Risk Assessment Model for Venous Thromboembolism in Acute Lymphoblastic Leukemia

Subcommittee: Hemostasis & Malignancy

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Description Abstract

BACKGROUND

Patients with acute lymphoblastic leukemia (ALL) are at increased risk of thrombotic and or bleeding events during chemotherapy, especially when receiving L-Asparaginase (ASP). Thrombosis in ALL has a significant impact on patients' lives, leading to increased length of hospital stay [1], need for central catheter removal [2], CNS complications [3], and increased mortality[4]. The incidence of venous thromboembolism (VTE) is in excess of 30% in some series of adult ALL patients, with a residual rate of thrombosis over 13% despite low molecular weight heparin (LMWH) thromboprophylaxis [5,6], which has been suggested by a recent ISTH SSC guidance for use in all adult patients with ALL during induction with ASP [7]. The TROMBOTECT study, a randomized controlled trial of thromboprophylaxis in pediatric ALL, demonstrated a decreased VTE incidence in patients receiving LMWH compared to the control arm [8]. However, this study did not utilize a risk assessment model (RAM) to stratify patients at risk. Stratifying the risk of VTE is crucial in developing thromboprophylaxis strategies which are able to intensify thromboprophylaxis in high-risk populations and avoid thromboprophylaxis in low-risk patients [9].

Several studies tried to identify variables associated with increased thrombotic and bleeding risk in ALL with varying results [10,11]. D-dimer, a fibrinogen degradation product, is a potential predictor of thrombosis in this population. D-dimer was associated with increased risk of thrombosis in outpatients with solid cancer [12], AML patients [13] and in a single-center pilot study of adult ALL patients [14]. Importantly, d-dimer was not associated with bleeding risk in the leukemia cohorts [13,14].

Risk Assessment Models (RAMs) predicting thrombosis have been developed for outpatients with solid cancers, and a general population of medically ill inpatients [15,16]. To date, no RAM has been developed specifically for ALL patients. Al-Ani et al completed a retrospective study consisting of 427 patients with AML and 74 patients with ALL, and derived and validated a prediction score consisting of: 1) history of venous thromboembolism (VTE); 2) ALL, 3) platelet count >50 x 10^9/L [17]. This study did not include d-dimer as a variable and has several limitations, first and foremost the inclusion of AML and ALL patients in the same cohort, despite these being distinct diseases with differences in treatment protocols, patient profiles and thrombotic risk.

STUDY AIMS:

1. Train and internally validate a RAM for VTE in ALL, using candidate demographic, clinical and biochemical factors identified in prior studies.
2. Assess whether the proposed VTE RAM is associated with an increased bleeding risk.

CLINICAL IMPLICATIONS:

Patients with ALL are at increased risk of thrombosis, even with LMWH thromboprophylaxis, which leads to significant morbidity and mortality [18]. A RAM which is able to stratify the VTE risk of in ALL patients, could help guide prospective studies evaluating risk-adapted thromboprophylaxis strategies. If the current study identifies a RAM which adequately stratifies the risk of VTE but not bleeding in ALL patients, the RAM will be externally validated in a planned prospective study of ALL patients. All candidate variables are being assessed in this study and VTE is among the secondary outcomes.

Design and methodology

DESIGN

Multicenter retrospective cohort study of all consecutive adult patients with ALL undergoing induction therapy. The study design is shown in Figure 1. Patients will be indexed on the first day of ALL diagnosis. All patients will be assessed for baseline characteristics at index, with an emphasis placed on variables associated with VTE in prior studies of ALL patients [6,10,11,17], as follows: age, sex, BMI, prior VTE, use of ASP, ponatinib treatment, hypertension, ALL phenotype and molecular subgroup, mediastinal mass, central venous catheter, platelet count, D-dimer level, fibrinogen level, DIC score. D-dimer values will only be documented at a given site, if d-dimer was routinely drawn for all ALL patients at diagnosis at that study center. Use of anticoagulation will be documented at index and during follow-up. Patients will be followed for 100 days post-index, and will be censored for VTE or use of therapeutic dose anticoagulation, with death prior VTE considered as a competing risk.

The main study outcome is symptomatic or incidental VTE at any site diagnosed using objective imaging studies. Secondary outcomes include major bleeding, clinically relevant non-major bleeding (using ISTH definitions) and arterial thrombosis. A RAM for VTE at 100 days post-diagnosis of ALL will be trained and internally validated. Since the two main decision-making junctions are at diagnosis and at the time of ASP initiation (in those who receive ASP), two different RAMs will be trained using each of these time-points.

Each center will use a locally-adapted screening strategy based upon diagnostic codes and prescription records to identify consecutive potential patients. Electronic medical records (EMRs) will be reviewed manually to ensure eligibility. Granular data will be extracted from the EMRs of each patient in the final cohort. VTE events will be adjudicated centrally using source documents.

STATISTICAL ANALYSIS

All analyses will be performed separately for PH-positive and PH-negative ALL patients, since these are distinctly different diseases with respect to biology and treatment. The cumulative incidence of VTE (and the other secondary endpoints) at 100 days will be calculated, with death as competing risk. Multivariate cox regression analysis will be used to calculate hazard ratios (95% confidence interval) for VTE at 100 days. Death before VTE will be considered as a competing

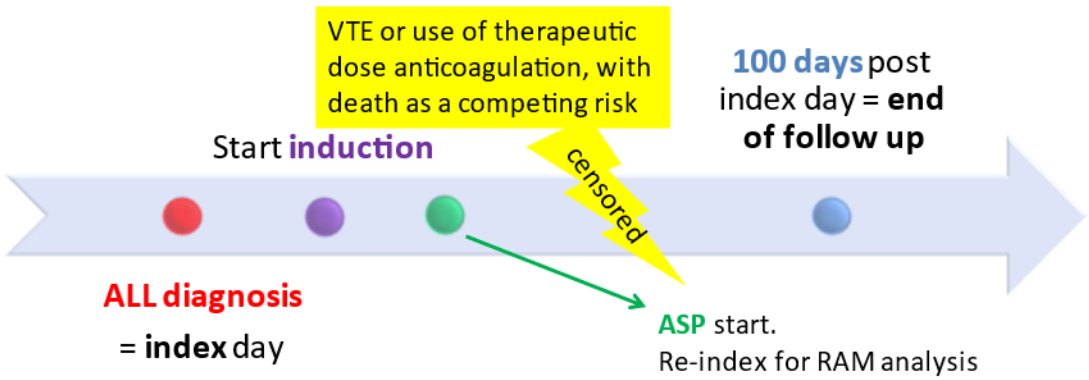
risk in all analyses (Fine and Gray model). The candidate variables (preselected based upon prior studies) will be considered in the regression models as fixed variables. Analyses will be adjusted for non-therapeutic anticoagulation during follow-up, as a time dependent variable. Analyses will be censored for VTE, use of therapeutic dose anticoagulation or loss to follow-up. Subsequently, a RAM aimed at predicting VTE at 100 days post ALL diagnosis will be trained and internally validated. The performance of the candidate VTE RAM for predicting major bleeding will be evaluated.

A secondary (landmark) analysis will be performed using the timepoint of ASP treatment as re-index date, and will include only patients starting ASP who did not experience VTE between ALL diagnosis and ASP treatment. A sensitivity analysis excluding centers without d-dimer data will be performed.

SAMPLE SIZE CONSIDERATIONS

Considering a 100-day VTE incidence of 20% and ten candidate variables for the VTE-RAM, we aim for a sample size of 500 patients.

Figure 1: Study Design



Covariates at index day:
age, sex, BMI, prior VTE, use of ASP/ ponatinib, ALL phenotype & molecular subgroup, HTN, mediastinal mass, CVC, platelet count, D -dimer level**, fibrinogen, DIC score, *Anticoagulation (time dependent over 100 days)*

Outcomes over 100 days:
VTE event, arterial thrombosis, death, bleeding (ISTH criteria)

Study population

SETTING AND SAMPLE

The cohort includes subjects treated as inpatients or outpatients in the hematology-oncology or oncology departments at the study centers between January 1st, 2008 and March 1st,

2021. Adult patients (≥18 years of age) will be eligible if the following inclusion criteria are met: 1) new diagnosis of ALL; 2) receiving induction therapy. Patients will be excluded from study participation in case of therapeutic dose anticoagulation (for any indication) at study index. Index day will be the day of ALL diagnosis.

PARTICIPATING INSTITUTIONS

The two lead centers are University of Chicago (Chicago, USA) and Rabin Medical Center (Petah Tikva, Israel). Additional centers currently participating are Northwestern University (Evanston, USA) and Dana Farber Cancer Institute (Boston, USA). Based on feasibility checks, at least 250 patients are anticipated to be included by these centers. Additional centers will be recruited via the ISTH SSC and through local and international networking (including hematology-oncology working groups). D-dimer at time of diagnosis is not a prerequisite for study participation, but this variable will only be considered at centers who routinely measure d-dimer adjacent to diagnosis.

Considering the sample size and number of patients per center to date, at least 5 ***additional centers*** are needed (9 in total), meaning that ***each*** center would have to include ***50 patients***. Considering the multinational make-up of the study team, we expect to meet this number of centers.

Expected timeline:

From set-up to publication of all related articles we anticipate a maximum of ***30 months, in total***:

1. PROJECT SET UP: ***3 months*** needed to adapt the protocol based on feedback and create a electronic CRF in REDCap.
2. LAUNCH: ***on September 1st 2021***. We anticipate that *6 months* will be needed until the full set of study centers is recruited and has local institutional/ethical approval
3. DURATION: ***September 1st – March 1st 2022*** (*6 months*) for data extraction
4. FINALIZATION/ANALYSIS: ***March 1st 2022 – September 1st 2022*** (*6 months*) for refinement of data and all statistical analyses.
5. REPORTING: ***September 1st – June 1st 2023*** (*9 months*) to write manuscript (see below)

Expected outcomes:

1. Publication of an original article: Risk stratification of VTE in patients with acute lymphoblastic leukemia receiving induction chemotherapy.
2. The VTE-RAM will be externally validated in an ongoing prospective study of adults with ALL, if the current study identifies a RAM which adequately stratifies the risk of VTE but not bleeding in patients with ALL.

Description of project set/up and management, needed infrastructure and resources

1. PROJECT SET UP
    a. The ***ISTH REDCap server*** would be needed to host this study.
2. LAUNCH: The ***ISTH networking capabilities*** needed to increase awareness and participation
3. DURATION: to be determined
4. FINALIZATION/ANALYSIS: Analyses will be performed in-house at the leading centers.

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