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Full Length Article

Risk factors for symptomatic venous thromboembolism during therapy for childhood acute lymphoblastic leukemia☆

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ABSTRACT

Background: Symptomatic venous thromboembolism (VTE) is an unpredictable and life-threatening toxicity, which occurs early in childhood acute lymphoblastic leukemia (ALL) therapy. Approximately 5% of children will experience VTE which is treated with anticoagulation. Asparaginase and corticosteroids are etiologic factors for VTE, however other clinical factors may modify this risk.

Procedure: We sought to i) assess published pre-treatment VTE risk factors ii) identify early clinical factors that were associated with VTE and iii) determine whether single nucleotide polymorphisms (SNPs) associated with VTE in non-cancer patients contributed to VTE in children with ALL. We performed a detailed, retrospective analysis of 1021 ALL patients treated between 1998 and 2013. Individual patient records were reviewed to ascertain VTE incidence and document treatment-related clinical variables.

Results: The incidence of VTE was 5.1%. Extremes of weight at diagnosis (< 5th or > 95th centile) was an independent risk factor in multivariable analysis, when added to published risk factors of age ≥10 years and mediastinal mass. When factors during induction/consolidation were considered separately: bacteremia, elevated serum gamma-glutamyl transferase and bilirubin were associated with VTE occurrence. None of the SNPs associated with VTE in non-cancer populations were significantly associated with VTE in our cohort.

Conclusion: We found two known risk factors (age ≥ 10 years and mediastinal mass) in a large cohort of children

Abbreviations: ALL, acute lymphoblastic leukemia; ANZCCSG, Australian and New Zealand Children's Cancer Study Group; ANZCHOG, Australian and New Zealand Children's Haematology and Oncology Group; BMI, body mass index; COG, Children's Oncology Group; CR1, first complete remission; CVL, central venous line; EFS, event-free survival; ERASE, Evaluation of Risk of ALL Treatment-related Side-Effects; GGT, gamma-glutamyl transferase; GWAS, genome wide association study; LFS, leukemia-free survival; MAF, minor allele frequency; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; RF, risk factor; SNP, single nucleotide polymorphism; VTE, symptomatic venous thromboembolism; TRT, treatment related toxicity; VTE, venous thromboembolism

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treated for ALL and identified other factors associated with VTE such as weight extremes at diagnosis, bacteremia, and abnormal liver function which warrant further study. These VTE risk factors may form the basis of future thromboprophylaxis trials.

1. Introduction

Symptomatic venous thromboembolism (VTE) is an unpredictable and life-threatening complication of therapy for childhood acute lymphoblastic leukemia (ALL), with an incidence of 5% [1–5]. Previously recognized factors associated with increased VTE risk include central venous lines (CVL), older age [2,6,7] and concomitant steroid and asparaginase therapy [1]. Additional factors such as T-immunophenotype [8], mediastinal mass [9], remission induction failure [6] and non-O blood type [10] may also play a role. In contrast, the incidence of VTE in the general pediatric hospitalized population is lower, approximately 5 VTE cases/100,000 children, with a frequently observed bimodal distribution in neonates and adolescents [11,12].

VTEs occur early in therapy, with the majority during induction and consolidation phases, coinciding with asparaginase and steroid treatment [1,9,13]. VTE, under normal physiological conditions, occurs as a result of platelet adhesion to exposed venous vascular endothelium, via a bridging molecule, von Willebrand factor [14]. In ALL, there are likely contributory host factors that increase the pro-inflammatory and pro-thrombotic milieu [15,16]. A nexus exists between CVL-related bacteremia and VTE [15,17]. Extremes of weight or body mass index (BMI) [18], drug-induced pro-coagulant mechanisms [19], liver dysfunction [20–22], hereditary thrombophilia and/or genetic polymorphisms may be additional factors [19,23]. While inherited thrombophilia increases VTE risk in the general population, there is uncertainty about the contribution of prothrombotic conditions such as Factor V Leiden mutation (known as c.1691 G > A, c.1601 G > A or rs6025 [24]) and the prothrombin gene G20210A polymorphism in ALL [1,4,25]. Genetic predisposition factors may also differ in ethnic populations, such as Factor V Leiden mutation which occurs in up to 15% of Turkish children diagnosed with ALL [26–28], as compared to Caucasian populations where the frequency is closer to 5% [26]. A prospective study of children treated on BFM-based ALL protocols found that hereditary thrombophilia only confers an additional VTE risk in the presence of combined asparaginase and steroid treatment [4].

The presence of a central venous line and the type of asparaginase used differ according to the protocol and national practices and there may be additional clinical factors that are important to consider in assessing a patient's risk of VTE. Recently, Rank et al showed that older age, presence of a mediastinal mass and lymphadenopathy at diagnosis were significantly associated with VTE risk in a prospective ALL study (NOPHO ALL2008) [9]. Thromboprophylaxis using enoxaparin in ALL induction therapy has been shown to be safe and to reduce incidence of VTE in children and adolescents, although the lack of acceptance of treatment allocation to the subcutaneous enoxaparin arm was high [29]. Therefore, identification of a high risk subgroup(s) could form the basis of targeted thromboprophylaxis strategies [4].

We sought to assess baseline clinical VTE risk variables shown to be important in other pediatric ALL regimes, in patients treated on BFM-based platforms and, secondly, to explore the association between selected early treatment-related clinical factors and development of VTE. Additionally we wished to determine if SNPs known to be associated with an increased VTE risk in the general population were associated with VTE in children and teenagers treated for ALL.

2. Materials and methods

The ERASE (Evaluation of Risk of ALL Treatment-related Side-Effects) study was designed to identify clinical and genetic risk factors for severe treatment related toxicity (TRT) in a retrospective cohort of consecutively diagnosed patients with acute lymphoblastic leukemia/lymphoma in 5 Australian hospitals between 1/1/1998 and 31/12/2013. Participating centers were Sydney Children's Hospital, Children's Hospital Westmead, John Hunter Children's Hospital, Royal Children's Hospital Melbourne, and Women's and Children's Hospital Adelaide. The ERASE study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Reference Number: 12/11/21/4.01). Targeted TRTs included, but were not limited to, VTE, bone toxicity and neurotoxicity. Patients were enrolled on, or treated according to, consecutive BFM-based ALL protocols used by Australian and New Zealand Children's Haematology Oncology Group (ANZCHOG) centres including ANZCCSG Study VII [30], ANZCHOG Study 8 [31], AIEOP-BFM ALL 2009-Study 9 [32], COG A5971 [33] and BFM-95 [34]. The protocols had similar four drug induction and consolidation phases (Supplementary Tables S1 and S2). Most patients in the cohort (96.08%) received *E. coli* L-asparaginase as standard therapy.

The ERASE study inclusion criteria included children and teenagers (1–18 years), diagnosed with primary ALL/lymphoma. Data was collected on every patient who experienced ≥1 TRT. Data on patients without any of the targeted TRTs was not collected unless there was follow up of ≥18 months from diagnosis, to ensure an adequate period during which TRTs were likely to have occurred. Exclusion criteria were designed to exclude patients who could not be reliably assessed in relation to experiencing TRT; and included lack of clinical data, early treatment related death (from a toxicity other than VTE or neurotoxicity) and/or < 18 months of follow-up from diagnosis in patients without documented TRT.

Individual clinical records, imaging and laboratory results were reviewed for the entire ERASE cohort, to systematically collect data on children who did and did not experience TRTs during firstline ALL therapy. Pre-treatment clinical variables that were specifically explored for the VTE analysis included age at diagnosis, immunophenotype (T vs B), presence of a mediastinal mass, weight, body mass index (BMI), and ABO blood group (O vs non-O). Early treatment-related variables were designated as those occurring during induction/consolidation, to allow a consistent time-frame for data capture for children who did and did not experience VTE. Data collected included remission status at end of induction (day 33), elevated creatinine levels (serum creatinine during induction/consolidation > 2× creatinine at ALL diagnosis), bacteremia and fungal infections in induction/consolidation; and presence of Grade 3 liver toxicities during induction/consolidation based on CTCAE criteria [35] – peak bilirubin > 3× upper limit normal (ULN), peak AST > 5× ULN, peak GGT > 5× ULN. These variables were chosen based on prior literature indicating potential association with VTE [6,15,17,18,22,23].

VTE cases were defined as patients with a documented VTE while undergoing treatment for newly diagnosed ALL whereas those without VTE were ALL patients who did not experience VTE (however these patients may have experienced other TRTs). VTE was confirmed by corroborating evidence including medical imaging (*e.g.* Doppler ultrasound, CT venography) and/or anticoagulant use (therapeutic dosing prescription and therapeutic anticoagulant monitoring, with confirmation in clinical notes). VTE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 [35]. Central venous line (CVL)-associated VTE was defined as a VTE occurring in the vein in which a CVL was placed.

Statistical analysis was performed using IBM SPSS for Macintosh, Versions 23.0 and 24.0. Overall survival (OS) was calculated from date of diagnosis through to last contact or death from any cause. Event-free

survival (EFS) was calculated as the time from diagnosis to first event or last contact in CR1. An event was defined as relapse, death from any cause or secondary malignancy. Leukemia-free survival (LFS) was determined from date of remission to first relapse or last contact in CR1. Comparison between groups, for categorical data, was conducted using Pearson Chi-squared analysis; or Fisher's exact test (2-sided) where expected values were < 5. Intergroup comparisons for continuous variables were performed using logistic regression. Analysis of OS, EFS, LFS for the cohort and cumulative event analysis for VTE was performed using the Kaplan Meier method.

Univariate and multivariable analysis was conducted to identify pre-treatment clinical factors associated with VTE. Individuals (with and without VTE) with incomplete data for variables of interest were censored. Categorical variables were assessed using Pearson Chi-squared analysis, with the use of Bonferroni correction. Pre-treatment variables with a significance level $P < 0.10$ were assessed for independent association with VTE development in multivariable regression analysis that included published risk factors age ≥10 years and mediastinal mass. Separately, an exploratory analysis was conducted to assess association of 7 chosen treatment-related variables (induction failure, bacteremia, fungal infection, renal impairment, hyperbilirubinemia, aspartate aminotransferase (AST) elevation, gamma glutamyl transferase (GGT) elevation) with VTE. Univariate analysis was performed, with Bonferroni correction, and significance level was set at $P < 0.007$ (0.05/7) [36]. Factors were also assessed for categorical variables in univariate logistic regression to determine odds ratios with 95% confidence intervals.

A germline genome wide association study (GWAS) was performed using remission bone marrow. From the 1021 patient cohort, remission DNA samples were available for 932. Genotyping was performed on the Illumina OncoArray platform at Genome Quebec, Canada. Samples from individuals of Caucasian ancestry, based on the 1000 Genomes [37], were analyzed. The GWAS analysis was restricted to a homogenous ethnic population group to reduce the risk of false positive results due to population stratification [38]. After sample quality control and exclusion of non-Caucasian samples, GWAS data were available for 707 individuals. At this point, one further individual was excluded due to lack of adequate clinical data (this patient did not experience a VTE). There were 31 with VTE and 675 without VTE that formed the ERASE GWAS cohort for exploration of germline contribution to VTE risk during ALL therapy. A list of germline SNPs associated with VTE in the non-cancer population was compiled based on several adult series, one pediatric study and SNPs identified through dbSNP build 149 (Supplementary Table S3, [39–46]). We identified 85 SNPs which was expanded to 356 SNPs by identifying additional SNPs in complete linkage disequilibrium (r2 = 1), using the SNAP (SNP annotation and proxy search) tool with HapMap genomic data [47]. A meta-analysis was performed using the ERASE GWAS and the 356 SNPs associated with VTE in the non-cancer population. The analysis had 80% power to replicate previously reported SNPs with a minor allele frequency (MAF) ≥4%, with a genotype relative risk (RR) of 3 for the minor allele; and an 80% power to replicate SNPs with a MAF ≥8% with a genotype relative risk of 2.4 for the minor allele [48].

3. Results

There were 1173 ALL patients identified for inclusion in our study; 152 were excluded leaving a final ERASE cohort of 1021 patients (Fig. 1). Main reasons for exclusion included follow up < 18 months in CR1 and no TRT (n = 70), lack of clinical information (n = 26), early death from treatment and no TRT (n = 21), treatment on non-included protocols (n = 9), and early death from relapse (n = 8).

Baseline demographics, treatment and outcome for the ERASE cohort are listed in Table 1.

Fifty-two VTEs were identified in our cohort of 1021 patients. The 2-year cumulative incidence of VTE was 5.1% ± 0.7%. All VTEs, except one, occurred during ALL therapy. The exception was a patient who had a prolonged work-up for ALL, during which a VTE was diagnosed, steroids were empirically used for symptom control and a second (intracardiac) thrombosis was suspected. The median time from ALL diagnosis to VTE was 1 month (range 0–24). The incidence of VTE according to ALL immunophenotype was: pre-B ALL (total n = 883), VTE n = 37 (4.2% of pre-B ALL patients); T-ALL (total n = 84), VTE n = 7 (8.3%); T-non Hodgkin lymphoma (total n = 28), VTE n = 7 (25%); other (ALL/LL not specified) (total n = 26), VTE n = 1 (3.8%). The severity, location and association of VTE with CVL are shown in Table 2. All patients had central venous lines (CVL) inserted early in therapy. Most VTE (n = 45, 86.5%) occurred during or immediately following asparaginase and steroid-related therapy blocks. There were 32 (61.5%) VTEs during induction, 6 (11.5%) during consolidation and 7 (13.5%) during re-induction. The remainder occurred during or immediately following high-risk chemotherapy (n = 3, 5.8%), around haematopoietic stem cell transplantation (n = 2, 3.8%); or during maintenance therapy (n = 1, 1.9%). All patients were retained in the analysis to determine risk associations for development of VTE as a result of ALL therapy. Family history was documented in 6 VTE patients, with the Factor V Leiden mutation (heterozygous) present in one patient. Thrombophilia screening results were recorded in 28 VTE patients. Of these, 3 had reduced protein S levels, and one had low antithrombin III levels, from samples taken at VTE diagnosis, therefore these changes could be attributed to drug therapy.

The majority of VTEs were treated with enoxaparin (n = 29, 55.8%), or unfractionated heparin followed by enoxaparin (n = 7, 13.5%). One patient received unfractionated heparin alone and another received alteplase. Four patients (7.7%) did not receive anticoagulation due to individual circumstances (*e.g.* intracerebral hemorrhage with cerebral venous sinus thrombosis). Ten patients (19.2%) did not have anticoagulant treatment clearly documented. Additional therapy included CVL removal (n = 5, 9.6%) and omission of asparaginase from subsequent treatment (n = 4, 7.7%).

There were three recurrent VTE events in three different patients. One patient experienced a recurrent CVST, one patient initially had a lower limb VTE and then a presumed left ventricular apical VTE, and the third patient had a recurrent internal jugular vein VTE on the

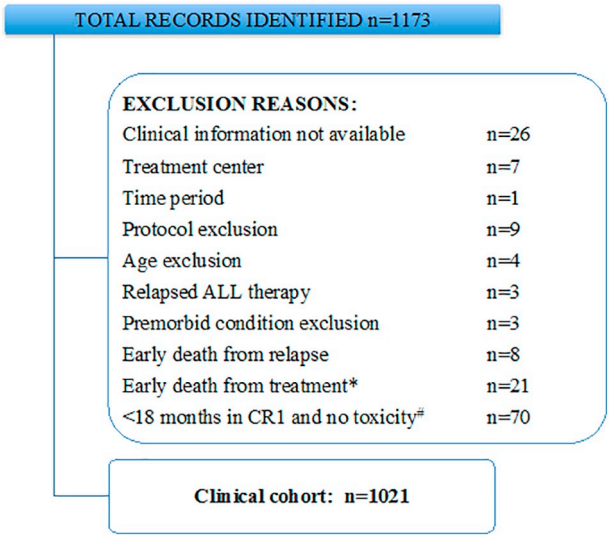

Fig. 1. Consort diagram for participant inclusion and exclusion in the ERASE study.
Patients without adequate clinical information to determine case or control status in first complete remission (CR1) were excluded. *Early death from treatment: patients who experienced treatment-related mortality not related to VTE or neurotoxicity were excluded. #Toxicities studied included VTE, bone toxicity and neurotoxicity.

Table 1
Baseline features of ERASE cohort (1021 patients).

Sex	Male	559 (54.8%)
	Female	462 (45.2%)
	Median age at diagnosis	58 months (range 12–227)
	Median follow up time from diagnosis (months)	78 months (range 3–184 months)
Diagnosis	Pre-B-ALL	883 (86.5%)
	T-ALL	84 (8.2%)
	T-non Hodgkin lymphoma	28 (2.7%)
	Other (ALL/LL, not specified)	26 (2.6%)
Treatment	ANZCCSG Study 7 (1998–2002) [30]	239 (23.4%)
	ANZCHOG Study 8 (2002 − 2012) [31]	608 (59.6%)
	AIEOP-BFM Study 9 (2012 − 2013) [32]	40 (3.9%)
	BFM-95 (1998–2002) [34]	125 (12.2%)
	COG A5971 (2003–2009) [33]	9 (0.9%)
Outcome	5 year overall survival	91.5 ± 1.0%
	5 year event-free survival	84.7 ± 1.2%
	5 year leukemia-free survival	82.6 ± 1.3%

ALL, acute lymphoblastic leukemia; LL, lymphoblastic lymphoma; ANZCCSG, Australian and New Zealand Children's Cancer Study Group; ANZCHOG, Australian and New Zealand Children's Haematology Oncology Group; AIEOP, Associazone Italiana Ematologia Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; COG, Children's Oncology Group.

Table 2
VTE severity, site and association with central venous lines in the ERASE cohort.

Severity		Site and association with CVL		
CTCAE Grade	N (%)	Site	Cases N (%)	Associated with CVL N (%)
Grade 2	24 (46.2%)	Cerebral venous sinus thrombosis	14 (26.9%)	
Grade 3	14 (26.9%)	Lower limb	12 (23.1%)	4 (7.7%)
		Neck veins	10 (19.2%)	8 (15.4%)
Grade 4	11 (21.2%)	Intrathoracic	8 (15.4%)	8 (15.4%)
		Upper limb	5 (9.6%)	2 (3.8%)
Grade 5	1 (1.9%)	Other[a]	3 (5.8%)	1 (1.9%)
Unknown	2 (3.8%)			
Total	52 (100%)	Total	52 (100%)	23 (44.2%)

Neck veins include internal jugular vein, external jugular vein and subclavian vein. Intrathoracic includes superior vena cava and intracardiac location (4/8 were in the right atrium); CVL-associated VTE: a VTE occurring in the vein into which the CVL was placed.
VTE events were graded according to NCI-CTCAE v4.03 [29]. Grade 1 is "mild", such as a superficial thrombosis; Grade 2 "moderate", requiring medical intervention, such as an uncomplicated deep venous thrombosis. Grade 3, "severe", includes uncomplicated pulmonary emboli or right atrial cardiac thrombosis requiring medical intervention. Grade 4, "life-threatening", includes pulmonary embolism, intracranial thrombosis such as cerebral venous sinus thrombosis (CVST), leading to hemodynamic or neurological instability, where urgent medical intervention is required. Grade 5 is death due to VTE.
[a] Other sites of VTE included portal vein thrombosis, one patient with simultaneous popliteal thrombosis and distal right internal jugular vein VTE; and another patient with concurrent cerebral venous sinus thrombosis and thrombotic emboli of cerebral end vessels.

contralateral side.

Overall survival (OS) analysis, adjusted for treatment risk group, showed that there was a significant difference in survival for children who did and did not experience VTE ($P = 0.004$).

Specifically, 5 year OS for children with high risk ALL (high or very high risk ALL according to treatment protocol) who experienced VTE was 61.9% ± 13.4% compared to 83.6% ± 3% for those who did not experience VTE ($P = 0.006$). In medium/standard risk ALL, 5 year OS for children who experienced VTE was 87.4% ± 7% compared to 94.1% ± 0.9% if no VTE occurred ($P = 0.224$) (Supplementary Fig. S1). There was no difference in LFS for children who did and did not experience VTE, adjusted for risk group ($P = 0.864$).

Analysis of published VTE risk factors in our BFM-treated cohort is presented in Table 3. We found a similar VTE incidence in patients with weight at extreme centiles at diagnosis, with an incidence of 9.7% and 10.1% for those with weights < 5th centile and > 95th centile respectively. We combined these two groups into an at-risk weight group (weight < 5th or > 95th centile at diagnosis), which was significantly associated with VTE ($P = 0.001$). Older age (as a continuous and categorical variable), risk group (high risk vs non-high risk), T-immunophenotype, and mediastinal mass were also significantly associated with VTE (Table 3). Mediastinal mass demonstrated the strongest effect (odds ratio (OR) 3.789, 95% confidence interval (CI) 1.81–7.95) followed by T-immunophenotype (OR 3.29, 95%CI 1.72–6.30) and weight extremes at diagnosis (OR 3.0, 95% CI 1.59–5.66). Treatment protocol ($P = 0.182$) was not associated with VTE.

Independent significance of variables was tested against a published backbone of known factors: age ≥10 years and mediastinal mass. In multivariable logistic regression analysis, extreme weight at diagnosis was the one variable that retained independent significance in addition to older age and presence of a mediastinal mass ($P = 0.001$, OR 2.95, 95%CI 1.54–5.59). The spearman rank correlation coefficient between mediastinal mass and T-immunophenotype was −0.767, indicating strong correlation.

Separate assessment of factors only during induction/consolidation is shown in Table 4. Failure to achieve a remission at end of induction ($P = 0.417$) was not associated with VTE. Bacteremia occurring in induction/consolidation was significantly associated with VTE ($P = 0.005$), however fungal infections alone were not ($P = 0.64$). In addition, ≥Grade 3 elevation of bilirubin ($P < 0.001$) and GGT ($P < 0.001$) during induction/consolidation were associated with VTE (Table 4).

Bacteremia occurred in 25/52 (48.1%) patients with VTE. Positive blood cultures were identified prior to VTE in 20/25 (80%) with VTE at a median of 29 days (range 3–668) before the VTE. For patients with bacteremia preceding VTE, 9 (45%) were CVL-associated, 18 (90%) were ≥grade 2, and the commonest organisms were gram-positive bacteria in 10 cases, 7 of which were Coagulase negative *Staphylococci* sp (CoNS). Gram-negative bacteria were found in 9 cases, 3 of which were *Escherichia coli*. One patient had two different organisms detected in the blood cultures. Peak GGT ≥grade 3 occurred in 17 of 52 (32.7%) VTE cases, with peak elevation occurring prior to VTE in 8 (47.1%) cases (median 93 days prior to VTE, range 1–195 days) and following VTE in 8 (47.1%) cases (median 17 days after VTE, range 6–41 days).

The possible contribution of 356 germline SNPs associated with VTE in the general population was examined in the ERASE cohort (Supplementary Table S4). No SNP reached significance, set at $P < 0.05/85$ ($< 5.8 \times 10^{-3}$) to correct for multiple testing the number of independent loci (n = 85) [36]. The top result from this analysis was rs13403289 ($P = 0.036$) (Supplementary Table S4). Specifically, previous genome-wide significant loci as documented by Hinds et al [39] were not replicated in our study, for the 6 of 8 genetic loci for which data were available in our study. Results were: rs6025 (Factor V Leiden mutation) $P = 0.27$, odds ratio (OR) 0.42, 95% confidence interval 0.1–1.74; rs529565 (ABO gene), $P = 0.44$, OR 1.22 (0.74–2.03); rs4444878 (Factor 11 gene) no results available, lead SNP in Factor 11 locus rs925451 (r2 = 0.7065, D′ = 0.8548 indicating linkage disequilibrium (LD) with the SNP rs4444878), $P = 0.31$, OR 0.75 (0.43–1.31); rs1799963 (Factor 2 gene) no relevant results available; rs7654093 (*FGG* gene), $P = 0.91$, OR 0.96 (0.50–1.84); rs114209171 (Factor 8 gene on X chromosome) no relevant results available; rs9797861 (*SLC44A2* gene) no results available, top SNP in same locus in LD rs8110055 (r2 = 0.989, D′ = 1.0), $P = 0.62$, OR 1.18 (0.60–2.31); rs34234989 (*PROCR* gene) no results available, top SNPs in same locus rs10747514 and rs6087685 in complete LD (r2 = 1.0,

Table 3
Baseline clinical factors associated with VTE in univariate and multivariable analysis.

Univariate analysis			Multivariable analysis		
Clinical factor	*P*	OR (95% CI)	Clinical factor	*P*	OR (95% CI)
Age (continuous)	0.016	1.01 (1.00–1.01)			
Older age (≥10 years vs < 10 years)	0.005	2.32 (1.30–4.13)	Age ≥10 years	0.036	1.97 (1.05–3.72)
T-immunophenotype	< 0.001	3.29 (1.72–6.30)			
High risk group (HR/VHR)[a]	0.027	2.08 (1.09–3.98)			
Mediastinal mass	< 0.001	3.79 (1.81–7.95)	Mediastinal mass	0.017	2.89 (1.21–6.95)
Weight < 5th or > 95th centile at diagnosis	0.001	3.00 (1.59–5.66)	Weight < 5th or > 95th centile at diagnosis	0.001	2.94 (1.54–5.59)
BMI > 95th centile at diagnosis (CDC)	0.062	2.14 (0.96–4.77)			
ABO blood group (non O vs O)	0.16	1.51 (0.85–1.70)			

P value level of significance < 0.05, 2-tailed. OR, odds ratio; 95% CI, 95% confidence interval for OR. HR indicates high-risk; VHR, very high-risk; BMI, body mass index; CDC, Centers for Disease Control and Prevention Growth charts.
[a] High risk (HR/VHR) groups were compared to combined standard and medium risk group.

Table 4
Risk associations for VTE in early therapy.

Clinical factor	*P*	OR (95% CI)
Positive blood culture[a]	0.005	2.3 (1.29–4.11)
Positive fungal infection[a]	0.64	1.24 (0.51–3.02)
Peak creatinine > 2× baseline[a]	0.51	1.51(0.45–5.07)
≥Grade 3 elevation in bilirubin[a]	< 0.001	4.81 (2.09–11.07)
≥Grade 3 elevation in GGT[a]	< 0.001	3.31 (1.74–6.30)
≥Grade 3 elevation in AST[a]	0.65	0.81(0.32–2.03)
Induction failure (day 33)	0.42	2.37(0.294–19.15)

Seven factors were assessed in univariate logistic regression for association with VTE incidence.
[a] Indicates laboratory result during induction/consolidation. *P* value level of significance < 0.007 (Bonferroni correction), 2-tailed. OR, odds ratio; 95% CI, 95% confidence interval for OR.

D′ = 1.0), *P* = 0.64, OR both loci 0.86 (0.47–1.60). A list of all available SNPs for analysis is contained in Supplementary Table S4.

4. Discussion

The 2-year cumulative incidence (5.1%) and timing of VTE (median onset 1 month from diagnosis) in the ERASE study is comparable to published studies [1,49]. We identified extreme weight (< 5th or > 95th centile) as an independent risk factor for VTE, beyond published risk factors of age ≥10 years and mediastinal mass, in a large cohort of 1021 children treated on BFM-based ALL protocols. During the early phases of therapy, bacteremia, ≥grade 3 bilirubin elevation and ≥grade 3 GGT elevation were also associated with VTE.

A major strength of this study was the availability of detailed information on both baseline and treatment-related variables for children who did and did not develop VTE, which has previously limited conclusions in relation to bacteremia in particular [9]. In our study, presence of bacteremia was associated with a 2-fold risk of VTE. The majority (80%) of bacteremia episodes occurred prior to the diagnosis of VTE. Bacteremia prior to VTE occurred in 20/52 (38.5%) cases of VTE in the ERASE study.

This study therefore shows a clear association between bacteremia and VTE in ALL, which has not previously been demonstrated. A previous study described an association between CVL dysfunction, CVL infection and VTE in children with various cancer diagnoses [5]. Others have reported significant associations with CVL dysfunction or infection and CVL-related VTE in adults [17,50] and children [15]. One recent publication found that 32% of patients aged 1–45 had bacteremia at the time of VTE, but did not have data on patients without VTE [9].

Extreme weight at diagnosis increases the risk of toxicities during ALL therapy [18] and nutritional interventions have been shown to reduce TRT [18]. We demonstrated that extreme weight constitutes a specific risk for VTE. Potential reasons include altered pharmacokinetics due to drug binding and/or distribution [51–53]. Hepatic metabolism is altered in underweight and obese patients [52–54] while glomerular filtration rate may decrease [53,54].

The association between older age and VTE risk in multivariable analysis is consistent with the literature [2,5,6,9]. Older children have altered coagulation profiles, with reduced anticoagulant factors and reduced fibrinolysis, similar to adults, which may explain the age-specific increased risk of VTE [55].

The association between peak GGT or bilirubin elevation and VTE incidence in children treated for ALL is novel. Baseline GGT correlates with mortality following pulmonary embolus in adults [56] while a prospective study in adults showed that elevated GGT was associated with risk of provoked VTE [22]. It is unclear what modulates this association in the ERASE study population and these changes may reflect drug-related liver abnormalities rather than imply causality. Areas of future study could include whether GGT elevation in particular is a marker of metabolic stress or a drug induction effect such as from glucocorticoids used in ALL therapy.

A goal of the ERASE GWAS was to determine whether SNPs associated with VTE in the general population were associated with VTE in children treated for ALL. We were not able to replicate any of the 356 SNPs associated with VTE in non-cancer studies in the ERASE GWAS, suggesting the pathogenesis and risk factors for VTE during ALL therapy may differ to those in the population with non-malignant disease.

There are limitations of the retrospective ERASE study. We were not able to replicate some risk factors previously associated with VTE, namely asparaginase therapy and combined asparaginase and steroid therapy [1,13], as the entire ERASE cohort were treated with a four drug induction therapy. Similarly, since it has been standard clinical practice in many Australian centres for the early insertion of central lines in ALL patients, we were not able to examine the additional VTE risk associated with the presence of a CVL. We identified a strong association between bacteremia and VTE but could not determine if bacteremia was confined to the CVL or systemic because most blood cultures were aspirated from the CVL without accompanying peripheral blood cultures. Documentation regarding family history of thrombophilia was limited, however this was overcome through the GWAS. The ERASE VTE risk factors were identified from data collected on > 1000 consecutive patients from 5 Australian hospitals using 5 BFM based treatment protocols between 1998 and 2013. A limitation of the work remains validation in an independent cohort. We were however able to validate two recently published risk factors for VTE – age ≥10 years and mediastinal mass, suggesting that there may be common risk factors across international treatment platforms. We were unable to identify a contemporaneous international dataset for validation of associated factors in induction/consolidation. Therefore, to address this limitation we have undertaken a prospective validation study, the ASSET study (Acute Leukaemia Subtype and Severe Side Effects from Treatment Study), across Australia and New Zealand. The main

limitation of the GWAS was small numbers for analysis (n = 31 with VTE, n = 675 without VTE), and thus the study was underpowered to detect a statistically significant difference for less common SNPs in the Caucasian population (MAF < 4%) or SNPs that did not exert a strong risk effect (RR < 2.4). As the GWAS was conducted in patients with Caucasian ancestry, the conclusions cannot be extrapolated to non-Caucasian populations.

This study emphasizes the dynamic evolution of VTE and the identification of new factors that are associated with risk of VTE in childhood ALL therapy. Importantly, clinicians should be made aware of the increased risk of VTE with bacteremia in this immunocompromised population, and where possible, health systems could look at methods to reduce occurrence of bacteremia with uniform asepsis and standardized central line care [57].

The risk factors highlighted in this study combined with those described [4] could be analyzed prospectively using common toxicity definitions [58] for VTE and if validated, used in a refined risk model for VTE in ALL. Future clinical challenges are determination of a suitable threshold for targeted thromboprophylaxis in patients at high risk of VTE within the context of a clinical trial, to balance the risk of bleeding against potential prevention of VTE, especially during periods of thrombocytopenia; and determining duration of prophylaxis to cover high-risk clinical periods. Recently published data show that the risk of major bleeding using thromboprophylaxis strategies in BFM ALL induction protocols is low (0.9%) [29]. Identification of additional biomarkers or pharmacogenomic factors may enhance clinical decision-making. Concurrent prospective measurement of health economic impact of future interventions and health-related quality of life will be important [59–61]. Further studies are required to assess genome-wide contribution of SNPs that predispose to VTE in pediatric ALL.

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Conflicts of interest

None to declare.

Author contributions

M.K.M developed study materials, collected data, extracted patient DNA samples, wrote the manuscript, analyzed data and helped with interpretation of SNP results. G.M.M and T.N.T wrote the study concept, supervised writing of the manuscript and assisted with interpretation of results. P.M.B, T.R, R.S.K collected data in the ERASE Study. M.C.J.Q performed the GWAS and SNP analysis. C.M assisted with statistical analysis. R.S, J.G, D.C helped with extraction of patient DNA samples. R.S, D.B, F.A, F.M, L.D.P assisted data collection processes. G.C.T and S.M provided assistance with the GWAS. All authors reviewed and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.011.

References

[1] V. Caruso, L. Iacoviello, A. Di Castelnuovo, S. Storti, G. Mariani, G. de Gaetano, M.B. Donati, Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients, Blood 108 (7) (2006) 2216–2222.
[2] R.F. Grace, S.E. Dahlberg, D. Neuberg, S.E. Sallan, J.M. Connors, E.J. Neufeld, D.J. DeAngelo, L.B. Silverman, The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols, Br. J. Haematol. 152 (4) (2011) 452–459.
[3] U. Nowak-Göttl, C. Wermes, R. Junker, H.-G. Koch, R. Schobess, G. Fleischhack, D. Schwabe, S. Ehrenforth, Prospective evaluation of the thrombotic risk in children with acute lymphoblastic leukemia carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors, Blood 93 (5) (1999) 1595–1599.
[4] L. Mitchell, M. Lambers, S. Flege, G. Kenet, V. Li-Thiao-Te, S. Holzhauer, C. Bidlingmaier, M.C. Frühwald, C. Heller, W. Schmidt, B. Pautard, U. Nowak-Göttl, Validation of a predictive model for identifying an increased risk for thromboembolism in children with acute lymphoblastic leukemia: results of a multicenter cohort study, Blood 115 (24) (2010) 4999–5004.
[5] U. Athale, S. Siciliano, L. Thabane, N. Pai, S. Cox, A. Lathia, A. Khan, A. Armstrong, A.K.C. Chan, Epidemiology and clinical risk factors predisposing to thromboembolism in children with cancer, Pediatr. Blood Cancer 51 (6) (2008) 792–797.
[6] R. Tuckuviene, S. Ranta, B.K. Albertsen, N.G. Andersson, M.D. Bendtsen, T. Frisk, M.W. Gunnes, J. Helgestad, M.M. Heyman, O.G. Jonsson, A. Mäkipernaa, K. Pruunsild, U. Tedgård, S.S. Trakymiene, E. Ruud, Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia - a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study, J. Thromb. Haemost. 14 (3) (2016) 485–494.
[7] L.B. Silverman, R.D. Gelber, V.K. Dalton, B.L. Asselin, R.D. Barr, L.A. Clavell, C.A. Hurwitz, A. Moghrabi, Y. Samson, M.A. Schorin, Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01, Blood 97 (5) (2001) 1211–1218.
[8] P. Giordano, N. Santoro, G.C. Del Vecchio, C. Rizzari, G. Masera, D. De Mattia, T-immunophenotype is associated with an increased prevalence of thrombosis in children with acute lymphoblastic leukemia. A retrospective study, Haematologica 88 (9) (2003) 1079–1080.
[9] C.U. Rank, N. Toft, R. Tuckuviene, K. Grell, O.J. Nielsen, T.L. Frandsen, H.V.H. Marquart, B.K. Albertsen, U. Tedgård, H. Hallböök, E. Ruud, K.B. Jarvis, P. Quist-Paulsen, P. Huttunen, U. Wartiovaara-Kautto, Ó.G. Jónsson, S.S. Trakymiene, L. Griškevičius, K. Saks, M. Punab, K. Schmiegelow, Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 protocol treatment in patients 1-45 years, Blood 131 (22) (2018) 2475–2484.
[10] F. Dentali, A.P. Sironi, W. Ageno, S. Turato, C. Bonfanti, F. Frattini, S. Crestani, M. Franchini, Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature, Semin. Thromb. Hemost. (2012) 535.
[11] M. Andrew, M. David, M. Adams, K. Ali, R. Anderson, D. Barnard, M. Bernstein, L. Brisson, B. Cairney, D. DeSai, Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE, Blood 83 (5) (1994) 1251–1257.
[12] P.D. Stein, F. Kayali, R.E. Olson, Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey, J. Pediatr. 145 (4) (2004) 563–565.
[13] J.H. Payne, A.J. Vora, Thrombosis and acute lymphoblastic leukaemia, Br. J. Haematol. 138 (4) (2007) 430–445.
[14] P.J. Lenting, J.N. Pegon, E. Groot, P.G. de Groot, Regulation of von Willebrand factor-platelet interactions, Thromb. Haemost. 104 (3) (2010) 449.
[15] J.M. Journeycake, G.R. Buchanan, Catheter-related deep venous thrombosis and other catheter complications in children with cancer, J. Clin. Oncol. 24 (28) (2006) 4575–4580.
[16] D. Piovesan, C. Attard, P. Monagle, V. Ignjatovic, Epidemiology of venous thrombosis in children with cancer, Thromb. Haemost. 111 (6) (2014) 1015–1021.
[17] C.J. van Rooden, E.F. Schippers, R.M. Barge, F.R. Rosendaal, H.F. Guiot, F.J. van der Meer, A.E. Meinders, M.V. Huisman, Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study, J. Clin. Oncol. 23 (12) (2005) 2655–2660.
[18] E. Orgel, R. Sposto, J. Malvar, N.L. Seibel, E. Ladas, P.S. Gaynon, D.R. Freyer, Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: a report from the children's oncology group, J. Clin. Oncol. 32 (13) (2014) 1331–1337.
[19] U.H. Athale, A.K. Chan, Thrombosis in children with acute lymphoblastic leukemia: part II. Pathogenesis of thrombosis in children with acute lymphoblastic leukemia: effects of the disease and therapy, Thromb. Res. 111 (4) (2003) 199–212.
[20] B.M. Wicklund, Bleeding and clotting disorders in pediatric liver disease, Hematology Am. Soc. Hematol. Educ. Program 2011 (2011) 170–177.
[21] O. Dabbagh, A. Oza, S. Prakash, R. Sunna, T.M. Saettele, Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease, Chest 137 (5) (2010) 1145–1149.

[22] A.R. Folsom, P.L. Lutsey, N.S. Roetker, W.D. Rosamond, M. Lazo, S.R. Heckbert, S. Basu, M. Cushman, E. Selvin, Elevated hepatic enzymes and incidence of venous thromboembolism: a prospective study, Ann. Epidemiol. 24 (11) (2014) 817–821.e2.
[23] C.M. Takemoto, S. Sohi, K. Desai, R. Bharaj, A. Khanna, S. McFarland, S. Klaus, A. Irshad, N.A. Goldenberg, J.J. Strouse, M.B. Streiff, Hospital-associated venous thromboembolism in children: incidence and clinical characteristics, J. Pediatr. 164 (2) (2014) 332–338.
[24] S. Zhang, A.K. Taylor, X. Huang, B. Luo, E.B. Spector, P. Fang, C.S. Richards, A.L.Q.A.C. on behalf of the, Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G > A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG), Genet. Med. 20 (12) (2018) 1489–1498.
[25] S. Unal, A. Varan, B. Yalcin, M. Buyukpamukcu, A. Gurgey, Evaluation of thrombotic children with malignancy, Ann. Hematol. 84 (6) (2005) 395–399.
[26] D.F. Akin, N. Akar, Effect of Factor V Leiden on thrombosis in childhood leukemia, Open J. Blood Dis. 03 (03) (2013) 4.
[27] S. Sivasliooglu, T. Gursel, U. Kocak, Z. Kaya, The risk factors for thrombosis in children with acute lymphoblastic leukemia, Clin. Appl. Thromb. Hemost. 20 (6) (2014) 651–653.
[28] Y.n.A. Torun, T. Patıroglu, M.A. Ozdemir, Y. Ozkul, A. Ekici, M. Karakukcu, Inherited prothrombotic risk factors in Turkish children with acute lymphoblastic leukemia:significance of concomitant genetic mutation, Clin. Appl. Thromb. Hemost. 18 (2) (2012) 218–221.
[29] J. Greiner, M. Schrappe, A. Claviez, M. Zimmermann, C. Niemeyer, R. Kolb, W. Eberl, F. Berthold, E. Bergsträsser, A. Gnekow, E. Lassay, P. Vorwerk, M. Lauten, A. Sauerbrey, J. Rischewski, A. Beilken, G. Henze, W. Korte, A. Möricke, THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents, Haematologica 104 (4) (2018) 756–765 (haematol. 2018.194175).
[30] R. Sutton, N.C. Venn, J. Tolisano, A.Y. Bahar, J.E. Giles, L.J. Ashton, L. Teague, G. Rigutto, K. Waters, G.M. Marshall, Clinical significance of minimal residual disease at day 15 and at the end of therapy in childhood acute lymphoblastic leukaemia, Br. J. Haematol. 146 (3) (2009) 292–299.
[31] G. Marshall, L. Dalla Pozza, R. Sutton, A. Ng, H. de Groot-Kruseman, V. van der Velden, N. Venn, H. van den Berg, E. De Bont, R.M. Egeler, High-risk childhood acute lymphoblastic leukemia in first remission treated with novel intensive chemotherapy and allogeneic transplantation, Leukemia 27 (7) (2013) 1497–1503.
[32] V. Conter, M.G. Valsecchi, B. Buldini, R. Parasole, F. Locatelli, A. Colombini, C. Rizzari, M.C. Putti, E. Barisone, L.L. Nigro, Early T-cell precursor acute lymphoblastic leukaemia in children treated in AIEOP centres with AIEOP-BFM protocols: a retrospective analysis, Lancet Haematol. 3 (2) (2016) e80–e86.
[33] A.M. Termuhlen, L.M. Smith, S.L. Perkins, M. Lones, J.L. Finlay, H. Weinstein, T.G. Gross, M. Abromowitch, Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group, Br. J. Haematol. 162 (6) (2013) 792–801.
[34] A. Möricke, A. Reiter, M. Zimmermann, H. Gadner, M. Stanulla, M. Dördelmann, L. Löning, R. Beier, W.-D. Ludwig, R. Ratei, Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95, Blood 111 (9) (2008) 4477–4489.
[35] National Cancer Institute Common Terminology Criteria for Adverse Events v4.0, NCI, NIH, DHHS. NIH publication # 09–7473, 2009.
[36] E. Evangelou, J.P. Ioannidis, Meta-analysis methods for genome-wide association studies and beyond, Nat. Rev. Genet. 14 (6) (2013) 379–389.
[37] G.P. Consortium, A map of human genome variation from population-scale sequencing, Nature 467 (7319) (2010) 1061–1073.
[38] M.I. McCarthy, G.R. Abecasis, L.R. Cardon, D.B. Goldstein, J. Little, J.P. Ioannidis, J.N. Hirschhorn, Genome-wide association studies for complex traits: consensus, uncertainty and challenges, Nat. Rev. Genet. 9 (5) (2008) 356–369.
[39] D.A. Hinds, A. Buil, D. Ziemek, A. Martinez-Perez, R. Malik, L. Folkersen, M. Germain, A. Mälarstig, A. Brown, J.M. Soria, Genome-wide association analysis of self-reported events in 6135 individuals and 252 827 controls identifies 8 loci associated with thrombosis, Hum. Mol. Genet. (2016) ddw037.
[40] M. Germain, D.I. Chasman, H. De Haan, W. Tang, S. Lindström, L.-C. Weng, M. De Andrade, M.C. De Visser, K.L. Wiggins, P. Suchon, Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism, Am. J. Hum. Genet. 96 (4) (2015) 532–542.
[41] M. Germain, N. Saut, T. Oudot-Mellakh, L. Letenneur, A.-M. Dupuy, M. Bertrand, M.-C. Alessi, J.-C. Lambert, D. Zelenika, J. Emmerich, Caution in interpreting results from imputation analysis when linkage disequilibrium extends over a large distance: a case study on venous thrombosis, PLoS One 7 (6) (2012) e38538.
[42] J. Dennis, C.Y. Johnson, A.S. Adediran, M. De Andrade, J.A. Heit, P.-E. Morange, D.-A. Trégouët, F. Gagnon, The endothelial protein C receptor (PROCR) Ser219Gly variant and risk of common thrombotic disorders: a HuGE review and meta-analysis of evidence from observational studies, Blood 119 (10) (2012) 2392–2400.
[43] J.A. Heit, S.M. Armasu, Y.W. Asmann, J.M. Cunningham, M.E. Matsumoto, T.M. Petterson, M. De Andrade, A genome-wide association study of venous thromboembolism identifies risk variants in chromosomes 1q24. 2 and 9q, J. Thromb. Haemost. 10 (8) (2012) 1521–1531.
[44] P.-E. Morange, I. Bezemer, N. Saut, L. Bare, G. Burgos, J. Brocheton, H. Durand, C. Biron-Andreani, J.-F. Schved, G. Pernod, A follow-up study of a genome-wide association scan identifies a susceptibility locus for venous thrombosis on chromosome 6p24. 1, Am. J. Hum. Genet. 86 (4) (2010) 592–595.
[45] A. Buil, D.-A. Trégouët, J.C. Souto, N. Saut, M. Germain, M. Rotival, L. Tiret, F. Cambien, M. Lathrop, T. Zeller, C4BPB/C4BPA is a new susceptibility locus for venous thrombosis with unknown protein S–independent mechanism: results from genome-wide association and gene expression analyses followed by case-control studies, Blood 115 (23) (2010) 4644–4650.
[46] F. Rühle, A. Witten, A. Barysenka, A. Huge, A. Arning, C. Heller, A. Krümpel, R. Mesters, A. Franke, W. Lieb, Rare genetic variants in SMAP1, B3GAT2 and RIMS1 contribute to pediatric venous thromboembolism, Blood 129 (6) (2017) 783–790 (blood-2016-07-728840).
[47] A.D. Johnson, R.E. Handsaker, S.L. Pulit, M.M. Nizzari, C.J. O'donnell, P.I. De Bakker, SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap, Bioinformatics 24 (24) (2008) 2938–2939.
[48] S. Purcell, S.S. Cherny, P.C. Sham, Genetic power calculator: design of linkage and association genetic mapping studies of complex traits, Bioinformatics 19 (1) (2003) 149–150.
[49] N. Santoro, A. Colombini, D. Silvestri, M. Grassi, P. Giordano, R. Parasole, E. Barisone, R. Caruso, V. Conter, M.G. Valsecchi, Screening for coagulopathy and identification of children with acute lymphoblastic leukemia at a higher risk of symptomatic venous thrombosis: an AIEOP experience, J. Pediatr. Hematol. Oncol. 35 (5) (2013) 348–355.
[50] B. Tolar, J.R. Gould, The timing and sequence of multiple device-related complications in patients with long term indwelling Groshong catheters, Cancer 78 (6) (1996) 1308–1313.
[51] P.C.J. Rogers, Nutritional status as a prognostic indicator for pediatric malignancies, J. Clin. Oncol. 32 (13) (2014) 1292–1294.
[52] G. Cheymol, Effects of obesity on pharmacokinetics, Clin. Pharmacokinet. 39 (3) (2000) 215–231.
[53] D.J. Murry, L. Riva, D.G. Poplack, Impact of nutrition on pharmacokinetics of antineoplastic agents, Int. J. Cancer 78 (S11) (1998) 48–51.
[54] K.A. Oshikoya, H.M. Sammons, I. Choonara, A systematic review of pharmacokinetics studies in children with protein-energy malnutrition, Eur. J. Clin. Pharmacol. 66 (10) (2010) 1025–1035.
[55] I.M. Appel, W.C. Hop, C. van Kessel-Bakvis, R. Stigter, R. Pieters, L-asparaginase and the effect of age on coagulation and fibrinolysis in childhood acute lymphoblastic leukemia, Thromb. Haemost. 100(2) (2008) 330–337.
[56] A. Zorlu, H. Yucel, G. Bektasoglu, K.A. Turkdogan, U. Eryigit, S. Sarikaya, M.R. Ege, I. Tandogan, M.B. Yilmaz, Increased γ-glutamyl transferase levels predict early mortality in patients with acute pulmonary embolism, Am. J. Emerg. Med. 30 (6) (2012) 908–915.
[57] A. Bhutta, C. Gilliam, M. Honeycutt, S. Schexnayder, J. Green, M. Moss, K. Anand, Reduction of bloodstream infections associated with catheters in paediatric intensive care unit: stepwise approach, Br. Med. J. 334 (7589) (2007) 362–365.
[58] K. Schmiegelow, A. Attarbaschi, S. Barzilai, G. Escherich, T.L. Frandsen, C. Halsey, R. Hough, S. Jeha, M. Kato, D.-C. Liang, Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus, Lancet Oncol. 17 (6) (2016) e231–e239.
[59] N.M. Kuderer, A.C. Wolff, Enhancing therapeutic decision making when options abound: toxicities matter, J. Clin. Oncol. 32 (19) (2014) 1990–1993.
[60] H.R. Mitchell, X. Lu, R.M. Myers, L. Sung, L.M. Balsamo, W.L. Carroll, E. Raetz, M.L. Loh, L.A. Mattano, N.J. Winick, Prospective, longitudinal assessment of quality of life in children from diagnosis to 3 months off treatment for standard risk acute lymphoblastic leukemia: results of Children's Oncology Group study AALL0331, Int. J. Cancer 138 (2) (2016) 332–339.
[61] J. Fardell, J. Vetsch, T. Trahair, M. Mateos, M. Grootenhuis, L. Touyz, G. Marshall, C. Wakefield, Health-related quality of life of children on treatment for acute lymphoblastic leukemia: a systematic review, Pediatr. Blood Cancer 64 (9) (2017) e26489.