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ORIGINAL ARTICLE

E-PASS scoring system serves as a predictor of short- and long-term outcomes in gastric cancer surgery

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Abstract

Purposes This study aimed to evaluate the estimation of the physiological ability and surgical stress (E-PASS) scoring system for predicting the short- and long-term outcomes in gastric cancer (GC) surgery.

Methods We analyzed a multi-institutional dataset to study patients who underwent gastrectomy with a curative intent between 2010 and 2014. This study evaluated the associations between the optimal E-PASS score cutoff value and the following outcomes: (1) the incidence of postoperative complications in stage I–III GC patients and (2) the prognosis in stage II–III GC patients.

Results A total of 2495 GC patients were included. A cutoff value of 0.419 was determined using the ROC curve analysis. Postoperative complications were observed more frequently in the E-PASS-high group than that in the E-PASS-low group (30% vs. 17%, $p<0.0001$). Among pStage II–III GC patients ($n=1009$), the overall survival time of the E-PASS-high group was significantly shorter than that of the E-PASS-low group (hazard ratio 2.08; 95% confidence interval 1.64–2.65; $p<0.0001$). A forest plot revealed that E-PASS-high was associated with a greater prognostic factor for overall survival in most subgroups.

Conclusions The E-PASS scoring system may therefore be a useful predictor of the short- and long-term outcomes in patients with GC who have undergone radical gastrectomy.

Keywords Postoperative complication · Prognosis · Gastrectomy · Risk assessment

Introduction

Despite advances in surgical and anesthetic techniques, surgical devices, and perioperative management, the incidence of postoperative complications following gastrectomy with systemic lymph node dissection for gastric cancer (GC) patients remains a major concern. The recently reported overall postoperative complication rates after gastrectomy for GC are 17.4–23% in East Asia and 13.6–46% in Western countries [1–4]. Predicting the

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occurrence of clinically relevant postoperative complications is useful to prevent complications by encouraging personalized postoperative care, precautionary measures, and early interventions, and also helps minimize medical costs.

In order to accurately predict postoperative complications, it is necessary to consider the patient's physiological capacity and the degree of surgical stress. The currently available factors for predicting postoperative complications after gastrectomy include the operation time, blood transfusions, intraoperative blood loss, reconstructive methods, and various preoperative laboratory values reflecting the patient's physiological capacity [5–8]. Patients with poor physiological conditions are more sensitive to surgical stress than those with good physiological conditions. Postoperative complications lead to prolonged hospitalization, an impaired quality of life, and delayed adjuvant treatment; thus, resulting in a poor prognosis [3, 9]. The establishment of objective prognostic markers is becoming increasingly important for effective patient management [8, 10, 11].

We utilized the physiologic ability and surgical stress (E-PASS) scoring system, which takes into consideration the patient's preoperative physiological capacity and the degree of surgical stress. This scale has attracted attention not only as a predictor of postoperative complications, but also as a prognostic indicator for cancer patients [12–18]. However, the past studies are limited as they most were conducted before the popularization of laparoscopic surgery, historical changes in surgical treatment, and were single institution studies with small sample size. Thus, validating their findings with a larger modern cohort is mandatory.

This study aimed to analyze a multicenter dataset to evaluate the value of the E-PASS scoring system for predicting the short- and long-term outcomes in GC patients who underwent gastrectomy.

Patients and methods

Ethics

All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Written informed consent for surgery and the use of the patients' clinical data were obtained from patients as required by the Institutional Review Board of each participating institution. We used an opt-out recruitment strategy in accordance with the Japanese government policy because the study exclusively analyzed retrospective clinical data without any intervention by the investigators.

Patient selection

We retrospectively reviewed the clinical data of 3575 patients who underwent gastrectomy for GC between January 2010 and December 2014, acquired from nine institutions. We retrieved medical records to identify patients eligible for analysis based on the criteria that included no preoperative treatment and an R0 resection. We excluded patients who underwent concurrent surgical procedures except for cholecystectomy, thoraco-abdominal approach, extended surgery (e.g., pancreaticoduodenectomy and Appleby's procedure), or modified surgery without systemic lymphadenectomy (Fig. 1). We also excluded patients with missing pathological findings or insufficient data to calculate the E-PASS score.

Surgery and postoperative management

The clinical and histopathological factors were determined according to the 15th edition of the Japanese Classification of Gastric Carcinoma [19]. Gastrectomy with proper systematic lymphadenectomy was performed in accordance with the Japanese Gastric Cancer Treatment Guidelines [20]. Postoperative chemotherapy with S-1 monotherapy has been recommended for all patients with pathological stages II/III, except T1 and T3N0 gastric cancer, unless contraindicated by the patient's condition [20]. Patient follow-up was performed in accordance with the Japanese Gastric Cancer Treatment Guidelines [20, 21]. We analyzed the data regarding postoperative complications occurring within 30 days following surgery—even of the patients treated in the outpatient clinics—in accordance with the Clavien–Dindo classification system [22, 23]. We considered the Clavien–Dindo grade ≥ II postoperative

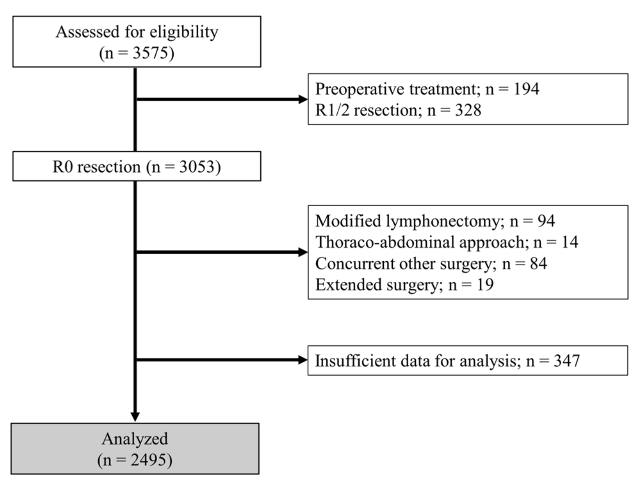

Fig. 1 Flow chart of patient enrolment

complications as clinically relevant. The adverse effects of postoperative adjuvant chemotherapy were excluded from the study.

E-PASS scoring systems

The physiological and operative variables for scoring the E-PASS were retrospectively collected. The preoperative risk score (PRS), surgical stress score (SSS), and comprehensive risk score (CRS) were calculated using Haga's equations for E-PASS, as shown below:

$$\begin{aligned}\text{PRS} = & -0.0686 + 0.00345X_1 + 0.323X_2 + 0.205X_3 \\ & + 0.153X_4 + 0.148X_5 + 0.0666X_6,\end{aligned}$$

wherein X_1 is the patient age; X_2 is the presence (1) or absence (0) of severe heart disease, X_3 is the presence (1) or absence (0) of severe pulmonary disease; X_4 is the presence (1) or absence (0) of diabetes mellitus, X_5 is the performance status index (0–4), and X_6 is the American Society of Anesthesiologists physiological status classification (1–5).

$$\text{SSS} = -0.342 + 0.0139X_1 + 0.0392X_2 + 0.352X_3,$$

wherein X_1 is blood loss/body weight (g/kg), X_2 is the operation time (h), and X_3 is the extent of skin incision (0, laparoscopic surgery; 1, laparotomy).

$$\text{CRS} = 0.052 + 0.58(\text{PRS}) + 0.83(\text{SSS}).$$

We calculated the E-PASS score and evaluated the association between CRS and the incidence of postoperative complications and prognosis.

Statistical analysis

The area under the curve (AUC) to predict postoperative complications was calculated using the receiver-operating characteristic (ROC) curve analysis. The optimal cutoff value was determined using the Youden index. Correlations between each group and qualitative variables were analyzed using either the Chi-squared test or Fisher's exact test for categorical variables, as appropriate, and the Mann–Whitney test for continuous variables. Survival rates were estimated using the Kaplan–Meier method, and the overall differences between survival curves were compared using the Cox proportional hazards model. We performed a multivariate analysis using a Cox proportional hazards model, after significant prognostic variables were defined using a univariate analysis. The data were analyzed using JMP version 15 software program (JMP, SAS Institute, Cary, NC, USA), and $p < 0.05$, indicated a significant difference.

Results

Patient characteristics and postoperative course

Based on the inclusion and exclusion criteria of the present study, 2495 patients were included in the final analysis (Fig. 1). The number of patients who underwent total gastrectomy including complete gastrectomy was 710 (28%), while 781 (31%) patients underwent laparoscopic surgery. Postoperative complications were observed in 578 patients (23%); and a total of 641 patients (26%) received postoperative adjuvant chemotherapy. The patients were followed up for a median of 62.3 months (range, 0.2–123 months).

Determination of the optimal E-PASS cutoff value

ROC curves were generated to evaluate the predictive value of E-PASS for postoperative complications (Fig. 2A). The optimal cutoff value of the CRS was 0.4179 for predicting overall postoperative complications (AUC, 0.609; sensitivity, 59.9%; specificity, 57.6%).

The AUC values categorized by postoperative complications were as follows: 0.579 for abdominal postoperative complications (cutoff value, 0.4179; sensitivity, 57.8%; specificity, 56.3%) and 0.676 for nonabdominal postoperative complications (cutoff value, 0.5050; sensitivity, 54.3%; specificity, 74.5%).

Comparing the predictive values for postoperative complications of different indicators

To evaluate the predictive value of E-PASS for postoperative complications, we compared AUC values among E-PASS, E-PASS constituents, and other indicators (Fig. 2B). The AUC values for overall postoperative complications of indicators are shown below in descending order: intraoperative blood loss (0.621), E-PASS (0.609), operation time (0.603). For the categorized complications, the AUC values of operation time (0.616) and intraoperative blood loss (0.611) were higher for abdominal postoperative complications than the E-PASS value (0.579). However, a higher AUC value of E-PASS (0.676) for nonabdominal postoperative complications was observed than that of both operation time (0.518) and intraoperative blood loss (0.612). These results indicated that the predictive value of E-PASS was superior to that of E-PASS constituents, and other indicators, as it predicted both abdominal and nonabdominal postoperative complications.

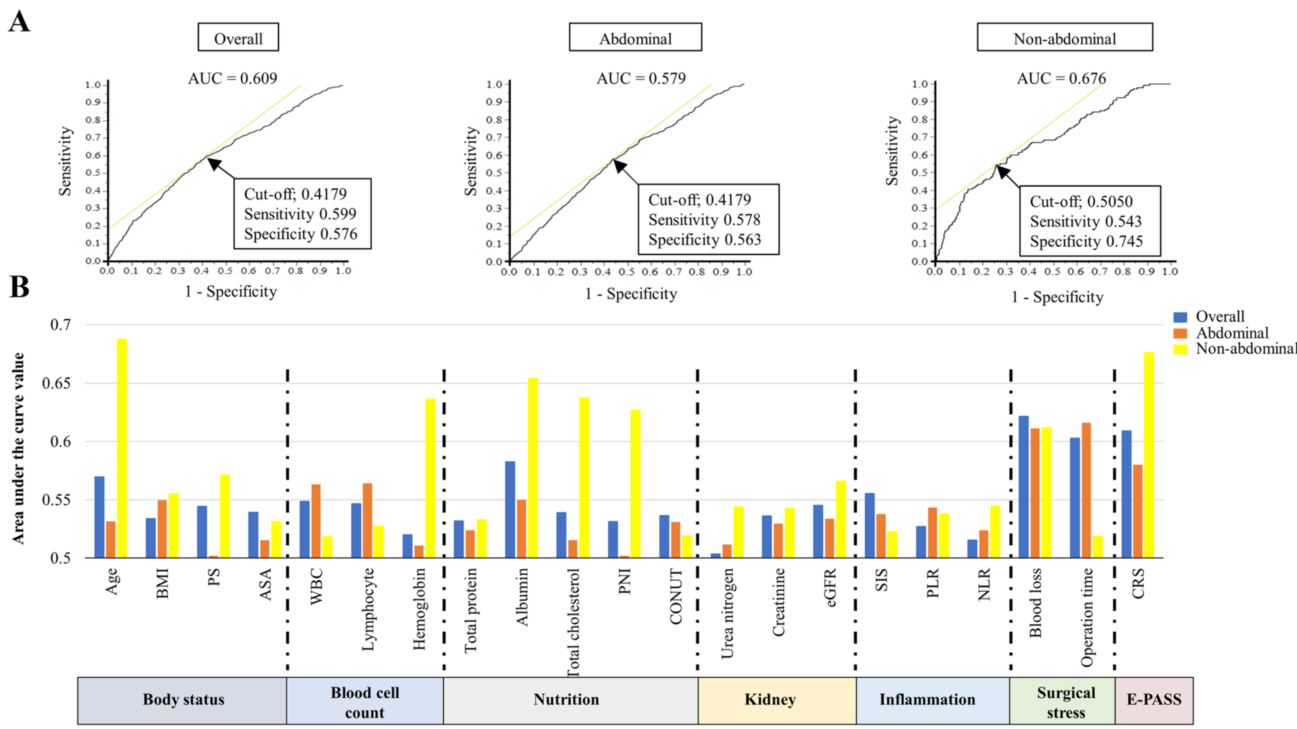

Fig. 2 **A** Receiver operating characteristic curve of the E-PASS as a predictive factor of overall-, abdominal-, and nonabdominal postoperative complications. The arrow indicates the optimal cutoff value. **B** Comparison of the area under the curve values of potential predictors

E-PASS and clinicopathological characteristics

Based on the optimal cutoff value of E-PASS, we classified 2495 patients into the E-PASS-low group (CRS < 0.4179, $n = 1335$) and the E-PASS-high group (CRS ≥ 0.4179, $n = 1160$). A comparison between the two groups revealed that E-PASS was significantly associated with certain clinicopathological characteristics. For example, when compared with patients in the E-PASS-low group, those in the E-PASS-high group were significantly older, had larger-sized tumors, and more advanced TNM stages (Table 1). We found a significant difference associated with the surgical approach, type of gastrectomy, degree of lymphadenectomy, operation time, and intraoperative blood loss.

E-PASS and postoperative complications

Postoperative complications were observed more frequently in the E-PASS-high group (17% vs. 30%, $p < 0.0001$) (Table 1). The incidence of grade ≥ III postoperative complications in the E-PASS-high group was significantly higher than that in the E-PASS-low group (7.2% vs. 14.1%, $p < 0.0001$).

The breakdown of the incidence of each postoperative complication is summarized in Supplemental Table 1. Among abdominal postoperative complications, the incidence of pancreatic fluid leakage in the E-PASS-high group was significantly higher than that in the E-PASS-low group (5.3% vs. 1.7%, $p < 0.0001$). Among nonabdominal postoperative complications, we found a significant difference in pneumonia (E-PASS-low, 25 patients [1.9%]; E-PASS-high, 58 patients [5.0%]; $p < 0.0001$).

We performed subgroup analyses to evaluate the association between E-PASS and the incidence of overall postoperative complications. The 2495 patients were subdivided according to age (< 70 or ≥ 70 years), surgical approach (laparoscopy or laparotomy), operative procedure (partial or total gastrectomy), and clinical disease stage. Our results showed that patients with a high E-PASS score experienced a significantly higher incidence of postoperative complications in all subgroups (Fig. 3).

E-PASS and prognosis

Because there was a large bias in the TNM stage between the two groups, we compared the prognosis of patients with pStage II–III GC ($n = 1009$). The overall survival (OS) time of the E-PASS-high group patients was significantly shorter than of those in the E-PASS-low group (hazard ratio [HR], 2.08; 95% confidence interval [CI] 1.64–2.65; $p < 0.0001$; Fig. 4A). The E-PASS-high group

Table 1 Comparison of the clinicopathological factors between the two groups

	E-PASS-low (n = 1335)	E-PASS-high (n = 1160)	p value
Clinicopathological factors			
Sex, (male/female)	882/453	908/252	< 0.0001
Age, (years), mean ± SD	64.8 ± 10.6	71.1 ± 9.3	< 0.0001
BMI, (kg/m^2), mean ± SD	22.1 ± 3.0	22.4 ± 3.5	0.0108
Tumor location, (upper/middle/lower/entire/remnant)	188/707/428/8/4	313/381/404/37/25	< 0.0001
Tumor size (mm), mean ± SD	32 ± 20	46 ± 27	< 0.0001
pT category, (1/2/3/4)	926/156/124/129	430/153/271/306	< 0.0001
pN category, (0/1/2/3)	1007/163/87/78	573/221/184/182	< 0.0001
Intraoperative data			
Approach, (laparotomy/laparoscopy)	572/763	1142/18	< 0.0001
Surgical procedure, (TG/PG/DG/PPG)	232/41/975/87	479/29/647/5	< 0.0001
Lymphadenectomy, (D1, D1+/≥ D2)	870/465	464/696	< 0.0001
Operative time (min), mean ± SD	252 ± 70	270 ± 72	< 0.0001
Intraoperative blood loss (ml), mean ± SD	121 ± 120	457 ± 422	< 0.0001
Resected lymph nodes, mean ± SD	33 ± 14	34 ± 16	0.6446
Postoperative course			
Hospital stay after surgery (days), mean ± SD	14 ± 13	21 ± 22	< 0.0001
Postoperative complications	232 (17%)	346 (30%)	< 0.0001
Clavien–Dindo classification (II/IIIa/IIIb/IVa/IVb)	136/65/24//5/1	180/116/26/12/3	< 0.0001
Mortality	1	9	0.0077
E-PASS score			
Preoperative risk score (PRS)	0.2990 ± 0.1170	0.4968 ± 0.2162	< 0.0001
Surgical risk score (SSS)	0.0011 ± 0.1704	0.2735 ± 0.1265	< 0.0001
Comprehensive risk score (CRS)	0.2254 ± 0.1390	0.5671 ± 0.1329	< 0.0001

SD standard deviation, *BMI* body mass index, *TG* total gastrectomy, *PG* proximal gastrectomy, *DG* distal gastrectomy, *PPG* pylorus-preserving gastrectomy

also had a significantly shorter disease-free survival (DFS) time (HR, 1.84; 95% CI 1.42–2.38; $p < 0.0001$; Fig. 4B).

A multivariate analysis revealed the following predictive factors to be significant for OS: total gastrectomy, pStage III, postoperative chemotherapy, and E-PASS (E-PASS-high: HR, 1.58; 95% CI 1.22–2.03; $p = 0.0004$; Table 2).

Subgroup analyses to evaluate the predictive value of the E-PASS score on OS are shown in Fig. 5. No interaction was observed between any of the subgroups.

The comparisons made based on the TNM stage are shown in Supplementary Figs. 1 and 2. The E-PASS-high group had a significantly shorter OS time when compared with the E-PASS-low group, associated with pStage I (HR, 2.94; 95% CI 2.16–4.00; $p < 0.0001$), pStage II (HR, 2.45; 95% CI 1.62–3.72; $p < 0.0001$), and pStage III (HR, 1.68; 95% CI 1.25–2.27; $p = 0.0006$). Regarding DFS, this trend was the same, the E-PASS-high group had a significantly shorter DFS time as compared to the E-PASS-low group (pStage I: HR, 2.81; 95% CI 2.09–3.80; $p < 0.0090$; pStage II: HR, 2.52; 95% CI 1.69–3.77; $p < 0.0001$; pStage III: HR, 1.69; 95% CI 1.28–2.21; $p = 0.0002$).

Discussion

The E-PASS scoring system was proposed by Haga et al. in 1999 as a predictive scoring system for postoperative morbidity and mortality in patients undergoing elective gastrointestinal surgery [17]. Recently, several studies have shown reproducible results suggesting that E-PASS scores can predict long-term outcomes in patients with cancer [14–16, 24]. We herein analyzed a multicenter dataset with a larger, modern cohort and found that the E-PASS score served as a predictor of postoperative complications in stage I–III GC patients, and a predictor of long-term postoperative survival in stage II–III GC patients.

A previous study suggested that the E-PASS score was associated with anastomotic leakage [18]. Consistent with this report, our data showed that the incidence of anastomotic leakage in the E-PASS-high group was higher than that in the E-PASS-low group (4.5% vs. 3.2%, $p = 0.1005$), although the difference was not significant. Furthermore, we found that the incidence of pancreatic fluid leakage and pneumonia was observed more frequently in the E-PASS-high group. To the best of our knowledge, this is the first

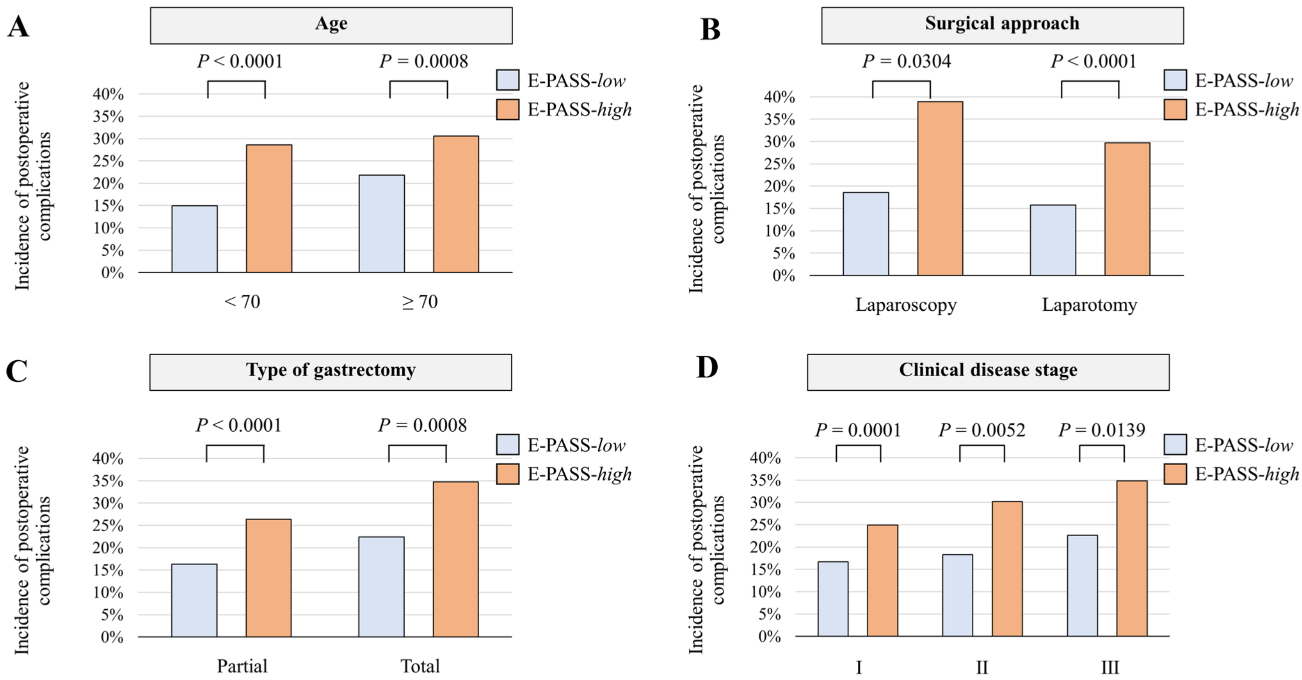

Fig. 3 Subgroup analyses of the impact of the E-PASS on postoperative complications. **A** Age. **B** Surgical approach. **C** Type of gastrectomy. **D** Clinical disease stage

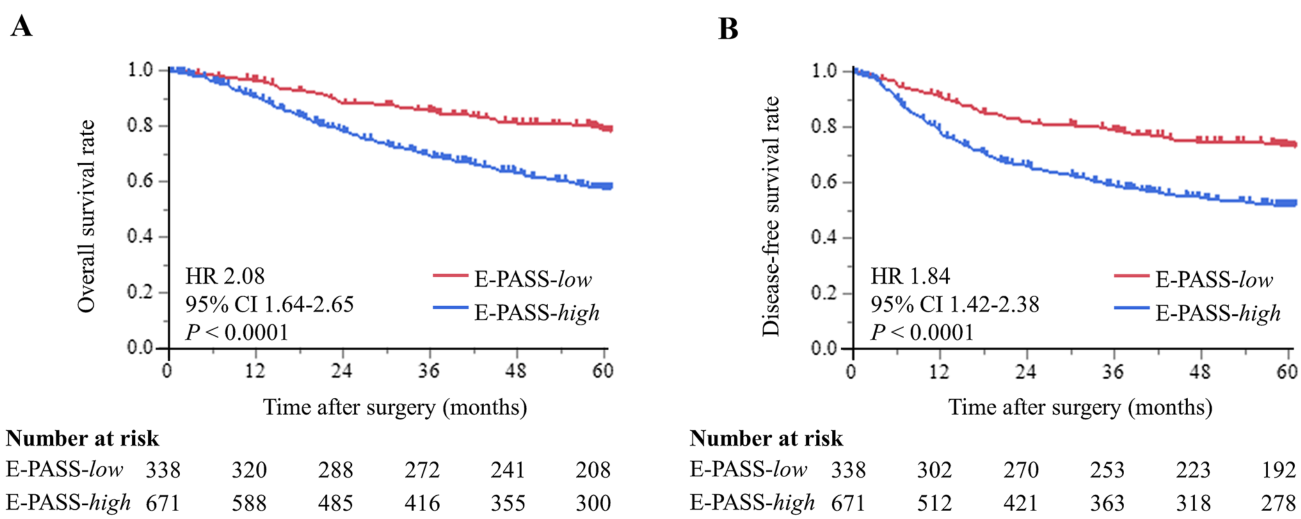

Fig. 4 **A** Overall and **B** disease-free survival curves after curative gastrectomy in patients with pStage II–III gastric cancer based on the E-PASS score

study to determine the correlations between E-PASS and either pancreatic fluid leakage or E-PASS and pneumonia. Previous studies have reported that the predictors of pancreatic fluid leakage after gastrectomy are age, operation time, body mass index, total gastrectomy, splenectomy, and a high drain amylase content [25]. The predictors of pneumonia after gastrectomy include age, diabetes mellitus, preoperative respiratory dysfunction, intraoperative blood loss, preoperative malnutrition, and inflammatory status [26, 27]. Many of these factors are common with E-PASS constituents. Therefore, E-PASS is strongly associated with the incidence of these postoperative complications. Our results therefore indicate that the E-PASS score is useful not only as a comprehensive scale for predicting overall postoperative complications but also as a disease-specific predictor.

Table 2 The prognostic factors of overall survival for 1009 patients with pStage II or III gastric cancer

Variables	Univariate		*p* value	Multivariable		*p* value
	OR	95% CI		OR	95% CI	
Sex						
Male	1.38	1.08–1.74	0.0086	1.15	0.90–1.47	0.2595
Age (years)						
≥ 70	1.93	1.57–2.38	< 0.0001			
BMI						
≥ 25	0.76	0.56–1.03	0.0728			
ASA-PS						
≥ 3	1.53	1.24–1.87	< 0.0001			
Tumor location						
Lower third	0.85	0.68–1.06	0.1418			
Tumor size						
≥ 50 mm	1.50	1.22–1.85	0.0001	1.11	0.89–1.37	0.3610
Surgical approach						
Laparotomy	1.98	1.25–3.14	0.0038			
Operative procedure						
Total gastrectomy	1.75	1.43–2.14	< 0.0001	1.48	1.20–1.82	0.0002
Intraoperative blood loss (ml)						
≥ 200	1.27	1.03–1.58	0.0286			
Operation time (min)						
≥ 240	1.17	0.95–1.45	0.1354			
pStage						
III	2.20	1.77–2.73	< 0.0001	2.26	1.79–2.85	< 0.0001
Postoperative complications*						
Present	1.29	1.04–1.60	0.0208	1.00	0.80–1.26	0.9651
Postoperative chemotherapy						
Performed	0.64	0.52–0.78	< 0.0001	0.53	0.43–0.66	< 0.0001
E-PASS						
CRS ≥ 0.4179	2.08	1.64–2.65	< 0.0001	1.58	1.22–2.03	0.0004

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *ASA-PS* American society of anesthesiologists physical status, *E-PASS* Estimation of Physiologic Ability and Surgical Stress, *CRS* comprehensive risk score

*According to the Clavien–Dindo classification

In this study, we found that E-PASS predicted the long-term survival of stage II–III GC patients who underwent gastrectomy. The E-PASS score, that is, CRS, comprises the PRS and SSS. The PRS includes age, severe heart disease, severe pulmonary disease, diabetes mellitus, performance status, and the American Society of Anesthesiologists physiological status classification. Therefore, it is reasonable to state that PRS is related to postoperative OS following surgery. Furthermore, our results indicate that CRS is related to the DFS time after gastrectomy. This may be explained using the close association of CRS with significantly advanced disease stages. The SSS is higher in patients with advanced GC than in those with early-stage GC because the surgery requires a longer operation time and causes greater intraoperative blood loss for advanced GC patients than for those with early GC. In addition, laparoscopic gastrectomy is performed more frequently to treat early GC. Most cases of laparoscopic gastrectomy were classified in the E-PASS-low group because the SSS for laparoscopic gastrectomy was lower owing to less intraoperative blood loss and a smaller skin incision despite the longer operation time. To overcome these confounding factors, we conducted a subgroup analysis and a multivariate analysis. Our results showed that the E-PASS was an independent prognostic factor throughout the disease stages, indicating that the association between the E-PASS and prognosis is not merely the result of advanced disease stages.

This method was found to be useful for predicting postoperative complications in laparoscopic surgery; however; long-term survival could not be fully evaluated owing to the small number of laparoscopic gastrectomies performed for advanced GC cases. In the future, if laparoscopic surgery

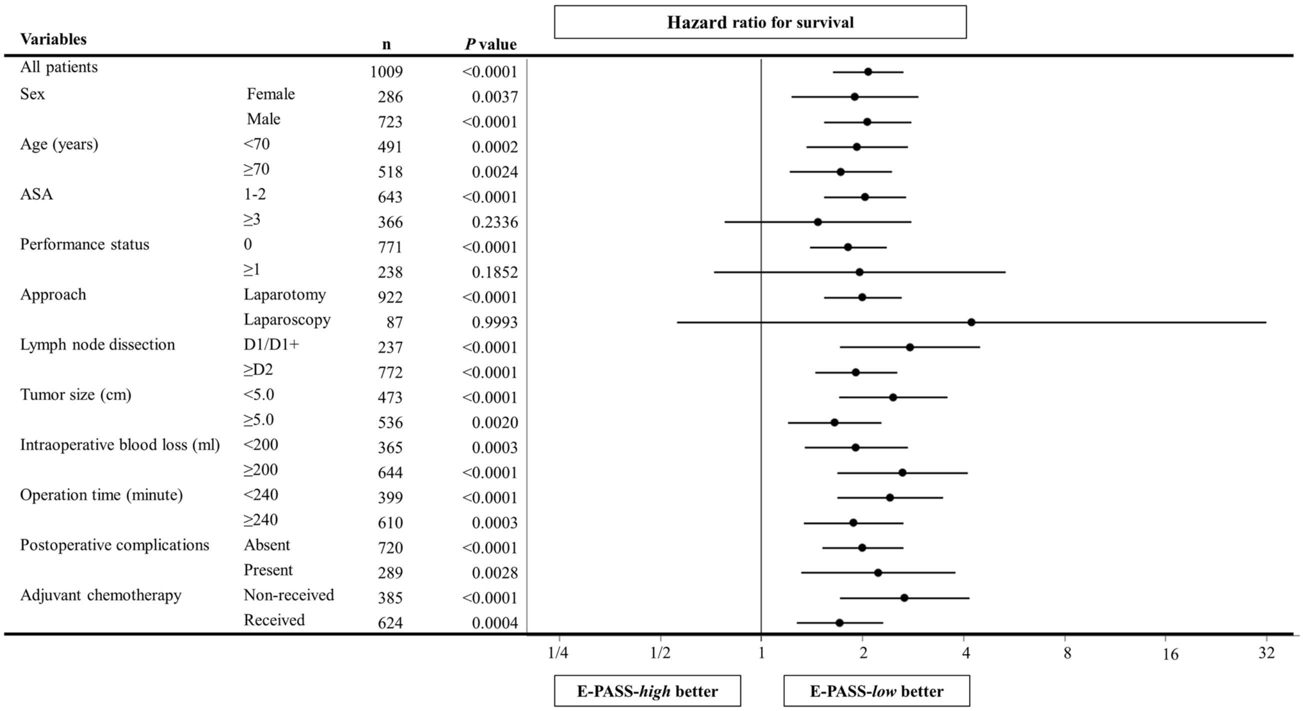

Fig. 5 A forest plot evaluating the impact of the E-PASS score on overall survival in patients with pStage II–III gastric cancer

is widely performed in patients with advanced GC, then it will be necessary to examine whether these results are reproducible.

The E-PASS is a comprehensive scale; therefore, it does not depend significantly on one factor. We performed a subgroup analysis and confirmed that it was useful beyond the surgical approach, procedure, age, and disease stage. The first advantage of E-PASS is that it provides the opportunity for more accurate informed consent, planning appropriate postoperative management, and safe discharge. Its usefulness may be further exploited in combination with the enhanced recovery after surgery (ERAS) program. Another advantage is the detailed postoperative follow-up and interventions for a patient with a high E-PASS score who is at higher risk of a shorter postoperative survival. Vulnerable patients may be selected based on the E-PASS score, which could potentially be an allocation criterion for clinical trials for nutritional support and the development of postoperative chemotherapy regimens.

Our study is associated with several limitations, the first being its retrospective nature. Research on independent prospective cohorts is required to validate our findings for a definitive conclusion regarding the clinical relevance of the E-PASS score and its optimal cut-off for this setting. However, our cutoff value of E-PASS for postoperative complications was close to that in a previous study [17] and it may be reproducible. Second, the E-PASS was useful for predicting postoperative complications in laparoscopic surgery; however; long-term survival could not be fully evaluated owing to the small number of laparoscopic gastrectomies performed for advanced GC cases. Our results may not be reproducible with the increasing popularization of laparoscopic surgery for advanced GC. Although our study has some limitations, it may still be a valuable conclusion for the next step. We plan to create a pre- and intraoperative risk model for postoperative complications after gastrectomy for gastric cancer based on our results.

In conclusion, these study results indicate that the E-PASS scoring system is useful as a potential predictor of the short- and long-term outcomes in GC surgery.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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