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Research Article

A Prospective Multicenter Observational Study of Venous Thromboembolism after Gastric Cancer Surgery (SHISA-1601)

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Keywords
Gastric cancer · Gastrectomy · Venous thromboembolism (VTE) · D-dimer · Soluble fibrin

Abstract
Introduction: This study aimed to clarify the frequency and risk factors of intercurrent venous thromboembolism (VTE) in patients undergoing major curative gastric cancer surgery. ***Methods:*** This prospective, multicenter, observational study included patients with gastric cancer who underwent radical gastrectomy at 5 hospitals between June 2016 and May 2018. Patients who were preoperatively administered anticoagulants were excluded. ***Results:*** A total of 126 patients were eligible to participate. VTE occurred within 9 days postoperatively in 5 cases (4.0%; 2 symptomatic and 3 asymptomatic). Postoperative day (POD) 1 plasma D-dimer and soluble fibrin (SF) levels were significantly higher in the VTE group than in the non-VTE group. Receiver-operating characteristic curve (ROC) analysis indicated a statistically significant ability of POD 1 D-dimer and SF levels to predict postoperative VTE development after gastrectomy; this finding was reflected by an area under the curve (AUC) of 0.97 (95% CI 0.92–1.0) and 0.87 (95% CI 0.74–1.0), respectively. Cutoff values of D-dimer (24.6 μg/mL) and SF (64.1 μg/mL) were determined. Intraoperative blood transfusion (odds ratio [OR] 7.86), POD 1 D-

This trial is registered with the UMIN Clinical Trials Registry (UMIN 000021702).

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dimer ≥24.6 μg/mL (OR 17.35), and POD 1 SF ≥64.1 μg/mL (OR 19.5) were independent predictive factors for postoperative VTE ($p < 0.05$). ***Conclusion:*** VTE occurred in 4.0% patients (1.6% symptomatic and 2.4% asymptomatic) after gastric cancer surgery; however, with an early diagnosis and anticoagulant therapy, no patients experienced progression. Careful observation of patients with a high risk for VTE, including intraoperative blood transfusion and high POD 1 D-dimer or SF levels, would contribute to the early detection of VTE.

Introduction

Venous thromboembolism (VTE) includes both pulmonary thromboembolism (PE) and deep vein thrombosis (DVT). A cancer-bearing condition is an independent risk factor for VTE [1–3]. In fact, cancer patients reportedly have a 4- to 7-times higher risk of experiencing VTE than healthy people [4, 5]. Moreover, surgery is also a major risk factor for VTE, a life-threating postoperative complication [6]. In previous reports, 24.7% of patients who underwent laparotomy due to malignant abdominal tumors developed VTE [7]. In the absence of an effective VTE prophylaxis, the rate of asymptomatic DVT is reportedly 15–40% in patients who undergo major abdominal or pelvic surgery, resulting in a 0.2–0.9% rate of fatal PE events [4, 8, 9].

Thus, VTE is well known worldwide as a postoperative complication to avoid, for which several prevention guidelines have been proposed. The American Society of Clinical Oncology (ASCO) has issued guidelines for preventing VTE in cancer patients [10]. The VTE prevention guidelines issued by the American College of Chest Physicians (ACCP) in 2012 also advocated a VTE prevention method based on a risk score [11]. However, surgery in the abdominal region is widely defined as "a major surgery for cancer over 40 years of age," and there are few reports on the risks, due to differences among races and organs.

Gastric cancer remains the leading cause of cancer-related death worldwide, and radical resection is the most promising treatment to ensure long-term survival [12, 13]. Many retrospective studies have examined VTE after gastrectomy. Tanizawa et al. [14] reported a 7.5% incidence of preoperative VTE with gastric cancer in Japan. Within 2 years after surgery for gastric cancer, 2.5–7% of patients with VTE had symptoms, or the condition was incidentally identified when imaging studies were performed to evaluate a tumor or other disease status [15]. However, the incidence of VTE after gastric cancer surgery including asymptomatic VTE remains unknown.

This multicenter study aimed to prospectively examine the precise incidence of symptomatic and asymptomatic VTE in patients undergoing radical gastric cancer surgery and then evaluate the risk factors for VTE.

Materials and Methods

Study Design

The Shiga Surgical Association-1601 study was a multicenter prospective observational study of postoperative VTE in patients who underwent gastrectomy for gastric cancer at 5 hospitals in Japan. Between June 2016 and May 2018, consecutive gastric cancer patients scheduled for radical surgery were enrolled.

The inclusion criteria were as follows: (1) diagnosis of histopathologically confirmed gastric cancer, (2) scheduled for curative gastrectomy and lymph node dissection, (3) an age ≥20 years at the time of consent, and (4) a performance status (PS) of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale. Those with a history of thromboembolic disease before surgery or severe renal insufficiency (creatinine clearance ≤30 mL/min), who were using any anticoagulant therapy before surgery, experienced severe complications, had a PS of ≥3 on the ECOG scale, or were pregnant were excluded. VTE prophylaxis after gastrectomy was chosen at the discretion of each facility.

Data Collection and Variables

Patient characteristics (age, sex, body mass index [BMI], ECOG PS, and disease progression), preoperative blood tests (hemoglobin, white blood cell [WBC] count, lymphocyte ratio, neutrophil ratio, platelet count, serum albumin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum creatinine, C-reactive protein [CRP], prothrombin time, activated partial thromboplastin time [APTT], and D-dimer), intraoperative outcomes (procedure, operation time, blood loss, and blood transfusions) and postoperative outcomes (complications including VTE; POD 1 blood tests: WBC, platelet count, hemoglobin, D-dimer, and soluble fibrin [SF]; POD 7 blood tests: WBC, platelet count, hemoglobin, CRP, and D-dimer) were recorded on standardized forms. The patients were enrolled on the day of surgery. Registration was completed when the patient characteristics were entered on the registration form specified in the research registration address. After registering, the patient was assigned a registration number.

Operative Technique

The standard procedure at our institutions was a distal, proximal, or total gastrectomy, with regional dissection of the lymph nodes according to the 15th edition of the Japanese Gastric Cancer Classification of Gastric Carcinoma [2]. In cases of clinical stage I tumors, laparoscopic gastrectomy with D1+ lymph node dissection was performed.

Outcome Measures

The primary end point of this study was to clarify the incidence of symptomatic and asymptomatic VTE during the observation period (30 days) after radical gastric cancer surgery. The secondary end point was to analyze the risk factors for VTE after gastric cancer surgery.

Surgical complications were classified according to the Clavien-Dindo (C-D) classification system [16]. Enhanced computed tomography (CT) or ultrasonography of the lower limb was performed to diagnose VTE postoperatively when symptoms of VTE such as respiratory distress, extremity edema, or leg pain were observed, or the postoperative blood test showed levels of SF ≥7.6 μg/mL or D-dimer ≥9.8 μg/mL on day 1 despite no symptoms of VTE based on past reports [17].

Since this was an exploratory study, we set the target number of cases based on feasibility, i.e., 80 patients per year were undergoing gastric cancer surgery at the participating facilities; taking into consideration the nonqualifying cases, the enrollment of 120 cases was estimated over a 2-year case accumulation period.

Statistical Analysis

STATISTICAL analyses were performed with the Fisher exact test or Mann-Whitney U test as appropriate. Statistical calculations were performed using the Statistical Package for the Social Sciences v22.0 (IBM Institute, Armonk, NY, USA) and GraphPad Prism v8.0 (GraphPad Software, San Diego, CA, USA). For all analyses, differences were considered statistically significant at $p < 0.05$. Using these parameters, receiver-operating characteristic (ROC) curves for D-dimer were constructed and quantified via area under the curve (AUC) analysis as well as the standard error of the mean and the corresponding 95% CI. The Youden Index was calculated as sensitivity + specificity – 1. Logistic regression models were used for the multivariate analyses to identify risk factors associated with the development of postoperative VTE. Two-sided p values <0.05 were considered statistically significant.

Results

Patients' Characteristics

A total of 136 patients were enrolled; 10 who were prospectively administered anticoagulants were excluded. Finally, 126 patients were enrolled in the study and followed up for 30 days postoperatively. Five patients developed VTE postoperatively; of these, 2 had symptomatic thrombosis. One patient had underlying hepatitis B and liver cirrhosis and showed no symptoms of VTE; however, the POD 1 D-dimer and SF levels were high, and enhanced CT revealed portal vein thrombosis on POD 1. In the other patient, who had a central venous port before surgery, POD 9 D-dimer and SF levels were increased, and enhanced CT revealed a small thrombus adhering to the catheter tip. Among the VTE cases, 4 patients were administered unfractionated heparin (UFH) for at least 1 week, so that the APTT was 1.5–2.5 times

Table 1. Patients' characteristics

	Non VTE group (n = 121)	VTE group (n = 5)	p value
Age, years	69 (24–91)	72 (66–77)	0.39
Sex			0.59
Male	92 (76)	3 (60)	
Body mass index	22.6 (16.2–32.2)	23.1 (19.0–24.7)	0.77
ECOG PS 0/1/2	101/14/6	3/1/1	0.28
Histological type			0.14
Differentiated	73 (60.3)	1 (20)	
Undifferentiated	44 (36.4)	4 (80)	
Other	4 (3.3)	0 (0)	
pT classification[1]			0.27
T1a/T1b	60 (49.6)	2 (40)	
T2	25 (20.7)	1 (20)	
T3	17 (14.0)	1 (20)	
T4	19 (15.7)	1 (20)	
pN classification[1]			0.86
N0	84 (69.4)	3 (60)	
N1	20 (16.5)	1 (20)	
N2	12 (9.9)	1 (20)	
N3	5 (4.1)	0 (0)	
pStaging[1]			0.085
I	78 (64.5)	1 (20)	
II	19 (15.7)	2 (40)	
III	20 (16.5)	1 (20)	
IV	4 (3.3)	1 (20)	

Values are expressed as n (%) or median (range). [1] According to the 15th Japanese Classification of Gastric Carcinoma.

the facility's upper limit. Another patient with DVT of the leg was followed up but did not require any additional treatments since the symptoms resolved. No cases of VTE progression were observed during follow-up.

Table 1 shows the characteristics of the VTE and non-VTE cases. There were no significant intergroup differences in patient background factors including age, sex, BMI, ECOG PS, histological type, clinical T classification, clinical N classification, or clinical stage according to the 15th Japanese Classification of Gastric Carcinoma. Table 2 compares the intraoperative outcomes and surgical procedures of the 2 groups. There were no significant intergroup differences in operative procedure, reconstruction method, percentage of open versus laparoscopic procedures, lymph node dissection, operation time, or blood loss. However, significantly more patients with VTE required intraoperative blood transfusions (7 cases [5.3%] vs. 3 cases [60%], p = 0.0034).

Pre- versus Postoperative Blood Test Results

Comparison of the blood test results revealed no significant intergroup difference in preoperative values. However, significant intergroup differences were observed in the POD 1 and POD 7 D-dimer and SF levels (Table 3).

VTE Prophylaxis and Postoperative Complications

VTE prophylaxis was performed by intermittent pneumatic compression (IPC) 126/126 [100%]), wearing elastic stockings (125/126 [99%]), or anticoagulant drugs (85/126

Table 2. Intraoperative outcomes and surgical procedures

	Non VTE group (n = 121)	VTE group (n = 5)	p value
Operative procedure			0.07
Distal gastrectomy	81 (66.9)	2 (40)	
Total gastrectomy	37 (30.6)	2 (40)	
Proximal gastrectomy	3 (2.5)	1 (20)	
Reconstruction method			0.08
Billroth I	41 (33.9)	2 (40)	
Roux-en-Y	77 (63.6)	2 (40)	
Esophagogastrostomy	3 (2.5)	1 (20)	
Approach			>0.99
Open	63 (52.1)	3 (60)	
Laparoscopic	58 (47.9)	2 (40)	
Lymph node dissection			>0.99
D1/D1+	61 (50.4)	3 (60)	
D2	60 (49.6)	2 (40)	
Operation time, min	339 (165–652)	476 (252–602)	0.15
Bleeding, mL	200 (0–3695)	813 (18–2463)	0.18
Intraoperative blood transfusion	7 (5.8)	3 (60)	0.0034

Values are expressed as n (%) or median (range).

[67.4%]). Enoxaparin sodium was most frequently used as a prophylaxis anticoagulant, but there was no significant intergroup difference. There was no difference between institutions in postoperative antithrombotic therapy, and IPC was used in 100% of cases during surgery and 82.5% of cases after surgery. Regarding postoperative outcomes, patients without VTE had a significantly higher occurrence of postoperative non-VTE complications than patients with VTE (C-D classification, p = 0.0093).

Patients with Positive D-Dimer and SF Test Results

D-dimer and SF data sets were obtained for 81 patients (64.3%). The mean POD 1 plasma D-dimer level of the VTE group was significantly higher than that of the non-VTE group (Fig. 1a). POD 1 plasma SF levels in the VTE group were also significantly higher than those in the non-VTE group (Fig. 1b). The ROC curve analysis indicated a statistically significant ability of POD 1 D-dimer and SF levels to predict postoperative VTE development after gastrectomy; these findings were reflected by an AUC value of 0.97 (95% CI 0.92–1.0) (Fig. 1c) and 0.87 (95% CI 0.74–1.0; Fig. 1d), respectively. The cutoff values of D-dimer (24.6 μg/mL) and SF (64.1 μg/mL) were determined.

Uni- and Multivariate Analyses of VTE Predictive Factors

Results from the univariate analysis of the risk factors associated with the postoperative development of VTE are shown in Table 4. Age ≥70 years (p = 0.0425), intraoperative blood transfusion (p < 0.0001), POD 1 D-dimer level ≥24.6 μg/mL (p < 0.0001), and POD 1 SF ≥64.1 μg/mL (p < 0.0001) were predictive of an increased risk of VTE development. However, no other clinical parameters were predictive of postoperative VTE development.

The multivariate analysis included only the 4 variables that showed statistical significance in the univariate analyses: age ≥70 years, intraoperative blood transfusion, and POD 1 D-dimer and SF levels. Among them, intraoperative blood transfusion (odds ratio [OR] 7.86; 95% CI 1.09–56.59; p = 0.0405), POD 1 D-dimer level ≥24.6 μg/mL (OR 17.35;

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Table 3. Preoperative and postoperative blood test outcomes

	Preoperative			Postoperative (POD 1)			Postoperative (POD 7)		
	Non VTE group (n = 121)	VTE group (n = 5)	p value	Non VTE group (n = 121)	VTE group (n = 5)	p value	Non VTE group (n = 121)	VTE group (n = 5)	p value
Hemoglobin, g/dL	12.7 (7.3–16.8)	12.4 (10.8–13.5)	0.37	11.8 (7.5–15.5)	11.7 (9.1–12.5)	0.35	10.9 (7.5–15.5)	10.1 (8.7–13.6)	0.66
White blood cells (*100)	53 (22–222)	46 (38–77)	0.78	96.4 (14.3–337)	107 (86–164)	0.29	60.5 (12.1–232)	87 (58–110)	0.12
Lymphocytes (*100/µL)	15.2 (2.73–40.4)	13.3 (6.84–21.4)	0.49						
Neutrophils (*100/µL)	30.1 (9.79–184.2)	31.8 (26.5–57.2)	0.47						
Platelets (*1,000/µL)	167 (13.3–501)	153 (22–211)	0.81	200 (11.3–523)	121 (15–165)	0.53	198.5 (11.3–523)	188 (26–261)	0.81
Serum albumin, g/dL	3.9 (2.2–4.8)	3.6 (3.0- 4.1)	0.33						
Aspartate aminotransferase, IU/L	20 (10–90)	21 (16–30)	0.7						
Alanine transaminase, IU/L	17 (5–68)	17 (10–28)	0.85						
Total bilirubin, mg/dL	0.6 (0.2–1.86)	0.4 (0.78–1.25)	0.52						
Creatinine, mg/dL	0.79 (0.51–5.09)	0.7 (0.47–0.94)	0.6						
C-reactive protein, mg/dL	0.2 (0.2–33.5)	0.12 (0.03–1.09)	>0.99				2.84 (0.2–33.5)	2.39 (0.75–7.48)	0.66
Prothrombin time, %	12.2 (10.2–120.5)	11.9 (11.3–100)	0.67						
APTT, s	27.9 (20–43.2)	29.3 (24.2–31.5)	0.93						
D-dimer, µg/mL	0.6 (0.1–9.2)	1.3 (0.2–2.9)	0.17	4.65 (1.3–19.6)	18.4 (13.6–29.9)	<0.0001	8.0 (0.2–51.0)	13.1 (8.6–56.9)	0.0279
Soluble fibrin, µg/mL				10.0 (2.3–80.0)	80.0 (12.0–80.0)	<0.0001			

Values are expressed as median (range). APTT, activated partial thromboplastin time; POD, postoperative day.

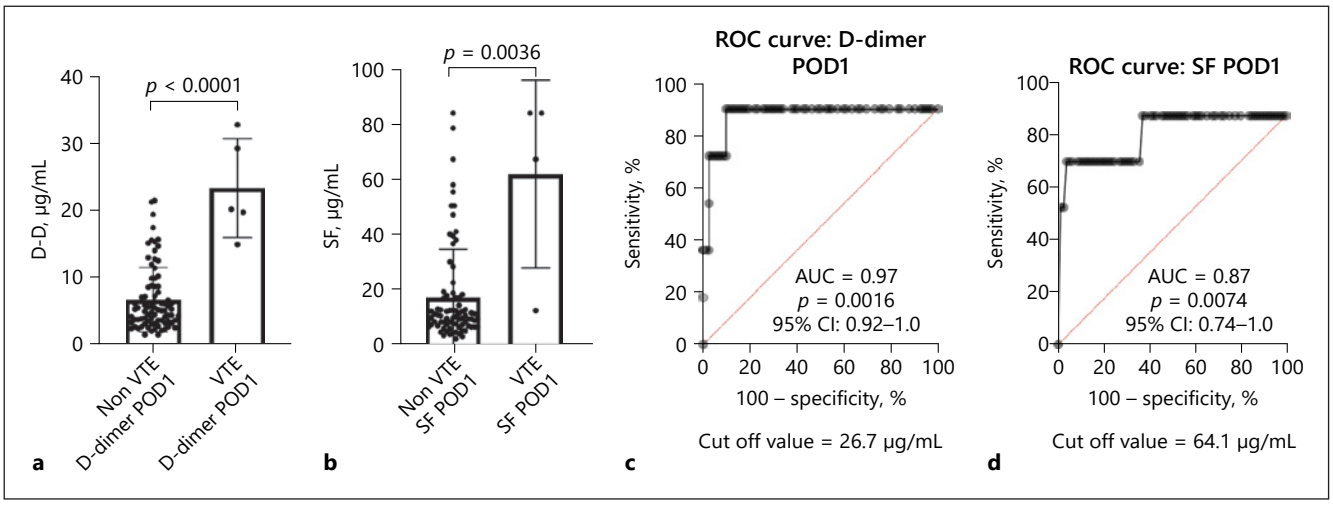

Fig. 1. Comparison of D-dimer (**a**) and SF (**b**) values on the first day after surgery. The ROC curve for the recognition of D-dimer (**c**) and SF (**d**). AUC, area under the curve; CI, confidence interval; POD, postoperative day; ROC, receiver-operating characteristic; SF, soluble fibrin.

Table 4. Univariate and multivariate analysis for VTE risk factors

	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Age ≥70 years	1.21	0.20–7.11	0.0425	1.31	0.13–13.65	0.8212
Male sex	2.1	0.27–16.17	0.4061			
ECOG PS ≥2	4.17	0.09–185.5	0.1622			
BMI ≥22	1.17	0.20–6.829	0.8615			
Intraoperative blood transfusion +	18.01	0.67–483.5	<0.0001	7.86	1.09–56.59	0.0405
Operation time ≥300 min	2.1	0.33–13.3	0.485			
Bleeding ≥300 mL	2.6	0.642–16.1	0.2808			
Open surgery	1.35	0.23–7.83	0.7506			
Pathological stage ≥III	0.21	0.03–1.62	0.0575			
D-dimer ≥24.6 μg/mL on POD1	34.85	0.06–22232	<0.0001	17.35	2.49–120.8	0.004
Soluble fibrin ≥64.1 μg/mL on POD1	38.45	0.38–3868	<0.0001	19.5	1.81–209.6	0.0142

95% CI 2.49–120.8, $p = 0.00395$), and POD 1 SF level ≥64.1 μg/mL (OR 19.5; 95% CI 1.81–209.6, $p = 0.0142$) were independent predictive factors for postoperative VTE development.

Discussion

The frequency of VTE after gastric cancer surgery has been reported in a randomized controlled trial in Korea [18]. The overall VTE frequency was 2.1%. All patients underwent duplex ultrasonography (DUS) routinely on postoperative day 4, after which they were followed up for clinical symptoms to identify VTE. In Japan, it has been reported that 7.2% of DVT was found by lower limb echo on 7 days after surgery for gastric cancer in a single-center study [19]. However, the incidence of VTE after gastric cancer surgery, including asymptomatic VTE diagnosed by more objective and sensitive images of CT scans, remains unknown. Therefore, it is worthwhile to report the frequency of symptomatic VTE confirmed by ultrasonography or a CT scan and asymptomatic VTE confirmed

by a contrast CT scan taken based on elevated of D-dimer and/or SF levels after gastric cancer surgery in a multicenter prospective study. In this study, we found VTE in 4.0% patients (1.6% symptomatic and 2.4% asymptomatic) after gastric cancer surgery.

There are many research reports on perioperative VTE prophylaxis in gastrointestinal surgery, and the ASCO guidelines suggest that VTE prophylaxis be administered at least 7–10 days after cancer surgery [10]. Especially in patients with a high risk of VTE, a maximum of 4 weeks of continuous VTE prophylaxis should be considered. The ACCP guidelines for the prevention of VTE recommend low-molecular-weight heparin (LMWH) for patients undergoing abdominal surgery for cancer [20]. Widely used LMWH is characterized as having a high anti-Xa/thrombin activity ratio compared to UFH and relatively less able to inhibit thrombin; it therefore has less influence on platelets and fewer hemorrhage-related side effects [21–23]. In a large randomized controlled trial in South Korea, postoperative VTE occurred significantly higher frequently in the IPC-only group compared to the IPC + LMWH group (3.6 vs. 0.6%; p = 0.008), and the incidence of postoperative bleeding complications was significantly higher in the IPC + LMWH group than in the IPC-only group (9.1 vs. 1.2%; p <0.001) after gastric cancer surgery [18]. From Japan, Osaki et al. [19] performed lower limb echo before and 7 days after surgery for gastric cancer, and reported a DVT of 4.4 and 7.2%, respectively.

We conducted this study to determine the incidence of patients who develop VTE after radical surgery for gastric cancer through a multicenter study in Japan. In this study, all surgeons at the 5 institutes used enoxaparin sodium postoperatively and no adverse bleeding events occurred. This study clarified that the incidence of VTE after radical gastric cancer surgery was 4.0%. Of the 5 VTE cases (4.0%), 3 (60%) were identified within 2 days after surgery; in all 3, enoxaparin sodium was used only once. This study found that LMWH administered from POD 2 could not completely prevent postoperative VTE.

Li et al. [24] reviewed 8,611 reports and identified the positive risk factors for VTE of age, radiation, need for blood transfusion, and operative time. Nielsen et al. [25] also reported that blood transfusion was a major risk factor for VTE in bariatric surgery. These reports demonstrated the need to monitor thrombosis markers and patient symptoms in cases in which blood transfusion was performed during surgery, and to evaluate imaging studies immediately to diagnose VTE and start treatment. Our study also showed that in elderly patients (≥70 years old), intraoperative blood transfusion could be a risk factor for VTE development after gastrectomy.

D-dimer is generally thought to increase in patients who are old, have a history of cancer, and undergo surgery [5]. In this study, D-dimer on days 1 and 7 after surgery for gastric cancer was also increased in patients who did not develop VTE, compared to preoperatively (Table 3). However, patients with high D-dimer on the first day after surgery still had a significantly higher incidence of VTE. This is a new finding that goes beyond the conventional knowledge of high D-dimer level after cancer surgery. Together with the SF levels, high D-dimer levels on the first day after surgery could be used as a high predictor of VTE development after surgery.

For predicting VTE, no previous reports suggested a detailed cutoff value for postoperative VTE in gastric cancer patients. Kimura et al. [26] reported that after gastrointestinal cancer surgery, D-dimer on the 7th day after the operation was significantly higher than that on the 3rd day after the operation. However, there has been no report showing the cut-off value of D-dimer that predicts VTE on the first day after surgery. Therefore, we focused on the blood test results from POD 1 for early VTE detection. The POD 1 D-dimer and SF levels were significantly higher in the VTE group, and the cutoff values obtained by drawing the ROC curve were 24.6 μg/mL for D-dimer and 64.1 μg/mL for SF. Imaging tests based on the elevated POD 1 D-dimer and SF levels could enable the early detection of VTE, which may lead to early anticoagulant therapy. Even in this study, an abnormal POD 1 D-dimer or SF levels led to the early diagnosis of asymptomatic VTE; as a result, rapid anticoagulation treatment was provided, resulting in a good prognosis without VTE deterioration.

One of the limitations of this study was that prophylaxis anticoagulants to prevent postoperative VTE were used only in 67.4% of patients. It is unclear whether the low incidence of VTE was related to postoperative prophylaxis anticoagulant use starting on POD 2. In addition, 5 cases of VTE were insufficiently powered to analyze the risk factors for VTE. It is expected that cases will be further accumulated under the unified use of postoperative prophylaxis anticoagulants and that the risk factors for VTE development will be analyzed in detail.

Another limitation was that POD 1 and POD 7 D-dimer and SF levels were obtained in 64.3% of cases. This was because the measurements could not be taken at some general hospitals due to medical insurance problems. However, our study findings suggest the significance of a high D-dimer or SF value in the early postoperative period and demonstrate the real incidence of VTE after radical gastric cancer surgery; therefore, we will be able to conduct this validation study to confirm the significance of early postoperative D-dimer and SF levels as risk factors for the development of postoperative DVT in gastric cancer surgery.

Conclusion

VTE occurred in 4.0% of patients (1.6% symptomatic and 2.4% asymptomatic) after gastric cancer surgery, without VTE deterioration due to the early diagnosis of VTE and early anticoagulant therapy. The careful observation of patients with high-risk factors and predictive factors for VTE, including intraoperative blood transfusion and high POD 1 D-dimer or SF level, would contribute to the early detection of VTE.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable standards. Informed consent was obtained from all individual participants included in the study. This study was approved by the Research Ethics Committee of Shiga University of Medical Science (No. R2015-228).

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

S.K.: conceptualization, methodology, and writing of the original draft; T.M.: validation and formal analysis; S.M.: writing (review and editing); T.Y., T.T., and S.N.: investigation and resources; K.M., H.O., H.O., H.T., M.K., and K.T.: data curation and resources; T.S.: software, supervision, and project administration; M.T.: supervision, writing (review and editing), and funding acquisition.

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