Turk Neurosurg, 2021

Original Investigation

DOI: 10.5137/1019-5149.JTN.32962-20.2

Received: 03.11.2020
Accepted: 05.02.2021

Published Online: 02.07.2021

# Prevalence and Screening of Deep Vein Thrombosis in Patients with Osteoporotic Vertebral Fracture

Isamu MIURA[1,2], Motoo KUBOTA[1], Nobuhiko MOMOZAKI[1,2], Takakazu KAWAMATA[2], Masahito YUZURIHARA[1]

[1]Kameda Medical Center, Department of Spinal Surgery, Chiba, Japan
[2]Tokyo Women's Medical University, Department of Neurosurgery, Tokyo, Japan

**Corresponding author:** Isamu MIURA ✉ isamu2345@yahoo.co.jp

## ABSTRACT

**AIM:** To determine the prevalence of a deep vein thrombosis (DVT) in osteoporotic vertebral fractures.

**MATERIAL and METHODS:** Data were retrospectively collected from the medical records of 50 patients who were admitted to the Kameda Medical Center for osteoporotic vertebral fracture from 2019 to 2020. Inpatients were screened for DVT using D-dimer, and those who were screened positive underwent lower extremity venous ultrasonography to confirm DVT. Associations between various clinical factors and DVT were analyzed.

**RESULTS:** Six (12.0%) inpatients with osteoporotic vertebral fractures were found to have DVT. Two (33.3%) of the six had proximal DVT, although no pulmonary embolism was detected by chest computed tomography angiography. Univariate analysis showed that D-dimer values and duration from onset to hospitalization were predictive of DVT ($p<0.05$).

**CONCLUSION:** The prevalence of DVT among inpatients with osteoporotic vertebral fractures was 12.0%. This finding emphasizes the importance of DVT screening using D-dimer in those with osteoporotic vertebral fractures.

**KEYWORDS:** D-dimer, Deep vein thrombosis, Osteoporotic vertebral fracture, Screening, Thoracolumbar fracture

**ABBREVIATIONS: AUC:** Area under the curve, **BKP:** Balloon kyphoplasty, **BMI:** Body mass index, **CKD:** Chronic kidney disease, **CT:** Computed tomography, **DVT:** Deep vein thrombosis, **NRS:** Numerical rating scale score, **ROC:** Receiver operating characteristic curve, **SD:** Standard deviation, **VTE:** Venous thromboembolism, **YAM:** Young adult means

## INTRODUCTION

Osteoporotic vertebral fracture is a common disease in older adults. More than 50% of postmenopausal women sustain mild to severe fractures because of osteoporosis (15). Vertebral compression fractures are a common type of osteoporotic fracture that severely compromises the patient's quality of life (1-4,6). Venous thromboembolism (VTE), including pulmonary embolism and deep vein thrombosis (DVT), is one of the most common and potentially fatal diseases that occur after vertebral fractures (2). However, the incidence and natural history of DVT in osteoporotic vertebral fractures are unclear, and conclusions regarding the need for screening have not been reached. Therefore, we examined cases of DVT among patients hospitalized for osteoporotic vertebral fractures including the incidence and potential risk factors of these fractures.

## MATERIAL and METHODS

We retrospectively reviewed the records of consecutive patients admitted to the Kameda Medical Center for osteoporotic vertebral fractures between April 2019 and September 2020. The diagnosis of osteoporotic vertebral

Isamu MIURA : 0000-0001-5231-5862
Motoo KUBOTA : 0000-0002-8403-9230
Nobuhiko MOMOZAKI : 0000-0002-5555-5228
Takakazu KAWAMATA : 0000-0002-6076-7065
Masahito YUZURIHARA : 0000-0002-8971-7707

fracture was based on clinical symptoms, episodes of low-velocity trauma or atraumatic causes and imaging studies, including plain radiography, computed tomography (CT), magnetic resonance imaging and young adult means (YAM) of bone mineral density measured by dual-energy X-ray absorptiometry at the lumbar spine and proximal femur. Fifty-one patients were eligible for inclusion; however, we excluded one patient who did not undergo screening. Therefore, 50 patients were included for analysis. This study was approved by the institutional review board of the Kameda Medical Center (No.19-177).

In our hospital, osteoporotic vertebral fractures are basically treated using conservative therapy and outpatient care. The main indications for hospitalization are surgical treatment because of pain refractory to conservative therapy, paresis, vertebral instability, and social problems such as living alone. At our hospital, inpatients were screened for DVT using D-dimer. D-dimer was measured once per week during hospitalization. In cases of abnormal D-dimer values (>4.0 μg/mL), we performed lower extremity venous ultrasound to evaluate for DVT or obtained a D-dimer level 1 week later. Neither mechanical (intermittent pneumatic compression device) nor chemical prophylaxis to prevent DVT was routinely conducted.

We collected information on body mass index (BMI), smoking and alcohol use, comorbidities, such as diabetes mellitus, chronic kidney disease (CKD), cancer history, steroid use, and YAM.

Statistical analysis was conducted using R statistical software. Results are reported as means ± standard deviation (SD) for continuous variables. We used Fisher's exact test to examine the differences between the DVT and non-DVT patient groups for binary variables. Pearson's chi-square test was used to compare the duration from onset to hospitalization between the three groups. For continuous variables, Student's t- test was used. *P* values of <0.05 were considered statistically significant. Receiver operating characteristic curve (ROC) analyses were used to evaluate the diagnostic value of predictors.

## RESULTS

Figure 1 displays the participant selection process for this study. D-dimer measurements were obtained from 50 patients. The participants comprised 17 men and 33 women with a mean age (± SD) of 77.9 ± 8.6 (range: 60–96) years. Thirty-two patients had a negative screen, 10 of whom showed transient elevation of D-dimer; however, the D-dimer values normalized without subsequent intervention. Eighteen patients underwent lower extremity venous ultrasonography. Six patients were diagnosed with DVT. Two of these six patients had proximal DVT, although no pulmonary embolism was detected on CT angiography. Four of the six patients had distal DVT only. After the diagnosis of DVT, five patients were treated with anticoagulants (n=4, apixaban; n=1, edoxaban). The other patient with DVT who did not take anticoagulants was followed-up because of old age (96-year-old). Four patients with DVT underwent surgery. Two patients with DVT, including one with proximal DVT were treated with anticoagulants before surgery, which was performed after the D-dimer value normalized. In contrast, five of six patients had elevated D-dimer level upon admission. This suggests that five of the six patients had DVT upon admission. One of the six patients showed normal values of D-dimer at admission; however, D-dimer levels were elevated after balloon kyphoplasty (BKP). This indicates that DVT developed in this patient perioperatively during hospitalization.

In this study, the mean duration from onset to the first visit to our hospital (± SD) was 64.3 ± 115.4 (range: 0-570) days, and the mean duration from onset to hospitalization (± SD) was 82.0 ± 123.1 (range: 0-600) days. Forty-two patients had a single-level vertebral fracture, and eight had multilevel fractures. L1 was the most commonly affected level (Figure 2). Thirty-four patients underwent surgery, and the mean duration from onset to surgery (± SD) was 116.5 ± 137.6 (range: 11-602) days. BKP was the most frequently conducted procedure (23 patients [67.6%]), and percutaneous pedicle screw (PPS) alone was conducted in two patients (5.9%). Five patients (14.7%) underwent a combined BKP and PPS, and two patients (5.9%) had a combined corpectomy and PPS. Another operation, such as transforaminal lumbar interbody fusion was conducted in two patients (5.9%).

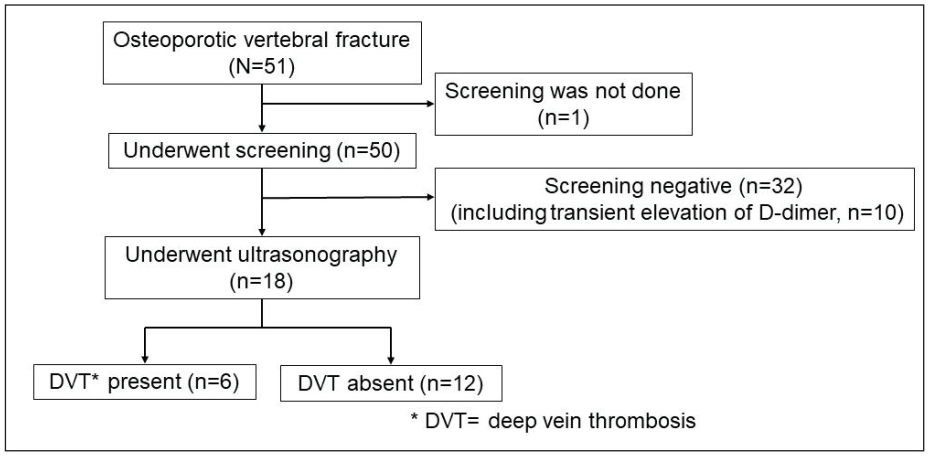


**Figure 1:** Participant selection. Throughout the study period, 51 patients with osteoporotic vertebral fractures were hospitalized at Kameda Medical Center. Fifty patients underwent screening for deep vein thrombosis (DVT). Eighteen patients underwent lower extremity venous ultrasound to examine DVT. Six patients had DVT.

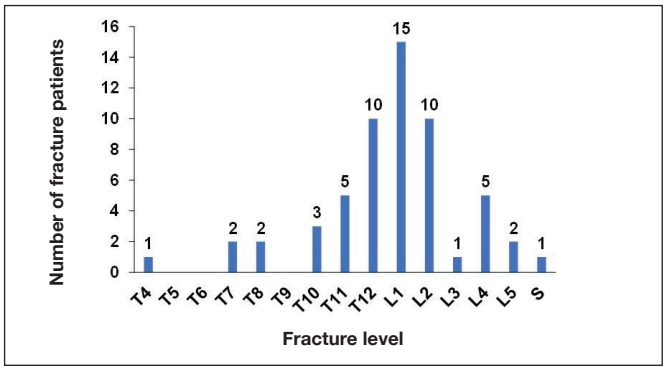


**Figure 2:** Distribution of involved levels in osteoporotic vertebral fractures.

Table I presents the results of the univariate analysis. The D-dimer level and duration from onset to hospitalization were considered predictive factors of DVT according to a univariate analysis ($p<0.05$). Based on an ROC analysis, the area under the curve (AUC) was 0.8561 (Table II and Figure 3). Age, sex, BMI, alcohol, smoking, diabetes mellitus, CKD, a history of cancer, steroid use, hospitalization, single-level vertebral fracture, numerical rating scale score (NRS), YAM, paresis, undergoing surgery, and taking an anticoagulant and/or antiplatelet medication were not significantly associated with DVT.

**Table I:** Patient Characteristics Stratified by Deep Vein Thrombosis

| | Deep Vein Thrombosis | | |
|---|---|---|---|
| **Characteristics** | **Present n=6** | **Absent n=44** | **P value** |
| Mean age, years, ±SD | 81.5 ± 9.3 | 77.4 ± 8.5 | 0.28 |
| Men, n (%) | 2 (33.3) | 15 (34) | 0.97 |
| Mean body mass index, ±SD | 23.1 ± 4.5 | 22.8 ± 4.2 | 0.88 |
| Health behaviors, n (%) | | | |
| Alcohol | 2 (33.3) | 11 (25.0) | 0.64 |
| Smoking | 0 (0) | 7 (15.9) | 0.58 |
| Chronic condition, n (%) | | | |
| Diabetes mellitus | 1 (16.7) | 9 (20.5) | 1.00 |
| Chronic kidney disease | 0 (0) | 7 (15.9) | 0.58 |
| History of cancer | 1 (16.7) | 10 (22.7) | 1.00 |
| Steroid user | 1 (16.7) | 2 (4.5) | 0.32 |
| Duration from onset to the first visit | | | |
| Mean days ± SD | 38.8 ± 41.8 | 67.7 ± 121.9 | 0.43 |
| Numbers of days, n (%) | | | |
| 0-10 | 1 (16.7) | 14 (31.8) | |
| 11-60 | 4 (66.7) | 17 (38.6) | |
| >60 | 1 (16.7) | 13 (29.5) | |
| Duration from onset to hospitalization | | | |
| Mean days ± SD | 53.0 ± 43.9 | 86.0 ± 130.1 | 0.033* |
| Numbers of days, n (%) | | | |
| 0-10 | 0 (0) | 12 (27.3) | |
| 11-60 | 5 (83.3) | 13 (29.5) | |
| >60 | 1 (16.7) | 19 (43.2) | |
| Mean hospitalization days, ±SD | 18.7 ± 5.6 | 27.0 ± 24.6 | 0.43 |
| Single-level vertebral fracture, n (%) | 4 (66.7) | 38 (86.4) | 0.24 |
| Numerical Rating Scale at admission, mean±SD | 5.7 ± 2.7 | 7.4 ± 2.0 | 0.06 |
| Young adult mean, %, ±SD | 60.7 ± 16.1 | 65.3 ± 15.7 | 0.56 |
| Paresis, n (%) | 0 (0) | 4 (9.1) | 1.00 |
| Underwent surgery, n (%) | 4 (66.7) | 30 (68.2) | 1 |
| Mean D-dimer level, µg/mL, ±SD | 10.7 ± 6.8 | 4.1 ± 4.2 | 0.0015* |
| Anti-coagulant and/or anti-platelet medications, n (%) | 1 (16.7) | 10 (22.7) | 1.000 |

**Table II:** Receiver Operating Characteristic Curve Result of D-Dimer

| | Cutoff value | Sensitivity | Specificity | 95% CI | AUC |
|---|---|---|---|---|---|
| D-dimer | 4.00 | 72.70 | 100.00 | 0.7412-0.9709 | 0.8561 |

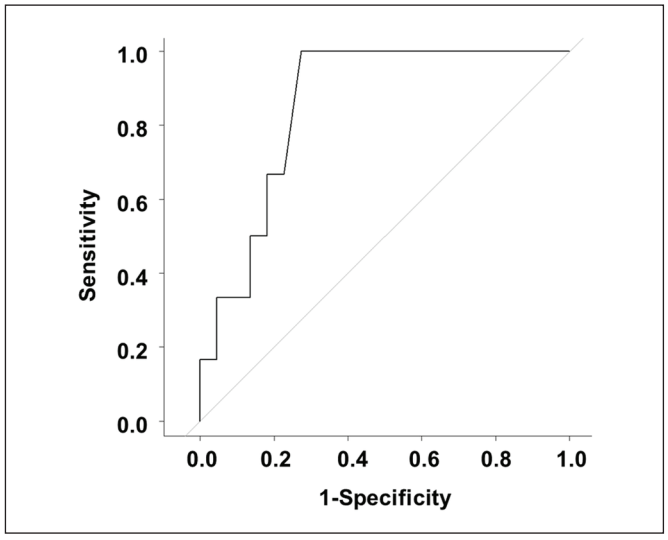


**Figure 3:** Receiver operating characteristic curve of D-dimer as a predictor of deep vein thrombosis.

## DISCUSSION

Our data showed that 12.0% of inpatients with osteoporotic vertebral fracture had DVT. To our knowledge, this is the first retrospective study to examine screening for and prevalence of DVT in inpatients with osteoporotic vertebral fracture. Previous studies have focused on the incidence of DVT after high-energy injuries or spinal surgery (11,13,16). In their retrospective study, Schulte et al. reported that the incidence of VTE was 1.1% in patients undergoing spine surgery (13). Samuel et al. reported that the overall rate of VTE was 2.5% in patients with traumatic vertebral fractures, a common high-energy injury that sometimes results in spinal cord injury (11). Wang et al. reported that 14% of patients with thoracolumbar fractures caused by high-energy injuries had DVT (15). In our study, the total incidence of DVT was six (12.0%) of 50 patients. Furthermore, two of the six patients had proximal DVT. In contrast to high-energy injuries, low-energy injuries may not be associated with endothelial disruption and thus do not increase the risk of DVT (20). However, osteoporotic vertebral fracture is common in older individuals. Advanced age is believed to be one of the risk factors of DVT (18). This incidence of DVT in inpatients with osteoporotic vertebral fracture cannot be ignored; thus, the detection of DVT in patients with osteoporotic vertebral fractures should be given more attention.

In this study, two of the six patients with DVT were treated with anticoagulants before surgery. Higo et al. evaluated the efficacy of anticoagulants for isolated distal DVT diagnosed before orthopedic surgery, including that for the spine or lower extremity (5). They reported that the size of an isolated distal DVT diagnosed before orthopedic surgery was significantly larger in the postoperative treated group than in the preoperative treated group (p=0.026). However, there were only few reports on the timing of anticoagulant therapy. Thus, whether patients with DVT diagnosed prior to surgery should receive preoperative anticoagulant must be validated in the future.

In the univariate analysis, we confirmed that D-dimer was significantly associated with DVT (p=0.02). Based on the ROC analysis, AUC was 0.86. The Youden index was used to determine the D-dimer cutoff values (10). Coincidentally, it showed that the cutoff value of D-dimer was 4.00 μg/mL. The sensitivity and specificity of D-dimer in diagnosing DVT were 72.7% and 100%, respectively. Similarly, Wang et al reported that D-dimer was one of the predictors for DVT (15). When the D-dimer cutoff value was set at 1.81 μg/mL (AUC, 0.769), the sensitivity and specificity were 66.1% and 79.8%, respectively. Song et al. reported that the sensitivity and specificity of D-dimer for the diagnosis of DVT were 71.4% and 78.6%, respectively when the cutoff value was set 2.79 μg/mL (14). The mean age (77.9 ± 8.6; range, 60–96 years) in our study was older than that in other studies. D-dimer is known to be associated with age (12); therefore, our results can be considered reliable even though our D-dimer cutoff was higher than that compared with other studies.

We found a statistically significant association between duration from onset to hospitalization and DVT ($P$ = 0.033). In a previous study of patients with leg injury, the authors reported that venous hypostasis with associated bed rest or prolonged immobilization was an important risk factor for the development of thrombosis (8). Xia et al. reported that patients with femoral neck fractures with a preoperative waiting time of longer than 7 days were at a twofold higher risk for preoperative VT (17). Wang et al. also reported that the time from injury to operation in patients with thoracolumbar fractures was a predictor of DVT (15). In our study, patients who had a duration from onset to hospitalization ranging from 10 to 60 days had the highest prevalence of DVT (Table I). This result is consistent with previous reports, and patients with subacute presentations in need of hospitalization might have increased risk of DVT because of longer periods of bed rests. None of the patients with duration from onset to hospitalization ranging from 0 to 10 days presented with DVT, and only one patient with a duration ranging from 61 to 600 days developed the condition. Rehabilitation as a DVT prophylaxis may be effective for patients with acute presentation (9), and DVT may disappear in chronic presentation (7). Nevertheless, further studies should be conducted to confirm these findings.

In our study, the mean age of the patients with and without DVT was 81.5 ± 9.3 and 77.4 ± 8.5 years, retrospectively. Although advanced age is considered a risk factor, we did

not find a statistically significant difference in terms of age and incidence of DVT (18). This may be a consequence of our small sample and the fact that osteoporotic vertebral fractures are common among older populations. We found that sex, BMI, comorbidities such as diabetes mellitus, CKD and cancer, alcohol and steroid use were not significantly associated with DVT, although CKD is known to increase the risk of DVT (16). We also found that hospitalization, single-level vertebral fracture, NRS, undergoing operation, and taking an anticoagulant and/or antiplatelet medication were not significantly associated with surgical outcome. In our study, we did not show a statistically significant difference between paralysis of the lower limbs and DVT. We know that lower limb paralysis is a risk factor for DVT because muscle pumping decreases blood flow and promotes the formation of DVT (15,19). Our results did not reach statistical significance because of the small number of patients.

Our study was limited by its retrospective single-center design and the small sample size. Future large-scale investigations are needed to validate our findings.

## CONCLUSION

Among inpatients with osteoporotic vertebral fracture, we found a DVT prevalence of 12.0 %. D-dimer values and the duration from onset to hospitalization can be predicting factors of DVT. These findings emphasize the importance of DVT screening using D-dimer in patients with osteoporotic vertebral fractures.

## ACKNOWLEDGMENTS

We would like to thank Enago Company and Sandra Moody for editing and reviewing this manuscript for English language.

## REFERENCES

1. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA: Mortality after all major types of osteoporotic fracture in men and women: An observational study. Lancet 353:878-882, 1999
2. Edidin AA, Ong KL, Lau E, Kurtz SM: Morbidity and mortality after vertebral fractures: Comparison of vertebral augmentation and nonoperative management in the medicare population. Spine (Phila Pa 1976) 40:1228-1241, 2015
3. Hasserius R, Karlsson MK, Jónsson B, Redlund-Johnell I, Johnell O: Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly-a 12- and 22-year follow-up of 257 patients. Calcif Tissue Int 76:235-242, 2005
4. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O; European Vertebral Osteoporosis Study: Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: A 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int 14:61-68, 2003
5. Higo K, Tokushige A, Tezuka A, Ojima S, Miyauchi T, Saihara K, Sunahara N, Taketomi E, Ohishi M: Isolated distal deep vein thrombus detected before orthopedic surgery: Is preoperative anticoagulation preferable? Ann Vasc Dis 12:354-361, 2019
6. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR: Vertebral fractures and mortality in older women: A prospective study. Study of osteoporotic fractures research group. Arch Intern Med 159:1215-1220, 1999
7. Kim YH, Kim JS: Incidence and natural history of deep-vein thrombosis after total knee arthroplasty. A prospective, randomised study. J Bone Joint Surg Br 84:566-570, 2002
8. Lassen MR, Borris LC, Nakov RL: Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med 347:726-730, 2002
9. Li Y, Guan XH, Wang R, Li B, Ning B, Su W, Sun T, Li HY: Active ankle movements prevent formation of lower-extremity deep venous thrombosis after orthopedic surgery. Med Sci Monit 7:3169-3176, 2016
10. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF: Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. Biom J 50:419-430, 2008
11. Samuel AM, Diaz-Collado PJ, Gala RJ, Webb ML, Lukasiewicz AM, Basques BA, Bohl DD, Kim HJ, Grauer JN: Thromboembolic events after taumatic vertebral fractures: An analysis of 190,192 patients. Spine (Phila Pa 1976) 43:1289-1295, 2018
12. Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, van Delden JJ, Moons KG, Reitsma JB: Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: Systematic review and meta-analysis. BMJ 346:f2492, 2013
13. Schulte LM, O'Brien JR, Bean MC, Pierce TP, Yu WD, Meals C: Deep vein thrombosis and pulmonary embolism after spine surgery: Incidence and patient risk factors. Am J Orthop (Belle Mead NJ) 42:267-270, 2013
14. Song K, Yao Y, Rong Z, Shen Y, Zheng M, Jiang Q: The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. Arch Orthop Trauma Surg 136:1459-1464, 2016
15. Wang H, Lv B, Zhang Z, Wang S, Ding W: Prevalence and predictors for preoperative deep vein thrombosis in patients with thoracolumbar fractures caused by high-energy injuries. World Neurosurg 141:e431-436, 2020
16. Wang Z, Xiao J, Zhang Z, Qiu X, Chen Y: Chronic kidney disease can increase the risk of preoperative deep vein thrombosis in middle-aged and elderly patients with hip fractures. Clin Interv Aging 13:1669-1674, 2018
17. Xia ZN, Xiao K, Zhu W, Feng B, Zhang BZ, Lin J, Qian WW, Jin J, Gao N, Qiu GX, Weng XS: Risk assessment and management of preoperative venous thromboembolism following femoral neck fracture. J Orthop Surg Res 13:291, 2018

18. Yang SD, Ding WY, Yang DL, Shen Y, Zhang YZ, Feng SQ, Zhao FD: Prevalence and risk factors of deep vein thrombosis in patients undergoing lumbar interbody fusion surgery: A single-center cross-sectional study. Medicine (Baltimore) 94:e2205, 2015
19. Yoshioka K, Murakami H, Demura S, Kato S, Hayashi H, Inoue K, Ota T, Shinmura K, Yokogawa N, Fang X, Tsuchiya H: Comparative study of the prevalence of venous thromboembolism after elective spinal surgery. Orthopedics 36:e223-228, 2013
20. Zhang W, Huai Y, Wang W, Xue K, Chen L, Chen C, Qian A: A retrospective cohort study on the risk factors of deep vein thrombosis (DVT) for patients with traumatic fracture at Honghui Hospital. BMJ Open 9:e024247, 2019