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Authors

Prasca, Saskia
Carmona, Roxana
Ji, Lingyun
et al.

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Obesity and risk for venous thromboembolism from contemporary therapy for pediatric acute lymphoblastic leukemia

Saskia Prasca[a], **Roxana Carmona**[a], **Lingyun Ji**[b], **Richard H. Ko**[a,c,1], **Deepa Bhojwani**[a,c], **Yasmin A. Rawlins**[d], **Steven D. Mittelman**[e,2], **Guy Young**[a,c], **Etan Orgel**[a,c,*]

[a]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, 4650 Sunset Blvd, Los Angeles, 90027, CA, USA

[b]Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, 1441 Eastlake Ave, Los Angeles, 90033, CA, USA

[c]Keck School of Medicine, University of Southern California, 1975 Zonal Ave, Los Angeles, 90033, CA, USA

[d]College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York, 10032, NY, USA

[e]Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles, Los Angeles, 4650 Sunset Blvd, Los Angeles, 90027, CA, USA

Abstract

Introduction: Acute lymphoblastic leukemia (ALL) therapy confers risk for venous thromboembolism (VTE) and associated acute and long-term morbidity. Obesity increases VTE risk in the general population but its impact on ALL therapy-associated VTE is unknown.

Methods: In a retrospective cohort of children treated for ALL between 2008 and 2016 (n = 294), we analyzed obesity at diagnosis (body mass index [BMI] ≥95%) and subsequent development of VTE. A subset participated in two concurrent prospective ALL trials studying body composition via dual-energy X-ray absorptiometry (DXA) (n = 35) and hypercoagulability via thromboelastography (TEG) (n = 46). Secondary analyses explored whether precise measurement of body fat and/or global hemostasis ex vivo by TEG could further delineate VTE risk in the obese.

*Corresponding author at: Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, 4650 Sunset Blvd., Los Angeles, CA 90027, USA. rcarmona@chla.usc.edu (R. Carmona), lingyun.ji@med.usc.edu (L. Ji), dbhojwani@chla.usc.edu (D. Bhojwani), yar2111@cumc.columbia.edu (Y.A. Rawlins), smittelman@mednet.ucla.edu (S.D. Mittelman), gyoung@chla.usc.edu (G. Young), eorgel@chla.usc.edu (E. Orgel).

[1]Present address: Genentech, Inc., South San Francisco, 410 Allerton Ave, South San Francisco, 94080, CA, USA.

[2]Present address: Division of Pediatric Endocrinology, UCLA Mattel Children's Hospital, 10833 Le Conte Ave, MDCC 22-315, Los Angeles, 90095, CA, USA.

Conflicts of interest

The authors declare that do not have potential conflicts of interest or financial involvement with any organization with an interest in the specific subject discussed. E.O. served on an Advisory Board for Jazz Pharmaceuticals and is on the Children's Oncology Group study committee for apixaban (referenced in the Discussion).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.02.150.

Results: Overall, we found 27/294 (9.2%) patients developed symptomatic VTE during therapy, 19/27 (70%) occurred during Induction. Study-defined “serious” VTE developed in 4/294 (1.4%) of patients. Obesity but not overweight was strongly predictive of symptomatic VTE (obesity odds ratio = 3.8, 95% confidence interval 1.5–9.6, $p = 0.008$). In the DXA subset, only 2/35 patients developed symptomatic VTE. However, within those prospectively screened during Induction, 30% (14/46) developed VTE; eight (17%) of these were asymptomatic and found only via screening.

Conclusions: In this pediatric ALL cohort, obesity conferred more than a three-fold increased risk for symptomatic VTE. In a subgroup of patients who underwent active screening, up to a third were noted to have VTE (symptomatic and asymptomatic). TEG did not predict VTE. Additional studies are necessary to validate these findings and to further refine a risk-stratified approach to thrombo-prevention during ALL therapy.

Keywords

Obesity; Venous thromboembolism; Thrombosis; Acute lymphoblastic leukemia; Asparaginase; Body mass index

1. Introduction

Pediatric venous thromboembolism (VTE) has an estimated incidence of 0.07 to 0.49 per 10,000 children in developed countries [1], The incidence is much higher in hospitalized children with a reported rate of 58 in 10,000 admissions [2,3]. The current widespread use of central venous catheters (CVC) during hospitalizations likely contributes to this risk [4]; children with leukemia and other chronic comorbidities and malignancies are at even greater risk [5–7]. In acute lymphoblastic leukemia (ALL), the inclusion of L-Asparaginase is associated with the development of VTE [8]. Asparaginase exposure begins at the outset of therapy during the Induction phase (the first month of chemotherapy) and continues through the intensive six to eight months of pre-Maintenance treatment phases. Estimates for prevalence of VTE during ALL therapy range from ~5–37% depending on regimen, asparaginase formulation, and surveillance methodology (i.e. use of screening versus symptomatic reporting) [9,10]. Only limited reports describe VTE risk from PEGylated L-asparaginase (PEG-ASP), the most common, contemporary formulation of asparaginase now used internationally in nearly all pediatric ALL regimens. The pro-thrombotic effect of asparaginase consists of an acquired antithrombin deficiency, among others [11].

Obesity is a well-described risk factor for VTE in children, particularly in those with increased adiposity [12,13]. While both obesity and fat gain are common during pediatric ALL therapy [14,15], their specific contribution to risk for therapy-associated VTE is unknown. To better understand the risk factors contributing to thrombosis in this patient population, we examined the impact of obesity and other clinical and laboratory predictors of VTE. Improved understanding of the potentiating factors for therapy-associated VTE is essential to develop risk-stratified approaches to thrombo-prevention in this population.

2. Methods

2.1. Retrospective study cohort

A retrospective cohort study was conducted for patients 1–21 years of age diagnosed with ALL between January 2008 and November 2016. Patients with a height and weight measurement at diagnosis and follow-up through the intensive pre-Maintenance chemotherapy treatment phases (Induction, Consolidation, Interim Maintenance 1, Delayed Intensification, ± Interim Maintenance 2) were included. All patients were treated using Children's Oncology Group (COG) regimens for frontline ALL therapy for NCI/Rome Standard-Risk (SR-ALL: CCG1991, AALL0331, AALL0932), High-Risk B-ALL (HR-ALL: modified CCG1961 [PEG-ASP during Induction], AALL08P1, AALL0232, AALL1131), or T-ALL (AALL0434) (complete details for each regimen accessible on the trial registry website: https://clinicaltrials.gov). Demographic data included sex, age, self-reported ethnicity, and body mass index percentile [BMI%] at diagnosis. Clinical information consisted of leukemia phenotype [B-ALL or T-ALL], Induction chemotherapy intensity (i.e. a three-drug [vincristine, steroid, PEG-ASP] or four-drug Induction [+anthracycline]), and Induction steroid (dexamethasone or prednisone). Data for study endpoints consisted of presence of symptomatic VTE (yes/no), phase of therapy when VTE occurred, whether related to the presence of a CVC, and whether the VTE was considered "serious" (defined as sinus venous thrombosis, other intracranial thrombus, pulmonary embolus [PE], or requiring critical care).

2.2. Description of prospective cohort

A subset of patients was also enrolled on either of two concurrent prospective studies in pediatric ALL that were accruing patients during the study period. Germane aspects of these studies and data for secondary analyses are summarized here. The first was a clinical trial [16] testing Vitamin D and calcium supplementation in 10–21 year old ALL patients after Induction to preserve bone health (Trial #1); a key secondary aim of the trial focused on assessment of body fat during the ALL Induction phase and prior to the randomized intervention. As described in the primary manuscript, body fat was directly measured at diagnosis and at end of Induction with the gold-standard of body composition assessment using a fan beam dual energy x-ray absorptiometry (DXA) densitometer (Delphi W; Hologic, Inc., Waltham, MA) in array mode. Body fat was calculated from manufacturer software for body fat percentage (BF%) and total fat mass (FM). In this trial, only information for symptomatic VTE were collected. The second prospective study [17] explored the use of thromboelastography (TEG) as a measure of global hemostasis to predict VTE during Induction for pediatric ALL in children 1–21 years of age (Trial #2). Blood samples were collected at diagnosis and weekly from CVCs into sodium citrate tubes. As previously described [18], tubes for TEG analysis were pre-filled with 50 μg/mL corn trypsin inhibitor (CTI). Analyses were run with 340 μL of blood added to TEG cups containing 20 μL of CaCl2. Both heparinase cups and pins and plain cups and pins were utilized. All samples were run in duplicate. All patients without symptomatic VTE were then screened at the end of Induction via ultrasound of the CVC-containing extremity. Presence of VTE was therefore further classified as symptomatic or asymptomatic (i.e. found only on screening). Additional hypercoagulability markers were drawn weekly (thrombin-

antithrombin complexes [TAT], prothrombin fragment 1 + 2 [PTF1 + 2]). For this post-hoc analysis, BF%, FM, and the principal TEG parameters (R = reaction time, K time = speed of clot formation, and MA = clot strength) were extracted. Patients co-enrolled on both trials were identified for further comparison of predictors of VTE. All studies were approved by the Institutional Review Board. Informed consent with appropriate documentation was obtained prior to enrollment for the prospective studies. The clinical trial for body composition was registered prior to first patient enrollment (NCT01317940).

2.3. Statistical methods

The study's primary objective was to investigate the association between obesity defined by BMI% at diagnosis and the risk for developing VTE during ALL therapy. Secondary objectives included assessment of the association of VTE with other candidate clinical predictors and/or TEG parameters for hemostasis. Additional descriptive aims included evaluation of phase of first VTE, CVC-related versus not-related, and incidence of study-defined "serious" VTE. BMI% was classified according to CDC age/sex norms (normal < 85%, overweight 85–94.9%, obese ≥95%) [19] with "length for weight" for patients 1–2 years old. Univariable and multivariable logistic regression models were used to examine the association between patient characteristics as described in Table 1 and risk for symptomatic VTE. To then analyze the predictive utility of TEG in the smaller prospective cohort, a second multivariable model was constructed limited to the strongest predictors. To do so, the initial model was refined using reverse stepwise selection with elimination and re-fitting of candidate variables (retention in model set at $p \leq 0.20$). Each TEG parameter was then tested against the resulting minimal multivariable model for the endpoint of any VTE (symptomatic or asymptomatic) and retained using the same threshold. A Weibull parametric survival model was used to assess if the risk for a first VTE (i.e. the "failure event") decreased over subsequent treatment phases (constrained as time 1, time 2, etc.) as indicated in the model by a shape parameter $p < 1$. For assessment of the predictive value of FM, BF%, and serum hypercoagulable measures (TAT, PTF1 + 2) in the prospectively screened cohort, non-parametric Wilcoxon rank-sum tests were used to analyze their association with occurrence of any VTE (symptomatic or asymptomatic). All p-values are two-sided with $p \leq 0.05$ considered statistically significant. All statistical analyses were performed using STATA software (StataCorp 2015, Stata Statistical Software: Release 11, College Station, TX: StataCorp LP).

3. Results

A total of 294 patients with ALL were included in the retrospective cohort (Table 1). In the cohort, 36% of patients were either overweight or obese. As per overall institutional demographics, the majority of patients self-identified as Hispanic (77%). The prospective sub-cohort (Suppl. Table 1) included 35 patients enrolled on Trial #1 (body composition), 46 patients enrolled on Trial #2 (TEG/VTE), and 13 subjects co-enrolled on both prospective studies (Trial #1 and #2, Suppl. Table 2). Out of 294 patients, 27 (9.2%) developed symptomatic thrombosis during treatment for ALL. The majority of VTE were associated with a CVC (20/27, 74%) and developed at the onset of therapy following the first dose of PEG-ASP during the initial Induction phase (19/27, 70%). Seven of the VTE were not

related to a CVC. Four of these occurred in the lower extremity, one of which was associated with a PE, and three patients developed sinus venous thrombosis. No other intracranial thrombosis or critical care admissions occurred in the cohort. The total "serious" VTE rate was 1.4% (4/294).

3.1. Obesity and risk for VTE

A clear correlation between obesity and VTE was found in the overall cohort. Nearly one in five patients who were obese to start Induction had a symptomatic VTE during therapy (19%, 12/64). The prevalence of symptomatic VTE in obese patients was more than twice that of patients who were either normal (6%) or overweight (7%) at diagnosis (Table 1). Induction remained the highest risk phase for obesity-associated first VTE with 9/12 (75%) symptomatic VTE in this group occurring within the first month (Table 2). In the Weibull model, the risk for developing a first VTE significantly decreased over consecutive treatment phases ($p = 0.047$). On multivariable analyses, compared to normal weight patients, being obese at diagnosis remained strongly associated with development of a symptomatic VTE; no difference was found in those only overweight (overweight odds ratio [OR] = 1.1, 95% confidence interval [95%CI] 0.28–4.1; obese OR = 3.8, 95%CI 1.5–9.6; global $p = 0.008$). After accounting for the impact of obesity, no other candidate predictors were significantly associated with symptomatic VTE. Notably, ethnicity, older age, Induction type (addition of anthracycline or steroid formulation), and treatment intensity were not associated with VTE (Table 3). No interaction between BMI and age or ethnicity was found (BMI/age: $p = 0.38$; BMI/ethnicity: $p = 0.24$).

3.2. Prediction of VTE in obese

In patients who received screening for VTE on Trial #2, 13% (6/46) had symptomatic VTE and an additional 8 patients had asymptomatic thrombosis for a total prevalence of ~30% (14/46). The distribution of VTE on Trial #2 is described in Table 4. After adjusting for BMI category and age, no TEG parameters were independently associated with the probability of developing a VTE (R time: OR 0.05, 95%CI 0.001–3.0; K time: OR 0.17, 95%CI 0.01–2.4; MA: OR 2.9, 95%CI 0.25–33) (Table 4). For the 35 patients with direct measurement of body fat from Trial #1, only two patients developed symptomatic VTE, one of which occurred in an obese patient (by BF% on DXA and by BMI %). For the patients co-enrolled on both trials and prospectively screened, four additional patients in this sub-cohort were found to have asymptomatic VTE ($n = 6/13$) (Suppl. Table 2). In co-enrolled patients, no significant differences were found between patients who developed VTE versus those who did not in terms of TEG parameters (all $p > 0.5$), FM ($p = 0.78$), BF% ($p = 0.89$), TAT ($p = 0.43$) or PTF1 + 2 ($p = 0.47$). No radiographic or laboratory biomarkers of adiposity or hypercoagulability were associated with VTE.

4. Discussion

Pediatric patients being treated for ALL are at significant risk for developing a VTE during therapy [20] resulting in acute and long-term morbidity [21]. We found obesity in newly diagnosed pediatric ALL patients to be strongly associated with symptomatic VTE. The heightened risk for obesity-associated VTE during ALL therapy observed here is close to

twice that reported in non-oncology obese populations [22,23]. Although adiposity is a well-characterized risk factor for VTE in the general population [24,25], FM% was not associated with symptomatic VTE in our cohort. VTE events were unexpectedly sparse in the DXA trial during ALL therapy despite the increases in FM% seen in the study cohort [15]. Many patients lost corresponding amounts of muscle mass during therapy ("sarcopenic obesity"), and this might have potentially influenced the association of FM% and VTE risk. Additional investigation is necessary to further define the contribution of directly-measured adiposity during ALL therapy to hypercoagulability. Nonetheless, the more than three-fold greater risk for VTE found in the cohort's obese patients strongly supports VTE as an obesity-associated treatment-related toxicity from contemporary ALL regimens.

In our cohort, the majority of VTE occurred during Induction. It is possible that the presence of leukemia is associated with a hypercoagulable state. As three-quarters of the VTE were CVC-associated, a portion of the Induction-associated risk is also likely due to disruption of the vascular endothelium from the initial CVC placement at time of diagnosis. However, this increased VTE risk is not replicated when CVCs are replaced later in therapy, or as per institutional practice in our cohort, changed for a portacath at start of Consolidation. Similarly, the Induction VTE risk is unlikely to be entirely a chemotherapy effect. PEG-ASP is incorporated intermittently throughout the first year of treatment with only rare PEG-ASP associated VTE post-Induction. Prolonged glucocorticoid exposure may contribute to increasing susceptibility to VTE in Induction, but exposure to glucocorticoids later in therapy during the Delayed Intensification phase resulted in only minimal rates of new VTE. In older ALL trials inclusive of non-pegylated L-asparaginase, type of glucocorticoid impacted risk for VTE; patients receiving dexamethasone-based Induction regimens were at greater risk for VTE [26]. We did not find a significant difference in patients receiving prednisone versus dexamethasone for Induction, but additional larger studies are necessary to fully address this question for contemporary ALL regimens.

Increased precision in determining the risk for VTE in obese patients would facilitate further refinement of targeted thrombo-prevention in this at-risk group. Previous studies of hemostatic alterations in the obese [27], and of a thrombin generation assay and elevated fibrinogen in pediatric ALL, suggest hypercoagulability in these populations, and hence, a means to measure for potential increased risk for thrombosis [28–31]. Traditionally, TEG is a reliable assay to evaluate global hemostasis and hyperfibrinolytic conditions [32]. Despite increased thrombin detection sensitivity from the addition of CTI, while TEG indicated hypercoagulability it unfortunately did not predict or differentiate those patients who developed a VTE versus those who did not. Previous studies assessing the predictive value of TEG for thrombosis are scarce, conflicting, and dissimilar to our target population of pediatric ALL [33–35]. We cannot exclude that this small pilot study of obesity, TEG, and VTE may underestimate the ability of TEG to predict VTE, yet the relatively high prevalence of VTE without an associated TEG signal suggests this is likely not the case. Although markers of hypercoagulability such as TAT and PTF1 + 2 have been associated with presence of VTE in other oncology populations [36,37], we did not see a trend for VTE within the limited co-enrolled cohort. Even with the relatively high prevalence of VTE in this subset, interpretation of this negative finding is challenging given the smaller sample size.

Comparison of VTE rates described here from the use of PEG-ASP on the included contemporary regimens versus reports of earlier asparaginase formulations demonstrates no clear differences in VTE risk. While < 2% of patients experienced a “serious” VTE, we found approximately one in ten children treated for ALL experienced symptomatic VTE, a rate similar to prior reports inclusive of childhood ALL [38,39]. The incidence for VTE found via screening was significantly higher with 30% of the cohort developing a symptomatic or asymptomatic VTE. Surprisingly, only age was significantly associated with VTE in the prospectively screened cohort, and this was irrespective of leukemia risk category, Induction regimen, and even weight category at diagnosis. The last finding is in contrast with the larger retrospective cohort where a clear association was found between obesity and symptomatic VTE. An explanation for this discrepancy is not readily apparent. As the direction of effect for age and obesity is consistent across models, this might be a limitation of the smaller prospective trial size. However, if a difference is truly present and replicated in larger cohorts, one also might postulate that obesity-associated inflammation may be associated with a greater likelihood of developing a symptomatic VTE.

Despite the low rate of acute “serious” morbidity and mortality, VTE significantly influences immediate and long-term quality of life. In pediatric patients, the current standard approaches to anticoagulation utilizes low-molecular weight heparin (LMWH), thereby necessitating months of painful injections. Many patients who develop ALL therapy-associated VTE and become long-term survivors will then develop post-thrombotic syndrome (PTS) as a late complication. Of note, in survivors of pediatric ALL, the incidence of PTS after asymptomatic VTE (54%) can be as high as that for symptomatic VTE (63%) [40]. PTS adversely impacts long-term quality of life and, specifically, results in size discrepancies of the affected limbs, chronic pain, functional impact, and potential VTE recurrence [41]. Effective and safe thrombo-prophylaxis for children undergoing ALL treatment is necessary. Use of LMWH for thrombo-prophylaxis for this purpose is controversial with evidence to date limited to small non-randomized studies [42,43]. The first randomized clinical trial assessing the efficacy and safety of LMWH thrombo-prophylaxis during treatment for pediatric ALL in children is currently in progress [44]. A similar, open-label randomized clinical trial being conducted in collaboration with the COG is currently evaluating the safety and efficacy of thrombo-prophylaxis with the oral agent apixaban during Induction therapy for children with ALL (NCT02369653). Understanding which patients are at high risk for VTE would help inform the design and clinical application of these and future randomized trials of thrombo-prophylaxis. As VTE during ALL therapy is often asymptomatic, predicting which patients are at risk for thromboembolism would allow targeted screening and/or implementation of thrombo-prophylaxis [45].

Combining a broad retrospective cohort with detailed prospective secondary analyses provided new insights into obesity and hypercoagulability during ALL therapy. However, several limitations are inherent to this approach. We would note the dataset only includes assessment of obesity at diagnosis and at the end of induction. This therefore precluded calculating the attributable risk to VTE during Induction from changes in body fat. Similarly, fewer than expected patients developed symptomatic VTE in the DXA cohort from Trial #1, limiting the in-depth analyses of fat quantification and symptomatic VTE. No

discernable trends were present in the co-enrolled prospective cohort. Patients at our institution near uniformly receive a single-lumen PICC for the duration of the Induction phase thereby precluding comment on the contribution of type of CVC to therapy-associated VTE risk in obese patients. Similarly, a small minority of patients might have transferred to an alternative asparaginase formulation later in therapy due to PEG-ASP allergy; this data was not available for comparison. We also cannot exclude the possibility that a subtle benefit from direct measurement of body fat and/or laboratory assessment of hemostasis were not detected due to the smaller samples sizes of the prospective sub-cohorts. We found no significant interaction between ethnicity, obesity, and VTE; of note, the lower incidence of VTE typically present in Hispanic populations may even suggest under-representation of the VTE risk in this study as compared to the general ALL population [46]. We conclude that obesity is an independent, strong risk factor for developing VTE during ALL therapy, and particularly during the Induction phase. This risk is present irrespective of ethnicity, age, leukemia phenotype, and treatment intensity. Obese children newly diagnosed with ALL may benefit from preventive prophylaxis regimens. Prospective, multicenter studies are needed to validate this latest finding and to develop risk-stratified approaches to thrombo-prediction during chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of retrospective cohort.

Variables	Cohort	Symptomatic VTE			
	N	Yes		No	
		n	(%[a])	*n*	(%[a])
All patients	294	27	9.2	267	90.8
Age					
Median (range)	7.0	10.0	(1.1–19.6)	8.3	(1.3–18.8)
< 10 years	177	12	(6.8)	165	(93.2)
≥10 years	117	15	(12.8)	102	(87.2)
Sex					
Female	131	12	(9.2)	119	(90.8)
Male	163	15	(9.2)	148	(90.8)
Ethnicity					
Non-Hispanic	68	7	(10.3)	61	(89.7)
Hispanic	226	20	(8.9)	206	(91.1)
NCI/Rome risk group					
Standard risk B-ALL	137	8	(5.8)	129	(94.2)
High risk B-ALL	132	17	(12.9)	115	(87.1)
T-ALL	25	2	(8.0)	23	(92.0)
Induction type					
3-drug, Dex	137	8	(5.8)	129	(94.2)
4-drug, Dex	26	2	(7.7)	24	(92.3)
4-drug, Pred	131	17	(13.0)	114	(87.0)
Weight category at diagnosis[b]					
Normal	188	12	(6.4)	176	(93.6)
Overweight	42	3	(7.1)	39	(92.9)
Obese	64	12	(18.8)	52	(81.3)
Treatment phase of first VTE					
Induction	294	19	(6.5)	275	(93.5)
Consolidation	275[c]	4	(1.5)	271	(98.5)
Interim Maintenance I	271[c]	2	(0.7)	269	(99.3)
Delayed Intensification	269[c]	2	(0.7)	267	(99.3)
Interim Maintenance II	267[c]	0	(0)	267	(100)
Start of maintenance	267[c]	–	–	–	–

[a]%VTE reports the percent of each variable who developed VTE.

[b]According to CDC age/sex norms, body mass index percentile; normal ≤85%, overweight 85– < 95%, obese≥95%.

[c]*n* = remaining patients without thrombosis. NCI = National Cancer Institute, Dex = dexamethasone, Pred = prednisone, BMI = Body mass index, VTE = venous thromboembolism.

Table 2

Distribution of patients in the retrospective cohort by timing of first symptomatic venous thromboembolism.

Variables	VTE+				
	Total	Treatment phase			
		Induction		Post-induction	
	n	*n*	(%[a])	*n*	(%[a])
All patients with VTE	27	19	(70)	8	(30)
Age					
< 10 years	12	10	(83)	2	(17)
≥10 years	15	9	(60)	6	(40)
Sex					
Female	12	8	(67)	4	(33)
Male	15	11	(73)	4	(27)
Ethnicity					
Non-Hispanic	7	6	(86)	1	(14)
Hispanic	20	13	(65)	7	(35)
NCI/Rome risk group					
Standard risk B-ALL	8	7	(88)	1	(12)
High risk B-ALL	17	10	(59)	7	(41)
T-ALL	2	2	(100)	0	(0)
Induction type					
3-drug, Dex	8	7	(88)	1	(12)
4-drug, Dex	2	2	(100)	0	(0)
4-drug, Pred	17	10	(59)	7	(41)
Weight category at diagnosis[b]					
Normal	12	8	(67)	4	(33)
Overweight	3	2	(67)	1	(33)
Obese	12	9	(75)	3	(25)

[a]Proportion of patients within each category who developed VTE.

[b]According to CDC age/sex norms, body mass index percentile; normal ≤85%, overweight 85– < 95%, obese≥95%, VTE = venous thromboembolism, OR = Odds ratio, 95%CI = 95% Confidence Interval, NCI = National Cancer Institute, Dex = dexamethasone, Pred = prednisone.

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Table 3

Multivariable analyses for risk of symptomatic venous thromboembolism ($n = 294$).

Variables	*n*	Univariable			Multivariable Model#1[a]			Multivariable Model #2[b]		
		OR	(95%CI)	*p*	OR	(95%CI)	*p*	OR	(95%CI)	*p*
Age										
< 10 years	177	1.0		0.083	1.0		0.610	1.0		0.197
≥10 years	117	2.0	(0.91, 4.5)		0.64	(0.12, 3.3)		1.7	(0.76, 3.9)	
Sex								Excluded		
Female	131	1.0		0.990	1.0		0.338			
Male	163	1.0	(0.45, 2.2)		0.65	(0.27, 1.6)				
Ethnicity								Excluded		
Non-Hispanic	68	1.0		0.721	1.0		0.404			
Hispanic	226	0.85	(0.34, 2.1)		0.66	(0.25, 1.7)				
Treatment intensity								Excluded		
NCI SR B-ALL	137	1.0		0.059	Omitted due to collinearity					
NCI HR B-ALL/T-ALL	157	2.2	(0.94, 5.2)							
Induction type								Excluded		
3-drug, Dex	137	1.0		0.124	1.0		0.315			
4-drug, Dex	26	1.0	(0.26, 6.4)		1.1	(0.20, 5.6)				
4-drug, Pred	131	2.4	(0.99, 5.8)		3.3	(0.59, 18)				
Weight category at diagnosis[c]										
Normal	188	1.0		0.008[d]	1.0		0.008[d]	1.0		0.015[d]
Overweight	42	1.1	(0.29, 4.1)		1.1	(0.28, 4.1)		1.1	(0.30, 4.1)	
Obese	64	3.4	(1.4, 7.9)		3.8	(1.5, 9.6)		3.1	(1.3, 7.3)	

[a] Multivariable model #1 includes all candidate variables.

[b] Multivariable Model #2 is a minimal model from stepwise reverse selection (retention $p \leq 0.20$). See methods for additional detail.

[c] According to CDC age/sex norms, body mass index percentile; normal ≤85%, overweight 85– < 95%, obese ≥ 95%, OR = Odds ratio, 95%CI = 95% Confidence Interval, NCI = National Cancer Institute, Dex = dexamethasone, Pred = prednisone.

[d] *p*-Value from trend test.

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Table 4

Multivariable analysis for risk of symptomatic or asymptomatic venous thromboembolism in prospectively screened cohort ($n = 46$).

Variables	Cohort (n)	VTE		Univariable Analysis			Multivariable analysis[a]		
		(*n*)	(%[b])	OR	(95%CI)	*p*	OR	(95%CI)	*p*
Age									
< 10 years	33	7	(21)	1.0		0.034	1.0		0.030
≥10 years	13	7	(54)	4.3	(1.1, 17)		5.0	(1.1, 22)	
Sex									
Female	17	6	(35)	1.0		0.585	Excluded		
Male	29	8	(28)	0.70	(0.19, 2.5)				
Ethnicity									
Non-Hispanic	9	3	(33)	1.0		0.834	Excluded		
Hispanic	37	11	(30)	0.85	(0.18, 4.0)				
Treatment intensity									
NCI/Rome SR B-ALL	26	6	(23)	1.0		0.217	Excluded		
NCI/Rome HR B-ALL/T-ALL	20	8	(40)	2.2	(0.62, 8.0)				
Induction type									
3-drug, Dex	26	6	(23)	1.0		0.093	Excluded		
4-drug, Dex	7	1	(14)	0.56	(0.06, 5.6)				
4-drug, Pred	13	7	(54)	3.9	(0.94, 16.0)				
Weight category at diagnosis[c]									
Normal	28	6	(21)	1.0		0.158[d]	1.0		0.306[d]
Overweight	6	3	(50)	3.7	(0.58, 23)		3.1	(0.38, 25)	
Obese	12	5	(42)	2.6	(0.61, 11)		2.1	(0.45, 10)	
TEG R time at baseline									
For every doubling	n/a			0.05	(0.001, 3.0)	0.155	0.05	(0.001, 4.0)	0.176
TEG K time at baseline	n/a								
For every doubling		0.17	(0.01, 2.4)	0.178			Excluded		
TEG MA at baseline	n/a								
For every doubling		2.9	(0.25, 33)	0.381			Excluded		

[a] This multivariable model included age and weight category that were in the minimal model in Table 3, and TEG parameters (R time, K time, or MA) were then individually tested and retained if $p \leq 0.20$. See methods for additional detail.

[b] Proportion of patients within each category who developed VTE.

[c] According to CDC age/sex norms, body mass index percentile; normal ≤ 85%, overweight 85– < 95%, obese ≥ 95%.

[d] p-Value from trend test. VTE = venous thromboembolism, OR = Odds ratio, 95%CI = 95% Confidence Interval, NCI = National Cancer Institute, Dex = dexamethasone, Pred = prednisone, TEG = thromboelastography. n/a = not applicable.