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REVIEW ARTICLE

# Risk factors and predictors for venous thromboembolism in people with ischemic stroke: A systematic review

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## Abstract

Identification of individuals with ischemic stroke at particularly high risk of venous thromboembolism (VTE) is crucial for targeted thromboprophylaxis. To guide clinical decision-making and development of risk prediction models, increased knowledge on risk factors and biomarkers is needed. Therefore, we set out to identify risk factors and predictors for VTE in people with ischemic stroke by conducting a systematic review of the literature. Medline and Embase were searched from January 1990 and onwards. Studies investigating demographic, clinical, and/or laboratory factors for stroke-related VTE were considered. Two reviewers screened all retrieved records, independently and in duplicate. Risk of bias assessments were guided by a structured framework (PROSPERO-ID: CRD42020176361). Of 4674 identified records, 26 studies were included. Twenty-six demographic, clinical, and laboratory factors associated with increased risk of stroke-related VTE after multivariable adjustments were identified. The following factors were reported by ≥2 studies: prior VTE, cancer, prestroke disability, leg weakness, increasing lesion volume of the brain infarct, infection, low Barthel Index, increasing length of hospital stay, biochemical indices of dehydration, as well as elevated levels of D-dimer, C-reactive protein, and homocysteine. The majority of the studies were of poor quality with moderate or high risk of bias. In conclusion, this systematic review informs on several potential risk factors and predictors for VTE in people with ischemic stroke. To improve risk stratification and guide development of risk prediction models, further confirmation is needed because there were few high-quality studies on each factor.

**KEYWORDS**
ischemic stroke, pulmonary embolism, risk factors, venous thromboembolism, venous thrombosis

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## 1 | BACKGROUND

Ischemic stroke is among the leading causes of death and disability worldwide.[1] Stroke recovery can be complicated by the development of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).[2–5] The risk of VTE is highest in the acute phase and the initial 3 months following an acute stroke event and declines rapidly thereafter.[3,5] Although symptomatic PE may occur in only 1% of stroke survivors during the first 2 to 4 weeks after the event,[2,4,6,7] PE is an important cause of avoidable death, accounting for up to 30% of deaths after acute stroke.[4,8,9] Moreover, development of stroke-related VTE has been associated with greater disability at 6 months after stroke,[10] and lower survival at 30 days and even at 1 year after the stroke event.[7]

Decisions on initiation and duration of pharmacological thromboprophylaxis in patients with ischemic stroke is a long-standing clinical dilemma, as the benefits of reducing the VTE risk may be offset by bleeding complications.[11,12] Several guidelines recommend prophylactic anticoagulation with low molecular weight heparin or unfractionated heparin only in selected individuals where the risk of VTE is particularly high and the risk of bleeding complications is low.[13–15] Currently, no reliable clinical algorithm to identify ischemic stroke patients at high VTE risk exists.

Data on prediction of stroke-related VTE are scarce, and prediction models based on clinical factors alone discriminate poorly between individuals at high and low risk of VTE.[16] Summarizing current literature on clinical risk factors and biomarkers for stroke-related VTE may identify knowledge gaps and guide future research and development of successful risk prediction models. Therefore, we performed a systematic review of the available literature on risk factors and predictors for VTE in people with ischemic stroke.

## 2 | METHODS

This systematic review was conducted and reported in accordance with PRISMA 2020 (Preferred Reporting Items for Systematic Review and Meta-analyses)[17] and COSMOS-E (Conducting Systematic Reviews and Meta-analyses of Observational Studies of Etiology)[18] recommendations. The prespecified study protocol was published in the PROSPERO database in July 2020 (ID: CRD42020176361, available at https://www.crd.york.ac.uk/prospero).

### 2.1 | Data sources and search strategy

A systematic literature search of Medline and Embase was conducted in February 2020. The search strategy applied in each database was composed of a combination of subject heading terms and free text words related to ischemic stroke and VTE. We did not limit the literature search to specific exposures, thus enabling the search strategy to capture all potential demographic, clinical, and laboratory factors associated with increased risk of stroke-related VTE. We did not prespecify any restrictions regarding minimum or maximum length of follow-up after the ischemic stroke event. The search was limited to records published from the first of January 1990 and onwards because of the extensive introduction of thromboprophylaxis with LMHW in the clinics during the 1990s.[19] In addition, the search was restricted to studies on humans, published in the English language. In Embase, an additional limitation on publication type was applied to exclude conference abstracts from the search, and the focus function was applied on subject heading terms to limit the number of records retrieved. The detailed search strategies for Medline and Embase can be found in Tables S1 and S2. The electronic searches were supplemented by a manual search of reference lists of all included studies and relevant review papers identified through the original search.

### 2.2 | Study selection

Two reviewers (B.G.T. and V.M.M.) screened titles and abstracts of all retrieved records, and subsequently, full-text articles, independently and in duplicate. A third reviewer (S.K.B.) resolved discrepancies when necessary. To aid the screening process, the reviewers used a standardized, prepiloted screening form.

We included studies that enrolled adults (≥18 years) with objectively confirmed ischemic stroke (regardless of being incident cases). Studies compromising individuals with both ischemic and hemorrhagic stroke were included as long as the majority had ischemic stroke (i.e., >50%). Studies were included regardless of clinical setting (i.e., hospital or rehabilitation center) or length of follow-up after the ischemic stroke event. We excluded studies restricted to selected subgroups of ischemic stroke (e.g., cryptogenic stroke, stroke, concurrent cancer) because such subgroups do not reflect the general population of people with ischemic stroke.

To be included, studies had to investigate demographic, clinical, and/or laboratory factors for the risk of VTE and report asymptomatic or symptomatic DVT of the lower limbs and/or fatal or nonfatal PE as predefined outcomes (regardless of being incident cases). All outcomes had to be objectively confirmed by radiological procedures or autopsy.

Only full-text articles were assessed for eligibility. Cross-sectional studies, case series, case reports, and review articles were excluded. If more than one record reported on the same study population, we included both studies as long as the exposure(s) and/or outcome(s) under investigation were different. In case of doubt of a study's eligibility for the review, we attempted to contact the corresponding author for clarification.

### 2.3 | Data extraction

Using a standardized, prepiloted form, data from the included studies were extracted by B.G.T. and reviewed by V.M.M. The following data were extracted: (1) study setting (e.g., country,

year of publication, clinical setting, number of centers), (2) study design including length of follow-up, (3) study population characteristics (e.g., sample size, age, sex, stroke type), (4) study outcome (DVT and/or PE), (5) exposure(s) of interest (e.g., definition, measurement method, number of exposed participants), (6) measures of association (e.g., relative risk estimates with confidence intervals).

### 2.4 | Assessment of risk of bias in individual studies

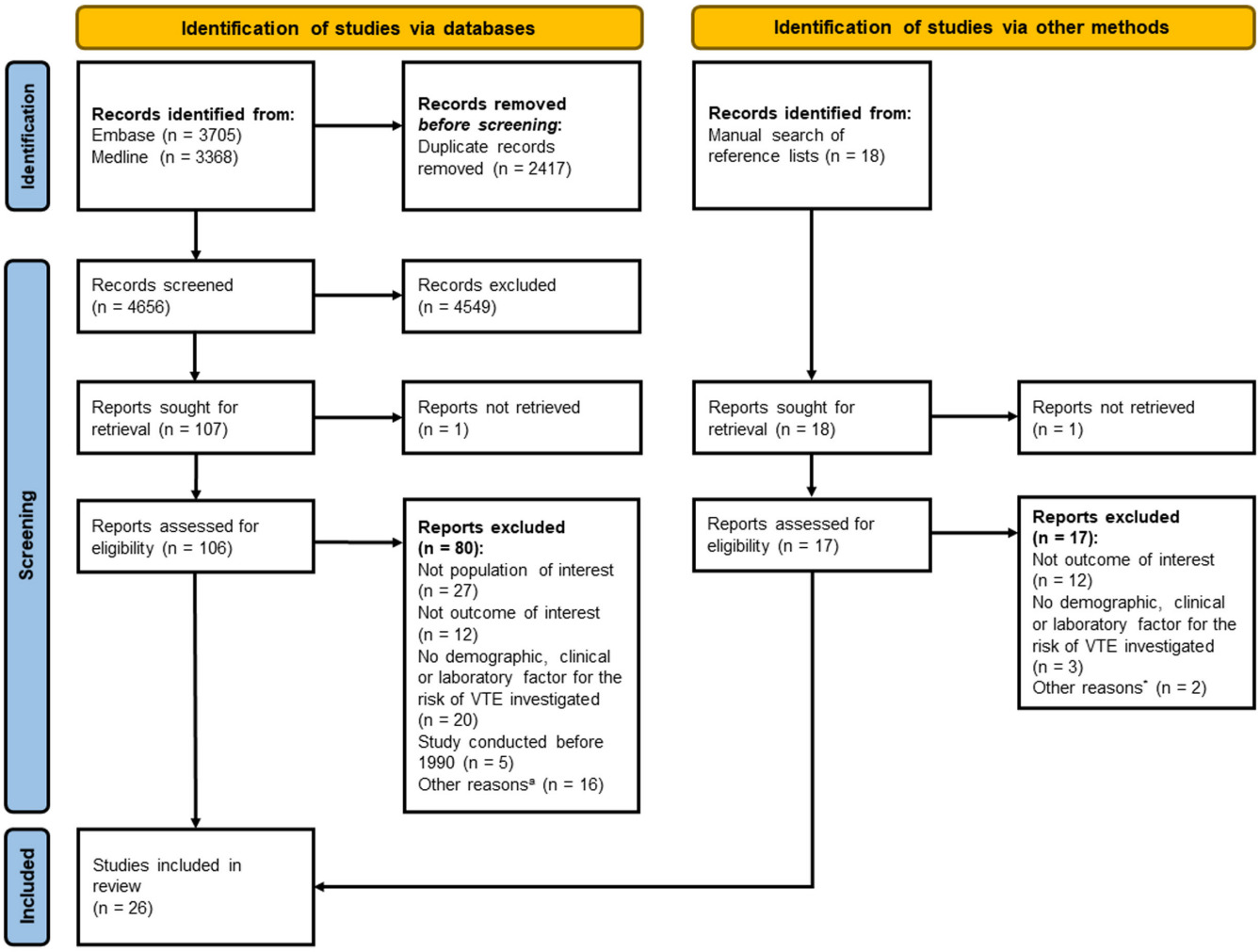
We assessed the risk of bias in each individual study by using the Quality in Prognosis Studies tool, which consists of six bias domains to be considered: participation, attrition, exposure measurement, outcome measurement, confounding measurement and account, and statistical analysis and reporting.[20] Judgments were made with consensus among two reviewers (B.G.T. and V.M.M.), with involvement of a third reviewer (S.K.B.) when necessary.

### 2.5 | Data synthesis

We prespecified that only a qualitative synthesis would be carried out in case of insufficient data on each risk factor and/or substantial clinical and methodological heterogeneity across the included studies. For a qualitative synthesis, characteristics, results, and risk of bias of the included studies were presented in tabular and narrative formats. For risk factors and predictors associated with increased VTE risk in multivariable models in two or more studies, an overview of the range of the reported relative risks (RR) was provided.

## 3 | RESULTS

Our systematic search of electronic databases and manual review of reference lists identified in total 4674 nonduplicate records. After title and abstract screening, we included 123 studies for full-text assessment (see Figure 1 for PRISMA flowchart). Twenty-six




*Other reasons (n = 18): No objective confirmation of stroke and/or VTE diagnosis, or missing information on how the diagnosis was objectively confirmed (n = 8), diagnostic study aim (n = 4), not full-text article (n = 3), full-text article not available in English (n = 2), and duplicate population (n = 1).

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart

studies met all eligibility criteria and were therefore included in the review.

### 3.1 | Study characteristics

Characteristics of the included studies are reported in Table 1. All studies were cohort studies, of which 5[7,16,21–23] were multicenter. The studies were conducted in China ($n = 9$),[21–29] United States ($n = 5$),[30–34] United Kingdom ($n = 4$),[35–38] Poland ($n = 2$),[39,40] Canada ($n = 1$),[7] Japan ($n = 1$),[41] Korea ($n = 1$),[42] Norway ($n = 1$),[43] and Singapore ($n = 1$),[10] and in an international multicenter setting ($n = 1$).[16]

Twenty-one studies had a study population consisting of ≥80% ischemic stroke patients. In the remaining five studies,[23,24,31,33,41] the proportion with ischemic stroke ranged from 64% to 75%. Stroke severity in the study populations varied because of heterogeneity in eligibility criteria and study design. Additionally, the studies were highly heterogenous in their reporting and use of pharmacological thromboprophylaxis.

Time from stroke onset to study inclusion ranged from 48 h to 30 days in the in-hospital studies[7,10,16,21–27,29,30,34–43] ($n = 22$). In the rehabilitation center-based studies[28,31–33] ($n = 4$), participants were included if the stroke event occurred within the prior 30–90 days before admission to rehabilitation. VTE assessments were either carried out via a systematic screening program[10,16,22,23,25–29,32,35–41] ($n = 17$) or based on clinical suspicion during stroke hospitalization or rehabilitation[7,21,24,30,31,33,34,42,43] ($n = 9$). Sixteen studies[10,16,22–29,32,35,37,39–41] reported on DVT as an outcome, whereas one study[7] reported on PE and nine studies[21,30,31,33,34,36,38,42,43] reported on VTE.

In the majority of the included studies ($n = 15$), demographic, clinical, and laboratory factors were investigated as potential risk factors or predictors for VTE. Nine studies[7,10,16,21,24,31,33,34,43] investigated only demographic and clinical factors and one study[30] investigated only laboratory factors. Most studies investigated the relationship between risk factors/predictors and VTE in multivariable models. However, six studies[10,30–32,34,37] only reported results from bivariable analyses (i.e., $t$ test/$\chi^2$ analyses).

### 3.2 | Risk of bias assessment

All studies were considered to have either moderate ($n = 13$) or high ($n = 13$) overall risk of bias. Summary assessments for risk of bias are shown in Figure 2, and detailed judgments for each study are provided in Figure S1. Twenty-four of the 26 included studies had unclear descriptions of the inclusion process and follow-up period (e.g., not reporting number of initially eligible study subjects, reasons for exclusions, number of individuals included in final analyses). Most studies had clear descriptions of exposure and outcome assessments. However, five studies[21,23,25,27,30] did not report the timing and/or method of the exposure measurement. Also, two studies[21,25] did not report the timing of the VTE assessment adequately, and one study[31] did not assess VTE with the same method in all participants. Twenty-three studies[7,10,21,23–25,27–30,32–44] were considered to have moderate or high risk of bias in the domains concerning confounding, statistical analysis and reporting of results, mainly because of unclear descriptions of the model building process and inadequate reporting of results.

### 3.3 | Risk factors and predictors for VTE in people with ischemic stroke reported by two or more studies

Sixteen demographic, clinical, and laboratory factors were reported to be associated with increased VTE risk in multivariable models in two or more studies. In light of few studies on each factor, as well as high clinical and methodological heterogeneity across the included studies, we did not use statistical techniques to combine and summarize the results of multiple studies on a risk factor/predictor for VTE. An overview of these factors and the corresponding range of the reported RRs are shown in Table 2 and described in the following paragraphs (with RR ranges in brackets). The main results of each individual study are reported in detail in Table S3.

#### 3.3.1 | Demographics

Eight studies[22–26,28,29,36] reported an association between advancing age and VTE (RR per 1-year increase: 1.03–1.11, RR for age ≥60 to 70 years: 1.8–4.0), whereas three[27,40,41] reported no association. Three studies[22,26,41] found an association between female sex and VTE (RR: 1.7–5.0), whereas three[27,28,40] reported no association.

#### 3.3.2 | Clinical factors

Both previous and current medical illnesses were reported to be associated with an increased VTE risk. All three studies[7,16,29] investigating a previous history of VTE and the risk of VTE after stroke reported an association (RR: 1.1–3.7). Three studies[7,22,26] found an association between cancer and VTE (RR: 3.3–5.2), whereas one[38] did not. Two studies[16,39] investigated prestroke disability (defined as "prestroke dependency in activities of daily living" and "prestroke disability") and the risk of VTE, and both found an association (RR: 2.9–3.6). Two studies[26,29] reported an association between atrial fibrillation and VTE (RR: 1.3–1.9), whereas 5[21,22,27,36,40] reported no association.

Several measures reflecting stroke severity were found to be associated with increased VTE risk. Two studies[25,29] investigated increasing lesion volume of the brain infarct (assessed by diffusion-weighted magnetic resonance imaging) and the risk of VTE, and both reported an association (RR per 1-ml increase: 1.02–1.14). Four studies[24,25,27,29] reported an association between VTE and an increasing/increased National Institutes of Health Stroke Scale (NIHSS) score (RR per 1-unit increase: 1.1–1.3, RR for NIHSS score >5: 1.1), whereas four

**TABLE 1** Characteristics of included studies

| First author, publication year, country | Timeframe | Setting (number of centers) | Population | Exposure assessment | VTE assessment and length of follow-up/hospital stay | VTE events |
|---|---|---|---|---|---|---|
| In-hospital screening studies | | | | | | |
| Dennis et al,[16] 2011, CLOTS Trials Collaboration[73,74] | 2001–2009 | Hospital (multicenter) | 1242 stroke patients (85% ischemic), age 76 (68–82) years, 50% men | Demographic and clinical factors | Screening by CUS at days 7–10 and 25–30 after randomization in the CLOTS Trials | 122 DVT patients with proximal DVT |
| De Silva et al,[10] 2006, Singapore | 2002 | Hospital, neurology department (single center) | 105 stroke patients (100% ischemic) | Demographic and clinical factors | Screening by CUS at days 7–10 after stroke | 31 DVT patients (26% proximal), 26% men, age 74 years (IQR NR) |
| Kuwashiro et al,[41] 2012, Japan | 2004–2006 | Hospital, stroke unit (single center) | 133 stroke patients (75% ischemic), age 72 ± 10 years, 50% men | Demographic and clinical factors<br>Laboratory factors: routine laboratory tests, global coagulation tests, D-dimer, thrombin-antithrombin complex | Screening by CUS at day 7 (4–15) after stroke | 61 DVT patients, age 73 ± 10 years, 41% men |
| Liu et al,[22] 2014, China | 2007 | Hospital (multicenter) | 575 stroke patients (80% ischemic), 63% men, 60% of the included were ≥65 years old | Demographic and clinical factors<br>Laboratory factors: routine laboratory tests | Screening by CUS 14 ± 3 days after stroke | 76 DVT patients |
| Bembenek et al,[39,40b] 2011 and 2012, Poland | 2007–2009 | Hospital, neurology department (single center) | 323 stroke patients[39] (93% ischemic), age 75 (64–82) years, 49% men.<br>Of the 323 stroke patients, 299 were included in a study on "early stroke-related DVT,"[40] see VTE assessment and VTE events | Demographic and clinical factors<br>Laboratory factors: CRP, fibrinogen | Screening by CUS at day 3 (2–5) after stroke,[39,40] then at day 9 (8–9) if possible[40] (to identify patients in whom DVT occurred between the first and second ultrasound examination) | 28 DVT patients[39] (21% proximal), 76 (69–87) years, 29% men.<br>Of the 28 DVT patients, 9 developed DVT after the first ultrasound examination[40] |
| Yi et al,[23] 2012, China | 2009–2010 | Hospital (multicenter) | 1380 stroke patients (70% ischemic), age 70 ± 12 years, age range 45–92, 64% men | Demographic and clinical factors<br>Laboratory factors: D-dimer, fibrinogen | Screening by CUS at days 10–14 after stroke | 62 DVT patients (15% had accompanying PE) and 11 PE patients |
| Balogun et al,[35,53a] 2016, UK | 2009–2011 | Hospital (single center) | 92 stroke patients (90% ischemic), 48% men | Demographic and clinical factors<br>Laboratory factors: D-dimer, thrombin generation, fibrinogen | Screening by CUS at day 9 (7–11) after stroke | 18 DVT patients (33% proximal), age 70 ± 13 years, 50% men |
| Kong et al,[25] 2016, China | 2013–2014 | Hospital (single center) | 255 stroke patients (100% ischemic), age (55–69) years, 51% men | Demographic and clinical factors<br>Laboratory factors: D-dimer, hs-CRP, homocysteine | Screening by CUS (timing of screening and length of follow-up NR) | 56 patients with proximal DVT |

(Continues)

TABLE 1 (Continued)

| First author, publication year, country | Timeframe | Setting (number of centers) | Population | Exposure assessment | VTE assessment and length of follow-up/hospital stay | VTE events |
|---|---|---|---|---|---|---|
| Yin et al,[29] 2016, China | 2013–2014 | Hospital (single center) | 232 stroke patients (100% ischemic), age 59 (52–71) years, 50% men | Demographic and clinical factors<br>Laboratory factors: global coagulation tests, fibrinogen, D-dimer, CRP, homocysteine, lipoprotein (a) | Screening by CUS at day 15 after stroke | 44 patients with proximal DVT |
| Li et al,[26] 2017, China | 2016 | Hospital, neurology department (single center) | 450 stroke patients (100% ischemic), age 70 ± 12 years, 60% men | Demographic and clinical factors<br>Laboratory factors: routine laboratory tests, D-dimer, homocysteine | Screening by CUS 10 ± 2 days after stroke | 98 patients with isolated distal DVT |
| Wang et al,[27] 2019, China | 2017–2018 | Hospital (single center) | 452 stroke patients (85% ischemic stroke), age 64 ± 14 years, 69% men | Demographic and clinical factors<br>Laboratory factors: routine tests, D-dimer | Screening by CUS within the first 7 days after stroke admission, and every 7 days during the next 14 days.<br>LOS: 15 (10–22) days in DVT+, 9 (7–12) days in DVT− | 52 patients developed DVT (mainly distal) within 21 days after hospital admission, age 71 (61–79) years, 58% men |
| Kelly et al,[36,38c] 2004, UK | NR | Hospital (single center) | 102 stroke patients (100% ischemic), age 70 ± 12 years, 46% men | Demographic and clinical factors[36,38]<br>Laboratory factors: urea, osmolality, serum urea/creatinine ratio[36] | Screening by MRDTI at days 7–14 and 21–28 (where possible) after stroke.<br>Follow-up: 21 ± 6 days | 41 VTE patients (44% proximal DVT) |
| Kelly et al,[37c] 2004, UK | NR | Hospital (single center) | 54 severe stroke patients (100% ischemic) | Demographic and clinical factors<br>Laboratory factors: D-dimer | Screening by MRDTI at days 7–14 and 21–28 (where possible) after stroke.<br>Follow-up: 21 ± 6 days | 16 patients with proximal DVT |
| In-hospital clinical follow-up studies | | | | | | |
| Pongmoragot et al,[7] 2013, Canada | 2003–2008 | Hospital, stroke unit (multicenter) | 11 287 stroke patients (100% ischemic), 52% men | Demographic and clinical factors | Patients with clinically suspected PE underwent CTPA.<br>Follow-up: up to 30 days after stroke admission | 89 PE patients, age range 60–79 years, 52% men |
| Novotny et al,[43] 2019, Norway | 2006–2017 | Hospital, stroke unit (single center) | 3343 stroke patients (100% ischemic), 66% men, age among patients with stroke in multiple or single arterial territories: 75 (64–82) and 71 (59–81) years, respectively | Clinical factors | Patients with clinically suspected VTE underwent imaging methods.<br>Follow-up/LOS NR | 8 DVT patients and 14 PE patients |

TABLE 1 (Continued)

| First author, publication year, country | Timeframe | Setting (number of centers) | Population | Exposure assessment | VTE assessment and length of follow-up/hospital stay | VTE events |
|---|---|---|---|---|---|---|
| Ji et al,[21] 2013, China | 2007–2008 | Hospital (multicenter) | 14 702 stroke patients (100% ischemic) | Clinical factors | Patients with clinically suspected VTE underwent imaging methods.<br>LOS: 14 (10–20) days | 63 DVT patients and 52 PE patients |
| Stecker et al,[34] 2014, USA | 2008–2012 | Hospital, stroke unit (single center) | 1333 stroke patients (100% ischemic) | Demographic and clinical factors | Patients with clinically suspected VTE underwent imaging methods.<br>Follow-up/LOS NR | 16 VTE patients |
| Gouse et al,[30] 2014, USA | 2008–2013 | Hospital, stroke unit (single center) | 298 stroke patients (100% ischemic), 49% men, age among patients with normal and elevated Factor VIII, respectively: 52 (26–85) and 54 (19–90) years | Laboratory factor: Factor VIII | Patients with clinically suspected VTE underwent imaging methods.<br>Follow-up/LOS NR | 10 VTE patients |
| Kim et al,[42] 2017, Korea | 2012–2013 | Hospital, stroke unit (single center) | 182 stroke patients (100% ischemic), 54% men | Clinical factors<br>Laboratory factors: blood urea nitrogen/creatinine ratio, osmolality | Patients with clinically suspected VTE underwent imaging methods.<br>VTE was diagnosed at a mean of 21 days (range 11–39) | 17 VTE patients, 74 ± 10 years, 35% men |
| Ji et al,[24] 2019, China | 2016 | Hospital, neurology department (single center) | 1771 stroke patients (64% ischemic), age 57 ± 13 years, 73% men | Demographic and clinical factors | Patients with clinically suspected DVT underwent CUS.<br>LOS: 14 (11–26) days | 66 DVT patients |
| Rehabilitation center-based screening studies | | | | | | |
| Pambianco et al,[32] 1995, USA | 1988–1991 | Rehabilitation center (single center) | 360 patients (100% ischemic), age 72 ± 10 years, 41% men | Demographic and clinical factors<br>Laboratory factors: routine tests, Antithrombin III, lactic dehydrogenase | Screening by CUS twice a week for 4 weeks or until discharge | 20 patients with proximal DVT |
| Wu et al,[28] 2018, China | 2015 | Hospital, rehabilitation unit (single center) | 180 patients (100% ischemic), age 65 ± 11 years, 64% men | Demographic and clinical factors<br>Laboratory factors: hematocrit, platelets, fibrinogen, vitamin D | Screening by CUS at days 14–21 after stroke, but before systematic rehabilitation.<br>Follow-up/LOS NR | 47 DVT patients (13% proximal), age 68 ± 8 years, 51% men |

(Continues)

TABLE 1 (Continued)

| First author, publication year, country | Timeframe | Setting (number of centers) | Population | Exposure assessment | VTE assessment and length of follow-up/hospital stay | VTE events |
|---|---|---|---|---|---|---|
| Rehabilitation center-based clinical follow-up studies | | | | | | |
| Roth et al,[33] 2001, USA | 1993–1997 | Rehabilitation hospital (single center) | 1029 stroke patients (71% ischemic), age 64 ± 15 years, 47% men | Clinical factors | Patients with clinically suspected VTE underwent imaging methods<br>LOS: 28 ± 14 days | 53 VTE patients (21% PE) |
| Harvey et al,[31] 2004, USA | 1994–1998 | Rehabilitation hospital (single center) | 1506 stroke patients admitted for rehabilitation (71% ischemic) | Demographic and clinical factors | Imaging was either ordered at the discretion of the patients' attending physicians or as part of a concurrent open-label research trial.[75]<br>Follow-up/LOS NR | 58 VTE patients (PE occurred in 24%), age 64 ± 15 years |

*Note*: Age and length of follow-up/hospital stay is reported as mean ± standard deviation or median (interquartile range). DVT+/DVT− indicates patients with radiological confirmed or excluded deep venous thrombosis, respectively.

Abbreviations: CLOTS trials, The Clots in Legs Or sTockings after Stroke Trials; CTPA, computed tomography pulmonary angiogram; CUS, compression ultrasound; DVT, deep venous thrombosis; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LOS, length of hospital stay; MRDTI, magnetic resonance direct thrombus imaging; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Corrigendum notice.[53]

[b,c]Overlapping study populations, but exposure(s) and/or outcome(s) under investigation are different.

[Correction added on 8 September 2022, after first online publication: Table 1 has been reformatted in this version.]

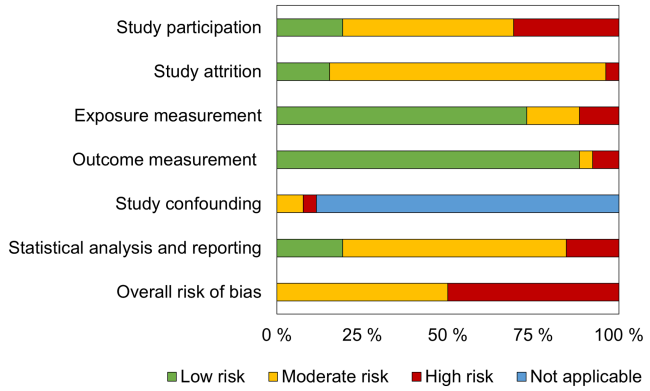



**FIGURE 2** Risk of bias graph: review author's judgments on each risk of bias domain in the Quality In Prognosis Studies tool, presented as percentages across all included studies.

studies[35,40–42] did not. Leg weakness, defined as a NIHSS score of lower limbs ≥2 to 3, was reported to be associated with VTE in three studies[22,23,28] (RR: 1.9–4.6), whereas one study[26] found no association. Two studies[23,38] reported an association between a low Barthel Index (BI) (defined as BI ≤9 and "low BI") and VTE (RR: 3.0–8.3), whereas one[35] did not. Infection (defined as "pneumonia," "acute infection" [including pulmonary, urinary, or skin infection and septicemia], and "infection" [including pulmonary and urinary tract infection]) was associated with increased VTE risk in two studies[21,26] (RR: 2.2–4.3), whereas one study[22] reported no association. Two studies[24,27] investigated an increasing length of hospital stay and the risk of VTE, and both reported an association (RR per 1-day increase: 1.06–1.07).

### 3.3.3 | Laboratory factors

Six studies[23,25,27,29,35,41] reported an association between elevated levels of D-dimer and VTE (RR: 1.1–3.5), whereas one[26] did not find an association. The range includes reported RRs for D-dimer analyzed both as a continuous and categorical variable because of inadequate reporting in several studies. Three studies[25,29,40] investigated the association between elevated baseline levels of C-reactive protein (CRP) and the risk of VTE, and all of them reported an association (RR per 1-mg/dL increase: 1.35–1.44, RR for CRP >10 mg/dl: 10.1). Two studies[25,29] found an association between homocysteine and VTE (RR per 1-unit increase: 1.14–1.15). Biochemical indices of dehydration measured at baseline (blood urea nitrogen/creatinine ratio >15) and 9 days poststroke (urea/creatinine ratio >80, urea>7.5 mmol/L and osmolality ≥297 mOsm/kg) were reported to be associated with VTE in two studies[36,42] (RR: 2.8–8.8).

## 3.4 | Risk factors and predictors for VTE in people with ischemic stroke reported by one study only

Ten clinical and laboratory factors were found to be associated with VTE in multivariable models in one study only, and the reported RRs for these factors are provided in Table 3, along with the number of studies reporting null findings. The main results of each individual study are reported in detail in Table S3.

Some factors associated with increased VTE risk were only investigated in one study, including ischemic stroke in multiple arterial territories,[43] poststroke hydrocephalus,[21] inability to lift arms off bed,[16] varicose veins in lower limbs,[28] vitamin D deficiency,[28] as well as elevated levels of low-density lipoprotein[26] and lipoprotein (a).[29] Other factors, including overweight/obesity,[22] being bedridden,[23] and elevated levels of blood glucose[27] were investigated in two to three studies, but only reported to be significantly associated with VTE in one of the studies.

# 4 | DISCUSSION

## 4.1 | Summary of main findings

In this systematic review, we identified in total 26 demographic, clinical, and laboratory factors associated with increased VTE risk in people with ischemic stroke after multivariable adjustments, of which 16 were reported by two or more studies. A previous history of VTE, cancer, prestroke disability, leg weakness, increasing lesion volume of the brain infarct, increasing length of hospital stay, infection, low BI, biochemical indices of dehydration as well as elevated levels of D-dimer, CRP, and homocysteine were associated with increased VTE risk in two or more studies, with 0–1 studies reporting null findings. For other factors, the results were inconsistent, and further investigation of these factors is therefore needed. Unfortunately, there were few high-quality studies on each factor, and all included studies were considered to have either moderate or high overall risk of bias.

# 5 | STRENGTHS AND LIMITATIONS

The systematic, thorough, and transparent methods are the major strengths of this study, including a comprehensive search strategy, duplicate and independent screening of records, data extraction using a standardized, prepiloted form, and risk of bias assessments guided by the Quality in Prognosis Studies tool. The application of the focus function in Embase could be a potential limitation to the completeness of our literature search. However, we tried to account for this by including a wide variety of free text words in the search strategy, and we also checked that our final search could identify 22 papers on ischemic stroke and VTE that we were aware of before the literature search was conducted. Also, we restricted the search to records published in English because of time and resource limitations. However, we believe it is unlikely that this restriction led to the omission of any major articles on this topic.

Limitations related to the included studies were heterogeneity in eligibility criteria, study design, outcome assessment (screening versus clinical follow-up studies), and study setting (acute stroke versus stroke rehabilitation), in addition to inconsistency in definitions and measurement methods (including timing of measurements)

**TABLE 2** Risk factors and predictors associated with increased risk of venous thromboembolism (VTE) in multivariable models in two or more studies

| Risk factors and predictors | No. of studies with positive findings | Ranges of reported relative risks in studies with positive findings (when applicable) | No. of studies with null findings |
|---|---|---|---|
| Demographic and clinical factors | | | |
| Advancing age | 8[22–26,28,29,36] | 1.03–1.11, per 1-year increase<br>1.8–4.0, for age ≥60 to 70 years | 3[27,40,41] |
| Previous history of VTE | 3[7,16,29] | 1.1–3.7 | 0 |
| Cancer | 3[7,22,26] | 3.3–5.2 | 1[38] |
| Leg weakness[a] | 3[22,23,28b] | 1.9–4.6 | 1[26] |
| Prestroke disability[c] | 2[16,39] | 2.9–3.6 | 0 |
| Increasing lesion volume of the brain infarct[d] | 2[25,29] | 1.02–1.14, per 1 ml-increase | 0 |
| Increasing length of hospital stay | 2[24,27] | 1.06–1.07, per 1-day increase | 0 |
| Infection[e] | 2[21,26] | 2.2–4.3 | 1[22] |
| Low Barthel Index[f] | 2[23,38] | 3.0–8.3 | 1[35] |
| Increasing/increased NIHSS score | 4[24,25,27,29] | 1.1–1.3, per 1-unit increase<br>1.1, for NIHSS score >5 | 4[35,40–42] |
| Female | 3[22,26,41] | 1.7–5.0 | 3[27,28,40] |
| Atrial fibrillation | 2[26,29] | 1.3–1.9 | 5[21,22,27,36,40] |
| Laboratory factors | | | |
| Elevated D-dimer level | 6[23,25,27,29,35,41] | 1.1–3.5[g] | 1[26] |
| Elevated CRP level | 3[25,29,40] | 1.35–1.44, per 1 mg/dl increase<br>10.1, for CRP >10 mg/dl | 0 |
| Elevated homocysteine level | 2[25,29] | 1.14–1.15, per 1-unit increase | 0 |
| Biochemical indices of dehydration | 2[36,42] | Blood urea nitrogen/creatinine ratio >15 at baseline: 8.8<br>serum urea/creatinine ratio >80, day 9 poststroke: 3.4<br>Osmolality >297 mOsm/kg, day 9 poststroke: 4.7<br>urea >7.5 mmol/L, day 9 poststroke: 2.8 | 0 |

Abbreviations: CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; VTE, venous thromboembolism.

[a]Defined as NIHSS score of lower limbs ≥2[22,28] and ≥3.[23,26]

[b]One study[28] was conducted in a rehabilitation center-setting.

[c]Defined as "prestroke dependency in activities of daily living"[16] and "prestroke disability" (modified Rankin Scale score of 3–5).[39]

[d]Assessed by diffusion-weighted magnetic resonance imaging in both studies.[25,29]

[e]Defined as "pneumonia,"[21] "acute infection" (including pulmonary infection, urinary infection, skin infection, and septicemia),[26] and "infection" (including pneumonia and urinary tract infection).[22]

[f]Defined as Barthel Index ≤9[38] and "low Barthel Index."[23]

[g]Because of large heterogeneity across included studies in how D-dimer was analyzed and reported, the relative risk (RR) range includes RRs obtained from analyses of D-dimer modeled both as a categorical and a continuous variable.

of the investigated factors. Several of the studies were small and had limited statistical power. Further, most studies were screening studies reporting only DVT as an outcome, and thus did not separate between asymptomatic and symptomatic events, which may influence the clinical relevance of the observed associations. Also, compression ultrasound used to screen for DVT in asymptomatic individuals has less diagnostic accuracy than in symptomatic ones, and some asymptomatic DVT episodes could therefore have been missed. Finally, most studies were considered to have moderate or high risk of bias in the domains concerning confounding, statistical analysis and reporting of results.

## 5.1 | Clinical factors

The included studies showed somewhat inconsistent results for advancing age and sex as risk factors for stroke-related VTE. Because the incidence of both stroke and VTE varies across age in men and women,[45–50] the observed inconsistency may be partly explained by differences in age and sex distributions in the study populations, and differences in the statistical modeling of age. Several factors reflecting stroke severity were associated with increased VTE risk in the included studies, although the results were conflicting for some of these. Differences in

**TABLE 3** Risk factors and predictors associated with increased risk of venous thromboembolism (VTE) in multivariable models in one study

| Risk factors and predictors | Reported relative risks | No. of studies with null findings |
|---|---|---|
| Clinical factors | | |
| Ischemic stroke in multiple arterial territories[43] | 6.6 | 0 |
| Poststroke hydrocephalus[21] | 4.5 | 0 |
| Unable to lift arms off bed[16] | 1.9 | 0 |
| Varicose veins in lower limbs[a28] | 2.8 | 0 |
| Overweight/obesity (BMI ≥25 kg/m$^2$)[22] | 2.0 | 1[b,c35,53] |
| Bedridden[d23] | 2.1 | 2[27,41] |
| Laboratory factors | | |
| Elevated Lp(a) level (≥300 mg/L)[29] | 12.1 | 0 |
| Vitamin D deficiency (25-hydroxyvitamin D ≤20 ng/ml)[28a] | 4.7 | 0 |
| Elevated LDL level (≥2.6 mmol/L)[26] | 1.9 | 0 |
| Elevated glucose level[e27] | 1.2 | 1[22] |

Abbreviations: BMI, body mass index; Lp(a), lipoprotein (a); LDL, low-density lipoprotein.

[a]The study was conducted in a rehabilitation-center setting.

[b]A 3-fold increased risk for VTE was reported (per 10-unit increase in BMI), but the association did not retain statistical significance in the multivariable model.

[c]Corrigendum notice.[53]

[d]Defined as being "bedridden,"[23] being "immobilized,"[27] and "bedridden period" (days).[41]

[e]Unit and cutoff value not reported.

severity definitions, as well as selected study populations (i.e., restricted to either low- or high-severity stroke), may partially explain this inconsistency. Future studies should assess the predictive performance of stroke severity measures in unselected populations of people with ischemic stroke. Even though obesity is prevalent in people with ischemic stroke and a major risk factor for VTE in the general population,[51,52] only two of the included studies investigated the role of overweight and obesity in stroke-related VTE. Liu et al[22] reported a 2-fold increased VTE risk in individuals with stroke and a body mass index ≥25 kg/m$^2$, whereas Balogun et al[35,3] reported a 3-fold increased VTE risk per 10-unit increase in body mass index ($p$ = .16). Future studies should investigate the risk according to commonly used clinical cutoffs of obesity to assess its role in the context of stroke-related VTE. Infection is a common complication of acute stroke,[54–56] and infection was associated with a 2- to 4-fold increased VTE risk.[21,26] These results are supported by a population-based case-crossover study reporting that the association between stroke and VTE was largely mediated by infection and immobilization.[57]

### 5.2 | Laboratory factors

An acute stroke event normally triggers an acute inflammatory response.[58–62] In the included studies, elevated levels of CRP and D-dimer were associated with increased VTE risk. However, because differences in statistical modeling, the optimal cut-off levels of CRP and D-dimer for discriminating between individuals at high and low risk of stroke-related VTE remains unclear, and further investigations of the predictive capability of these biomarkers in ischemic stroke are therefore warranted.

### 5.3 | Genetic factors

VTE is a disease with a strong hereditary component,[63–68] and some recognized prothrombotic genotypes are also associated with increased risk of stroke.[69–71] None of the included studies evaluated the association between a genetic factor and stroke-related VTE. However, a population-based case-cohort study investigating the combined effect of prothrombotic genotypes and ischemic stroke using a genetic risk score, suggested that genetic risk factors may be important in VTE development following an acute ischemic stroke event.[72] Future studies should investigate the predictive capability of prothrombotic genotypes on stroke-related VTE risk.

### 5.4 | Risk prediction models for VTE in ischemic stroke

Currently, no algorithm to predict VTE in people with ischemic stroke is implemented in clinical practice. Among the studies included in the review, five[16,22,24,26,27] reported multivariable models for prediction of DVT along with measures of discriminatory powers (i.e., area under the receiver operating curve). All of these studies were considered to have several methodological concerns and a moderate or high overall risk of bias. Moreover, these models lack external and robust validation in new, independent cohorts, and cannot be considered ready for use in clinical practice. The risk factors and predictors found to be associated with increased VTE risk in this review, should be considered in any development of new prediction models, or in the reevaluation of existing ones.

## 6 | CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH

This systematic review summarizes current knowledge on risk factors and predictors for VTE in people with ischemic stroke. Most

of the identified factors, including the biomarkers, can easily be obtained in clinical practice, which is beneficial in the context of risk prediction model development and implementation. However, because there were few high-quality studies on each factor, future research should also focus on further identification and confirmation of clinical risk factors and biomarkers that can improve patient stratification and guide the development of successful risk prediction models.

## AUTHOR CONTRIBUTIONS

Conception and design of the study: B.G.T., V.M.M., J.B.H., S.K.B.; literature search: B.G.T., V.M.M.; screening and inclusion: B.G.T., V.M.M., S.K.B.; data extraction: B.G.T., V.M.M.; interpretation of results: B.G.T., V.M.M., J.B.H., S.K.B.; manuscript draft: B.G.T., S.K.B.; critical revision of manuscript: S.K.B., V.M.M., J.B.H. All authors approved the submitted version of the manuscript.

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## CONFLICT OF INTEREST

There are no conflicts of interest reported by the authors.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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