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原　著

Clinical significance of soluble fibrin in coagulopathy caused by highly invasive surgery

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Abstract

Objective : The clinical attention of soluble fibrin (SF) as a coagulation marker is increasing. However, its diagnostic role in coagulopathy during invasive abdominal surgery has not been examined. I evaluated the clinical significance of SF in coagulopathy cased by highly invasive surgery.

Method : 44 highly invasive surgeries (segmental hepatectomy or more, 28 ; pancreaticoduodenectomy, 9 ; and so on) were included. After excluding 7 patients who did not develop DIC through out the course, 37 patients were classified into 2 groups : the SAC (n=16), and the DIC group (n=21).

Result : All patients in each group were diagnosed as SAC on POD1 and as DIC on POD2 respectively. Multivariate analyses revealed significant differences in SF and FDP for predicting DIC development (odds ratio at 14.4 and 7.8). A prediction formula was then prepared based on the β value : $P=1/[1+\exp\{-(2.665\times SF+2.049\times FDP-1.309)\}]$. According to the formula, Ps always showed above 0.7, if SF was above the cut-off value regardless of FDP levels, indicating a high probability of predicting DIC. This result showed SF being the stronger predictive factor for advancing DIC.

Conclusion : Operative stress can be quantified using SF on POD1, enabling more specific postoperative coagulopathy management.

Key Words : Soluble fibrin (SF), Disseminated intravascular coagulation (DIC), Highly invasive surgery

Introduction

The outcomes of highly invasive surgeries, such as major hepatectomy and pancreaticoduodenectomy, have recently been improved with optimization of their indications for surgeries and improvement in the perioperative management. Nevertheless, postoperative complications could occur, some cases result in fatal. Postoperative systematic inflammatory response syndrome (SIRS) is often inevitable[1], while 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 condition, 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.

Materials and Methods

Subjects

44 patients undergoing 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),

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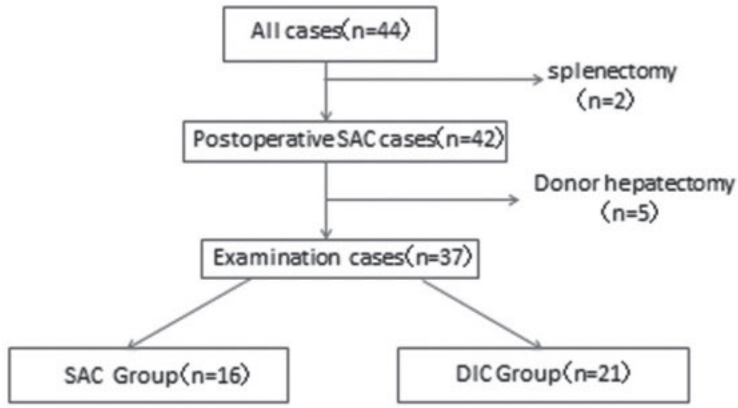

Fig. 1. Algorithm
44 highly invasive surgeries conducted in our department from April 2012 to April 2014 were evaluated: hepatectomy (segmental resection or more severe cases, including biliary duct reconstruction) (23 cases), pancreaticoduodenectomy (9 cases) and so on.
After excluding 2 patients with splenectomy with postoperative DIC scores of 0 points and 5 patients with donor hepatectomy who did not develop to DIC, finally, 37 patients remained and were classified into 2 groups: the SAC group, in which SAC remained after surgery, and the DIC group, which developed to DIC.

platelet count, fibrinogen degradation products (FDP), 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 afterward (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, chi-squared 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 institutional Review Board.

Result

Result 1

As shown by the changes in the DIC scores, all patients were diagnosed with SAC on POD1 and with DIC on POD2 (Fig. 2). On POD1, the SF level, 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, two inflammatory markers, and four coagulofibrinolytic markers revealed significant differences in the SF level, FDP, and PT-INR between the two groups (Table 2).

Multivariate analysis with cut-off values based on the ROC analysis of the three 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: $P = 1/[1 + \exp\{-(2.665 \times SF + 2.049 \times FDP - 1.309)\}]$.

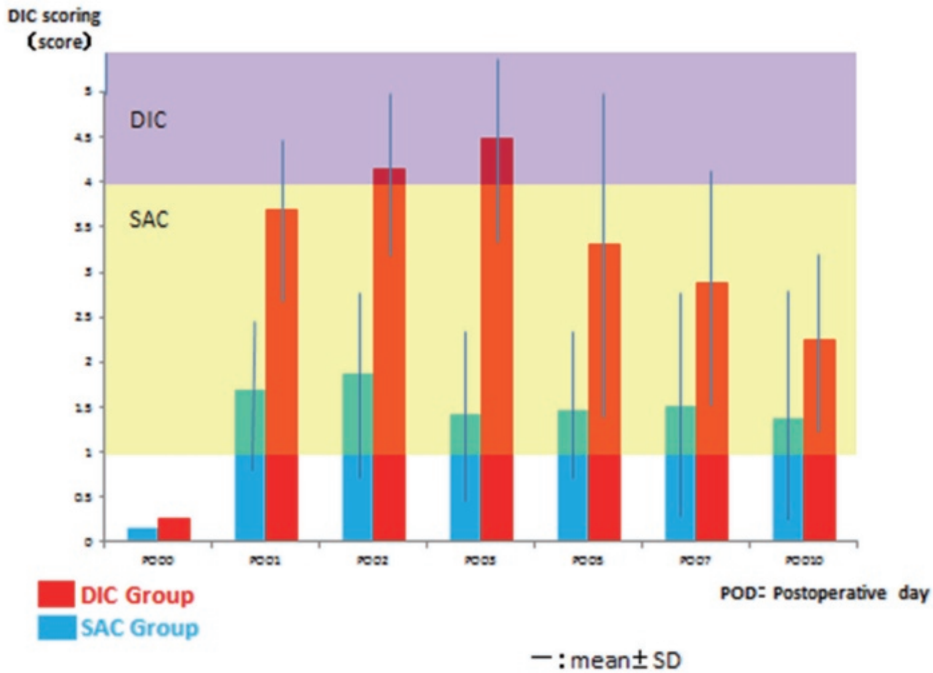

Fig. 2. The postoperative change of DIC score
As shown by the changes in the DIC scores, all patients were diagnosed with SAC on POD1 and with DIC on POD2.

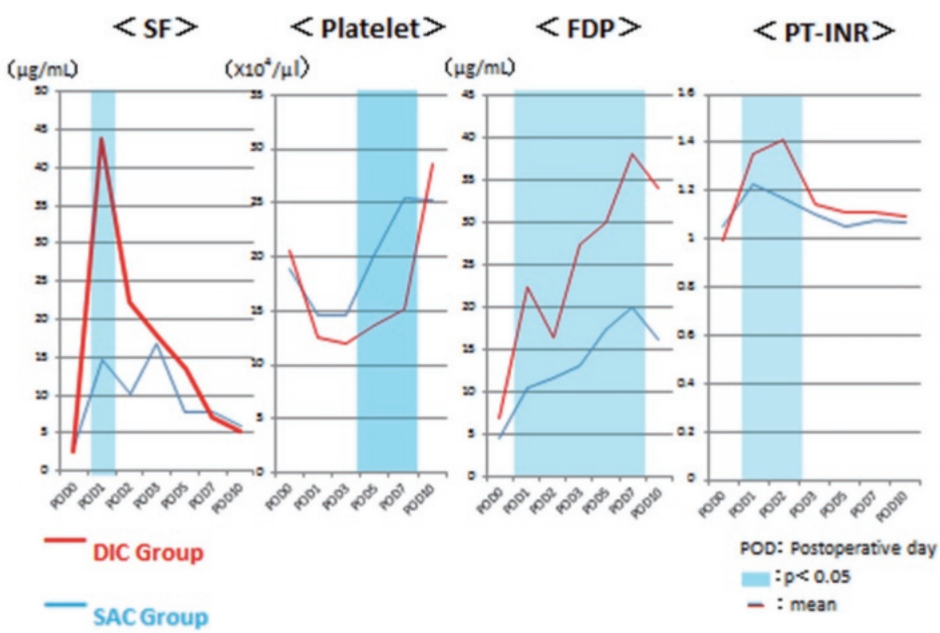

Fig. 3. The postoperative change of coagulofibrinolytic markers
Postoperative changes of each coagulofibrinolytic parameter are shown in this figure, blue zone is significant different between the DIC group (red line) and the SAC group (blue line).
The SF level was significantly higher in the DIC group than in the SAC group on POD1.
Platelet count was significantly lower in the DIC group than in the SAC group on POD5～POD7.
FDP was significantly higher in the DIC group than in the SAC group on POD1～POD 10.
PT-INR was significantly higher in the DIC group than in the SAC group on POD1～POD2.

Table 1. Patient characteristics (n = 37)

	SAC Group (n=16)	DIC Group (n=21)	p-value
< Patient factor >			
Gender (male/female)	8/8	7/14	0.336
Age	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-Bil (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
Intra-operative blood loss (ml)	702 ± 608	958 ± 1030	0.384

Correletion of the background in two groups is shown in this table.
There were no significant differences in the patient-or surgery-related factors between the groups.

Table 2. Univariate analysis of postoperative clinical findings on POD1

	SAC Group (n=16)	DIC Group (n=21)	p-value
Vital sign			
BT (Body temparature)	37.9 ± 0.456	37.9 ± 0.437	0.885
HR (Heart rate)	97.13 ± 7.94	100.04 ± 21.8	0.625
RR (Respiratory rate)	28.93 ± 11.42	34.33 ± 9.19	0.125
Inflammatory response			
WBC (μ/L)	10268 ± 3608	10223 ± 3179	0.968
CRP (mg/dL)	5.70 ± 5.36	5.27 ± 2.80	0.751
Coagulation factor			
Plt (x10000/μL)	14.51 ± 4.58	12.45 ± 5.66	0.245
PT-INR	1.23 ± 0.17	1.35 ± 0.17	0.033
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

Univariate analysis of the vital signs, two inflammatory markers, and four coagulofibrinolytic markers on POD1 revealed significant differences in the SF level, FDP, and PT-INR between the two groups.

When using this formula, the values of SF, FDP should be substituted as binary variables of 1 or 0, converted from continuous values depending on their respective cut-off values. A $P>0.7$ indicates the prospective incidence of DIC whereas $P<0.5$ indicates SAC. We found the incidence of DIC could be predicted using this formula shown herein. When the binary value of the two significant factors were substituted into the formula, P always showed above 0.7, if SF was above the cut-off value regardless of FDP, indicating a high probability of DIC. On the other hand, P always showed under 0.5 if SF and FDP were lower than their cut-off value, indicating a high probability of SAC (Fig. 5). The classification table based on the results of the predicitive probability demonstrated sensitivity, specificity, positive predictive value, negative predictive value were 66.7%, 93.8%, 93.3%, 68.1% (Table 4). Moreover, the AUC value for the results of the constructed formula obtained by the multivariate logistic regression analysis was 0.93. Thus, the prediction we showed was accurate.

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

	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

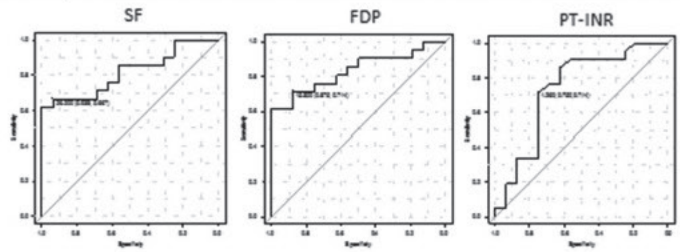

Fig. 4. ROC analysis for prediction of DIC
ROC analysis of the three factors (SF, FDP and PT-INR) revealed FDP had the highest AUC at 0.833 and the SF had 0.818.

Table 3. Multivariate logistic regression analysis and prediction formula

	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	

⇒ Predicted probability is calculated by the following formula

$$P=1/[1+\exp\{-(2.665\times SF+2.049\times FDP-1.309)\}]$$

Based on the ROC analysis of the three factors, multivariate analysis with cut-off values revealed significant differences only in the SF level and FDP.
And, the SF level had the highest odds ratio at 14.4.
Based on the results of the logistic regression analysis, the predicted probability is calculated by the following formula: $P=1/[1+\exp\{-(2.665\times SF+2.049\times FDP-1.309)\}]$.

stronger risk factor.

Discussion

It is thought that inflammatory cytokines cause a series of excessive systematic responses[10] and that SIRS triggers a hypercoagulable condition (SAC)[1]. The more invasive surgery, the more frequently coagulofibrinolytic abnormalities induce the progression of SAC to DIC[11].

This study has three main findings. First, postoperative SAC occurred in 95% of patients who underwent highly invasive surgeries, and the fact that a half of the patients developed DIC on POD2 demonstrates the significantly high occurrence of coagulopathy after highly invasive surgery. Interestingly, in the operations performed, although DIC was most frequent in patients who underwent hepatectomy for removing tumors, 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

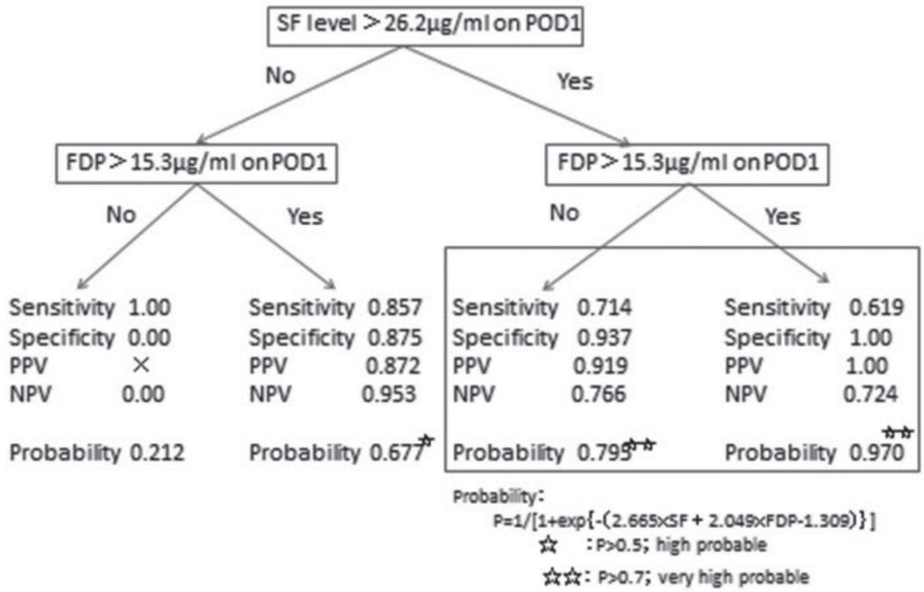

Fig. 5. The prediction chart for occurrence of DIC by constructed formula
When the binary values of two predictors were substained into the formula, P always showed above 0.7 if SF was above their cut-off value regardless of FDP, indicating a high probability of DIC.
On the other hand, P always showed under 0.5 if SF and FDP were lower than their cut-off values, indicating a high probability of SAC.

Table 4. Screening accuracy and predictive power of prediction formula

Observed	Predicted	
	SAC Group	DIC Group
SAC Group (n=16)	15	1
DIC Group (n=21)	7	14

Sensitivity	66.7%
Specificity	93.8 %
PPV	93.3%
NPV	68.1%

NPV: negative predictive value
PPV: positive predictive value

The classification table based on the results of the predicitive probability demonstrated sensitivity, specificity, positive predictive value, negative predictive value were 66.7%, 93.8%, 93.3%, 68.1%.

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 the highly invasive surgery, especially SF. Hematologically, FDP is a fibrinolysis marker while SF is a coagulation marker, reflecting early intravascular hypercoagulation before thrombi formation.

Third, operative stress can be quantified using the SF levels on POD1, enabling us to do more specific perioperative managements from the perspective of postoperative coagulopathy changes. Figure 6 shows a potential chart for initiating treatments of coagulopathy at the time of SAC after highly invasive surgery. According to the chart, it is suspected that DIC would occur with a high probability if SF being above the cut-off value regardless of FDP levels. Therefore, we believe that it is useful to treat SAC earlier using of ulinastatin[12], protease inhibitor and sivelestat sodium hydrate[13]. However, there is no evidence of improvements in survival with treatment-induced improvement in the DIC score, unlike the effect of AT-Ⅲ[14] and recombinant human soluble thrombomodulin[15] to septic DIC. Prospective clinical trials of these agents are required to perform in the future.

Summary

SF as a coagulation marker can predict postoperative DIC cased by highly invasive surgeries. Operative stress can be quantified using the SF levels on POD1, enabling us to do more specific perioperative managements from the perspective of postoperative coagulopathy changes.

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The article has been checked by a Statistician. None of authors has any financial or personal conflicts of interest of any kind.

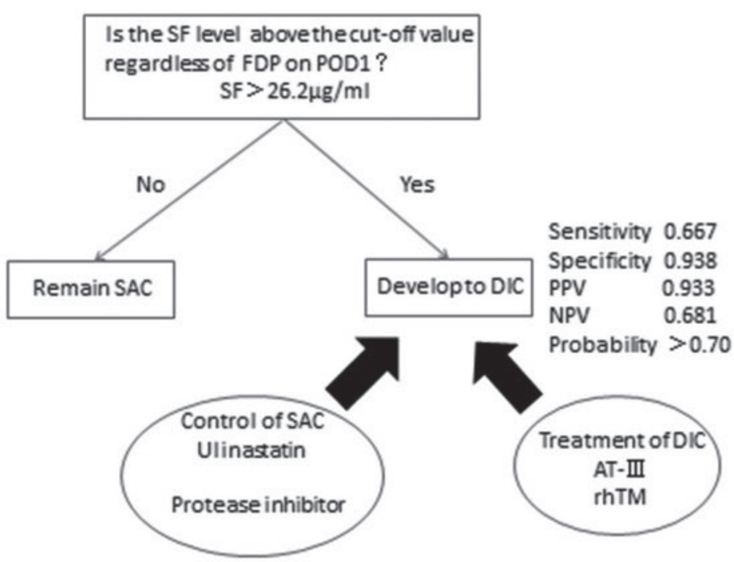

Fig. 6 . A potential management chart for postoperative coagulopathy after highly invasive surgery
I propose a chart of for initiating treatment of postoperative coagulopathy at the SAC after highly invasive surgeries.
According to the chart, it is suspected that DIC would occur with a high probability if SF being above the cut-off value regardless of FDP levels.
Therefore, the early use of Ulinastatin, Protease inhibitor and/or rhTM, AT-Ⅲ can be recommended in such cases.

References

1. Ogura H, Gando S, Iba T et al : SIRS -associated coagulopathy and organ dysfunction in critically ill patients with thrombocytopenia. Shock 2007 ; 28 : 411－7.
2. Nakahara K : Measurement of soluble fibrin monomer-fibrinogen complex in plasmas derived from patients with various underlying clinical situation. Thromb Haemost 2003 ; 89 : 832－6.
3. Niimi R, Hasegawa M, Sudoh Y et al : Usefulness of a soluble fibrin monomer complex（SFMC）and a D-dimer assay for screening of deep vein thrombosis following total hip arthroplasty. Hip Joint 2006 ; 32 : 667－72.
4. Wada H, Wakita Y : Increased plasma-soluble fibrin monomer levels in patients with disseminated intravascular coagulation. Am J Hematol 1996 ; 51 : 255－60.
5. Oda S, Aibiki M, Ikeda T et al : The Japanese Society of Intensive Care Medicine, Sepsis Registry Committee : The Japanese Guidelines for the management of sepsis. Journal of Intensive Care Medicine 2013 ; 20 : 124－73.
6. Gando S : Diagnosis and management of disseminated intravascular coagulation in critically ill patients. Journal of the Japanese Society on Thrombosis and Hemostasis 2008 ; 19 : 353－7.
7. Kobayashi N, Maekawa T, Takada M : Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. Bibl Haematol 1983 ; 49 : 265－75.
8. Maruyama M, Sakata Y, Wada H et al : The Japanese Society on Thrombosis and Haemostasis DIC study Group : Expert consensus based on the evidence for the treatment of disseminated intravascular coagulation due to infection intravascular. Journal of the Japanese Society on Thrombosis and Hemostasis 2009 ; 20 : 77－113.
9. Kanda Y : Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplantation 2013 ; 48 : 452－8.
10. Gando S, Iba T, Eguchi Y et al : Japanese association for acute medicine Disseminated Intravascular Coagulation（JAAM DIC）Study Group : A multicenter prospective validation of DIC diagnostic criteria for critically ill patients : comparing current criteria. Critical Care Medicine 2006 ; 34 : 625－31.
11. Gando S, Saitoh D, Ogura H et al : Japanese association for acute medicine Disseminated Intravascular Coagulation（JAAM DIC）Study Group : Natural history of disseminated intravascular coagulation diagnosed based on the Newly established diagnostic criteria for critically ill patients : results of Multicenter, prospective survey. Critical Care Medicine 2008 ; 36 : 145－50.
12. Inoue K, Takano H : Ulinary trypsin inhibitor as a therapeutic option for endotoxin-related inflammatory disorders. Expert Opin Investig Drugs 2010 ; 19 : 513－20.
13. Henriksen PA : The potential of neutrophil elastase inhibitors as anti-inflammatory therapies. Curr Opin Hematol 2014 ; 21 : 23－8.
14. Gando S, Saitoh D, Ishikura H et al : Japanese Association for Acute Medicine Disseminated Intravascular Coagulation（JAAM DIC）Study Group : Effect of AT-Ⅲ to septic DIC diagnosed by JAAM DIC diagnostic criteria. Journal of Japanese Association for Acute Medicine 2013 ; 24 : 105－15.
15. Saito H, Maruyama I, Shimazaki S et al : Efficacy and safety of recombinant human soluble thrombomodulin（ART-123）in disseminated intravascular coagulation : results of a phaseⅢrandomized, double-blind clinical trial. J Thromb Haemost 2007 ; 5 : 31－41.

外科大侵襲手術術後凝固異常における
可溶性フィブリンモノマー（SF）の臨床的有用性

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要　旨

目的：近年，可溶性フィブリンモノマー（Soluble　Fibrin；SF）の凝固マーカーとしての臨床的有用性が報告されその使用頻度が増加しているが外科大侵襲手術術後におけるその臨床的意義に関する検討は未だなされていない．今回当科における外科大侵襲手術症例を対象に，術後凝固異常におけるSFの臨床的意義を検討した．

方法：44例の外科大侵襲手術（区域切除以上の肝切除28例，膵頭十二指腸切除９例など）を対象としretrospectiveな検討を行った．術後経過中DICに至らなかった７例を除く37例を，術後SIRS関連凝固異常（SIRS associated Coagulopathy；SAC）にとどまった16例とDICにまで至った21例の２群に割り付けた．

結果：術後全ての患者が術後１日目にSACに至り，DIC移行群は術後２日目にDICへ移行した．多変量解析の結果，術後１日目のSFとFDPの２因子がDIC移行群の危険因子として有意差を認めた（オッズ比14.4，7.8）．そこでβ値を用いて予測式を作成した（P＝１/［１＋exp ｛−(2.665×SF＋2.049×FDP−1.309)｝］．この予測式を用いると，DICの発症確率は，FDPの値にかかわらずSFがカットオフ値以上であれば常に0.7を超えており，この結果からDIC発症の予測因子は術後１日目のSFとFDPであり，特にSFが最も強い予測因子である可能性が示された．

結論：術後１日目のSF値により手術の侵襲度を把握し，術後の凝固異常を早期に予測することが可能であり，これにより凝固異常にも配慮したよりきめ細かい術後管理が可能になる可能性がある．

Key Words：可溶性フィブリンモノマー（SF），播種性血管内凝固症候群（DIC），大侵襲外科手術