Incidence and Related Factors for Low-Extremity Deep Vein Thrombosis in Breast Cancer Patients Who Underwent Surgical Resection: What Do We Know and What Should We Care

Liqiang Chen¹, Qiang Feng², Wenjuan Wang³ and Lanbo Liu*¹

¹ Department of Cardiovascular, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China, ² Department of Cardiovascular, Handan Central Hospital, Handan, China, ³ Department of Emergency, 982 Hospital of the Joint Logistics Support Force of The Chinese People’s Liberation Army, Tangshan, China

Malignancy, surgical resection, and neoadjuvant and/or adjuvant chemotherapy increase the low-extremity deep vein thrombosis (LDVT) risk in patients with breast cancer, bringing in great physical burdens, disabilities, and worse survivals. However, LDVT in surgical breast cancer patients is scarcely reported. Therefore, this study aimed to evaluate the incidence and related factors for LDVT in these patients. Patients with breast cancer who underwent surgical resection were included. LDVT was examined on the day of discharge and 1 month after the discharge. A total of 491 eligible patients were included, among which 11 (2.2%) patients occurred LDVT. Besides, higher age, history of diabetes mellitus, advanced T and tumor node metastasis (TNM) stages, higher platelet count, and shorter activated partial thromboplastin time (APTT) were correlated with increased LDVT incidence (all \(p < 0.05\)). Additionally, higher age \(p = 0.004\), odds ratio (OR) (95% CI): 1.082 (1.023–1.144), history of diabetes mellitus \(p = 0.003\), OR (95% CI): 10.426 (2.219–48.986), and a higher platelet count \(p = 0.008\), OR (95% CI): 1.017 (1.004–1.029) were independent factors for increased LDVT incidence, while higher APTT \(p = 0.004\), OR (95% CI): 0.636 (0.467–0.866) was an independent factor for decreased LDVT incidence. Lastly, the risk prediction model involving age, history of diabetes mellitus, platelet count, and APTT showed a good ability to predict LDVT occurrence (area under curve: 0.919, 95% CI: 0.869–0.968). In conclusion, the LDVT incidence is 2.2%, and its independent factors consist of age, history of diabetes mellitus, platelet count, and APTT in patients with breast cancer who underwent surgical resection, which provides evidence for the prevention and surveillance of LDVT in surgical breast cancer.

Keywords: risk factor, incidence, predict model, low-extremity deep vein thrombosis, breast cancer
INTRODUCTION

Breast cancer is the most common carcinoma and a leading cause of cancer mortality in women, with ~2,000,000 new cases and 626,000 fatalities globally every year (1, 2). So far, great progress has been made on the treatments for breast cancer, such as surgical resection, neoadjuvant therapy, adjuvant therapy, endocrinotherapy, and targeted therapy (3–7). Among these treatments, resection is a predominant strategy. Unfortunately, patients with breast cancer after resection may experience severe postoperative complications (8–11). One of the most threatening complications is deep vein thrombosis (DVT), a severe disease in the venous system, which is a vital cause of high mortality of breast cancer (10, 12, 13).

Among DVT, low-extremity DVT (LDVT) occurs more frequently because the venous blood viscosity of low-extremity is obviously higher than that of upper-extremity (14). According to previous studies, the risk factors of LDVT include major surgery, malignant tumor, older age, diabetes mellitus, etc. (15–19). Meanwhile, it is worth noting that patients with LDVT often suffer from physical burdens, such as Neuh of positive and Homans signs, superficial varicosities, stasis pigmentation, edema and pain of lower limbs, and low-extremity paralysis, resulting in treatment difficulty, reduced quality of life, worse survivals, or sudden death (9, 20–25).

The common LDVT incidence is low in patients with breast cancer (26), but this incidence risk is higher for those who received surgical resection, neoadjuvant, and/or adjuvant chemotherapy (27, 28). Therefore, great attention should still be attached to LDVT in surgical breast cancer patients. However, few such studies have been reported on this.

Therefore, this study aimed to evaluate the incidence of LDVT and its related factors in surgical breast cancer patients.

MATERIALS AND METHODS

Patients

After approval by the Institutional Review Board of The Fourth Hospital of Hebei Medical University, a total of 491 patients with breast cancer who underwent surgical resection in our hospital from January 2016 to September 2020 were included consecutively in this study. The inclusion criteria were as follows: (i) diagnosed as primary breast cancer by the histopathological examination; (ii) scheduled for surgical resection; (iii) aged older than 18 years; and (iv) able to understand the study contents and willing to participate in the study. The exclusion criteria were as follows: (i) presented with thrombosis before surgery or had a history of thromboembolism; (ii) known cardiovascular diseases, cerebrovascular diseases, or hematological diseases; (iii) complicated with other cancers; (iv) received treatment with anticoagulant within 3 months before surgery; and (v) pregnant or lactating women. Written informed consents were obtained from all patients.

Collection of Clinical Features

Clinical features of patients were documented before discharge from the hospital, which included demographic characteristics, medical history, tumor characteristics, blood routine & blood lipid indexes, and blood coagulation indexes.

Diagnosis of LDVT

In order to avoid LDVT incidence, patients received routine perioperative low molecular weight heparin according to the guideline in China and clinicians’ experience. All patients received LDVT examination on the day of discharge from the hospital and 1 month after the discharge. The diagnostic procedures of LDVT were performed as recommended in the clinical guideline (29). In brief, for patients with signs or symptoms of LDVT, a 2-level DVT Wells score was used to estimate the clinical probability of LDVT, then D-dimer test, and compression ultrasonography (gray scale, B-mode, and color Doppler) were carried out depending on the Wells score. If patients are with high clinical suspicion of LDVT but in a negative ultrasound scan, the angiography was implied to further confirm the diagnosis.

Statistical Analysis

Data were described as count with percentage, mean with SD, or median with interquartile range (IQR). A comparison was determined by the chi-square test or the Wilcoxon rank-sum test. Univariate and multivariate logistic regression analyses were carried out to evaluate the factors affecting the LDVT occurrence and to construct the LDVT prediction model. The performance of the LDVT prediction model was estimated by the receiver operating characteristic (ROC) curve analysis. SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, CA, USA) were applied for data analysis and graph making. A p < 0.05 indicated statistical significance.

RESULTS

Clinical Features

In the analyzed patients with breast cancer, their mean age was 52.7 ± 12.3 years, and the number of these patients with diabetes mellitus history was 47 (9.6%). Regarding the pathological grade, the number of patients with grade 1, grade 2, and grade 3 was 99 (20.2), 286 (58.2), and 106 (21.6%), respectively. With respect to the tumor size, tumor node metastasis (TNM) stage, there were 69 (14.1), 310 (63.1), and 112 (22.8%) patients with TNM stages I, II, and III, respectively. In terms of blood routine, blood lipid and blood coagulation indexes, the median (IQR) value of platelet count was 237.9 (191.6–272.9) × 10^9/L, and the median (IQR) value of activated partial thromboplastin time (APTT) was 28.5 (27.0–30.2) s in patients. More detailed demographic characteristics, medical history, tumor characteristics, blood routine indexes, blood lipid indexes, and blood coagulation indexes in patients are presented in (Table 1).

LDVT Incidence

Low-extremity deep vein thrombosis was examined on the day of discharge from the hospital and 1 month after the discharge. Among 491 patients with breast cancer who underwent surgical resection, there were only 11 (2.2%) patients who occurred LDVT.
TABLE 1 | Clinical features.

| Items                                      | Breast cancer patients (N = 491) |
|--------------------------------------------|----------------------------------|
| Demographic characteristics                |                                  |
| Age (years), mean ± SD                     | 52.7 ± 12.3                      |
| BMI (kg/m²), mean ± SD                     | 22.8 ± 2.3                       |
| History of smoking, No. (%)                | 61 (12.4)                        |
| History of drinking, No. (%)               | 97 (19.8)                        |
| Medical history                            |                                  |
| History of hypertension, No. (%)           | 155 (31.6)                       |
| History of hypercholesteremia, No. (%)     | 69 (14.1)                        |
| History of diabetes mellitus, No. (%)      | 47 (9.6)                         |
| Tumor characteristics                      |                                  |
| Pathological grade, No. (%)                |                                  |
| Grade 1                                    | 99 (20.2)                        |
| Grade 2                                    | 286 (58.2)                       |
| Grade 3                                    | 106 (21.6)                       |
| Molecular subtype, No. (%)                 |                                  |
| Luminal-A                                  | 187 (38.1)                       |
| Luminal-B                                  | 130 (26.5)                       |
| HER2+                                      | 83 (16.9)                        |
| Basal-like                                 | 91 (18.5)                        |
| T stage, No. (%)                           |                                  |
| T1                                         | 105 (21.4)                       |
| T2                                         | 323 (65.8)                       |
| T3                                         | 63 (12.8)                        |
| N stage, No. (%)                           |                                  |
| N0                                         | 276 (56.2)                       |
| N1                                         | 116 (23.6)                       |
| N2                                         | 89 (18.1)                        |
| N3                                         | 10 (2.0)                         |
| TNM stage, No. (%)                         |                                  |
| I                                          | 69 (14.1)                        |
| II                                         | 310 (63.1)                       |
| III                                        | 112 (22.8)                       |
| Blood routine and blood lipid indexes      |                                  |
| WBC (x10⁹/L), median (IQR)                 | 6.6 (5.4–7.6)                    |
| Hemoglobin (g/dL), median (IQR)            | 128.5 (118.4–137.3)              |
| Platelet count (x10⁹/L), median (IQR)      | 237.9 (191.6–272.9)              |
| TG (mmol/L), median (IQR)                  | 1.2 (1.0–1.7)                    |
| TC (mmol/L), median (IQR)                  | 4.6 (3.9–5.2)                    |
| LDL-C (mmol/L), median (IQR)               | 2.8 (2.4–3.3)                    |
| HDL-C (mmol/L), median (IQR)               | 1.5 (1.1–1.8)                    |
| Blood coagulation indexes                  |                                  |
| PT (sec), median (IQR)                     | 11.2 (9.9–12.7)                  |
| APTT (sec), median (IQR)                   | 28.5 (27.0–30.2)                 |
| TT (sec), median (IQR)                     | 16.4 (15.4–17.5)                 |
| FIB (g/L), median (IQR)                    | 2.9 (2.5–3.4)                    |
| Khorana score (or CONKO score)             |                                  |
| 0                                          | 432 (88.0)                       |
| 1                                          | 56 (11.4)                        |
| 2                                          | 3 (0.6)                          |

(Continued)

and 480 (97.8%) patients who did not occur LDVT (Figure 1). Meanwhile, the incidence of venous thromboembolism (VTE) in cancer patients from previous studies (10, 26, 30–34) is listed in Supplementary Table S1.

**Correlations Between Clinical Characteristics and LDVT**

In terms of demographic characteristics and medical history, higher age (p = 0.002) and history of diabetes mellitus (p = 0.011) were correlated with increased LDVT incidence (Table 2). With respect to tumor characteristics, higher T stage (p = 0.038) and advanced TNM stage (p = 0.040) were correlated with increased LDVT incidence (Table 3). Concerning the blood routine/blood lipid indexes, higher platelet count (p = 0.038) was correlated with higher LDVT incidence (Table 4). Regarding the blood coagulation indexes, higher APTT (p = 0.001) was correlated with lower LDVT incidence (Table 5).

**Factors Related to the LDVT Incidence**

From the univariate logistic regression model analysis, higher age (p = 0.004, OR (95% CI): 1.085 (1.027–1.147)), T stage [p = 0.039, OR (95% CI): 3.021 (1.056–8.638)], TNM stage [p...
**TABLE 2** | Correlation between demographic characteristics/medical history and LDVT.

| Items                          | LDVT, No. (%) | P-value |
|-------------------------------|---------------|---------|
| Age (years), mean ± SD        | No            | Yes     | 0.002   |
| 52.4 ± 12.2                  | 64.1 ± 9.0    |         |
| BMI (kg/m²), mean ± SD       | No            | Yes     | 0.245   |
| 22.8 ± 2.3                   | 23.6 ± 2.2    |         |
| History of smoking           | No            | Yes     | 0.423   |
| No                           | 419 (87.3)    | 11 (100.0) |
| Yes                          | 61 (12.7)     | 0 (0.0)  |
| History of drinking          | No            | Yes     | 0.606   |
| No                           | 384 (80.0)    | 10 (90.9) |
| Yes                          | 96 (20.0)     | 1 (9.1)  |
| History of hypertension      | No            | Yes     | 0.500   |
| No                           | 330 (88.8)    | 6 (54.5) |
| Yes                          | 150 (31.2)    | 5 (45.5) |
| History of hypercholesteremia| No            | Yes     | 0.402   |
| No                           | 414 (86.3)    | 8 (72.7) |
| Yes                          | 66 (13.7)     | 3 (27.3) |
| History of diabetes mellitus | No            | Yes     | 0.011   |
| No                           | 437 (91.0)    | 7 (63.6) |
| Yes                          | 43 (9.0)      | 4 (36.4) |

LDVT, low-extremity deep vein thrombosis; SD, standard deviation; BMI, body mass indexes.

**TABLE 3** | Correlation between tumor characteristics and LDVT.

| Items                          | LDVT, No. (%) | P-value |
|-------------------------------|---------------|---------|
| Paternal grade                | No            | Yes     | 0.382   |
| Grade 1                       | 97 (20.2)     | 2 (18.2) |
| Grade 2                       | 281 (58.5)    | 5 (45.4) |
| Grade 3                       | 102 (21.3)    | 4 (36.4) |
| Molecular subtype             | No            | Yes     | 0.830   |
| Luminal-A                     | 183 (38.1)    | 4 (36.4) |
| Luminal-B                     | 127 (26.5)    | 3 (27.3) |
| HER2+                         | 82 (17.1)     | 1 (9.1)  |
| Basal-like                    | 88 (18.3)     | 3 (27.3) |
| T stage                       | No            | Yes     | 0.038   |
| T1                            | 105 (21.9)    | 0 (0.0)  |
| T2                            | 315 (65.6)    | 8 (72.7) |
| T3                            | 60 (12.5)     | 3 (27.3) |
| N stage                       | No            | Yes     | 0.151   |
| N0                            | 272 (56.7)    | 4 (36.4) |
| N1                            | 113 (23.5)    | 3 (27.3) |
| N2                            | 85 (17.7)     | 4 (36.4) |
| N3                            | 10 (2.1)      | 0 (0.0)  |
| TNM stage                     | No            | Yes     | 0.040   |
| I                             | 69 (14.4)     | 0 (0.0)  |
| II                            | 304 (63.3)    | 6 (54.5) |
| III                           | 107 (22.3)    | 5 (45.5) |

LDVT, low-extremity deep vein thrombosis; HER2+, Human Epidermal Growth Factor Receptor 2-positive; TNM, tumor, node, and metastasis.

**DISCUSSION**

The primary findings were listed as follows: in 491 patients with breast cancer who underwent surgical resection, (i) the incidence of LDVT was 2.2%, (ii) higher age, history of diabetes mellitus, and higher platelet count were independent factors for higher LDVT incidence, while higher APTT was an independent factor for lower LDVT incidence, (iii) the risk prediction model involving age, history of diabetes mellitus, platelet count, and APTT showed a good ability to predict LDVT occurrence.

According to previous studies, DVT rarely occurs in patients with various cancers, such as breast, prostate, and colorectal cancers (10, 18, 26, 30, 36). A study shows that in 9,735 patients with cancer (such as colorectal, lung, stomach, pancreatic, breast, and gynecologic cancers), the DVT incidence is 5.2% in Japan (37). In terms of patients with breast cancer who underwent surgery, another study exhibits that the 2-month cumulative DVT incidence is ~0.15% in the USA (26). However, limited studies estimated the LDVT incidence in patients with breast cancer. In this study, the 1-month incidence of LDVT was 2.2% (11 cases) in 491 patients with breast cancer who underwent surgical resection, which was within the range of previous studies. It could be explained by that the conditions of medical care varied in different countries, resulting in the different LDVT incidences in breast cancer.
With respect to the demographic and tumor features, they are related to DVT in patients with cancer (18, 30, 38–41). For instance, older age, obesity, and hyperlipidemia are independent risk factors for DVT in surgical colorectal cancer patients (18, 30). Moreover, the preoperative Frankel score, blood transfusion, Charlson comorbidity index, and operative time are four independent risk factors for DVT in patients with postoperative breast and cervical cancer (41). Partly in line with these reports, the current study discovered that in patients with breast cancer who underwent surgical resection, higher age, history of diabetes mellitus, T stage, and TNM stage were correlated with a higher risk of LDVT occurrence, among which higher age and history of diabetes mellitus were independent risk factors for LDVT incidence. The explanations might be as follows: (1) with the increase of age, venous thrombosis became more aggressive due to a more severe vasculopathy (17, 18), bringing in a high risk of LDVT in these patients. (2) Diabetes mellitus caused vasculopathy, neuropathy, and insufficient blood supply for extremities (42–44), enhancing the risk of LDVT in these patients. Moreover, other factors might influence the risk of LDVT, such as the application of operative mechanical pumping, which could be investigated in further studies.

Regarding the blood routine, lipid, and coagulation indexes, the present study discovered that in patients with breast cancer who underwent surgical resection, higher platelet count was an independent factor for higher LDVT incidence, while higher APTT was an independent factor for lower LDVT incidence within 1 month after discharge from the hospital. This could be attributed to the (1) higher platelet count that exerted a strong coagulation effect to form the thrombus more easily (45, 46), thus patients were at a high risk of LDVT. (2) The higher APTT indicated poor thromboplastic activity and weak coagulation effect (47, 48), which lowered the risk of thrombosis and LDVT in patients. Previous studies have also suggested platelet count as a predictor of VTE in patients with cancer (49, 50); while APTT is not commonly reported (51).

To further prevent and early predict LDVT and minimize the consequence of LDVT in surgical breast cancer patients, the current study used univariate and multivariate logistic regression analyses to construct the LDVT prediction model, which discovered that the risk prediction model involves age, history of diabetes mellitus, platelet count, and APTT showed a good ability to predict LDVT occurrence. This provided evidence for the prevention and surveillance of LDVT in surgical breast cancer. Besides, previous studies also mention several risk factors for VTE, such as individual patient risk factors (such as age, sex, race, and comorbidities), cancer-associated risk factors (such as the site of cancer and the stage of cancer), and cancer-treatment-associated risk factors (such as surgery, hospitalization, and chemotherapy) (52). Some of these factors have already been included in the present study, such as age, comorbidities, and the stage of cancer. Meanwhile, considering that all the patients enrolled in this study were female breast cancer patients who underwent surgery, some of the abovementioned risk factors were not applicable in this study. Immobility is also considered as a risk factor for VTE in cancer patients (33). In the current study, we enrolled early-stage operable breast cancer patients, and the performance status was relatively satisfactory. Thus, immobility was quite rare in the current study. Several scores have been established to predict the VTE risk in patients with cancer, such as the Khorana score and the CONKO score (35). However, these scores are mainly applied in cancer patients who receive chemotherapy, while rare predictive models were established for LDVT risk in patients with breast cancer receiving surgery. Moreover, it is also suggested that chemotherapy is a considerable risk factor for VTE in patients with cancer (33, 35, 52); in the current study, all patients received surgical resection, and the administration of adjuvant therapy was given after their recoveries from the surgery, which would be 3–6 weeks after surgery, while the evaluation time of LDVT was within 1 month after surgery. Therefore, adjuvant therapy is not likely to affect the incidence of LDVT in the current study.

In spite of these findings, there were still a few limitations in this study: (1) The LDVT incidence was relatively low, so it is inadequate to evaluate the incidence and the related factors of LDVT in 491 patients with breast cancer who underwent

### TABLE 4 | Correlation between blood routine/blood lipid indexes and LDVT.

| Items                                | LDVT, No. (%) | P-value |
|--------------------------------------|---------------|---------|
|                                      | No            | Yes     |         |
| WBC (x10³/L), median (IQR)           | 6.6 (5.3–7.6) | 7.5 (6.5–7.9) | 0.108   |
| Hemoglobin (g/dL), median (IQR)      | 128.6 (118.4–137.3) | 127.1 (109.2–133.1) | 0.553   |
| Platelet count (x10³/L), median (IQR)| 237.0 (191.2–272.0) | 253.4 (244.0–319.3) | 0.038   |
| TG (mmol/L), median (IQR)            | 1.2 (1.0–1.7) | 1.2 (1.0–1.6) | 0.838   |
| TC (mmol/L), median (IQR)            | 4.6 (3.9–5.2) | 4.7 (4.2–5.6) | 0.241   |
| LDL-C (mmol/L), median (IQR)         | 2.8 (2.4–3.2) | 3.2 (2.5–3.8) | 0.133   |
| HDL-C (mmol/L), median (IQR)         | 1.5 (1.1–1.8) | 1.3 (1.2–1.5) | 0.433   |

**LDVT**, low-extremity deep vein thrombosis; **WBC**, white blood cell; **IQR**, interquartile range; **TG**, triglyceride; **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol.

### TABLE 5 | Correlation between blood coagulation indexes and LDVT.

| Items                | LDVT, No. (%) | P-value |
|----------------------|---------------|---------|
| PT (sec), median (IQR)| 11.2 (9.9–12.7) | 10.3 (9.2–11.8) | 0.142 |
| APTT (sec), median (IQR)| 28.6 (27.1–30.2) | 26.5 (24.9–27.8) | 0.001 |
| TT (sec), median (IQR)  | 16.4 (15.4–17.6) | 15.9 (15.3–16.2) | 0.103 |
| FIB (g/L), median (IQR) | 2.9 (2.5–3.4) | 3.3 (3.0–3.5) | 0.080 |

**LDVT**, low-extremity deep vein thrombosis; **PT**, prothrombin time; **Sec**, second; **IQR**, interquartile range; **APTT**, activated partial thromboplastin time; **TT**, thrombin time; **FIB**, fibrinogen.
surgical resection. (2) The current study evaluated risk factors for LDVT in breast cancer patients after resection within only a month after discharge from the hospital. Further study with a long-term follow-up was supposed to be conducted. (3) This study only evaluated the LDVT incidence and its related factors, while pulmonary embolism (PE) was also an important part.
of DVT. Further study should focus on the PE incidence and its related factors in surgical breast cancer patients. (4) Further studies conducted in multiple centers were needed to verify our findings.

CONCLUSION

This study reveals that the LDVT incidence is 2.2%, and its independent factors consist of age, history of diabetes mellitus, platelet count, and APTT in breast cancer patients who underwent surgical resection. Although previous studies have constructed several scores to predict the risk of VTE in cancer patients, none of them are designed for patients with breast cancer who underwent surgery. The current study constructs a specific predictive model for LDVT risk in patients with breast cancer who underwent surgical resection, which provides evidence for the prevention and surveillance of LDVT in surgical breast cancer. Moreover, diabetes mellitus and APTT are recognized as risk factors for LDVT, which are seldom reported.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

REFERENCES

1. Zeng L, Li W, Chen CS. Breast cancer animal models and applications. Zool Res. (2020) 41:477–94. doi: 10.24272/zir.2020.095
2. Li K, Zhang TT, Zhao CX, Wang F, Cui B, Yang ZN, et al. Faciogenital dysplasia 5 supports cancer stem cell traits in basal-like breast cancer by enhancing EGFR stability. Sci Transl Med. (2021) 13:eabb2914. doi: 10.1126/scitranslmed.abb2914
3. Wang H, Chen S, Li J, Shao ZM. [Neoadjuvant chemotherapy in breast cancer of consensuses and controversial perspectives]. Zhonghua Zhong Liu Za Zhi. (2021) 43:504–9. doi: 10.3760/cma.j.cn112152-20190214-00086
4. Li J, Yang Y, Wan Q, Li H, Long QM, Zhang PR. Clinical observation of the regeneration process of defects after breast cancer resection. BMC Womens Health. (2021) 21:99. doi: 10.1186/s12905-021-01219-2
5. Antunes MV, Raymundo S, de Oliveira V, Staudt DE, Gossling G, Petefi GP, et al. Ultra-high performance liquid chromatography tandem spectrometric method for the determination of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen in dried blood spots—development, validation and clinical application during breast cancer adjuvant therapy. *Talanta*. (2015) 132:775–84. doi:10.1016/j.talanta.2014.10.040

6. Wang X, Fang Y, Sun W, Xu Z, Zhang Y, Wei X, et al. Endocrinotherapy resistance of prostate and breast cancer: Importance of the NFκB pathway (review). *Int J Onkol.* (2020) 56:1064–74. doi:10.3892/ijio.2020.4990

7. Metawe OA, Abdelmoneem MA, Haiba NS, Khalil HH, Teleb M, Elzoghy AO, et al. A novel smart PNIPAM-based copolymer for breast cancer targeted therapy: Synthesis, and characterization of dual pH/temperature-responsive lactoferrin-targeted PNIPAM-co-AA. *Colloids Surf B Biointerfaces*. (2021) 202:111694. doi:10.1016/j.colsurfb.2021.111694

8. Bonvivini D, De Cassai A, Andreotta G, Savigno M, Carbonari I, Carea A, et al. Breast Regional Anesthesia Practice in the Italian Public Health System (BRA-SURVEY): a survey-based national study. *Anesth Analg*. (2021) 133:772–80. doi:10.1213/ANE.0000000000005649

9. Koop Y, van Zadelhof N, Maas A, Atsma F, El Messaoudi S, Vermeulen C, et al. Effects of age on the risk of dying from pulmonary embolism or medical malpractice. *J Thromb Haemost.* (2012) 10:56–63. doi:10.1111/j.1538-7836.2011.04555.x

10. Deng W, Huo L, Yuan Q, Huang D, Li Q, Tian W. Risk factors for venous thrombosis in cancer: A protocol for systematic review and meta-analysis. *Medicine*. (2021) 100:e26454. doi:10.1097/MD.00000000000026454

11. Hirmerova J, Seidlerova J, Subrt I, Hajsmanova Z. Prevalence of cancer in patients receiving outpatient cancer therapy in Iran. *Tunaflos*. (2019) 18:244–53.

12. Henriet JP. [Pain in venous thrombosis of the leg]. *Phlébologie*. (1992) 45:67–6; discussion-7.

13. Yamaki T, Nozaki M, Sasaki K. Acute massive pulmonary embolism following hight ligation combined with compression sclerotherapy for varicose veins report of a case. *Dermatol Surg*. (1999) 25:321–5. doi:10.1097/00001106-199906020-00024.x

14. Lu L, Liu Y, Li J. Thrombogenic cause of low extremity veins in patients with deep venous thrombosis: a retrospective study. *Emerg Surg*. (2016) 24:446. doi:10.1186/s13018-021-02595-z

15. Munoz-Torrero JF, Bounameaux H, Pedrajas JM, Lorenzo A, Rubio S, Kearon C, et al. Acute massive pulmonary embolism in patients with diabetes undergoing joint arthroplasty. *J Orthop Surg Res*. (2021) 16:446. doi:10.1186/s13018-021-02595-z

16. Ohya H, Kimura H, Watanabe J, Nakagawa K, Suwa Y, Ozawa M, et al. The incidence of deep vein thrombosis in breast cancer patients receiving outpatient cancer therapy in Iran. *Tunaflos*. (2019) 18:244–53.

17. Xiao S, Geng X, Zhao J, Fu L. Risk factors for potential pulmonary embolism in patients undergoing breast cancer surgery and treated according to clinical pathways. *Ann Surg*. (2006) 243:98–101. doi:10.1097/01.sla.0000193959.44677.48

18. Brea EI, Tiu BC, Connors JM. A comprehensive review of DOACs for cancer associated VTE prophylaxis or treatment. *Postgrad Med*. (2021) 53:71–9. doi:10.1002/ps.32548.1.20195542

19. Yamashita S, Nishi M, Ikemoto T, Yoshikawa K, Higashijima J, Tomakunai T, et al. Clinical analysis of postoperative venous thromboembolism in Japanese patients after colorectal cancer surgery. *Surg Today*. (2021) 51:1022–7. doi:10.1007/s00595-020-02201-5

20. Walker AJ, West J, Card TR, Crooks C, Kirwan CC, Grainge MJ. When are breast cancer patients at highest risk of venous thromboembolism? a cohort study using English health care data. *Blood*. (2016) 127:849–57; quiz 953. doi:10.1182/blood-2015-01-625582

21. Momeni A, Fox JP. Venous thromboembolism after surgical treatment of breast cancer. *Ann Plast Surg*. (2018) 80:188–92. doi:10.1097/SAP.0000000000001249

22. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzi E, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the RISTOS project. *Ann Surg*. (2006) 243:89–95. doi:10.1097/01.sla.0000193959.44677.48

23. Kimura CC, McDowell G, McCallum CN, Byrne GJ. Incidence of venous thromboembolism during chemotherapy for breast cancer: impact on cancer outcome. *Anticancer Res*. (2011) 31:2383–8.

24. van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahe I, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica*. (2017) 102:1494–501. doi:10.3324/haematol.2017.169060

25. Chen DQ, Montgomery SR Jr, Cancienne JM, Werner BC. Postoperative venous thromboembolism and other complications after anatomic total shoulder arthroplasty in patients with a history of prostate or breast cancer. *J Am Acad Orthop Surg*. (2020) 28:75–80. doi:10.5435/JAAOS-D-18-00777

26. Ohashi Y, Ikeda M, Kunitoh H, Sasaki M, Okusaka T, Mukai H, et al. Venous thromboembolism in cancer patients: report of baseline data from the multicentre, prospective Cancer-VTE Registry. *Jpn J Clin Oncol*. (2020) 50:1246–53. doi:10.1093/jjco/hyy112

27. Xiao S, Geng X, Zhao J, Fu L. Risk factors for potential pulmonary embolism in the patients with deep venous thrombosis: a retrospective study. *J Vasc Surg*. (2020) 66:1944–9. doi:10.1016/j.vascup.2019.09.035

28. Kerget B, Erol Afsin D, Aksakal A, Kerget F, Askin S, Yilmazel Ucar E, et al. Could VEGF-D level have a role in clinical risk scoring, estimation of thrombus burden, and treatment in acute pulmonary thromboembolism? *Int J Clin Pract*. (2021) 75:e14601. doi:10.1111/ijcp.14601

29. Lee CH, Cheng CL, Chang CH, Kao Yang YH, Lin LJ, Lin TC, et al. Universal pharmacological thromboprophylaxis for total knee arthroplasty may not be necessary in low-risk populations: a nationwide study in Taiwan. *J Thromb Haemost*. (2012) 10:56–63. doi:10.1111/j.1538-7836.2011.04555.x

30. De Donno A, Favia M, Martini A, Calvano M, Galeandro C, Angilletta D, Phlegmatisa Cerulea Dolens: a sudden unexpected death with hypothesis of medical malpractice. *Clin Ter*. (2021) 172:256–9. doi:10.7417/CT.2021.2326
42. Wan J, Liu B. Construction of lncRNA-related ceRNA regulatory network in diabetic subdermal endothelial cells. *Bioengineered*. (2021) 12:2592–602. doi: 10.1080/21655979.2021.1936892

43. Schneider C, Stratman S, Kirsner RS. Lower Extremity Ulcers. *Med Clin North Am.* (2021) 105:663–79. doi: 10.1016/j.mcna.2021.04.006

44. Kale MB, Bajaj K, Umare M, Wankhede NL, Taksande BG, Umekar MJ, et al. Exercise and nutraceuticals: eminent approach for diabetic neuropathy. *Curr Mol Pharmacol.* (2022) 15:108–28. doi: 10.2174/187446721466610629123010

45. Taruya A, Hatada A, Nishimura Y, Uchita S, Toguchi K, Honda K, et al. Left ventricular ball-like thrombus after acute myocardial infarction with essential thrombocytopenia. *J Cardiol Cases*. (2014) 10:1–3. doi: 10.1016/j.jccase.2014.01.005

46. Fang L, Liu J, Zhu FB. [Effect of Xinfeng Capsule on Related Factors of Thrombus Formation and Inflammatory Cytokines in Active Ankylosing Spondylitis Patients]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. (2016) 36:1202–7.

47. Ahmad I, Sharma S, Gupta N, Rashid Q, Abid M, Ashraf MZ, et al. Antithrombotic potential of esculin 7, 3', 4', 5', 6'-O-pentasulfate (EPS) for its role in thrombus reduction using rat thrombosis model. *Int J Biol Macromol*. (2018) 119:360–8. doi: 10.1016/j.ijbiomac.2018.07.048

48. Breitenstein A, Sluka SH, Akhmedov A, Stivala S, Steffel J, Camici GG, et al. Dronedarone reduces arterial thrombus formation. *Basic Res Cardiol*. (2012) 107:302. doi: 10.1007/s00395-012-0302-4

49. Squizzato A, Galliazzo S, Rancan E, Di Pilla M, Micucci G, Poddà G, et al. Current management of cancer-associated venous thromboembolism in patients with thrombocytopenia: a retrospective cohort study. *Intern Emerg Med*. (2021). doi: 10.1007/s11739-021-02771-3. [Epub ahead of print].

50. Kenmotsu H, Notsu A, Mori K, Omori S, Tsushima T, Satake Y, et al. Cumulative incidence of venous thromboembolism in patients with advanced cancer in prospective observational study. *Cancer Med*. (2021) 10:895–904. doi: 10.1002/cam4.3670

51. Sun W, Ren H, Gao CT, Ma WD, Luo L, Liu Y, et al. Clinical and prognostic significance of coagulation assays in pancreatic cancer patients with absence of venous thromboembolism. *Am J Clin Oncol*. (2015) 38:550–6. doi: 10.1097/01.coc.0000436088.69084.22

52. Abdul Razak NR, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers*. (2018) 10:380. doi: 10.3390/cancers10030080

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