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CLINICAL STUDY

# Incidence, risk factors and management of venous thromboembolism in patients with primary CNS lymphoma

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## Abstract

**Introduction** Venous thromboembolism (VTE) is a known complication of malignancy. While brain tumors in general predispose to VTE, the incidence in primary central nervous system lymphoma (PCNSL) is poorly characterized. We sought to characterize incidence, risk factors, management, and outcome of VTE in PCNSL

**Method** Retrospective study of 78 PCNSL patients from 2/1/2002 to 4/1/2020 at the University of Virginia

**Results** 31% (24/78) of patients developed VTE. 12.8% (10/78) had deep venous thrombosis (DVT) alone, 11.5% (9/78) isolated pulmonary embolism (PE) and 6.4% (5/78) both. The median time from PCNSL diagnosis to VTE was 3 months. In a univariate competing risks analysis, previous VTE ($p < 0.001$), impaired ambulation ($p = 0.035$), baseline hemoglobin < 10 g/dL ($p = 0.025$) and history of diabetes mellitus (type 1 or 2) ($p = 0.007$) were associated with increased VTE risk. 34.8% were anticoagulated acutely with heparin (8/23) or 65.2% LMWH (15/23), and 25.0% (6/24) received warfarin, 41.7% (10/24) LMWH, and 33.3% (8/24) DOACs long-term. One adverse event was attributable to anticoagulation (arm hematoma with hemoglobin decrease). Five patients received IVC filters with concomitant oral anticoagulation; one experienced IVC thrombosis after anticoagulation discontinuation. Six of the 24 patients experienced recurrent VTE, four while anticoagulated.

**Conclusion** Patients with PCNSL are at high risk of VTE, most of which accrues in the first few months. History of VTE, diabetes mellitus (type 1 or 2), impaired ambulatory status, or hemoglobin < 10 g/dL may predispose patients to this complication. While optimal management is uncertain, anticoagulation prevented recurrent VTE in most patients without intracranial bleeding.

**Keywords** Venous thromboembolism · Pulmonary embolus · Deep venous thrombosis · Primary central nervous system lymphoma · Brain tumor

## Background

Venous thromboembolism (VTE) is a known complication in many malignancies such as glioblastoma and adenocarcinomas such as pancreatic and ovarian that significantly affect patient mortality and morbidity. For example, a national study of all hospitalizations in England over 13 years found a risk ratio of VTE in cancer patients of 3.6 compared to patients without cancer; the highest risk ratios were in malignant brain tumors (21.4) and pancreatic cancer (12.0) [1]. In high-grade glioma, even outside of a 6-week perioperative window in which VTE incidence is as high as 60% with radiolabeled fibrinogen studies, approximately one-quarter of patients develop VTE over the ensuing 17 months [2].

The increased risk of VTE in cancer likely relates to alterations in various aspects of Virchow's triad [3]. Hypercoagulability may result from tumor secretion of tissue factors or other procoagulant molecules and various cytokine-mediated interactions of neoplastic cells with platelets and leukocytes [3]. Age, medical comorbidity, and previous history of thrombosis are risk factors common to VTE in general. However, the high incidence seen in patients with

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brain tumors may be due to other factors more specific to the disease. For example, the particularly elevated incidence in those with high-grade gliomas may be due in part to neurologic disabilities and perioperative immobility that come with the diagnosis. Large tumors may have a high risk due to increased production of procoagulant molecules, hemiparesis, or high levels of dexamethasone, resulting in myopathy [3]. Tissue factor plays a significant role in the coagulation cascade, and its expression is correlated with glioma grade [3].

Systemic lymphomas are among the malignancies associated with increased risk for VTE, and incidence ranges from 3 to 13% [4]. In a meta-analysis of 18 published studies, the incidence rate of VTE for patients with non-Hodgkin lymphoma was 6.5% [5], similar to the 4% reported in another large population study by Mahajan [6]. In patients with aggressive histologies like diffuse large B cell lymphoma, the incidence rate increases to 10–12% [4].

Primary CNS lymphoma (PCNSL) is a rare but aggressive type of non-Hodgkin lymphoma that accounts for ~ 4% of CNS tumors [7]. Treatment regimens usually include high-dose methotrexate along with other agents and/or radiation [8]. Although there are long-term survivors, prognosis is poor, with a median survival of those treated with MTX ranging from 14 months to 5 years [9].

There is little literature on the incidence, and particularly risk factors and management, of VTE in PCNSL. A retrospective study of CNSL patients, some with metastatic brain disease, reported that 24/42 (59.5%) developed VTE in the first three months after diagnosis [10]. A multicenter study of 235 Korean patients identified 33 patients (14%) with VTE in the 21 months since diagnosis [11]. Another single-center study of 33 patients with PCNSL found a VTE incidence of 27.2% [4].

Given the wide range of incidence and paucity of data on management and outcome, in the setting of our group's longstanding interest in VTE [12], we sought to describe the incidence, risk factor, and VTE management in patients with PCNSL.

## Methods

After obtaining institutional review board (IRB) approval, we retrospectively identified 137 patients diagnosed with CNS lymphoma between 2/1/2002 and 4/1/2020 in the University of Virginia IRB-approved neuro-oncology database. Adult patients, defined as 18 years or older, with pathologically confirmed PCNSL were included, while cases with secondary/metastatic CNS lymphoma, history of HIV infection, history of organ transplant or other immunosuppression, as well as those with insufficient medical record data were excluded (Fig. 1). We reviewed the medical records of

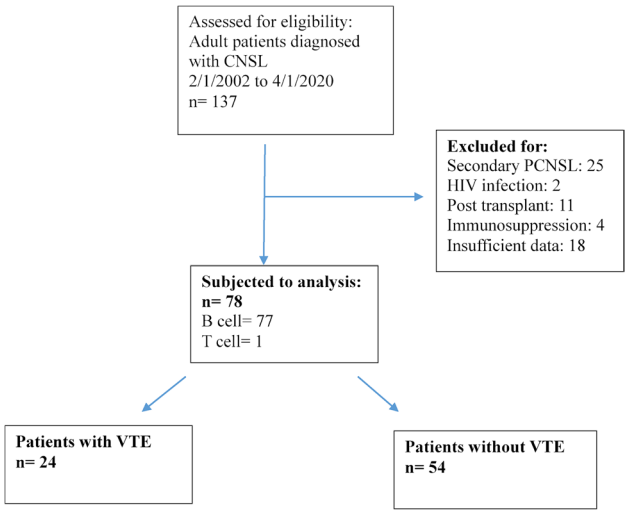


**Fig. 1** CONSORT diagram

the qualified 78 patients and collected various data regarding past medical history, diagnostic procedures, and characteristics surrounding the development and management of VTE, as confirmed by Doppler ultrasound or pulmonary CT angiography.

### Statistical analysis

An independent statistician performed all statistical analyses using the R statistical programming language (R Core Team version 4.0.2). The primary outcome was time to VTE after diagnosis of CNS lymphoma, with death as a competing event. Competing-risks regressions, specifically Fine and Gray models, were used to compare the cumulative incidence of VTE between groups in the presence of the competing risk of death. Competing risks analysis was conducted using the cmprsk package. P values of $\leq 0.05$ were considered statistically significant.

## Results

### Baseline characteristics

Of the 137 initially identified cases, data from 78 patients were evaluated according to demographics, laboratory, and clinical data based on inclusion criteria. Table 1 summarizes the characteristics of the selected patients. The mean age of diagnosis was 60.5 years, and the average BMI was 28.9 kg/m$^2$. Median follow-up for non-deceased patients was 3.7 years (range 0.1–14.5 years). Only 5.1% (4/78) of the patients had a previous history of VTE prior to diagnosis; however, those who did had a higher likelihood of a subsequent VTE event ($p < 0.001$). 65.4% (51/78) had a

**Table 1** Baseline characteristics among PCNSL patients

| Variables | All (n = 78) | | VTE (n = 24) | | No VTE (n = 54) | | p value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Gender | | | | | | | |
| Male | 44 | 56.4 | 16 | 66.7 | 28 | 51.9 | 0.22 |
| Female | 34 | 43.6 | 8 | 33.3 | 26 | 48.1 | |
| Age at diagnosis (mean) | | | | | | | |
| < 50 | 13 | 16.7 | 4 | 16.7 | 9 | 16.7 | 0.99 |
| 50–59 | 19 | 24.3 | 6 | 25.0 | 13 | 24.1 | |
| 60–69 | 30 | 38.5 | 10 | 41.7 | 20 | 37.0 | |
| 70–79 | 12 | 15.4 | 3 | 12.5 | 9 | 16.7 | |
| > 80 | 4 | 5.1 | 1 | 4.1 | 3 | 5.5 | |
| Average BMI at diagnosis ($kg/m^2$)[a] | | | | | | | |
| Underweight < 18.5 | 2 | 2.8 | 0 | 0 | 2 | 4.1 | 0.56 |
| Normal 18.5–24.9 | 15 | 21.1 | 6 | 26.1 | 9 | 18.8 | |
| Overweight 25–29.9 | 33 | 46.5 | 9 | 39.1 | 24 | 50 | |
| Obese > 30 | 21 | 29.6 | 8 | 34.8 | 13 | 27.1 | |
| Blood type[b] | | | | | | | |
| A | 25 | 38.5 | 9 | 42.9 | 16 | 36.4 | 0.50 |
| B | 4 | 6.1 | 0 | 0 | 4 | 9.1 | |
| AB | 2 | 3.1 | 1 | 4.7 | 1 | 2.2 | |
| O | 34 | 52.3 | 11 | 52.4 | 23 | 52.3 | |
| Previous hx of VTE | | | | | | | |
| Yes | 4 | 5.1 | 3 | 12.5 | 1 | 1.9 | 0.05 |
| No | 74 | 94.9 | 21 | 87.5 | 53 | 98.1 | |
| Previous hx of HTN | | | | | | | |
| Yes | 51 | 65.4 | 19 | 79.2 | 32 | 59.3 | 0.09 |
| No | 27 | 34.6 | 5 | 20.8 | 22 | 40.7 | |
| Previous hx of DM | | | | | | | |
| Yes | 17 | 21.8 | 8 | 33.3 | 9 | 16.7 | 0.10 |
| No | 61 | 78.2 | 16 | 66.7 | 45 | 83.3 | |
| Previous hx of smoking | | | | | | | |
| Yes | 44 | 56.4 | 15 | 62.5 | 29 | 53.7 | 0.47 |
| No | 34 | 43.5 | 9 | 37.5 | 25 | 46.3 | |
| Surgery type | | | | | | | |
| Resection | 8 | 10.3 | 2 | 8.3 | 6 | 11.1 | 0.79 |
| Biopsy | 68 | 87.2 | 21 | 87.5 | 47 | 87.0 | |
| None/other | 2 | 2.6 | 1 | 4.2 | 1 | 1.9 | |
| Perioperative prophylaxis[c] | | | | | | | |
| Mechanical only | 24 | 57.1 | 7 | 46.6 | 17 | 64.0 | 0.13 |
| Heparin/LMWH only | 15 | 35.7 | 8 | 53.3 | 7 | 25.9 | |
| Mechanical + heparin/LMWH | 3 | 7.1 | 0 | 0 | 3 | 11.1 | |
| KPS score[d] | | | | | | | |
| Low risk >/= 90 | 11 | 15.1 | 3 | 14.2 | 8 | 15.4 | 0.40 |
| Medium risk 70–80 | 39 | 53.4 | 9 | 42.9 | 30 | 57.7 | |
| High risk </= 60 | 23 | 31.5 | 9 | 42.9 | 14 | 26.9 | |
| ECOG performance score[e] | | | | | | | |
| >/= 2 | 57 | 80.3 | 16 | 76.2 | 41 | 82.0 | 0.57 |

**Table 1** (continued)

| Variables | All (n = 78) | | VTE (n = 24) | | No VTE (n = 54) | | p value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| < 2 | 14 | 19.7 | 5 | 23.8 | 9 | 18.0 | |
| MSKCC prognostic class | | | | | | | |
| 1 | 12 | 16.4 | 4 | 18.2 | 8 | 15.7 | 0.94 |
| 2 | 42 | 57.5 | 12 | 54.5 | 30 | 58.8 | |
| 3 | 19 | 26.1 | 6 | 27.3 | 13 | 25.5 | |
| Initial hemoglobin (g/dL)[g] | | | | | | | |
| </= 10 | 3 | 3.9 | 2 | 8.3 | 1 | 1.9 | 0.18 |
| > 10 | 74 | 96.1 | 22 | 91.7 | 52 | 98.1 | |
| Initial albumin (g/dL)[h] | | | | | | | |
| </= 4 | 42 | 55.3 | 16 | 66.7 | 26 | 50.0 | 0.17 |
| > 4 | 34 | 44.7 | 8 | 33.3 | 26 | 50.0 | |
| Impaired ambulation | | | | | | | |
| Ambulatory without assistance | 60 | 76.9 | 15 | 62.5 | 45 | 83.3 | 0.07 |
| Ambulatory with assistance | 4 | 5.1 | 3 | 12.5 | 1 | 1.9 | |
| Nonambulatory | 14 | 17.9 | 6 | 25.0 | 8 | 14.8 | |
| Chemotherapy regimen[i] | | | | | | | |
| R-MPV | 53 | 71.6 | 16 | 66.7 | 37 | 74.0 | 0.91 |
| R-MTV | 6 | 8.1 | 3 | 12.5 | 3 | 6.0 | |
| MPV | 6 | 8.1 | 2 | 8.3 | 4 | 8.0 | |
| MTV | 0 | 0 | 0 | 0 | 0 | 0 | |
| Chemo without MTX | 3 | 4.1 | 1 | 4.2 | 2 | 4.0 | |
| Other | 6 | 8.1 | 2 | 8.3 | 4 | 8.0 | |
| Length of chemotherapy (days)[j] | | | | | | | |
| </= 90 | 39 | 56.5 | 12 | 52.2 | 27 | 58.7 | 0.61 |
| > 90 | 30 | 43.5 | 11 | 47.8 | 19 | 41.3 | |
| Initial dexamethasone dose (mg) | | | | | | | |
| </= 12 | 55 | 70.5 | 17 | 70.8 | 38 | 70.4 | 0.97 |
| > 12 | 23 | 29.5 | 7 | 29.2 | 16 | 29.6 | |
| Radiation | | | | | | | |
| Yes | 19 | 24.4 | 8 | 33.3 | 11 | 20.4 | 0.22 |
| No | 59 | 75.6 | 16 | 66.7 | 43 | 79.6 | |

[a]Missing data on 7 patients
[b]Missing data on 13 patients
[c]Missing data on 36 patients
[d]Missing data on 5 patients
[e]Missing data on 7 patients
[f]Missing data on 5 patients
[g]Missing data on 1 patient
[h]Missing data on 2 patients
[i]Missing data on 4 patients
[j]Missing data on 9 patients

past medical history of hypertension, 21.8% (17/78) diabetes mellitus (type 1 or 2), and 56.4% (44/78) prior tobacco use. Initial laboratory findings at time of diagnosis revealed that 3.9% (3/77 patients) were anemic (Hgb < 10 mg/dL) and 55.3% (42/76) had hypoalbuminemia. 87.2% (68/78) of patients were diagnosed by either open or stereotactic brain biopsy, while 10.3% (8/78) patients underwent resection, and 2.6% (2/78) were diagnosed via CSF analysis. Among the 42 patients with perioperative prophylaxis for DVT data available, 57.1% (24/42) received mechanical

support, while 35.7% (15/42) received heparin or LMWH. Only 7.1% (3/42) received prophylaxis with both methods. At the first follow-up visit post-diagnosis, 76.9% (60/78) were ambulatory without assistance, 5.1% (4/78) were ambulatory with assistance, and 17.9% (14/78) were nonambulatory on physical exam. Treatment regimens for PCNSL generally include high dose methotrexate, a potential risk factor for developing VTE through elevation of homocysteine levels [6]. Among the 74 patients with available data on the type of chemotherapy received, a multi-drug therapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) was the most common treatment regimen (71.6%, 53/74). Other regimens included R-MTV (temozolomide in lieu of procarbazine) 8.1% (6/74) MPV 8.1% (6/74), MTV 4.1% (4/74) and non-methotrexate containing regimens 8.1% (6/74). 24.4% (19/78) also received radiation as part of their therapy.

## Incidence

31% (24/78) of patients developed confirmed VTE. 41.7% (10/24) patients developed isolated DVT, 37.5% (9/24) PE, and 20.8% (5/24) both DVT and PE. DVT was diagnosed via Doppler ultrasound and PE via CT pulmonary angiography in all cases. The median time between PCNSL diagnosis and VTE development was 3 months; 20 of the 24 events were within the first 6 months (Fig. 2). Most of the events developed during chemotherapy treatment; however, 1 patient had DVT and PE prior to chemotherapy, and 5 events occurred

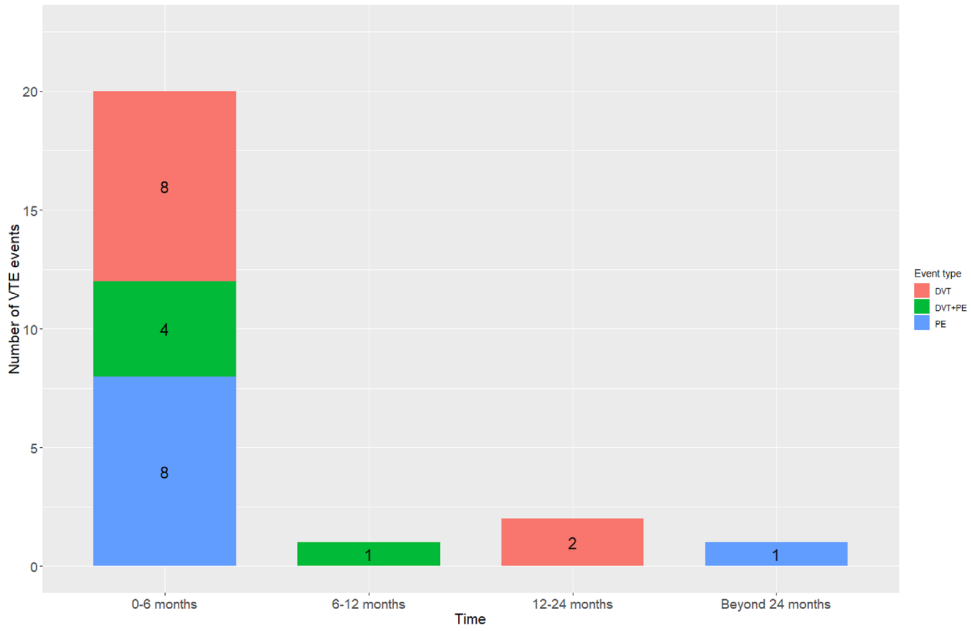


**Fig. 2** Timeline for the onset of VTE events

**Table 2** Management of VTE

| | Total with VTE (n = 24) | | With recurrence (n = 6) | | Without recurrence (n = 18) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Treated with IVC | | | | | | |
| Yes | 5 | 20.8 | 4 | 66.7 | 1 | 5.6 |
| No | 19 | 79.2 | 2 | 33.3 | 17 | 94.4 |
| Acute anticoagulant* | | | | | | |
| Heparin | 8 | 34.8 | 2 | 40.0 | 6 | 35.3 |
| LMWH | 15 | 65.2 | 2 | 40.0 | 13 | 47.1 |
| Chronic anticoagulants | | | | | | |
| Warfarin | 6 | 25.0 | 2 | 33.3 | 4 | 22.2 |
| LMWH | 10 | 41.7 | 3 | 50.0 | 7 | 38.9 |
| DOAC | 8 | 33.3 | 1 | 16.7 | 7 | 38.9 |

*One patient not acutely anticoagulated

post-treatment. One of the 5 post-treatment cases developed PE 10 years post-diagnosis.

In terms of VTE management (Table 2), acute treatment included 34.8% (8/23) with heparin and 65.2% (15/23) with low molecular weight heparin (LMWH). 25.0% (6/24) were treated chronically with warfarin, 41.7% (10/24) with LMWH, and 33.3% (8/24) with direct oral anticoagulants (DOACs). The median duration of anticoagulant treatment was 6.1 months. 5 patients also received an IVC filter in addition to anticoagulation treatment. One adverse event was attributable to anticoagulation (arm hematoma with hemoglobin decrease). Five patients received IVC filters with concomitant oral anticoagulation; one experienced IVC thrombosis after anticoagulation discontinuation. Six of the 24 patients experienced recurrent VTE, four while anticoagulated. Most VTE recurrence (4 of 6) occurred within 6 months of the first VTE. Two patients developed a third VTE.

### Competing-risks analysis

Univariate competing risks regression (Table 3) demonstrated that previous VTE (hazard ratio [HR] 4.28, 95% confidence interval [CI] 2.42–7.58, $p < 0.001$), ambulatory status (HR 5.16, 95% CI 1.56–17.13, $p = 0.007$), initial hemoglobin < 10 g/dL (HR 7.7, 95% CI 2.05–28.9, $p = 0.003$), and previous history of diabetes (HR 2.49, 95% CI 1.07–5.79, $p = 0.04$) were associated with an increased risk for developing VTE. Prior history of hypertension and hypoalbuminemia (< 4 g/dL) had hazard ratios that trended towards an increased risk of VTE development. Gender, age, BMI, and type of treatment were not associated with VTE development.

### Impact on survival

Overall, 24 patients died without developing VTE, and 30 were alive as of June 2020 without developing VTE. Of those who developed a VTE, 9 patients subsequently died. However, none of the deaths were attributable to VTE.

## Discussion

Our findings of a VTE incidence in PCNSL patients of 31% with a mean time to development of 3 months support the high prevalence (25%) and early occurrence (70 days) found in another retrospective study that looked at VTE prevalence in PCNSL patients between 1997 and 2018 who received methotrexate, procarbazine, and vincristine ± rituximab [13]. A similar VTE incidence (30%) was reported in another single-center retrospective study of 33 patients [14]. Though these values are significantly lower than the 59% reported by Goldschmidt et al., the retrospective study of 42 PCNSL patients has some generalizability limitations [10]. Six of the 42 patients had CNS non-Hodgkin lymphoma arising in the setting of prior systemic NHL, suggesting they did not have PCNSL; furthermore, 20 of these patients were treated with intraarterial chemotherapy, which may result in a different risk profile [10].

In terms of individual risk factors, we report previous VTE, ambulatory status, initial hemoglobin < 10 g/dL, and previous history of diabetes as potential risk factors for developing VTE. We did not find any significant difference in VTE development based on tumor treatment modality, supporting the results of an earlier study [11] that identified female sex, poor ECOG performance scores, older age, and anemia (Hgb < 10 mg/dL) as VTE risk factors. Low hemoglobin is a component of the Khorana Risk score for VTE development in cancer patients [15]. No patient in our study died from VTE.

Our high VTE incidence rates suggest that current perioperative prophylaxis regimens may be inadequate. Only 3 patients in this study received both mechanical and pharmacological prophylaxis perioperatively. Hemorrhage from a biopsy of PCNSL is a well-recognized complication [16, 17]. Yuen et al. found no intracranial hemorrhage from prophylactic LMWH, though patients known to be contraindicated against the use were not given anticoagulants [13]. No patients in our study developed intracranial hemorrhage. The role of various methods of prophylaxis is an area for further research.

In terms of treatment, most patients received anticoagulants and tolerated the treatment well. There was only one adverse event associated with treatment; an arm hematoma associated with LMWH use. Five patients were concomitantly treated with an IVC filter; VTE recurred in 4 of these 5 patients, suggesting IVC filters may not effectively prevent VTE in this population. This result is in concordance with a meta-analysis of IVC filter efficacy, which, although revealing some reduction in risk of recurrent PE (OR 0.5), identified an increased risk of subsequent DVT (OR 1.70) [18].

**Table 3** Univariate competing risks analysis for VTE development

| | Hazard ratio | Confidence interval | P value |
|---|---|---|---|
| Previous history of VTE | 4.28 | 2.42–7.58 | < 0.001 |
| Previous history of diabetes | 2.49 | 1.07–5.79 | 0.035 |
| Initial hemoglobin < 10(g/dL) | 7.7 | 2.05–28.9 | 0.0025 |
| Ambulatory with assistance | 5.16 | 1.56–17.13 | 0.007 |

Though anticoagulation was not 100% effective in preventing VTE recurrence, our findings indicate that most patients can be safely and effectively treated with anticoagulation. The retrospective nature of our study does not shed light on the optimal form of anticoagulation.

Strengths of this study include the large sample size for a single institutional study, the vigilance in VTE ascertainment in the study population, and a median follow-up duration of 4 years. We acknowledge various limitations of this study, including its retrospective nature contributing to missing patient data. Furthermore, it is conceivable some patients had VTE diagnosed at outside hospitals without our knowledge. Lastly, as a univariate method was used for competing risks analysis instead of a multivariate method due to an insufficient number of events, there may have been confounding factors. Nonetheless, our results highlight the strikingly high VTE incidence in PCNSL and indicate the need for further studies to identify those patients at the highest risk of VTE to develop more effective preventive strategies.

**Author contributions** MS abstracted the data and co-wrote the manuscript. NAW performed statistical analysis and edited the manuscript. DS conceived of the study, provided the data, and co-wrote the manuscript.

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**Availability of data and materials** This dataset does not reside in a publicly available repository but is available upon request.

## Declarations

**Conflict of interest** The authors declare no conflicts of interest.

**Consent to publish** Each author (MS, NAW, and DS) approves of the content and provides consent to publish.

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