Genomic analysis of venous thrombosis in children with acute lymphoblastic leukemia from diverse ancestries

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Abstract

Venous thrombosis is a common adverse effect of modern therapy for acute lymphoblastic leukemia (ALL). Prior studies to identify risks of thrombosis in pediatric ALL have been limited by genetic screens of pre-identified genetic variants or genome-wide association studies (GWAS) in ancestrally uniform populations. To address this, we performed a retrospective cohort evaluation of thrombosis risk in 1,005 children treated for newly diagnosed ALL. Genetic risk factors were comprehensively evaluated from genome-wide single nucleotide polymorphism (SNP) arrays and were evaluated using Cox regression adjusting for identified clinical risk factors and genetic ancestry. The cumulative incidence of thrombosis was 7.8%. In multivariate analysis, older age, T-lineage ALL, and non-O blood group were associated with increased thrombosis while non-low-risk treatment and higher presenting white blood cell count trended toward increased thrombosis. No SNP reached genome-wide significance. The SNP most strongly associated with thrombosis was rs2874964 near *RFXAP* (G risk allele; $P=4x10^{-7}$; hazard ratio [HR] =2.8). In patients of non-European ancestry, rs55689276 near the α globin cluster ($P=1.28x10^{-6}$; HR=27) was most strongly associated with thrombosis. Among GWAS catalogue SNP reported to be associated with thrombosis, rs2519093 (T risk allele, $P=4.8x10^{-4}$; HR=2.1), an intronic variant in *ABO*, was most strongly associated with risk in this cohort. Classic thrombophilia risks were not associated with thrombosis. Our study confirms known clinical risk features associated with thrombosis risk in children with ALL. In this ancestrally diverse cohort, genetic risks linked to thrombosis risk aggregated in erythrocyte-related SNP, suggesting the critical role of this tissue in thrombosis risk.

Introduction

Contemporary treatment for children with acute lymphoblastic leukemia (ALL) cures more than 90% of patients.[1,2] However, therapy-related toxicities including venous thrombosis can reduce event-free survival and overall survival as well as quality of life of patients and survivors. The risk of thrombosis in children with ALL is dramatically higher than the general pediatric population, likely related to a combination of known prothrombotic risk factors, including the presence of central venous catheters, inflammation and other direct effects from leukemia, and chemotherapy, particularly glucocorticoids and asparaginase.[3] As pediatric therapeutic strategies have expanded to treat young adults, thrombosis is increasingly occurring in this population.[4] Prior studies of the association between inherited thrombophilia variants such as prothrombin G20210A and factor V Leiden have yielded inconsistent results.[5-9] However, several of these studies have only ascertained thrombophilia genetics in patients who developed thromboses.[7,8] Other studies used targeted screening but lacked genome-wide assessments.[10] Prior genome-wide assessments of thrombosis risk in ALL have been limited by homogenous population selection, with analyses limited to patients of European ancestry.[4,11,12] As a result, there have been no comprehensive genetic evaluations of the risk of thrombosis during ALL therapy in genetically diverse cohorts. Because studies have demonstrated an increased risk of venous thrombosis among Americans of African ancestry as compared to those with European ancestry in both the general population[13,14] and adults with cancer,[15] assessment of this risk factor in the context of ALL therapy and identification of any genetic features driving such differences are needed.

Methods

Patients and clinical trials

All patients were treated at our institution and enrolled on the Total XV (*change both to: clinicaltrials gov. Identifier: NCT00137111*) or Total XVI (*change both to: clinicaltrials gov. Identifier: NCT00549848*) studies for newly diagnosed ALL. Details of these cohorts and their treatment characteristics have been previously reported and are included in the *Online Supplementary Appendix*.[1,16] Neither trial included recommendations for thromboprophylaxis. Prospective thrombophilia screening was not routinely performed in patients.

All clinically significant thromboses (Common Terminology Criteria for Adverse Events versions 2 [Total XV] or 3 [Total XVI] grade 2 or higher) occurring on therapy were prospectively gathered in research databases and were independently reviewed for accuracy. Thrombosis-associated symptoms were assessed at the time of data collection. Data used in the current analyses was current as of 20 January 2023.

All studies were approved by the institutional review boards of participating institutions. Patients and/or legal guardians provided informed written consent/assent consistent with the Declaration of Helsinki.

Genotyping and genomic analyses

Germline DNA for patients was collected from peripheral blood following remission induction and genotyping was performed in a research setting without return of results to clinicians or patients. Details of genotyping and assessment of genetic ancestry are available in the *Online Supplementary Appendix*.

Statistics

Risk for thrombosis was assessed using time-dependent Cox proportional hazard models until the occurrence of the first thrombosis with death in remission, relapse, and termination of protocol therapy treated as competing events. For each single nucleotide polymorphism (SNP), Cox proportional-hazard regressions were performed separately for patients treated on Total XV and Total XVI adjusting for age, ancestry, and risk arm. The results were then combined in a meta-analysis weighted by square-root of the number of patients included in each protocol. Analyses were performed in R[17] 4.1.1 and Stata 16.1 (StataCorp LLC, College Station, TX). The threshold of statistical significance was $P<0.05$ for clinical analyses and $P<5x10^{-8}$ for GWAS analyses.

In multivariate analysis, first all factors associated at $P<0.05$ in univariate analysis were included to define the initial model. Then, the final model was determined by removing factors showing $P<0.2$ in the initial model.

In order to identify variants previously associated with thrombosis or associated phenotypes, we extracted relevant diseases/traits from the GWAS catalogue version 1.02 with data present on 26 March 2020.[18] Identified traits and SNP linked to thrombosis are found in the *Online Supplementary Table S1*.

Results

Clinical associations with thrombosis

Thrombosis was detected in 79 of 1,005 evaluated patients. Thrombosis was detected by imaging without clinical symptoms in seven patients, including three patients with cerebral sinus thrombosis discovered on magnetic resonance imaging (MRI) and four with line-associated thromboses. A second episode of thrombosis occurred in nine of 79 patients (11.4% of thromboses), including two patients with three episodes of thrombosis. Subsequent thromboses were at discreet sites from the initial thrombosis in ten of 11 subsequent episodes; seven occurred after completion of the initial anticoagulation course and four occurred while patients were still receiving anticoagulation. Thromboses included 27 central venous line-associated thromboses, eight pulmonary emboli, 21 cerebral venous thromboses, and 34 other deep vein thromboses. Thrombosis was fatal in two cases, including a patient with a fungal pulmonary thrombosis during high-risk pretransplant re-intensification therapy and a patient with Trisomy 21 who developed a saddle pulmonary embolus during week 11 of standard-risk continuation therapy.

Univariate analysis showed that older age, T-ALL, and standard- or high-risk therapy were risk factors for thrombosis development (Table 1). Patients who developed thrombosis were older (mean 11 *vs*. 6.9 years; $P<0.001$; hazard ratio [HR] =1.17; 95% confidence interval [CI]: 1.12-1.22%; *Online Supplementary Figure S1*). Thrombosis occurred in 4.3% of children 1-9.99 years old at diagnosis, 8.3% of infants less than 1 year old at diagnosis (HR=2.3; 95% CI: 0.3-16.5 *vs*. children; $P=0.4$), and in 17.3% of adolescents 10 years old and older at diagnosis (HR=4.5; 95% CI: 2.9-7.1 *vs*. children, $P<0.001$). There was no difference by patients' genetic ancestry, with 5.5% of African ancestry, 8.7% of Hispanic/Native American ancestry, 8.8% of European ancestry, and 4.9% of patients with other ancestries developing thrombosis ($P=0.4$; *Online Supplemental Figure S2*). There was also no difference by sex, with 7.7% of females and 7.8% of males developing thrombosis ($P=0.9$).

Thrombosis rates were similar across protocol, with 7.4% of Total XV and 8.2% of Total XVI patients developing thrombosis ($P=0.7$). However, certain disease and therapy characteristics were associated with thrombosis risk. Patients treated with standard- or high-risk therapy had a higher thrombosis rate (11.5%) than those treated with low-risk therapy (3.5%, HR=3.6; 95% CI: 2.1-6.2; $P<0.001$). Thrombosis risk was higher in patients with T-ALL than B-cell precursor ALL (16.8% *vs*. 6.1%, HR=3; 95% CI: 1.9-4.8; $P<0.001$).

Since all patients with T-ALL received intensified asparagi-

nase and dexamethasone treatment in standard-/high-risk arm, comparison was also made between patients with T-ALL and those with B-ALL treated in standard-/high-risk arm and showed a persistent significant increased thrombosis risk for patients with T-ALL (16.8% *vs*. 9.2%, HR=1.9; 95% CI: 1.2-3.2; *P*=0.009). There was a non-significant increase in thrombosis in patients with central nervous system 3 (CNS3) status (cerebrospinal fluid [CSF] white blood cell count [WBC] ≥5/μL with blasts) compared to other patients (17% *vs*. 7.6%, HR=2.4; 95% CI: 0.97-5.9; *P*=0.06). Intensified intrathecal (IT) treatment was associated with increased thrombosis risk (9.7% in those receiving 4 to 7 doses during induction *vs*. 6.3% in those receiving 2 to 3 doses, HR=1.56; 95% CI: 1-2.44; *P*=0.048). Patients

Table 1. Analysis of risk factors for thrombosis development in children with acute lymphoblastic leukemia.

	No thrombosis N=926	Thrombosis N=79 (% with thrombosis)	Univariate *P*	Multivariate *P* without ABO type	Multivariate *P* with ABO type	Multivariate *P* with blood type and rs2519093
Age in years at diagnosis, mean (SD)	6.9 (4.6)	11 (5.1)	<0.001	<0.001	<0.001	<0.001
Age in years at diagnosis						
0-0.99	11	1 (8.3)	<0.001	NA	NA	NA
1-9.99	691	31 (4.3)				
10-18.99	224	47 (17.3)				
Sex						
F	394	34 (7.9)	0.97	NA	NA	NA
M	532	45 (7.8)				
Study						
Total XV	377	30 (7.4)	0.69	NA	NA	NA
Total XVI	549	49 (8.2)				
Immunophenotype and risk						
B low-risk	442	16 (3.5)	Ref	Ref	Ref	Ref
B SH-risk	345	35 (9.2)	<0.001	*	*	0.15
T lineage, SH-risk	139	28 (16.8)	<0.001	0.021	0.014	0.008
CNS3 status at diagnosis						
Yes	24	5 (17.2)	0.093	NA	NA	NA
No	902	74 (7.6)				
Intrathecal therapy in induction, N of doses						
2-3	517	35 (6.3)	0.047	*	*	*
4-7	409	44 (9.7)				
WBC count x10^3/mm^3 at diagnosis, mean (SD)	52 (104.4)	93.7 (194.3)	<0.001	0.045	0.011	0.025
Mediastinal mass on initial chest x-ray						
Yes	92	14 (13.2)	0.033	*	*	*
No	830	63 (7.1)				
Unavailable	4	2 (33.3)				
Genetic ancestry						
African	138	8 (5.5)	0.21	NA	NA	NA
Hispanic/ Native American	84	8 (8.7)	0.99	NA	NA	NA
Other ancestry	77	4 (4.9)	0.26	NA	NA	NA
European	612	59 (8.8)	Ref	NA	NA	NA
Unavailable	15	0 (0)	NA	NA	NA	NA
Blood type OO						
No	444	49 (10)	0.007	NA	0.001	0.11
Yes	442	25 (5.4)				
Unavailable	40	5 (11.1%)				
rs2519093						
TT	35	4 (10.3)	<0.001	NA	NA	0.05
TC	215	36 (14.3)				
CC	656	38 (5.5)				
Unavailable	20	1 (4.8)				

SD: standard deviation; NA: factor not considered in multivariate analysis; *: not selected in multivariate analysis; CNS: central nervous system; WBC: white blood cell; M: male; F: female.

who developed thrombosis also had a higher presenting WBC count (mean 93.7 *vs*. 52x10^3/mm^3, HR=1.25; 95% CI: 1.1-1.41 per 100x10^3/mm^3; *P*<0.001) and were more likely to have a mediastinal mass on initial chest x-ray (13.2% *vs*. 7.1%, HR=1.97; 95% CI: 1.1-3.52; *P*=0.02).

In order to identify factors associated which might mediate the increased risk of thrombosis in T-ALL compared to standard/high-risk B-ALL, we assessed factors reported to be more common in T-ALL than B-ALL including CNS status and CNS-directed therapy, presenting WBC count, and the presence of mediastinal mass for their association with thrombosis development. Among patients treated on the standard- or high-risk arm, there was no increase in CNS3 status (CSF WBC count ≥5/μL with blasts) comparing B-ALL to T-ALL (5% *vs*. 6%; *P*=0.63). More patients with T-ALL received intensified CNS-directed therapy with 82% receiving at least four intrathecal therapies during induction compared to 50% among standard/high-risk B-ALL (*P*<0.001). Patients with T-ALL were also more likely to have a mediastinal mass (53.6% *vs*. 1.3%; *P*<0.001) and had a higher mean presenting WBC count (154 *vs*. 57.2x10^3/mm^3; *P*<0.001). In this subset of patients, only WBC count was associated with increased thrombosis risk (HR=1.15 per 100x10^3/mm^3; 95% CI: 1.003-1.32; *P*=0.045).

In multivariate analysis, age (HR=1.15 for each additional 1 year; 95% CI: 1.09-1.2; *P*<0.001) and T-ALL (HR=2.69; 95% CI: 1.29-5.62; *P*=0.009) remained associated with increased thrombosis risk while B-ALL receiving standard/high-risk therapy (HR=1.63; 95% CI: 0.83-3.2; *P*=0.16) and presenting WBC count (HR=1.15; 95% CI: 0.99-1.34 per 100x10^3/mm^3; *P*=0.07) were also retained in the model but did not reach the threshold of statistical significance (Table 1).

Genetic associations with thrombosis

Genotype data were available on 983 patients, including 387 treated on Total XV and 596 treated on Total XVI. No SNP were associated with thrombosis at the genome-wide association threshold of 5x10^{-8} (Figure 1). The SNP most strongly associated with thrombosis in the meta-analysis was rs2874964 near *RFXAP* (G risk allele, *P*=4x10^{-7}; HR=2.8; 95% CI: 1.9-4.2), a variant which decreases SREBP binding.[19] The coding variant most strongly associated with thrombosis was rs11540822 in *CCHCR1* (T risk allele, *P*=1.1x10^{-5}; HR=3.4; 95% CI: 2-5.9). This missense variant is predicted to be damaging to CCHCR1 function (Ensembl release 10920), and is an expression quantitative trait locus for *HLA-C* and *HCG27* in whole blood (GTeX accessed May 14, 2023).[21]

Among GWAS catalogue SNP, 279 previously reported to be associated with thrombosis were typed or imputed in our cohort (*Online Supplementary Table S1*). The GWAS catalog thrombosis SNP most strongly associated with thrombosis in this cohort was rs2519093 (T risk allele, *P*=4.8x10^{-4}; HR=2.1; 95% CI: 1.4-3.1), an intronic variant in *ABO*. Notably, there was no association between rs6025 (Leiden mutation) in factor V (*P*=0.4), rs1799963 (G2020A) in prothrombin (*P*=0.3), or rs1801133 (C677T) in *MTHFR* on the development

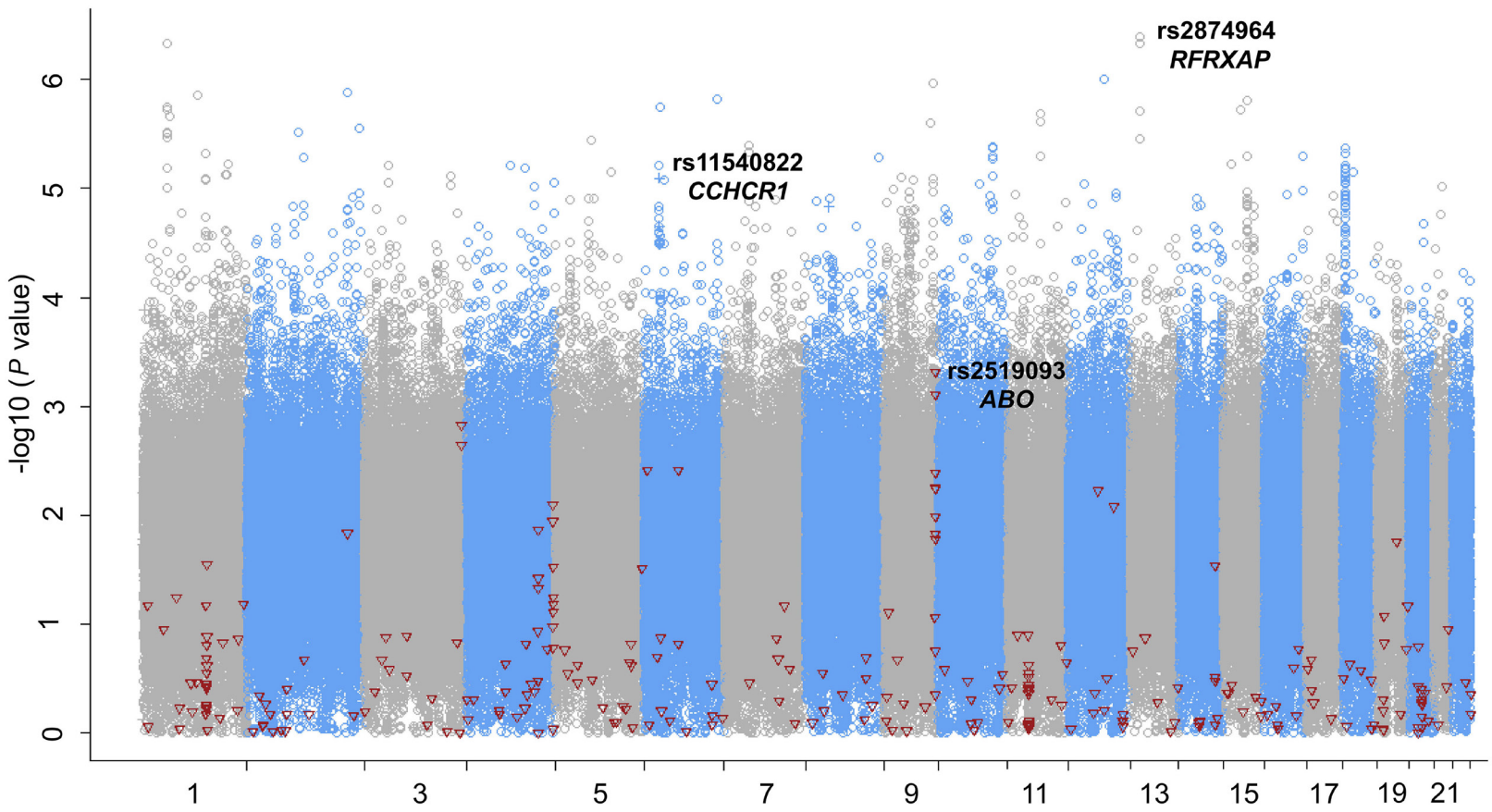

Figure 1. Manhattan plot of venous thrombosis risk in children with acute lymphoblastic leukemia. Non-coding variants are shown as blue and gray circles. The top variant is rs2874964 near *RFXAP* (*P*=4x10^{-7}). Coding variates are shown with blue and gray crosses and the top variant is rs11540822 in *CCHCR1* (*P*=1.1x10^{-5}). Variants previously associated with thrombosis in the genome-wide association studies catalogue are shown as red triangles, with rs2519093 in *ABO* the top ranked single nucleotide polymorphism (*P*=4.8x10^{-4}).

of thrombosis. Prior GWAS SNP12 rs1804772 and rs570684 were not associated with thrombosis in our cohort (*P*=0.41 and *P*=0.82, respectively; *Online Supplementary Table S1*). When the analysis was restricted to 317 patients of non-European ancestry (CEU <90%), the top SNP was rs55689276 near the α globin cluster (P=1.28x10^{-6}; HR=27; 95% CI: 7.2-105; *Online Supplementary Figure S3*). This SNP had a weak trend in the same direction in European ancestry patients (*P*=0.19; HR=1.5; 95% CI: 0.83-2.6) and is an eQTL for Z globin in whole blood.

Because of the association between rs2519093 in *ABO* with thrombosis in our cohort, we assessed the impact of blood type on thrombosis risk. Clinical blood types were available for 960 patients, including 493 with type non-O blood and 467 with O blood. Non-type O blood was associated with an increased risk of thrombosis (HR=1.89; 95% CI: 1.17-3.07; *P*=0.007), an association which was retained in multivariate analysis (HR=2.34; 95% CI: 1.42-3.87; *P*=0.001; Table 1). Despite the strong correlation between rs2519093 genotype and blood group, both factors retained strong trends toward association in multivariable models. (Table 1; *Online Supplementary Table S2*).

Discussion

Despite excellent cure rates, therapy for children with ALL can result in life-threatening consequences. Within our cohort, symptomatic venous thrombosis occurred in 7.8% of 1,004 patients and was fatal in two patients (0.2%). Older age, T-ALL immunophenotype, higher WBC count at diagnosis, standard-/high-risk therapy, and non-O blood group were all associated with increased with thrombosis and retained in multivariate analysis. No genetic variant reached genome-wide significance; the GWAS catalog SNP most strongly associated with thrombosis was the *ABO* variant rs2519093.

In this cohort with diverse ancestries, no genetic ancestry group experienced an increased risk of thrombosis. This contrasts with increased risks of thrombosis in self-identified Blacks in adults with cancer[15] and the general population.[13,14] This suggests that risk factors associated with ALL therapy override any genetic contribution to the increased risk of thrombosis experienced by Blacks in those studies. A related explanation is that social determinants of health may play a larger role in thrombosis risk in adults than in children receiving therapy for ALL. Interestingly, the SNP most strongly associated with thrombosis in non-European ancestry patients in our cohort differed from that seen in the population at large, suggesting the drivers of thrombosis may differ in patients of different ancestries being treated with ALL. This provides a potential explanation for our failure to replicate thrombosis SNP from a previously published ALL cohort.[12] Notably, although this cohort is more ancestrally diverse than prior analyses of European ancestry patients, our genomic ancestry classification does not differentiate patients of Middle Eastern ancestry from other patients and this population is not a large portion of the communities contributing patients to these trials. This is notable because patients of Middle Eastern ancestry have previously been reported to have a higher incidence of classic thrombophilia genetic variants than the European population.[9,10,22,23] Whether our genomic findings are extensible to this population is unknown and requires further study.

No SNP reached genome-wide significance in this analysis, suggesting that therapy factors and physiological changes with age are the dominant drivers of thrombosis risk during ALL therapy. Classic thrombophilia polymorphisms in prothrombin, factor V, and MTHFR were not associated with an increased risk of thrombosis during therapy in this cohort, consistent with some prior findings.[11,12] This supports our clinical practice to not routinely test for these variants in patients at diagnosis, although such routine testing may be indicated in populations with high rates of thrombophilia variants as noted above.

Non-O blood type was associated with a 2-fold increased incidence of thrombosis in this cohort. Non-O blood has previously been associated with an increased risk of thrombosis in children treated on Dana Farber trials for newly diagnosed ALL.[24] This increased risk of thrombosis is consistent with the increased risk thrombotic complications observed in individuals with non-O blood type in the general population.[25] The preservation of this risk in multivariable analysis and despite the strong impact of therapy suggests that the mechanism of increased risk associated with non-O blood is additive with the risks imposed by ALL therapy. Non-O blood type is associated with elevated levels of factor VIII and von Willebrand factor[26] and appears to increase thrombosis risk through this and other mechanisms.[25] Interestingly, the intronic rs2519093 variant in ABO increased thrombosis risk despite imperfect correlation with blood type (*Online Supplementary Table S2*) and in multivariate analysis including blood type. Prior work has linked this variant to increased soluble E-selectin and soluble intercellular adhesion molecule-1 independent of its association with blood group.[27] These two adhesion molecules have been associated with increased intravascular inflammation and thrombosis risk,[28] suggesting an alternative biological pathway driving thrombosis risk in this population.

Limitations of this study include its moderate size relative to most genomic discovery studies. This may limit our ability to identify new genetic variants associated with thrombosis. We addressed this limitation in part by evaluating variants previously associated with thrombosis risk in prior published GWAS. Findings in this asparaginase intensive regimen may be attenuated in children with ALL treated with less asparaginase-intensive therapy. However, because the rs2519093 variant and non-O blood are known to be risk factors in the general population (who receive no asparaginase), we

believe these findings are applicable to all children receiving ALL treatment. Interestingly, a variant in the α globin cluster rs55689276 was the top SNP in analyses limited to the non-European population, suggesting genetic risks of thrombosis converge on erythrocytes. The contribution of erythrocytes to thrombosis is now being documented in multiple contexts. Interactions between erythrocytes and oxidative stress contribute to thrombosis initiation and expansion,[29] erythrocyte transfusion increases the risk of thrombosis after orthopedic surgery,[30] and dysfunctional interactions between erythrocytes and vascular endothelium appear to contribute to COVID-19 associated thrombosis.[31] While the findings of this study suggest that age, disease, and treatment factors predominate in modulating the risk of thrombosis in children with ALL, it is possible that genetic risks may play a larger role in cohorts treated with less asparaginase. The increased risk associated with T-immunophenotype, older age, and non-O blood group are all likely to be maintained across cohorts due to their confirmation in multiple other settings. The convergence of genetic risks from this study around erythrocyte characteristics including ABO and globin SNP suggests a consistent impact from this tissue on thrombosis risk, consistent with identified risks in other settings. Further research is needed to understand the interaction of demographic, phenotypic, therapeutic, and genomic contributors to thrombosis risk in the ALL population, and whether the transfusions frequently given to this population impacts this risk.

In this large, ancestrally diverse cohort of children treated for ALL, clinical rather than genetic risk factors dominated the risk of thrombosis. This study both identifies easily assessable factors (older age, T immunophenotype, and non-O blood type) to further refine thrombosis risk while providing areas for future evaluation in other diverse cohorts. Such work may provide opportunities to target prophylactic interventions to reduce the frequency of this common toxicity from ALL therapy.

Disclosures

SEK has served as a consultant to Servier and on an advisory board for Jazz Pharmaceuticals. All other authors have no conflicts of interest to disclose.

Contributions

WY, MVR and SEK designed the study. YZ, SJ and CHP provided data and/or supervised the clinical trials. WY, DP, CC and SEK performed analyses. YZ, WY and SEK drafted the manuscript which was finalized with input from all authors.

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Data-sharing statement

De-identified data used in the preparation of this manuscript are available from the authors upon reasonable request for non-commercial use.

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