Research Article

Sickle Cell Disease and Risk of Venous Thromboembolism: A Systematic Review

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Abstract

Background: Sickle cell disease (SCD) is associated with a prothrombotic state, but clinical venous thromboembolism (VTE) estimates differ markedly between population-based, inpatient, paediatric, maternity and referral-care settings.
Objective: To critically synthesise evidence on deep vein thrombosis (DVT), pulmonary embolism (PE) and VTE in SCD, prioritising comparative risk and interpretable incidence; recurrence and associated clinical factors were secondary outcomes.
Methods: Primary clinical studies published between 1 January 2000 and 30 June 2025 were identified through targeted biomedical index, publisher-record and citation searching. Fifteen individually logged candidate reports were assessed; twelve original studies with clinical VTE data met the review criteria. Published denominators, effect estimates and study methods were compared narratively using PRISMA 2020 and SWiM reporting principles. Meta-analysis was not performed.
Results: Among 1,523 adolescents and adults with SCD, first-VTE incidence was 5.2 per 1,000 person-years (95% CI 3.8–6.9). A California cohort reported 696 incident cases among 6,237 patients (11.2%). Pregnancy-related VTE was recorded in 720/6,388 people with SCD (11.3%) versus 202/17,110 controls (1.2%; reported OR 10.6, 95% CI 9.1–12.5). Paediatric cohorts reported 181/10,454 (1.7%) and 12/414 (2.9%) events. Greater disease severity, central venous catheters and pregnancy were recurrently associated with VTE; recurrence and mortality also carried a substantial burden.
Conclusion: The available observational evidence indicates an important VTE burden in SCD, especially in particular adult and pregnancy populations. Interpretation depends on whether the denominator is patients, hospital admissions, person-time or patients surviving a prior event. Heterogeneous designs and incomplete ascertainment of the full literature limit the precision and generalisability of any single risk estimate.

Keywords: sickle cell disease; venous thromboembolism; pulmonary embolism; deep vein thrombosis; risk factors; pregnancy; evidence synthesis.

Introduction

Background

Sickle cell disease (SCD) comprises inherited haemoglobin disorders in which polymerisation of haemoglobin S under deoxygenated conditions promotes erythrocyte sickling, haemolysis, endothelial injury and recurrent vaso-occlusion. Beyond its established effects on the microcirculation, SCD is associated with a prothrombotic phenotype involving endothelial activation, inflammation, altered platelet function and coagulation activation. These mechanisms are plausible contributors to venous thromboembolism (VTE), but biological plausibility alone does not specify the magnitude of clinically recognised deep vein thrombosis (DVT) or pulmonary embolism (PE). A previous systematic review identified an association between SCD and VTE while also considering sickle cell trait, a distinct exposure that should not be conflated with SCD [1].

The population in which a VTE risk is measured matters as much as the numerical estimate. A national US discharge analysis found more PE-coded admissions in younger patients with SCD than among African-American patients without SCD, whereas coded DVT proportions were similar [2]. A Pennsylvania study likewise showed higher estimated population incidence of PE in SCD, but similar PE prevalence per hospital discharge after restricting to those aged 50 years or younger [3]. These apparent differences are not necessarily contradictory: people, admissions and population-at-risk years are different denominators, and acute chest syndrome or pulmonary thrombosis in situ may complicate PE diagnosis.

Longitudinal cohorts give a different view. In the Cooperative Study of Sickle Cell Disease, the rate of first VTE was 5.2 events per 1,000 person-years among individuals aged 15 years or older [4]. A large California claims cohort showed a substantial cumulative burden and more events among those with severe, frequently hospitalised SCD [5]. These studies place thrombotic disease within the course of a chronic inherited condition, but they also illustrate how severity, healthcare exposure and event ascertainment may influence measured risk.

Paediatric evidence is particularly important because children with SCD encounter different treatment exposures and a different baseline risk of thrombosis. A multicentre administrative study documented incident VTE in 1.7% of more than 10,000 children with SCD [6], while a smaller tertiary-centre cohort described a 2.9% event history and a strong relationship with central venous catheters [7]. Catheter exposure can represent a potentially modifiable clinical risk, but the effects of disease severity and treatment selection must be considered before drawing causal conclusions.

Recurrent thrombosis is another aspect of the overall burden. A follow-up analysis of California data found a five-year VTE recurrence incidence of 24.1% after an index event [8]. Tertiary-centre cohorts also implicate renal impairment, genotype, leucocytosis and clinical severity, although associations with treatment markers such as hydroxyurea may be confounded by indication [9]. Regional evidence offers useful contrasts: a Nigerian multicentre series reported VTE in 2.0% of recorded adult SCD patients [10], whereas a Saudi inpatient study recorded VTE in 3.0% of admissions, rather than 3.0% of unique patients [11].

Pregnancy introduces a clearly defined period of additional thrombotic vulnerability. A US Medicaid cohort documented a higher recorded risk of VTE during pregnancy and the first postpartum year in patients with SCD than in matched pregnant controls [12]. In women attending a US tertiary centre, a history of thrombosis was most strongly associated with increasing SCD clinical severity [13]. These findings highlight the need to separate pregnancy-related risk, lifetime event history and incidence during prospective follow-up. The present review therefore focuses on clinically interpretable comparisons and systematically distinguishes the populations, outcomes and denominators that underlie apparently dissimilar figures.

Objectives

Primary objective. To critically evaluate published observational evidence on the association between SCD and clinical VTE, including PE and DVT, prioritising between-population comparisons and directly interpretable incidence measures.

Secondary objectives. To describe VTE occurrence within defined SCD cohorts; compare patterns in adults, children, pregnancy and hospital settings; identify reported associations with genotype, hospital utilisation, disease severity, central venous catheters and laboratory or treatment variables; and summarise recurrence and mortality outcomes without conflating event, patient and admission denominators.

PECO. Population: patients with confirmed SCD (including HbSS, HbSC and S/β-thalassaemia). Exposure: SCD or defined severity/exposure factors within SCD. Comparator: patients without SCD or clinically meaningful within-SCD strata, where available. Outcomes: first VTE, DVT, PE, relevant event rates, risk ratios/odds ratios/hazard ratios and specified recurrence or mortality estimates. Studies restricted to sickle cell trait were not eligible for the SCD evidence set.

Literature Review

Earlier work approached the SCD–VTE relationship through contrasting study designs. Discharge-based epidemiology demonstrated that coded PE may occur more frequently in young patients with SCD than in patients without the disease, but also raised an unresolved diagnostic distinction between embolic disease and pulmonary thrombosis in situ. Stein and colleagues found PE recorded in 0.44% of weighted SCD discharges compared with 0.12% among African-American non-SCD discharges in patients younger than 40 years; by contrast, DVT codes were present in approximately 0.44% and 0.40%, respectively [2]. Novelli and colleagues used Pennsylvania hospital records and a smaller institutional case-control component. Their age-restricted PE discharge proportions were 0.57% with SCD and 0.60% without SCD despite increased estimated population incidence [3]. These studies cannot be understood properly if a prevalence per discharge is interpreted as a cumulative incidence per patient.

By observing persons over time, Naik and colleagues made possible an incidence estimate denominated by person-years. Among 1,523 adults and adolescents with SCD, 8,862 person-years yielded a first-VTE rate of 5.2 per 1,000 person-years, and the estimated cumulative incidence reached 11.3% by age 40. The investigators also found higher post-VTE mortality, an association that makes incident VTE clinically important beyond an isolated diagnostic label [4]. A population-based California comparison extended this work by accounting for the frequency of hospitalisation, reporting an overall 11.2% incident VTE proportion and a pronounced difference between severe SCD and matched asthma controls by age 40 [5]. Even there, hospitalisation is both a marker of clinical severity and a circumstance in which diagnostic testing and thrombosis-provoking interventions are more likely to occur.

The paediatric literature identified clinically distinct risk patterns. In a study spanning 48 paediatric hospitals, Kumar and colleagues recorded VTE in 181 of 10,454 children with SCD, and found associations with central venous lines, age, renal disease, previous stroke and indicators of hospital intensity [6]. Woods and colleagues

identified only 12 VTE events among 414 children, nine of which were associated with a central venous catheter. Despite the striking reported adjusted odds ratio for catheter exposure, the small event count and broad confidence interval argue against viewing that number as a precise universal effect [7]. The consistency of the catheter association across settings is more useful than treating the magnitude from a small retrospective centre as definitive.

A second evidence stream considers the long-term course after a first event. In an expanded California analysis, Brunson and colleagues described 877 patients with index VTE and a recurrence incidence of 13.2% at one year and 24.1% at five years; severe disease, lower-limb index DVT and acute chest syndrome/pneumonia were associated with recurrence [8]. These patients may overlap with those in the earlier California report, meaning that a simple sum of the two published denominators would double-count individuals. Recurrence is also conditional on having had a first VTE and therefore addresses a different question from first-event risk. The investigators observed bleeding as well, underscoring the balance between prevention of recurrent thrombosis and harm from anticoagulation.

Clinical and laboratory predictors have been assessed in tertiary cohorts. Srisuwananukorn and colleagues examined 1,193 patients and reported 208 patients experiencing any thrombotic event, including 288 individual VTE events across the cohort. Associations with estimated glomerular filtration rate, genotype, white blood cell count and hydroxyurea use suggested multiple interacting pathways [9]. However, medication exposure is not randomly assigned; patients receiving hydroxyurea may have more severe SCD before treatment. Without appropriate causal methods, a positive treatment association cannot be interpreted as evidence that the treatment causes VTE. Similarly, genetic and clinical associations must be interpreted with attention to multiple testing and to whether venous and arterial events were separated.

Regional estimates highlight the effect of healthcare systems and sampling. In Nigeria, a multicentre review found ten VTE cases in 509 adults with SCD, nine involving DVT; several reported clinical associations had wide confidence limits consistent with the small number of events [10]. In Saudi Arabia, Ziyadah and colleagues followed 394 unique patients through 1,054 admissions and observed 32 VTE-associated admissions. The reported 3.0% refers to admissions and therefore cannot be compared as if it were the same patient-level two-year prevalence described in Nigeria [11]. Differences in hospital prophylaxis, obstetric care, access to imaging and selection of admissions may all contribute to the contrast, but the included designs cannot isolate their individual effects.

Pregnancy-related thrombosis offers direct contemporary comparison with an unexposed population. Agarwal and colleagues evaluated 6,388 people with SCD with a recorded delivery and 17,110 pregnant controls without SCD. Venous thrombosis was recorded in 11.3% versus 1.2% during the defined pregnancy/postpartum observation period [12]. Importantly, the source description of an eight- to eleven-fold increase pertains to thromboembolism outcomes as reported and is not automatically a single adjusted VTE-specific odds ratio. In a separate women-only tertiary cohort, Light and colleagues found previous thrombosis in 25.1% of 370 women; disease severity was a stronger correlate than contraceptive exposure after adjustment [13]. One cohort measures events arising during a defined reproductive interval; the other records history in a selected clinical population. Their percentages should not be quantitatively compared as though they are interchangeable.

The 2018 review by Noubiap and colleagues already synthesised aspects of SCD, sickle cell trait and VTE [1]. A new synthesis is warranted not because a previous pooled effect should simply be repeated, but because newer cohorts clarify the roles of paediatric catheters, pregnancy, recurrence and regional variation. The present appraisal deliberately avoids combining estimates from non-exchangeable populations or denominators. Its intended contribution is a clinically organised account of the direction and credibility of associations and an explicit description of where the public evidence permits—and does not permit—a precise risk statement.

Methods

Study design and reporting

This systematic evidence synthesis used a structured, non-quantitative approach informed by PRISMA 2020 [14], SWiM reporting guidance [15], the Cochrane Handbook [16] and the JBI Manual [17]. The publication window was 1 January 2000 to 30 June 2025. Primary articles and indexed records were examined on 3 November 2026. Searches of accessible PubMed records, journal websites and the references of relevant primary and secondary publications were used for source identification; a prospective protocol was not registered. Fifteen individually identified candidate reports were logged for eligibility assessment.

The identifiable selection pathway comprised 15 candidate reports: two were excluded at record screening (one earlier systematic review and one report published after the date limit), and one case-only study without a source-population denominator was excluded after detailed eligibility assessment. Twelve primary publications were retained for the narrative evidence tables. Figure 1 reports the pathway for this individually logged set; it is not a comprehensive database-export PRISMA tally. Study screening and data abstraction were undertaken within one analytical workflow and checked against original publication records.

Eligibility criteria and sources

Eligible studies were original observational cohorts, comparative discharge studies, case-control investigations and analytical cross-sectional studies involving people with diagnosed SCD and measured clinical VTE, PE or DVT. A defined SCD cohort denominator, a relevant unexposed comparator or a longitudinal denominator was required. Paediatric, maternal, hospital-based and recurrence cohorts were retained as distinct evidence streams. Reviews, isolated sickle cell trait analyses, exclusively arterial thrombosis, isolated case reports and case-only series unable to estimate frequency or comparative risk were excluded from the core table.

Indexing concepts included “Anemia, Sickle Cell”, sickle cell disease/anaemia, HbSS, HbSC, HbS/β-thalassaemia, venous thromboembolism, pulmonary embolism and deep vein thrombosis. Candidate publications were checked against indexed citations, publisher pages and available primary articles. The concept syntax and platform-specific translations are presented in Appendix A. Neither the search date nor the available candidate set should be interpreted as proof of exhaustive coverage of all subscription databases.

Data extraction and narrative synthesis

For each included report, study setting, population, design, exposure or comparison, clinical endpoint, denominator, reported effect estimate and main limitations were extracted. Patients, admissions, events and person-years were not treated as exchangeable units. Recurrence following an index VTE, pregnancy-specific outcomes and first-event risk were handled separately. Published estimates with confidence intervals were retained when available; study samples were not summed because repeated hospital visits and overlapping cohorts preclude a valid aggregate denominator.

Results were synthesised by clinical contrast: comparative SCD versus non-SCD risk; longitudinal incidence; hospital and paediatric observations; clinical risk factors; and recurrence or mortality. Direct comparative evidence received greatest weight for the primary objective. Differences in study design, diagnostic ascertainment, risk adjustment, participant age and follow-up were examined narratively. No meta-analysis, pooled prevalence estimate, funnel plot or statistical significance vote-counting was performed.

Risk-of-bias assessment

Studies were appraised across selection, comparability/confounding, VTE ascertainment and reporting domains informed by the Newcastle–Ottawa Scale (NOS) [18], with additional attention to exposure classification and time-related bias. The risk-of-bias tables present qualitative judgements and study-specific reasons instead of unsupported aggregate NOS star scores. ROBINS-I was considered as background methodological guidance for confounding in observational comparisons, while recognising that its intervention-specific framework is not directly interchangeable with exposure-epidemiology appraisal [19]. Unreported source information was not assumed to be free of bias.

Results

Identification and selection of studies

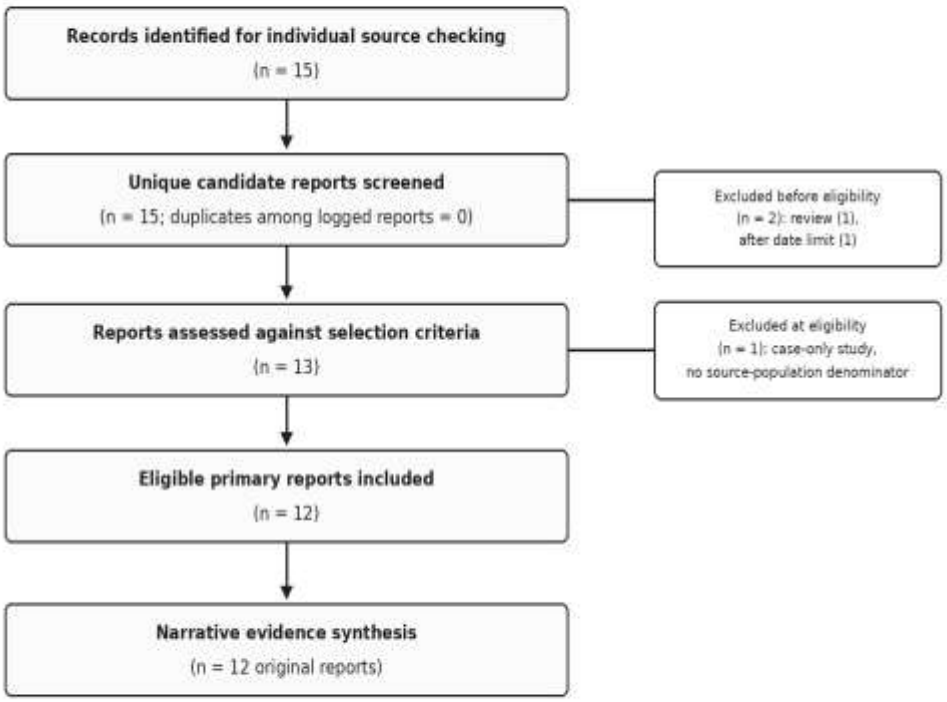
Fifteen candidate publications were individually logged during targeted identification and citation checking. Two did not proceed beyond record screening because one was a previous systematic review and the other was published after 30 June 2025. Thirteen reports were examined for eligibility, and the hospital-acquired paediatric case series without a population-at-risk denominator was excluded from risk estimation. Twelve original reports published from 2006 to 2024 form the narrative evidence set (Figure 1; Table 1). Publications came from the USA, Nigeria and Saudi Arabia and included comparative discharge studies, cohorts, pregnancy analyses and recurrence research.

Table (1): Individually logged identification and selection counts

Selection stage	n	Selection basis
Individually logged candidate reports	15	Targeted indexing, publisher and citation identification
Duplicate publications within logged set	0	Distinct publication identifiers
Records screened	15	Title, abstract and publication date
Excluded before detailed eligibility	2	Earlier systematic review (1); publication beyond cutoff (1)
Reports assessed for detailed eligibility	13	Original study eligibility and denominator
Excluded during detailed eligibility	1	Hospital-acquired paediatric VTE case-only series
Original reports included in synthesis	12	Retained for chronological evidence and appraisal

Figure 1. Study-selection pathway

PRISMA 2020-informed display of individually logged candidates



Counts refer to the 15 individually logged candidate publications, not a pooled database export.

Figure (1): Identification and selection of individually logged candidate reports

Included studies are described chronologically in Table 2. Two California analyses use related administrative data and should not be counted as independent patient cohorts; the Saudi study measures admissions rather than new unique patients; and a recurrence cohort begins with participants who have already had VTE. The evidence-map in Figure 2 makes the different clinical comparisons explicit.

Characteristics of the source-verified studies

Table (2): Chronological evidence table of included original studies

Study / setting	Design and sample	Exposure / comparator	Numerical outcomes	Interpretive context
Stein 2006 [2] USA; National Hospital Discharge Survey	Comparative discharge-based epidemiology; weighted inpatient estimates 1,581,000 weighted SCD discharges in patients <40 years; comparator 48,611,000 African-American non-SCD discharges	SCD versus African-American non-SCD discharges (<40 years)	PE: 0.44% of SCD discharges versus 0.12% of non-SCD discharges. DVT: 0.44% versus 0.40%.	Discharges, not unique persons; PE may represent in-situ pulmonary thrombosis; imaging validation NR.
Novelli 2012 [3] USA; Pennsylvania discharge data and Pittsburgh case-control sample	Discharge-level comparative epidemiology plus case-control analysis Pennsylvania discharges, 2001–2006; 14 PE cases and 28 controls in institutional case-control subset	SCD versus non-SCD PA admissions; matched hospital cases	Among discharges aged ≤50 years, PE prevalence 0.57% in SCD versus 0.60% in non-SCD; population-based PE incidence was higher in SCD.	Population incidence uses an external SCD denominator; hospitalisation-based prevalence differs from population incidence.
Naik 2014 [4] USA; Cooperative Study of Sickle Cell Disease	Longitudinal retrospective cohort analysis 1,523 individuals with SCD, age ≥15 years; 8,862 person-years	First VTE and Hb genotype; no external comparator	First VTE: 5.2/1,000 person-years (95% CI 3.8–6.9); cumulative incidence by age 40: 11.3% (95% CI 8.3–15.3); mortality aHR 2.32 (1.20–4.46).	Historical cohort and code-based event ascertainment; not directly comparable to inpatient discharge proportions.
Brunson 2017 [5] USA; California administrative cohort	Population-based matched comparative cohort 6,237 individuals with SCD; 696 with incident VTE	SCD versus matched asthma controls; severity within SCD	Incident VTE 11.2%. By age 40: 17.1% in severe SCD versus 8.0% in matched asthma controls. Severe SCD: HR 2.86 (2.42–3.37); mortality HR 2.88 (2.35–3.52).	Hospitalisation-defined severity and coding-derived outcomes; potential residual confounding. Cohort overlaps with Brunson 2019.
Kumar 2018 [6] USA; 48 tertiary children's hospitals (PHIS)	Multicentre retrospective administrative cohort 10,454 children and young people with SCD	Paediatric SCD: VTE versus no VTE, 48 hospitals	181 (1.7%) had index VTE; older age, female sex, central line placement, stroke, renal disease and illness severity indicators were associated.	Hospital-selected population, billing-code outcomes; no unexposed population comparator.
Woods 2018 [7] USA; single tertiary paediatric centre	Retrospective cohort with within-SCD case comparison 414 children with SCD; 12 VTE events	Paediatric SCD: catheter exposure within cohort	12/414 (2.9%) developed VTE; nine were CVC-associated. CVC remained associated in multivariable model: OR 33.8 (95% CI 8.7–130.9).	Only 12 events; wide interval and instability of multivariable estimates; referral-centre selection.
Brunson 2019 [8] USA; California statewide SCD cohort	Retrospective cohort of individuals after first VTE 877 SCD patients with incident VTE	First-event SCD VTE survivors followed for recurrence	Recurrence: 13.2% at 1 year (95% CI 11.0–15.5) and 24.1% at 5 years (21.2–27.1); severe SCD associated with recurrence, HR 2.41 (1.67–3.47).	Recurrence-only denominator; overlap with prior California data; not an independent set of first-VTE participants.

Srisuwananukorn 2020 [9] USA; Illinois tertiary SCD centre	Longitudinal retrospective cohort; chart-verified events 1,193 children and adults with SCD	Clinical and laboratory factors within SCD cohort	208 (17.4%) experienced 352 thrombotic events, including 288 VTE events and 64 strokes. VTE associations included eGFR, HbSS/Sβ0, WBC and hydroxyurea use.	288 counts VTE EVENTS, not patients; indication confounding may affect hydroxyurea association.
Okoye 2022 [10] Nigeria; multicentre adult services	Retrospective medical-record cohort 509 adults with SCD	Within-SCD VTE and complications	10/509 (2.0%) had VTE: nine DVT and one PE; ACS association OR 8.0 (95% CI 2.2–28.9).	Only 10 events; retrospective capture and very wide intervals; estimates do not establish population incidence.
Ziyadah 2023 [11] Saudi Arabia; single teaching hospital	Retrospective admissions-based observational study 394 unique adult patients; 1,054 hospital admissions	VTE associated with inpatient admissions	32 of 1,054 admissions (3.0%) involved VTE; PE represented 50% of events; 6.4% of pregnant SCD admissions had VTE.	Denominator is ADMISSIONS, not unique patients; repeated admissions may cluster within patients.
Agarwal 2023 [12] USA; Medicaid pregnancy claims	Matched retrospective pregnancy/postpartum comparative cohort 6,388 pregnant people with SCD; 17,110 matched controls without SCD	SCD versus no SCD in pregnancy and postpartum	VTE in 720/6,388 (11.3%) versus 202/17,110 (1.2%) (reported OR 10.6, 95% CI 9.1–12.5) through 1 year postpartum; study reports 8–11-fold greater odds of thromboembolism overall.	Pregnancy-specific cohort; 8–11-fold statement encompasses TE outcomes and must not be relabelled a VTE-only adjusted OR.
Light 2024 [13] USA; tertiary centre, women aged 15–49	Retrospective single-centre cohort 370 women with SCD	Severity/contraception in SCD women aged 15–49	93/370 (25.1%) had a HISTORY of VTE. Severe versus mild disease: OR 11.79 (95% CI 5.14–27.06); moderate versus mild: OR 4.37 (1.77–10.76).	Selected referral sample; history of events rather than new-event incidence; broad record-based thrombotic outcome definition.

Figure 2. How the evidence addresses different questions



Figure (2): Evidence map by clinical question and outcome denominator

Risk of VTE in SCD compared with people without SCD

The most directly comparative observations support an increased VTE burden in several clinical settings, but do not yield a single transportable relative-risk value. National weighted discharge figures for patients younger than 40 years showed PE in 0.44% of SCD discharges and 0.12% of African-American non-SCD discharges; DVT percentages were similar at 0.44% and 0.40% [2]. Conversely, among Pennsylvania hospital discharges from people aged 50 years or younger, the corresponding PE proportions were 0.57% with SCD and 0.60% without,

while estimated population incidence was higher in SCD [3]. These outcomes have different admission and population denominators and different susceptibility to PE ascertainment.
The large California cohort reported 696 incident VTE cases among 6,237 people with SCD. For severe SCD, the estimated cumulative VTE incidence by age 40 was 17.1%, compared with 8.0% in matched asthma controls [5]. The pregnancy comparator provided particularly pronounced separation: 720 of 6,388 pregnant people with SCD had VTE (11.3%), compared with 202 of 17,110 controls (1.2%) from pregnancy through one year postpartum (reported OR 10.6, 95% CI 9.1–12.5) [12]. These results support the direction of increased risk in defined populations but should not be treated as a pooled SCD-versus-control estimate.

Occurrence within SCD cohorts and differences in denominator
In the longitudinal Cooperative Study, first-VTE incidence was 5.2 events per 1,000 person-years (95% CI 3.8–6.9), increasing to 7.6 per 1,000 person-years in patients with HbSS/Sβ0-thalassaemia; PE was detected more often than isolated DVT, although the difference was not statistically significant [4]. In contrast, selected tertiary-care cohorts reported case-history proportions. Srisuwananukorn and colleagues found any thrombosis in 208 of 1,193 patients but counted 288 VTE events, a number that must not be described as 288 unique people with VTE [9]. Light and colleagues found recorded VTE history in 93 of 370 women (25.1%) [13]. These figures do not measure equivalent observation intervals or clinical populations.
Geographical differences were notable but not directly causal. In Nigeria, ten of 509 adults had a recorded VTE history (2.0%), most involving DVT [10]. A Saudi analysis observed VTE during 32 of 1,054 admissions (3.0%) among 394 unique patients [11]. The latter result is a proportion of admissions, and treating it as a cumulative risk among patients would bias cross-study comparisons.

Paediatric SCD and central venous catheters
In 48 US paediatric hospitals, 181 of 10,454 patients with SCD (1.7%) had a coded index VTE during the study observation period [6]. In a separate 414-child tertiary cohort, 12 developed VTE (2.9%), including nine central-line-related cases. Catheter presence was associated with VTE on multivariable analysis (OR 33.8, 95% CI 8.7–130.9), although the small number of events makes the estimate imprecise [7]. These cohorts agree that vascular access and complex care matter, but cannot establish that removing catheters would eliminate the background thrombotic risk of SCD.

Disease severity, recurrence and mortality
The California cohort identified frequent hospitalisation as a marker of markedly higher VTE risk: the severe-disease hazard ratio was 2.86 (95% CI 2.42–3.37) in within-SCD analysis [5]. Women in the same cohort had a modestly higher hazard of VTE (HR 1.22, 95% CI 1.05–1.43). Post-event mortality was increased in both major longitudinal sources: adjusted HR 2.32 (95% CI 1.20–4.46) in the Cooperative Study [4] and HR 2.88 (95% CI 2.35–3.52) in the California study [5]. These are associations rather than proof that VTE alone caused subsequent deaths.
Among 877 California SCD patients with first VTE, recurrence incidence reached 13.2% (95% CI 11.0–15.5) by one year and 24.1% (95% CI 21.2–27.1) by five years. Severe SCD (HR 2.41, 95% CI 1.67–3.47), lower-extremity index DVT and pneumonia/acute chest syndrome were associated with recurrence [8]. These recurrence patients potentially overlap with patients contributing to the 2017 first-event cohort; summation would not produce a valid larger sample. Additionally, antithrombotic management must account for bleeding risk, which the recurrence investigators also measured.
Within-SCD clinical associations varied by cohort. In Nigeria, acute chest syndrome was associated with VTE (OR 8.0, 95% CI 2.2–28.9), but this involved only ten events [10]. Light and colleagues reported much higher odds of recorded thrombosis among women with severe (OR 11.79, 95% CI 5.14–27.06) or moderate (OR 4.37, 95% CI 1.77–10.76) disease versus mild disease [13]. In the Illinois cohort, genotype, leucocytosis, lower kidney function and hydroxyurea exposure were associated with VTE; treatment associations must be interpreted in the light of confounding by indication [9].

Critical appraisal
The risk-of-bias profile was heterogeneous (Tables 3 and 4). Retrospective designs, coding-based VTE identification, tertiary-centre selection and uncontrolled disease severity frequently affected comparability. Larger datasets provide broad reach but may miss imaging-adjudicated event confirmation; smaller clinical series provide finer phenotype detail at the cost of precision. The judgements were made for interpreting clinical VTE outcomes rather than as pooled quality scores.

Table (3): NOS-informed domain appraisal of included observational studies

Study	Selection	Confounding	Outcome	Reporting	Overall
Stein 2006	High	High	High	NR	High
Novelli 2012	High	High	Some	Some	High
Naik 2014	Some	Some	Some	Some	Some
Brunson 2017	Some	High	Some	Some	High
Kumar 2018	Some	High	Some	Some	High
Woods 2018	High	High	Some	Some	High
Brunson 2019	Some	High	Some	Some	High
Srisuwananukorn 2020	Some	High	Some	Some	High
Okoye 2022	High	High	Some	Some	High
Ziyadah 2023	High	High	Some	Some	High
Agarwal 2023	Some	Some	Some	Some	Some
Light 2024	High	High	Some	Some	High

Table (4): Study-specific reasons for risk-of-bias judgements

Study	Reason for judgement
Stein 2006	Discharge weighting and different likelihood of PE testing; patient linkage and adjustment incomplete.
Novelli 2012	Hospital-based sampling and externally estimated incidence denominator; small case-control component.
Naik 2014	Longitudinal denominator and genotype data strengthen inference; retrospective coding remains.
Brunson 2017	Very large cohort, but claims and hospitalisation-defined severity may introduce differential detection.
Kumar 2018	Hospital-selected children, coded VTE and care-intensity confounding.
Woods 2018	Only twelve cases and strong catheter indication/clinical-severity confounding.
Brunson 2019	Retrospective recurrence coding, survivor selection and overlap with prior report.
Srisuwananukorn 2020	Chart-verified events but clinic selection and confounding by hydroxyurea indication.
Okoye 2022	Ten events only; retrospective records and unstable adjusted associations.
Ziyadah 2023	Admissions are repeated within patients; event ascertainment and follow-up reflect inpatient care.
Agarwal 2023	Matched pregnancy cohort provides comparison, but claims coding and residual obstetric confounding remain.

Light 2024	Selected centre; recorded history, broad thrombus definition and time-dependent exposure uncertainty.

Low risk was not assigned when details were absent. “Some concerns” indicates limitations unlikely to be resolvable from the reported methods alone; “High” indicates selection, confounding, ascertainment or denominator problems important to the interpretation of the target outcome. The judgements are qualitative and study-specific, not a numerical synthesis of study quality.

Discussion

The evidence consistently points to a clinically important burden of venous thromboembolism in sickle cell disease, although the strength and size of the association vary across clinical settings. Large comparative cohorts show excess events in some groups of people with SCD, while other hospital-based comparisons report similar proportions of coded pulmonary embolism once the analysis is restricted to admissions [5]. These findings are not contradictory if their populations, time at risk and outcome definitions differ. In particular, a patient-level risk, an admission-level proportion and a pregnancy-specific risk answer different questions; none should be substituted for another. The pregnancy cohort illustrates how a defined observation period can reveal a pronounced between-group contrast without producing a lifetime estimate applicable to all people with SCD [12].

Comparative investigations should be prioritised when interpreting the relationship between SCD and VTE. A national hospital-discharge study showed greater PE-coded prevalence in SCD admissions than in non-SCD admissions, even though DVT-coded prevalence was similar [2]. In Pennsylvania, hospitalised patients with and without SCD had similar proportions of PE-coded discharges, while a separate population-based rate analysis suggested higher PE incidence in SCD [3]. California cohort and Medicaid pregnancy data further indicate excess events in defined clinical populations; these comparisons are not measurements of one identical underlying risk.

The apparent difference between pulmonary embolism and deep vein thrombosis warrants separate interpretation. Stein and colleagues reported a substantially higher proportion of PE-coded discharges in SCD while DVT-coded proportions were nearly the same in the comparison population [2]. Pulmonary vascular occlusion arising locally during sickling and inflammation is biologically plausible, but administrative diagnoses do not reliably distinguish thrombosis in situ from thromboembolism originating in a peripheral vein. Novelli and colleagues also noted differences in computed tomography use between patients with and without SCD [3]. Therefore, neither the absence of an accompanying DVT code nor a rise in PE coding is conclusive evidence for a specific mechanism. Comparable imaging criteria and clinical adjudication would strengthen the interpretation of future PE studies.

A limitation that is easily missed is differential surveillance. Patients with SCD may be hospitalised more often, undergo more imaging, and have more indwelling vascular devices. Consequently, they may be more likely to have thrombosis identified even after adjusting for selected covariates. Conversely, diagnostic overlap between acute chest syndrome, pulmonary infarction and embolic PE can cause under- or over-identification in administrative codes. The broader vascular pathology of SCD means that thrombosis in situ may be clinically relevant, but it is not always equivalent to an embolus originating in a peripheral deep vein. Source definitions and adjudication should therefore be explicit in future comparisons.

The longitudinal study of Naik and colleagues illustrates why incidence density is valuable for counselling: 5.2 events per 1,000 person-years is not the same as a 5.2% risk, and their estimated 11.3% cumulative incidence by age 40 uses a particular age-time analysis [4]. Similarly, the 11.2% proportion in the California cohort reflects a different study window and claims capture [5]. Their value lies in consistent identification of a sustained burden from adolescence into adulthood, rather than in whether one point estimate numerically exceeds another.

An additional statistical issue is that cumulative incidence is sensitive to the time origin, the follow-up window and events that prevent later observation. In the Cooperative Study, the age-specific cumulative incidence was estimated longitudinally, whereas the California proportion was obtained from a different administrative observation period [4,5]. A simple division of events by enrolled patients does not reproduce the underlying time-to-event analysis. In more severe disease, competing mortality, changes in health-care coverage and repeated admissions can further affect which events are recorded. Consequently, numerical differences between cohorts should not be treated as trends over calendar time or evidence of regional superiority without harmonised case ascertainment and follow-up.

Paediatric studies provide a clinically actionable secondary theme. Both the 48-centre PHIS study and the smaller clinical series implicated central vascular access [6,7]. The latter reported a very large association with catheter exposure, but the confidence interval was wide and catheter placement marks severe illness and transfusion needs. A policy of carefully considering vascular access, insertion duration and prophylactic care is reasonable to investigate. It would not be justified to infer from these non-randomised observations that catheters alone caused all recorded events.

The very wide catheter-related estimate from the paediatric clinical cohort is informative about uncertainty as well as association. The odds ratio of 33.8 had a 95% confidence interval from 8.7 to 130.9, reflecting only twelve thrombotic events [7]. It is therefore unsuitable as a precise prediction for an individual child. The larger PHIS cohort supports the clinical relevance of vascular access across hospitals, but catheter insertion also tracks the need for transfusion, intensive treatment and hospital exposure [6]. These findings support carefully defined, prospective evaluation of catheter-associated prevention strategies, with attention to line type, dwell time, indication and concomitant illness rather than assuming a uniform effect across all children.

The range of reported frequencies across Nigeria, Saudi Arabia and United States centres illustrates the denominator problem. A Nigerian multicentre study documented 10 VTE cases among 509 individuals with SCD [10], whereas a Saudi inpatient study recorded 32 VTE-associated admissions among 1,054 total admissions [11]. A selected tertiary-care study of 370 women described 93 patients with a thrombosis history labelled VTE; its event classification included a small number of intracardiac thrombi, making the broad endpoint less directly comparable with strictly defined DVT or PE [13]. Those figures should not be juxtaposed as equivalent lifetime risks.

SCD disease severity appears repeatedly as an important correlate of VTE. Hospital utilisation was associated with events in the California study, and severity strata had large associations in the women-only cohort [5,13]. This concordance improves the plausibility of a connection between cumulative disease burden and thrombosis. Nevertheless, severity measures can be complex mixtures of biology, access to care and decisions to admit, and may change over time. Future studies should prespecify severity and collect time-updated exposure measures to distinguish predictive associations from causal relationships.

Differences between regional cohorts should also be considered in light of care pathways and observation intensity. The Nigerian series relied on available clinical records for 509 patients, whereas the Saudi study considered more than a thousand inpatient episodes contributed by fewer than four hundred individuals [10,11]. Repeated admissions from one patient are correlated observations, so a percentage calculated per admission cannot be used as a probability that an individual will experience VTE. Variation in imaging availability, referral patterns, prophylaxis practices and inpatient exposure may contribute to the contrast. These differences do not establish that the underlying biological susceptibility is lower in one country; instead, they define the limits of an international numerical comparison.

Recurrence deserves particular attention because it changes the clinical question from prevention of a first event to secondary prevention after a diagnosed VTE. The California recurrence cohort recorded about one-quarter of individuals experiencing recurrent VTE by five years, with a higher hazard in severe SCD [8]. Decisions on anticoagulation duration require balancing this risk against bleeding, age, provoking factors and patient preferences; the observational recurrence data alone cannot specify an optimal anticoagulation regimen. The elevated mortality associations in the Cooperative Study and California cohort underline clinical importance but remain susceptible to confounding by underlying SCD severity [4,5].

Risk factors reported across studies—genotype, leucocytosis, kidney function, acute chest syndrome, previous stroke and treatment exposures—may help define populations for future validation [9,10]. An association of hydroxyurea with VTE should not be interpreted as drug-induced harm in the absence of careful adjustment for disease severity and treatment indication. Likewise, the high odds ratios derived from very few events in regional cohorts may be unstable. A risk model suitable for preventive decisions would require prospective validation, uniform clinical outcome definitions and assessment of calibration as well as discrimination.

The balance between recurrent thrombosis and treatment-related bleeding is important when translating epidemiological associations into clinical decisions. In the California recurrence cohort, first recurrence affected 13.2% within one year and 24.1% within five years after the index event; the same investigators reported a one-year cumulative bleeding incidence of 7.9% [8]. These are outcomes in a selected population with prior thrombosis, rather than estimates for primary prevention in all patients with SCD. The data justify individualised consideration of provoking circumstances and bleeding risk, but do not establish that a particular duration or intensity of anticoagulation is best. Direct comparisons of treatment strategies would be needed before drawing a prescriptive conclusion.

Pregnancy-specific findings have particular relevance to counselling, antenatal planning and postpartum monitoring. The large Medicaid comparison suggests excess VTE in people with SCD, but it covers pregnancy

through one year postpartum rather than lifetime risk [12]. Additional pregnancy confounders, recurrent deliveries, prophylactic regimens and pre-existing thrombosis history may affect claims estimates. The women-only contraception cohort argues that underlying disease severity can dominate an apparent hormonal association after adjustment [13]. These findings should be presented together without implying that pregnancy and contraception represent equivalent exposures or that a retrospective association dictates a universal prophylaxis strategy.

The pregnancy evidence is notable for both its size and the clarity of its comparator. Agarwal and colleagues observed VTE in 720 of 6,388 pregnant people with SCD and in 202 of 17,110 matched controls; the reported VTE-specific odds ratio was 10.6 (95% CI 9.1–12.5) [12]. The absolute event proportions carry clinical meaning, but the odds ratio should not be interpreted as a lifetime relative risk, nor does it identify a universal prophylaxis threshold. In the women-only SCD cohort, associations between hormonal contraception and thrombosis changed after accounting for disease severity, showing how exposure selection can distort an unadjusted comparison [13]. These results favour assessment that considers baseline SCD severity, prior thrombosis and the specific pregnancy or treatment window.

Important limitations stem from observational designs, heterogeneous time at risk, clinical selection and diagnostic coding. Although the twelve studies were individually checked against their original records, source ascertainment used targeted publicly accessible searching rather than complete exported retrieval sets from all bibliographic databases, so an exhaustive universe of eligible studies cannot be established. Some evaluations relied primarily on published abstracts, restricting detailed bias appraisal. Misclassified PE, overlapping administrative cohorts and residual confounding reduce causal certainty. A numerical pooled estimate would obscure rather than resolve these differences.

An important implication for future research is the need to move beyond a single yes-or-no VTE variable. Studies should distinguish first DVT, first PE, catheter-associated thrombosis, cerebral venous thrombosis and recurrence, and should report how diagnoses were established. The denominator must be prespecified at the same level as the question being addressed: person-time for incidence density, people for cumulative risk, and admissions only for admission-related outcomes. When multiple admissions or pregnancies arise from the same person, statistical methods should account for clustering. Consistent reporting of confidence intervals, competing events and follow-up completeness would allow more credible comparisons and, if clinically compatible datasets become available, a defensible quantitative synthesis.

Future epidemiological studies would benefit from population linkage, prospective adjudication of PE and DVT, clear distinction between patients and admissions, person-time denominators, reproducible ascertainment of genotype and hospital exposure, and explicit reporting of both recurrence and anticoagulant-associated bleeding. Prospective maternal and paediatric cohorts are especially valuable for evaluating thrombotic risk modification while accounting for clinical severity and central venous access.

Conclusion

Across the observational literature, sickle cell disease is associated with a clinically important burden of venous thromboembolism, but the extent of excess risk depends strongly on the population and the measure used. Comparative discharge investigations yielded different pulmonary embolism patterns from longitudinal and pregnancy cohorts, while the strongest contemporary pregnancy comparison identified a markedly higher risk of VTE in people with SCD. Clinical thrombotic events occur in children as well as adults; central venous access is a prominent correlate in paediatric care, and more severe SCD, recurrent hospitalisation and selected clinical complications are repeatedly associated with events in adult cohorts. After an initial VTE, recurrence and bleeding become additional concerns that cannot be inferred from first-event frequencies alone.

The evidence also shows why apparently divergent percentages should be interpreted with caution. Estimates based on person-years, unique patients, hospital admissions, pregnancy and postpartum observation periods, and cohorts already selected by a prior VTE have different meanings. Diagnostic coding, referral selection, varying use of chest imaging and residual confounding further limit direct numerical comparisons. Cohorts drawn from overlapping administrative sources should not be counted as independent participant samples. The available findings support the clinical importance of recognising thrombosis in SCD, but they do not establish a single transferable incidence or an optimal prevention regimen for every patient.

Clinical implications are therefore best framed around risk awareness and careful identification of the setting in which an estimate was obtained. Assessment of symptoms compatible with DVT or PE, attention to vascular access and prior thromboembolic history, and consideration of pregnancy-related risk are reasonable themes for multidisciplinary care; however, observational associations alone cannot dictate the use or duration of anticoagulation. Future prospective, multicentre studies with validated diagnoses, clear population

denominators, consistent severity measures and longitudinal follow-up would better quantify absolute risk and help evaluate strategies to prevent first and recurrent events while balancing bleeding complications.

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Appendix A. Search syntax and evidence identification

The eligibility window was 1 January 2000 to 30 June 2025. Targeted identification drew on publicly accessible PubMed indexing records, original articles and citation lists. Below are the PubMed concept syntax and equivalent platform-specific formulations that specify the same disease and VTE question. The documented source-checking date was 3 November 2026. These expressions describe the reproducible scope of the search, not counts from a combined export of subscription databases.

PubMed concept syntax

(("Anemia, Sickle Cell"[MeSH] OR "sickle cell disease"[tiab] OR "sickle cell anaemia"[tiab] OR "sickle cell anemia"[tiab] OR HbSS[tiab] OR HbSC[tiab] OR "sickle beta thalassemia"[tiab]) AND ("Venous Thromboembolism"[MeSH] OR "Pulmonary Embolism"[MeSH] OR "Venous Thrombosis"[MeSH] OR "venous thromboembol*"[tiab] OR "deep vein thromb*"[tiab] OR "pulmonary embol*"[tiab] OR DVT[tiab] OR VTE[tiab])) AND ("2000/01/01"[dp]:"2025/06/30"[dp])

Scopus-equivalent syntax

TITLE-ABS-KEY("sickle cell disease" OR "sickle cell anemia" OR "sickle cell anaemia" OR HbSS OR HbSC OR "sickle beta thalassemia") AND TITLE-ABS-KEY("venous thromboembolism" OR "deep vein thrombosis" OR "pulmonary embolism" OR VTE OR DVT) AND PUBYEAR > 1999 AND PUBYEAR < 2026

Web of Science Core Collection-equivalent syntax

TS=("sickle cell disease" OR "sickle cell anaemia" OR "sickle cell anemia" OR HbSS OR HbSC OR "sickle beta thalassemia") AND TS=("venous thromboembol*" OR "deep vein thromb*" OR "pulmonary embol*" OR VTE OR DVT); years 2000–2025, manually exclude publications after 30 June 2025

LILACS / BVS multilingual syntax

(("sickle cell disease" OR "anemia falciforme" OR "anemia de células falciformes" OR "doença falciforme") AND ("venous thromboembolism" OR "tromboembolismo venoso" OR "trombose venosa profunda" OR "embolia pulmonar")); apply publication dates 2000-01-01 to 2025-06-30

Appendix B. Source and eligibility audit

Table B1. Included primary-study source records

Study	Source location	Source evidence level
Stein 2006	https://pubmed.ncbi.nlm.nih.gov/17000225/	Primary abstract
Novelli 2012	https://pubmed.ncbi.nlm.nih.gov/22417249/	Full text / primary abstract
Naik 2014	https://pmc.ncbi.nlm.nih.gov/articles/PMC4268385/	Full text
Brunson 2017	https://pubmed.ncbi.nlm.nih.gov/28369826/	Primary abstract
Kumar 2018	https://pubmed.ncbi.nlm.nih.gov/29431623/	Full text
Woods 2018	https://pubmed.ncbi.nlm.nih.gov/29605397/	Primary abstract

Brunson 2019	https://pmc.ncbi.nlm.nih.gov/articles/PMC6876692/	Full text
Srisuwananukorn 2020	https://pubmed.ncbi.nlm.nih.gov/32384541/	Full text
Okoye 2022	https://pubmed.ncbi.nlm.nih.gov/35687045/	Primary abstract
Ziyadah 2023	https://pmc.ncbi.nlm.nih.gov/articles/PMC10607487/	Full text
Agarwal 2023	https://pubmed.ncbi.nlm.nih.gov/37551881/	Full text
Light 2024	https://pubmed.ncbi.nlm.nih.gov/39099800/	Full text

Table B2. Individually logged reports excluded from the primary evidence set

Candidate report	Record	Reason for exclusion
Noubiap et al. 2018	Previous systematic review/meta-analysis	Secondary evidence; discussed in background, not primary study
Agarwal et al. 2024	Hospital-acquired paediatric VTE case-only series (20 events)	No denominator of hospitalised SCD patients at risk; descriptive context only
Bhasin et al. 2026	Risk factors for VTE in SCD (719-patient clinical cohort)	Published after 30 June 2025 publication eligibility cutoff

Each source is identified by a publication record or original article. Distinct participant, event, admission and follow-up denominators were retained as reported. Study-level limitations in case selection, validation and comparative adjustment are presented in Tables 2–4.