Prevalence of and Risk Factors for Venous Thromboembolism in Patients With Lymphoma: A Meta-Analysis

Cuiting Jiang, MSN, RN, Tingting Liu, BSN, RN, Luxiang Xu, BSN, RN, Jing Lv, BSN, RN, and Yao Liu, PhD

Venous thromboembolism (VTE), which consists of deep venous thrombosis and pulmonary embolism, is a significant global burden and ranks as the third leading cause of death worldwide (Klemen et al., 2020). Lymphoma is a malignancy that carries a high risk of VTE, with an incidence ranging from 5.3% to 59.5% (Caruso et al., 2010; Goldschmidt et al., 2003). VTE in patients with lymphoma is associated with prolonged hospitalization, bleeding-related complications, and mortality, all of which can severely affect prognosis (Kirkizlar et al., 2020). Therefore, it is crucial to determine the prevalence of VTE, identify risk factors in a timely manner, and implement targeted preventive measures to reduce the occurrence of VTE in patients with lymphoma.

VTE incidence across different lymphoma subtypes varies alongside tumor characteristics, such as metastatic spread and growth rate. In a meta-analysis of 18 published studies (Caruso et al., 2010), the prevalence of VTE in patients with non-Hodgkin lymphoma (NHL) was 6.5%, which was significantly higher than the 4.7% prevalence rate observed in patients with Hodgkin lymphoma (HL). An incidence rate of 10%–12% has been reported in patients with aggressive histology, including diffuse large B-cell lymphoma (DLBCL) (Hohaus et al., 2018), and in patients with primary central nervous system lymphoma, the incidence rate is as high as 31% (Saito et al., 2021). Because of its high incidence rate, it is important to identify risk factors associated with VTE to ensure early prevention. Therefore, routine assessment of the risk of VTE in patients with newly diagnosed lymphoma is recommended.

Numerous studies have examined risk factors associated with VTE in patients with lymphoma, with inconsistent results. Previous studies (Borg et al., 2016; Chen et al., 2022) have suggested that age,
history of VTE, and Ann Arbor stage are associated with an increased risk of VTE, whereas other studies (Lund et al., 2015; Saito et al., 2021) have reported a higher risk of VTE in patients with central venous catheterization, a history of diabetes mellitus, a hemoglobin level less than 10 g/dl, and impaired ambulation. These factors can significantly affect cancer treatment, cause a greater financial burden on patients, increase the risk of bleeding, and, ultimately, lead to increased mortality. As a result, systematically summarizing identified risk factors and quantitatively exploring their correlation with VTE is of great significance for the evidence-based management of VTE in patients with lymphoma.

To date, many studies have examined the prevalence of and risk factors associated with VTE in patients with lymphoma, but the quality of these studies is inconsistent, the prevalence of VTE varies greatly, and the results are often inconclusive. Because of the inconsistencies and disagreements in the existing literature, the purpose of this study was to conduct a meta-analysis to identify the prevalence of and risk factors for VTE in patients with lymphoma. This meta-analysis provides a theoretical foundation for clinicians to conduct early assessments and identify patients at risk for VTE, allowing for timely intervention.

Methods

Search Strategy

This meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2015). However, the study protocol was not registered on any platform. Two investigators (C.J. and T.L.) systematically searched Embase®, Web of Science, PubMed®, and Cochrane Library databases from inception to February 2023 to identify all potentially eligible studies about VTE in patients with lymphoma. The search was conducted using a combination of MeSH (Medical Subject Headings) terms and free-text words. Specifically, the following key terms were used: thrombosis, venous thrombosis, venous thrombosis events, venous thromboembolism, pulmonary embolism, deep vein thromboses, VTE, DVT, PE, and lymphoma. In addition, the reference lists of the records identified for inclusion were independently reviewed, and any discrepancies were resolved through consultation with a third investigator (Y.L.). Because this study is based entirely on previously published studies, it did not require the approval of an ethics committee.

Study Selection

After removing duplicate records, two investigators (C.J. and T.L.) independently assessed the eligible studies by screening the titles, abstracts, and full texts. Any discrepancies regarding study inclusion were resolved by consulting a third investigator (Y.L.). This study included only observational studies, such as cohort or case-control studies, that met the following criteria: (a) investigated risk factors for VTE in patients with lymphoma, (b) included participants who were pathologically diagnosed with lymphoma, (c) included participants aged 18 years or older, and (d) had clear diagnostic criteria for VTE. Studies were excluded if they had no eligible data for extraction; if they were review articles, meta-analyses, or case reports; or if the full text was unavailable.

Quality Assessment

The methodologic quality of eligible observational studies was assessed using the Newcastle-Ottawa Scale (Lo et al., 2014). The Newcastle-Ottawa Scale consists of eight items that measure the following three dimensions: selection criteria of participants, comparability, and outcome or exposure factor measurement. Each study’s methodologic quality is calculated by summing the scores for each domain, with the maximum obtainable score being 9. A score of 7 or greater is considered good quality, a score of 5–6 is considered fair quality, and a score of 4 or less is considered poor quality (Stang, 2010).

Data Extraction

A standardized data extraction table was used to extract the following data: authors’ names, publication year, country, study design, lymphoma subtype, VTE diagnostic criteria, sample size, VTE prevalence, and risk factors for VTE. Only adjusted relative risk or odds ratios (ORs) with 95% confidence intervals (CIs) from multivariate analyses were extracted.

Data Analysis

Stata, version 12.0, was used to perform the meta-analysis. The heterogeneity among studies was assessed using Cochran’s Q test, and the degree of heterogeneity was evaluated using the I² statistic. When significant heterogeneity was detected (p < 0.1 or I² > 50%), a random-effects model was applied to combine the effect sizes of the included studies; otherwise, a fixed-effects model was used. Statistical significance was set at p < 0.05. The pooled prevalence of VTE was calculated by extracting the proportions
of participants diagnosed with VTE from all included studies. To evaluate the risk factors for VTE, the relative risk or OR and 95% CI from all included studies were extracted, and all eligible available data were summarized. In addition, sensitivity analysis was conducted to assess the robustness of the study findings by comparing the results before and after the removal of low-quality studies or studies with the highest prevalence of VTE. Publication bias was identified using a funnel plot, and the asymmetry was tested using Egger’s test, with significance set at p < 0.1.

Results
Selection of Studies
The initial literature database search retrieved 4,983 records. After removing 1,032 duplicates, the titles and abstracts of the remaining 3,951 records were screened. After screening, 3,867 unrelated studies, reviews, meta-analyses, and case reports were excluded. The full text of the remaining 84 records was reviewed, and 67 records were excluded. In total, 17 studies were included in the meta-analysis. The PRISMA flow diagram is illustrated in Figure 1.

Characteristics of Studies
Of the 17 included studies, 9 were cohort studies, and 8 were case-control studies. The diagnosis of VTE was mainly based on ultrasound imaging and computed tomography. The total sample size of this meta-analysis was 21,125, which consisted of 1,728 VTE cases and 19,397 non-VTE cases. Table 1 presents the detailed characteristics of the included studies, and Table 2 presents the methodologic quality of the studies based on Newcastle-Ottawa Scale scores. Of the 17 studies, 14 were good quality and 3 were fair quality, indicating that the overall quality of the included studies was high.

Prevalence of and Risk Factors for VTE
Across all studies, the reported VTE prevalence rate ranged from 3.09% to 30.77%. The pooled prevalence of VTE was 12% (range = 9%-15%), with substantial heterogeneity (I² = 98.3%). One study did not provide the prevalence of VTE in patients with HL or NHL (Zhou et al., 2010), so a subgroup analysis of the remaining 16 studies was performed according to the two main types of lymphoma: HL and NHL (Shi, 2018). The subgroup analysis showed that the prevalence of VTE in patients with NHL (12%) was higher than in patients with HL (10%).

In the included studies, a total of 25 risk factors associated with VTE were identified. Of these, 12 were mentioned in a single study, so a meta-analysis could not be performed. Therefore, these 12 risk factors were excluded, and a meta-analysis was performed on the remaining 13 risk factors. Heterogeneity analysis revealed no heterogeneity among the following 10 risk factors: female sex, older age, history of VTE, a diagnosis of DLBCL, bulky disease, central nervous system involvement, a white blood cell count greater than 11 x 10⁹/L, a D-dimer level greater than 0.5 mg/L, central venous catheterization, and treatment with doxorubicin (I² < 50%). These risk factors were analyzed using a fixed-effects model. The heterogeneity of the other factors was large (I² > 50%); therefore, a random-effects model was used for analysis. The
<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Design, Lymphoma Subtype, and VTE Diagnostic Criteria</th>
<th>Population and VTE Prevalence</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borg et al., 2016 (Denmark)</td>
<td>Design: case-control study; Lymphoma subtype: DLBCL; VTE diagnostic criteria: Doppler ultrasound; CT</td>
<td>Population: VTE group (N = 32); non-VTE group (N = 257); VTE prevalence: 11.07%</td>
<td>A history of VTE; Ann Arbor stage III–IV disease; a higher ECOG-PS score</td>
</tr>
<tr>
<td>Byun et al., 2019 (Korea)</td>
<td>Design: case-control study; Lymphoma subtype: PCNSL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 33); non-VTE group (N = 202); VTE prevalence: 14.04%</td>
<td>Female sex; older age; a higher ECOG-PS score; a hemoglobin level less than 10 g/dl</td>
</tr>
<tr>
<td>Chen et al., 2022 (China)</td>
<td>Design: cohort study; Lymphoma subtype: HL or NHL; VTE diagnostic criteria: Doppler ultrasound; angiography; CT; ventilation perfusion scans</td>
<td>Population: VTE group (N = 52); non-VTE group (N = 635); VTE prevalence: 4.94%</td>
<td>Male sex; older age; a D-dimer level greater than 0.5 mg/L; number of cycles of chemotherapy; a platelet count greater than or equal to 350 × 10⁹/L; a diagnosis of PCNSL</td>
</tr>
<tr>
<td>Hohaus et al., 2018 (Italy)</td>
<td>Design: case-control study; Lymphoma subtype: HL or NHL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 95); non-VTE group (N = 762); VTE prevalence: 11.09%</td>
<td>A higher ECOG-PS score; a mass greater than 10 cm (bulky disease); a diagnosis of PCNSL</td>
</tr>
<tr>
<td>Lan et al., 2021 (China)</td>
<td>Design: case-control study; Lymphoma subtype: T cell; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 33); non-VTE group (N = 635); VTE prevalence: 4.94%</td>
<td>Central venous catheterization; Ann Arbor stage III–IV disease</td>
</tr>
<tr>
<td>Lim et al., 2016 (Korea)</td>
<td>Design: cohort study; Lymphoma subtype: DLBCL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 34); non-VTE group (N = 288); VTE prevalence: 10.56%</td>
<td>Number of extranodal sites (2 or more); a white blood cell count greater than 10 × 10⁹/L; Ann Arbor stage III–IV disease</td>
</tr>
<tr>
<td>Liu &amp; Yang, 2015 (China)</td>
<td>Design: cohort study; Lymphoma subtype: DLBCL; VTE diagnostic criteria: ultrasound imaging</td>
<td>Population: VTE group (N = 14); non-VTE group (N = 128); VTE prevalence: 9.86%</td>
<td>A higher ECOG-PS score; 3–4 courses of chemotherapy; incomplete remission</td>
</tr>
<tr>
<td>Lund et al., 2015 (Denmark)</td>
<td>Design: cohort study; Lymphoma subtype: HL or NHL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 55); non-VTE group (N = 10,020); VTE prevalence: 3.42%</td>
<td>Central nervous system involvement; a higher ECOG-PS score; a higher level of lactate dehydrogenase; a diagnosis of T-cell lymphoma, DLBCL, or HL</td>
</tr>
<tr>
<td>Park et al., 2012 (Korea)</td>
<td>Design: cohort study; Lymphoma subtype: HL or NHL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 54); non-VTE group (N = 632); VTE prevalence: 7.87%</td>
<td>Central nervous system involvement; older age; central venous catheterization</td>
</tr>
<tr>
<td>Qian et al., 2021 (China)</td>
<td>Design: cohort study; Lymphoma subtype: NHL; VTE diagnostic criteria: ultrasound imaging; CT</td>
<td>Population: VTE group (N = 53); non-VTE group (N = 317); VTE prevalence: 14.32%</td>
<td>A hemoglobin level less than 100 g/L; a D-dimer level greater than 0.5 mg/L; Ann Arbor stage III–IV disease; a higher ECOG-PS score</td>
</tr>
</tbody>
</table>

Continued on the next page
results of the meta-analysis indicated that female sex, older age, history of VTE, a diagnosis of DLBCL, Ann Arbor stage III–IV disease, a higher Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, bulky disease, central nervous system involvement, a white blood cell count greater than \(11 \times 10^9/L\), a D-dimer level greater than 0.5 mg/L, central venous catheterization, and treatment with doxorubicin were all significant risk factors for VTE in patients with lymphoma (\(p < 0.05\)). Comparatively, a hemoglobin level less than 10 g/dl was not associated with VTE in patients with lymphoma (\(p = 0.857\)). The pooled results of the VTE prevalence and risk factor analysis are presented in Table 3.

### Sensitivity Analysis

Sensitivity analysis was conducted on the meta-analysis results for risk factors that were included in more than two studies, as well as for the prevalence of VTE. The results of the sensitivity analysis indicated that there was no significant difference among all results after removing the study that reported the
highest incidence of VTE (p < 0.05). This finding suggests that the results of this meta-analysis are reliable. The results of the sensitivity analysis are shown in Table 4.

**Publication Bias Analysis**
Egger’s test revealed potential publication bias in the current meta-analysis (p < 0.001). To explore the effect of “missing studies” on the pooled prevalence of VTE, the trim-and-fill method was employed. The results showed that nine studies were missing from this meta-analysis, but the new pooled estimate (OR = 1.05, 95% CI [1.02, 1.08]) was consistent with the previous estimate (OR = 1.04, 95% CI [1.03, 1.04]).

**Discussion**
This meta-analysis investigated the prevalence of and risk factors for VTE in patients with lymphoma. Data from seven countries across three continents (America, Europe, and Asia) were included, and the results suggest that VTE is a relatively common complication in this patient population. The study also identified several significant risk factors for VTE in patients with lymphoma, including female sex, older age, history of VTE, a diagnosis of DLBCL, Ann Arbor stage III–IV disease, a higher ECOG-PS score, bulky disease, central nervous system involvement, a white blood cell count greater than 11 × 10^9/L, a D-dimer level greater than 0.5 mg/L, central venous catheterization, and treatment with doxorubicin.

In this meta-analysis, the overall pooled prevalence of VTE in patients with lymphoma was about 12%, with significant heterogeneity (I^2 = 98.3%). The pooled prevalence of VTE in this study was lower than the 30.77% prevalence reported by Saito et al. (2021) in their study of 78 patients with primary lymphoma.

**TABLE 2. Newcastle-Ottawa Scale Scores of Included Studies (N = 17)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/ Exposure</th>
<th>Total Score</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borg et al., 2016</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Byun et al., 2019</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Chen et al., 2022</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>Good</td>
</tr>
<tr>
<td>Hohaus et al., 2018</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Lan et al., 2021</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>Good</td>
</tr>
<tr>
<td>Lim et al., 2016</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Liu &amp; Yang, 2015</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>Good</td>
</tr>
<tr>
<td>Lund et al., 2015</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Park et al., 2012</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Qian et al., 2021</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>Fair</td>
</tr>
<tr>
<td>Rupa-Matysek et al., 2017</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>Good</td>
</tr>
<tr>
<td>Saito et al., 2021</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Sanfilippo et al., 2016</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Santi et al., 2017</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>Fair</td>
</tr>
<tr>
<td>Yang et al., 2021</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>Fair</td>
</tr>
<tr>
<td>Yokoyama et al., 2012</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Zhou et al., 2010</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Note.** The Newcastle-Ottawa Scale was used to determine each study’s methodologic quality. The maximum score is 9, with a score of 7 or greater indicating good quality, a score of 5–6 indicating fair quality, and a score of 4 or less indicating poor quality.
Central nervous system lymphoma, but it was higher than the 4.94% prevalence reported by Lan et al. (2021) in their study of 668 patients with T-cell lymphoma. Differences in VTE prevalence among the studies may be related to the inconsistent lymphoma subtypes and sample sizes. Subgroup analysis based on lymphoma subtypes showed that the prevalence of VTE in patients with NHL was higher than that in patients with HL, and the relationship between lymphoma subtypes and VTE has been discussed in previous studies (Lund et al., 2015; Santi et al., 2017; Yang et al., 2021), all of which indicated that the DLBCL subtype was a risk factor for VTE. In addition, a meta-analysis of thrombotic complications in adult patients with lymphoma showed that the prevalence of thrombosis observed in patients with NHL was 6.5%, which was significantly greater than that observed in patients with HL (Caruso et al., 2010). However, another meta-analysis showed no difference based on histologic subtype (Sorigue et al., 2018). Therefore, it is necessary to identify the risk of VTE for patients with varying lymphoma subtypes to provide targeted measures to prevent its occurrence.

This study suggests that patients with lymphoma who are female, are older, and have a history of VTE are more susceptible to VTE. Female sex may be a potential risk factor for VTE because of endogenous estrogen and its impact on coagulation factors (Simon et al., 2006). However, a study of 1,069 patients with lymphoma undergoing chemotherapy found that the prevalence of VTE was higher in male patients (Chen et al., 2022). Several other studies did not find an association between sex and VTE, which requires further validation in additional studies (Hohaus et al., 2018; Rupa-Matysek et al., 2017; Sanfilippo et al., 2016).

Most studies suggest that older patients are at greater risk for VTE, but there is no exact statistical data on the age of highest incidence of VTE. Previous

**TABLE 3. Meta-Analysis of the Prevalence of and Risk Factors for VTE in Patients With Lymphoma**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studies</th>
<th>I²</th>
<th>p</th>
<th>Model Type</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE prevalence</td>
<td>17</td>
<td>98.3</td>
<td>&lt; 0.001</td>
<td>Random</td>
<td>0.12</td>
<td>[0.09, 0.15]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Risk factor**

- Higher ECOG-PS score: 7, 67.3, 0.005, Random, 3.05, [1.74, 5.36], < 0.001
- Ann Arbor stage III–IV: 6, 72.6, 0.003, Random, 3, [1.8, 4.98], < 0.001
- Hemoglobin level < 10 g/dl: 4, 88.4, < 0.001, Random, 1.14, [0.27, 4.9], 0.857
- Older age: 4, –, 0.927, Fixed, 2.55, [1.67, 3.88], < 0.001
- CNS involvement: 3, –, 0.563, Fixed, 2.95, [1.98, 4.38], < 0.001
- Diagnosis of DLBCL: 3, –, < 0.439, Fixed, 1.93, [1.49, 2.51], < 0.001
- History of VTE: 3, –, 0.698, Fixed, 3.9, [2.6, 5.83], < 0.001
- Bulky disease: 2, –, 0.508, Fixed, 3.64, [2.37, 5.59], < 0.001
- CVC: 2, –, 0.439, Fixed, 2.67, [1.47, 4.84], 0.001
- D-dimer level > 0.5 mg/L: 2, –, 0.45, Fixed, 5.16, [2.91, 9.18], < 0.001
- Female sex: 2, –, 0.456, Fixed, 2.34, [1.69, 4.89], < 0.001
- Treatment with doxorubicin: 2, 14.7, 0.279, Fixed, 2.443, [1.48, 4.04], 0.001
- WBC count > 11 × 10⁹/L: 2, –, 0.436, Fixed, 2.05, [1.26, 3.36], 0.004

CI—confidence interval; CNS—central nervous system; CVC—central venous catheterization; DLBCL—diffuse large B-cell lymphoma; ECOG-PS—Eastern Cooperative Oncology Group Performance Status; OR—odds ratio; VTE—venous thromboembolism; WBC—white blood cell
studies have reported that the risk of VTE is greatest at different ages. Chen et al. (2022) identified being aged older than 64 years as a risk factor for VTE, and another study confirmed that patients aged older than 60 years were at increased risk for VTE (Park et al., 2012). With increasing age, various substances in the blood system change, such as decreased fibrinogen dissolution and increased platelet aggregation, making the body more prone to VTE (Favaloro et al., 2014).

A prior history of VTE is a known risk factor for VTE in the general population (Brink et al., 2023; Chen et al., 2023). Similarly, VTE risk in the current study increased 3.9 times in patients with lymphoma with a history of VTE. Therefore, clinical attention should be paid to older female patients with lymphoma with a previous history of VTE, and preventive measures should be taken to mitigate thrombosis.

This study demonstrated that Ann Arbor stage III–IV disease, a higher ECOG-PS score, bulky disease, and central nervous system involvement were all risk factors for VTE in patients with lymphoma. A deeper evaluation indicated that patients with DLBCL and central nervous system involvement developed more severe VTE compared to patients with other lymphoma subtypes. This was expected because multiple studies have shown that patients diagnosed with aggressive lymphomas tend to be more frequently affected by VTE (Lund et al., 2015; Park et al., 2012; Santi et al., 2017). Stage of disease and poor performance status have also been identified as risk factors for VTE (Byun et al., 2019; Yang et al., 2021). The higher the Ann Arbor stage and ECOG-PS scores are, the greater the malignancy of tumor, the invasion taking place within the body, and the damage caused to peripheral blood vessels, all of which increase the viscosity of blood and increase the risk of thrombosis (Mahajan et al., 2014; Yokoyama et al., 2012). In addition, larger tumors result in more damage to the surrounding vascular tissue, which promotes the occurrence of thrombosis (Rupa-Matysek et al., 2017). Therefore, a comprehensive assessment of the patient’s condition should be performed during hospitalization to identify any risk factors for VTE in a timely manner.

This study also found that treatment with doxorubicin and central venous catheterization were significant risk factors for VTE in patients with lymphoma. Chemotherapy is the main treatment for lymphoma, and doxorubicin-containing regimens often require central venous catheterization. Chemotherapy can decrease levels of protein C and protein S, leading to endothelial damage and increased platelet adhesion, resulting in a hypercoagulable state (Park et al., 2012; Zhou et al., 2010). In addition, central venous catheterization can

TABLE 4. Sensitivity Analysis of the Prevalence of and Risk Factors for VTE in Patients With Lymphoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p</td>
<td>OR 95% CI p</td>
</tr>
<tr>
<td>VTE prevalence</td>
<td>0.12 [0.09, 0.15] &lt; 0.001</td>
<td>0.11 [0.08, 0.14] &lt; 0.001</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ann Arbor stage III–IV</td>
<td>3 [1.8, 4.98] &lt; 0.001</td>
<td>3.72 [2.68, 5.15] &lt; 0.001</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>2.95 [1.98, 4.38] &lt; 0.001</td>
<td>2.81 [1.82, 4.35] &lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis of DLBCL</td>
<td>1.93 [1.49, 2.51] &lt; 0.001</td>
<td>1.9 [1.42, 2.55] &lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 10 g/dl</td>
<td>1.14 [0.27, 4.9] 0.857</td>
<td>0.63 [0.17, 2.31] 0.48</td>
</tr>
<tr>
<td>Higher ECOG-PS score</td>
<td>3.05 [1.74, 5.36] &lt; 0.001</td>
<td>2.86 [1.58, 5.17] &lt; 0.001</td>
</tr>
<tr>
<td>History of VTE</td>
<td>3.9 [2.6, 5.83] &lt; 0.001</td>
<td>4.63 [2.62, 8.18] &lt; 0.001</td>
</tr>
<tr>
<td>Older age</td>
<td>2.55 [1.67, 3.88] &lt; 0.001</td>
<td>2.38 [1.48, 3.82] &lt; 0.001</td>
</tr>
</tbody>
</table>

CI—confidence interval; CNS—central nervous system; DLBCL—diffuse large B-cell lymphoma; ECOG-PS—Eastern Cooperative Oncology Group Performance Status; OR—odds ratio; VTE—venous thromboembolism

Note. Model 1 depicts the statistics with the inclusion of the study with the highest reported prevalence of VTE, whereas model 2 depicts the statistics for each variable after the removal of the study with the highest reported prevalence of VTE. All variables were stable.
mechanically damage the vascular endothelium and increase the risk of catheter-related thrombosis (Ellis et al., 2020; Lanza et al., 2016). Therefore, it is important to monitor patients with lymphoma receiving doxorubicin-containing treatments and central venous catheterization, consider prophylactic use of anticoagulant drugs, and promote functional exercise following catheterization to prevent VTE occurrence.

A white blood cell count greater than $11 \times 10^9/L$ and a D-dimer level greater than $0.5 \text{mg/L}$ were associated with VTE development, which is consistent with previous studies (Chen et al., 2022; Rupa-Matysek et al., 2017). An elevated white blood cell count can promote thrombin activity and stimulate the synthesis of platelet-activating factors, leading to the formation of thrombosis (Martella et al., 2022). D-dimer is a well-established marker of VTE, and its level has been shown to be strongly associated with the risk of VTE in patients with lymphoma (Chen et al., 2022). However, the current study did not find a significant association between a hemoglobin level less than $10 \text{g/dL}$ and VTE risk, although other studies have suggested a potential link (Mackman, 2008; Saito et al., 2021). Additional research is needed to confirm this relationship. Regular monitoring of white blood cell count and D-dimer levels may help to identify high-risk patients and implement preventive measures to reduce the incidence of VTE in patients with lymphoma.

Limitations

This meta-analysis reviewed studies on VTE in patients with lymphoma and integrated results of clinical significance, but there were some limitations. First, this study retrieved only literature published in English, which may present a certain selection bias. Second, the lymphoma type, sample size, and risk factors included in each study were not the same, which may account for a large part of the heterogeneity of this study. Five studies did not specify the lymphoma type, so further subgroup analysis could not be performed. Third, Khorana Risk Score and results from the Vienna Cancer and Thrombosis Study were not evaluated. Khorana Risk Scores were not found to be risk factors for VTE in the included studies; however, they are commonly used as risk prediction tools for VTE in clinical practice (Gerotziafas et al., 2020). This may reduce the generalization of the findings. In the future, more multicenter, high-quality studies with larger samples are needed to further explore risk factors for VTE in patients with lymphoma.

**Implications for Nursing**

The prevalence of and risk factors for VTE in patients with lymphoma have been extensively studied, with varying degrees of research quality and inconsistent findings. Thromboprophylaxis for patients with lymphoma is often contraindicated because of the risk of thrombocytopenia from the disease or chemotherapy (Zwicker et al., 2014), which ignores the risk of VTE and can lead to prophylaxis regimens performing inadequately. It is crucial to strengthen the prevention and management of VTE in clinical practice. Depending on the patient’s condition, subcutaneous injection of heparin, compression therapy, and increased physical activity may be employed (Bauersachs, 2022). Further research is needed in the areas of the various prevention methods of VTE and the risk of bleeding because of thrombocytopenia. In addition, there is currently no VTE risk assessment scale specifically for patients with lymphoma. Identifying risk factors for VTE may provide a theoretical foundation for clinical staff to conduct early assessment and identification of high-risk VTE groups, allowing for timely intervention.

In conclusion, this meta-analysis showed that the pooled prevalence of VTE in patients with lymphoma was about 12%. Several risk factors were identified as significant predictors of VTE, including female sex, older age, a history of VTE, a diagnosis of DLBCL, Ann Arbor stage III–IV disease, a higher ECOG-PS score, bulky disease, central nervous system involvement, a white blood cell count greater than $11 \times 10^9/L$, a D-dimer level greater than $0.5 \text{mg/L}$, central venous catheterization, and treatment with doxorubicin. However, more high-quality studies are needed to
confirm these risk factors and provide effective early warning and preventive measures for VTE in patients with lymphoma, thereby reducing the incidence and mortality of VTE in clinical practice.

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