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ONCOLOGY: RESEARCH ARTICLE

# Treatment-induced cerebral sinus venous thrombosis in childhood acute lymphoblastic malignancies: New risk factors to consider

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## Abstract

**Background:** Cerebral sinus venous thrombosis (CSVT) is one of the many side effects encountered during acute lymphoblastic leukemia (ALL) therapy. Due to the rarity of cases, lack of data, and consensus management, no recommendations exist to target the population at risk.

**Methods:** This is a retrospective chart review of 229 consecutive patients diagnosed with ALL with an age range of 1–21 years, treated at the Children's Cancer Center of Lebanon between October 2007 and February 2018.

**Results:** The incidence of CSVT was 10.5%. Using univariate analysis, increased risk of CSVT was observed with male gender, age >10 years, T-cell immunophenotype, intermediate/high-risk disease, maximum triglyceride (TG) level of >615 mg/dl, presence of mediastinal mass, and larger body surface area (BSA). With multivariate analysis, the only statistically significant risk factors were maximum TG level, BSA, presence of mediastinal mass, and risk stratification (intermediate/high risk).

**Conclusion:** Our study was able to unveil TG level of >615 mg/dl, mediastinal mass, and a larger BSA as novel risk factors that have not been previously discussed in the literature.

KEYWORDS
ALL, asparaginase, Children's Cancer Center of Lebanon, CSVT, Lebanon, pediatric ALL

## 1 | INTRODUCTION

Leukemia is the most common childhood cancer today, representing 25% of all childhood cancers. Acute lymphoblastic leukemia (ALL) is the most common type of childhood leukemia. Cure rates for children with ALL have currently reached 90% following multiagent intensive chemotherapy.[1] Today, efforts are directed toward controlling for toxicities that result from such aggressive therapies that can lead to serious complications and thus treatment cessation.

Cerebral sinus venous thrombosis (CSVT) is one of the many side effects encountered during ALL therapy. CSVT was shown to complicate therapy in 1%–2% of children being treated for ALL.[2] In childhood, CSVT has a mortality rate of 8%–13%[2] and can cause serious neurological morbidity. In addition, CSVT was shown to compromise ALL therapy by a reluctance to interrupt anticoagulation for

**Abbreviations:** ALL, acute lymphoblastic leukemia; ASP, asparaginase; CSVT, cerebral sinus venous thrombosis; MRD, minimal residual disease; TG, triglyceride.

intrathecal treatment and/or delayed/missed doses of L-asparaginase due to concern about thrombus progression or recurrence.[3] Thus, CSVT development during ALL therapy is not only limited to its own complications but extends to its potential negative impact on treatment, which makes it a rare but serious complication. There is still no consensus in the literature regarding identification of high-risk groups, potential risk factors, and prophylaxis.

Moreover, the most recent guidelines for the management of venous thromboembolism in pediatric population did not find enough accord in the literature to recommend CSVT prophylaxis in children being treated for ALL.

The aim of this manuscript is to explore potential risk factors for the development of CSVT in children with lymphoid malignancies undergoing treatment and to augment our previous findings[4] with additional risk factors based on a larger and more representative sample.

## 2 | METHODS

### 2.1 | Patient population

The study is a retrospective chart review of consecutive patients treated for ALL and lymphoblastic lymphoma at the Children's Cancer Center of Lebanon. Children and adolescents aged 1–21 years who were diagnosed between October 2007 and February 2018 were retrospectively reviewed. They were all treated with the same protocol. Patients who developed CSVT during treatment were identified. Relevant information such as patient characteristics, treatment regimen, and clinical outcome were collected and compared between two groups: patients who developed CSVT during treatment versus those who did not. CT venography and/or MRI were used to diagnose CSVT.

This study builds on a previous one done at our institution that described certain potential risk factors for the development of CSVT in children being treated for ALL. It showed that age above 10 years at diagnosis, T-cell immunophenotype, and risk stratification (intermediate/high risk) were statistically significant risk factors for CSVT.[4]

Our study was reviewed and approved by the Institutional Review Board at the American University of Beirut Medical Center.

### 2.2 | Treatment protocol

Our treatment protocol was adopted from the St. Jude Total XV therapy with minor modifications.[5,6] Remission induction therapy began with prednisone, vincristine, daunorubicin, and asparaginase (ASP). Patients with ≥1% minimal residual disease (MRD) on day 15 received three additional doses of ASP. The second part of induction therapy consisted of cyclophosphamide, mercaptopurine, and cytarabine. Upon hematopoietic recovery (between days 43 and 46), MRD is assessed and consolidation therapy initiated.

After induction, patients are stratified into three risk groups (low, intermediate, high) and two protocol arms (low risk and intermediate/high risk). The consolidation phase of 8 weeks consists of a 24-hour IV infusion of methotrexate at a dose of 2.5 g/m$^2$ for low-risk patients and 5 g/m$^2$ for intermediate-/high-risk individuals every 2 weeks for four doses in combination with 6-MP 50 mg/m$^2$ orally once daily. The continuation phase consists of 120 weeks for females and 146 weeks for males. A more intensive therapy termed "reinduction" is given for both risk groups. Reinduction I and II phases last for 3 weeks each and occur at weeks 7–9 and 17–19, respectively, during continuation therapy. Low-risk patients receive nine doses of IM ASP at 10,000 units/m$^2$/dose in combination with dexamethasone 8 mg/m$^2$/day for 2 weeks in each reinduction phase. Intermediate-/high-risk patients receive an intensive once weekly IM ASP treatment of 25,000 units/m$^2$/dose for the first 20 weeks of continuation in combination with once monthly dexamethasone pulses of 12 mg/m$^2$/day over 5 days. During reinduction phases (weeks 7–9 and 17–19), intermediate-/high-risk patients receive twice-monthly dexamethasone pulses at the same dose over 7 days.

In case of allergy to *Escherichia coli* (*E. coli*) ASP, Erwinia-derived ASP was used at a dose of 20,000 units/m$^2$ three times weekly to replace the 10,000 units/m$^2$ of *E. coli* ASP during induction and reinductions 1 and 2 for low-risk patients and 30,000 units/m$^2$/dose twice weekly instead of once weekly 25,000 units/m$^2$ of *E. coli* ASP for intermediate-/high-risk patients. In case of allergy to both products, we used pegylated ASP at a dose of 2500 units/m$^2$ once every other week. Low-risk patients are those aged 1–9.9 years with precursor B-cell ALL and presenting white blood count of less than 50,000/$\mu$l, DNA index of ≥1.16 or t(12,21). Low-risk patients must not have extramedullary disease, t(1,19), or mixed-lineage leukemia (MLL) rearrangement. High-risk patients are those with t(9,22) or failure of induction (>1% of leukemic lymphoblasts at remission date). Intermediate-risk patients are all T-cell patients and precursor B-cell patients who do not meet the low-risk criteria.[4]

### 2.3 | CSVT prophylaxis and treatment

The standard CSVT treatment in our organization comprises of low molecular weight heparin (LMWH). First choice is enoxaparin with a dose of 1 mg/kg twice daily administered subcutaneously. We aim for therapeutic target of anti-Xa activity level that ranges between 0.5 and 1 IU/ml, and we stop treatment after a minimal period of 3 months when CT scan or brain MRI shows complete resolution or significant improvement of the filling defect. Treatment is halted for 24 hours pre and 6 hours post some procedures such as lumbar puncture.

For primary prophylaxis, we did not utilize anticoagulation treatment. Neither antithrombin replacement was given for low antithrombin (AT) levels nor fresh frozen plasma was provided when fibrinogen levels were low.

Anticoagulation was given for at least 3 months and until radiological resolution. It was continued as well throughout the ASP therapy. There was no maximum enoxaparin dose. Patients were started on 1 mg/kg twice daily and then doses were adjusted according to anti-Xa levels. Therapy was modified in case of CSVT; for low-risk patients, dexamethasone was omitted in the third week of each reinduction, and ASP was omitted from the first week of each reinduction. In intermediate- and high-risk patients, dexamethasone was omitted

from weeks 4 and 9 and low molecular weight heparin was given during the first 19 weeks of continuation.

### 2.4 | Thrombophilia screening

All patients who developed CSVT underwent screening for inherited thrombophilia via Strip Assay (reverse hybridization-SSOP) to look for factor V Leiden (G1691A), factor V (H1299R), MTHFR (C677T), MTHFR (A1298C), and factor II (G20210A). These genetic studies come under one code of Inherited Thrombophilia at our Lab. MTHFR polymorphisms (C677T and A1298C), although unlikely to cause thrombosis in the pediatric population, are included in the test bundle at no extra cost. Due to the lack of solid evidence for screening all children during ALL therapy for inherited thrombophilia, only patients who developed CSVT underwent the above screening.

Protein C, protein S, and antithrombin were not performed routinely on CSVT patients because of cost and limited resources. Triglyceride (TG) levels were measured before each ASP dose.

### 2.5 | Statistical analysis

Statistical analysis was performed using IBM SPSS statistical software for Windows version 22 (SPSS for Windows, version 22; SPSS, Inc., Chicago, IL). Descriptive statistics were summarized by presenting the number and percentage for categorical variables, whereas the mean and standard deviation (±SD) were calculated for continuous ones. The comparison between the CSVT outcome and categorical variables was assessed by Pearson chi-square test, whereas the Student's *t*-test was used for the continuous variables. Multivariate stepwise logistic regression was used to identify the predictors of CSVT. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). *p*-Value less than .05 is considered statistically significant. The optimal cutoff that differentiates between CSVT outcome and TG level was found by Youden's index from the ROC analysis.

## 3 | RESULTS

### 3.1 | Patient characteristics

A total of 24 (10.5%) patients developed CSVT during treatment, of those, nine (37.5%) occurred during the induction phase of treatment and 15 (62.5%) during reinduction phases (reinduction 1 or reinduction 2). Clinical features of all patients are summarized in Table 1.

### 3.2 | Risk factors

With univariate analysis, male gender ($p = .004$), age >10 years at diagnosis ($p = .002$), T-cell immunophenotype ($p \leq .0001$), intermediate-/high-risk disease ($p = 0.05$), maximum TG levels of >615 mg/dl ($p = .012$), presence of mediastinal mass ($p \leq .0001$), and body surface area ($p \leq .0001$) were significantly associated with increased risk of CSVT. On the other hand, initial blast count ($p = .765$), non-O blood group ($p = .843$) were not significantly associated with increased risk of CSVT. Although BMI (mean 18.2, median 16.5, and SD 9.3) was not significant as a continuous variable, however when grouped into four groups underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obese (>30), it was significant for CSVT ($p = .05$) in univariate analysis.

With multivariate analysis using Cox regression model considering age at diagnosis, gender, immunophenotype, risk stratification, mediastinal mass, BSA, BMI, and maximal TG level as variables, only intermediate-/high-risk disease (OR: 6.879, 95% CI: 1.235–38.304, $p = .028$), presence of mediastinal mass (OR: 23.949, 95% CI: 5.606–102.316, $p < .001$), maximum TG levels of >615 mg/dl (OR: 3.732, 95% CI: 1.007–13.836, $p = .049$), and larger BSA (one unit increase as a continuous variable) (OR: 6.234, 95% CI: 1.694–22.921, $p = .006$) retained significance. Detailed results are shown in Table 2.

### 3.3 | Symptoms and signs of patients with CSVT

All patients who were identified as developing CSVT were symptomatic. The most common clinical presentations were seizures and headache.

### 3.4 | L-asparaginase and steroids

CSVT developed in patients receiving a combined therapy of ASP and steroids. The most commonly used ASP product was that of the native *E. coli* (KidrolaseR; EUSA Pharma, France). CSVT rates were observed to differ with different treatment regimens depending on the type of ASP or steroid used. CSVT occurred in patients who received either native L-asparaginase or pegylated ASP as the predominant ASP product, whereas none of the 42 patients who received Erwinia-derived ASP as the predominant ASP product developed CSVT. Furthermore, 77% of CSVT events occurred while receiving combined ASP and dexamethasone treatment (during reinduction I or II or the first 20 weeks of continuation therapy in intermediate-/high-risk patients) compared to 23% of events that occurred during combined ASP and prednisone therapy (induction). Of note is that all patients treated as per our protocol received only 2 or 3 weeks of combined ASP and prednisone (40 mg/m$^2$/day), whereas they received 4 weeks of dexamethasone if they were classified as low risk or 19 weeks of combined dexamethasone and ASP if classified as intermediate/high risk, thus resulting in more exposure to the dexamethasone/ASP combination.

### 3.5 | Impact on ALL protocol

All 24 patients who developed CSVT had delays and/or interruption of ASP and dexamethasone therapy. Treatment was suspended upon

**TABLE 1** Clinical features of all patients with and without CSVT

| | | CSVT | | |
|---|---|---|---|---|
| **Variables** | | **No *N* = 205** | **Yes *N* = 24** | ***p*-Value** |
| Gender | Male | 117 (57.1%) | 21 (87.5%) | **.004** |
| | Female | 88 (42.9%) | 3 (12.5%) | |
| Age at diagnosis | Mean (± SD) | 6.3 ± 4.7 | 10.2 ± 4.7 | **<.0001** |
| | <10 | 154 (75.1%) | 11 (45.8%) | **.002** |
| | ≥10 | 51 (24.9%) | 13 (54.2%) | |
| Phenotype | B | 177 (86.3%) | 10 (41.7%) | |
| | T | 28 (13.7%) | 14 (58.3%) | **<.0001** |
| Risk | Low | 106 (51.7%) | 8 (33.3%) | **.05** |
| | High/standard | 99 (48.3%) | 16 (66.7%) | |
| Max TG level (mg/dl)[a] | <615 | 127 (74.3%) | 8 (44.4%) | **.012** |
| | ≥615 | 44 (25.7%) | 10 (55.6%) | |
| Mediastinal mass | Yes | 15 (7.3%) | 11 (45.8%) | **<.0001** |
| | No | 190 (92.7%) | 13 (54.2%) | |
| Initial blasts | Mean (± SD) | 28714 ± 68119 | 28021 ± 55536 | .96 |
| | <10,000 | 136 (66.3%) | 17 (70.8%) | |
| | 10,000–50,000 | 38 (18.5%) | 3 (12.5%) | .765 |
| | >500,000 | 31 (15.1%) | 4 (16.7%) | |
| BMI (kg/m$^2$) | Mean (± SD) | 17.9841 ± 9.63414 | 20.5706 ± 5.77814 | .209 |
| BSA (m$^2$) | Mean (± SD) | 0.9210 ± 0.42238 | 1.3313 ± 0.50235 | **<.0001** |
| Blood group | O | 63 (31.3%) | 8 (33.3%) | .843 |
| | Non-O | 138 (68.7%) | 16 (66.6%) | |

*Note*: Risk stratification of patients was defined as per the low- versus standard-/high-risk protocol. The initial blast count was calculated as the percentage of blasts multiplied by the total white blood cells upon presentation of patients.
Abbreviations: BMI, body mass index; BSA, body surface area; TG, triglycerides.
[a]Maximal triglycerides level during induction or reinduction of treatment.

**TABLE 2** Stepwise multivariate logistic regression of some potential CSVT risk factors

| **Multivariate analysis** | | |
|---|---|---|
| **Variables** | **OR (95% CI)** | ***p*-Value** |
| Max TG level (mg/dl) | 3.732 (1.007–13.836) | .049 |
| Mediastinal mass | 23.949 (5.606–102.316) | .000 |
| BSA (m$^2$) | 6.234 (1.694–22.921) | .006 |
| Protocol treatment arm | 6.879 (1.235–38.304) | .028 |

*Note*: Variables included in the multivariate model were stepwise: gender, age, disease phenotype, risk stratification, mediastinal mass, BSA, body mass index, maximal TG level, and protocol treatment arm (low-risk vs. intermediate-/high-risk arm).
Abbreviations: BSA, body surface area; CSVT, cerebral sinus venous thrombosis; TG, triglycerides.

CSVT diagnosis until clinically stable. Also, our protocol omits dexamethasone from weeks 4 and 9 in intermediate-/high-risk patients who develop CSVT. The protocol also omits dexamethasone during week 3 and ASP during week 1 of maintenance in the case of CSVT in low-risk patients. ASP was completely omitted from the entire treatment regimen for one patient who had a life-threatening superior sagittal sinus thrombosis that was complicated by a large intracranial hemorrhage (ICH) and who required two craniotomies.

## 3.6 | Thrombophilia screening and coagulopathy studies

The results of the genetic screening in our patients mentioned in the methodology section are shown in Table 3. Due to the high cost of genetic tests and the lack of evidence for screening all ALL children during treatment for inherited thrombophilia, we only screened patients who developed symptomatic CSVT. Of those, we were only able to retrieve results on 20 patients.

The genetic test results that were included namely factor V Leiden, factor II, MTHFR, were selected because they are results that may explain the increased rate of CSVT in our patients. All are included under one "inherited thrombophilia" test option with one code at our lab and MTHFR with its two polymorphisms (C677T and A1298C) despite being unlikely to cause thrombosis in the pediatric population

**TABLE 3** Findings of thrombophilia screening of 20 cerebral sinus venous thrombosis (CSVT) patients

| Inherited thrombophilia | Heterozygous | Homozygous |
|---|---|---|
| | *N* (%) | *N* (%) |
| A. Factor V Leiden (G1691A) | 3 (15) | 0 (0) |
| B. Factor V (H1299R) | 1 (5) | 0 (0) |
| C. MTHFR (C677T) | 11 (55) | 0 (0) |
| D. MTHFR (A1298C) | 2 (10) | 1 (5) |
| E. Factor II (G20210A) | 1 (5) | 0 (0) |

**TABLE 4** Correlation between BMI and CSVT

| BMI category | CSVT | | Total | *p*-Value |
|---|---|---|---|---|
| | No | Yes | | |
| Underweight (<18.5) | 157 | 12 | 169 | .002 |
| | 77.3% | 52.2% | 74.8% | |
| Normal (18.5–24.9) | 33 | 5 | 38 | |
| | 16.3% | 21.7% | 16.8% | |
| Overweight (25–29.9) | 7 | 5 | 12 | |
| | 3.4% | 21.7% | 5.3% | |
| Obese (>30) | 6 | 1 | 7 | |
| | 3.0% | 4.3% | 3.1% | |

Abbreviations: BMI, body mass index; CSVT, cerebral sinus venous thrombosis.

are included in the same test order panel at no extra cost. Protein C, protein S, and antithrombin were not performed routinely for CSVT patients because of cost and limited resources.

### 3.7 | Outcomes due to CSVT

Neuroimaging (CT and MR venography) was used for follow-up.

Twenty-two out of 24 patients with CSVT had complete resolution of CSVT on follow-up imaging. Two patients whose CSVT were complicated by secondary hemorrhage still had abnormal imaging. The first patient had no evidence of thrombosis but had a stable posthemorrhagic infarct and the second had recanalization of the anterior cortical veins, which however appeared smaller with patent major sinuses.

Duration of therapy was for 3 months at least and until radiological resolution of CSVT.

Neurological exam was done by our pediatric neurologist for all patients upon CSVT diagnosis and was not repeated if deemed normal. None of the patients passed and only one had minor neurologic sequalae.

## 4 | DISCUSSION

We report a CSVT incidence of 10.5% in children and young adults with ALL/LBL at the Children Cancer Center of Lebanon treated on a common protocol based on the original Total XV St. Jude study. This incidence seems unacceptably high.

A global CSVT rate of 2.9% was reported in a meta-analysis of 17 prospective studies that included 1752 pediatric patients with childhood ALL.[7] Two recent studies have reported incidences of 1.4% and 1.9% from the United Kingdom and the Nordic Society of Pediatric Hematology and Oncology (NOPHO).[2,8] However, we report an incidence of 10.5% for CSVT during treatment of our ALL patients, which is much higher than that of the literature. This may be related to the treatment protocol that we use, in addition to our patients' characteristics.[9] Caruso et al. found that a combination of ASP and steroids in the presence of other prothrombotic factors like inherited thrombophilia were significantly associated with thrombosis (OR: 34.5; 95% CI: 4.39–271.42; $p = .0008$).[7] These studies have reported the incidence of thrombosis during ALL treatment to be highest during the induction phase, whereas in our study, most CSVT events occurred during early continuation and reinductions I and II. This might be explained by the lower prednisone dose that we use during the induction phase compared to the BFM protocols reported by Nowak-GöTtl et al.[10] (40 mg/m$^2$/day vs. 60 mg/m$^2$/day). However, we use higher doses of dexamethasone during early continuation (12 mg/m$^2$/day vs. 10 mg/m$^2$/day). Moreover, the duration of the combined treatment (steroids + ASP) given was longer in the postinduction phase compared to the induction phase.

In Lebanon, the carrier rate of factor V Leiden is 14.4% compared to 3%–8% in Europe and the United States.[11] Similarly, the carrier rate of prothrombin G20210A in Lebanon is 3% similar to that in Europe but higher than what is reported in the United States.[9] There is no solid evidence for screening all ALL children during treatment for heritable thrombophilia.[12,13] Because such screening is of a high financial burden in a middle-income country like Lebanon, we screened only patients who developed CSVT. The lack of thrombophilia status in patients who did not develop CSVT prevented us from investigating thrombophilia as a risk factor and integrating it into our analysis. FVL prevalence was 15% in this study and 14.4% in the general Lebanese population. Although very similar, this is still among the highest prevalences for FVL in the world. Due to the higher incidence of CSVT compared to other studies and the high thrombophilia rate in our country, we suggest revisiting the role of thrombophilia screening in countries with high prevalence of inherited thrombophilia especially if their treatment protocol relies on intensive combined ASP and steroids therapy.[4]

The incidence of CSVT in our patient population is higher than that of the original Total XV St. Jude study (NCT00137111). Possible explanations are that our patient population included patients with lymphoblastic lymphoma as they were all treated on the same protocol, whereas only ALL patients were treated on the original (NCT00137111) protocol. Also, the native L ASP used in Lebanon is the French preparation "Kidrolase" whereas that used in the NCT00137111 study was Elspar. Although both are native ASP preparations, they may have different potencies regarding asparagine depletion and/or silent activation rates. The prevalence of factor V Leiden (15%) in Lebanon is among the highest in the world. Although factor V Leiden was not performed for all treated patients, the

difference between the prevalence of factor V Leiden in Lebanese patients and that of the original (NCT00137111) patients may have contributed to the high CSVT rates in our study.

The strong association between CSVT during childhood ALL treatment and older age at diagnosis, T-cell immunophenotype, and an intermediate/higher risk disease that is observed in our univariate analysis has been well described previously.[2,10] In our study, T-cell phenotype and BMI were only significant in the univariate analysis, whereas intermediate-/high-risk disease and mediastinal mass retained significance in multivariate analysis. The protocol used in our patient population has two treatment arms: low and intermediate/high arms. Patients who have T-cell ALL are all treated on the intermediate-/high-risk arm even if they had low counts or were below 10 years of age. Those with B lineage were treated on the intermediate-/high-risk arm if they were above 10 years of age or if they had higher risk criteria. There was a statistical difference between patients receiving the intermediate-/high-risk protocol arm compared to those receiving the low-risk protocol arm despite the fact that having T-cell phenotype did not maintain significance with multivariate analysis. When BMI was grouped into four groups (underweight, normal, overweight, and obese), the results were significant with CSVT in univariate analysis ($p = .05$). However, this did not retain significance in multivariate analysis. Larger number of patients in future studies may determine if T-cell phenotype and BMI would remain significant in multivariate analysis.

Studies have linked ASP and corticosteroids treatment to an increase in TG level in ALL patients.[14,15] Hypertriglyceridemia induced by ASP was recently reported to be significantly associated with thrombosis in childhood ALL.[16] Hypertriglyceridemia induced by peg ASP was more prevalent than that induced by native L-asparaginase, by native ASP more than by dexamethasone and by drug effects more than by genetics.[16] A TG level above 1000 mg/dl has been associated with thrombosis.[16,17] We describe a maximum TG level of more than 615 mg/dl (3× the upper normal limit) to be associated with CSVT (Youden's index from the ROC analysis). Further studies with larger sample sizes are recommended to confirm this cutoff. It is still not clear whether TGs contribute to thrombosis or are biomarkers of toxicity of therapy.[16]

*Our study was the first to describe a significant association between BSA and CSVT*. Larger BSA requires higher doses of therapeutic drugs, and hence possibility of more frequent side effects. Similar findings were observed in a previous study where moderate-dose methotrexate caused toxicity in patients with larger body size upon treating non-Hodgkin's lymphoma.[18] Further studies on larger patient samples are recommended to find an appropriate cutoff for BSA. When BMI was grouped into four groups: underweight BMI (<18.5%), normal BMI (18.5–24.9), overweight (25–29.9), and obese BMI (>30), the results were significant with CSVT as an outcome ($p = .05$). However, this did not retain significance in multivariate analysis. We recommend investigating further BSA and BMI as CSVT risk factors in future studies, as it may help in choosing groups for prophylactic anticoagulation or capping of chemotherapy doses. Overweight/obese children with ALL have lower OS than healthy-weight children. This may be partially due to complications of therapy. OS and EFS may be improved by decreasing treatment toxicity in overweight patients. Several current pediatric ALL protocols measure ASP activity, which in future studies could also be used to compare with both toxicity and outcome.

A previous study described the link between the presence of mediastinal mass in Nordic children with ALL and overall thrombotic events in general but not CSVT specifically.[10] To the best of our knowledge, we are the first to describe the presence of mediastinal mass as a significant risk factor for the development of CSVT in children treated for ALL/LL. As expected, patients with mediastinal mass who developed CSVT did so during induction phase rather than later during therapy (maintenance/reinductions I or II).

Initial blast count was not significant as a risk factor for CSVT in our study. This is supported by the Nordic study while exploring its relation to any thrombotic event.[10] Non-O blood group has been reported to be an important genetic risk factor for venous thromboembolism.[19] In our previous report, we reported lack of significance of non-O blood group for the development of CSVT in our patient population.[4] This factor was reinvestigated in our population and found to be not significant.

Given the significant delay that CSVT has on treatment, and the higher chances of disease relapse from early discontinuation of ASP as reported from the Dana-Farber Cancer Institute,[3] we believe that this issue is of significant importance and needs further investigation and future guideline modifications in areas where thrombosis/CSVT incidence is high. The incidence of CSVT is protocol-specific and seems to be affected by factors such as the use of prednisone or dexamethasone and their respective doses, the intensity and duration of ASP therapy and concomitant (ASP plus steroid) therapy, as well as ethnic specificities.

Thrombosis and CSVT have been reported with both native ASP as well as Erwinia ASP. Erwinia ASP has a shorter half-life compared to native ASP so a higher dose and an increased frequency of therapy is required to ensure asparagine depletion. In the EORTC study, Duval[20] concluded that using equal doses of 10,000 IU/m$^2$ twice weekly of *E. coli* and Erwinia ASP resulted in significantly more coagulation abnormalities in *E. coli* ASP than in Erwinia ASP. The incidence of venous thromboembolism was the same in the DFCI Consortium Protocols (1991–2008) between L ASP and Erwinia ASP.[21] Plourde et al. in a large study (the EMTP trial) where Erwinia ASP was used at doses that adequately deplete asparagine reported a thrombosis rate of 2.1% and a grades 3 and 4 toxicity of 0.9%.[22] The dose of Erwinia used in our protocol was twice that of native L-ASP; however, no patient developed CSVT while receiving Erwinia ASP. This could be due to the small number of patients who received Erwinia ASP in our patient population.

## 5 | CONCLUSION

CSVT is an important complication of ALL treatment, especially in areas where its incidence is reported to be high as in Lebanon. Some risk factors have been previously identified and our study was able to shed light on novel risk factors that have not been previously described: TGs level >615 mg/dl, mediastinal mass, and body surface area. Given the poor literature and recommendation consensus in relation to CSVT

prophylaxis and the newly suggested risk factors that are highlighted in our study, we recommend further prospective studies with larger samples to confirm our findings and help identify the subgroup of patients that qualify for CSVT prophylaxis during ALL treatment.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

## AUTHOR CONTRIBUTIONS

All authors have contributed to the production of this manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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