BMJ Open

Impact of treatment-induced thrombosis on the prognosis of acute lymphoblastic leukaemia: a protocol for a systematic review and meta-analysis

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To cite: Mkhwanazi ZA, Fabunmi OA, Nkambule BB. Impact of treatment-induced thrombosis on the prognosis of acute lymphoblastic leukaemia: a protocol for a systematic review and meta-analysis. *BMJ Open* 2026;**16**:e106123. doi:10.1136/bmjopen-2025-106123

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-106123).

Received 05 June 2025
Accepted 29 January 2026

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ABSTRACT

Introduction Therapy-associated thrombosis remains a challenge in the management of patients with acute lymphoblastic leukaemia (ALL). Thrombosis associated with asparaginase-containing chemotherapy complicates patient management strategies, prompting the need for effective prophylaxis. Assessing the relationship between chemotherapy-induced thrombosis and patient outcomes is crucial for optimising ALL management strategies. The aim of this systematic review is to provide a synthesis on whether the development of thrombosis during asparaginase-containing chemotherapy regimens impacts the overall and event-free survival of patients with ALL.

Methods and analysis *Data sources*: to identify relevant studies, a comprehensive search will be conducted on the major electronic databases, including MEDLINE (PubMed), Web of Science (Clarivate), Academic Search Complete (EBSCOhost), clinicaltrial.gov and the Cochrane Central Register of Controlled Trials from inception to 30 January 2026.

Inclusion criteria for selecting studies: randomised and non-randomised clinical studies evaluating the impact of asparaginase-containing chemotherapy-associated thrombosis on survival outcomes in patients with ALL will be included. Two reviewers will independently screen the retrieved studies, extract data and assess study quality using a predefined criteria. A narrative synthesis will be undertaken, and if feasible, meta-analyses will be conducted. A subgroup and sensitivity analysis will be performed to explain the sources of heterogeneity. The quality of cumulative evidence will be assessed using the grading of recommendations assessment, development and evaluation tool. The findings from this systematic review will inform evidence-based clinical guidelines for thrombosis risk assessment and management in patients with ALL, potentially improving treatment outcomes and reducing thrombosis-related morbidity.

Ethics and dissemination No ethical approval will be required and the findings of this meta-analysis will be published in a peer-reviewed journal.

Trial registration number CRD42024532665.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The review will be conducted according to a predefined protocol with systematic searching, dual independent screening, data extraction and risk-of-bias assessment.
⇒ Both narrative synthesis and meta-analysis will be undertaken where appropriate, with statistical heterogeneity assessed and explored using predefined subgroup and sensitivity analyses.
⇒ Randomised controlled trials and non-randomised cohort studies involving participants across all age groups will be included.
⇒ Mortality outcomes will be synthesised using reported overall survival and event-free survival at comparable follow-up time points.
⇒ Variability in thrombosis definitions, diagnostic criteria and outcome reporting across studies may limit study comparability and the precision of pooled estimates.

INTRODUCTION

The advancements in the treatment modalities available for patients with acute lymphoblastic leukaemia (ALL) have significantly improved the overall survival (OS) outcomes.[1] However, thrombotic events during treatment significantly reduce the OS rates.[2–5] Chemotherapy-induced thrombosis often develops with aggressive chemotherapy regimens and central venous catheter use, affecting 15% of patients, with 69% of cases occurring during induction therapy.[6–8] Notably, cerebral venous thrombosis constitutes a large proportion of these occurrences.[9] The pathophysiology of chemotherapy-induced thrombosis is complex and involves patient-specific factors, treatment modalities and underlying disease biology.[2 7 10 11]

The onset of thrombosis in children with ALL often occurs after the initiation of chemotherapy, which highlights an interplay between the disease and treatment.[12] Chemotherapeutic agents, particularly those with a high pro-thrombotic potential such as asparaginase and steroids, can disrupt haemostasis of coagulation and fibrinolysis pathways.[13] Consequently, predisposing patients to

thrombotic events.[13 14] Mitigating the risk of thrombosis in patients with ALL on treatment requires a careful selection of chemotherapeutic drugs and frequent monitoring of thrombotic complications. While thromboprophylaxis has been explored in selected high-risk patients, there is limited and inconclusive evidence supporting its safety and efficacy.[15 16] Despite these preventive measures, thrombotic events continue to pose a significant concern in the clinical management of ALL, particularly in paediatric cases where the risk is notably elevated.[16] This underscores the need for ongoing research and innovation within this domain to address the persistent challenges associated with thrombosis in ALL treatment.

The Khorana score, a validated scoring system, predicts thrombosis risk in solid tumours, but its reliance on elevated leucocyte or platelet counts limits its applicability to acute leukaemia.[17] Thrombotic events not only contribute to treatment-related morbidity and mortality but also pose challenges to the delivery of optimal leukaemia therapy.[18] Patients who develop thrombosis during treatment may require dose adjustments, premature discontinuation of ALL treatment or the need for anticoagulation, all of which can potentially compromise treatment efficacy and OS.[9 19–21] The impact of thrombosis on the survival outcomes of patients with ALL remains unclear. Hence, systematic reviews are crucial to assess the effect of thrombosis on survival during ALL treatment.

Review question

Does the development of thrombosis during asparaginase-chemotherapy impact the OS and event-free survival (EFS) of patients with ALL?

METHODS AND ANALYSIS

Protocol registration

This protocol for a systematic review and meta-analysis has been prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 (PRISMA-P) guidelines.[22] The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) registry (Registration number: CRD42024532665).

Eligibility criteria

Study design

Randomised controlled trials (RCTs) and observational cohort studies evaluating patients with ALL receiving asparaginase-containing chemotherapy will be eligible for inclusion. Interventional studies will not be required to include a comparator arm, and observational studies comparing outcomes in patients with and without thrombotic events will be included. Studies must report whether anticoagulant thromboprophylaxis was used or not during treatment. Studies lacking information on chemotherapy composition or thromboprophylaxis status will be excluded. Studies reporting thrombosis present at diagnosis or prior to the start of chemotherapy will be excluded where timing is specified. Thrombotic events will be classified based on their temporal relationship to chemotherapy initiation rather than inferred causality. Full-length articles will be reviewed for outcome data. Studies will be excluded if they do not report thrombotic events, or if outcome measures relevant to thrombosis (incidence, timing or survival outcomes) are not reported. Other exclusion criteria include studies limited to lymphoblastic lymphoma without leukemic presentation, reviews, editorials, commentaries and conference abstracts.

Participants

The population of interest will include patients of any age with newly diagnosed or relapsed B cell or T-cell ALL and who have received asparaginase-containing chemotherapy as part of their treatment.

Exposure

Studies reporting thrombotic events occurring after initiation of asparaginase-containing chemotherapy will be eligible, including both symptomatic and incidentally detected thromboses.

Comparator

The comparator group will be patients with ALL who do not develop thrombosis at any point during or following treatment with asparaginase-containing chemotherapy.

Outcomes

Primary outcome(s)

The primary outcome will include the all-cause mortality (reported as 2–5 year OS and EFS). OS is defined as the time from initiation of chemotherapy to death from any cause. Patients who are alive at the end of follow-up will be censored at the last known date of follow-up. EFS will be defined as the time from initiation of chemotherapy to the first occurrence of relapse, disease progression, thrombotic event or death from any cause. Where studies report alternative definitions of EFS, these will be extracted and documented.

Surrogate outcome(s)

The surrogate outcome(s) related to OS and EFS will include complete remission rates and relapse incidence. Additional intermediate outcomes will include treatment interruptions or delays attributable to thrombotic events and quality-of-life measures, where reported, as these may indirectly influence survival outcomes through effects on treatment delivery and tolerability.

Prioritisation and rationale

Survival outcomes were prioritised as primary endpoints because they represent the ultimate goals of ALL treatment and are most relevant for clinical decision-making regarding thrombosis management. Understanding whether thrombotic events adversely affect long-term survival will directly inform clinical practice regarding the need for more aggressive thrombosis prevention

strategies or modifications to treatment protocols. Surrogate outcomes provide important context for understanding the mechanisms through which thrombosis may impact survival and help identify intermediate endpoints that could serve as early indicators of poor prognosis in future studies. All outcome definitions as reported in individual studies will be extracted to account for potential variations in endpoint definitions across studies. Data will be extracted in their original format (dichotomous, continuous or time-to-event) as reported, with appropriate statistical measures including hazards ratios (HR), odds ratios (OR), 95% confidence intervals (CI) and p values where available.

Information sources

A literature search will be conducted in MEDLINE, Academic Search Complete, Web of Science, clinicaltrial.gov and the Cochrane Central Register of Controlled Trials from inception to 30 January 2026. To be comprehensive, we will examine reference lists of included studies or relevant reviews identified through the search. The literature search will be conducted without language restrictions, with the literature restricted to human subject studies. To achieve comprehensive literature saturation, we will review the reference lists of the included studies and any relevant reviews identified during our search.

Search strategy

Systematic searches will be conducted using PubMed and EBSCOhost interfaces. The search strategy will be developed using medical subject headings for MEDLINE. The search terms will also be applied to retrieve studies from EBSCOhost. The following search terms and combinations will be used, "Precursor cell lymphoblastic leukaemia", "thrombosis" (see online supplemental file 1).

Data extraction and management

All identified records from the database searches will be imported into Mendeley reference management software for initial organisation and duplicate removal. Following duplication, the study selection process will be conducted in two phases by two independent reviewers (ZAM, OAF). In the first phase, titles and abstracts of all identified records will be screened against the predefined eligibility criteria. Records deemed potentially relevant by either reviewer will proceed to full-text assessment. In the second phase, full-text articles will be independently evaluated for final inclusion. Any disagreements between the two primary reviewers at either screening phase will be resolved through discussion, and if consensus cannot be reached, a third reviewer (BBN) will make the final decision. The study selection process will be documented using a PRISMA flow diagram, detailing the number of records at each stage and reasons for exclusion.

Data items

A standardised data extraction form will be developed and piloted on a subset of included studies to ensure consistency and completeness. Data extraction will be performed independently by two reviewers (ZAM, OAF) using the structured form, which will capture publication details, study characteristics, participant demographics, intervention details, outcome measures and results. For treatment-related variables, we will extract details on chemotherapy protocols used, dosage variations, intensity of treatment, duration and cycles of therapy. Studies that evaluate the treatment of thrombosis (eg, anticoagulants, thrombolytic therapy) will be included to allow for the assessment of how effective thrombosis treatments are in mitigating the negative impact of thrombosis on OS. Thrombosis-related data will include the type of thrombotic event (venous thromboembolism, cerebral venous thrombosis, arterial thrombosis), timing of thrombosis onset relative to treatment initiation, diagnostic methods used and any thrombosis treatment administered. Any discrepancies in extracted data will be resolved through discussion between the two extractors, with consultation of the third reviewer (BBN) if needed. When key information is missing or unclear, study authors will be contacted via email with up to two follow-up attempts to obtain additional data or clarification.

Risk of bias in individual studies

The risk of bias for each included study will be independently assessed by two reviewers (ZAM, OAF). RCTs will be evaluated using the Cochrane Risk of Bias 2 tool, which assesses bias across domains including the randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes and selection of the reported result. Non-randomised cohort studies will be assessed using the Newcastle-Ottawa Scale, examining selection, comparability and outcome domains, with studies rated as good, fair or poor quality. Disagreements between reviewers will be resolved through discussion, with a third reviewer consulted where necessary. All assessments will be documented to ensure transparency and reproducibility.

Data synthesis and meta-analyses

A narrative synthesis of clinical studies will be undertaken to present comprehensive findings, with an emphasis on clarity and coherence. The results will be organised and summarised in tabular form. Where sufficient data are available, meta-analyses will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions using study-level summary data. For dichotomous outcomes, pooled effect estimates will be calculated using reported numbers of events and total participants. For time-to-event outcomes, HRs and 95% CIs will be extracted from individual studies or estimated from published survival data using established methods when required. Individual patient-level data will not be sought. To pool outcomes, we will employ a random effects model. All data analysis will be performed using R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The Cochrane I^2 and χ^2

statistical tests will be used to analyse statistical heterogeneity between studies.[23 24] If substantial heterogeneity is present, we will explore potential sources through subgroup analyses or sensitivity analyses.[25]

Subgroup and sensitivity analyses

Where sufficient and comparable data are available, subgroup analyses will be performed based on age group (paediatric/adolescent vs adult), type of thrombotic event (venous vs arterial), and remission status (complete remission vs no complete remission) and reported diagnostic methods for ALL and thrombotic events. However, subgroup analyses based on ALL risk category will only be undertaken if consistently reported across studies. If data are insufficient to support quantitative subgroup analyses, these factors will be explored qualitatively in the narrative synthesis and discussed as potential sources of heterogeneity.

Confidence in the cumulative estimate

The overall quality and strength of the cumulative evidence will be systematically evaluated using the grading of recommendations assessment, development and evaluation (GRADE) approach.[26] The GRADE assessment will be conducted independently by two reviewers (ZAM, OAF) for each primary outcome, with any disagreements resolved through discussion or consultation with the third reviewer (BBN). Each outcome will be assigned a GRADE rating of very low, low, moderate or high quality, reflecting our confidence in the effect estimate. The rationale for each GRADE decision will be documented and presented in evidence profile tables accompanying the results.

DISCUSSION

Chemotherapy-induced thrombosis is an important complication in patients with ALL and may influence survival outcomes. This systematic review and meta-analysis will comprehensively evaluate how chemotherapy-associated thrombosis affects OS and EFS in this population. Existing thrombosis risk prediction models, such as the Khorana score, have limited applicability in acute leukaemia due to differences in disease biology, treatment intensity and baseline haematological parameters. By focusing specifically on patients with B/T-ALL receiving asparaginase-containing chemotherapy, this review aims to generate evidence that is more directly applicable to contemporary treatment settings. Where data permit, planned subgroup analyses will explore differences in outcomes based on age group, type of thrombotic event (venous vs arterial) and remission status (complete remission vs no complete remission). These analyses may provide insights into the relationship between thrombosis, treatment modalities and survival outcomes, informing strategies for monitoring and managing thrombotic complications during chemotherapy.

Several limitations of this review are anticipated. Included studies are expected to vary in design, patient populations, chemotherapy protocols and definitions of thrombotic events, which may contribute to statistical heterogeneity. Inconsistent reporting of anticoagulant prophylaxis use, timing of thrombosis relative to chemotherapy initiation and outcome definitions may further limit the precision of pooled estimates. Additionally, the inclusion of non-randomised studies may introduce residual confounding, and the possibility of publication bias cannot be excluded.

Despite these limitations, this review will provide a comprehensive synthesis of the available evidence and help inform clinical decision-making regarding thrombosis monitoring and management during ALL treatment, while highlighting areas where future prospective studies are needed.

Contributors ZAM and BBN: Conceptualisation, BBN: Supervision, ZAM: Protocol draft. All authors read, provided feedback and approved the final manuscript. BBN is the guarantor of the review.

Funding This review is funded by the University of KwaZulu-Natal (UKZN) staff research productivity units (Awarded to Prof. BBN). ZAM is funded by the National Research Foundation (NRF). The funding body(s) did not play a role in any aspect of this review.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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