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Original Research Article

Efficacy of Coagulofibrinolytic Markers for Postoperative Prediction of Venous Thromboembolism in Colorectal Surgery Patients: A Retrospective Observational Study

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Abstract

Objectives: A low rate of the incidence of venous thromboembolism (VTE) after surgeries that are preoperatively classified as having high risk of VTE has been reported in recent years. We seek to identify the optimal cases to receive perioperative pharmacologic thromboprophylaxis. In this study, we evaluated the incidence rate of VTE among patients undergoing colorectal surgery who did not receive perioperative pharmacologic thromboprophylaxis, and the ability of coagulofibrinolytic markers to predict the postoperative development of VTE.

Methods: We retrospectively analyzed the rate of postoperative development of VTE in 70 patients undergoing elective colorectal surgery without perioperative pharmacologic thromboprophylaxis and the ability of coagulofibrinolytic markers to predict the development of VTE.

Results: The incidence of VTE was observed in 11 patients (15.7%); all cases were asymptomatic and distal-type deep vein thrombosis (DVT). Comparisons of time course changes in perioperative coagulofibrinolytic markers between patients with and without DVT revealed significant differences in soluble fibrin (SF), thrombin-antithrombin complex (TAT), fibrin/fibrinogen degradation product (FDP) and D-dimer. Dynamic postoperative physiological coagulofibrinolytic responses were shown, but all four markers at each postoperative point demonstrated moderate accuracy (median area under the curve [AUC]: 0.788, median sensitivity: 0.865, median specificity: 0.644) for predicting the development of DVT.

Conclusions: The incidence of postoperative VTE was low in patients with colorectal surgery even in those who did not receive perioperative pharmacologic thromboprophylaxis. SF, TAT, FDP and D-dimer were useful for predicting the development of DVT when we set cut-off values taking the physiological perioperative coagulofibrinolytic responses into consideration.

Keywords

D-dimer, deep vein thrombosis, fibrin/fibrinogen degradation product, soluble fibrin, thrombin-antithrombin complex

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Introduction

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is uncommon, but lead to severe morbidity and mortality after surgery[1-4]. In some major surgery such as colorectal surgery, the risk of the development of VTE is relatively high, and perioperative pharmacologic thromboprophylaxis is recommended[5-8]. However, in recent years, some reports have shown a low incidence rate of VTE, even after surgeries that are preoperatively classified as having high risk for VTE[9,10]. Against this background, it is important to identify the optimal cases in which to perform perioperative pharmacologic thromboprophylaxis.

The prediction and early diagnosis of VTE is needed for the appropriate determination of thromboprophylaxis or anticoagulant therapy even after surgery. As one of the indicators of the development of VTE, the assessment of coagulofibrinolytic markers such as D-dimer is well known to be effective[11,12]. However, its diagnostic accuracy after surgery is suboptimal since the perioperative coagulofibrinolytic alteration leads to a high rate of false-positive results[13]. We need to consider this physiological response when we attempt to employ coagulofibrinolytic markers to predict the development of VTE.

We previously reported the dynamic perioperative coagulofibrinolytic changes, namely, coagulation activation and the tri-phasic responses of fibrinolytic activity[14]. As an additional consideration, we evaluated the rate of VTE development among patients undergoing colorectal surgery who did not receive pharmacologic thromboprophylaxis during the perioperative period, and the ability of coagulofibrinolytic markers to predict the development of VTE in this study. Here, we considered the perioperative coagulofibrinolytic responses by setting cut-off values at each postoperative timing.

Methods

Study design

This was a single-center, retrospective, observational study of patients undergoing elective colorectal surgery between September 2016 and December 2017 in Ehime University Hospital in Japan. In accordance with our hospital policy during the study period, pharmacologic thromboprophylaxis was not generally implemented for all patients unless continuous anticoagulant therapy was required for comorbidities. In addition, we routinely screened patients for DVT using coagulofibrinolytic markers and ultrasonography. We shared a decision-making process with all patients, and obtained informed consent from them. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Clinical Research of Ehime University Hospital (No. 1902015). The requirement to obtain informed consent for this study was waived because of the retrospective design.

Patients

We included patients undergoing elective colorectal surgery, which is known to be a high VTE-risk operation. In addition, we evaluated patients who did not receive pharmacologic thromboprophylaxis so that we could analyze sophisticated perioperative coagulofibrinolytic responses using markers. Perioperative mechanical thromboprophylaxis was applied to all patients using sequential compression devices, and patients were encouraged to ambulate from postoperative day (POD) 1. Exclusion criteria were active bleeding, high risk of thrombosis due to comorbidities if a patient discontinued anticoagulant or antiplatelet drugs, a history of thromboembolic disease within 3 months before surgery, and a history of a coagulation disorder such as liver cirrhosis.

Data collection and definition

Data on the patients' characteristics were collected at the presurgical screening. Colorectal cancer was graded according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum[15]. Postoperative complications were classified according to the Clavien-Dindo classification[16], and we defined significant complications when the grade was ≥2.

We measured routine blood counts using a TBA-c16000 analyzer (Toshiba Medical Systems, Tochigi, Japan), biochemistry markers using an XE-5000 automated hematology system (Sysmex, Hyogo, Japan), and coagulofibrinolytic markers with the STACIA immunoanalyzer (LSI Medience, Tokyo, Japan) and CP-2000 coagulation instrument (Sekisui Medical, Tokyo, Japan) before and immediately after surgery, and on PODs 1, 3, and 7. Blood sampling was performed preoperatively (from a few days before surgery to the day of surgery), immediately after surgery, and on PODs 1, 3, and 7. The coagulofibrinolytic markers measured during the study period were as follows: activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (Fbg), soluble fibrin (SF), thrombin-antithrombin complex (TAT), protein C (PC), antithrombin (AT), plasminogen (PLG), α_2-plasmin inhibitor (α_2PI), plasmin-α_2-plasmin inhibitor complex (PIC), fibrin/fibrinogen degradation product (FDP), and D-dimer.

DVT screening was performed using ultrasonography of the lower extremities (Aplio 400: TUS-A400, Toshiba Medical Systems, Tochigi, Japan) equipped with a 7.5-MHz probe (PLT-704SBT, Toshiba Medical Systems, Tochigi, Japan) by experienced sonographers before surgery and on POD 7. Color and pulse Doppler and the compression method were used to search for thrombus formation.

Whether a thrombus was in an acute or a chronic phase was estimated based on findings such as echogenicity in changes of shape upon compression by the probe. DVT was classified as proximal or distal DVT, based on the location of thrombus: proximal DVT if the thrombus was in the popliteal or more proximal veins, and distal if the thrombus was found in the calf veins. Development of DVT was defined as a new venous blood clot formation that was not detected before surgery.

Statistical analysis

IBM SPSS Statistics 22 package (IBM, Tokyo, Japan) was used for all statistical analyses. All data are expressed as median and interquartile range (IQR). The statistical significances of differences between groups were assessed with the Student's *t*-test, Mann-Whitney *U* test or Fisher exact test, as appropriate. Time course changes of the values were assessed by one-way repeated measures analysis of variance (ANOVA). The longitudinal differences between groups were analyzed by two-way repeated measures ANOVA, and pairwise comparisons were made by Mann-Whitney U test. Receiver operating characteristic (ROC) curves were used to determine the ability of coagulofibrinolytic markers to predict the development of DVT. The cutoff values of the markers for DVT screening were also determined by the ROC analysis using the Youden index. A p value less than 0.05 was considered to denote statistical significance.

Results

Patient characteristics (Table 1)

We included 70 patients in this study (Table 1). The median age was 70 years old, the median body mass index (BMI) was 22.4 kg/m^2, and 58.6% were men. Seventeen patients used anticoagulant and/or antiplatelet drugs, but all patients included in this study were allowed to discontinue the drugs during the perioperative period at the discretion of their neurologists or cardiologists. All except 4 patients had surgery for cancer (94.3%), and most surgeries were performed laparoscopically (88.6%). The median operation time was 305.5 min, and the amount of bleeding was negligible in many operations (median value: 0 mL). The median postoperative hospitalization duration was 12 days.

Chronic asymptomatic distal DVT was incidentally detected in 3 patients (4.3%) preoperatively, but all patients were followed without any anticoagulant therapy according to their cardiologists' decision. Eleven patients (15.7%) were diagnosed with development of DVT on POD 7, and all DVT cases were asymptomatic and distal-type. No patients developed symptomatic PE or DVT on POD 7 or throughout 30-day postsurgical observation period. There were no significant differences in the characteristics of patients with VTE and without VTE.

Comparisons of perioperative changes in coagulofibrinolytic markers between the patients with and without DVT (Table 1, 2, Figure 1)

A comparison of preoperative laboratory data revealed that they were similar (Table 2). However, there was a small, but statistically significant difference between the two groups only in TAT values even though the values were within the normal range. Comparisons of time course changes in perioperative coagulofibrinolytic markers between the two groups revealed significant differences in SF, TAT, FDP and D-dimer (Figure 1). SF and TAT, the parameters of coagulation activation, increased after surgery and then decreased gradually to their normal ranges. In patients with DVT, SF and TAT elevations were significantly higher than those in patients without DVT throughout the postoperative period. FDP and D-dimer continued to increase during the study period, and these elevations in patients with DVT were significantly greater than those in patients without DVT throughout the postoperative period.

ROC analyses for predicting DVT using four coagulofibrinolytic markers: SF, TAT, FDP and D-dimer (Figure 2, 3, Table 3)

To determine the diagnostic accuracy of SF, TAT, FDP and D-dimer which revealed significant differences in postoperative time course changes between patients with and without DVT, ROC analyses of the four markers at each postoperative point were performed. As presented in Figure 2, Table 3, all four markers during the entire postoperative point demonstrated moderate accuracy (median AUC: 0.788, median sensitivity: 0.865, median specificity: 0.644). The best cut-off values were shown in Table 3, and their longitudinal changes were depicted in Figure 3.

Discussion

In this study, we evaluated the incidence rate of VTE among patients undergoing colorectal surgery who did not receive perioperative pharmacologic thromboprophylaxis, and the ability of coagulofibrinolytic markers to predict the postoperative development of VTE. Even though 94.3% of all patients underwent surgery for cancer, which is preoperatively classified as having high risk for the development of VTE according to the guidelines[8], no symptomatic PE and proximal-type DVT occurred, and only asymptomatic and distal-type DVT was observed in 11 patients (15.7%). Against this background, we might need to reconsider the optimal indications for perioperative pharmacologic thromboprophylaxis in colorectal surgery rather than routine prophylaxis based on surgical procedures. In terms of postoperative VTE risk assessment, our results demonstrated that

Table 1. Patient Characteristics and Outcomes.

	Total patients: n=70	Development of VTE		
		VTE (+): n=11	VTE (-): n=59	*p* value
Sex (male/female), n (%)	41 (58.6)/29 (41.4)	5 (45.5)/6 (54.5)	36 (61.0)/23 (39.0)	0.263
Age, years	70 (64.8–77)	75 (67–81)	70 (63–76)	0.188
BMI, kg/m^2	22.4 (20.3–24.3)	23.6 (21.0–25.2)	22.2 (20.2–24.3)	0.410
Smoking history, n (%)				0.422
Never	37 (52.9)	7 (63.6)	30 (50.8)	
Former	29 (41.4)	4 (36.4)	25 (42.4)	
Current	4 (5.7)	0 (0.0)	4 (6.8)	
Comorbidities, n (%)				
Heart diseases	19 (27.1)	2 (18.2)	17 (28.9)	0.375
Respiratory diseases	2 (2.9)	0 (0.0)	2 (3.4)	0.708
Chronic renal failure	0 (0.0)	0 (0.0)	0 (0.0)	*n.d.*
Diabetes	12 (17.1)	3 (27.3)	9 (15.3)	0.281
Liver cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	*n.d.*
Neurological disorders	1 (1.4)	0 (0.0)	1 (1.7)	0.843
Use of steroid	2 (2.9)	0 (0.0)	2 (3.4)	0.708
Use of anticoagulants and/or antiplatelet agents	17 (24.3)	2 (18.2)	15 (25.4)	0.467
Cause, n (%)				0.539
Cancer	66 (94.3)	10 (90.9)	56 (94.9)	
the Japanese Society for Cancer of the Colon and Rectum guidelines				
Stage I	16 (22.9)	3 (27.3)	13 (22.0)	
Stage II	26 (37.1)	3 (27.3)	23 (39.0)	
Stage III	17 (24.3)	4 (36.4)	13 (22.0)	
Stage IV	7 (10.0)	0 (0.0)	7 (11.9)	
Adenoma	1 (1.4)	0 (0.0)	1 (1.7)	
Mucocele of the appendix	2 (2.9)	1 (9.1)	1 (1.7)	
Malignant lymphoma	1 (1.4)	0 (0.0)	1 (1.7)	
Surgical Approach (Open/Laparoscopic)	8 (11.4)/62 (88.6)	3 (27.2)/8 (72.7)	5 (8.5)/54 (91.5)	0.105
Surgical Intervention, n (%)				0.070
Ileocecal resection	8 (11.4)	2 (18.2)	6 (10.2)	
Right hemicolectomy	12 (17.1)	1 (9.1)	11 (18.6)	
Transverse colectomy	1 (1.4)	0 (0.0)	1 (1.7)	
Left hemicolectomy	4 (5.7)	0 (0.0)	4 (6.8)	
Sigmoidectomy	11 (15.7)	2 (18.2)	9 (15.3)	
High anterior resection	4 (5.7)	0 (0.0)	4 (6.8)	
Low anterior resection	20 (28.6)	2 (18.2)	18 (30.5)	
Abdomino-perineal resection	6 (8.6)	3 (27.3)	3 (5.1)	
Hartmann operation	4 (5.7)	1 (9.1)	3 (5.1)	
Operation time, min	305.5 (210.8–371.3)	330.0 (169.0–439.0)	304.0 (212.0–366.0)	0.846
Amount of bleeding, mL	0 (0–105)	0 (0–535)	0 (0–100)	0.345
Transfusion, n (%)	3 (4.3)	1 (9.1)	2 (3.4)	0.406
PRBC, U	0 (0–0)	0 (0–0)	0 (0–0)	
FFP, U	none	none	none	
PC, U	none	none	none	
Postoperative hospitalization, days	12 (7–199)	18 (10–34)	11 (10–16)	0.249
Outcome, n (%)				
In hospital mortality	0 (0.0)	0 (0.0)	0 (0.0)	*n.d.*
Development of PE	0 (0.0)	0 (0.0)	0 (0.0)	*n.d.*
Development of DVT	11 (15.7)			
Proximal/Distal	0 (0.0)/11 (15.7)			
Symptomatic/Asymptomatic	0 (0.0)/11 (15.7)			
Complications (Clavien-Dindo classification ≥grade 2)	21 (30.0)	3 (27.3)	18 (30.5)	0.570
Paralytic ileus	9 (12.9)	1 (9.1)	8 (13.6)	0.568
Surgical site infection	4 (5.7)	0 (0.0)	4 (6.8)	0.496
Anastomotic leakage	4 (5.7)	1 (9.1)	3 (5.1)	0.503
Anastomotic bleeding	2 (2.9)	0 (0.0)	2 (3.4)	0.708
Urinary tract infection	1 (1.4)	0 (0.0)	1 (1.7)	0.843
Bacterial translocation	1 (1.4)	1 (9.1)	0 (0.0)	0.157

Values are presented as the median (interquartile range: IQR) or number (%), if appropriate. VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep venous thrombosis; BMI, body mass index; PRBC, packed red blood cells; FFP, fresh frozen plasma; PC, platelet concentrates

Table 2. Preoperative Laboratory Data.

[Normal range]	Total (n=70)	DVT (+) (n=11)	DVT (-) (n=59)	*p* value
WBC [3500–9000]/μL	5400 (4800–6725)	6000 (4900–7500)	5400 (4800–6700)	0.286
HGB [11.3–15.2] g/dL	12.1 (10.3–14.1)	12.8 (10.5–14.3)	11.9 (10.2–14.0)	0.737
HCT [35.0–52.0] %	36.9 (32.5–42.0)	39.0 (30.7–43.9)	36.1 (32.5–41.9)	0.617
PLT [15.0–40.0]×10^4/μL	22.4 (17.2–30.5)	22.3 (18.7–33.4)	22.5 (16.9–30.0)	0.735
SF [<7.0] μg/mL	3.0 (3.0–3.0)	3.0 (3.0–3.8)	3.0 (3.0–3.0)	0.694
TAT [<3.0] μg/L	1.2 (0.9–1.6)	1.7 (1.2–2.2)	1.1 (0.9–1.5)	0.036
APTT [21.5–43.1] sec	26.7 (25.4–29.4)	26.5 (25.4–28.2)	26.8 (25.4–29.5)	0.594
PT [80.0–120.0] %	95.8 (86.7–112.0)	100.1 (94.1–120.3)	94.1 (85.5–106.9)	0.098
HPT [70.0–130.0] %	101.8 (92.5–123.5)	99.2 (94.0–123.3)	101.8 (92.3–124.0)	0.968
Fbg [200–400] mg/dL	333.5 (298.3–403.8)	368 (315–510)	323 (296–403)	0.276
AT [80.0–120.0] %	95.5 (85.9–108.2)	93.9 (82.7–107.8)	95.7 (86.0–108.3)	0.910
PC [82.0–112.0] %	97.3 (86.0–109.4)	99.2 (84.1–120.1)	96.9 (86.6–109.2)	0.646
PLG [80.0–130.0] %	100.4 (90.6–112.3)	105.9 (95.5–115.3)	100.2 (90.0–110.7)	0.463
α_2PI [80.0–130.0] %	102.1 (91.7–109.7)	102.3 (92.8–112.3)	101.8 (90.6–109.4)	0.923
FDP [<5.0] μg/mL	3.2 (2.5–4.5)	4.4 (2.4–6.1)	3.0 (2.5–4.1)	0.131
D-dimer [<1.0] μg/mL	0.9 (0.6–1.3)	1.1 (0.7–2.0)	0.8 (0.6–1.2)	0.102
PIC [0.0–0.8] μg/mL	1.0 (0.8–1.5)	1.2 (0.9–1.8)	1.0 (0.8–1.4)	0.112
CRP [<0.3] mg/dL	0.1 (0.1–0.4)	0.09 (0.05–0.43)	0.13 (0.05–0.42)	0.809

WBC: white blood cell; HGB: hemoglobin; HCT: hematocrit; PLT: platelet; SF: soluble fibrin; TAT: thrombin-antithrombin complex; APTT: activated partial thromboplastin time; PT: prothrombin time; HPT: hepaplastin test; Fbg: fibrinogen; AT: antithrombin; PC: protein C; PLG: plasminogen; α_2PI: α_2-plasmin inhibitor; FDP: fibrin/fibrinogen degradation product; PIC: plasmin-α_2-plasmin inhibitor complex; CRP: C-reactive protein

SF, TAT, FDP and D-dimer were independently useful for predicting the new onset of thrombosis at each postoperative point. The evaluation of these markers might be effective in the management of postoperative thromboprophylaxis.

In the current study, almost all patients underwent surgery for cancer without pharmacologic thromboprophylaxis, asymptomatic and distal-type DVT, which is frequently diagnosed in clinical practice, was observed in a small number of cases. The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines consider patients with a fatal PE risk of 0.4 to 1.0%, symptomatic PE risk of 2 to 4%, proximal DVT risk of 4 to 8% or distal DVT risk of 20 to 40% without prophylaxis to be at high risk and recommend perioperative pharmacologic thromboprophylaxis[8]. According to this risk assessment, the distal DVT incidence of 15.7% in the present study was relatively low and would be categorized as a moderate risk of VTE. So far, a high incidence of VTE after colorectal surgery has been reported in previous studies[5-7,17]. Moreover, patients with cancer are at increased risk of VTE[18]. VTE incidence in Japan has been thought to be almost the same as that in Western countries[5], however, some recent Japanese reports demonstrated that the incidence of VTE after colorectal surgery was much lower than expected[3,9,10]. They suggested that perioperative pharmacologic thromboprophylaxis following colorectal surgery may be restricted in Japanese patients. Many risk factors, such as malignancy, major surgery, increasing age, prolonged immobility, prior VTE and chronic heart failure have been convincingly demonstrated for VTE[8]. Identically, the incidence rate of VTE is heterogeneous among races, and is lower in Asian subjects than in European subjects[19]. In recent years, laparoscopic surgery has been widely performed for various cancers, including colorectal cancer, which is associated with a lower VTE rate than open surgery[20]. In this context, the perioperative VTE risk might have come to be more strongly influenced by individual factors including race than surgical factors in the evolution of minimally invasive surgery which can reduce the rate of VTE development. We need to consider the strength of individual risk factors and risk-stratified applications of perioperative pharmacologic thromboprophylaxis rather than routine prophylaxis in colorectal surgery. Even though anticoagulation is cautiously recommended for high-risk distal DVT, such as that seen in patients with active cancer, unprovoked DVT, and inpatient status by the international guidelines[21], the optimal management of isolated distal DVT remains undefined[22-24]. Under such circumstances, electing not to implement perioperative pharmacologic thromboprophylaxis might be an option. For such cases, VTE risk assessment of postoperative factors should be considered to determine the appropriate thromboprophylaxis.

The new development of DVT after surgery may indicate the presence of perioperative excessive thrombotic tendency. The evaluation of this thrombotic tendency using the coagulofibrinolytic markers in this study revealed that four mark-

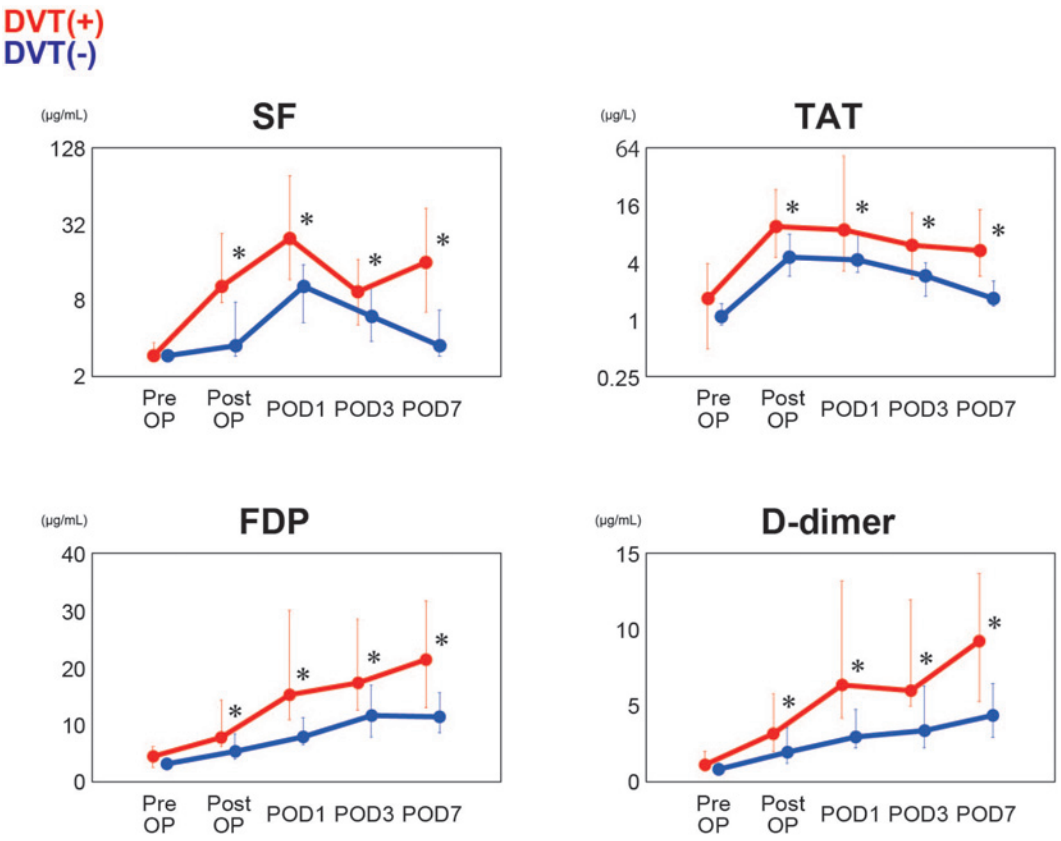

Figure 1. Comparisons of time course changes in SF, TAT, FDP and D-dimer between patients with and without DVT.

Central marks represent median values, and upper and lower whiskers represent 25th to 75th percentiles, respectively. The red lines represent the values of the patients with DVT, and the blue lines represent those without DVT. DVT: deep vein thrombosis; SF: soluble fibrin; TAT: thrombin-antithrombin complex; FDP: fibrin/fibrinogen degradation product. *p<0.05.

ers, SF, TAT, FDP and D-dimer, were significantly higher in patients with DVT than those without DVT during the postoperative period, and each marker changed in a mutual relationship. We measured the values of SF and TAT as parameters of coagulation activation. SF is generated during thrombin-fibrinogen reactions, and its elevation reflects hypercoagulation. Thrombin is inactivated by forming TAT with antithrombin; thus, TAT values reflect thrombin activity. Activated plasmin lyses fibrinogen and fibrin to make FDP and D-dimer, so these two markers reflect coagulofibrinolytic activation. In such a situation, our results clearly demonstrated that the excessive postoperative coagulofibrinolytic responses that can cause the development of DVT were sensitively detected using these markers.

To date, D-dimer is used internationally used as one indicator of the development of VTE[11,12]; however, its diagnostic accuracy after surgery is suboptimal because perioperative coagulofibrinolytic changes lead to a high rate of false-positive results[13]. We demonstrated that coagulofibrinolytic markers were useful for predicting the development of postoperative DVT when we set cut-off values taking the physiological perioperative coagulofibrinolytic responses into consideration. These markers change due to surgical stress[14]. In the current study, coagulation activation shown by SF and TAT values was observed immediately after operation to POD 1. In contrast, FDP and D-dimer continued to increase until POD 7, which might be due to a relationship between initial coagulation activation and delayed physiological fibrinolytic activation. In this situation, these four markers showed significant differences at each point of postoperative timing between patients with and without DVT. These physiological coagulofibrinolytic responses lead to a high rate of false-positive results for diagnosing VTE, but our results demonstrated that SF, TAT, FDP and D-dimer were useful for predicting the development of DVT when we set cut-off values that take the perioperative coagulofibrinolytic responses and evaluation timing into consideration. Furthermore, each marker changes in relation to each other, thus we can predict DVT by measuring any one of the four markers at each postoperative point. The four markers detected asymptomatic and distal-type DVT, indicating that they were extremely sensitive for predicting the development

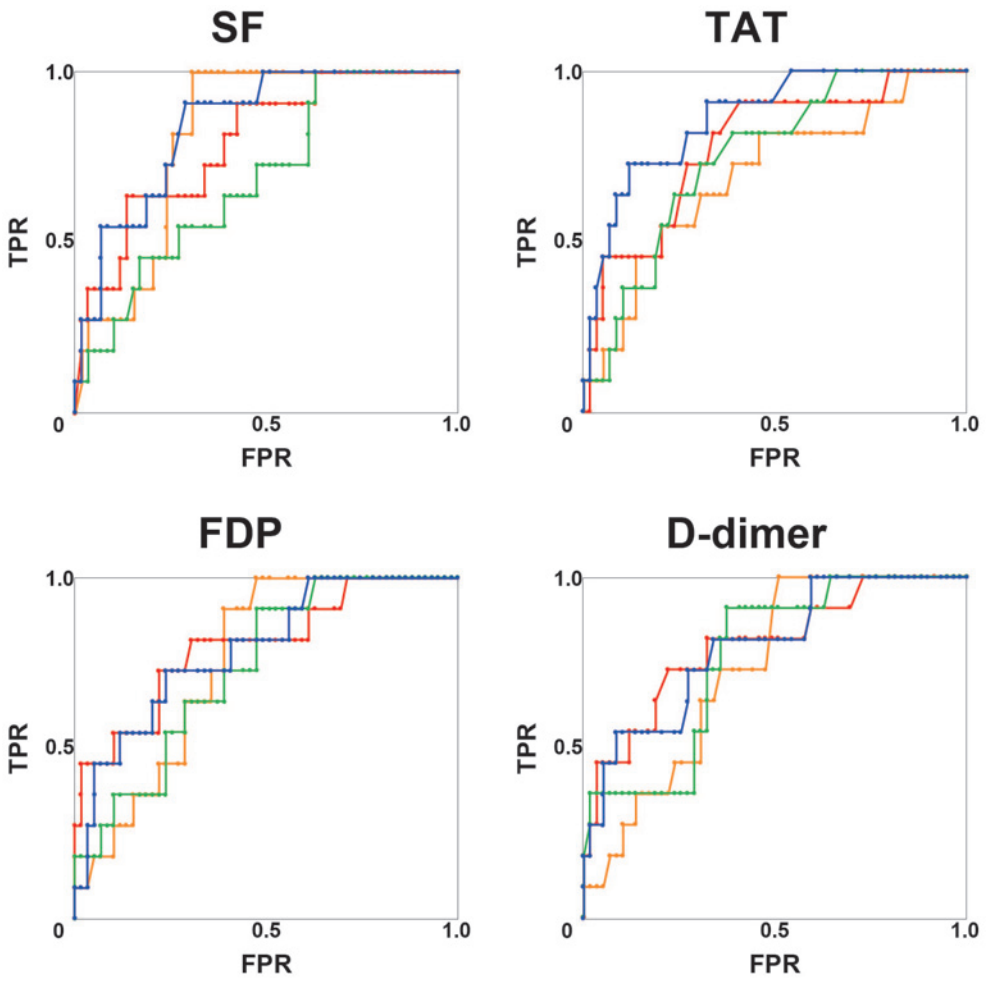

Figure 2. ROC analyses for predicting DVT using four coagulofibrinolytic markers: SF, TAT, FDP and D-dimer.
ROC curves immediately after surgery (Post OP), and on PODs 1, 3 and 7. Yellow lines represent the values of Post OP; red, POD1; green, POD3; and blue, POD7, respectively. ROC: receiver-operating-characteristic; TPR: true positive rate; FPR: false positive rate

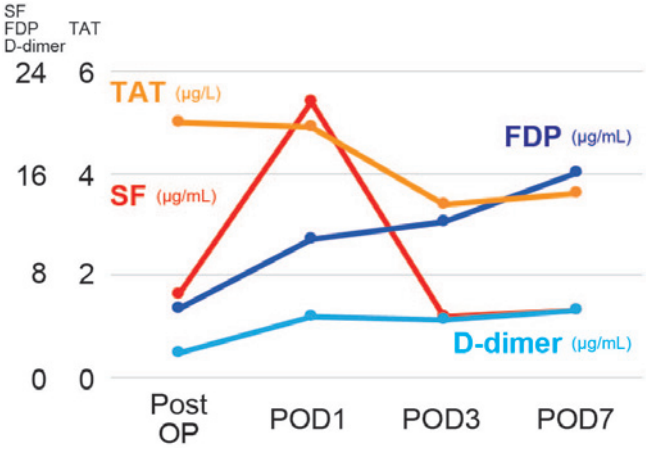

Figure 3. Longitudinal changes of cut-off values for predicting the development of DVT in SF, TAT, FDP and D-dimer.

of VTE. It is assumed that the markers can more sensitively detect the development of symptomatic DVT or PE than distal-type DVT. The perioperative coagulofibrinolytic responses are similar, but the degree or duration of their alternations may differ depending on the cause of insults, surgical method or anesthesia[25,26]. Indeed, the positive predictive cut-off values of D-dimer for VTE varied widely in previous studies of various types of operations[27-30]. As such, we need to select a condition such as a surgical procedure so as to be able to adequately evaluate the perioperative changes in the coagulofibrinolytic markers. The evaluation of coagulofibrinolytic markers showed high predictive ability for a tendency of thrombosis immediately after surgery, so anticoagulant therapy should be considered for patients whose markers show elevated levels beyond the physiological ranges. The incidence of VTE was reduced with perioperative thromboprophylaxis; however, subsequently, it

Table 3. Cut-off Value, Sensitivity and Specificity of SF, TAT, FDP and D-dimer for Predicting the Development of DVT.

		Cut-off value	Sensitivity (%)	Specificity (%)	AUC	Standard error	*p* value	95%CI	
								Lower limit	Upper limit
SF (μg/mL)	Post OP	6.5	1.000	0.695	0.819	0.051	0.001	0.718	0.920
	POD1	21.6	0.636	0.847	0.797	0.068	0.002	0.663	0.930
	POD3	4.8	1.000	0.373	0.688	0.080	0.049	0.532	0.844
	POD7	5.3	0.910	0.711	0.847	0.053	<0.001	0.742	0.952
TAT (μg/L)	Post OP	5	0.818	0.542	0.700	0.087	0.040	0.525	0.867
	POD1	4.9	0.909	0.593	0.784	0.074	0.003	0.638	0.929
	POD3	3.4	0.818	0.576	0.751	0.070	0.009	0.613	0.889
	POD7	3.6	0.727	0.881	0.865	0.054	<0.001	0.759	0.972
FDP (μg/mL)	Post OP	5.4	1.000	0.530	0.755	0.061	0.008	0.635	0.875
	POD1	10.8	0.820	0.695	0.801	0.077	0.002	0.651	0.952
	POD3	12.2	0.910	0.525	0.737	0.071	0.013	0.597	0.877
	POD7	16.0	0.727	0.762	0.791	0.071	0.002	0.653	0.930
D-dimer (μg/mL)	Post OP	1.9	1.000	0.492	0.732	0.066	0.015	0.602	0.862
	POD1	4.8	0.727	0.780	0.799	0.076	0.002	0.650	0.947
	POD3	4.5	0.91	0.627	0.763	0.070	0.006	0.626	0.900
	POD7	5.2	0.82	0.661	0.796	0.071	0.002	0.656	0.935

AUC: area under the curve; CI, confidence interval

has remained largely unchanged despite increases in pharmacologic prophylaxis[17,31]. In addition to the conventional preoperative VTE risk assessment, multifaceted risk assessment including postoperative factors might be necessary. The real benefit of measuring coagulofibrinolytic markers is to sensitively detect the thrombogenic tendency and to evaluate the management of postoperative thromboprophylaxis regardless of whether or not perioperative pharmacologic thromboprophylaxis is implemented. We recommend the evaluation of coagulofibrinolytic markers at least once after surgery for patients who are at high risk of developing of VTE or who do not receive pharmacologic thromboprophylaxis. Imaging evaluation of the development of VTE using ultrasonography or enhanced CT should be considered, and pharmacologic thromboprophylaxis should be implemented (or the dose increased) when any of the four markers (SF, TAT, FDP and D-dimer) increase beyond the perioperative physiological response. In terms of thromboprophylaxis, it is reasonable that we should predict the thrombogenic tendency to develop VTE based on the level of sensitivity of detecting asymptomatic and distal-type DVT.

This study has some limitations. First, it was a retrospective single-center study with a small sample size, and the cases were heterogeneous in terms of surgical indication and procedure. A large-scale, prospective study adjusted for factors associated with perioperative coagulofibrinolytic responses is needed to confirm the results. Second, we demonstrated that the four coagulofibrinolytic markers could predict the thrombogenic tendency to develop VTE, although whether evaluation of the markers can reduce symptomatic VTE has not been validated. Additional research is needed to verify the effect of assessing the markers for reducing VTE development is needed. Finally, we excluded patients who were unable to discontinue anticoagulant and/or antiplatelet medications during the study period due to a high risk of exacerbation of thromboembolic complications associated with comorbidities. Although we could have included the patients with a relatively low risk of VTE, our aim of this study was to evaluate the rate of VTE development among patients who did not receive pharmacologic thromboprophylaxis during the perioperative period, as well as the ability of coagulofibrinolytic markers to predict VTE development under the natural coagulofibrinolytic responses to surgery.

Conclusion

The incidence of postoperative VTE was low in patients with colorectal surgery, even in those who did not receive perioperative pharmacologic thromboprophylaxis. We might need to consider the individual risk-stratified applications of perioperative pharmacologic thromboprophylaxis rather than routine prophylaxis in colorectal surgery. SF, TAT, FDP and D-dimer were independently useful for predicting the postoperative development of DVT at each postoperative point when we set cut-off values that take the physiological perioperative coagulofibrinolytic responses into consideration. Measuring coagulofibrinolytic markers might be effective for detecting postoperative VTE and evaluating the management of postoperative thromboprophylaxis, regardless of whether

or not perioperative pharmacologic thromboprophylaxis is implemented.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

All authors contributed to conceive and design the study. HM, YY, KI, SK and SA prepared the data. HM and KI analyzed the date. SK, MY, HE and YW assisted and supervised the study. HM and KI wrote the manuscript. All authors read the manuscript and agree with the contents.

Approval by Institutional Review Board (IRB)

This study was approved by the Ethics Committee for Clinical Research of Ehime University Hospital (No. 1902015). The requirement to obtain informed consent for this study was waived because of the retrospective design.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets for the current study are available from the corresponding author upon reasonable request.

References

1. Lindblad B, Eriksson A, Bergqvist D. Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988. Br J Surg. 1991 Jul; 78(7): 849-52.
2. Kuroiwa M, Morimatsu H, Tsuzaki K, et al. Changes in the incidence, case fatality rate, and characteristics of symptomatic perioperative pulmonary thromboembolism in Japan: results of the 2002-2011 Japanese Society of Anesthesiologists perioperative pulmonary thromboembolism (JSA-PTE) study. J Anesth. 2015 Jun; 29(3): 433-41.
3. Takeda C, Yamashita Y, Takeuchi M, et al. Incidence, clinical characteristics and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study. BMJ Open. 2022 Feb; 12(2): e055090.
4. Kunisawa S, Ikai H, Imanaka Y. Incidence and prevention of postoperative venous thromboembolism: are they meaningful quality indicators in Japanese health care settings? World J Surg. 2012 Feb; 36(2): 280-6.
5. Sakon M, Maehara Y, Yoshikawa H, et al. Incidence of venous thromboembolism following major abdominal surgery: a multicenter, prospective epidemiological study in Japan. J Thromb Haemost. 2006 Mar; 4(3): 581-6.
6. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, et al. A nationwide analysis of postoperative deep vein thrombosis and pulmonary embolism in colon and rectal surgery. J Gastrointest Surg. 2014 Dec; 18(12): 2169-77.
7. Bouras G, Burns EM, Howell A-M, et al. Risk of Post-Discharge Venous Thromboembolism and Associated Mortality in General Surgery: A Population-Based Cohort Study Using Linked Hospital and Primary Care Data in England. PLoS One. 2015 Dec; 10(12): e0145759.
8. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2 Suppl): e227S-77S.
9. Kamachi H, Homma S, Kawamura H, et al. Intermittent pneumatic compression versus additional prophylaxis with enoxaparin for prevention of venous thromboembolism after laparoscopic surgery for gastric and colorectal malignancies: multicentre randomized clinical trial. BJS open. 2020 Oct; 4(5): 804-10.
10. Hata T, Yasui M, Ikeda M, et al. Efficacy and safety of anticoagulant prophylaxis for prevention of postoperative venous thromboembolism in Japanese patients undergoing laparoscopic colorectal cancer surgery. Ann Gastroenterol Surg. 2019 Jul; 3(5): 568-75.
11. Wada H, Kobayashi T, Abe Y, et al. Elevated levels of soluble fibrin or D-dimer indicate high risk of thrombosis. J Thromb Haemost. 2006 Jun; 4(6): 1253-8.
12. de Moerloose P, Desmarais S, Bounameaux H, et al. Contribution of a new, rapid, individual and quantitative automated D-dimer ELISA to exclude pulmonary embolism. Thromb Haemost. 1996 Jan; 75(1): 11-3.
13. Chen CJ, Wang CJ, Huang CC. The value of D-dimer in the detection of early deep-vein thrombosis after total knee arthroplasty in Asian patients: a cohort study. Thromb J. 2018 May; 6: 5.
14. Matsumoto H, Ishimaru K, Kikuchi S, et al. Perioperative coagulofibrinolytic responses in colorectal surgery patients without chemical thromboprophylaxis: a retrospective observational study. Surgery Today. 2022 Jun; 52(6): 904-13.
15. Watanabe T, Itabashi M, Shimada Y, et al; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2010 for the Treatment of Colorectal Cancer. J Clin Oncol. 2012 Feb; 17(1): 1-29.
16. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2004 Aug; 240 (2): 205-13.
17. Colorectal Writing Group for Surgical Care and Outcomes Assessment Program-Comparative Effectiveness Research Translation Network (SCOAP-CERTAIN) Collaborative. Thromboembolic Complications and Prophylaxis Patterns in Colorectal Surgery. JAMA Surg. 2015 Aug; 150(8): 712-20.
18. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. Blood. 2013 Sep; 122(10): 1712-23.
19. Liao S, Woulfe T, Hyder S, et al. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. J Thromb Haemost. 2014 Feb; 12(2): 214-9.
20. Nguyen NT, Hinojosa MW, Fayad C, et al. Laparoscopic surgery is associated with a lower incidence of venous thromboembolism compared with open surgery. Ann Surg. 2007 Dec; 246(6): 1021-7.
21. Chopard R, Albertsen IE, Piazza G. Diagnosis and treatment of lower extremity venous thromboembolism: A review. JAMA. 2020 Nov; 324(17): 1765-76.
22. Franco L, Giustozzi M, Agnelli G, et al. Anticoagulation in patients with isolated distal deep vein thrombosis: a meta-analysis. J Thromb Haemost. 2017 Jun; 15: 1142-54.
23. Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant ther-

apy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol. 2016 Dec; 3(12): e556-62.

24. Luo X, Zhang L, Hou C, et al. Hospitalized patients with isolated distal deep vein thrombosis: anticoagulation therapy or not? Thromb J. 2022 Sep; 20(1): 52.

25. López Y, Páramo JA, Valentí JR, et al. Hemostatic markers in surgery: a different fibrinolytic activity may be of pathophysiological significance in orthopedic versus abdominal surgery. Int J Clin Lab Res. 1997; 27(4): 233-7.

26. Schietroma M, Carlei F, Mownah A, et al. Changes in the blood coagulation, fibrinolysis, and cytokine profile during laparoscopic and open cholecystectomy. Surg Endosc. 2004 Jul; 18(7): 1090-6.

27. Mitani G, Takagaki T, Hamahashi K, et al. Associations between venous thromboembolism onset, D-dimer, and soluble fibrin monomer complex after total knee arthroplasty. J Orthop Surg Res. 2015 Nov; 10: 172.

28. Natsumeda M, Uzuka T, Watanabe J, et al. High Incidence of Deep Vein Thrombosis in the Perioperative Period of Neurosurgical Patients. World Neurosurg. 2018 Apr; 112: e103-12.

29. Shi A, Huang J, Wang X, et al. Postoperative D-dimer predicts venous thromboembolism in patients undergoing urologic tumor surgery. Urol Oncol. 2018 Jun; 36(6): 307.e15-21.

30. Tian B, Song C, Li H, et al. The significance of perioperative coagulation and fibrinolysis related parameters after lung surgery for predicting venous thromboembolism: a prospective, single center study. J Thorac Dis. 2018 Apr; 10(4): 2223-30.

31. Konstantinides SV, Barco S, Lankeit M, et al. Management of Pulmonary Embolism: An Update. J Am Coll Cardiol. 2016 Mar; 67 (8): 976-90.