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REVIEW ARTICLE

The risk of venous thromboembolism in primary central nervous system lymphoma: a systematic review and meta-analysis

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare extranodal lymphoma localized to the central nervous system. Small single-center studies have suggested that patients with PCNSL may be at high risk of venous thromboembolism (VTE). This systematic review aimed to estimate the risk of VTE in patients with PCNSL. A systematic review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. MEDLINE, Embase, and CINAHL were searched from 1990 to 2022. Prospective and retrospective observational studies as well as clinical trials were included. The primary efficacy outcome was VTE, and the primary safety outcome was major bleeding as defined by the individual studies. After screening 883 studies, 46 studies (3688 patients) with PCNSL were included. Mean age was 62.4 years. Five studies explored the use of thromboprophylaxis (acetyl salicylic acid or anticoagulation [n = 1]) and low-molecular-weight heparin (n = 4). Overall, 420 patients developed VTE (11.4%), including 17 fatal events (4% of all VTE). Two studies that reported on VTE prophylaxis representing 77 patients identified 8 breakthrough VTE events (10.4%). Most studies (n = 34; 74.5%) did not report major bleeding complications. Among studies reporting on bleeding, 174 major bleeding (7.4%) events were reported out of 2361 patients, 3 of which were attributed to thromboprophylaxis. Patients with PCNSL seem to be at high risk of both VTE and bleeding complications. Future clinical trials in this population should routinely collect data on incidence of VTE and bleeding to help clinicians assess the risk-to-benefit ratio of thromboprophylaxis in this high-risk patient population.

KEYWORDS
bleeding, hemorrhage, lymphoma, thrombosis, vascular diseases

Adam Suleman and Rachel Wine are co-first authors.

Essentials

- Patients with primary central nervous system lymphoma (PCNSL) are at risk of venous thromboembolism (VTE).
- This systematic review identified 46 studies of patients with PCNSL that reported on VTE outcomes.
- The rate of VTE was 11.4% in patients with PCNSL, but bleeding event rates appeared to be high.
- Detailed reporting on VTE and bleeding outcomes is needed in trials of patients with PCNSL.

1 | INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma accounting for 3% to 4% of central nervous system (CNS) tumors [1]. Most cases of PCNSL involve the brain, but the eyes, leptomeninges, and/or spinal cord can also be involved [2]. Treatment most often includes high-dose methotrexate as a backbone of multiagent-based chemotherapy [3]. The past decade has shown advances in the treatment of PCNSL resulting in significantly improved overall survival, albeit with increased toxicity from treatment [4].

Venous thromboembolism (VTE) is a known complication of malignancy due to recognized pathogenic mechanisms including tissue factors, endothelial damage, and alteration in coagulation factors [5]. Immobilization, surgery, and chemotherapy also increase the risk of VTE in patients with cancer [6]. In patients with PCNSL, VTE results in significant morbidity and mortality, and highest risk of VTE has been shown to be during early periods of therapy [7]. While VTE has been studied in the context of various malignancies, its incidence, risk factors, and clinical implications in patients with PCNSL are not well-defined. The risk of VTE in patients with PCNSL has been reported in few small single-center studies suggesting a high risk between 14% and 60% [8,9].

Patients with cancer who develop VTE have an increased risk of bleeding complications while on anticoagulation therapy [10]. Patients with PCNSL are at risk for major bleeding including intracranial hemorrhage, which is associated with significant morbidity and mortality. Incidence of major bleeding events in patients with PCNSL is not well established, and few studies report bleeding complications. Reports from 1 study found major bleeding events in 15% of the cohort [11].

Assessment of VTE risk is important for medical management and as a foundation for future studies of VTE prophylaxis. While various study guidelines support the use of thromboprophylaxis in high-risk ambulatory cancer patients, the studies influencing guidelines have not specifically included patients with PCNSL [12]. Information on the incidence of VTE as well as risk of bleeding in patients with PCNSL will help inform decisions regarding use of VTE prophylaxis in these patients. This systematic review was conducted to determine the incidence of VTE in patients with PCNSL to understand how it impacts outcomes and provider practices.

2 | METHODS

This systematic review and meta-analysis is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

2.1 | Identification and selection of articles

The medical databases MEDLINE, Embase, and CINAHL were searched from January 1990 to March 2022. The description of PCNSL as a separate biological entity is relatively new, and 1990 was chosen to obtain data that accurately identifies this population. A full search strategy is shown in the Supplementary Search Strategy.

Studies were included if they reported on adult patients aged ≥18 years with a diagnosis of PCNSL, either newly diagnosed or relapsed/refractory. Studies were excluded if they reported on patients aged <18 years or on patients with secondary CNS involvement for their lymphoma.

Retrospective, prospective, and phase 2/3 clinical trials were included. Case reports were excluded. Abstract-only articles were included if they specifically reported on clear VTE outcomes, and no full manuscript was identified on detailed search.

Title and abstract screening was performed by 2 authors (A.S. and R.W.) and a third author (L.K.H.) was available to resolve any discrepancies through joint discussion. As VTE is often a secondary outcome in trials of patients with PCNSL, studies were included if they reported on patients with PCNSL and reported any toxicities, even if VTE was not a specified toxicity in the abstract. Full-text review was performed by 2 authors (A.S. and R.W.), and a third author (L.K.H.) was available to discuss discrepancies. Abstract-only papers were included if they reported in detail on VTE outcomes in patients with PCNSL. Data extraction was performed by 2 authors (A.S. and R.W.) using prespecified extraction forms to capture baseline demographic and outcome data.

2.2 | Study outcomes

The main outcome of this study was the incidence of VTE (pulmonary embolism [PE], deep vein thrombosis [DVT], central venous sinus thrombosis, or other thrombosis of the venous system) in patients with PCNSL. Secondary outcomes included VTE-related mortality, breakthrough thrombosis on prophylaxis, bleeding, and bleed-related mortality. Incidence of these outcomes could be at diagnosis, during treatment, or after treatment for PCNSL.

2.3 | Synthesis of evidence

The primary and secondary outcomes were described as incidence rates with 95% CIs. Secondary outcomes were described using incidence rates when possible, or descriptively when insufficient data

were available. I^2 tests were performed to assess for heterogeneity, where values of 25%, 50% and 75% correspond to low, moderate, and high levels of heterogeneity, respectively.

For the primary and secondary outcomes, meta-analysis was performed using a random-effects model (DerSimonian and Laird) using the MetaXL add-in for Microsoft Excel (www.epigear.com).

2.4 | Evaluation of study quality

Two authors (A.S. and R.W.) independently conducted quality assessment for each study included in the review. The Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data was used to assess risk of bias [13].

3 | RESULTS

3.1 | Study selection

Our initial search yielded 883 abstracts after removal of duplicate records (Figure 1). Of these, 793 were removed after title and abstract screening as they did not report on VTE outcomes. A total of 90 studies were included in full-text review, of which 44 studies were excluded as they did not accurately report on VTE outcomes, did not report on patients with PCNSL, or were conference abstracts that contained incomplete information on the main outcome. A total of 46 studies were included in this review.

3.2 | Characteristics of included studies

In total, there were 3688 patients with PCNSL across 46 studies (Table 1). The mean age of patients across all studies was 62.4 years. Most studies were conducted in North America (n = 13, 28%) or Europe (n = 21, 46%), and most studies were retrospective cohort studies (n = 25, 54%). One study included was an abstract-only publication. A description of studies is shown in Table 2.

3.3 | Study quality assessment

Quality of the included studies was assessed using the Joanna Briggs Institute risk of bias assessment tools (Supplementary Table S1). The studies were evaluated using the checklist for prevalence studies or the checklist for experimental studies based on the study design

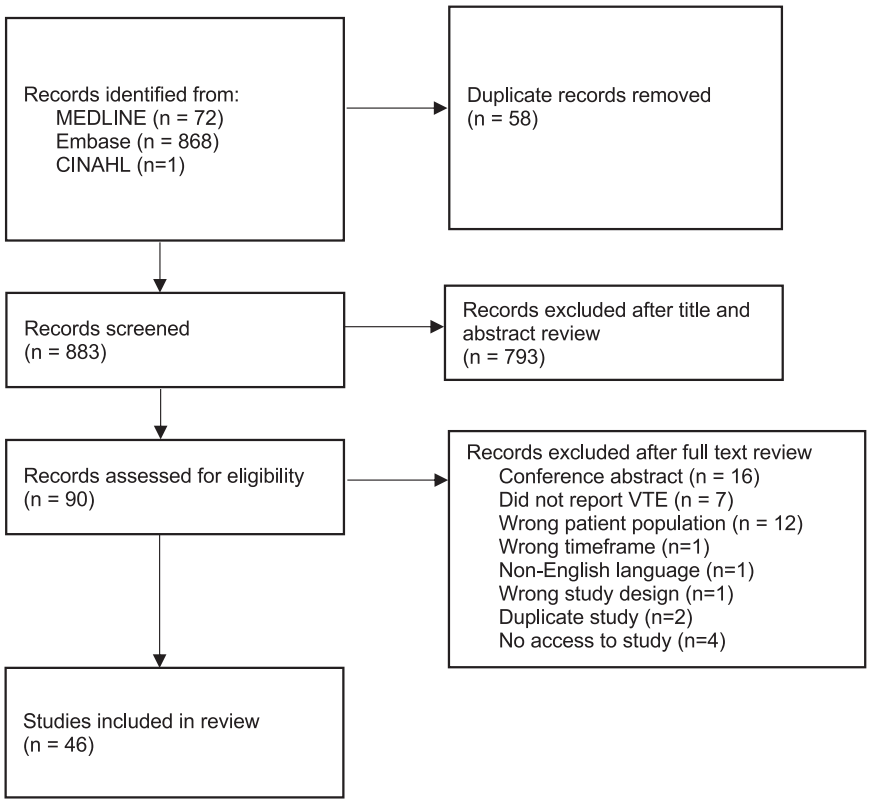

FIGURE 1 Flowchart of studies included in the systematic review and meta-analysis. VTE, venous thromboembolism.

TABLE 1 Description of studies included in the systematic review and meta-analysis.

Site of publication	
North America	13
Europe	21
Asia	9
Australia	1
Multinational	2
Mean age across studies	62.4 y
Sample size range	
Minimum	3
Maximum	551
Study design	
Randomized trial	1
Phase 1 or 2 trial	10
Prospective	5
Retrospective	30

(Supplementary Table S2). Out of the prevalence studies, 17 of 26 (65%) were found to have high risk of bias. Out of the experimental studies, 10 of 20 (50%) were found to have low risk of bias.

3.4 | Primary outcome

Of the 46 studies representing 3688 patients included in this study, the pooled incidence of VTE across studies was 11% (95% CI, 9%-14%), as shown in Figure 2. There was a high degree of heterogeneity across studies (I^2, 81%; $P < .001$). Crude patient data also showed a VTE incidence of 11% (420 out of 3688 patients). Seventeen of the thrombotic events were fatal PEs (4.05%), though only 33 studies reported VTE fatalities. The definition of VTE was inconsistent across studies with limited information on whether patients were symptomatic, and the methodology used for detection of VTE was not consistently reported (Supplementary Table S3).

The type of VTE was reported in 33 studies, with isolated DVT being the most common, followed by a combination of DVT and PE, or isolated PE. VTE timing was reported in 35 studies, representing 189 patients. A majority of VTE events occurred while on treatment (n = 167, 88.4%), with some occurring before treatment (n = 15, 7.9%) or after treatment (n = 7, 3.7%).

3.5 | Bleeding complications

A total of 12 of the 46 included studies (26.1%) reported on bleeding outcomes. The criteria used for bleeding were not standardized across studies (Supplementary Table S4). The pooled incidence of bleeding was 3% (95% CI, 1%-8%), with a high degree of heterogeneity across studies (I^2, 94%; $P < .001$), shown in Figure 3. When assessing crude rates of bleeding, there were 174 bleeding events reported in 2361 patients (7.4%). Three of these events (1.7%) occurred in patients receiving VTE prophylaxis. Description of sites of bleeding was available for 14 patients. CNS bleeding was most common (n = 9), including 2 postoperative bleeds. Two fatal CNS bleeds were reported, 1 during treatment and 1 in the postoperative setting. One intracranial hemorrhage occurred in a patient on therapeutic anticoagulation. Other reported bleeding events included 2 hematomas, 1 retroperitoneal bleed, and 2 gastrointestinal bleeds.

3.6 | Thromboprophylaxis

There were 5 studies of the 46 included (10.9%) that described the use of thromboprophylaxis. Four studies described the use of low-molecular-weight heparin as prophylaxis, with 1 study describing the use of either acetyl salicylic acid or low-molecular-weight heparin for VTE prophylaxis. Out of the 77 patients represented in the 5 studies, 8 had breakthrough VTEs (10.4%).

4 | DISCUSSION

This is the first systematic review that assesses the risk of VTE in patients with PCNSL. The pooled incidence rate of 11% (95% CI, 9%-14%) may be underestimated given the lack of reporting of VTE in studies of patients with PCNSL. Isolated DVT appeared to be the most common thrombotic event; however, fatal PEs occurred in 4.05% of patients with VTE. This is higher than what has been described in large registries, with a VTE mortality rate of 3% at 3 months [56].

The risk of thrombosis seen in this study is similar to the risk of thrombosis seen in retrospective studies of patients with diffuse large B-cell lymphoma [57–59]. However, Medicare data suggest a lower rate of thrombosis of 8.3% for all patients with diffuse large B-cell lymphoma [60]. Patients with PCNSL often present with severe neurologic deficits, are immobile, and often require neurosurgery for diagnosis, providing many additional risk factors for VTE compared with other patients with lymphoma [3,61,62].

Given the lack of reporting of thrombosis outcomes trials of PCNSL, the true risk of VTE is likely underestimated. The widely used Khorana score for prediction of patients at high risk of VTE did not include patients with PCNSL in its derivation, and its applicability to patients with PCNSL has not been validated [63]. The currently existing lymphoma-specific thrombosis prediction models have rarely included patients with PCNSL [64,65,16]. There is an ongoing need to understand the true risk of VTE in this population as patients with PCNSL may benefit from a routine thromboprophylaxis strategy.

TABLE 2 Characteristics of included studies.

First author/ year	Location	Type of study	Sample size (PCNSL only)	VTE incidence (*n*)	Fatal VTE events (*n*)	Type of VTE	Bleeding reported	Bleeding events (*n*)	VTE prophylaxis reported
Aoki, 2013 [14]	Japan	Prospective	38	1	0	DVT	N	N/R	N
Asano, 2022 [15]	Japan	Retrospective	133	15	1	Unclear	Y	2	N
Bastos-Oreiro, 2021 [16]	Spain	Retrospective	3	2	N/R	Unclear	N	N/R	N
Bimbaum, 2012 [17]	Germany	Retrospective	36	1	N/R	PE	N	N/R	N
Byun, 2019 [9]	Korea	Retrospective	235	33	1	11 DVT 15 PE 7 DVT + PE	Y	5	N
Calderoni, 2002 [18]	Switzerland	Prospective	14	1	1	1 PE	N	N/R	N
Chamberlain, 2014 [19]	United States	Retrospective	12	1	N/R	Thrombophlebitis	N	N/R	N
Depil, 2022 [20]	France	Retrospective	34	7	N/R	4 PE 1 lower limb phlebitis 2 CVST	N	N/R	Y
Ferreri, 2020 [21]	Italy	Phase 2 trial	28	2	0	DVT	N	N/R	N
Ferreri, 2006 [22]	Italy	Phase 2 trial	41	5	1	DVT	Y	3	N
Ferreri, 2011 [23]	Italy	Prospective	59	0	0	N/A	N	N/R	N
Ferreri, 2001 [24]	Italy	Prospective	13	1	1	PE	N	N/R	N
Ferreri, 2016 [25]	Europe	Randomized phase 2 trial	219	19	0	DVT and PE	N	N/R	N
Fritsch, 2011 [26]	Germany	Prospective	28	1	1	Unclear	N	2	N
Glass, 1994 [27]	United States	Retrospective	25	3	N/R	2 DVT 1 PE	N	N/R	N
Glass, 1996 [28]	United States	Prospective	18	2	N/R	DVT	Y	1	N
Goldschmidt, 2003 [8]	Israel	Retrospective	43	25	3	14 DVT 11 PE	Y	N/R	N
Hohaus, 2018 [29]	Italy	Retrospective	33	9	N/R	Unclear	N	N/R	N
Iorio-Morin, 2020 [30]	Canada	Retrospective	44	1	0	PE	N	N/R	N
Korfel, 2016 [31]	Germany	Phase 2 trial	37	2	0	DVT	Y	1	N
Kuitunen, 2017 [32]	Finland	Retrospective	25	2	0	SVT	N	N/R	N
Mahajan, 2020 [11]	United States	Retrospective	992	143	N/R	75 PE ± DVT 32 proximal DVT 36 distal DVT	Y	156	N
Mocikova, 2016 [33]	Czech Republic	Retrospective	164	14	N/R	DVT	N	N/R	N

(Continues)

TABLE 2 (Continued)

First author/ year	Location	Type of study	Sample size (PCNSL only)	VTE incidence (*n*)	Fatal VTE events (*n*)	Type of VTE	Bleeding reported	Bleeding events (*n*)	VTE prophylaxis reported
Montemurro, 2007 [34]	Germany	Prospective	23	2	1	PE	N	N/R	N
Olivier, 2014 [35]	France	Phase 1 trial	35	1	1	PE	N	N/R	N
Omuro, 2015 [36]	USA	Phase 2 trial	32	3	0	Not reported	N	N/R	N
Park, 2012 [37]	Korea	Prospective	51	10	N/R	Not reported	N	N/R	N
Pentsova, 2014 [38]	United States	Retrospective	39	1	0	DVT	N	N/R	N
Plotkin, 2004 [39]	United States	Retrospective	22	3	0	Not reported	N	N/R	N
Pulczynski, 2015 [40]	Norway	Phase 2 trial	66	7	0	DVT	N	N/R	N
Ravi, 2014 [41]	United States	Retrospective	30	6	0	Not reported	N	N/R	N
Saito, 2021 [42]	United States	Retrospective	78	24	N/R	9 PE 10 DVT 5 DVT and PE	Y	1	Y
Salamoon, 2013 [43]	Syria	Prospective	40	3	0	DVT	N	N/R	N
Sarid, 2021 [44]	Israel	Retrospective	73	17	0	8 DVT (4 catheter-related) 2 SVT 7 DVT and PE	N	N/R	N
Seidel, 2020 [45]	Germany	Retrospective	43	8	0	DVT	Y	1	Y
Silvani, 2007 [46]	Italy	Prospective	38	2	0	DVT	Y	0	N
Simonetti, 2015 [47]	Italy	Retrospective	17	2	0	1 DVT 1 PE	N	N/R	N
Sonoda, 2007 [48]	Japan	Retrospective	63	1	0	PE	N	N/R	N
Swinnen, 2018 [49]	United States	Phase 2 trial	26	3	0	Not reported	N	N/R	N
Thiel, 2010 [50]	Germany	Randomized phase 3 trial	551	16	5	PE	Y	1	N
Tun, 2018 [51]	United States	Phase 1 trial	25	2	0	Not reported	N	N/R	Y
Tyson, 2003 [52]	United States and Israel	Retrospective	37	3	0	2 DVT 1 PE	N	N/R	N
Welch, 2012 [53]	United States	Retrospective	24	1	0	Not reported	N	N/R	N
Yamanaka, 2005 [54]	Japan	Prospective	32	1	0	Not reported	N	N/R	N
Yuen, 2020 [7]	Australia	Retrospective	51	13	0	8 DVT 3 DVT and PE	Y	4	Y
Zhang, 2013 [55]	United States and China	Retrospective	18	1	1	PE	N	N/R	N

CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; N, no; N/R, not reported; PCNSL, primary central nervous system lymphoma; PE, pulmonary embolism; SVT, superficial vein thrombosis; VTE, venous thromboembolism; Y, yes.

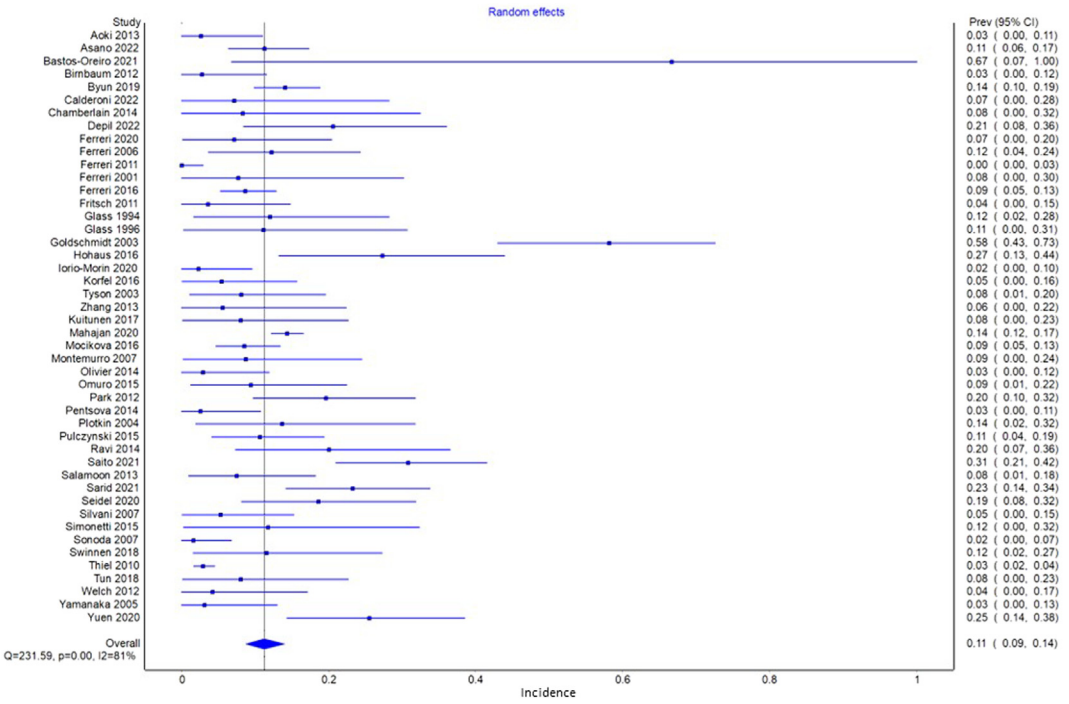

FIGURE 2 Forest plot of venous thromboembolism incidence.

The pooled bleeding rate in this study was low at 3% (95% CI, 1%-8%), though crude bleeding events were higher at 7.4%. Patients with PCNSL at baseline may have bleeding at their tumor sites and therefore may be at increased risk of bleeding compared with patients with other types of cancer [66]. Treatment for PCNSL often involves very myelotoxic chemotherapy, which increases a bleed risk through severe thrombocytopenia [25,67]. The bleed risk is also likely underestimated from a lack of reporting, and the true risk has yet to be determined.

This review has several limitations. Given the paucity of high-quality data specifically focused on thrombosis in patients with PCNSL, we included manuscripts that had VTE as a secondary outcome and abstracts that specifically reported on VTE in PCNSL. A majority of the studies included were at high risk of bias, and there was significant heterogeneity between studies (I^2, 81%). This likely reflects the small sample size in studies that assess outcomes of patients with PCNSL. The largest sample size in our current study comes from 1 registry study, and the presented risk is largely impacted by this 1 study [11]. Our pooled estimates of VTE and bleeding should be interpreted with caution, and it is possible that the true estimate is higher than what is reported. There was significant heterogeneity in the definitions of both VTE and bleeding. It was not possible to stratify bleeding further based on prognosis, and therefore is challenging to balance with the risk of VTE. These limitations highlight the need for studies to capture outcomes with standardized definitions.

In conclusion, this systematic review and meta-analysis found a high rate of thrombosis among patients with PCNSL, as well as a potentially high bleeding rate. Importantly, both thrombosis and bleeding appear to be underreported in trials of patients with PCNSL,

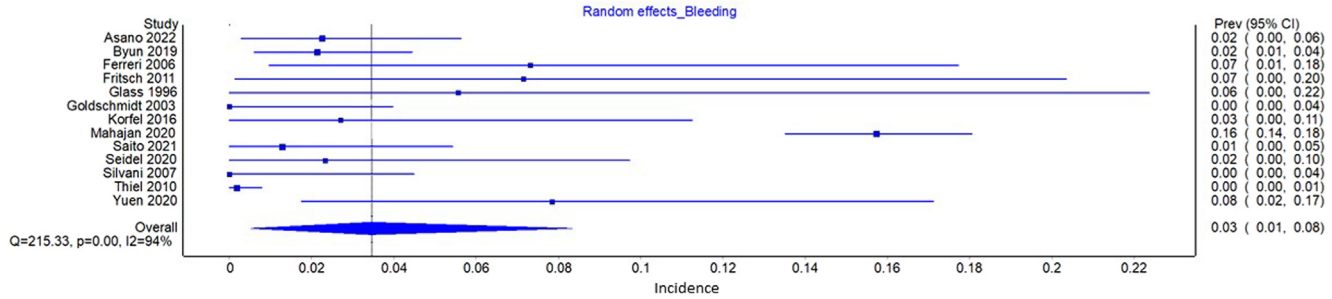

FIGURE 3 Forest plot of bleeding incidence.

with very few trials tracking bleeding events in particular; thus, the true estimates of VTE and bleeding are likely higher than those reported. Ongoing trials of patients with PCNSL need clear reporting of VTE and bleeding complications for the true risk to be ascertained. This is a necessary first step to inform future trials of VTE prophylaxis in this high-risk population.

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AUTHOR CONTRIBUTIONS

A.S. and R.W. performed the search and data extraction. L.K.H. was available to resolve any disputes. All authors were involved in interpretation of data and manuscript writing.

RELATIONSHIP DISCLOSURE

M.C. reports grants from BMS, Leo Pharma, and Pfizer and personal fees from BMS, Leo Pharma, Bayer, Pfizer, Servier, and Sanofi. A.S., L.K.H., and R.W. do not have any conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

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