

Intraoperative Blood Loss is Associated with Shortened Postoperative Survival of Patients with Stage II/III Gastric Cancer: Analysis of a Multi-institutional Dataset

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Published online: 30 October 2018
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Abstract

Background The influence of intraoperative blood loss (IBL) on postoperative long-term outcomes of patients with gastric cancer is controversial. Here, we used a large multicenter dataset from nine institutes to evaluate the prognostic impact of IBL on patients with stage II/III gastric cancer.

Methods The study analyzed 1013 patients with stage II/III gastric cancer who underwent gastrectomy without preoperative treatment and intraoperative transfusion. Patients were equally divided into learning and validation cohorts using a table of random numbers. The optimal cutoff value of IBL to predict recurrence was determined using the learning cohort, and the prognostic significance of the proposed cutoff was validated using the second cohort.

Results The optimal cutoff value of IBL determined with the learning cohort using the receiver operating characteristic curve analysis was 330 ml. In the validation cohort, IBL > 330 ml was significantly associated with high body mass index, total gastrectomy, and postoperative complications, but not disease stage and the frequency of adjuvant chemotherapy. The disease-free and disease-specific survival rates of patients in the IBL > 330 ml (IBL-high) group were significantly shorter compared with those in the IBL ≤ 330 ml group. IBL-high was identified as an independent prognostic factor of disease recurrence (hazard ratio 1.45, 95% confidence interval 1.01–2.09, $P = 0.0420$). The hazard ratio of the IBL-high group was greater in the surgery-alone subgroup compared with that of the postoperative adjuvant-chemotherapy subgroup.

Conclusions Our analysis of a multicenter dataset indicates that IBL adversely influenced long-term outcomes of patients with stage II/III gastric cancer.

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Introduction

Gastric cancer remains one of the leading causes of cancer-related death worldwide [1, 2]. Endoscopic or surgical resection can cure early gastric cancer diagnosed at the earliest stage [3]. Unfortunately, many patients with stage II or III disease suffer disease recurrence even after curative resection [4, 5]. Therefore, the identification of predictors of recurrence is essential to provide such patients with appropriate treatment that prolongs their survival and improves their quality of life.

The influence of intraoperative blood loss (IBL) on postoperative long-term outcomes of patients with cancer has long been controversial [6–8]. Nevertheless, this topic continues to be an issue as the standard practice changes such as frequent use of postoperative adjuvant chemotherapy and improvements in surgical devices. Our previous retrospective analysis of 203 patients with stage II/III gastric cancer revealed IBL ≥ 400 ml as a significant predictor of cancer recurrence and, consequently, an independent prognostic factor [9]. However, this effort suffered from being a single-institution study with the small number of patients and the patient accrual over a 16-year period.

To overcome these limitations, we compiled a multi-center dataset analysis comprising a larger number of patients with stage II/III gastric cancer who underwent gastrectomy between 2010 and 2014. The aim of this study was to confirm our previous findings of the adverse effects of IBL on prognosis using this dataset.

Materials and methods

Patients

We retrospectively reviewed clinical data of 3484 patients who underwent gastrectomy for gastric cancer between January 2010 and December 2014 acquired from medical records from nine institutions. We retrieved 1013 patients for analysis according to the criteria as follows: no preoperative treatment, R0 gastrectomy with systematic D2 lymphadenectomy performed according to the Japanese Gastric Cancer Treatment Guidelines [10], pathological stage II–III gastric cancer according to the TNM Classification of Malignant Tumors, 8th Edition [11], and sufficient data for analysis (Fig. 1a). We excluded patients with gastric stump cancer, those who underwent extended surgery (e.g., pancreaticoduodenectomy and Appleby's procedure) and postoperative follow-up <3 months. Patients who received intraoperative blood transfusions were also excluded to eliminate a potential confounding bias due to

its prognostic impact [12]. This study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Patients provided written informed consent for surgery and use of clinical data as required by the Institutional Review Board of each participating institute.

Patient management

Patients underwent gastrectomy with systematic D2 lymphadenectomy according to the Japanese Gastric Cancer Treatment Guidelines. The method of reconstruction was selected at the surgeon's discretion. Patients received postoperative follow-up that included physical examinations, laboratory tests, and enhanced computed tomography (chest and abdominal cavity) once in every 6 months for 5 years or until recurrences [13]. Postoperative 12 months of S-1 (an oral fluoropyrimidine derivative) or capecitabine plus oxaliplatin was recommended to patients as postoperative adjuvant treatments, unless contraindicated by the patient's condition or refusal [14–16]. Treatment after recurrence was determined according to the evidence available at the time of treatment, the patient's condition, and with the patient's consent.

Definition of IBL

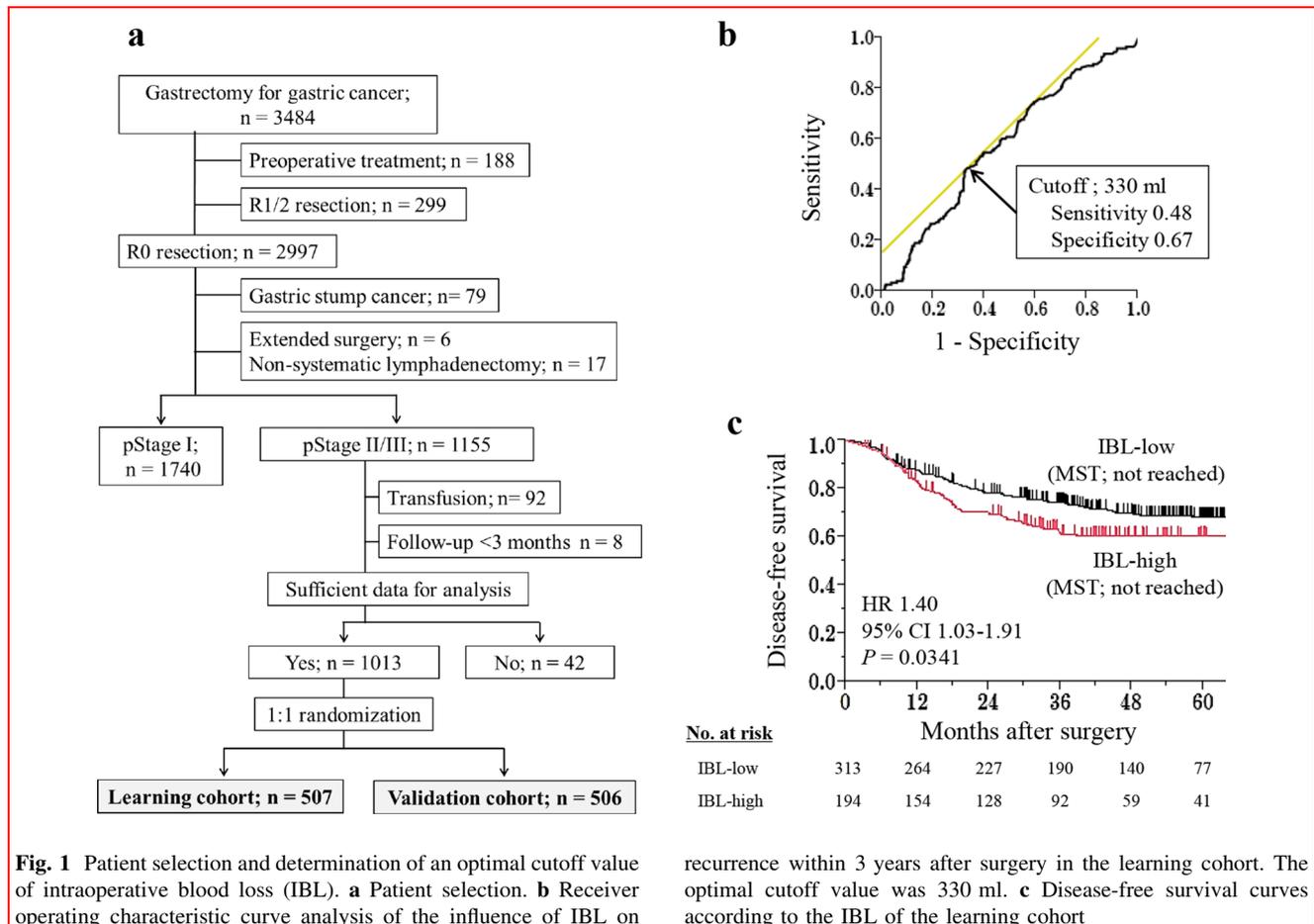
IBL was determined according to the volumes and weights of suction pumps and surgical gauze, respectively, during gastrectomy. The volume of blood absorbed by gauze was measured by weighing every tenth gauze pad, or every hour, and before closure of the abdominal wall [9].

Determination and validation of an optimal cutoff volume of IBL to predict survival

We used a table of randomly generated numbers to equally divide patients into the learning cohort ($N = 507$) and validation cohort ($N = 506$) (Fig. 1a). Using the learning cohort, cutoff value of the IBL most suitable for prediction of long-term outcome was determined by using receiver operating characteristic (ROC) curve analysis of the postoperative disease recurrence within 3 years after surgery. Next, the prognostic significance of the proposed cutoff value was validated using the validation cohort.

Statistical analysis

Qualitative variables were compared between the two groups using the χ^2 test, quantitative variables were compared using the Mann–Whitney test, and survival rates were estimated using the Kaplan–Meier method. When



calculating disease-specific survival, only gastric cancer-related deaths were counted, and subjects who died of some other cause were censored. The Cox proportional hazards model was used to evaluate the hazard ratio relative to each variable and for multivariable analysis. Statistical analysis was performed using JMP 10 software (SAS Institute Inc., NC, USA). A statistically significant difference is indicated by $p < 0.05$.

Results

Determination of the optimal IBL cutoff value

There were no significant differences in clinicopathological factors including surgical procedures, disease stage, and whether the postoperative adjuvant chemotherapy was given between the learning and validation cohorts (Table 1). ROC curve analysis of the learning cohort yielded an IBL cutoff value = 330 ml to predict disease recurrence within 3 years after surgery (Fig. 1b). Disease-free survival time was significantly shorter in the IBL >

recurrence within 3 years after surgery in the learning cohort. The optimal cutoff value was 330 ml. **c** Disease-free survival curves according to the IBL of the learning cohort

330 ml (IBL-high) group compared with that of the IBL \leq 330 ml (IBL-low) group (median survival time not reached for both, hazard ratio 1.40, 95% confidence interval 1.03–1.91, $P = 0.0341$; Fig. 1c).

Significance of IBL for predicting outcomes of the validation cohort

Next, we validated the cutoff value of the IBL using the second cohort. Compared with patients in the IBL-low group, patients in the IBL-high ml group were characterized by male gender, higher body mass index, larger macroscopic tumor size, higher incidence of total gastrectomy and splenectomy, longer operative time, more frequent postoperative complications, and advanced disease stage. In contrast, there were no significant differences between the groups in age, pathological tumor depth and differentiation, lymph node metastasis, and whether the postoperative adjuvant chemotherapy was administered (Table 2).

The IBL-high group experienced significantly shorter disease-free survival compared with that of the IBL-low

Table 1 Characteristics of patients in the learning and validation cohorts

	Learning set (<i>n</i> = 507)	Validation set (<i>n</i> = 506)	<i>P</i>
Age (years), mean ± SD	68.5 ± 10.3	68.6 ± 11.0	0.8276
Sex (male/female)	346/161	352/154	0.6498
Tumor size			
<50 mm	247	252	0.7768
≥50 mm	258	254	
Macroscopic type			
Borrmann type 4/5	39	37	0.8184
Others	468	469	
Type of gastrectomy			
Total gastrectomy	181	197	0.2874
Partial gastrectomy	326	309	
Surgical approach			
Open	456	459	0.6782
Laparoscopic	51	47	
Operative time (min), mean ± SD	257 ± 64	260 ± 70	0.6917
Intraoperative blood loss (ml), median (range)	242 (0–2400)	250 (0–1924)	0.8710
UICC stage			
IIA	129	124	
IIB	108	120	0.8734
IIIA	154	145	
IIIB	80	84	
IIIC	36	33	
Adjuvant chemotherapy (%)	321 (63.3%)	313 (61.9%)	0.632

SD standard deviation

group (hazard ratio 1.76, 95% confidence interval 1.25–2.48, *P* = 0.0012) (Fig. 2a). Proportions of censored cases within 5 years of the IBL-low and IBL-high groups were 54.4% and 58.7%, respectively. Multivariable analysis using a stepwise regression model identified IBL-high as an independent prognostic factor for disease recurrence after curative gastrectomy (hazard ratio 1.45, 95% confidence interval 1.01–2.09, *P* = 0.0420) (Table 3). The disease-specific survival rates of patients in the IBL-high group were significantly inferior to those in the IBL-low group (hazard ratio 1.86, 95% confidence interval 1.23–2.84, *P* = 0.0036) (Fig. 2b).

We next investigated the patterns of the initial recurrence after gastrectomy and found that the prevalence of overall recurrence in the IBL-high group was 33% and that of the IBL-low group was 21% (Fig. 2c). The IBL-high group had an increased incidence of recurrences at the peritoneum, lymph nodes, liver, as well as a significantly

higher prevalence of lung recurrence compared with that of the IBL-low ml group (4% vs. 0.7%, respectively) (Fig. 2c).

Subgroup analyses

Subgroup analyses of the validation cohort were conducted based on whether the postoperative adjuvant chemotherapy was given. Patients were stratified into a subgroup that underwent surgery alone (*n* = 193) and those who underwent gastrectomy followed by adjuvant chemotherapy (*n* = 313). The IBL-low group was significantly superior in terms of disease-free survival in either of the subgroups, with the hazard ratio of 2.00 (95% CI 1.17–3.46) in the surgery-alone subgroup and 1.61 (95% CI 1.04–2.51) in the adjuvant chemotherapy subgroup (Fig. 3). Subgroup analyses according to the pathological stage revealed that the IBL was a significant prognostic factor in Stage III but not in Stage II (hazard ratios 1.77 and 1.29, respectively) (Fig. 4).

Discussion

In the present study, we sought to clarify whether IBL is associated with long-term outcomes of patients with stage II/III gastric cancer. We designed a two-step evaluation protocol to determine and validate the optimal cutoff value of IBL to predict disease recurrence. The IBL cutoff value of the learning cohort was 330 ml. Moreover, patients underwent surgery between 2010 and 2014, indicating that our present findings can be translated to clinical practice. Prognostic value of this cutoff value was reproducible in the validation set, and IBL-high was identified as an independent prognostic factor of disease recurrence after curative gastrectomy.

Evidence conflicts about the influence of IBL on the postoperative prognosis of patients with gastric cancer [17, 18]. Intraoperative blood transfusion should be considered as an important confounding factor to this conundrum [12, 19]. Blood transfusion causes dysfunction of the immune system and may adversely affect the outcomes of patients with cancer [20–22]. Considering the possible linkage of this phenomenon with IBL, we conducted the current analyses only among patients who did not receive intraoperative blood transfusion. We found that the IBL nevertheless remained to be an independent determinant of cancer recurrence and survival in gastric cancer.

There are numerous theories that explain why high IBL is associated with an increased risk of death and recurrence of gastric cancer. Blood loss may promote tumor spillage and hematogenous spread during surgery, which may generate micrometastases that accelerate disease

Table 2 Patients' demographics and perioperative clinical characteristics

Variables	IBL-low (n = 305)	IBL-high (n = 201)	P
Age, mean \pm SD	68.5 \pm 11.2	68.7 \pm 10.7	0.8010
Sex			
Male	193	159	0.0001
Female	112	42	
Preoperative symptom			
Absent	171	107	0.5311
Present	134	94	
Preoperative body mass index, mean \pm SD	21.6 \pm 3.3	22.5 \pm 3.1	0.0007
Tumor size (mm)			
< 50	167	85	0.0060
\geq 50	138	116	
Type of gastrectomy			
Total gastrectomy	89	108	<0.0001
Partial gastrectomy	216	93	
Surgical approach			
Open	259	200	<0.0001
Laparoscopic	46	1	
Splenectomy			
Performed	29	64	<0.0001
Not performed	276	137	
Dissected lymph nodes, mean \pm SD	36.4 \pm 16.0	40.2 \pm 17.8	0.0094
Operative time (min), mean \pm SD	239 \pm 60	292 \pm 71	<0.0001
Estimated blood loss (ml), median (range)	145 (0–330)	521 (334–1924)	<0.0001
Postoperative complication*			
Absent	273	158	0.0008
Present	32	43	
T factor			
pT1	17	15	
pT2	45	20	0.0857
pT3	124	69	
pT4	119	97	
Differentiation			
Differentiated	132	88	0.9112
Undifferentiated	173	113	
Lymph node metastasis			
Absent	70	36	0.1697
Present	235	165	
TNM stage			
II	159	85	0.0299
III	146	116	
Adjuvant chemotherapy			
Absent	114	79	0.6626
Present	191	122	

IBL intraoperative blood loss, SD standard deviation

*Grade III–IV of the Clavien–Dindo classification

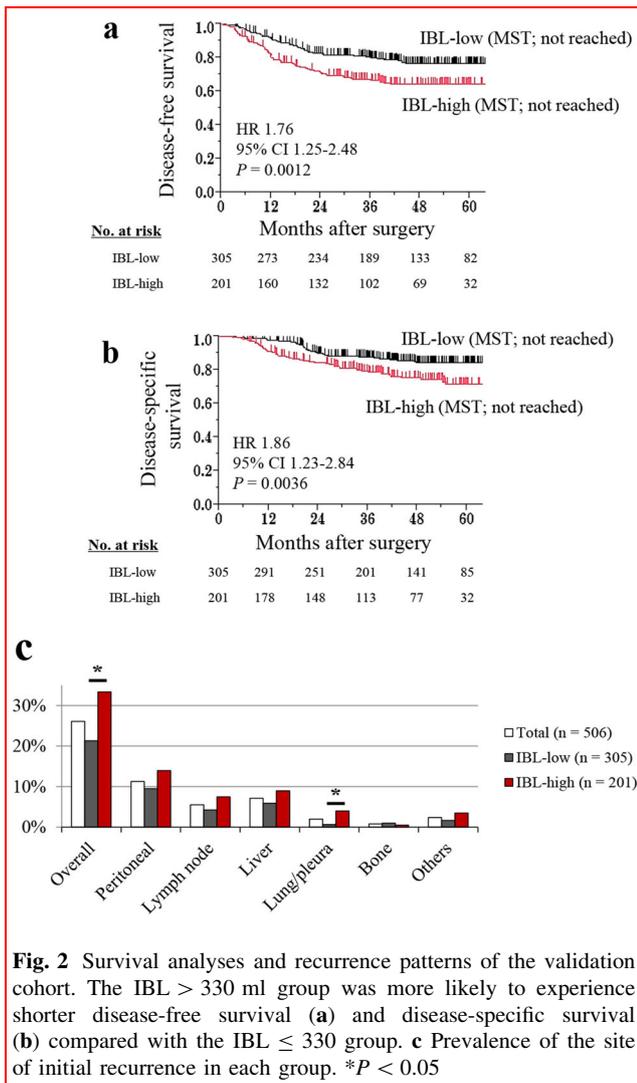


Fig. 2 Survival analyses and recurrence patterns of the validation cohort. The IBL > 330 ml group was more likely to experience shorter disease-free survival (a) and disease-specific survival (b) compared with the IBL ≤ 330 group. c Prevalence of the site of initial recurrence in each group. *P < 0.05

recurrence [7, 8, 23, 24]. Alternatively, a large volume of blood loss may impede antitumor immunity as indicated by Bruns et al. [25] who found that increased IBL during gastrointestinal surgery is associated with a significant decrease in natural killer cell activity. In support of this concept, we show here that the prevalence of recurrence at the lung, a major hematogenous metastatic sites, was significantly higher in the IBL-high group.

According to the findings of our previous single-center study, we reasoned that the differences in the prognostic significance of the volume of IBL may be influenced by adjuvant chemotherapy [9]. Differences between survival curves of the IBL-high and IBL-low groups were reduced in the subgroup of patients who underwent surgery followed by adjuvant chemotherapy, indicating that the negative effect of IBL on prognosis might be partially compensated by adjuvant chemotherapy. This finding may provide one of explanations that adjuvant chemotherapy confers survival benefit for patients with stage II/III gastric cancer.

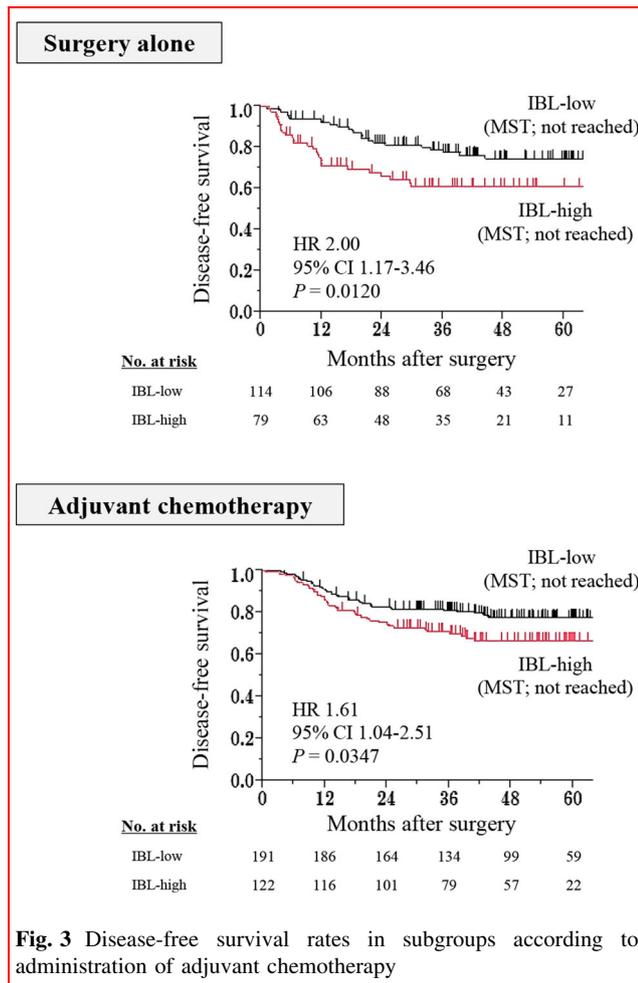
In contrast, subgroup analysis according to disease stage revealed that the survival difference between the IBL-high and IBL-low groups was greater for patients with stage III disease, suggesting that individuals with more advanced cancer are susceptible to the adverse effects of IBL. This finding may be explained, in part, by increased tumor spillage and hematogenous spread, which accompanies excessive blood loss.

The limitations of the present study include its retrospective nature and lack of external validation. Moreover, the absence of immunonutritional data, such as serum cytokine concentrations, limited our ability to decipher the underlying mechanism of immunosuppression associated

Table 3 Prognostic factors of disease-free survival of 506 patients with stage II/III gastric cancer

Variables	Univariate			Multivariable			
	HR	95% CI	P	HR	95% CI	P	
Age	≥65	1.72	1.17–2.58	0.0051	1.76	1.20–2.66	0.0035
Sex	Male	1.16	0.81–1.72	0.4149			
Tumor size	≥50 mm	1.75	1.24–2.49	0.0015	1.30	0.91–1.87	0.1568
Type of gastrectomy	Total	1.55	1.10–2.19	0.0121	1.20	0.84–1.72	0.3107
Surgical approach	Open	2.39	1.15–6.10	0.0121	1.47	0.68–3.82	0.3479
Operative time	≥240 min	1.21	0.86–1.73	0.2787			
Intraoperative blood loss	>330 ml	1.76	1.25–2.48	0.0012	1.45	1.01–2.09	0.0420
Postoperative complication*	Present	1.27	0.87–1.82	0.2083			
Lymphatic involvement	Present	1.69	0.94–3.44	0.0853			
Vascular invasion	Present	1.21	0.84–1.78	0.3185			
Pathological disease stage	III	1.70	1.07–2.84	0.0237	2.70	1.84–4.05	<0.0001
Adjuvant chemotherapy	Performed	0.81	0.57–1.15	0.2323			

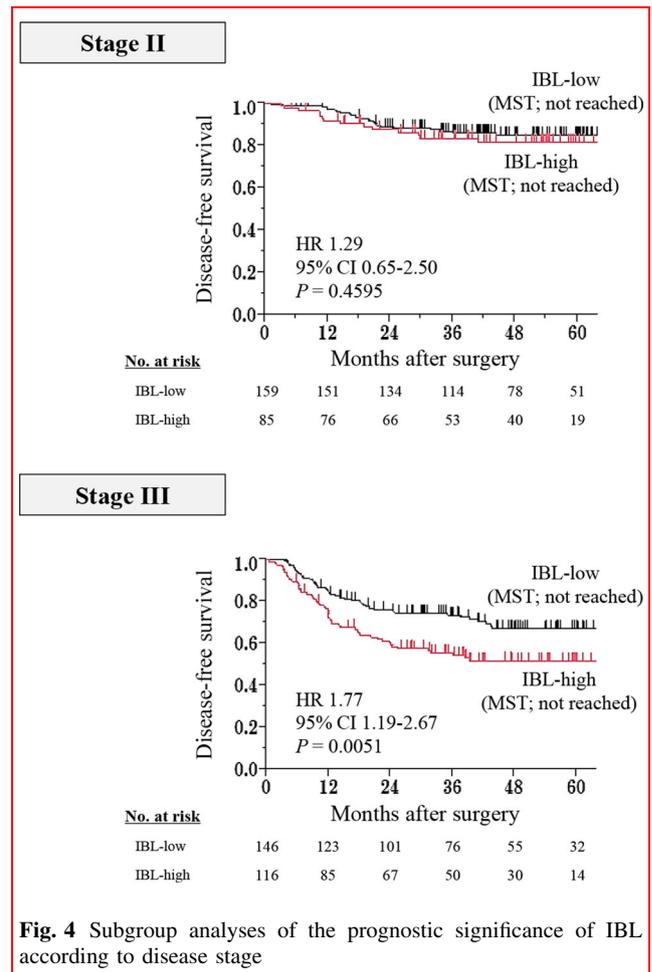
*Surgery-related complications graded II–IV in the Clavien–Dindo classification
HR hazard ratio, CI confidence interval



with IBL. In clinical practice, IBL, blood transfusion, anemia, and postoperative complications are strongly related in a complex pattern. The individual effects of these factors on long-term survival are probably impossible to define. Nevertheless, continuous and untiring efforts to minimize IBL (e.g., improvement of surgical techniques and devices, down-staging using neoadjuvant treatment, and appropriate physical therapy) are required to improve patients' outcomes.

Conclusion

Our analysis of a multicenter dataset using a two-step evaluation protocol reveals that IBL had an adverse effect on the long-term outcomes of patients with stage II/III gastric cancer. The adverse effects of IBL must be eliminated through a multifactorial approach to reduce the risk of recurrence of advanced gastric cancer



Acknowledgements We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Compliance with ethical standards

Conflict of interest The authors do not have any conflicts of interest or financial or material support to disclose.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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