Proposal of the Coagulation Score as a Predictor for Short-term and Long-term Outcomes of Patients with Resectable Gastric Cancer

Short title: Coagulation Score in Gastric Cancer

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Synopsis

We evaluated the clinical significance of preoperative coagulation factors in patients with stage II/III gastric cancer. The Coagulation Score, formulated according to preoperative fibrinogen and d-dimer levels, is a promising predictive marker for short- and long-term outcomes after curative gastrectomy.

ABSTRACT

Background. Systemic hemostasis and thrombosis activation has been implicated in tumor progression and metastasis. This study aimed to investigate the use of coagulation factors as a novel prediction method for postoperative outcomes after curative gastrectomy in patients with stage II/III gastric cancer (GC).

Methods. One hundred twenty-six patients with stage II/III GC who underwent gastrectomy between May 2003 and February 2016 were eligible for study inclusion. We retrospectively evaluated the predictive value of preoperative platelet count, plasma fibrinogen and d-dimer levels, and Coagulation Score (0: fibrinogen and d-dimer both below upper limits; 1: either fibrinogen or d-dimer over upper limits; 2: both fibrinogen and d-dimer over upper limits) for short- and long-term outcomes.

Results. Postoperative complications were significantly more frequent in patients with elevated preoperative d-dimer levels compared with those with normal d-dimer levels (26% vs. 10%, p=0.032). The prevalence of postoperative complications showed a stepwise increase in proportion to the Coagulation Score. Patients with Coagulation Score 2 had significantly larger tumors (p=0.013) and significantly greater intraoperative blood loss (p=0.004) than those who scored 0–1. Coagulation Score showed the highest values to distinguish high-risk patients in overall and disease-free survival, and Coagulation Score 2 was an independent prognostic factor for recurrence. Patients with Coagulation Score 2 experienced a

significantly higher prevalence of liver metastasis as an initial recurrence than those who scored 0–1 (p=0.019).

Conclusions. The Coagulation Score is a simple and promising predictor for postoperative complications and recurrence after gastrectomy in stage II/III GC patients.

INTRODUCTION

Gastric cancer (GC) is a major world health burden, rated as the second-leading cause of cancer death worldwide.[1,2] D2 gastrectomy is the mainstay of therapeutic strategy for advanced but localized GC; however, it has been associated with recurrence after surgery.[3,4] Management of patients with stage II/III GC would benefit from accurate risk stratification, as the prognoses are highly variable and range from complete cure to early recurrence.[5,6] Therefore, the development of sensitive preoperative predictive markers is warranted.

Hemostatic alterations occur during the development of cancer.[7] Even in the absence of venous thromboembolism, the systemic activation of blood coagulation and procoagulant changes in the hemostatic system are frequently observed in cancer patients.[8] In a cancer-bearing host, coagulation facilitates tumor progression through release of platelet granule contents, inhibition of natural killer cells, and recruitment of macrophages.[9] A number of studies have reported that levels of coagulation factors, such as platelet count, fibrinogen and d-dimer levels, are associated with tumor stage, metastasis, and survival in patients with solid tumors including GC.[10-12] However, most previous investigations have looked only at relevance of each one of these factors. As cancer progression may closely be associated with activation of the coagulation system, it could be useful to formulate an integrated score system of coagulation markers to maximize their predictive performance. Additionally, the predictive value of preoperative coagulation factors for postoperative complications has not

been well-explored.

This study evaluated the clinical significance of coagulation factors to identify predictors of both short-term and long-term outcomes after curative gastrectomy in patients with stage II/III GC.

PATIENTS AND METHODS

Patients

Between May 2003 and February 2016, 886 patients underwent gastrectomy for GC without preoperative treatment at the Department of Gastroenterological Surgery, Nagoya University. Of these, 208 were diagnosed with stage II/III disease according to the TNM Classification of Malignant Tumours, 7th Edition,[13] and this retrospective study included a final total of 126 patients for whom both the plasma fibrinogen level and d-dimer level were available. Written informed consent for surgery and use of clinical data was obtained from all patients as required by the Institutional Review Board of Nagoya University.[14]

Treatment

All patients underwent gastrectomy with D2 lymphadenectomy according to the Japanese Gastric Cancer Treatment Guidelines.[15] Since 2007, adjuvant chemotherapy with S-1 (an oral fluoropyrimidine derivative) has been administered to all patients with stage II/III GC at our

institution unless contraindicated by a patient's condition or patient refusal.[16-18] The treatment after recurrence was determined at the discretion of physicians.[19]

Investigational variables

Clinical data were retrospectively collected from medical records. The variables investigated as preoperative coagulation factors were platelet count (upper limit of normal 350,000/mm^3), plasma fibrinogen (upper limit of normal 400 mg/dl) and d-dimer level (latex agglutination method, upper limit of normal 1.0 μg/ml). Coagulation factors were measured within 3 days before surgery. The Coagulation Score was formulated as follows: a score of 0 indicated that both fibrinogen and d-dimer levels were lower than the upper limits; 1 indicated that either the fibrinogen or d-dimer level was over the upper limit; 2 indicated that both fibrinogen and d-dimer levels were over the upper limits. Patients in whom hemoglobin was lower than 13.0 g/dl for men and 11.0 g/dl for women were diagnosed as anemia. Postoperative complications evaluated as Clavien-Dindo grade III–IV were regarded as clinically relevant.[20]

Statistical analysis

The qualitative χ^2 and quantitative Mann–Whitney U tests were used to compare the two groups. Survival rates were estimated using the Kaplan–Meier method, and the overall differences between curves were compared using the log-rank test. In survival analyses,

patients with perioperative (within 90 days) mortality were recognized as censored cases to assess the oncological predictive ability of the variables. The univariate Cox proportional hazards model was used to evaluate the hazard ratio for recurrence-free survival relative to each variable.[21] Variables with $p < 0.05$ were included in the multivariate analysis to identify independent factors. Statistical analysis was performed using JMP 10 software (SAS Institute Inc., NC, USA), and $p < 0.05$ was taken to represent a statistically significant difference.

RESULTS

Patient characteristics

The demographics and oncological characteristics of the 126 included patients are shown in Supplementary Table 1. Patients were diagnosed with stages IIA (n = 28), IIB (n = 28), IIIA (n = 25), IIIB (n = 25), and IIIC (n = 20). Total gastrectomy was performed in 44 patients (35%). The median preoperative platelet count, fibrinogen and d-dimer levels were 222,000/mm^3 (range 98,000–1,120,000/mm^3), 357 mg/dl (range 206–729 mg/dl), and 0.72 μg/ml (range < 0.25–10.1 μg/ml), respectively.

Association between coagulation factors and postoperative complications

Nineteen patients (15%) experienced postoperative complications, including anastomotic leakage in seven patients (6%), intra-abdominal abscess in five patients (4%), leakage of

pancreatic fluids in four patients (3%), and bowel obstruction in two patients (2%). The incidence of postoperative complications was similar in patients with and without increased platelet count (14% vs 15% respectively), tended to be lower in those without increased fibrinogen levels than in those with increased fibrinogen (12% vs 22% respectively), and was significantly lower in those without increased d-dimer levels than in those with increased d-dimer levels (10% vs 26% respectively; $p = 0.032$; Fig. 1A). There was a stepwise increase in the prevalence of postoperative complications in proportion to the Coagulation Score (Fig. 1B).

Patient characteristics in each Coagulation Score (0, 1, and 2) are shown in Table 1. When variables were compared between patients with a Coagulation Score of 0/1 and 2, those with the Score of 2 had significantly higher prevalence of preoperative anemia ($p = 0.019$), larger macroscopic tumor sizes ($p = 0.013$) and a significantly greater amount of intraoperative blood loss ($p = 0.004$) than those with the Score of 0/1 (Table 1). Conversely, there was no significant difference between patients with Coagulation Score 0/1 and 2 regarding age, comorbidity, tumor location, and disease stage (Table 1).

Impact of coagulation factors on probability of survival

There was no significant difference in overall survival rate between patients with and without increased platelet count. Patients with elevated fibrinogen had a significantly worse overall

survival than those without elevated fibrinogen (5-year survival rate 56% and 75%, respectively, $p = 0.028$; Fig. 2a). Overall survival tended to be lower in those with d-dimer levels below the upper limit compared with those with elevated d-dimer levels (5-year survival rates 53% and 74%, respectively, $p = 0.132$; Fig. 2a).

The Coagulation Score identified high risk patients, in that the overall survival of patients in the Coagulation Score 2 group was significantly shorter after curative gastrectomy compared with those who scored 0 and 1 (5-year survival rates of those with a Coagulation Score of 0, 1, and 2 were 77%, 67% and 39%, respectively; $p = 0.003$; Fig. 2b). The Coagulation Score 2 group also experienced significantly shorter disease-free survival compared with those who scored 0 and 1 (3-year survival rates of those with a Coagulation Score of 0, 1, and 2 were 73%, 76% and 37%, respectively; $p = 0.005$; Fig. 3a). Multivariable analysis using a stepwise regression model identified Coagulation Score 2 as an independent prognostic factor for recurrence after curative gastrectomy (hazard ratio [HR] 2.44, 95% confidence interval [CI] 1.04–5.32, $p = 0.042$; Table 2). Eighty-two patients were excluded from this study because of lack of data for the Coagulation Score. To further validate the data regarding survival analyses, we evaluated the similarity of characteristics between the 126 patients included and the 82 excluded from the analysis. We then analyzed the “missingness” corresponding to the 82 patients in all 208 patients. In the univariate Cox proportional hazards model, missingness (corresponding to the 82 excluded patients) was not a significant

prognostic factor for recurrence-free survival in all 208 patients (HR 1.03, 95%CI 0.61–1.75, $p = 0.900$). In addition, we conducted multivariable Cox proportional hazards regression analysis using missingness, tumor size, and pathological tumor depth (pT4), whereby missingness was not identified as a significant factor for recurrence-free survival (HR 1.21, 95%CI 0.71–2.06, $p = 0.488$). These findings indicated that although approximately 40% of patients were excluded because of a lack of coagulation data, the validity of our results was not jeopardized.

The overall recurrence rate of patients with a Coagulation Score of 2 was 53%, which was significantly higher than those with a Coagulation Score of 0 or 1 (22% and 21%, respectively; $p = 0.045$; Fig. 3b). Patients with a Coagulation Score of 2 experienced a significantly higher prevalence of liver metastasis as an initial recurrence compared with those who scored 0 or 1 (prevalence of liver metastasis in those with Coagulation Score 0, 1, and 2 was 6%, 2% and 27%, respectively; $p = 0.019$; Fig. 3b), whereas the frequencies of peritoneal and nodal recurrences were similar between Coagulation Score groups (Fig. 3b).

Further evaluation of clinical implications of the Coagulation Score

To further evaluate the individual role of fibrinogen and d-dimer, we subdivided the Coagulation Score of 1 as follows: a Score of 1a indicated that the fibrinogen was over the upper limit but the d-dimer level was lower than the upper limits; and 1b indicated that the

fibrinogen was lower than the upper limit but the d-dimer level was over the upper limit. Patients with a Coagulation Score of 1a and 1b had similar overall and recurrence-free survival (Supplementary Fig. 1). In addition, a subgroup analysis to evaluate the prognostic impact of the Coagulation Score according to pathological nodal status was performed. A coherent tendency of recurrence-free survival (comparable between Scores 0 and 1, with a poorer prognosis for Score2) was observed in pN0, pN1/2, and pN3 (Supplementary Fig. 2).

DISCUSSION

Little is known about the influences of preoperative hypercoagulability on postoperative morbidity in the field of oncological surgery. In the present study, preoperative d-dimer level was a significant predictor of postoperative complications, while platelet count was not. The literature contains many reports on the association between preoperative d-dimer and postoperative thrombosis.[22,23] Interestingly, our data demonstrated that elevated d-dimer was correlated with the incidence of surgery-related complications such as anastomotic leakage. One possible explanation for this finding is that hypercoagulation status induced formation of microthrombus, leading to tissue ischemia and impaired wound healing and, eventually, the development of severe complications.[24] Our findings offered a valuable insight into the clinical implications of perioperative anticoagulation therapy, not only for the prevention of thrombosis but also the reduction of surgery-related complications. Moreover, the use of an

integrated index was justified, as there was a stepwise increase in the incidence of postoperative complications in accordance with an increase in Coagulation Score. These findings indicate that preoperative coagulation factors may aid in the informed consent process and perioperative management by predicting short-term outcomes after gastrectomy.

The formation of platelet-fibrin-tumor cell aggregates may play a causal role in endothelial adhesion and metastatic potential.[25] Fibrinogen is a crucial source of bioavailable fibrin to tumor cells in the vasculature, which is necessary for tumor cell extravasation, and metastasis formation.[10,26] D-dimer is a stable end-product of the degradation of cross-linked fibrin, which results from enhanced fibrin formation and fibrinolysis.[27,28] We evaluated the association between preoperative platelet count, fibrinogen and d-dimer levels to test our hypothesis that these coagulation factors may be involved in the promotion of a metastatic phenotype in the bloodstream of patients with GC. In the present study, preoperative coagulation factors were linked to long-term outcomes, both overall and recurrence-free survival, of patients with stage II/III GC. Notably, the Coagulation Score demonstrated a high performance for patient stratification, and was identified as an independent prognostic factor for recurrence after curative gastrectomy. Moreover, a high Coagulation Score was linked to increased risk of liver metastasis (representative of hematogenous metastasis), but not nodal and peritoneal metastasis. Fibrinogen and d-dimer levels are routinely measured and reproducibly detected without additional laborious efforts, and the Coagulation Score is easily

calculated. Our results indicate that the Coagulation Score can be used to predict patients with micrometastasis, which contributes to early tumor recurrence postoperatively. In clinical practice, intensive postoperative surveillance for liver metastasis (including Gd-EOB-DTPA enhanced magnetic resonance imaging or contrast-enhanced ultrasound of the liver) may be advisable for patients with a high Coagulation Score.[29]

Our results raised two important questions. The first relates to how the coagulation pathways might engage an aggressive phenotype of GC cells; the other pertains to why hypercoagulation might facilitate hematogenous metastasis rather than peritoneal and lymphatic metastasis. It has been reported that coagulation factors and progression of GC interact with and stimulate each other.[9] Cancer cells facilitate coagulation via diverse processes as follows. Because cancer cells can convert fibrinogen to fibrin, the levels of d-dimer, which is a stable fibrinogen degradation product and reflects ongoing fibrinogen metabolism, are increased within active remodeling of the stroma of progressive tumors.[27,30] Cancer cells express tissue factor, an activator of coagulation cascades that leads to fibrin deposition.[31] Moreover, platelet aggregation is triggered by cancer cells by expressing cytochrome c oxidase (COX), which produces prostaglandins and thromboxanes.[9,32] However, multiple mechanisms have the potential to contribute to metastasis enhancement by coagulation. Activation of platelets and the presence of fibrinogen have been shown to help tumor cells to evade immune surveillance mechanisms, protecting them from killing by NK

cells, by both physical means and through signaling that leads to NK quiescence.[25,33,34] Thus the cancer cells are allowed to survive in the bloodstream as circulating tumor cells (CTCs), which may be responsible for hematogenous metastasis and recurrence. Furthermore, coagulation activation not only generates a protective barrier against immune surveillance but also facilitates the initial steps of tumor cell extravasation, such as cell adherence at the distant organ and spreading, and epithelial-mesenchymal transition.[35,36] Besides this, we need to consider the reasons why the Coagulation Score showed closer association with hematogenous metastasis rather than peritoneal or lymphatic metastasis. One possible explanation is that coagulation status may partly reflect the amount and activity of CTCs because it is activated by stimulating factors released from CTCs.[37] In contrast, when cancer cells metastasize through the other major metastatic routes of GC, peritoneal and lymphatic metastasis, without entering the bloodstream, direct interference between cancer cells and the coagulation system would be relatively small. The other possible explanation is that metastasis requires a complex set of cellular functions mediated by key molecules that are often peculiar to each step of the metastatic process and routes.[2] The unique characteristics in relevant molecules such as cytokines by three metastatic routes may lead to differences in the stimulation of coagulation systems by cancer cells.[38] Clinical and experimental evidence supporting these concepts is anticipated.

Another question raised from our results is whether an anticoagulant treatment can be

used in the treatment of cancer. Previous preclinical models have reported that inhibition of coagulation suppresses cancer metastasis.[9,39] In the field of colorectal neoplasms, several clinical trials have evaluated the effect of low dose aspirin on cancer prevention and prognosis; colorectal cancer incidence appears to be substantially reduced by prophylactic aspirin use.[40] A randomized clinical trial found that celecoxib, a COX-2 inhibitor exhibiting anticoagulant activity through inhibiting synthesis of TAX2, reduced the incidence of colorectal adenomas in a dose-dependent manner.[32,41] It is desirable to conduct large-scale clinical trials evaluating the efficacy of anticoagulant agents in patients with GC.

Limitation of the study includes the retrospective design, long enrollment period, and small sample size. A large-scale prospective study is warranted to validate role of the coagulation factor-related score in predicting recurrence in patients with GC. Furthermore, coagulation factors were tested only once in each patient and were not examined during follow-up, and we did not collect data regarding venous thromboembolism events. In this study, S-1 monotherapy was employed for adjuvant therapy, in contrast to the established Western experience of using multi-drug regimens.[17] Thus, an external validation is needed to generalize our findings.

Our results suggest that the Coagulation Score is a promising prognostic biomarker associated with disease-free and overall survival. The Coagulation Score may represent an easy to measure and low-cost marker for the testing of GC patients to predict postoperative

morbidity and asymptomatic hematogenous metastasis, and could be considered during routine testing.

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Figure Legends

Fig. 1 Incidence of clinically relevant postoperative complications. **a.** Patients were categorized by platelet count, fibrinogen and d-dimer levels. **b.** Morbidity rate increased along with the Coagulation Score.

Fig. 2 Comparison of survival according to preoperative coagulation factors. **a.** Overall survival associated with the preoperative fibrinogen and d-dimer levels. **b** Patients with a Coagulation Score of 2 were more likely to have shortened overall survival.

Fig. 3 a. Patients with a Coagulation Score of 2 had significantly shorter recurrence-free survival compared with those with a Coagulation Score of 0 or 1. **b.** Frequencies of the sites of initial recurrence in each Coagulation Score group.

Supplementary Fig. 1 Survival analyses according to the Coagulation Score when patients with the Score of 1 are subdivided. **a**. Overall survival. **b**. Recurrence-free survival.

Supplementary Fig. 2 Impact of the Coagulation Score on recurrence-free survival according to pathological nodal status.

Table 1. Patient characteristics according to the Coagulation Score

Variables	Score 0 (n = 63)	Score 1 (n = 48)	Score 2 (n = 15)	*P* value*
Age, median (range)	66 (26-86)	71 (56-96)	70 (53-84)	0.415
Sex (male/female)	49/14	35/13	12/3	0.707
Cardiovascular comorbidity (%)	25 (40%)	15 (31%)	4 (27%)	0.467
Diabetes mellitus (%)	15 (24%)	6 (13%)	3 (20%)	0.921
Preoperative symptom (%)	27 (43%)	23 (48%)	8 (53%)	0.546
Preoperative body mass index, mean ± SD	23.1 ± 2.9	21.9 ± 3.5	21.7 ± 4.1	0.456
Preoperative anemia (%)	17 (27%)	29 (60%)	11 (73%)	0.019
Tumor location				
Entire	1	2	1	
Upper third	14	18	5	0.705
Middle third	22	14	3	
Lower third	26	14	6	
Tumor size (mm), mean ± SD	44.9 ± 17.7	56.1 ± 29.4	77.9 ± 42.8	0.013
Type of gastrectomy				
Total gastrectomy	16	22	6	0.663
Partial gastrectomy	47	26	9	
Splenectomy (%)	10 (16%)	14 (29%)	6 (40%)	0.136
Dissected lymph nodes, mean ± SD	37.1 ± 18.1	39.9 ± 18.6	34.5 ± 18.8	0.233
Operative time (min), mean ± SD	234 ± 41	249 ± 56	300 ± 167	0.094
Intraoperative blood loss (ml), median (range)	251 (17-4267)	415 (20-3698)	721 (62-2350)	0.004
Differentiation				
Differentiated	21	19	7	0.430
Undifferentiated	42	29	8	
UICC T factor				
pT1	2	4	0	
pT2	10	9	3	0.452
pT3	27	15	4	
pT4	24	20	8	
UICC N factor				
pN0	15	8	4	0.450
pN1	14	12	3	

pN2	15	14	6	
pN3	19	14	2	
UICC stage				
IIA	14	13	1	
IIB	15	10	3	0.369
IIIA	13	8	4	
IIIB	11	9	5	
IIIC	10	8	2	
Postoperative stay (day) mean ± SD	17.3 ± 12.1	23.8 ± 20.8	20.7 ± 11.9	0.463
Adjuvant chemotherapy (%)	41 (65%)	22 (46%)	11 (73%)	0.210

*Comparison between patients with the Coagulation Score 0–1 and those with the Coagulation Score 2. SD, standard deviation; UICC, Union for International Cancer Control.

Table 2. Prognostic factors for recurrence-free survival of 126 patients with stage II/III gastric cancer

Variables	Univariate			Multivariate		
	Hazards ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (≥65 years)	1.60	0.75 – 3.81	0.231			
Male sex	1.91	0.80 – 5.63	0.155			
Preoperative symptoms	1.06	0.53 – 2.16	0.871			
Preoperative body mass index (≥22)	1.32	0.66 – 2.69	0.441			
Preoperative anemia	1.31	0.66 – 2.61	0.446			
Preoperative Coagulation Score (2)	3.34	1.47 – 6.97	0.006	2.44	1.04 – 5.32	0.042
CEA (>5 ng/ml)	2.14	0.97 – 4.41	0.060			
CA19-9 (>37 IU/ml)	1.87	0.82 – 3.92	0.133			
Tumor location (lower third)	0.94	0.45 – 1.91	0.875			
Tumor size (≥50 mm)	2.74	1.31 – 6.25	0.007	1.66	0.75 – 3.85	0.214
Total gastrectomy	1.95	0.97 – 3.92	0.062			
Operative time (≥240 min)	1.13	0.56 – 2.28	0.739			
Intraoperative blood loss (≥400 ml)	1.82	0.91 – 3.69	0.091			
Postoperative complication	1.80	0.64 – 7.53	0.293			
Pathological tumor depth (pT4)	2.91	1.44 – 6.14	0.003	2.10	1.02 – 4.50	0.045
Undifferentiated tumor	1.39	0.66 – 2.82	0.374			
Lymphatic involvement	1.40	0.30 – 25.0	0.727			
Vessel invasion	1.17	0.57 – 2.60	0.671			
Invasive growth	1.06	0.52 – 2.13	0.866			
Pathological lymph node metastasis	2.09	0.82 – 7.06	0.131			
Adjuvant chemotherapy	0.84	0.39 – 1.71	0.637			

CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Supplementary Table 1. Demographics and perioperative clinical characteristics of the 126 included patients

Variables	Values
Age, median (range)	68 (26-96)
Sex (male/female)	96/30
Cardiovascular comorbidity (%)	44 (35%)
Diabetes mellitus (%)	24 (19%)
Preoperative symptom (%)	58 (46%)
Preoperative body mass index, mean ± SD	22.5 ± 3.8
Preoperative anemia (%)	57 (45%)
Tumor location	
Entire	4
Upper third	37
Middle third	39
Lower third	46
Tumor size (mm), mean ± SD	53.1 ± 28.2
Type of gastrectomy	
Total gastrectomy	44
Partial gastrectomy	82
Splenectomy (%)	30 (24%)
Dissected lymph nodes, mean ± SD	37.9 ± 18.3
Operative time (min), mean ± SD	248 ± 75
Intraoperative blood loss (ml), median (range)	309 (17-4267)
UICC T factor	
pT1	6
pT2	22
pT3	46
pT4	52
Differentiation	
Differentiated	47
Undifferentiated	79
Lymph node metastasis (%)	99 (79%)
UICC stage	
IIA	28
IIB	28
IIIA	25
IIIB	25
IIIC	20

Postoperative stay (day), mean ± SD	20.2 ± 16.1
Adjuvant chemotherapy (%)	74 (59%)

SD, standard deviation; UICC, Union for International Cancer Control.

FIG. 1

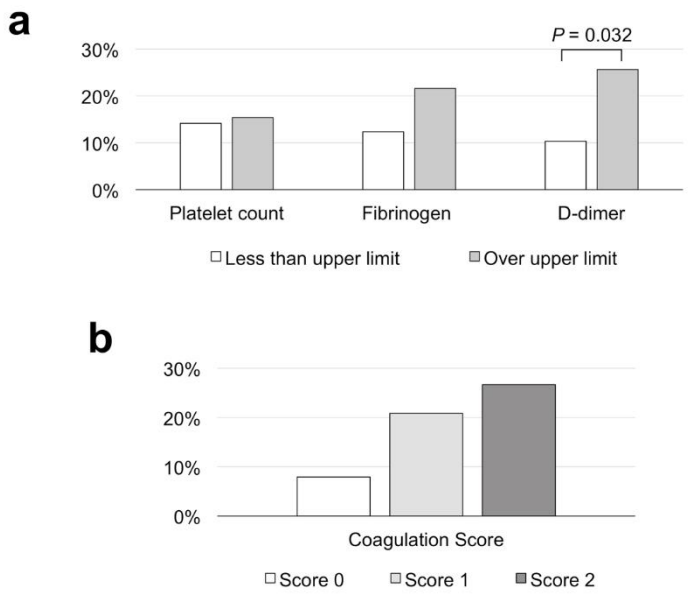
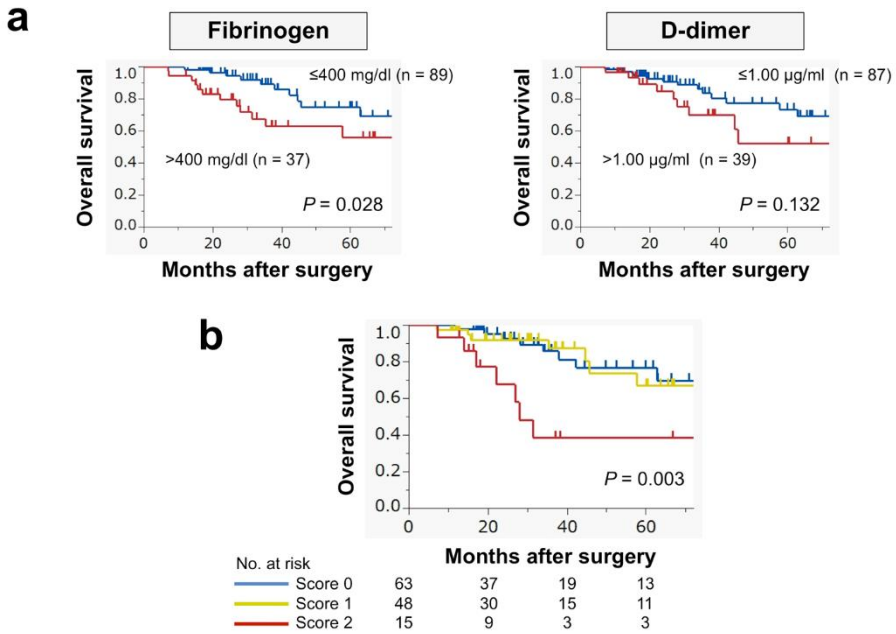
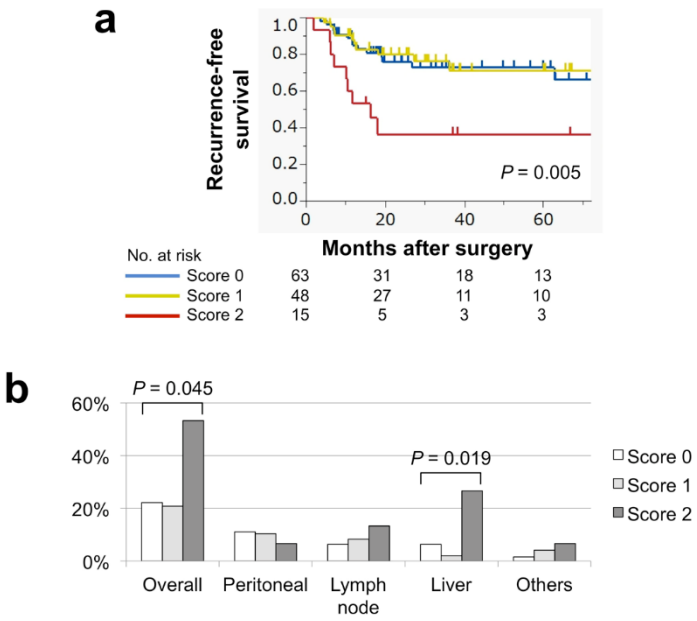

a
P = 0.032
30%
20%
10%
0%
Platelet count
Fibrinogen
D-dimer
Less than upper limit
Over upper limit
b
30%
20%
10%
0%
Coagulation Score
Score 0
Score 1
Score 2

FIG. 2

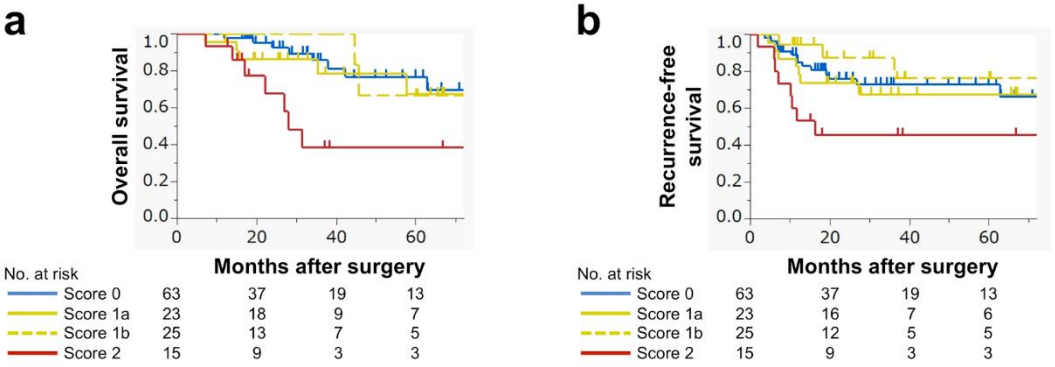

a
Fibrinogen
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
≤400 mg/dl (n = 89)
>400 mg/dl (n = 37)
P = 0.028
0
20
40
60
Months after surgery
D-dimer
Overall survival
≤1.00 μg/ml (n = 87)
>1.00 μg/ml (n = 39)
P = 0.132
Months after surgery

b
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
P = 0.003
0
20
40
60
Months after surgery
No. at risk
Score 0 63 37 19 13
Score 1 48 30 15 11
Score 2 15 9 3 3

FIG. 3


a
Recurrence-free survival
1.0
0.8
0.6
0.4
0.2
0.0
P = 0.005
0
20
40
60
Months after surgery
No. at risk
Score 0 63 31 18 13
Score 1 48 27 11 10
Score 2 15 5 3 3
b
P = 0.045
P = 0.019
60%
40%
20%
0%
Overall
Peritoneal
Lymph node
Liver
Others
Score 0
Score 1
Score 2

Supplementary FIG 1



Supplementary FIG 2