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Asymptomatic Venous Thromboembolism After Hepatobiliary–Pancreatic Surgery: Early Detection Using D-dimer and Soluble Fibrin Monomer Complex Levels

Hikaru Hayashi | Akira Shimizu [ID] | Koji Kubota | Tsuyoshi Notake | Shinsuke Sugenoya | Hitoshi Masuo | Kiyotaka Hosoda | Koya Yasukawa | Ryoichiro Kobayashi | Yuji Soejima

Division of Gastroenterological, Hepato-Biliary-Pancreatic, Transplantation and Pediatric Surgery, Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Correspondence
Akira Shimizu, Division of Gastroenterological, Hepato-Biliary-Pancreatic, Transplantation and Pediatric Surgery, Department of Surgery, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto, Nagano, 390-8621, Japan
Email: ashimizu@shinshu-u.ac.jp

Abstract

Aim: The aim was to investigate the usefulness of a preemptive management strategy that includes monitoring serum D-dimer (DD) and soluble fibrin monomer complex (SFMC) levels for early detection and treatment of venous thromboembolism (VTE) after hepatobiliary–pancreatic (HBP) surgery.

Methods: Overall, 678 patients who underwent HBP surgery between January 2010 and March 2020 were enrolled. Patients with increased postoperative serum DD or SFMC levels underwent contrast-enhanced computed tomography, and those with VTE received anticoagulant agents. The VTE risk factors were investigated using multivariable analysis. Postoperative changes in DD and SFMC levels were verified, and their ability to identify VTE was evaluated using receiver operating characteristic (ROC) analysis.

Results: VTE developed in 83 patients (12.2%), and no symptomatic VTE or death due to VTE was observed. Multivariable analysis identified female sex (odds ratio [OR] 2.26; 95% confidence interval [CI] 1.41–3.60; $P < .001$) and surgery duration of ≥401 min (OR 2.07; 95% CI 1.27–3.35; $P < .001$) as independent risk factors for VTE. Maximum serum DD and SFMC levels in patients who developed VTE were significantly higher than those in patients without VTE (DD, 15.1 vs 8.9 μg/mL, $P < .001$; SFMC, 18.0 vs 10.2 μg/mL, $P < .001$, respectively). Both DD (n = 678) and the combination of DD and SFMC levels (n = 230) showed a good ability to detect VTE (area under the ROC curve, 0.804 and 0.761, respectively).

Conclusion: Our preemptive strategy of monitoring serum DD and SFMC levels enables early detection and treatment intervention of VTE after HBP surgery.

KEYWORDS
D-dimer, hepatobiliary–pancreatic surgery, prophylactic anticoagulation, soluble fibrin monomer complex, venous thromboembolism

1 | INTRODUCTION

The overall incidence of venous thromboembolism (VTE) in patients who underwent general surgery without prophylactic treatment is approximately 20%–30%.[1] Thromboembolism is a potentially fatal postoperative event; therefore, patients should be managed on the basis of strategies including compression stockings, intermittent pneumatic compression (IPC) devices, and anticoagulant therapy.[2,3] For example, the incidence of deep vein thrombosis (DVT) in patients receiving anticoagulant therapy is approximately 10%.[4] Particularly in the field of orthopedic surgery, postoperative chemoprophylaxis is a widely accepted procedure to minimize the incidence of postoperative VTE events; however, strategies for perioperative management to prevent VTE in patients undergoing hepatobiliary–pancreatic (HBP) surgery remain controversial. Although patients undergoing HBP surgery often have comorbidities that are commonly associated with VTE, the risk of bleeding is perceived by some surgeons to outweigh the risk of postoperative VTE in some cases.[5] Furthermore, prophylactic anticoagulant therapy may be a disadvantage because of the high medical cost or interference when removing the epidural catheter. Early therapeutic intervention is required after VTE development; however, clinical symptoms alone will not likely lead to early detection of VTE. Therefore, the establishment of strategies to manage VTE using effective and appropriate indicators in patients who underwent HBP surgery is required.

D-dimer (DD) and soluble fibrin monomer complex (SFMC) levels are useful clinical biomarkers to exclude VTE, including DVT and pulmonary thromboembolism (PTE).[6] We hypothesized that measurement of these markers is beneficial after HBP surgery, and thus, we routinely measured serum DD levels after HBP surgery since January 2010 (SFMC in addition to DD, which has been measurable since July 2016 at our institute), and we have used these markers as indicators to detect and treat VTE without the routine use of postoperative chemoprophylaxis. Patients with increased serum DD or SFMC levels undergo contrast-enhanced computed tomography (CT) unless they have an allergy to the contrast medium to confirm the existence and location of VTE. When this VTE is identified via this imaging study, patients are treated using anticoagulant agents.

The present study aimed to investigate the clinical benefit, safety, and usefulness of the aforementioned preemptive management strategy that includes monitoring of DD and SFMC levels for the early detection and treatment of VTE after HBP surgery.

2 | METHODS

There were 829 patients who underwent liver resection and/or pancreatectomy and/or bile duct resection between January 2010 and March 2020 who were identified as candidates for the present study. Among them, patients who had DVT and/or PTE at the time of surgery, had abnormal coagulability, or received anticoagulation therapy and/or antiplatelet drugs without a VTE diagnosis were excluded. Finally, 678 patients were enrolled in this study and were categorized into two groups on the basis of the presence or absence of VTE within 30 d after surgery. Demographic and clinicopathological variables, including age, sex, body mass index, surgical details (type and extent of resection), and short-term outcomes, such as postoperative complications, were recorded. The Caprini score[3] and the data elements contributing to the Caprini score were also recorded. This study was approved by the Ethics Committee of Shinshu University School of Medicine (approval no. 4841) and conducted in accordance with the principles of the Declaration of Helsinki.

2.1 | Perioperative management

All patients in this study underwent mechanical prophylaxis, including compression stockings and IPC devices, from induction of general anesthesia to postoperative ambulation. No patient received anticoagulation therapy for prophylaxis against VTE. Each day for at least 1 wk after surgery, serum DD levels were measured, and if the serum DD level increased by >10 µg/mL or if a clinical finding strongly suggested VTE, contrast-enhanced chest-to-lower-extremity CT was performed to evaluate the presence or absence and location of VTE unless the patient had an allergy to the contrast medium. The SFMC level was also routinely measured from July 2016, and if the serum SFMC level increased by >10 µg/mL, a CT was performed even if the DD level was low. Furthermore, the level of antithrombin III (AT III), which is primarily a potent anticoagulant with independent antiinflammatory properties, has been routinely measured, and it has been routinely administered if AT III levels are <70%. Moreover, 2–3 wk after discharge from the hospital, patients were followed-up and serum DD and SFMC levels were assessed. If abnormal findings were observed, CT was performed.

Serum DD and SFMC levels were measured using the Nano-pia kit (Sekisui Medical, Tokyo, Japan), both of which were based on the latex agglutination immunoassay. All qualified laboratory technicians who interpreted both test results were unaware of the patients' clinical presentation or the results of other objective tests. On the basis of the manufacturer's information, the DD and SFMC reference ranges were <1.0 and <7.0 µg/mL, respectively.

2.2 | Definition

Postoperative complications were defined and classified in accordance with the Clavien–Dindo classification.[7] VTE was categorized into DVT and/or PTE and others. Posthepatectomy liver failure (PHLF), posthepatectomy bile leak (PHBL), and postoperative pancreatic fistula (POPF) were diagnosed and graded in accordance with the criteria of the International Study Group of Liver Surgery[8] and the updated criteria of the International Study Criteria of Pancreatic Surgery.[9]

2.3 | Data handling and statistical analysis

All data were retrospectively collected by a research assistant and stored in a computer database. Statistical analysis was performed using the chi-square test or Fisher's exact test to compare categorical variables and the Mann–Whitney U-test to compare continuous variables. A multivariate analysis using logistic regression analysis was conducted to identify independent significant factors for VTE following HBP surgery, including all variables with P-values of <.05 in the univariable analysis. A P-value of <.05 was considered statistically significant. The detection power of DD and SFMC for VTE was examined using a receiver operating characteristic (ROC) analysis, and the cutoff values were also determined using ROC analysis and the Youden index. All statistical data analyses were performed using JMP 14 (SAS Institute, Cary, NC).

3 | RESULTS

Overall, VTE was observed in 83 patients (12.2%), and the median surgery duration was 401 min, median inflow occlusion time was 32 min, and median blood loss was 300 mL. The comparison of background characteristics, preoperative laboratory data, surgical outcomes, and postoperative outcomes between patients with (n = 83) and without (n = 595) VTE is summarized in Table 1. In patients with VTE, the ratio of females to males was significantly higher (52% vs 33%, P = .001) and the surgery duration was significantly longer (503 vs 395 min, P = .005) than that in patients without VTE. No significant difference was observed between the two groups for the other parameters, which were age, preoperative comorbidities, laboratory data including preoperative DD and SFMC levels, and operative procedures. The Caprini score was also comparable between the two groups (P = .675), and ≥95% of patients had a high risk (Caprini score ≥5 points) of developing VTE in this study. Although the mortality rate, proportion of complications that were Clavien–Dindo Grade III or higher, and incidence of other complications, including hemorrhage, PHLF, POPF, and PHBL, were all comparable between patients with and without VTE; the duration of postoperative hospital stay in patients with VTE was significantly longer than that in patients without VTE (20 vs 14 d, P = .001). Multivariable analysis revealed that the female sex (odds ratio [OR] 2.26; 95% confidence interval [CI] 1.41–3.60; P < .001) and a surgery duration of ≥401 min (OR 2.07; 95% CI 1.27–3.35; P < .001) were the independent risk factors for VTE (data not shown).

3.1 | Treatments and outcomes in patients who developed VTE

Treatment interventions for VTE, outcomes, and adverse events are summarized in Table 2. VTE developed in 83 patients (12.2%), including DVT and/or PTE in 56 (8.3%), portal vein thrombosis (PVT)

TABLE 1 Patients' characteristics, clinicopathological findings, and surgical and short-term outcomes

	VTE (−)	VTE (+)	
	(n = 595)	(n = 83)	P
Age (y)[a]	69 (20-89)	69 (42-85)	.670
Sex (male:female)	399:196	40:43	.001
Body mass index (kg/m^2)			
<25	474 (80)	62 (75)	.307
≥25	121 (20)	21 (25)	
Social history			
Smoking	342 (58)	41 (49)	.161
Drinking	407 (69)	55 (66)	.681
Preoperative comorbidity			
Hypertension	266 (45)	37 (45)	.983
Diabetes mellitus	153 (26)	28 (34)	.130
Atrial fibrillation	8 (1)	3 (4)	.175
Dialysis	3 (1)	0 (0)	.376
Abnormal pulmonary function	56 (9)	8 (10)	.955
Post PCI or CABG	21 (4)	1 (1)	.206
Anticoagulant	18 (5)	7 (11)	.096
Cerebral vascular accident	19 (3)	3 (4)	.844
History of VTE	1 (1)	0 (0)	.609
Family history of clotting disorder	0 (0)	0 (0)	—
Laboratory data			
Albumin (g/dL)[a]	4.0 (2.4–5.2)	4.1 (2.6–4.7)	.685
AST (units/L)[a]	25 (6–310)	25 (12–75)	.714
ALT (units/L)[a]	27 (4–450)	28 (7–189)	.822
Creatinine (mg/dL)[a]	0.76 (0.35–150)	0.74 (0.34–1.25)	.287
PLT (×10^3/μL)[a]	17.8 (4.0–49.1)	19.7 (5.3–53.2)	.058
PT-INR[a]	1.04 (0.89–1.27)	1.03 (0.92–1.20)	.619
DD (μg/mL)[a]	0.8 (0.3–7.3)	0.9 (0.5–3.7)	.257
SFMC (μg/mL)[a]	3.0 (3.0–10.4)	3.0 (3.0–8.1)	.148
AT III[a]	94.1 (52–120)	97.1 (71–120)	.054
Preoperative central venous catheter	46 (55)	37 (45)	.001
Caprini score			
0-2 (Low risk)	3 (1)	0 (0)	.675[b]
3-4 (Moderate risk)	21 (4)	3 (4)	
≥5 (High risk)	571 (95)	80 (96)	
Diagnosis			
Hepatocellular carcinoma	279 (47)	28 (34)	.105
Colorectal liver metastasis	63 (10)	8 (10)	
Intrahepatic cholangiocarcinoma	15 (3)	3 (4)	
Extrahepatic cholangiocarcinoma	57 (10)	11 (13)	
Ampullary cancer	19 (3)	2 (2)	

TABLE 1 (Continued)

	VTE (–)	VTE (+)	
	(n = 595)	(n = 83)	P
Gallbladder cancer	16 (3)	4 (5)	
Pancreatic cancer	67 (11)	19 (23)	
PNET	40 (6)	2 (2)	
IPMN	29 (5)	5 (6)	
Others	10 (2)	1 (1)	
Surgical procedure			
Hepatectomy	388 (65)	47 (58)	.378
Hepato-pancreatoduodenectomy	8 (1)	1 (1)	
Bile duct resection	20 (3)	6 (7)	
Pancreatoduodenectomy	92 (16)	17 (20)	
Distal pancreatectomy	70 (12)	11 (13)	
Partial pancreatectomy	17 (3)	1 (1)	
Preoperative portal vein embolization	13 (2)	1 (1)	.524
Duration of operation (min)[a]	395 (82–1297)	503 (110–1026)	.005
Inflow occlusion time (min)[a]	32 (0–247)	40 (0–143)	.894
Blood loss (mL)[a]	300 (0–3250)	350 (0–5100)	.091
Intraoperative blood transfusion	71 (12)	12 (14)	.520
Clavien–Dindo classification			
Grade 0	247 (41)	0 (0)	.137[c]
Grade I	87 (15)	1 (1)	
Grade II	140 (23)	59 (71)	
Grade III	114 (19)	21 (26)	
Grade IV	6 (1)	1 (1)	
Grade V	1 (1)	1 (1)	
Post-operative hemorrhage	28 (5)	6 (7)	.364
Post-hepatectomy liver failure	54 (9)	6 (7)	.569
Post-operative pancreatic fistula	85 (14)	17 (20)	.154
Post-hepatectomy bile leak	62 (10)	7 (8)	.566
Incisional surgical site infection	39 (7)	8 (10)	.322
Mortality	1 (1)	1 (1)	.193
Post-operative hospital stay (d)[a]	14 (4–198)	20 (7–130)	.001

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT III, antithrombin III; CABG, coronary artery bypass graft; DD, D-dimer; IPMN, intraductal papillary mucinous neoplasm; PCI, percutaneous coronary intervention; PLT, platelet; PNET, pancreatic neuroendocrine tumor; PT-INR, prothrombin time-international normalized ratio; SFMC, soluble fibrin monomer complex; VTE, venous thromboembolism.

[a]Median (range).

[b]Comparison between Caprini score ≤4 and ≥5.

[c]Comparison between Clavien–Dindo Grade ≤II and ≥III.

in 23 (3.4%), hepatic vein thrombosis (HVT) in one (0.1%), pelvic vein thrombosis in two (0.3%), and internal jugular vein thrombosis in one (0.1%) patient. All DVTs were located below the knee. All 83 patients with VTE were asymptomatic and had high DD and/or SFMC levels. The median postoperative day (POD) upon which the VTE diagnosis was made was 4 (range, 1–14 d). Although only one patient (0.1%) who developed PVT required thrombectomy, for the other patients anticoagulant therapies were immediately started, and no patient died of VTE. Almost 90% of patients with VTE received intravenous administration of unfractionated heparin or low molecular-weight heparin. Among the 83 patients who developed VTE, hemorrhage as an adverse event that was associated with anticoagulation was observed only in six patients (7.2%), two of whom required blood transfusion. No patient showed thrombocytopenia associated with anticoagulation therapy, and liver dysfunction was observed in only one patient (1.2%).

3.2 | Postoperative serum DD and SFMC levels

The change over time in the serum DD and SFMC levels is shown in Figure 1. DD and SFMC levels at POD1 in the VTE (+) group were significantly higher than those in the VTE (–) group (DD, 7.7 vs 4.3 µg/mL, $P < .001$; SFMC, 16.2 vs 7.1 µg/mL, $P < .001$). Regardless of the day that VTE was diagnosed, maximum DD and SFMC levels in the VTE (+) group were significantly higher than those in VTE (–) group (DD, 15.1 vs 8.9 µg/mL, $P < .001$; SFMC, 18.0 vs 10.2 µg/mL, $P < .001$). ROC curve analysis results that were used to estimate the discrimination ability of DD, SFMC, and the combination of these factors for VTE are shown in Figure 2. The area under the ROC (AUROC) curve for the serum DD level was 0.804 (Figure 2A). The optimal cutoff DD level for diagnosing VTE onset was 11.4 µg/mL. At this level, the sensitivity and specificity were 79.5% and 69.9%, respectively, with a positive predictive value (PPV) of 26.9% and a negative predictive value (NPV) of 96.1%. Furthermore, the AUROC of SFMC was 0.696 (Figure 2B). The optimal cutoff serum SFMC level for diagnosing VTE onset was 16.8 µg/mL. At this level, the sensitivity and specificity were 56.3% and 80.2%, respectively, with a PPV of 42.9% and an NPV of 87.4%.

The analysis also focused on patients in whom both DD and SFMC levels were measured (n = 230 patients). VTE developed in 48 of 230 patients (20.9%), although 32 patients (66.7%) exhibited 10 µg/mL or more for both DD and SFMC levels, four patients (8.3%) showed <10 µg/mL of both, and eight patients (16.7%) showed DD levels of <10 µg/mL. When the cutoff values for both DD and SFMC were used to detect VTE, the AUROC was 0.761 (Figure 2C), the sensitivity was increased to 83.3%, the specificity was decreased to 60.4%, the PPV was 35.7%, and the NPV was 93.2%. Furthermore, a scatter diagram of the correlation between the maximum DD and SFMC levels was created (Figure 3). The Spearman rank correlation analysis showed that the maximum DD levels were positively correlated with those of SFMC ($r = .424$, $P < .01$).

TABLE 2 Treatment, outcomes, and adverse events in patients with venous thromboembolism

	Total (n = 83)	DVT only (n = 16)	PTE only (n = 25)	DVT+PTE (n = 15)	PVT (n = 23)	Others[a] (n = 4)
Symptomatic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
The day of diagnosis from operation	4 (1–14)	3 (1–14)	5 (1–10)	2 (1–7)	4 (1–10)	6 (2–14)
Induction treatment						
UFH	17 (20)	4 (25)	3 (12)	5 (33)	5 (22)	0 (0)
LMWH	57 (69)	11 (69)	22 (88)	9 (60)	14 (61)	1 (25)
DOAC	8 (10)	1 (6)	0 (0)	1 (7)	3 (13)	3 (75)
Thrombectomy	1 (1)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)
Duration of treatment						
≤6 mo	25 (30)	4 (25)	6 (24)	7 (47)	6 (26)	2 (50)
>6 mo, ≤12 mo	37 (45)	5 (31)	13 (52)	7 (47)	12 (52)	0 (0)
>12 mo	21 (25)	7 (44)	6 (24)	1 (6)	5 (22)	2 (50)
Outcome						
Disappeared	73 (88)	14 (88)	22 (88)	13 (87)	20 (87)	4 (100)
Reduced	5 (6)	0 (0)	2 (8)	0 (0)	3 (13)	0 (0)
No change	5 (6)	2 (12)	1 (4)	2 (13)	0 (0)	0 (0)
Adverse events associated with anticoagulation						
Hemorrhage	6 (7)	1 (6)	1 (4)	2 (13)	2 (9)	0 (0)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver dysfunction	1 (1)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)

Note: Values in parentheses are percentages.

Abbreviations: DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low molecule weight heparin; PTE, pulmonary thromboembolism; PVT, portal vein thrombosis; UFH, unfractionated heparin.

[a]Hepatic vein thrombosis (n = 1), pelvic vein thrombosis (n = 2), internal jugular vein thrombosis (n = 1).

4 | DISCUSSION

For postoperative VTE, the Caprini score[3] is one of the most well-known preventive scoring systems worldwide. However, most patients who undergo digestive surgery for a malignant tumor will be categorized into the high-risk group for VTE using this scoring system, and prophylactic anticoagulant therapy is recommended for these patients. In patients who undergo orthopedic surgery, prophylactic anticoagulation therapy is widely accepted for preventing the occurrence of postoperative VTE. However, postoperative hemorrhage is a serious complication of HBP surgery; therefore, routine application of chemoprophylaxis has not been the standard treatment for managing VTE after HBP surgery. We monitored serum DD and SFMC levels after HBP surgery without the routine use of chemoprophylaxis and evaluated the presence of VTE using contrast-enhanced CT in patients who had high serum DD or SFMC levels. In this study, 83 (12.2%) of 678 patients who underwent HBP surgery had asymptomatic VTE, and no death associated with VTE was observed in these patients. The incidence of hemorrhage in patients with VTE was 7.2%, which was comparable to that in patients without postoperative VTE (4.7%, P = .364).

We reviewed previous studies that compared postoperative outcomes between the presence and absence of prophylactic anticoagulation therapy in patients who underwent abdominal surgery, including four randomized control trials (RCTs) and two retrospective cohort studies (Table 3).[10-15] Among them, the four RCTs that were conducted in patients who underwent general abdominal or pelvic surgery showed a lower incidence of VTE in the prophylactic anticoagulation group than in the control group, with a comparable incidence of hemorrhage. Conversely, one study[15] conducted in patients who underwent HBP surgery showed a high incidence of hemorrhage (26.6%) in the prophylactic anticoagulation therapy group. In the present study, anticoagulation therapy was applied only in patients who were diagnosed with VTE using contrast-enhanced CT and in whom the incidence of hemorrhage was only 7.2%, and only two patients (2.4%) required blood transfusion. On the basis of these findings, the combination management of early VTE detection through monitoring DD and SFMC levels and early treatment intervention after confirmation of VTE is considered more reasonable and appropriate than routine application of prophylactic anticoagulation in patients who undergo surgery with a high risk of postoperative hemorrhage, such as HBP surgery. However, Sakon et al[14] reported that prophylactic anticoagulation therapy (darexaban) was a safe and efficient method for preventing VTE in patients who underwent major abdominal surgery and who had a high risk of developing VTE. In the present study, we focused on the usefulness of the preemptive management strategy by monitoring DD and SFMC levels, and thus, the
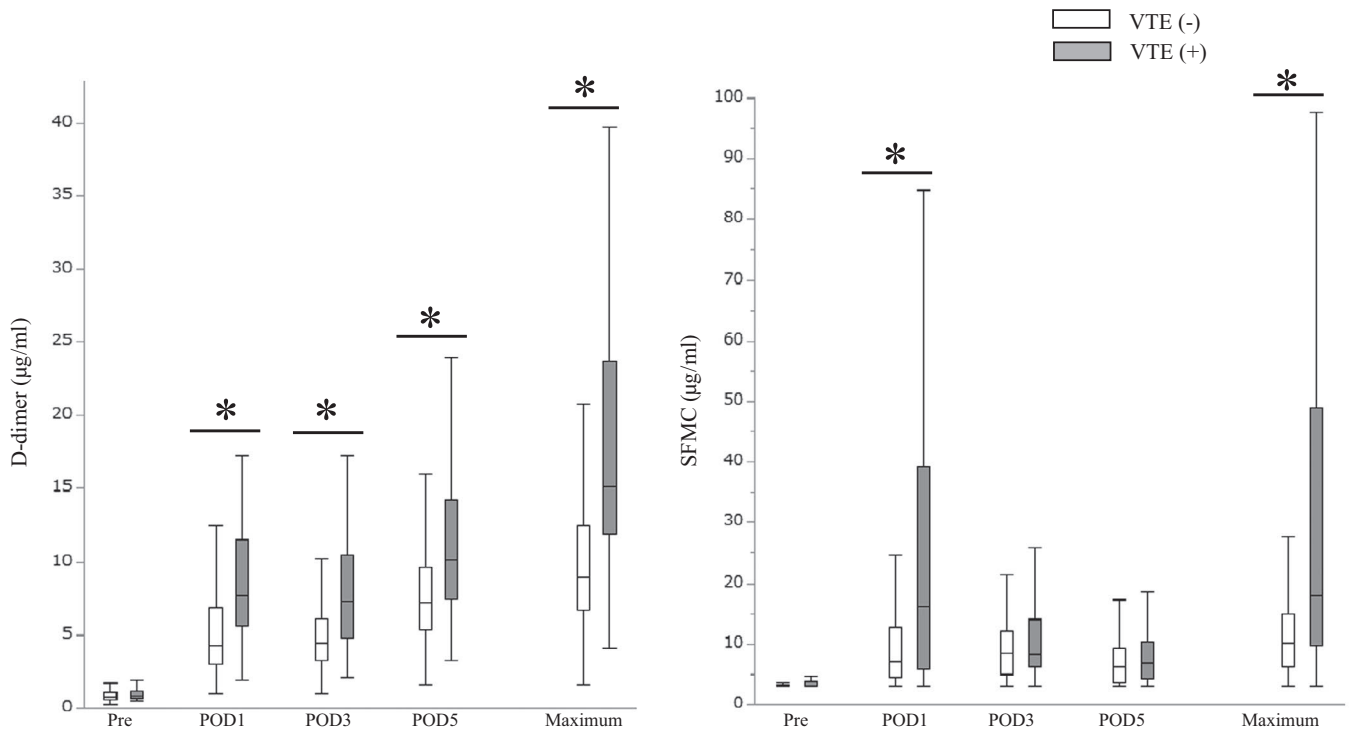
FIGURE 1 Preoperative and postoperative D-dimer and soluble fibrin monomer complex levels. White boxes, patients without venous thromboembolism (VTE); gray boxes, patients with VTE. *P < .05, patients without VTE versus patients with VTE by the Mann–Whitney U-test
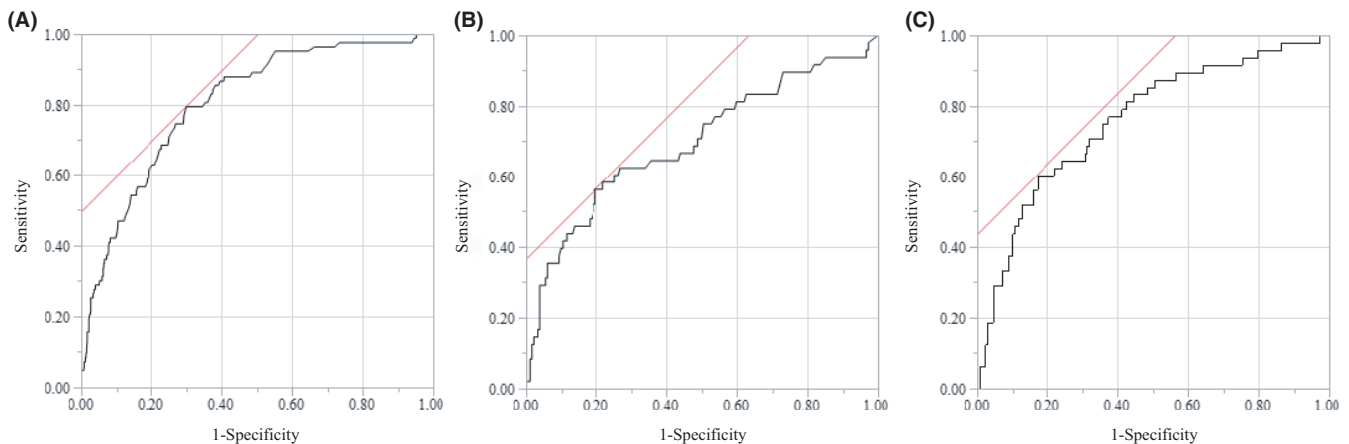

FIGURE 2 Receiver operating characteristics curves. A: At a cutoff value of 11.4 µg/mL for the maximum D-dimer (DD) level, the area under the receiver operating characteristic (AUROC) is 0.804, the sensitivity is 79.5%, and the specificity is 69.9%. B: At a cutoff value of 16.8 µg/mL for the maximum soluble fibrin monomer complex (SFMC) level, the AUROC is 0.696, the sensitivity is 56.3%, and the specificity is 80.2%. C: At a cutoff value of 11.4 µg/mL for the maximum DD level or 16.8 µg/mL for the maximum SFMC level, respectively, the AUROC is 0.761, the sensitivity is 83.3%, and the specificity is 60.4%

use of anticoagulant agents was not evaluated. Seventy-two of 83 patients (87%) had either of the two risk factors that were identified using multivariate analysis, which are female sex and a surgery duration of ≥401 min. However, this result of multivariate analysis cannot be applied unconditionally. Although prophylactic postoperative anticoagulation therapy might be one option in high-risk cases, it is desirable to use anticoagulation therapy on the basis of the individual disease and surgical procedure. To establish a more efficient and effective strategy for preventing VTE using the

combination of routine DD and SFMC monitoring and prophylactic anticoagulation, large-scale and prospective studies are required.

We focused on serum DD and SFMC levels as indicators for the early detection of VTE. SFMC levels reflect the early phase of a thrombotic event, whereas DD levels reflect secondary fibrinolysis after clot formation.[16] Elevated SFMC levels indicate the conversion of fibrinogen to fibrin by thrombin. In our study, most patients showed a rapidly increased SFMC level, which decreased soon thereafter, whereas high DD levels were maintained for

FIGURE 3 Scatter diagram of the correlation between the maximum levels of D-dimer and soluble fibrin monomer complex. Coefficients (r) and P-values were calculated using the Spearman rank correlation analysis. White circles indicate patients without venous thromboembolism (VTE), and black circles indicate patients with VTE
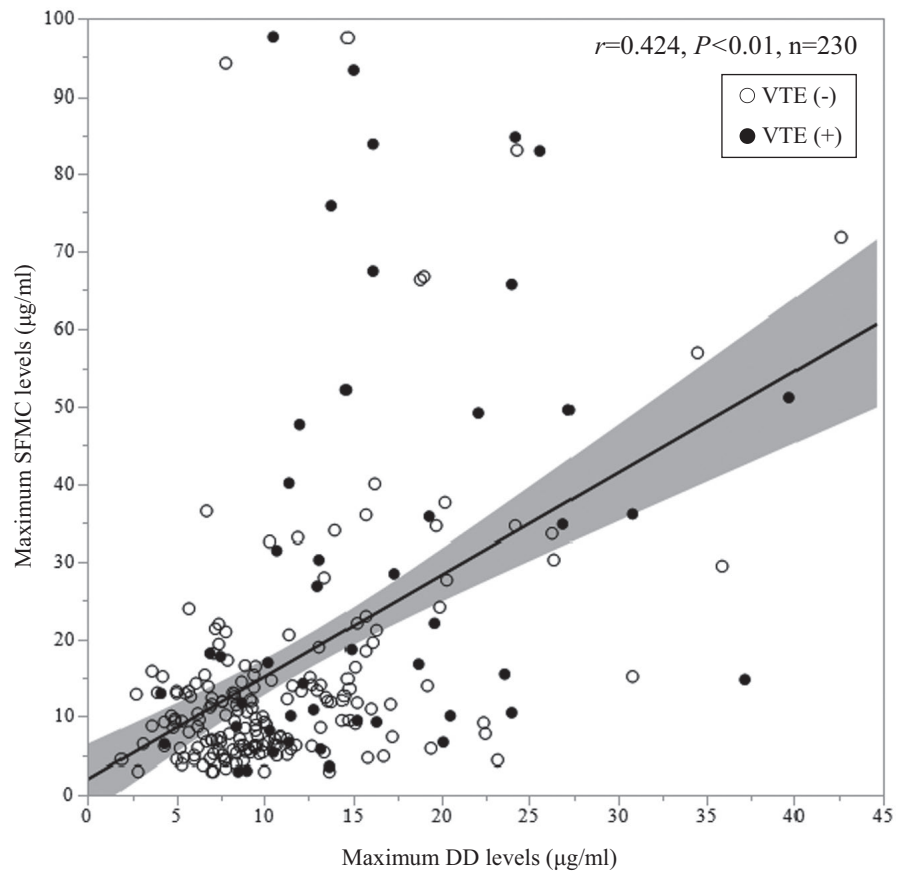
longer periods than SFMC levels because of the long half-life of DD. This result is similar to those of previously published studies.[17,18] Furthermore, when anticoagulant therapy, such as heparin administration, improves hypercoagulability, the SFMC levels improve relatively quickly; conversely, DD levels remain elevated for some time. SFMC levels reflect abnormal fibrin formation in the hypercoagulation phase and may fall within the normal range after amelioration of the hypercoagulation phase, even if VTE is present. Therefore, simultaneous measurement of both serum DD and SFMC levels reduces the chances of missing a VTE diagnosis.[19]

We summarized the results from previous studies that investigated the cutoff DD and/or SFMC levels to detect VTE and the results of the present study (Table 4).[20-26] Clinical trials on anticoagulant therapy before the detection of VTE were excluded. Although there were several studies in the field of orthopedics, only three studies, which were conducted in patients who underwent surgery for portal hypertension or liver transplantation,[21,23,26] have been reported in the field of gastroenterological surgery. In addition, no study has been conducted on the serum DD and/or SFMC level in patients who underwent HBP surgery. In most studies, the serum DD or SFMC level showed a high AUROC to identify VTE; therefore, monitoring these parameters is considered a useful tool to detect and diagnose VTE. Although our management setting, ie, serum DD level of >10 μg/mL or SFMC level of >10 μg/mL for the application of contrast-enhanced CT, demonstrated high sensitivity (91.7%) and a high NPV (93.8%) to detect VTE, it showed a relatively low specificity (33.5%). However, the cutoff values of a serum DD level of >11.4 μg/mL or an SFMC level of >16.8 μg/mL revealed a higher

specificity (60.4%) and a comparable NPV (93.2%), while the sensitivity (83.3%) was lower than the aforementioned cutoff values. Therefore, further investigation on the configuration of a more appropriate and efficient cutoff value to detect VTE is required. For example, a more useful cutoff value might be obtained by stratifying on the basis of disease or surgical procedure. The present study included DVT and PTE as well as HVT and PVT, which are complications that are specific to HBP surgery and are caused by surgical procedures. For the extracted patient data, except for patients with HVT and PVT, the AUROC curve for the serum DD level was 0.827, and the sensitivity and specificity were 85.0% and 69.9%, respectively, with a PPV of 22.2% and an NPV of 97.9%. Furthermore, the AUROC of SFMC was 0.733, and the sensitivity and specificity were 60.6% and 80.8%, respectively, with a PPV of 36.4% and an NPV of 91.9%. The study showed a good ability with high sensitivity and high NPV in any case, and thus, this preemptive management strategy enables early detection of VTE.

Venous thrombosis in the calf is generally asymptomatic and usually resolves spontaneously. However, it may propagate proximally, which leads to a risk of PTE.[27] Furthermore, 40% of PTEs develop within 24 h postoperatively, and the mortality rate of patients within 1 h after onset is 30%.[28] Therefore, a simple screening method for detection is important, even if the DVT is asymptomatic. In the present study, all patients with VTE were asymptomatic. This showed that our strategy of monitoring DD and SFMC levels could detect VTE before it led to fatal complications. Therefore, a routine measurement and surveillance system using appropriate cutoff values for DD and SFMC levels are useful for early detection of, and treatment intervention for,

TABLE 3 Literature review comparing the outcomes between the presence and absence of postoperative prophylactic anticoagulant therapy in patients who underwent abdominal surgery

Author	Year	Type of article	Operative procedure	Type of anticoagulation	Sample size		VTE			Postoperative hemorrhage		
					Anticoagulation	Control	Anticoagulation (%)	Control (%)	P	Anticoagulation (%)	Control (%)	P
Kakkar[10]	1977	RCT	Abdominal or pelvic[a]	Heparin	1998	2033	2 (0.1)	20 (0.9)	<.05	202[b] (10.1)	202[b] (9.9)	.34
Turpie[11]	2007	RCT	Abdominal or pelvic[a]	Fondaparinux	635	650	9 (1.4)	24 (3.7)	.012	10 (1.6)	1 (0.2)	.006
Sakon[12]	2010	RCT	Abdominal or pelvic[a]	Enoxaparin	83	31	1 (1.2)	6 (19.4)	NA	10 (12.0)	3 (9.7)	NA
Reddy[13]	2011	RCS	Hepatic	UFH or LMWH	275	144	6 (2.2)	9 (6.3)	.03	46[b] (16.7)	38[b] (26.6)	.02
Sakon[14]	2012	RCT	Abdominal or pelvic[a]	Darexaban	77 (105)[c]	40 (51)[c]	2 (2.6)	6 (15.0)	NA	10[c] (9.5)	2[c] (3.9)	NA
Hayashi[15]	2014	RCS	HBP	Enoxaparin or Fondaparinux	207	142	6 (2.9)	11 (7.7)	<.05	55 (26.6)	12 (8.5)	<.05

Abbreviations: VTE, venous thromboembolism; RCT, randomized control trial; RCS, retrospective cohort study; HBP, hepato-biliary-pancreatic; NA, not available; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

[a]Including gastrointestinal, hepato-biliary-pancreatic, urologic, and gynecologic surgery.

[b]The number of patients who required postoperative red-blood-cell transfusion.

[c]The incidence of hemorrhage was evaluated in the safety analysis set.

thrombosis. Although DD and SFMC levels are predictive parameters for detecting VTE, it is difficult to determine only the actual case in whom VTE is occurring only by measuring serum DD and SFMC levels. To comprehensively evaluate the results of imaging studies, other blood tests are necessary. For example, Righini et al[29] showed that DD must be integrated in comprehensive sequential diagnostic strategies, including a clinical probability assessment and imaging techniques, owing to its poor specificity. Thus, our perioperative management strategy along with monitoring of serum DD and SFMC levels and a dynamic imaging study for the early detection and treatment of VTE are considered useful. Furthermore, ultrasonography (US) and contrast-enhanced CT are usually performed to detect VTE. Ultrasonic color Doppler imaging is a noninvasive and convenient modality. However, for example, the sensitivity of detecting PVT in patients after hepatectomy is only 56%,[30] which is worrisome because PVT might be missed. Moreover, PTE cannot be diagnosed using US, and contrast-enhanced CT is superior to US for identifying the area of thrombosis or visualizing small thrombi, in addition to its high sensitivity. Thus, CT is used to diagnose VTE at our institute. However, contrast-enhanced CT cannot be performed in patients with renal dysfunction or in those with an allergy to the contrast medium. To diagnose PTE for those patients, lung perfusion scintigraphy is an alternative pulmonary imaging method. Sostman et al[31] reported that lung perfusion scintigraphy to diagnose acute PTE had a sensitivity of 77.4% and a high specificity of 97.7%. Although the imaging method is very effective without the risk of exposure, there are a limited number of facilities that can perform this technique in an emergency case.

A combination management strategy to monitor serum DD and SFMC levels using contrast-enhanced CT following confirmed high DD and/or SFMC levels enables early detection of, and treatment intervention for, VTE before symptom onset without the routine use of postoperative chemoprophylaxis.

The present study has several limitations. First, this was a single-center retrospective study, and it may include a selection bias. Second, contrast-enhanced CT was not performed in all patients; therefore, the true incidence of VTE may be different from the incidence that was noted in this study. Low DD and SFMC levels do not mean no thrombosis, and potentially fatal VTE patients can be missed. A prospective study in which CT scans are performed in all patients on a fixed postoperative day is required. Despite these drawbacks, we believe that our findings are of interest to HBP surgeons because, to the best of our knowledge, this is the first report evaluating VTE by measuring both DD and SFMC levels in patients who underwent HBP surgery.

In conclusion, the management strategy of monitoring serum DD and SFMC levels enables early detection of, and treatment intervention for, VTE before symptom onset without the routine use of postoperative chemoprophylaxis. Further prospective studies are needed to establish a more appropriate and efficient cutoff value for DD and SFMC levels to detect VTE.

TABLE 4 Cutoff values of D-dimer and soluble fibrin monomer complex levels to diagnose venous thromboembolism and literature review

Author	Year	Operative procedure	Sample size	Incidence of VTE (%)	POD[a]	Cut-off value DD (µg/mL)	SFMC (µg/mL)	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Efficacy (%)
Yoshioka[20]	2010	Orthopedics	72	8.3	7	6.5	–	0.858	83.3	75.7	23.8	98.0	76.4
					1	–	20.8	0.932	100	86.3	40.0	100	87.5
Wang[21]	2010	Splenectomy[b]	82	30.1[c]	Any	500	–	0.880	88.9	78.2	66.7	93.5	81.7
Niimi[22]	2010	Orthopedics	207	50.2	1	4.88	–	0.683	91.4	28.2	56.5	78.4	60.4
					1	–	4.00	0.730	90.4	33.0	57.7	77.3	61.8
Fei[23]	2016	SDPD[d]	137	27.7[e]	Any	0.5	–	0.826	83.8	76.0	81.3	80.7	NA
Natsumeda[24]	2018	Neurologic	92	26.1	7	2.65	–	0.841	85.7	72.3	NA	NA	NA
Inoue[25]	2018	Orthopedics	72	15.3	3	8.2	–	NA	83.3	84.4	NA	NA	NA
					7	10.8	–	NA	67.7	87.5	NA	NA	NA
Zhang[26]	2019	Liver transplantation	525	13.9	1	8.82	–	0.698	NA	NA	43.1	87.8	NA
Present	2020	HBP	678	12.2	Any	11.4	–	0.804	79.5	69.9	26.9	96.1	71.1
			230	20.9	Any	10.0	10.0	0.761	91.7	33.5	26.7	93.8	45.7
					Any	11.4	16.8		83.3	60.4	35.7	93.2	65.2

Abbreviations: VTE, venous thromboembolism; POD, postoperative day; DD, D-dimer; SFMC, soluble fibrin monomer complex; AUROC, area under the receiver operating characteristics curve; PPV, positive predictive value; NPV, negative predictive value; SDPD, selective double portazygous disconnection; HBP, hepato-biliary pancreatic; NA, not available.

[a]Postoperative day on which the cutoff value of D-dimer or soluble fibrin monomer complex was derived.

[b]Splenectomy for patients with portal hypertension.

[c]The incidence of splenic or portal vein thrombosis.

[d]Selective double portazygous disconnection for patients with portal hypertension

[e]The incidence of portal vein thrombosis.

DISCLOSURE

Conflict of interest: The authors have no conflicts of interest regarding the current study.

APPROVAL OF THE RESEARCH PROTOCOL

This study was approved by the Ethics Committee of Shinshu University School of Medicine and was conducted in accordance with the principles of the Declaration of Helsinki.

INFORMED CONSENT

All patients received complete information about the study and provided consent for participation.

ORCID

Akira Shimizu https://orcid.org/0000-0002-5015-1697

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