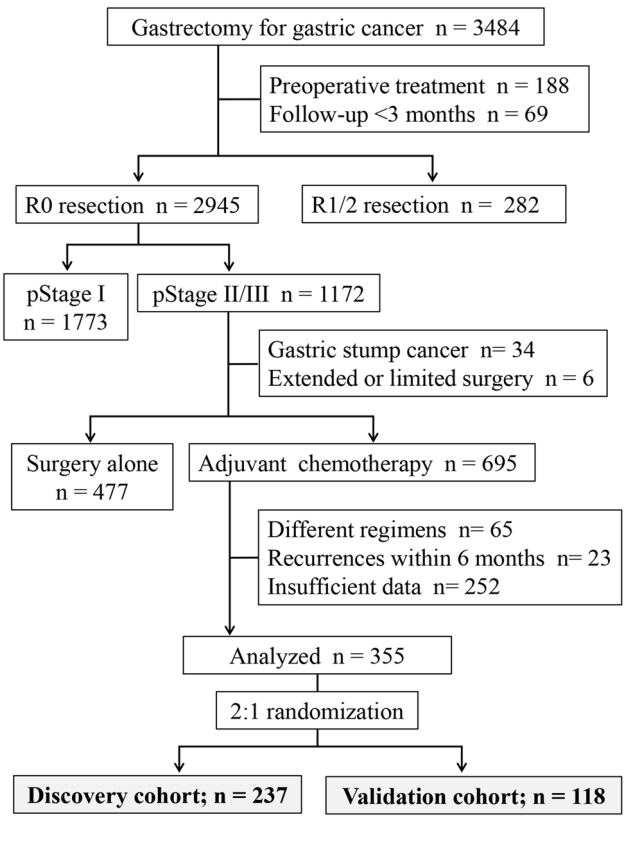

Fig. 1 Flow diagram of patient selection

Patient management

Gastrectomy with systematic lymphadenectomy was performed according to the Japanese Gastric Cancer Treatment Guidelines [16]. Reconstruction methods after removal of the specimens were designated at the surgeon's discretion. Patients received postoperative follow-up examinations that included physical examinations, laboratory tests and enhanced computed tomography (chest and abdominal cavity) once every 6 months for 5 years or until recurrence [14, 17]. Postoperative S-1 adjuvant therapy was usually commenced between 4 and 8 weeks after surgery [18]. A dose of S-1 was 80–120 mg/day according to the body surface area (BSA) (80 mg/day for BSA < 1.25 m^2, 100 mg/day for BSA of 1.25–1.5 m^2 and 120 mg/day for BSA > 1.5 m^2). Eight courses (6 weeks for a course) of S-1 were administered on days 1–28 unless in the absence of unacceptable side effects and disease recurrences [19]. Starting dose reduction, delay of treatment schedule and subsequent dose reduction were determined following the criteria of the ACTS-GC [7]. Briefly, the treatment was delayed when patients had hematological adverse events of grade 3 or more or non-hematological adverse events of grade 2 or more until all adverse events recovered to grade 0 or 1; treatment was restarted at a reduced dose of 100 mg, 80 mg or 50 mg based on the BSA [19]. Patients who experienced disease recurrence were treated according to the patient's condition and the evidence available at the time of treatment with the patient's consent [18, 20].

Study parameters

Data on physical status and blood test results, including blood cell counts, coagulation, nutrition, hepatorenal function and inflammation were collected and evaluated. We investigated 29 candidate parameters as predictive factors for the discontinuation of adjuvant S-1 monotherapy that can be rapidly measured in every hospital [21]. In addition, some simple indices were employed as candidate indicators: the estimated glomerular filtration rate (eGFR), the lymphocyte-to-monocyte ratio (LMR = total lymphocyte count (TLC)/monocyte count), the neutrophil-to-lymphocyte ratio (NLR = neutrophil count/TLC), the platelet-to-lymphocyte ratio (PLR = TLC/platelet count $\times$ 100), the platelet-to-neutrophil ratio (PNR = neutrophil count/platelet count $\times$ 100), Onodera's prognostic nutritional index (PNI = 10 $\times$ albumin g/dL + 0.005 $\times$ TLC/mm^3), the systemic inflammation score (SIS, formulated based on the serum albumin level and LMR), the albumin-to-bilirubin index (ALBI = (log10 bilirubin micromol/L) $\times$ 0.66) + (albumin g/L) $\times$ -0.085) and the Controlling Nutrition Status score (CONUT score, calculated from the TLC, serum albumin level and cholesterol level) [22–24]. Those candidate factors were evaluated both before and after surgery. Preoperative data were collected within five days before surgery, and postoperative data were collected within two days before the initiation of S-1 adjuvant therapy.

A scoring system for risk estimation

An integrated scoring system was introduced using risk factors for S-1 discontinuation identified as independent risk factors in the multivariate analysis of the discovery cohort. We allocated the individual scores to each parameter according to their odds ratios (ORs). We test the reproducibility of the scoring system in the validation cohort.

Statistical analysis

The area under the curve (AUC) to predict discontinuation of S-1 was calculated using a receiver operating characteristic (ROC) curve analysis. The optimal cutoff value was determined using the Youden index [21, 22]. A multivariate analysis was performed to identify independent risk factors for the discontinuation of S-1 adjuvant therapy using a binomial logistic analysis. Variables with a value of $P < 0.05$ in the univariate analysis were included as covariates in the final model [22]. All statistical analyses were performed using JMP 10 software (SAS Institute, Inc., NC, USA). Statistically significant differences were indicated by $P < 0.05$.

Results

Patient characteristics and S-1 adjuvant treatment profile

The demographics, pathological findings and perioperative characteristics of the 355 patients are presented in Table 1. The mean age was 65.4 years (±9.7 years; standard deviation [SD]), and the male-to-female ratio was 244:111. Total gastrectomy was performed in 140 patients. With respect to pathological staging, 59, 83, 111, 72 and 30 patients were classified as TNM stage IIA, IIB, IIIA, IIIB and IIIC, respectively. The median duration of S-1 adjuvant therapy was 10.7 months (range 0.03–23.5 months), and 92 (25.9%) patients discontinued S-1 adjuvant therapy within 6 months because of adverse effects (Table 1). The reasons for S-1 discontinuation were as follows: general fatigue ($n = 23$), anorexia ($n = 21$), diarrhea ($n = 8$), rash ($n = 8$), bone marrow suppression ($n = 7$), liver dysfunction ($n = 6$), oral mucositis ($n = 4$), vertigo ($n = 2$), heart

Table 1 Patient demographics and pathological characteristics

Variables		Values
Age (years)	Mean ± SD	65.4 ± 9.7
Sex	Male	244
	Female	111
Preoperative performance status	0	306
	1	41
	2	8
Preoperative symptoms	Absent	180
	Present	175
Cardiopulmonary comorbidities	Absent	306
	Present	49
Cerebrovascular disease	Absent	341
	Present	14
Diabetes mellitus	Absent	298
	Present	57
Preoperative body mass index,	Mean ± SD	22.3 ± 3.6
Tumor location	Entire	14
	Upper third	87
	Middle third	133
	Lower third	121
Tumor size (mm)	Median (range)	50 (10–180)
Type of gastrectomy	Total	140
	Non-total	215
Surgical approach	Open	323
	Laparoscopic	32
Operative time (min)	Median (range)	261 (134–560)
Intraoperative blood loss (ml)	Median (range)	270 (0–6362)
Splenectomy	Performed	77
	Not performed	278
Dissected lymph nodes	Mean ± SD	40.4 ± 15.9
Intraoperative transfusion	Performed	25
	Not performed	330
Postoperative complications[a]	Absent	260
	Present	95
Tumor differentiation	Differentiated	154
	Undifferentiated	201
Pathological stage	IIA	59
	IIB	83
	IIIA	111
	IIIB	72
	IIIC	30
Duration of S-1 adjuvant (months)	Median (range)	10.7 (0.03–23.5)
	<6 months	92
	≥6 months	263
Postoperative follow-up period (months)	Median (range)	51.5 (3.9–93.7)

SD standard deviation

[a]Grade III–IV by the Clavien–Dindo classification

failure ($n = 2$), pneumonia ($n = 2$), dacryorrhea ($n = 2$) and others ($n = 7$).

There were no significant differences in clinicopathologic factors including demographics, prevalence of comorbidities, surgical procedures, disease stage, postoperative complication rates and duration of S-1 adjuvant between the discovery and validation cohorts (Supplemental Table 1).

Comparison of predictive values among the candidate parameters

Candidate parameters were classified into three categories: body status, blood tests and indices, as shown in Fig. 2. The AUC, as an indicator of the power of the parameter to predict S-1 adjuvant discontinuation within 6 months, was analyzed for each of the 29 parameters in the discovery cohort. Age demonstrated the highest AUC (0.680) among the body status category. In the blood tests category, preoperative urea nitrogen (UN) exhibited the highest AUC (0.597). The ALBI had the highest AUC (0.613) in the indices category. Accordingly, three parameters, age, preoperative UN and preoperative ALBI, were selected for further evaluation.

Further analysis of age, preoperative UN and preoperative ALBI

In the discovery cohort, the optimal cutoff values of age, preoperative UN and preoperative ALBI for predicting the discontinuation of S-1 adjuvant therapy within 6 months were determined to be 64 years, 15.2 mg/dl and − 0.265, respectively. When stratified by these cutoff values, there were statistically significant differences in time to treatment discontinuation between the patient groups for each of the three variables (Fig. 3). Reflecting these findings, the univariate analysis to evaluate risk factors for the discontinuation of S-1 adjuvant therapy within 6 months revealed that age ≥ 64 years, preoperative UN ≥ 15.2 mg/dl and preoperative ALBI ≥ − 0.265 were significant risk factors (Table 2). Moreover, the multivariate analysis identified those four parameters as independent risk factors for the discontinuation of S-1 adjuvant therapy within 6 months (Table 2).

Risk scoring scale for S-1 adjuvant therapy discontinuation

A scoring scale for the prediction of S-1 adjuvant therapy discontinuation within 6 months was developed to enhance the clinical utility of the diagnostic factors identified in the discovery cohort. In accordance with the ORs of the factors in the multivariate analysis, individual scores were

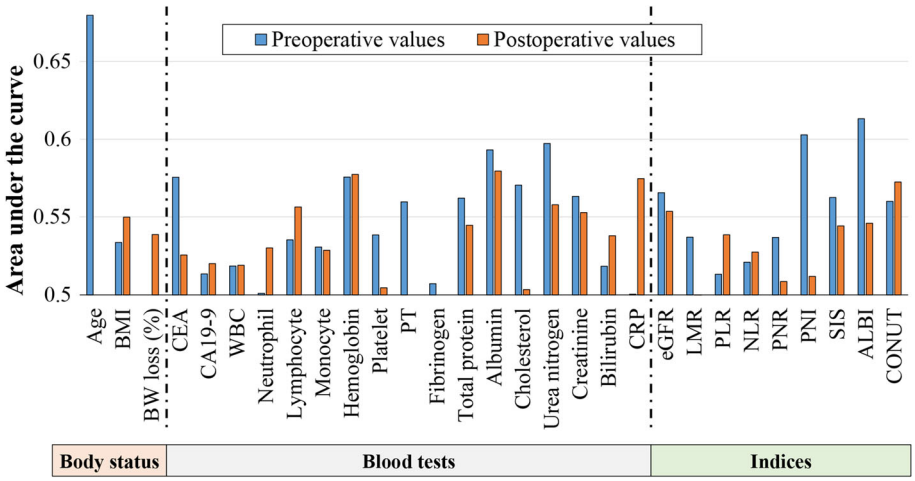

Fig. 2 Comparison of the predictive value of candidate parameters

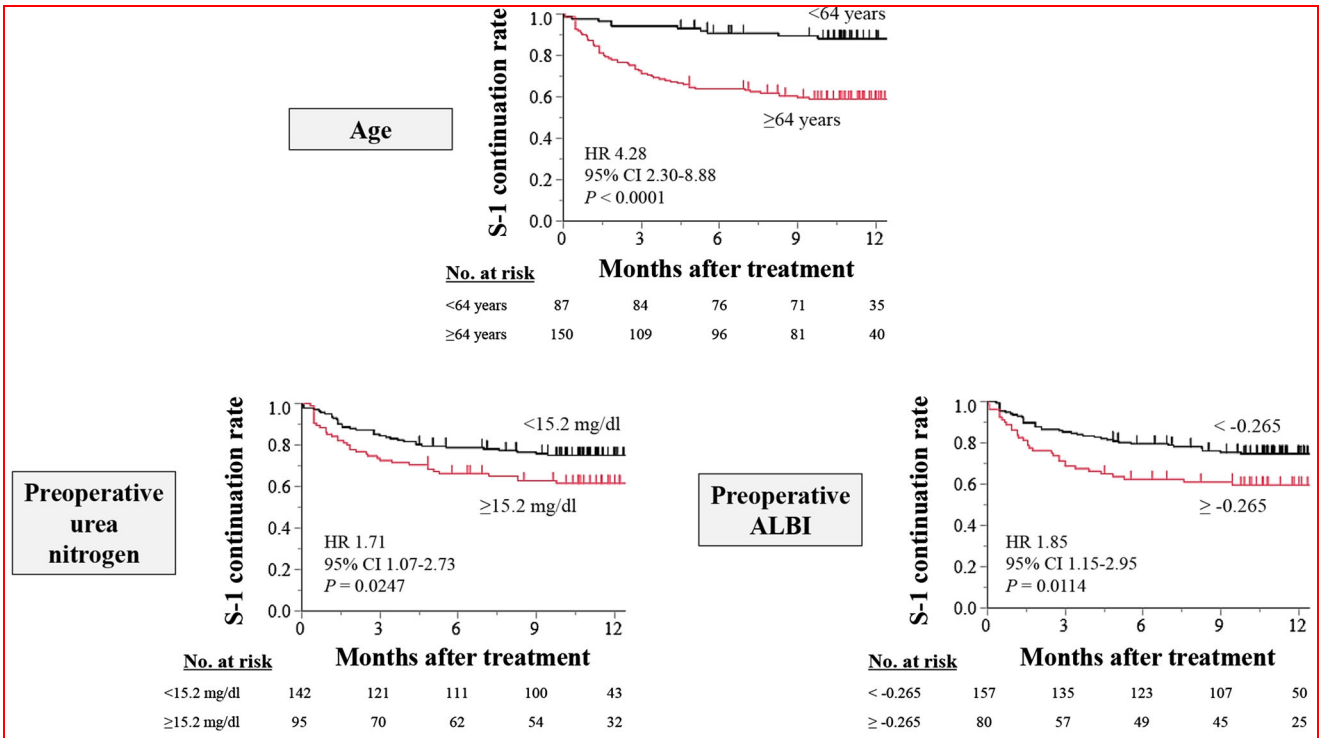

Fig. 3 Kaplan–Meier curves for S-1 continuation rate according to age, preoperative urea nitrogen (UN) and preoperative albumin-to-bilirubin index (ALBI). *HR* hazard ratio, *CI* confidence interval

allocated to each parameter as follows: a score of 4 for age ≥ 64 years and a score of 2 for preoperative UN ≥ 15.2 mg/dl and preoperative ALBI ≥ −0.265. The total score demonstrated a high goodness of fit for the discontinuation of S-1 adjuvant therapy within 6 months (AUC = 0.728) and was greater than the individual AUCs of the four components (Fig. 4a). The time to treatment discontinuation of S-1 monotherapy decreased incrementally with the increase in the risk score, thereby supporting the clinical utility of the scoring scale as an accurate risk stratification method (Fig. 4b). In the validation cohort consisted of 118 patients, the time to treatment discontinuation of S-1 monotherapy was altered according to the risk score in consistent with results in the discovery cohort (Fig. 4c).

Table 2 Potential risk factors for the discontinuation of S-1 adjuvant therapy in the discovery cohort

Variables		Univariate			Multivariate		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Age	≥64	5.55	2.50–12.4	< 0.0001	4.91	2.18–11.1	0.0001
Sex	Male	1.62	0.88–2.98	0.1182			
Preoperative symptoms	Present	1.53	0.85–2.76	0.1514			
Preoperative body mass index	≥22	0.81	0.45–1.45	0.4798			
Performance status	0	0.89	0.39–2.05	0.7858			
Cardiopulmonary comorbidities	Present	1.34	0.59–3.00	0.4823			
Cerebrovascular disease	Present	2.54	0.31–21.1	0.3875			
Diabetes mellitus	Present	1.51	0.70–3.24	0.2899			
Preoperative blood urea nitrogen	≥15.2 mg/dl	1.90	1.06–3.41	0.0323	1.97	1.04–3.74	0.0384
Preoperative albumin–bilirubin	≥ −0.265	2.34	1.29–4.26	0.0051	2.45	1.28–4.69	0.0067
Tumor location	Lower third	0.76	0.42–1.39	0.3819			
Multifocal lesions	Present	2.21	0.48–10.2	0.3088			
Tumor size	≥50 mm	1.37	0.76–2.46	0.2928			
Type of gastrectomy	Total	1.28	0.71–2.32	0.4075			
Surgical approach	Open	1.00	0.38–2.67	0.9933			
Splenectomy	Performed	1.03	0.50–2.15	0.9316			
Intraoperative transfusion	Performed	1.07	0.33–3.44	0.9129			
Tumor differentiation	Undifferentiated	1.07	0.60–1.91	0.8282			
Pathological stage	III	1.01	0.56–1.82	0.9837			
Postoperative complications[a]	Present	1.12	0.58–2.16	0.7247			

OR odds ratio, *CI* confidence interval

[a]Grade II–IV by the Clavien–Dindo classification

Discussion

Currently, limited information is available on the optimal management of S-1 adjuvant therapy in patients with gastric cancer. Using a large multicenter dataset, we explored predictive factors of S-1 discontinuation and found that age, preoperative UN and preoperative ALBI were independent risk factors for S-1 discontinuation. In addition, the risk score scale integrating the three parameters hierarchically stratified the risk levels of the patients in both the discovery and validation cohorts.

The ACTS-GC study successfully demonstrated the survival benefit of postoperative adjuvant S-1 monotherapy, but 34.2% of patients failed to continue S-1 for 12 months, and 46.5% of patients required a dose reduction from the recommended regimens due to adverse effects [7]. Aoyama et al. reported that the 6-month continuation rate was 72.9% in patients with CCr > 60 ml/min and 40.0% in patients with CCr < 60 ml/min [13]. In another study, it was reported that the 6-month continuation rate was 66.4% in patients with body weight loss < 15% and 36.4% in patients with body weight loss > 15% [12]. The 6-month continuation rate in the present study was 74.1% and was relatively high compared to those reports. We speculate that physicians have become accustomed to the management of S-1 (dose control and treatment of adverse effects) after the standardization of S-1 adjuvant therapy. Nevertheless, there is a room for further improvement in drug compliance as shown in the fact that the S-1 continuation rate in the high-risk patient group was quite low. Predictors with superior performance can increase the probability of supporting patients at a high risk of treatment discontinuation intensively.

In the present study, we exercised ingenuity in exploring predictors by cross-sectionally analyzing a total of 29 parameters comprising both preoperative and postoperative values. Age, preoperative UN and preoperative ALBI were identified as independent risk factors for S-1 discontinuation. Tsushima et al. [25] analyzed patients with metastatic gastric cancer to evaluate the toxicity of S-1 monotherapy and found that an advanced age corelated to a greater incidence of severe toxicity. Elderly patients frequently have age-related physiological problems and comorbidities [26–28]. S-1 was developed as an oral fluoropyrimidine containing tegafur, potassium oxonate and 5-chloro-2,4-dihydropyrimidine (CDHP) [29]. CDHP has an inhibitory effect of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme for the degradation of

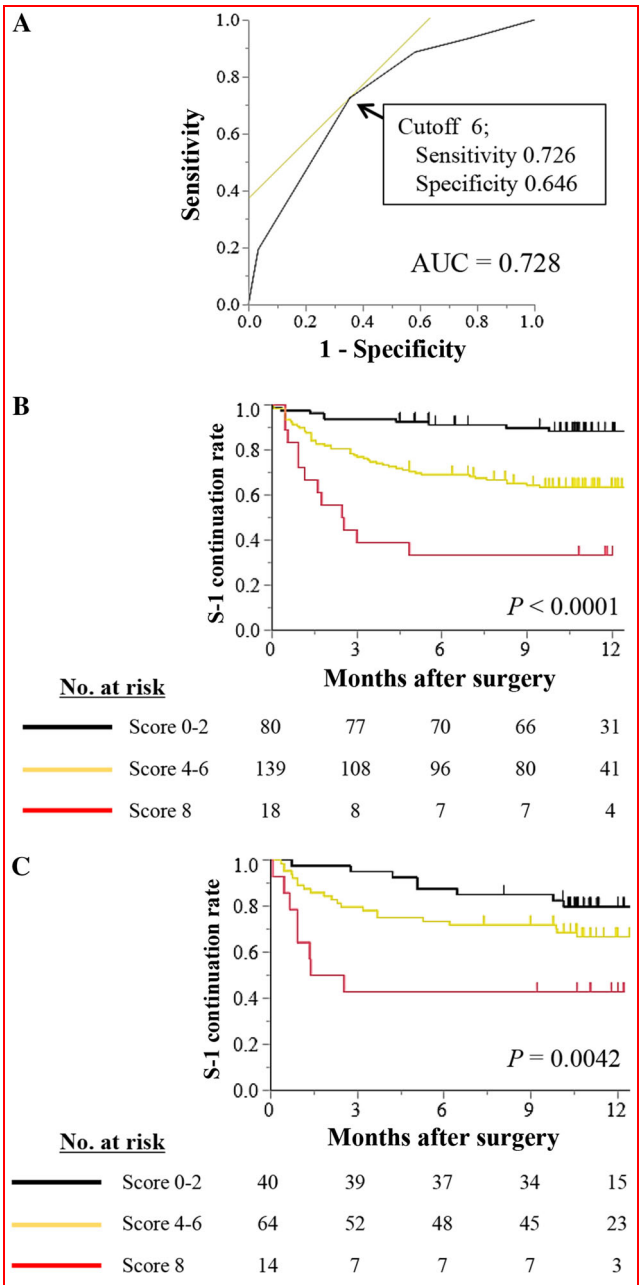

Fig. 4 Performance of the risk score scale. **a** Receiver operating characteristic curve analysis of S-1 adjuvant therapy discontinuation within 6 months in the discovery cohort. **b** S-1 continuation rate of patients with a risk score of 0–2, 4–6 and 8 in the discovery cohort. **c** S-1 continuation rate of patients with a risk score of 0–2, 4–6 and 8 in the validation cohort

fluorouracil [30]. Renal dysfunction can reduce a clearance of CDHP and increase a blood concentration of fluorouracil due to decreased DPD activity [29]. DPD inhibition occurs in liver cells, and liver dysfunction results in poor fluorouracil degradation. Because blood UN is an indicator of renal function and ALBI is an indicator of liver function, increased UN and ALBI are linked to poor fluorouracil degradation, thus provoking more frequent adverse events and S-1 discontinuation [23, 31]. For individuals with increased UN and ALBI, reduction in the initial S-1 dose might be justified to improve S-1 continuation rates in light of FU concentration rise in blood.

Most studies of predictive markers for S-1 tolerability have evaluated the performance of a single or a few parameters [12, 13, 32–34]. In the present study, a score scale for estimating the risk of S-1 adjuvant therapy discontinuation within 6 months was developed by integrating the three independent risk factors identified from different categories. In addition, the score was calculated with weighted scores based on the OR for S-1 discontinuation of each constituent. The patient's condition can be evaluated more precisely by comprehensively combining analyses of various factors from different categories, and the score scale proposed in the current study is just such as example. Precise risk stratification will help clinicians and community pharmacists identify patients whose drug compliance might be improved through more meticulous management through modification of dosage and treatment schedules as well as prescription of drugs that may ameliorate adverse reactions. For example, de-escalation of initial S-1 dosage (e.g., 100 mg, 80 mg or 50 mg/day) based on our risk scale might be justified to prevent early discontinuation of S-1 due to adverse effects. However, the possibility of diminished survival benefit by dose modification of S-1 adjuvant should be considered and further investigation addressing to this issue is desirable.

There are several limitations in the study. First, this was a retrospective study. Second, patients analyzed may already have been highly selected, given that as many as 477 of 1172 patients with stage II/III cancer in the current series did not receive the adjuvant chemotherapy. Third, the lack of data on body composition limited the discussion. Finally, detailed information on dose reduction and adverse effect management is missing.

Conclusion

Our results indicate that age, preoperative UN and preoperative ALBI, as well as a score scale consisting of these three parameters, may serve as useful predictors for the treatment discontinuation of adjuvant S-1 monotherapy within 6 months in patients with stage II to III gastric cancer.

Compliance with ethical standards

Conflict of interest The authors do not have any commercial interest or sources of financial or material support to report.

Human and animal rights This study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and with the ethical standards of the institutional committee

References

1. Van Cutsem E, Sagaert X, Topal B et al (2016) Gastric cancer. Lancet 388:2654–2664
2. Kanda M, Kobayashi D, Tanaka C et al (2016) Adverse prognostic impact of perioperative allogeneic transfusion on patients with stage II/III gastric cancer. Gastric Cancer 19:255–263
3. Shen L, Shan YS, Hu HM et al (2013) Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol 14:e535–e547
4. Ychou M, Boige V, Pignon JP et al (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29:1715–1721
5. Ashraf N, Hoffe S, Kim R (2013) Adjuvant treatment for gastric cancer: chemotherapy versus radiation. Oncologist 18:1013–1021
6. Kanda M, Kodera Y, Sakamoto J (2015) Updated evidence on adjuvant treatments for gastric cancer. Expert Rev Gastroenterol Hepatol 9:1–12
7. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820
8. Yoshikawa T, Terashima M, Mizusawa J et al (2017) A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1). Ann Oncol 28:626
9. Tanaka H, Kanda M, Morita S et al (2017) Randomized phase II study of daily and alternate-day administration of S-1 for advanced gastric cancer (JFMC43-1003). Int J Clin Oncol 22:1052–1059
10. Kanda M, Shimizu D, Tanaka H et al (2018) Significance of SYT8 for the detection, prediction, and treatment of peritoneal metastasis from gastric cancer. Ann Surg 267:495–503
11. Schuhmacher C, Gretschel S, Lordick F et al (2010) Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 28:5210–5218
12. Aoyama T, Yoshikawa T, Shirai J et al (2013) Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. Ann Surg Oncol 20:2000–2006
13. Aoyama T, Yoshikawa T, Hayashi T et al (2013) Risk factors for 6-month continuation of S-1 adjuvant chemotherapy for gastric cancer. Gastric Cancer 16:133–139
14. Ito Y, Kanda M, Ito S et al (2018) Intraoperative blood loss is associated with shortened postoperative survival of patients with stage II/III gastric cancer: analysis of a multi-institutional dataset. World J Surg 43:870–877
15. Liu JY, Peng CW, Yang XJ et al (2018) The prognosis role of AJCC/UICC 8(th) edition staging system in gastric cancer, a retrospective analysis. Am J Transl Res 10:292–303
16. Japanese Gastric Cancer Association (2014) Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 20:1–19
17. Kanda M, Mizuno A, Fujii T et al (2016) Tumor infiltrative pattern predicts sites of recurrence after curative gastrectomy for stages 2 and 3 gastric cancer. Ann Surg Oncol 23:1934–1940
18. Kanda M, Murotani K, Kobayashi D et al (2015) Postoperative adjuvant chemotherapy with S-1 alters recurrence patterns and prognostic factors among patients with stage II/III gastric cancer: a propensity score matching analysis. Surgery 158:1573–1580
19. Sasako M, Sakuramoto S, Katai H et al (2011) Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 29:4387–4393
20. Kanda M, Tanaka C, Kobayashi D et al (2017) Proposal of the coagulation score as a predictor for short-term and long-term outcomes of patients with resectable gastric cancer. Ann Surg Oncol 24:502–509
21. Inaoka K, Kanda M, Uda H et al (2017) Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer. World J Gastroenterol 23:2519–2526
22. Tanaka Y, Kanda M, Tanaka C et al (2017) Usefulness of preoperative estimated glomerular filtration rate to predict complications after curative gastrectomy in patients with clinical T2-4 gastric cancer. Gastric Cancer 20:736–743
23. Kanda M, Tanaka C, Kobayashi D et al (2018) Preoperative albumin–bilirubin grade predicts recurrences after radical gastrectomy in patients with pT2-4 gastric cancer. World J Surg 42:773–781
24. Kanda M, Mizuno A, Tanaka C et al (2016) Nutritional predictors for postoperative short-term and long-term outcomes of patients with gastric cancer. Medicine (Baltimore) 95:e3781
25. Tsushima T, Hironaka S, Boku N et al (2010) Safety and efficacy of S-1 monotherapy in elderly patients with advanced gastric cancer. Gastric Cancer 13:245–250
26. Jeong JW, Kwon IG, Son YG et al (2016) Could adjuvant chemotherapy after surgery benefit elderly patients with advanced gastric cancer? J Gastric Cancer 16:260–265
27. Hikage M, Tokunaga M, Makuuchi R et al (2018) Surgical outcomes after gastrectomy in very elderly patients with gastric cancer. Surg Today 48:773–782
28. Tanahashi T, Yoshida K, Yamaguchi K et al (2018) Questionnaire survey on adjuvant chemotherapy for elderly patients after gastrectomy indicates their vulnelabilities. Gastric Cancer 22:130–137
29. Peters GJ, Noordhuis P, Van Kuilenburg AB et al (2003) Pharmacokinetics of S-1, an oral formulation of ftorafur, oxonic acid and 5-chloro-2,4-dihydroxypyridine (molar ratio 1:0.4:1) in patients with solid tumors. Cancer Chemother Pharmacol 52:1–12
30. Ikeda M, Furukawa H, Imamura H et al (2002) Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor agent in animal model and in patients with impaired renal function. Cancer Chemother Pharmacol 50:25–32
31. Johnson PJ, Berhane S, Kagebayashi C et al (2015) Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 33:550–558
32. Yamanaka T, Matsumoto S, Teramukai S et al (2007) Analysis of risk factors for severe adverse effects of oral 5-fluorouracil S-1 in patients with advanced gastric cancer. Gastric Cancer 10:129–134
33. Tsujimoto H, Horiguchi H, Hiraki S et al (2012) Tolerability of adjuvant chemotherapy with S-1 after curative resection in patients with stage II/III gastric cancer. Oncol Lett 4:1135–1139

34. Yang J, Zhou Y, Min K et al (2014) S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer: a meta-analysis. World J Gastroenterol 20:11886–11893