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

Hikaru Hayashi | Akira Shimizu | 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
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).5 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 score6 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 Surgery8 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) (Continues)
TABLE 1 (Continued)

| Surgical procedure                  | VTE (−) (n = 595) | VTE (+) (n = 83) | P     |
|-------------------------------------|-------------------|------------------|-------|
| Gallbladder cancer                  | 16 (3)            | 4 (5)            | .378  |
| 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)**     | 395 (82–1297)     | 503 (110–1026)   | .005  |
| **Inflow occlusion time (min)**     | 32 (0–247)        | 40 (0–143)       | .894  |
| **Blood loss (mL)**                 | 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  |
| 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)     | 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; CAGB, 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.

*Median (range).

**Comparison between Caprini score ≤4 and ≥5.

*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).
DISCUSSION

For postoperative VTE, the Caprini score 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). 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 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 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

### 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.

aHepatic vein thrombosis (n = 1), pelvic vein thrombosis (n = 2), internal jugular vein thrombosis (n = 1).
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 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%
longer periods than SFMC levels because of the long half-life of DD. This result is similar to those of previously published studies.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{21,23,26} have been reported in the field of gastroenterological surgery. In addition, no study has been conducted on the serum DD 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.\textsuperscript{27} Furthermore, 40% of PTEs develop within 24 h postoperatively, and the mortality rate of patients within 1 h after onset is 30%.\textsuperscript{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,
| Author          | Year | Type of article | Operative procedure | Type of anticoagulation | Sample size | Anticoagulation (%) | Control (%) | P     | Anticoagulation (%) | Control (%) | P     | Postoperative hemorrhage |
|-----------------|------|-----------------|---------------------|-------------------------|-------------|---------------------|-------------|-------|---------------------|-------------|-------|-------------------------|
| Kakkar         | 1977 | RCT             | Abdominal or pelvic | Heparin                 | 1998        | 2 (0.1)             | 20 (0.9)    | <.05  | 202 (10.1)         | 202 (9.9)   | .34   |
| Turpie         | 2007 | RCT             | Abdominal or pelvic | Fondaparinux            | 635         | 9 (1.4)             | 24 (3.7)    | .012  | 10 (1.6)           | 1 (0.2)     | .006  |
| Sakon           | 2010 | RCT             | Abdominal or pelvic | Enoxaparin              | 83          | 1 (1.2)             | 6 (19.4)    | NA    | 10 (12.0)          | 3 (9.7)     | NA    |
| Reddy          | 2011 | RCS             | Hepatic             | UFH or LMWH             | 275         | 6 (2.2)             | 9 (6.3)     | .03   | 46 (16.7)          | 38 (26.6)   | .02   |
| Sakon           | 2012 | RCS             | Abdominal or pelvic | Darexaban               | 77 (105)    | 2 (2.6)             | 6 (15.0)    | NA    | 10 (9.5)           | 2 (3.9)     | NA    |
| Hayashi        | 2014 | RCS             | HBP                 | Enoxaparin or Fondaparinux | 207       | 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.

*aIncluding gastrointestinal, hepato-biliary-pancreatic, urologic, and gynecologic surgery.

*bThe number of patients who required postoperative red-blood-cell transfusion.

*cThe incidence of hemorrhage was evaluated in the safety analysis set.
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<sup>a</sup> | Cut-off value | AUROC | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Efficacy (%) |
|-------------|------|---------------------|-------------|----------------------|------------------|---------------|-------|----------------|----------------|--------|---------|--------------|
| Yoshioka<sup>20</sup> | 2010 | Orthopedics         | 72          | 8.3                  | 7                | 6.5           | —     | 0.858          | 83.3            | 75.7   | 23.8    | 98.0         |
| Wang<sup>21</sup>    | 2010 | Splenectomy<sup>b</sup> | 82          | 30.1<sup>c</sup>    | Any             | 500           | —     | 0.880          | 88.9            | 78.2   | 66.7    | 93.5         |
| Niimi<sup>22</sup>   | 2010 | Orthopedics         | 207         | 50.2                 | 1                | 4.88          | —     | 0.683          | 91.4            | 28.2   | 56.5    | 78.4         |
| Fei<sup>23</sup>     | 2016 | SDPD<sup>d</sup>    | 137         | 27.7<sup>e</sup>    | Any             | 0.5           | —     | 0.826          | 83.8            | 76.0   | 81.3    | 80.7         |
| Natsumeda<sup>24</sup> | 2018 | Neurologic          | 92          | 26.1                 | 7                | 2.65          | —     | 0.841          | 85.7            | 72.3   | NA      | NA           |
| Inoue<sup>25</sup>   | 2018 | Orthopedics         | 72          | 15.3                 | 3                | 8.2           | —     | NA             | 83.3            | 84.4   | NA      | NA           |
| Zhang<sup>26</sup>   | 2019 | Liver transplantation| 525         | 13.9                 | 1                | 8.82          | —     | 0.698          | NA             | NA     | 43.1    | 87.8         |
| Present             | 2020 | HBP                 | 678         | 12.2                 | Any             | 11.4          | —     | 0.804          | 79.5            | 69.9   | 26.9    | 96.1         |
|                      |      |                     | 230         | 20.9                 | Any             | 10.0          | 10.0  | 0.761          | 91.7            | 33.5   | 26.7    | 93.8         |
|                      |      |                     |             | 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.

<sup>a</sup>Postoperative day on which the cutoff value of D-dimer or soluble fibrin monomer complex was derived.

<sup>b</sup>Splenectomy for patients with portal hypertension.

<sup>c</sup>The incidence of splenic or portal vein thrombosis.

<sup>d</sup>Selective double portazygous disconnection for patients with portal hypertension.

<sup>e</sup>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

REFERENCES
1. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1988;208:227–40.
2. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:381S–453.
3. Caprini JA, Arcelus JI, Hasty JH, et al. Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost. 1991;17(Suppl 3):304–12.
4. Colditz GA, Tuden RL, Oster G. Rates of venous thrombosis after general surgery: combined results of randomised clinical trials. Lancet. 1986;2:143–6.
5. Vivarelli M, Zanello M, Zanfi C, et al. Prophylaxis for venous thromboembolism after resection of hepatocellular carcinoma on cirrhosis: is it necessary? World J Gastroenterol. 2010;16:2146–50.
6. Rathbun SW, Whitsett TL, Raskob GE. Negative D-dimer result to exclude recurrent deep venous thrombosis: a management trial. Ann Intern Med. 2004;141:839–45.
7. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187–96.
8. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149:713–24.
9. Bassi C, Marchegiani G, Dervenir C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161:584–91.
10. Kakkar VV, Corrigan TP, Fossard DP, et al. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet. 1977;1:567–9.
11. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. J Thromb Haemost. 2007;5:1854–61.
12. Sakon M, Kobayashi T, Shimazu T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. Thromb Res. 2010;125:e65–70.
13. Reddy SK, Turley RS, Barbas AS, et al. Post-operative pharmacologic thromboprophylaxis after major hepatectomy: does peripheral venous thromboembolism prevention outweigh bleeding risks? J Gastrointest Surg. 2011;15:1602–10.
14. Sakon M, Nakamura M. Darexaban (YM150) prevents venous thromboembolism in Japanese patients undergoing major abdominal surgery: Phase III randomized, mechanical prophylaxis-controlled, open-label study. Thromb Res. 2012;130:e52–9.
15. Hayashi H, Morikawa T, Yoshida H, et al. Safety of postoperative thromboprophylaxis after major hepatobiliopancreatic surgery in Japanese patients. Surg Today. 2014;44:1660–8.
16. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet. 1991;337:196–200.
17. Kodama J, Seki N, Masahiro S, et al. D-dimer level as a risk factor for postoperative venous thromboembolism in Japanese women with gynecologic cancer. Ann Oncol. 2010;21:1651–6.
18. Sudo A, Wada H, Nobori T, et al. Cut-off values of D-dimer and soluble fibrin for prediction of deep vein thrombosis after orthopaedic surgery. Int J Hematol. 2009;89:572–6.
19. Ota S, Wada H, Nobori T, et al. Diagnosis of deep vein thrombosis by plasma-soluble fibrin or D-dimer. Am J Hematol. 2005;79:274–80.
20. Yoshioka K, Kitajima I, Kabata T, et al. Venous thromboembolism after spine surgery: changes of the fibrin monomer complex and D-dimer level during the perioperative period. J Neurosurg Spine. 2010;13:594–9.
21. Wang L, Liu GJ, Chen YX, et al. Combined use of D-dimer and P-selectin for the diagnosis of splenic or portal vein thrombosis following splenectomy. Thromb Res. 2010;125:e206–9.
22. Niimi R, Hasegawa M, Sudo A, et al. Evaluation of soluble fibrin and D-dimer in the diagnosis of postoperative deep vein thrombosis. Biomarkers. 2010;15:149–57.
23. Fei Y, Zong GQ, Chen J, et al. Evaluation of the value of d-Dimer, P-selectin, and platelet count for prediction of portal vein thrombosis after devascularization. Clin Appl Thromb Hemost. 2016;22:471–5.
24. Natsume M, Uzuka T, Watanabe J, et al. High incidence of deep vein thrombosis in the perioperative period of neurosurgical patients. World Neurosurg. 2018;112:e103–12.
25. Inoue H, Watanabe H, Okami H, et al. D-dimer predicts pulmonary embolism after low-risk spine surgery. Spine Surg Relat Res. 2018;2:113–20.
26. Zhang Q, Guo R, Chen Y. D-dimer level in liver transplant recipients on the first day after surgery is correlated with postoperative thrombosis recurrence. J Clin Lab Anal. 2019;33:e22646.
27. Kakkar VV, Howe CT, Flanc C, et al. Natural history of postoperative deep-vein thrombosis. Lancet. 1969;2:230–2.
28. Cormican D, Morkos MS, Winter D, et al. Acute perioperative pulmonary embolism-management strategies and outcomes. J Cardiothorac Vasc Anesth. 2020;34:1972–84.
29. Righini M, Perrier A, De Moerloose P, et al. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost. 2008;6:1059–71.
30. Kuboki S, Shimizu H, Ohtsuka M, et al. Incidence, risk factors, and management options for portal vein thrombosis after hepatectomy: a 14-year, single-center experience. Am J Surg. 2015;210:878–85.e872.
31. Sostman HD, Stein PD, Gottschalk A, et al. Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. Radiology. 2008;246:941–6.

How to cite this article: Hayashi H, Shimizu A, Kubota K, Notake T, Sugenoya S, Masuo H, et al. Asymptomatic Venous Thromboembolism After Hepatobiliary–Pancreatic Surgery: Early Detection Using D-dimer and Soluble Fibrin Monomer Complex Levels. Ann Gastroenterol Surg. 2022;6:109–118. https://doi.org/10.1002/ags3.12495