D-dimer predicts pulmonary embolism after low-risk spine surgery

Hirokazu Inoue¹⁾, Hideaki Watanabe²⁾, Hitoshi Okami³⁾, Atsushi Kimura¹⁾, Atsushi Seichi⁴⁾ and Katsushi Takeshita¹⁾

1) Department of Orthopaedic Surgery, Jichi Medical University, Shimotsuke, Japan

2) Department of Pediatric Orthopaedic Surgery, Jichi Children's Medical Center, Shimotsuke, Japan

3) Department of Orthopaedic Surgery, Shinkaminokawa Hospital, Kaminokawa, Japan

4) Department of Orthopaedic Surgery, Mitsuikinen Hospital, Tokyo, Japan

Abstract:

Introduction: Pulmonary embolism (PE) is a risk of mortality following spine surgery. Many studies have demonstrated that deep venous thrombosis (DVT) may affect and actually advance to PE, but few studies have shown how venous thromboembolism (VTE), including PE and DVT, affect blood markers after spine surgery. In this study, we examined changes in blood markers with PE or DVT after low-risk spine surgery, namely cervical laminoplasty or lumbar laminectomy.

Methods: Seventy-two spine surgery patients were studied. A 16-row multidetector computed tomography was performed before and 3 d after the surgery. Patients with a history of cerebral vascular accident or arterial thrombotic episode or pre-surgical asymptomatic PE or DVT were excluded. Plasma levels of soluble fibrin monomer complex, D-dimer, plasminogen activator inhibitor type-1 (PAI-1), and white blood cell and platelet counts were measured preoperatively and postoperatively at days 1, 3, and 7.

Results: No patient developed symptomatic post-surgical VTE. Six patients with asymptomatic PE and six with asymptomatic DVT were detected post-surgery, including one patient with both. D-dimer postoperatively at days 3 and 7 was significantly higher in the post-op PE group than in the no-PE group. PAI-1 preoperatively was significantly higher in the DVT and VTE groups than in the no-DVT and no-VTE groups.

Conclusions: Elevated D-dimer at postoperative days 3 and 7 is a predictive factor for the early diagnosis of PE after spine surgery. Moreover, elevated PAI-1 preoperatively is a predictive factor for the early diagnosis of DVT and VTE. Consequently, PE may occur through a pathway other than DVT.

Keywords:

deep vein thrombosis, D-dimer, pulmonary embolism, soluble fibrin monomer complex, plasminogen activator inhibitor type-1, venous thromboembolism

Spine Surg Relat Res 2018; 2(2): 113-120

dx.doi.org/10.22603/ssrr.2017-0054

Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), is important to control during orthopedic surgery because PE is a mortal complication and DVT can advance to PE. There is a worldwide increase in low-risk spine surgery. The decision to employ thromboprophylaxis is made weighing the risks of epidural hematoma, which can have serious neurological consequences, versus VTE and possibly PE, which can be asymptomatic until fatal. Thus, reliable blood markers that predict asymptomatic PE or DVT are desirable.

In spine surgery, the incidence of DVT is 0.3%-15.5%¹⁻⁶⁾.

The reported incidence of all PE after spine surgery is 0.06%-18%^{4,5,7)}. The 30-day postoperative risks were 0.29% for symptomatic PE and 0.6% for symptomatic DVT⁶⁾. Venographic studies absent thromboprophylaxis show that the incidence of DVT and PE is 41%-85% and 0.9%-28%, respectively, for total knee arthroplasty⁸⁾. When severe PE occurred, fatal outcomes were reported in 0.3% of the patients after spine surgery⁹⁾. Therefore, a predictive diagnosis of PE after spinal surgery is important. In a study of 10 different types of orthopedic surgery, Lapidus et al. have found a wide variance in the incidence of VTE, from 0.3% in spine surgery with thromboprophylaxis to 7.2% in Achilles tendon repair without thromboprophylaxis¹⁰⁾. The same study

also found a wide variance in the ratio of PE to DVT from 0% to 350%. Spine surgery had the second highest ratio at 200%. Takahashi et al. have found an asymptomatic PE incidence of 18% and a ratio of PE to DVT of 360% in patients who received either no prophylaxis or mechanical prophylaxis after spine surgery⁵.

PE is preferentially detected by multidetector computed tomography (MDCT), which requires a contrast agent, or by scintigraphy, which requires a radioactive isotope. Both may be contraindicated for patients who are allergic or who have renal dysfunction. Many researchers have demonstrated that effective blood markers for DVT or VTE are D-dimer¹¹⁻¹³, soluble fibrin monomer complex (SFMC)¹², and plasminogen activator inhibitor type-1 (PAI-1)¹⁴. To the best of our knowledge, no studies have focused on examining biomarkers that might be of predictive value for asymptomatic PE or DVT after low-risk spine surgery. Therefore, the purpose of our study was to measure blood coagulation-fibrinolysis markers in patients undergoing such surgery to identify independent markers that will facilitate an early diagnosis of asymptomatic PE and DVT.

Materials and Methods

Patients

The study protocol was approved by the Ethics Review Board of the Jichi Medical University. This prospective, single-center study enrolled patients who underwent cervical laminoplasty or lumbar laminectomy at our institution from August 2013 to August 2014 and gave informed consent to participate. Our study is consistent with The World Medical Association Declaration of Helsinki principles for medical research involving human subjects.

Exclusion criteria included a past history of symptomatic VTE, cerebral vascular accident, cardiac infarction, or drug allergy to a contrast medium. In addition, we excluded patients with liver disease, renal disease, congenital clotting factor deficiencies, and those undergoing antithrombotic therapy or hemodialysis. We also excluded four patients with asymptomatic VTE by preoperative MDCT and enrolled the remaining patients as low-risk patients. No patients had symptomatic VTE.

We examined 72 patients (female, 27; male, 45) with a mean age of 68 (range, 38-88) years. Spine surgery was performed under general anesthesia in all patients. The patients wore elastic stockings on the legs during surgery. Later, they wore them on the legs and used an intermittent pneumatic compression device until ambulant training was initiated in accordance with the Japanese Guidelines for Prevention of Venous Thromboembolism. Then, they could stand and walk on postoperative day 2. No postoperative prophylactic antithrombotic therapy was provided. Any patient with VTE was given aggressive antithrombotic therapy.

Multidetector computed tomography

A pre-surgical MDCT screened any preexisting disease, and a post-surgical MDCT identified only those patients who developed DVT or PE after surgery. For the diagnosis of VTE, a 16-row MDCT (Eclos; Hitachi Medical System, Kashiwa, Japan) was performed before surgery and on postoperative day 3. The testing time points for the present study were taken from our previous study¹⁴.

MDCT was performed with patients in the supine position after injecting 150 ml (100 ml for patients weighing <50 kg) of iohexol (300 mg/ml; Daiichi-Sankyo Co, Ltd, Tokyo, Japan) at 3 ml/s. The thoracic region and the area from the diaphragm to the middle of the crural region were cranio-caudally examined. Bolus tracking was performed by setting the region of interest in the main trunk of the pulmonary artery, and scanning was started when the computed tomography level reached 100 in the thoracic region and, after 3.5 min, in the area from the abdomen to the lower limbs. MDCT slice thicknesses were 2 mm in the thoracic region and 5 mm from the abdomen to the lower limbs. The window levels were 40-60 and 40-50, and the window widths were 400-500 and 200-400, respectively. A single radiologist evaluated the MDCT images in a blinded manner before and after the surgery to determine postoperative asymptomatic PE and DVT. Patients were then classified into four groups: PE, no-PE, DVT, no-DVT.

Blood Coagulation-Fibrinolysis Markers

Plasma levels of SFMC, D-dimer, PAI-1, and platelet (Plt) count were measured before and on postoperative days 1, 3, and 7. SFMC levels were measured by a latex immunoagglutination assay (Mitsubishi Chemical Medience Corporation, Tokyo, Japan) using the monoclonal antibody IF-43¹⁵. D-dimer levels were measured by a latex immunoagglutination assay (Mitsubishi Chemical Medience Corporation) using the monoclonal antibody JIF-23¹⁶. PAI-1 levels were measured by a latex photometric immunoassay (Mitsubishi Chemical Medience Corporation) using the polyclonal antibody F(ab') fragment¹⁷. Blood markers were analyzed over time from preoperative day 1 to postoperative days 1, 3, and 7.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). SFMC, D-dimer, PAI-1, and Plt levels were analyzed by the Shapiro-Wilk test if they did not fit a normal distribution^{10,18}. SFMC, D-dimer, PAI-1, and Plt levels were compared before and on postoperative days 1, 3, and 7 using the Friedman test. If a significant difference was noted, then the data were compared using the Wilcoxon signed rank test and corrected using Bonferroni's inequality. SFMC, D-dimer, PAI-1, and Plt levels were compared between the thrombus and no-thrombus groups using the Mann-Whitney U-test. Age, volume of intraoperative hemorrhage, operation time, other pre-

Table 1. Baseline Characteristics of Patients with or without PE.

	PE (n=6)	No-PE (n=66)	P
Gender (Male:Female)	5:1	40:26	0.26
Age (years)	70 (56-82)	68 (38-88)	0.77
Volume of intraoperative hemorrhage (ml)	133 (55-210)	141 (20-565)	0.60
Operation time (min)	104 (72-149)	101 (37-226)	0.64
Height (cm)	163 (156-170)	159 (130-179)	0.37
Weight (kg)	64 (53-70)	63 (35-95)	0.73
BMI	24 (18-29)	25 (18-31)	0.64

PE, pulmonary embolism

Table 2. Baseline Characteristics of Patients with or without DVT.

	DVT (n=6)	No-DVT (n=66)	P
Gender (Male:Female)	4:2	41:25	0.83
Age (years)	70 (57-82)	68 (38-88)	0.74
Volume of intraoperative hemorrhage (ml)	103 (60-210)	143 (20-565)	0.43
Operation time (min)	94 (67-149)	102 (37-226)	0.70
Height (cm)	160 (145-170)	159 (130-179)	0.98
Weight (kg)	64 (56-70)	63 (35-95)	0.74
BMI	25 (21-29)	25 (18-31)	0.84

DVT, deep vein thrombosis

surgical factors, and blood markers were compared using an unpaired *t*-test. The level of statistical significance was set at $P < 0.05$ for all tests. Receiver operating characteristic (ROC) curves were plotted using SPSS software.

Results

We prospectively analyzed the collected data on 72 patients who underwent cervical laminoplasty or lumbar laminectomy from August 2013 to August 2014. No patient had symptomatic PE or DVT after spine surgery. Postoperative MDCT revealed asymptomatic PE in six (8.3%) and DVT in six (8.3%) patients. One patient was detected with both PE and DVT. The data for PE are summarized in Fig. 1, those for DVT in Fig. 3, and those for VTE in Fig. 5. Cervical laminoplasty was performed in 17 patients, which indicated asymptomatic PE in one (5.9%), DVT in one (5.9%), and VTE in two (11.8%) patients. Lumbar laminectomy was performed in 55 patients, which indicated asymptomatic PE in five (9.1%), DVT in five (9.1%), and VTE nine (16.3%) patients. PE, DVT, or VTE had no significant differences between cervical laminoplasty and lumbar laminectomy.

There were no significant differences in gender, age, intraoperative hemorrhage, operation time, height, weight, and body mass index between the PE and no-PE groups (Table 1), the DVT and no-DVT groups (Table 2), and the VTE and no-VTE groups (Table 3).

Table 3. Baseline Characteristics of Patients with or without VTE.

	VTE (n=11)	No-VTE (n=61)	P
Gender (Male:Female)	9:2	36:25	0.14
Age (years)	69 (56-82)	68 (38-88)	1.00
Volume of intraoperative hemorrhage (ml)	110 (55-210)	146 (20-565)	0.55
Operation time (min)	94 (67-149)	103 (37-226)	0.71
Height (cm)	162 (145-170)	159 (130-179)	0.36
Weight (kg)	63 (53-70)	63 (35-95)	0.81
BMI	24 (18-29)	25 (18-31)	0.55

VTE, venous thromboembolism

Pulmonary embolism

D-dimer was significantly higher in the PE group than in the no-PE group on postoperative days 3 and 7 ($p < 0.05$; Fig. 1). The median PE postoperative day 3 D-dimer was 4.3 $\mu\text{g/ml}$ [interquartile range, (IQR) 5.1 (3.3-8.3)] vs. 1.7 $\mu\text{g/ml}$ [IQR, 1.4 (1.2-2.5)]. The median PE postoperative day 7 D-dimer was 10.0 $\mu\text{g/ml}$ [IQR, 13.9 (4.6-18.4)] vs. 4.6 $\mu\text{g/ml}$ [IQR, 4.1 (2.7 to 6.8)]. There were no significant differences in SFMC, PAI-1, and Plt between the PE and no-PE groups.

ROC curves were postoperatively obtained for various cut-off values of D-dimer. The levels at days 3 and 7 were 8.2 and 10.8 $\mu\text{g/ml}$, with a sensitivity of 83.3% and 67.7% and a specificity of 84.4% and 87.5%, respectively (Fig. 2).

Deep vein thrombosis

Plt counts on both preoperative and postoperative days 1 and 3 were significantly higher in the DVT groups than in the non-DVT groups ($p < 0.05$; Fig. 3). The median preoperative Plt count was $27.8 \times 10^4/\mu\text{l}$ [IQR, 19.0 (24.4-43.4)] vs. $22.1 \times 10^4/\mu\text{l}$ [IQR, 8.6 (18.7-27.3)]. The median postoperative day 1 count was $23.3 \times 10^4/\mu\text{l}$ [IQR, 13.3 (20.1-33.4)] vs. $19.5 \times 10^4/\mu\text{l}$ [IQR, 6.7 (16.0-22.7)]. The median day 3 count was $23.2 \times 10^4/\mu\text{l}$ [IQR, 9.1 (19.7-28.8)] vs. $19.0 \times 10^4/\mu\text{l}$ [IQR, 7.4 (15.6-22.9)].

The median preoperative PAI-1 was significantly higher at 24.5 ng/ml [IQR, 15.5 (21.5-37.0)] in the DVT group than at 17.5 ng/ml [IQR, 9.3 (13.8-23.0)], in the no-DVT group ($p < 0.05$).

ROC curves were obtained for Plt cut-off values. The levels preoperatively and on postoperative days 1 and 3 were $42.3 \times 10^4/\mu\text{l}$, $24.3 \times 10^4/\mu\text{l}$, and $23.8 \times 10^4/\mu\text{l}$, with a sensitivity of 83.3%, 66.7%, and 67.7% and a specificity of 54.5%, 72.7%, and 74.2%, respectively (Fig. 4). These analyses revealed significant differences, but all were within the normal values. ROC curves were obtained for PAI-1 cut-off values. The preoperative cut-off level was 31 ng/ml, with a sensitivity of 83.3% and a specificity of 59.1% ($P < 0.05$; Fig. 4); this result was also within the normal range.

Figure 1. Preoperative and postoperative D-dimer, total plasminogen activator inhibitor type-1 (PAI-1), soluble fibrin monomer complex (SFMC), and platelet (Plt). White boxes, no-pulmonary embolism; gray boxes, pulmonary embolism. * $P < 0.05$, pulmonary embolism group vs. no-pulmonary embolism group by the Mann-Whitney U-test.

Figure 2. Receiver operating characteristic curves. Left: at a cut-off point of $8.2 \mu\text{g/ml}$ for the D-dimer level at postoperative day 3, the sensitivity is 83% and the specificity is 86%. Right: at a cut-off point of $10.8 \mu\text{g/ml}$ for the D-dimer level at postoperative day 7, the sensitivity is 67% and the specificity is 88%.

Venous thromboembolism

The median preoperative PAI-1 was significantly higher at 25.0 ng/ml [IQR, 17.0 (20.0-37.0)] in the VTE group than at 17.0 ng/ml [IQR, 9.5 (13.5-23.0)] in the no-VTE group ($p <$

0.05; Fig. 5). There were no significant differences in D-dimer, SFMC, and Plt between the VTE and no-VTE groups.

ROC curves were obtained for various cut-off values of PAI-1. The preoperative level was 31 ng/ml , with a sensitiv-

Figure 3. Preoperative and postoperative D-dimer, total plasminogen activator inhibitor type-1 (PAI-1), soluble fibrin monomer complex (SFMC), and platelet (Plt). White boxes, no-deep vein thrombosis; gray boxes, deep vein thrombosis. *P < 0.05, deep vein thrombosis group vs. no-deep vein thrombosis group by the Mann-Whitney U-test.

ity of 81.8% and a specificity of 54.1% ($P < 0.05$; Fig. 6). This result revealed a significant difference, but was within the normal range.

Discussion

We found that elevated D-dimer after low-risk spinal surgery on postoperative days 3 and 7 is a predictive marker for asymptomatic PE, whereas elevated PAI-1 is a preoperative predictive marker for asymptomatic DVT or VTE. We further found that the incidence of both asymptomatic PE and DVT was 8.3% (6/72); thus, the incidence of VTE was 15%, with one patient having both PE and DVT. Although DVT and PE are a part of the general spectrum of VTE, they are separate conditions in different microenvironments with different risks of mortality and morbidity. Therefore, it is possible that different biological mechanisms with corresponding biomarkers underlie each one. Furthermore, variations in the ratio of PE to DVT, irrespective of the prophylaxis seen in the Lapidus study, suggest that it is useful to separately consider examining these conditions for a possible biomarker involvement¹⁰.

PE is a fatal complication after spine surgery, and the prevalence of VTE after spine surgery is relatively high¹⁹. Takahashi et al. have demonstrated that asymptomatic PE or

DVT is detected in 18% and 5% of the patients, respectively, using contrast-enhanced computed tomography after spine surgery⁵. However, they did not exclude patients with a history of symptomatic VTE, cerebral vascular accident, or cardiac infarction. Thus, they possibly included patients at high risk and those with invasive spine surgery. We excluded patients with these histories and focused on decompression surgery including laminectomy and laminoplasty, which signifies low-risk surgery.

In total, 15% (11/72) of our patients had DVT or PE, including one with both. Six (8%) patients had DVT and six (8%) had PE. No patient had symptomatic post-surgical VTE. These results suggest that PE does not always develop from DVT.

MDCT can diagnose symptomatic PE to the level of sub-segmental pulmonary arteries. MDCT can also determine the size of thrombi and is capable of detecting both PE and DVT. The usefulness of MDCT is supported by its high sensitivity (100%) and specificity (96.6%) and moderate-to-high interobserver agreement rates, with kappa values ranging from 0.59 to 0.94 in symptomatic PE²⁰⁻²².

Many studies have shown D-dimer to be an effective blood marker for DVT in various surgeries^{11-13,23}. Post-surgical cut-off values after total knee or hip arthroplasty were 7.2 µg/ml on day 1, 7.0 µg/ml on day 4¹², and 10 µg/

Figure 4. Receiver operating characteristic curves. A: at a cut-off point of $42.3 \times 10^4/\mu\text{l}$ for the platelet level at preoperative days. B: at a cut-off point of $24.3 \times 10^4/\mu\text{l}$ for the platelet level at postoperative day 1. C: at a cut-off point of $23.8 \times 10^4/\mu\text{l}$ for the platelet level at postoperative day 3. D: at a cut-off point of 31 ng/ml for the PAI-1 level preoperatively.

ml on day 7²³). After spine surgery, the cut-off value was 10 $\mu\text{g}/\text{ml}$ ¹³). Few studies have reported cut-off values for PE. We demonstrated that D-dimer is an effective blood marker for detecting PE, with post-surgical cut-off values of 8.2 $\mu\text{g}/\text{ml}$ on day 3 and 10.8 $\mu\text{g}/\text{ml}$ on day 7.

In previous reports, high concentrations of SFMC and PAI-1 were considered to be markers of thrombosis, including VTE^{11,12,24,25}). Reber et al. have shown that SFMC level was significantly elevated in patients with asymptomatic DVT on postoperative days 3 and 6²⁵). PAI-1 inhibits plasminogen activator, which leads to the production of fibrin or thrombus²⁶). Plt have substantially higher PAI-1 concentrations than plasma, but 90% of Plt PAI-1 is inactive; whereas most plasma PAI-1 is active²⁷). Watanabe et al. have demonstrated that PAI-1 levels in patients with VTE increased higher than in those without VTE after pneumatic tourniquet release during total knee arthroplasty¹⁴). In that study, SFMC and PAI-1 were not effective in detecting PE. However, in our patients with DVT and VTE, preoperative PAI-1 was significantly increased with a cut-off value of 31 ng/ml. We believe that high preoperative PAI-1 is indicative of DVT or VTE.

In the present study, we detected that Plt was a marker for DVT because Plt levels preoperatively and at postoperative days 1 and 3 significantly differed between the patients with DVT and those without DVT, but the cut-off levels were in the normal range: $42.3 \times 10^4/\mu\text{l}$ preoperatively, $24.3 \times 10^4/\mu\text{l}$ on postoperative day 1, and $23.8 \times 10^4/\mu\text{l}$ on postoperative day 3. Therefore, Plt was an ineffective marker for DVT.

The variance found by Lapidus in the ratio of PE to DVT from 0% in Achilles tendon repair to 350% in lower limb amputation, which is a very high-risk surgery, is interesting because it lacks correlation to thromboprophylaxis¹⁰). In fact, spine surgery with thromboprophylaxis showed a 200% ratio of PE to DVT, and all lower ratios were under 54%, averaging at 16%. The Takahashi study of spine surgeries showed a similar ratio of PE to DVT at 360%⁵). These data suggested the occurrence of direct PE, not arising from DVT, in which case a blood marker specific to PE becomes increasingly important. This variation may be the result of different biological mechanisms that could imprint different biomarker levels. Thus, we segregated our analyses by PE and DVT to reveal whether some biomarkers are more or

Figure 5. Preoperative and postoperative D-dimer, total plasminogen activator inhibitor type-1 (PAI-1), soluble fibrin monomer complex (SFMC), and platelet (Plt). White boxes, no-venous thromboembolism; gray boxes, venous thromboembolism. * $P < 0.05$, venous thromboembolism group vs. no-venous thromboembolism group by the Mann-Whitney U-test.

Figure 6. Receiver operating characteristic curves. At a cut-off point of 31 ng/ml for the PAI-1 level preoperatively.

secure important differences in the biomarker thresholds between the two conditions. In fact, an analysis of VTE+ vs. VTE- groups revealed that there was only one significant difference in the higher preoperative PAI-1 levels compared with our original groupings. In the PE+DVT- vs. VTE- groups, D-dimer and SFMC were significantly higher. In the DVT+PE- vs. VTE- groups, Plt and PAI-1 were significantly higher.

The present study may be the first to definitively measure the incidence of PE in asymptomatic patients after low-risk spine surgery, but there are some limitations. We selected low-risk patients with less invasive spine surgery. High-risk patients or more invasive surgery may result in different cut-off values. Our study had six patients with PE and six with DVT; a greater number of subjects may yield more accurate results. It is possible that our results are because of chance, but we consider this only a remote possibility. Our findings, although not exact, may lay the groundwork toward a better understanding of the risks of asymptomatic VTE associated with low-risk spine surgery. Additional analyses with larger cohorts are needed to confirm our findings. Finally, because of a small sample size, ROC findings may be of limited value.

less specific to each condition. Combining DVT and PE patients into a single VTE group may increase the overall statistical power in the present study; however, it may also ob-

Conclusion

In low-risk spine surgery, we found that D-dimer is an effective marker for PE on postoperative days 3 and 7, with cut-off values of 8.2 µg/ml and 10.8 µg/ml, respectively. Preoperatively, PAI-1, with a cut-off value of 31 ng/ml, is an effective marker for both DVT and VTE. These differing blood markers suggest that PE does not invariably arise from DVT.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Acknowledgement: We thank Gary Baley for research and for being an academic editor of the manuscript.

References

1. Ferree BA, Stern PJ, Jolson RS, et al. Deep venous thrombosis after spinal surgery. *Spine (Phila Pa 1976)*. 1993;18(3):315-9.
2. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. *Spine (Phila Pa 1976)*. 1996;21(7):853-8.
3. Oda T, Fuji T, Kato Y, et al. Deep venous thrombosis after posterior spinal surgery. *Spine (Phila Pa 1976)*. 2000;25(22):2962-7.
4. Piasecki DP, Poynton AR, Mintz DN, et al. Thromboembolic disease after combined anterior/posterior reconstruction for adult spinal deformity: a prospective cohort study using magnetic resonance venography. *Spine (Phila Pa 1976)*. 2008;33(6):668-72.
5. Takahashi H, Yokoyama Y, Iida Y, et al. Incidence of venous thromboembolism after spine surgery. *J Orthop Sci*. 2012;17(2):114-7.
6. Bekelis K, Desai A, Bakhoun SF, et al. A predictive model of complications after spine surgery: the National Surgical Quality Improvement Program (NSQIP) 2005-2010. *Spine J*. 2014;14(7):1247-55.
7. Sansone JM, del Rio AM, Anderson PA. The prevalence of and specific risk factors for venous thromboembolic disease following elective spine surgery. *J Bone Joint Surg Am*. 2010;92(2):304-13.
8. Colwell CW. The ACCP guidelines for thromboprophylaxis in total hip and knee arthroplasty. *Orthopedics*. 2009;32(12 Suppl):67-73.
9. Schoenfeld AJ, Herzog JP, Dunn JC, et al. Patient-based and surgical characteristics associated with the acute development of deep venous thrombosis and pulmonary embolism after spine surgery. *Spine (Phila Pa 1976)*. 2013;38(21):1892-8.
10. Lapidus LJ, Ponzer S, Pettersson H, et al. Symptomatic venous thromboembolism and mortality in orthopaedic surgery - an observational study of 45 968 consecutive procedures. *BMC Musculoskelet Disord*. 2013;14:177.
11. Watanabe H, Madoiwa S, Sekiya H, et al. Predictive blood coagulation markers for early diagnosis of venous thromboembolism after total knee joint replacement. *Thromb Res*. 2011;128(6):e137-43.
12. 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(5):572-6.
13. Yoshiiwa T, Miyazaki M, Takita C, et al. Analysis of measured D-dimer levels for detection of deep venous thrombosis and pulmonary embolism after spinal surgery. *J Spinal Disord Tech*. 2011;24(4):E35-9.
14. Watanabe H, Kikkawa I, Madoiwa S, et al. Changes in blood coagulation-fibrinolysis markers by pneumatic tourniquet during total knee joint arthroplasty with venous thromboembolism. *J Arthroplasty*. 2014;29(3):569-73.
15. Soe G, Kohno I, Inuzuka K, et al. A monoclonal antibody that recognizes a neo-antigen exposed in the E domain of fibrin monomer complexed with fibrinogen or its derivatives: its application to the measurement of soluble fibrin in plasma. *Blood*. 1996;88(6):2109-17.
16. Madoiwa S, Someya T, Hironaka M, et al. Annexin 2 and hemorrhagic disorder in vascular intimal carcinomatosis. *Thromb Res*. 2007;119(2):229-40.
17. Ono T, Sogabe M, Ogura M, et al. Automated latex photometric immunoassay for total plasminogen activator inhibitor-1 in plasma. *Clin Chem*. 2003;49(6 Pt 1):987-9.
18. McPherson R PM, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 22nd ed. Philadelphia, PA: Saunders Elsevier; 2011.
19. Tominaga H, Setoguchi T, Tanabe F, et al. Risk factors for venous thromboembolism after spine surgery. *Medicine (Baltimore)*. 2015;94(5):e466.
20. Begemann PG, Bonacker M, Kemper J, et al. Evaluation of the deep venous system in patients with suspected pulmonary embolism with multi-detector CT: a prospective study in comparison to Doppler sonography. *J Comput Assist Tomogr*. 2003;27(3):399-409.
21. Coche EE, Hamoir XL, Hammer FD, et al. Using dual-detector helical CT angiography to detect deep venous thrombosis in patients with suspicion of pulmonary embolism: diagnostic value and additional findings. *AJR Am J Roentgenol*. 2001;176(4):1035-9.
22. Patel S, Kazerooni EA. Helical CT for the evaluation of acute pulmonary embolism. *AJR Am J Roentgenol*. 2005;185(1):135-49.
23. Shiota N, Sato T, Nishida K, et al. Changes in LPIA D-dimer levels after total hip or knee arthroplasty relevant to deep-vein thrombosis diagnosed by bilateral ascending venography. *J Orthop Sci*. 2002;7(4):444-50.
24. Yukizawa Y, Inaba Y, Kobayashi N, et al. Selective pharmacological prophylaxis based on individual risk assessment using plasma levels of soluble fibrin and plasminogen-activator inhibitor-1 following total hip arthroplasty. *Mod Rheumatol*. 2014;24(5):835-9.
25. Reber G, Blanchard J, Bounameaux H, et al. Inability of serial fibrin monomer measurements to predict or exclude deep venous thrombosis in asymptomatic patients undergoing total knee arthroplasty. *Blood Coagul Fibrinolysis*. 2000;11(3):305-8.
26. Watanabe H, Inoue H, Murayama A, et al. Prediction of venous thromboembolism after total knee arthroplasty using blood coagulation-fibrinolysis markers: a systematic review. *Int J of Orthopaedics*. 2015;2(3):280-3.
27. Declerck PJ, Alessi MC, Verstreken M, et al. Measurement of plasminogen activator inhibitor 1 in biologic fluids with a murine monoclonal antibody-based enzyme-linked immunosorbent assay. *Blood*. 1988;71(1):220-5.

Spine Surgery and Related Research is an Open Access article distributed under the Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).