Effects of computer-assisted navigation versus the conventional technique for total knee arthroplasty on levels of plasma thrombotic markers: a prospective study

Ka-Kit Siu1,2, Kwan-Ting Wu1,2, Jih-Yang Ko1,2,3*, Feng-Sheng Wang2, Wen-Yi Chou1, Ching-Jen Wang1,2 and Shu-Jui Kuo4,5*

Abstract

Background: Venous thromboembolism (VTE) is a major sequela after total knee arthroplasty (TKA). We prospectively compared the differences in the perioperative plasma d-dimer and fibrinogen levels between the individuals undergoing TKA via computer-assisted navigation and via a conventional method as the surrogate comparison for VTE. There were 174 patients fulfilling the inclusion criteria and providing valid informed consent between September 2011 and November 2013. There were 69 females and 20 males in the navigation-assisted group (median age: 71.00 years), while the conventional group was composed of 59 females and 26 males (median age: 69.00 years). Blood samples were obtained prior to and at 24 and 72 h after surgery for measurement of the levels of plasma d-dimer and fibrinogen.

Results: A significantly lower plasma d-dimer level 24 h after TKA (p = 0.001) and a milder postoperative surge 24 h after TKA (p = 0.002) were observed in patients undergoing navigation-assisted TKA. The proportions of subjects exceeding the plasma d-dimer cut-off values of 7.5, 8.6 and 10 mg/L 24 h after TKA were all significantly higher in the conventional group than in the navigation-assisted group (p = 0.024, 0.004, and 0.004, respectively).

Conclusions: A lower plasma d-dimer level and a milder surge in the plasma d-dimer level were observed in patients undergoing navigation-assisted TKA in comparison with patients undergoing conventional TKA 24 h after surgery. These findings may supplement the known advantages of navigation-assisted TKA.

Keywords: Navigation-assisted total knee arthroplasty, d-dimer, Fibrinogen
after TKA has been reported to be 30–50% [7, 12–14]. More than half of VTE cases are asymptomatic [15]. Acquired risk factors for VTE include hip or knee joint replacement, major trauma, lower limb fractures and spinal cord injury [9]. The American Academy of Orthopedic Surgeons (AAOS) clinical guidelines for VTE published in 2011 suggested that patients undergoing elective hip or knee replacement surgery are already at high risk of VTE, even if they do not possess any other acquired or hereditary factors [10].

No single assessment is adequate for the diagnosis of DVT, mandating a combination of clinical evaluation, laboratory testing and imaging studies. Computed tomography (CT) angiography is the gold standard for the diagnosis of PE, and Doppler ultrasound or venography is commonly utilized for imaging validation of DVT [6, 9, 15, 16]. Clinical scoring systems for VTE prediction include Wells score and the revised Geneva score [5, 9]. Clinically, the plasma d-dimer level is used effectively to exclude VTE [17–20]; it is also used as an indicator of thromboembolic events [20].

Using navigation-assisted TKA, femur and tibia cutting can be performed accurately in an extramedullary manner, hence mitigating the destruction of the bone marrow cavity. A significant decrease in systemic emboli was observed by transesophageal echocardiography [21] and transcranial Doppler [22] soon after surgery in previous pilot studies. Our previous studies showed milder increases in serum endothelial injury markers and inflammation markers in a navigation-assisted TKA cohort as compared with a conventional TKA group [2, 23].

Based upon the findings mentioned above, we hypothesized that the limited violation of the distal femoral bone marrow cavity in navigation-assisted TKA might mitigate the postoperative surge in the levels of thromboembolic markers, which has been proposed as an indicator of thromboembolism. In this study, we prospectively compared the levels of perioperative plasma thrombotic markers between patients undergoing navigation-assisted and conventional TKA as the surrogate comparison of VTE. We also investigated the incidence of VTE or PE within 5 to 7 years after surgery.

**Results**

A total of 174 patients who fulfilled the inclusion criteria and provided valid informed consent between September 2011 and November 2013 were recruited for the study. There were 69 females and 20 males in the navigation-assisted TKA group, with a median age of 71.00 years, while the conventional group was composed of 59 females and 26 males, with a median age of 69.00 years. There were no between-group differences in gender \( (p=0.225) \), age \( (p=0.980) \), operated side \( (p=0.368) \), preoperative deformity \( (p=0.916) \) or body mass index \( (p=0.246) \). The proportions of subjects afflicted with diabetes \( (p=0.992) \), hypertension \( (p=0.879) \) and coronary artery disease \( (p=0.696) \) were comparable between the two groups. A higher proportion of participants in the navigation-assisted group was afflicted with stroke before the surgery \( (p=0.015) \) (Table 1).

At baseline, the plasma levels of d-dimer \( (p=0.172) \) and fibrinogen \( (p=0.847) \) were comparable between the two groups. The Friedman \( p \)-values were < 0.001 and < 0.001 for d-dimer and fibrinogen in the conventional group and < 0.001 and < 0.001 in the navigation-assisted group, respectively. The \( p \)-values of post hoc Wilcoxon signed-rank tests
are shown in Tables 2, 3. Generally, the post-TKA plasma d-dimer and fibrinogen levels were all higher than those at baseline.

At 24 h after surgery, the median plasma d-dimer level in the navigation-assisted group was 36.0% \((p < 0.001)\), lower than that in the conventional group. The median postoperative increment in the plasma d-dimer level was 41.2% lower in the navigation-assisted group than in the conventional group; however, the between-group difference was diminished 72 h after surgery.

We also compared the proportions of subjects in whom various plasma d-dimer level cut-off values for VTE as described in the literature were exceeded \([20, 24–26]\). The proportions of subjects exceeding the cut-off values of 7.5 \((p = 0.024)\), 8.6 \((p = 0.004)\) and 10 mg/L \((p = 0.004)\) 24 h after TKA were all significantly higher in the conventional group than in the navigation-assisted group (Table 4).

### Table 1 Demographic profiles between the navigation and conventional groups

|                | Navigation \((n = 89)\) | Conventional \((n = 85)\) | \(p\)-value |
|----------------|--------------------------|---------------------------|-------------|
| Gender         | 69 F, 20 M               | 59 F, 26 M                | 0.225       |
| Age (years)    | 71.00 (63.00, 75.00)     | 69.00 (64.00, 75.00)      | 0.980       |
| Operated side  | 49 left, 40 right        | 41 left, 44 right         | 0.368       |
| Preoperative deformity | 77 varus, 12 valgus | 74 varus, 11 valgus       | 0.916       |
| BMI (kg/m²)    | 27.48 (25.11, 29.59)     | 27.59 (25.78, 30.85)      | 0.246       |
| Diabetes       | 21                       | 20                        | 0.992       |
| Hypertension   | 64                       | 62                        | 0.879       |
| CAD            | 5                        | 6                         | 0.696       |
| Stroke         | 6                        | 0                         | 0.015       |

\(F\) Female, \(M\) Male, BMI body mass index, CAD coronary artery disease

### Table 2 Plasma d-dimer concentrations (mg/L) prior to TKA, then at 24 and 72 h after TKA

|                | Navigation         | Conventional       | \(p\)-value |
|----------------|--------------------|--------------------|-------------|
| Baseline       | 0.55 (0.35, 0.98)\(^{ab}\) | 0.56 (0.36, 0.99)\(^{de}\) | 0.172       |
| 24 h after TKA | 4.60 (3.10, 8.83)\(^{ac}\) | 7.19 (3.89, 14.38)\(^{df}\) | 0.001       |
| 72 h after TKA | 3.11 (2.32, 3.99)\(^{bc}\) | 2.70 (2.06, 4.10)\(^{ef}\) | 0.531       |
| 24 h-baseline  | 3.97 (2.42, 7.78)   | 6.76 (3.17, 13.88)   | 0.002       |
| 72 h-baseline  | 2.43 (1.47, 3.36)   | 2.16 (1.40, 3.24)    | 0.446       |

\(^{a}\) \(p < 0.001\); \(^{b}\) \(p < 0.001\); \(^{c}\) \(p < 0.001\); \(^{d}\) \(p < 0.001\); \(^{e}\) \(p < 0.001\); \(^{f}\) \(p < 0.001\) by Wilcoxon signed-rank test for post hoc analysis

### Table 3 Plasma fibrinogen concentrations (mg/dL) prior to TKA, then at 24 and 72 h after TKA

|                | Navigation           | Conventional        | \(p\)-value |
|----------------|----------------------|---------------------|-------------|
| Baseline       | 282.00 (257.00, 330.00)\(^{gh}\) | 284.00 (248.50, 335.50)\(^{ik}\) | 0.847       |
| 24 h after TKA | 292.00 (257.00, 323.00)\(^{gi}\) | 303.00 (259.00, 332.00)\(^{jl}\) | 0.325       |
| 72 h after TKA | 523.00 (482.75, 589.25)\(^{hi}\) | 496.00 (469.00, 551.00)\(^{kl}\) | 0.232       |
| 24 h-baseline  | − 6.50 (− 4.25, 23.00) | 9.00 (− 17.00, 34.00) | 0.175       |
| 72 h-baseline  | 238.00 (166.25, 298.00) | 212.00 (169.00, 280.00) | 0.360       |

\(^{g}\) \(p = 0.099\); \(^{h}\) \(p < 0.001\); \(^{i}\) \(p < 0.001\); \(^{j}\) \(p = 0.412\); \(^{k}\) \(p < 0.001\); \(^{l}\) \(p < 0.001\) by Wilcoxon signed-rank test for post hoc analysis
Table 4 Between-group differences of the proportion of subjects exceeding the various cut-off values of plasma d-dimer (mg/L) 24 h after surgery

| d-dimer cut-off value | Navigation | Conventional | p-value |
|-----------------------|------------|--------------|---------|
| 7.5                   | 42         | 29           | 0.024   |
| 8.6                   | 40         | 23           | 0.004   |
| 10                    | 32         | 16           | 0.004   |

Table 5 Summary of the suspicious VTE events within post-op 7 months follow-up

| d-dimer (mg/L) | Timing (months) | Presentation | Surveys         |
|----------------|-----------------|--------------|-----------------|
| Case 1         | 7.19            | 1            | Leg swelling, redness | Duplex: negative |
| Case 2         | 16.01           | 4            | Leg swelling, redness | Duplex: negative |
| Case 3         | 18.25           | 7            | Leg swelling, dyspnea | Chest CT: negative |

All the three cases underwent conventional TKA

All of the participants were followed up for 5–7 years after surgery. None of the participants was readmitted due to acute postoperative complications such as hematoma, periprosthetic infection or fracture during the follow-up period. VTE was suspected in three patients in the conventional TKA group. The first patient was readmitted 1 month after surgery due to clinically suspected DVT (leg swelling and redness), with a preadmission plasma d-dimer level of 7.19 mg/L. Duplex scanning of the vein was arranged, and the result of which was negative. The second patient visited the cardiovascular surgery clinic for clinically suspected DVT (leg swelling and redness) 4 months after surgery. Her plasma d-dimer level was measured at 16.01 mg/L in the cardiovascular surgery clinic, and duplex scanning of the vein was arranged, with negative results. The third patient was referred to the Emergency Department 7 months after surgery (post-op d-dimer level: 18.25 mg/L) due to leg swelling and dyspnea. Under the impression of pulmonary embolism, chest CT was arranged, but no emboli were found (Table 5). The symptoms of these patients resolved after the administration of anticoagulants. None of the participants in the navigation-assisted TKA group visited the Emergency Department or the Outpatient Clinic due to symptoms of VTE.

Discussion

If not diagnosed and treated in a timely manner, the development of VTE after TKA may lead to a catastrophic outcome. Although certain regimens have been proposed for mechanical and pharmacological VTE prophylaxis, the ideal strategy for addressing VTE is to prevent rather than to treat. In our study, we attempted to demonstrate the reduced risk of VTE following TKA surgery using the reaming-free navigation technique by comparing proxy endpoints, consisting of the plasma d-dimer and fibrinogen levels, between a navigation-assisted TKA group and a conventional TKA group. We demonstrated a significantly lower plasma d-dimer level as well as a milder increase in the plasma d-dimer level 24 h after TKA in patients undergoing navigation-assisted TKA as compared with those undergoing conventional TKA. These results have not been published previously and are worthy of note.
D-dimer is the degradation product of fibrin that is formed immediately following the degradation of thrombin-generated fibrin clots, and the plasma concentration of D-dimer reflects the global activation of coagulation and fibrinolysis [18]. Other factors related to an elevated plasma D-dimer level include sepsis, inflammatory disease, malignancy, trauma, coagulation disorders and the aging process [17, 27]. The plasma D-dimer level is one of the most useful laboratory tests to supplement the diagnosis of VTE after TKA, and a normal plasma D-dimer safely excludes VTE [16]. Various cut-off values for the plasma D-dimer level for VTE evaluation have been reported in the literature. Watanabe et al. [20] showed that with a cut-off D-dimer value of 7.5 μg/mL, the sensitivity and specificity were 75% and 63% for VTE after TKA, respectively. For patients undergoing TKA with tourniquet use, the sensitivity, specificity and positive and negative predictive values for a D-dimer cut-off value of 8.6 mg/L were 100%, 82.5%, 30% and 100%, respectively, for symptomatic PE [25]. Meanwhile, Nakao et al. [24] showed that the plasma D-dimer cut-off value of 10 mg/L had a sensitivity and specificity of 94.4% and 90%, respectively, for the development of VTE among patients undergoing TKA. We utilized the various cut-off values mentioned above, and the proportions of subjects exceeding the three cut-off values were all significantly higher in the conventional group than in the navigation-assisted TKA group.

The differential extent of systemic embolization between navigation-assisted TKA and conventional TKA has been reported previously. Ooi et al. evaluated the degree, duration and size of the embolic shower using a transesophageal echocardiography probe after navigation-assisted and conventional TKA and demonstrated significant differences in the size of the emboli and the Mayo Clinic score between groups. There were also significant between-group differences in the pulse oximetry oxygen saturation and heart rate [21]. Kalairajah et al. undertook a prospective, randomized study using a transcranial Doppler device to compare the extent of cranial embolization in navigation-assisted (n = 14) and conventional TKA patients (n = 10). Doppler signals were obtained in 14 patients in the navigation-assisted group and nine (90%) in the conventional group, in whom high-intensity signals were detected in seven patients undergoing navigation-assisted TKA (50%) and all participants receiving conventional TKA. In the navigation-assisted group, no patient had more than two detectable emboli, with a mean of 0.64 (standard deviation: 0.74). In the conventional group, the number of emboli ranged from 1 to 43, and six patients had more than two detectable emboli, with a mean of 10.7 (standard deviation: 13.5). The between-group difference was highly significant (p < 0.001). The authors thus concluded that navigation-assisted TKA, when compared with the conventional technique, significantly reduces systemic emboli as detected by transcranial Doppler ultrasonography [22]. In keeping with the sonographic findings, our study showed that the plasma D-dimer level and the surge in the plasma D-dimer level 24 h after TKA were significantly higher in the conventional group. These combined findings cannot be extrapolated to conclude that navigation-assisted TKA leads to fewer postoperative thromboembolic complications; however, the correlations of the postoperative plasma D-dimer level with sonographically detected emboli and the occurrence of VTE warrant further study with a larger population for validation.

In addition to the correlation with thromboembolic events, Shahi et al. [28] suggested that a higher plasma D-dimer level is associated with a higher risk of periprosthetic joint
infection (PJI). Although the causal relationship between a higher postoperative plasma 
D-dimer level and a higher risk of PJI is not clear, the findings suggested that the inter-
pretation of a higher postoperative plasma D-dimer level among subjects undergoing
conventional TKA should not be limited to the perspective of thromboembolic activity.

The limitations of this study included non-randomization and a relatively small num-
ber of patients. Although measurement of thromboembolic markers alone is not suffi-
cient to diagnose VTE, it does represent activation of coagulation and the thrombotic
cascade. According to previous studies, the plasma D-dimer level is correlated with the
occurrence of VTE, as well as PJI. Although the lower perioperative plasma D-dimer
level observed in the navigation-assisted TKA group could not be extrapolated to the
conclusion that the incidences of VTE and PJI were lower in the navigation-assisted
TKA group, our study may allow orthopedic surgeons to reflect upon the possibility of
differential risks of VTE and PJI between navigation-assisted and conventional TKA
techniques and offers important pilot findings that will inform subsequent larger-scale
studies to compare the incidences of VTE and PJI between navigation-assisted TKA and
conventional TKA.

Conclusions
In our study, we demonstrated a lower plasma D-dimer level as well as a milder surge
in the plasma D-dimer level in patients receiving navigation-assisted TKA as compared
with those undergoing conventional TKA 24 h after surgery. The proportions of subjects
exceeding the plasma D-dimer level cut-off values of 7.5, 8.6 and 10 mg/L 24 h after TKA
were all significantly higher in the conventional group than in the navigation-assisted
group. These findings may supplement the known benefits of navigation-assisted TKA.

Methods
The study was approved by the Institutional Review Board of Chang Gung Memorial
Hospital (IRB number: 100-0038A3) and registered on the ClinicalTrials.gov website
(registration number: NCT02206321). Patients undergoing TKA surgery performed by
the two senior authors (JYK and CJW) between September 2011 and November 2013
were recruited. The patients were self-separated according to their clinic registration
to the two senior surgeons. One surgeon (JYK) performed navigation-assisted TKA,
and the other surgeon (CJW) performed conventional TKA; the two surgeons had per-
formed more than one thousand navigation-assisted or conventional TKA surgeries,
respectively. Patients aged > 85 years, those with autoimmune diseases, active infection,
malignancy, end-stage renal disease or a previous history of VTE, were excluded from
the study. Patients who had undergone previous surgeries, such as high tibia osteotomy
or fracture repair surgeries, on the same knee were also excluded. All participants pro-
vided valid informed consent and were aware of their surgical allocation prior to the
operation, as the participants undergoing navigation-assisted TKA required four addi-
tional small incisions for tracker pinning.

Navigation-assisted TKA was performed with the aid of a CT-free navigation system
(Vector Vision, Brain Lab, Heimstetten, Germany). Both femur cutting and tibia cutting
were performed in an extramedullary manner in the navigation-assisted group, whereas
intramedullary guided femur cutting was performed in the conventional TKA group.
Blood samples were obtained prior to and at 24 and 72 h after TKA surgery and were sent to the central laboratory in tubes loaded with sodium citrate for further analysis. The plasma D-dimer level was measured using a microlatex immunoturbidity technique (Dade Behring, Marburg, Germany), which employed a monoclonal antibody to detect only cross-linked D-dimer fragments, while fibrinogen was measured using a scattered light detection method.

Each patient began quadriceps exercise and continuous passive range of motion exercise 24 h after surgery, and most patients started off-bed ambulation on the same day. Oral aspirin at 500 mg per day was given for DVT prophylaxis. However, in patients with morbid obesity, lower leg swelling (Homan sign positive), or a plasma D-dimer level greater than 5 mg/L, oral rivaroxaban or subcutaneous enoxaparin was prescribed [19]. Venography or ultrasonography was arranged if DVT was clinically suspected, whereas chest CT angiography or lung perfusion scans were scheduled if PE was suspected. For patients without clinically suspected DVT, early off-bed ambulation and vigorous physiotherapy programs were encouraged as a mechanical VTE prophylaxis.

A packed red blood cell transfusion was given if the postoperative level of Hb < 7.0 g/dL or Hb < 8.0 g/dL with symptoms such as dizziness or generalized weakness. An oral iron supplement was prescribed for patients with asymptomatic anemia. Clinical assessments for DVT were performed daily until discharge and at regular outpatient follow-ups. Patients with postoperative comorbidities were advised to visit the Emergency Department.

The minimum sample size required for the navigation-assisted and control groups was determined using G*Power 3.1.9.2 software (http://www.gpower.hhu.de/en.html). The priori power calculation used a two-tailed Wilcoxon signed-rank test to calculate a sample size of at least 27 for each group (calculated effect size: 0.8; α level: 0.05; power: 80%; allocation ratio: 1) [22].

The data are presented as median values with lower and upper quartiles. Categorical variables were compared using the chi-square test, and the Mann–Whitney U test was employed to compare differences between groups. The Friedman test was used for repeated measures analysis of repeated within-group comparisons for continuous variables, and the Wilcoxon signed-rank test was used for post hoc analysis. All statistical analyses were performed using SPSS software, and a p-value of < 0.05 was considered to indicate statistical significance [2, 29, 30].

Abbreviations
AAOS: American Academy of Orthopedic Surgeons; BMI: body mass index; CAD: coronary artery disease; PE: pulmonary embolism; VTE: venous thromboembolism; TKA: total knee arthroplasty.

Acknowledgements
The study was sponsored by CMRP8G0051-CMRPG8E0152. We are thankful for the help by the Center for Shockwave Medicine and Tissue Engineering, Department of Medical Research, Kaohsiung Chang Gung Memorial Hospital, Taiwan.

Authors’ contributions
JYK and CJW conceptualize the study. KKS and KTW have made substantial contributions to the acquisition and analysis of the study. FSW and WYC interpreted the data. KKS drafted the work, and SJI substantively revised the manuscript. All authors read and approved the final manuscript.

Funding
The funding sources are from Chang Gung Medical Foundation (CMRP8G0051, CRRPG8F0461, CRRPG8F0462, CRRPG8F0463 and CLRPG8E0131).
Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB number: 100-0038A3) and registered in ClinicalTrials.gov website (registration number: NCT02206321).

Consent for publication
Not applicable in our study.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Orthopedic Surgery, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan. 2 Center for Shock-wave Medicine and Tissue Engineering, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan. 3 Department of Orthopedic Surgery, Xiamen Chang Gung Hospital, Xiamen, China. 4 School of Medicine, China Medical University, Taichung, Taiwan. 5 Department of Orthopedic Surgery, China Medical University Hospital, Taichung, Taiwan.

Received: 25 April 2019   Accepted: 24 September 2019

Published online: 14 October 2019

References
1. Kuo SJ, Liu SC, Huang YL, Tsai CH, Fong YC, Hsu HC, et al. TGF-β1 enhances FOXO3 expression in human synovial fibroblasts by inhibiting miR-92a through AMPK and p38 pathways. Aging. 2019;11(12):4075–89.
2. Kuo SJ, Wang FS, Wang CJ, Ko JY, Chen SH, Siu KK. Effects of computer navigation versus conventional total knee arthroplasty on endothelial damage marker levels: a prospective comparative study. PLoS ONE. 2015;10(5):e0126663.
3. Abraham P, Ternisien C, Hubert I, Pelhorz L, Saumet JL. Does venous microemboli detection add to the interpretation of D-dimer values following orthopedic surgery? Ultrasound Med Biol. 1999;25(4):637–40.
4. Bin Abd Razak HR, Soon AT, Dhanaraj ID, Tan AH. Does venous microemboli detection add to the interpretation of D-dimer values following orthopedic surgery? Ultrasound Med Biol. 1999;25(4):637–40.
5. Kessenich CR, Robelli SJ. D-dimer and deep vein thrombosis. Nurse Pract. 2011;36(6):10–1.
6. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood. 2009;113(13):2878–87.
7. Pabinger I, Ay C. Biomarkers and venous thromboembolism. Arterioscler Thromb Vasc Biol. 2009;29(3):332–6.
8. Thachil J, Fitzmaurice DA, Toth CH. Appropriate use of d-dimer in hospital patients. Am J Med. 2010;123(1):17–9.
9. Watanabe H, Madoiwa S, Sekiya H, Hoshino Y, Sugimoto H, Hayasaka S. The incidence of venous thromboembolism before and after total knee arthroplasty using 16-row multidetector computed tomography. J Arthroplasty. 2011;26(8):1488–93.
10. Wang CJ, Wang JW, Weng LH, Huang CC, Yu PC. Clinical significance of muscular deep-vein thrombosis after total knee arthroplasty. Chang Gung Med J. 2007;30(1):41–6.
11. Mont MA, Boggio LN, Bozic KJ, Watters WC Jr, Donnelly P, Patel N, AAOS. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Am Acad Orthop Surg. 2011;19(12):768–76.
12. Kanchanabat B, Stapanavat W, Meknavin S, Soorapanth C, Sumanasrethakul C, Kanchanasuttirak P. Systematic review and meta-analysis on the rate of postoperative venous thromboembolism in orthopaedic surgery in Asian patients without thromboprophylaxis. Br J Surg. 2011;98(10):1356–64.
13. Abraham P, Ternisien C, Hubert I, Pelhorz L, Saumet JL. Does venous microemboli detection add to the interpretation of D-dimer values following orthopedic surgery? Ultrasound Med Biol. 1999;25(4):637–40.
14. Watanabe H, Madoiwa S, Sekiya H, Hoshino Y, Sugimoto H, Hayasaka S. The incidence of venous thromboembolism before and after total knee arthroplasty using 16-row multidetector computed tomography. J Arthroplasty. 2011;26(8):1488–93.
15. Watanabe H, Madoiwa S, Sekiya H, Hoshino Y, Sugimoto H, Hayasaka S. The incidence of venous thromboembolism before and after total knee arthroplasty using 16-row multidetector computed tomography. J Arthroplasty. 2011;26(8):1488–93.
16. Watanabe H, Madoiwa S, Sekiya H, Hoshino Y, Sugimoto H, Hayasaka S. The incidence of venous thromboembolism before and after total knee arthroplasty using 16-row multidetector computed tomography. J Arthroplasty. 2011;26(8):1488–93.
17. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood. 2009;113(13):2878–87.
18. Pabinger I, Ay C. Biomarkers and venous thromboembolism. Arterioscler Thromb Vasc Biol. 2009;29(3):332–6.
19. Thachil J, Fitzmaurice DA, Toth CH. Appropriate use of D-dimer in hospital patients. Am J Med. 2010;123(1):17–9.
20. Watanabe H, Madoiwa S, Sekiya H, Hoshino Y, Sugimoto H, Hayasaka S, Kanyi Y, et al. Predictive blood coagulation markers for early diagnosis of venous thromboembolism after total knee joint replacement. Thromb Res. 2011;128(6):e137–43.
21. Ooi LH, Lo N, Yeo SJ, Ong BC, Ding ZP, Leif A. Does computer-assisted surgical navigation total knee arthroplasty reduce venous thromboembolism compared with conventional total knee arthroplasty? Singapore Med J. 2008;49(8):610–4.
24. Nakao STS, Uemura H, Nakano S, Egawa H, Kawasaki Y, Kashihara M, Yasui N. Early ambulation after total knee arthroplasty prevents patients with osteoarthritis and rheumatoid arthritis from developing postoperative higher levels of \( \alpha \)-dimer. J Med Invest. 2010;57(1–2):146–51.

25. Nishiguchi M, Takamura N, Abe Y, Kono M, Shinoda H, Aoyagi K. Pilot study on the use of tourniquet: a risk factor for pulmonary thromboembolism after total knee arthroplasty? Thromb Res. 2005;115(4):271–6.

26. Wada HKT, Abe Y, Hatada T, Yamada N, Sudo A, Uchida A, Nobori T. Elevated levels of soluble fibrin or \( \alpha \)-dimer indicate high risk of thrombosis. J Thromb Haemost. 2006;4(6):1253–8.

27. Ho CH. Can very high level of \( \alpha \)-dimer exclusively predict the presence of thromboembolic diseases? J Chin Med Assoc. 2011;74(4):151–4.

28. Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum \( \alpha \)-dimer test is promising for the diagnosis of periprosthetic joint infection and timing of reimplantation. J Bone Joint Surg Am. 2017;99(17):1419–27.

29. Hsu CC, Hsu HC, Lin CC, Wang YC, Chen HJ, Chiu YC, et al. Increased risk for hip fractures among patients with cholangitis: a nationwide population-based study. Biomed Res Int. 2018;2018:8928174.

30. Kuo SJ, Huang CC, Tsai CH, Hsu HC, Su CM, Tang CH. Chemokine C-C motif ligand 4 gene polymorphisms associated with susceptibility to rheumatoid arthritis. Biomed Res Int. 2018;2018:9181647.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.