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Clinical Significance of Soluble Fibrin in Coagulopathy Caused by Highly Invasive Surgery

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Background: The clinical use of soluble fibrin (SF) as a coagulation marker is increasing. However, its diagnostic role in critical coagulopathy during invasive abdominal surgery has not been examined.

Methods: In the present study we evaluated changes in SF and other conventional markers, and we performed statistical examination of risk factors in disseminated intravascular coagulation (DIC). A total of 44 highly invasive surgeries (segmental hepatectomy or more, 28; pancreaticoduodenectomy, 9; distal pancreatectomy, 5; and splenectomy, 2) were included. After excluding 7 patients who did not develop DIC, 37 patients were classified into 2 groups: the SIRS-associated coagulopathy (SAC) group, in which SAC remained after surgery ($n = 16$), and the DIC group, which developed DIC ($n = 21$). All patients received a diagnosis of SAC on postoperative day 1 (POD1) and DIC on POD2.

Results: Multivariate analysis revealed significant differences only in the SF level and fibrinogen degradation product (FDP; odds ratios, 14.4 and 7.8). A prediction formula was then prepared based on the β value: $P = 1 / [1 + \exp\{-(2.665 \times SF + 2.049 \times FDP - 1.309)\}]$. The sensitivity and specificity of the prediction formula were 71% and 94%, respectively.

Conclusions: These results showed that the risk factors in the DIC group were SF and FDP on POD1, with SF being the stronger risk factor. Operative stress can be quantified using the SF level on POD1, enabling more specific perioperative management from the perspective of postoperative coagulopathy control.

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The outcomes of highly invasive surgery, such as major hepatectomy and pancreaticoduodenectomy, have recently improved with optimization of the indications for surgery and improvement in perioperative management. Nevertheless, postoperative complications are frequent and result in many fatalities. Postoperative systematic inflammatory response syndrome (SIRS) is often inevitable,[1] whereas less is known about SIRS-associated coagulopathy (SAC).[1]

The clinical use of soluble fibrin (SF) as a coagulation marker is increasing.[2] SF is a polymer of fibrin monomers that directly reflects clotting, but its role during the perioperative period has not been examined, despite its use in diagnosing deep vein thrombosis[3] and disseminated intravascular coagulopathy (DIC),[4] as outlined in the diagnostic criteria of the Japanese Ministry of Health, Labour and Welfare.[5]

Therefore, this clinical study examined the role of SF and other coagulation factors in coagulopathy caused by highly invasive surgery.

Patients and Methods

Objective

This study aims to examine the clinical significance of SF and conventional coagulofibrinolytic markers in coagulopathy (SAC and DIC) caused by highly invasive surgery.

Patients

In total, 44 highly invasive surgeries conducted in our department from April 2011 to April 2014 were evaluated: hepatectomy (segmental resection or more severe cases, including biliary duct reconstruction; 23 cases), pancreaticoduodenectomy (9 cases), distal pancreatectomy (5 cases), hepatectomy for living-donor liver transplantation (5 cases), and splenectomy (splenomegaly/portal hypertension; 2 cases).

Methods

The DIC score was calculated according to the diagnostic criteria for acute DIC.[6–8] Peripheral venous blood was drawn preoperatively and on postoperative days (PODs) 1, 2, 3, 5, 7, and 10 to determine the SF level (latex immune nephelometry; normal level, <7 μg/mL: LSI Medience Corporation, Tokyo, Japan), platelet count, fibrinogen degradation products (FDPs), prothrombin time (PT), and SIRS parameters (body temperature, heart rate, respiration rate, and white blood cell count). A SIRS score of 1 to 3 points was defined as SAC, and a score of ≥4 points was defined as DIC.

After excluding 2 patients with splenectomy with postoperative DIC scores of 0 points and 5 patients with donor hepatectomy who did not develop DIC, 37 patients remained and were classified into 2 groups: the SAC group, in which SAC remained after surgery (n = 16), and the DIC group, which developed DIC (n = 21; Fig. 1).

Examination items

Examination 1: Changes in SF and other markers over time in the SAC and DIC groups.

Examination 2: Statistical examination of risk factors in the DIC group using univariate and multivariate analyses

For the statistical analysis, the *t*-test, χ^2 test, receiver-operating characteristic (ROC) analysis, and logistic regression analysis were performed using the medical statistical software EZR,[9] with significance defined as $P < 0.05$.

This study was approved by the medical faculty's ethics committee.

Results

Result 1

As shown by the changes in the DIC scores, all patients received a diagnosis of SAC on POD1 and of DIC on POD2 (Fig. 2). On POD1, the SF level,

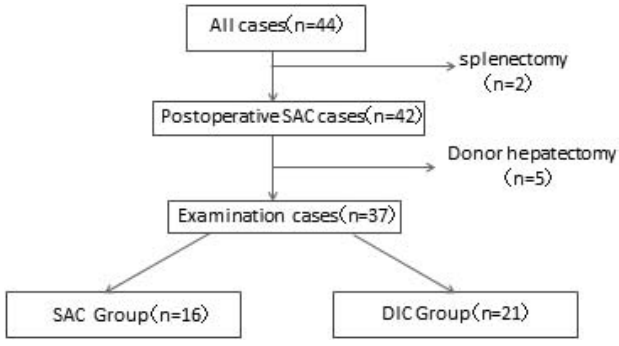


Fig. 1 Algorithm.

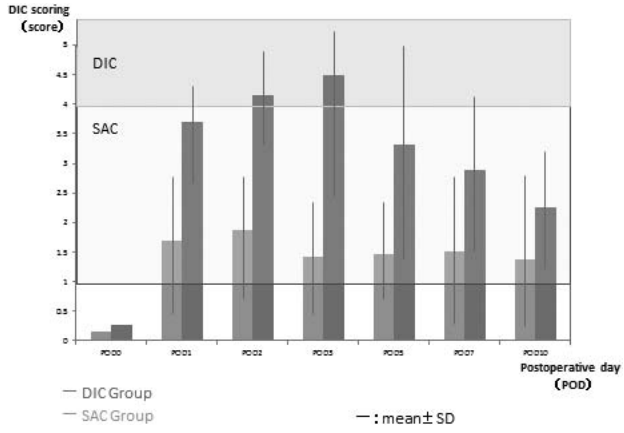


Fig. 2 The change of postoperative DIC score.

FDP, platelet count, and PT–international normalized ratio (INR) were significantly higher in the DIC group than in the SAC group (Fig. 3).

Result 2

There were no significant differences in the patient- or surgery-related factors between the groups (Table 1). Univariate analysis of the vital signs, 2 inflammatory markers, and 4 coagulofibrinolytic markers revealed significant differences in the SF level, FDP, and PT-INR between the 2 groups (Table 2).

Multivariate analysis with cutoff values based on the ROC analysis of the 3 factors revealed significant differences only in the SF level and FDP (Fig. 4). The SF level had the highest odds ratio at 14.4 (Table 3). A prediction formula was then prepared based on the β value: $P = 1 / [1 + \exp\{-(2.665 \times SF + 2.049 \times FDP - 1.309)\}]$.

In the ROC analysis based on the prediction formula, the area under the curve with the formula was 0.875, and the cutoff value was set to 94.5 (Fig. 5).

Next, multivariate analysis was performed for SF, FDP, and the prediction formula based on the cutoff value. A significant difference was observed only for the prediction formula (odds ratio, 17.2). The sensitivity and specificity of the prediction formula were 71% and 94%, respectively (Table 4).

These results showed that the risk factors in the DIC group were SF and FDP on POD1, with SF being the stronger risk factor.

Discussion

It is believed that inflammatory cytokines cause a series of excessive responses[10] and SAC.[1] The more invasive the surgery, the more frequently coagulofibrinolytic abnormalities induce the progression of SAC to DIC.[11] The rates of mortality and morbidity for highly invasive surgery, such as major hepatectomy and pancreaticoduodenectomy, have still been about 10 times higher than those of those of standard gastrointestinal surgery. There have been no molecular markers that can quantify postoperative surgical stress early.

The clinical use of SF as a coagulation marker is increasing.[2] SF is a polymer of fibrin monomers that directly reflects clotting, but its role during the

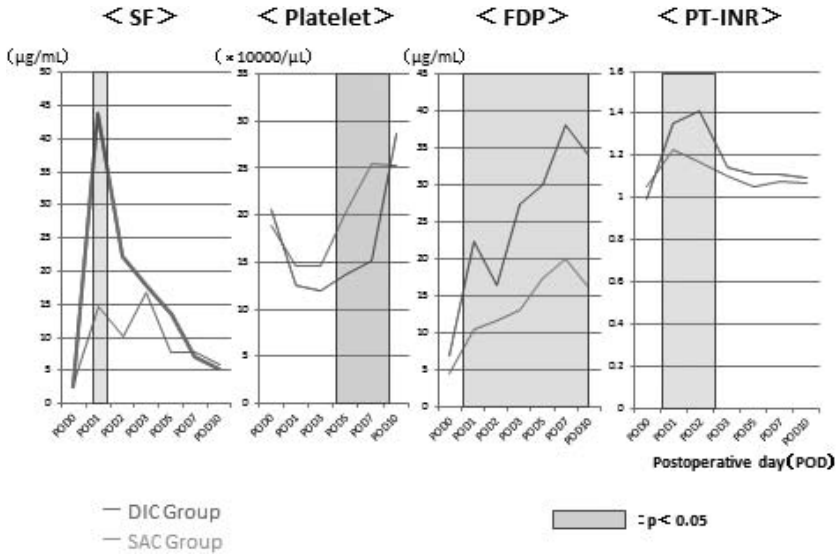


Fig. 3 The change of postoperative coagulofibrinolytic factors.

Table 1 Patient characteristics (n = 37)

Patient factor	SAC group (n = 16)	DIC group (n = 21)	*P* value
Sex, M/F	8/8	7/14	0.336
Age, y	63.8 ± 17.07	68.2 ± 9.79	0.35
BMI	22.69 ± 6.38	21.95 ± 2.39	0.628
Tumor character, malignant/benign	12/4	19/2	0.149
Preoperative blood examination			
T-Bill, mg/dL	0.87 ± 1.00	0.72 ± 0.28	0.501
Amylase, IU/L	100.68 ± 50.86	91.61 ± 38.86	0.542
HbA1c, %	5.72 ± 0.69	5.90 ± 0.81	0.482
ICGR15, %	9.66 ± 6.68	15.71 ± 9.26	0.168
Alb, g/dL	3.78 ± 0.46	3.52 ± 0.41	0.0943
Surgical factor			
Surgical treatment, liver/pancreas	7/9	16/5	0.0857
Operative time, min	460 ± 196	496 ± 155	0.537
Intraoperative blood loss, mL	702 ± 608	958 ± 1030	0.384

Alb, albumin; BMI, body mass index.

Table 2 Univariate analysis of postoperative clinical findings on POD1

Clinical finding	SAC group (n = 16)	DIC group (n = 21)	*P* value
Vital sign			
Body temperature	37.9 ± 0.456	37.9 ± 0.437	0.885
Heart rate	97.13 ± 7.94	100.04 ± 21.8	0.625
Respiratory rate	28.93 ± 11.42	34.33 ± 9.19	0.125
Inflammatory response			
WBC, μ/L	10,268 ± 3608	10,223 ± 3179	0.968
CRP, mg/dL	5.70 ± 5.36	5.27 ± 2.80	0.751
Coagulation factor			
Plt, $\times 10^3/\mu L$	14.51 ± 4.58	12.45 ± 5.66	0.245
PT-INR	1.23 ± 0.17	1.35 ± 0.17	0.33
FDP, μg/mL	10.45 ± 3.85	22.28 ± 12.24	0.000704
SF, μg/mL	14.76 ± 7.63	43.83 ± 28.10	0.000299

CRP, C-reactive protein; Plt, platelet; WBC, white blood cell.

	Cut-off value	AUC	Sensitivity	Specificity	CI
SF	26.2	0.818	0.667	0.938	0.682-0.955
FDP	15.3	0.833	0.714	0.875	0.701-0.966
PT-INR	1.26	0.737	0.714	0.750	0.558-0.915

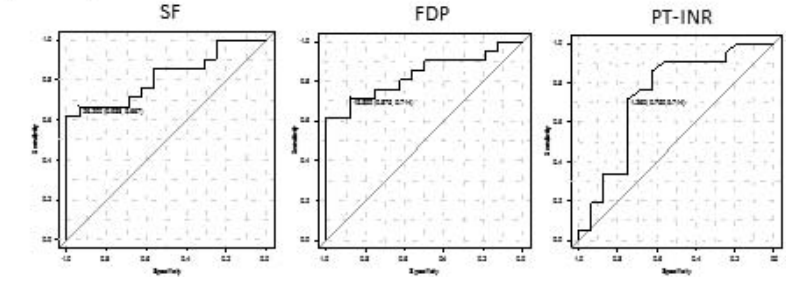


Fig. 4 ROC curve for SF, FDP, and PT-INR.

Table 3 Multivariate logistic regression analysis and prediction formula[a]

	β	*P* value	Odds ratio	CI
SF	2.67	0.0263	14.4	1.37–151
FDP	2.05	0.0403	7.76	1.10–55
Constant	−1.31	0.0228	0.27	

CI, confidence interval.

[a]Predicted probability is calculated by the following formula P = 1 / [1 + exp {–(2.665 × SF + 2.049 × FDP − 1.309}].

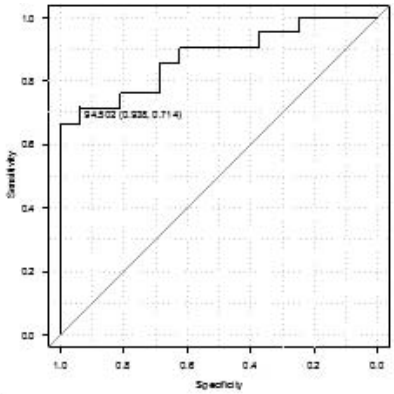
Table 4 Screening accuracy and predictive power of prediction formula

	Predicted	
Observed	Remaining SAC	Developing to DIC
SAC group	15	1
DIC group	6	15
Sensitivity, %	71.4	
Specificity, %	93.8	
PPV, %	71.4	
NPV, %	93.8	
Predictive accuracy, %	81.1	

NPV, negative predictive value; PPV, positive predictive value.

perioperative period has not been examined, despite its use in diagnosing deep vein thrombosis[3] and DIC.[4] Therefore, we evaluated changes in SF and other conventional markers, and statistical examination of risk factors in the DIC.

This study has 3 main findings. First, postoperative SAC occurred in 95% of patients who underwent highly invasive surgery, and the fact that half of the patients developed DIC on POD2 demonstrates the significantly high occurrence of coagulopathy after highly invasive surgery. Interestingly, among the operations performed, although DIC was most frequent in patients who underwent hepatectomy, including subsegmental resection, DIC did not occur in patients who underwent hepatectomy for living-donor liver transplantation, which involves essentially the same technique and amount of resection (data not shown). This finding suggests that even the same operative method has significantly different effects on the coagulofibrinolytic system. The difference in invasiveness might have been affected by differences in patient factors, such as injured versus normal livers; further consideration of this point is required. Second, SF and FDP appear to predict postoperative DIC after highly invasive surgery, especially SF. Hematologically, FDP is a fibrinolysis marker, whereas SF is a coagulation marker, reflecting early hypercoagulation before clotting. Third, operative stress can be quantified using the SF level on POD1, enabling more specific perioperative management from the perspective of postoperative coagulopathy control. Figure 6 shows a chart for initiating treatment of coagulopathy at the time of SAC. According to the chart, there is a 94% risk of remaining SAC if the predictive formula value on POD1 is less than or equal to the cutoff value; otherwise, there is a 71% risk of the development of DIC. Therefore, we believe that it is useful to treat SAC earlier using urinastatin[12] or sivelestat sodium hydrate.[13] However, there is no evidence of improvement in survival with treatment-induced improvement in the DIC score,



	Cut-off value	AUC	Sensitivity	Specificity	CI
Constructed formula	94.502	0.875	0.714	0.938	0.764-0.986

Fig. 5 ROC curve for prediction formula.

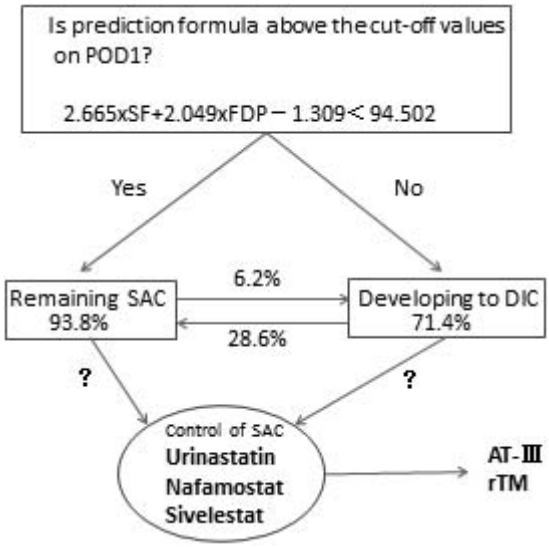


Fig. 6 Because of the use of the prediction formula on POD1, we can predict whether postoperative coagulopathy will develop to DIC or not.

unlike the effect of AT-III[14] and recombinant human soluble thrombomodulin[15] to septic DIC. Prospective clinical examinations of these agents must be performed in the future.

In conclusion, SF as a coagulation marker can predict postoperative DIC after highly invasive surgery, and it may quantify operative stress, enabling more specific perioperative management from the perspective of operative coagulopathy control.

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