Received: 23 January 2023 | Revised: 22 April 2023 | Accepted: 25 April 2023

DOI: 10.1002/pbc.30425

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

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RESEARCH ARTICLE

Central nervous system thrombosis in pediatric acute lymphoblastic leukemia in Turkey: A multicenter study

Zeliha Guzelkucuk[1] | Deniz Yılmaz Karapınar[2] | Sema Aylan Gelen[3] | Huseyin Tokgoz[4] | Alper Ozcan[5] | Yılmaz Ay[6] | Aysenur Bahadır[7] | Namik Yasar Ozbek[1] | Ayse Ceyda Oren[8] | Aylin Canbolat Ayhan[9] | Arzu Akyay[10] | Burcu Akıncı[11] | Nihal Karadas[2] | Aysegul Unuvar[12] | Hale Oren[13] | Ali Fettah[14] | Zuhre Kaya[15] | Bilgen Isık[16] | İbrahim Eker[17] | Serap Karaman[12] | Aysen Turedi Yıldırım[18] | Mehmet Fatih Orhan[19] | Yesim Oymak[20] | Cetin Timur[21] | Nalan Yazici[22] | Ayse Simsek[4] | Neslihan Karakurt[23] | Ersin Toret[24] | Melike Sezgin Evim[25]

[1]Department of Pediatric Hematology-Oncology, Ankara Bilkent City Hospital, Ankara, Turkey

[2]Department of Pediatric Hematology-Oncology, Ege University Faculty of Medicine, İzmir, Turkey

[3]Department of Pediatric Hematology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

[4]Department of Pediatric Hematology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey

[5]Department of Pediatric Hematology-Oncology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[6]Department of Pediatric Hematology, Pamukkale University Faculty of Medicine, Denizli, Turkey

[7]Faculty of Medicine, Department of Pediatric Hematology, Karadeniz Technical University, Trabzon, Turkey

[8]Department of Pediatric Hematology-Oncology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

[9]Faculty of Medicine, Department of Pediatric Hematology, Istanbul Medeniyet University, Istanbul, Turkey

[10]Department of Pediatric Hematology, Inonu University Faculty of Medicine, Malatya, Turkey

[11]Department of Pediatric Hematology-Oncology, Acıbadem University Faculty of Medicine, Istanbul, Turkey

[12]Department of Pediatric Hematology-Oncology, Istanbul University Faculty of Medicine, Istanbul, Turkey

[13]Department of Pediatric Hematology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

[14]Department of Pediatric Hematology, Dr. Sami Ulus Pediatric Health and Diseases Training and Research Hospital, Ankara, Turkey

[15]Department of Pediatric Hematology-Oncology, Gazi University Faculty of Medicine, Ankara, Turkey

[16]Department of Pediatric Hematology-Oncology, University of Health Sciences Bursa High Specialization Hospital, Bursa, Turkey

[17]Department of Pediatric Hematology-Oncology, Afyonkarahisar University Faculty of Medicine, Afyon, Turkey

[18]Department of Pediatric Hematology-Oncology, Celal Bayar University Faculty of Medicine, Manisa, Turkey

[19]Department of Pediatric Hematology-Oncology, Sakarya University Faculty of Medicine, Sakarya, Turkey

[20]University of Health Sciences Dr. Behçet Uz Pediatric Diseases and Pediatric Surgery Department of Pediatric Hematology, İzmir, Turkey

[21]Department of Pediatric Hematology-Oncology, Yeditepe Faculty of Medicine, Istanbul, Turkey

[22]Department of Pediatric Hematology, Baskent University Adana Dr. Turgut Noyan Application and Research Center, Adana, Turkey

[23]Department of Pediatric Hematology Oncology, Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital, Istanbul, Turkey

[24]Department of Pediatric Hematology-Oncology, Osmangazi University Faculty of Medicine, Eskişehir, Turkey

[25]Department of Pediatric Hematology-Oncology, Uludag University Faculty of Medicine, Bursa, Turkey

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin–Frankfurt–Münster; CNS, central nervous system; CSVT, cerebral sinus vein thrombosis; CVT, cerebral venous thrombosis; LMWH, low molecular weight heparin; NOACs, new oral anticoagulants; PAI, plasminogen activator inhibitor.

Correspondence
Zeliha Guzelkucuk, Department of Pediatric Hematology Oncology, Ankara Bilkent City Hospital, Ankara Şehir hastanesi, Çocuk Kulesi, Üniversiteler Mahallesi 1604, Cadde No: 9, Çankaya/Ankara, Turkey.
Email: drguzelkucuk@hotmail.com

Abstract

Background: In patients with acute lymphoblastic leukemia (ALL), the risk of thromboembolism increases due to hemostatic changes secondary to the primary disease and due to treatment-related factors. In this multicenter study, we aimed to research the frequency of central nervous system (CNS) thrombosis occurring during treatment, hereditary and acquired risk factors, clinical and laboratory features of patients with thrombosis, treatment approaches, and thrombosis-related mortality and morbidity rates in pediatric ALL patients.

Procedure: Pediatric patients who developed CNS thrombosis during ALL treatment from 2010 to 2021 were analyzed retrospectively in 25 different Pediatric Hematology Oncology centers in Türkiye. The demographic characteristics of the patients, symptoms associated with thrombosis, the stage of the leukemia treatment during thrombosis, the anticoagulant therapy applied for thrombosis, and the final status of the patients recorded through electronic medical records were determined.

Results: Data from 70 patients with CNS thrombosis during treatment, out of 3968 pediatric patients with ALL, were reviewed. The incidence of CNS thrombosis was 1.8% (venous: 1.5 %; arterial: 0.03%). Among patients with CNS thrombosis, 47 had the event in the first 2 months. Low molecular weight heparin (LMWH) was the most commonly used treatment with a median of 6 months (min–max: 3–28 months). No treatment-related complications occurred. Chronic thrombosis findings occurred in four patients (6%). In five (7%) patients who developed cerebral vein thrombosis, neurological sequelae (epilepsy and neurological deficit) remained. One patient died related to thrombosis, and the mortality rate was 1.4%.

Conclusion: Cerebral venous thrombosis and, less frequently, cerebral arterial thrombosis may develop in patients with ALL. The incidence of CNS thrombosis is higher during induction therapy than during other courses of treatment. Therefore, patients receiving induction therapy should be monitored carefully for clinical findings suggestive of CNS thrombosis.

KEYWORDS
acute lymphoblastic leukemia, central nervous system, thrombosis

1 | INTRODUCTION

Cancer is a well-known risk factor for thromboembolic events, especially in adults. Although thrombosis is relatively rare in the pediatric age group, it is reported that the frequency in the pediatric population is increased.[1] The diagnoses of leukemia and lymphoma are known as independent risk factors in patients with thrombosis, in which venous thromboembolism is predominant.[2] The estimated incidence of thrombosis in patients with leukemia has been reported in a fairly wide range, 5%–70%.[3] In the study of Caruso et al., in which 1752 ALL (acute lymphoblastic leukemia) patients were evaluated, the incidence of thrombosis was reported as 5.2%, and more than half of those cases (53.8%) were central nervous system (CNS) thrombosis.[4]

The hematological changes leading to a prothrombotic state can be related to the underlying diagnosis, chemotherapeutic agents used (e.g., asparaginase, type of steroids [prednisone vs. dexamethasone], and thrombophilia [inherited vs. acquired [e.g., obesity, older age]).[3,5–7] Hematological changes due to leukemia may be listed as increased factor VIII, factor IX, von Willebrand factor, alpha 2-macroglobulin levels, and decreased antithrombin, protein C, and S levels, and decreased fibrinolysis.[3] Endothelial damage secondary to chemotherapeutic drugs and increased infections on the background of bone marrow suppression are also important factors that facilitate the formation of thrombosis.[3]

Although there are studies on thrombosis in patients with ALL in the literature, studies evaluating only CNS thrombosis in ALL are relatively rare. Therefore, we aimed to research the frequency of CNS

thrombosis occurring during treatment, hereditary and acquired risk factors, clinical and laboratory features of the patients with thrombosis, thrombosis treatment approaches, thrombosis-related mortality and morbidity rates, and prognosis of pediatric ALL patients in this large multicenter study.

2 | METHODS

2.1 | Data collection

The study was planned by the Turkish Society of Pediatric Hematology, the Subcommittee of Early/Late Side Effects and Supportive Treatments. Data of patients from 25 pediatric hematology oncology centers in Turkey were evaluated. Demographic characteristics of the patients, hereditary and acquired risk factors, symptoms during thrombosis, laboratory-radiological findings, chemotherapy protocols, the time point of the chemotherapy when the thrombosis occurred, anticoagulant treatment, and the final status of the patients were examined from electronic medical records.

2.2 | Patient characteristics

Patients aged 0—18 years who were diagnosed with cerebral arterial and/or venous thrombosis while receiving ALL treatment between 2010 and 2021 were included in the study. Patients who were found to have CNS thrombosis during the relapse protocol were excluded from the study.

2.3 | Ethics committee approval

This study was approved by the Ankara City Hospital ethics committee (approval number: E2-23-3262).

2.4 | Statistical analyses

Descriptive statistics were used while assessing the data. Categorical measurements were expressed as numbers and percentages, and numerical measurements were expressed as means and standard deviations.

3 | RESULTS

The medical records of 3968 pediatric ALL patients from 25 centers were examined and the data of 74 patients diagnosed with CNS thrombosis were obtained. Four relapsed patients were excluded from the study; as a result, data from 70 patients were analyzed. The frequency of CNS thrombosis was calculated as 1.8% (venous: 1.5%; arterial: 0.03%). The median age of the patients was 8 years (min–max: 3—18 years), and 45 patients (64%) were male. Fifty-seven patients (81%) were diagnosed with B-ALL and 13 patients (19%) with T-ALL (four patients with a mediastinal mass). Clinical features, clinical risk factors, and chemotherapy protocols are shown in Table 1, and genetic risk factors that could be determined (in 53 patients) for thrombophilia are also shown in Table 2. Protein C resistance was detected in one patient, but factor V Leiden mutation was not detected. Patients were treated with Berlin–Frankfurt–Münster (BFM) ALL Intercontinental-2009, ALL BFM 2000, ALL BFM 1995, St Jude Total 13, Esph ALL, and NHL BFM 2012. Thrombosis was reported in the following phases of therapy: induction phase in 29 (42%) patients, early intensification in 18 (26%), consolidation in two (2.8%), reinduction in 18 (26%), and maintenance phase in two (2.8%) patients. The median administered number of L-asparaginase was eight doses (min–max: 1–12) until the development of thrombosis. Thrombosis was detected in one patient (Burkitt's leukemia) before treatment at the time of diagnosis.

Cerebral venous thrombosis (CVT) was detected in 58 patients (83%), arterial thrombosis in 11 patients (16%), and both arterial and venous thrombosis in one patient (1.4%). The diagnosis was made by computed tomography angiography in two patients and by magnetic resonance imaging angiography and venography imaging in the other patients. Control evaluations were made with the same radiological method.

The localizations of thrombosis are shown in Table 3, and the signs and symptoms of CNS thrombosis are shown in Table 4.

There were 14 patients (20%) observed to have bleeding with thrombosis. The median time between the onset of clinical findings and the diagnosis of thrombosis was 1 day (min–max: 1 hour to 17 days). While anticoagulant treatment was applied to all patients, the most commonly used agent (98.5%) was low molecular weight heparin (LMWH). The median duration of LMWH treatment was 6 months (min–max: 3—28 months). There was no side effect associated with LMWH treatment. Fresh frozen plasma and aspirin were used in one patient with arterial thrombosis, and unfractionated heparin was administered to another patient with arterial thrombosis. The mean clinical recovery time was 5.4 days (min–max: 1—30 days), and the mean recanalization time illustrated by radiological imaging techniques was 78.8 days (min–max: 15–217 days). Findings of chronic thrombosis were detected in four patients (6%). No neurological sequelae were observed in these patients with chronic thrombosis. It was determined that 28 (40%) patients experienced a delay in the implementation of the chemotherapy protocol due to thrombosis. The mean chemotherapy delay time due to thrombosis was 10 days (min–max: 2—30 days). One intrathecal treatment in one patient and two doses of L-asparaginase treatment in two patients could not be given. Recurrence of CNS thrombosis was observed in only one patient (1.4%), and in another patient (1.4%) thrombosis recurred outside of the CNS (in the central venous catheter). Neurological sequelae (epilepsy and neurological deficit) were detected in five patients (7%) with venous thrombosis. In total, eight patients died. Thrombosis-related death was observed in one patient, and the mortality rate was calculated at 1.4%. A 12-year-old male patient with T-ALL developed hemiparesis and delirium in the course of induction chemotherapy and died 2 days after being

TABLE 1 Clinical characteristics of patients with central nervous system thrombosis.

	Number of patients	%
Immunophenotype		
B-ALL	57	81
T-ALL	13	19
Diagnostic risk group		
SRG	4	6
IRG	49	70
HRG	17	24
CNS involvement at the time of diagnosis		
Positive	12	17
Negative	58	83
Treatment protocol		
ALLIC BFM 2009	58	83
ALLIC BFM 2000	5	7
St Jude	3	4.3
ALLIC BFM 95	2	2.9
EsphALL	1	1.4
NHL BFM	1	1.4
Number of asparaginase use (min–max) type of L-asparaginase	0–12	
Escherichia coli asparaginase	67	97
E. coli asparaginase + PEG asparaginase	1	1.4
PEG asparaginase	1	1.4
CNS radiotherapy		
Yes	1	1.4
No	69	98.6
Family history of thrombosis		
Yes	0	0
No	44	63
Unknown	26	37
Obesity		
Yes	2	3
No	68	97
Hyperlipidemia		
Yes	9	13
No	61	87
TPN		
Yes	2	3
No	68	97
Central venous catheter		
Yes	41	59
No	29	41
Infection (systemic-intracranial)		
Yes	17	24
No	52	74
Combined	1	1.4

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system; HRG, high-risk group; IRG, intermediate-risk group; PEG, polyethylene glycol; SRG, standard-risk group; T-ALL, T-cell acute lymphoblastic leukemia; TPN, total parenteral nutrition.

TABLE 2 Genetic risk factors for thrombophilia.

Thrombophilia risk factors	Number of patients ($n = 53$)	%
MTHFRC677T polymorphism (homozygous/heterozygous)	19	36
MTHFR 1298 polymorphism (homozygous/heterozygous)	17	32
Factor V Leiden (heterozygous)	7	13
PAI-1 (4G/5G) polymorphism	5	9
Factor XIII V34L polymorphism (heterozygous)	2	4
Protrombin mutasyonu (heterozygous)	1	2
Hyperhomocysteinemia	1	2
Hyperfibrinogenemia/increased vWF level	3	6

Abbreviations: MTHFR, methylene tetrahydrofolate reductase; PAI, plasminogen activator inhibitor; vWF, von Willebrand factor.

diagnosed with thrombosis in the superior sagittal sinus, medial left transverse sinus, and left posterior cerebral artery.

4 | DISCUSSION

CNS thrombosis has an important place in terms of symptomatic thromboembolic complications in patients with ALL.[3,8] Most studies investigating cases of thrombosis in patients with leukemia include data on cerebral sinus vein thrombosis (CSVT) because it is more common than arterial thrombosis.[2,9] Data on the frequency of arterial thrombosis are limited. In a meta-analysis by Caruso et al, the incidence of CNS thrombosis was reported in 49 patients out of 1752 pediatric patients with leukemia (2.49%).[4] The incidence of CSVT in ALL has been reported to be between 1.4% and 3.8%.[10,11] In our study, the data from 3968 pediatric ALL cases were analyzed and the incidence of CNS thrombosis was 1.8%. On the other hand, the incidence of arterial thrombosis (0.03%) was found to be comparatively low.

The incidence of thrombosis is increasing due to many risk factors in patients with leukemia.[12] Advancing age, male gender, and being in an intermediate-risk group at diagnosis are reported to be significant factors in the development of thrombosis in patients with ALL.[13] In our

TABLE 3 Localizations of central nervous system thrombosis.

Thrombosis localization	Number of patients	%
Cerebral venous thrombosis	**58**	**83**
Superior sagittal sinus	33	47
Right transverse sinus	15	21
Left transverse sinus	10	14
Right–left sigmoid sinus	15	21
Ethmoid sinus	1	1.4
Galen vein	1	1.4
Multifocal venous ınfarction	1	1.4
Cortical vein thrombosis	1	1.4
Dural vein thrombosis	1	1.4
Arterial thrombosis	**11**	**16**
Right middle cerebral artery	3	4.3
Left middle cerebral artery	3	4.3
Right posterior cerebral artery	1	1.4
Left posterior cerebral artery	1	1.4
Right anterior cerebral artery	1	1.4
Left anterior cerebral artery	1	1.4
Vertebrobasilar artery	1	1.4
Arterial and venous thrombosis	**1**	**1.4**
Superior sagittal sinus, left transverse sinus, left posterior cerebral artery	1	1.4

TABLE 4 Signs and symptoms seen in patients during central nervous system thrombosis.

Signs and symptoms	Number of patients	%
Headache	32	46
Convulsion	22	31
Loss of consciousness	16	23
Facial paralysis	8	11
Vomiting	6	8.6
Speech disorder	6	8.6
Defect of vision	5	7.1
Other (hemiparesis, weakness, personality changes, dizziness, numbness in extremities)	17	24

study, it was seen that most of the patients with thrombosis were in the median-risk group, the gender was male, and the median age was 8. The increase in the frequency of thrombosis after infancy and early childhood is attributed to the increase in thrombin-forming capacity with age.[13,14] There are controversial results regarding the relationship between the T-cell ALL phenotype and susceptibility to thrombosis. The main reason for the predisposition to thrombosis in these patients is currently unknown, but it has been reported that the risk of thrombosis may be increased due to the procoagulant effect of the blasts by the excess disease burden.[15] In addition, in a recently published study, the presence of a mediastinal mass, which is more commonly seen in patients with T-ALL, was identified as a new risk factor associated with an increased risk of thrombosis.[16] In our study, approximately 20% of the cases were in the T-ALL phenotype (four patients with a mediastinal mass). This rate is similar to the general incidence of T-ALL. The induction period is important, because of the risk of thrombosis due to the active disease process and the intensive use of L-asparaginase and corticosteroids.[10,17–20] Correspondingly, most of the patients with thrombosis in our study were diagnosed during the induction period. In our study, the presence of CNS thrombosis especially during reinduction therapy attracted our attention. We thought that the presence of central venous catheters, infections, and immobility may contribute to the development of thrombosis during this part of the treatment.[11]

The role of genetic thrombophilia in cancer-related thrombosis is controversial.[2] It has been reported that the risk of thrombosis increases in the presence of additional prothrombotic risks in patients with malignancy and that patients should be screened for these risk factors and necessary precautions should be taken.[2,21,22] Activated protein C resistance is the most frequent coagulation abnormality associated with CVT.[23] The rate of resistance to active protein C in patients with CVT is unknown. In a case-controlled study conducted by Zuber et al., four (21%) of 19 patients with CVT and only one (2%) of 57 patients in the control group had a heterozygous factor V Leiden mutation.[24] In our study, no patient was carrying a factor V Leiden homozygous mutation. Similarly, there were no patients with hereditary antithrombin III, protein C, or protein S deficiencies. However, heterozygous factor V Leiden mutation positivity was 13% in our patients whose genetic thrombophilia tests were determined. Genetic polymorphisms of plasminogen activator inhibitor (PAI)-1 675 4G/5G have been identified as a risk factor associated with CVST.[25] In the study by Gogu et al., it was indicated that PAI-1 gene mutations are associated with higher total cholesterol, low-density lipoprotein cholesterol, triglyceride, homocysteine level, and higher sensitive C-reactive protein levels.[25] In our study, PAI polymorphism was found to be 9%. Further studies are needed to evaluate the contribution of PAI polymorphisms to the development of thrombosis in children with leukemia.

Clinical findings of thrombosis may be confusing with drug-related neurologic side effects and symptoms of CNS involvement in ALL.[4,26] In our study, headache, seizure, and alternating consciousness were the most common clinical symptoms in patients with CNS thrombosis. However, different neurological symptoms such as vomiting, vision and speech disorder, facial paralysis, hemiparesis, weakness, personality changes, dizziness, and numbness in the extremities were observed at varying rates. It should be kept in mind that these findings could be a clue for cerebral thrombosis in patients with ALL. CNS thrombosis may result in neurological sequelae such as epilepsy, neurological deficits, and chronic headaches (20%).[13] In our study, neurological sequelae such as neurological deficit and epilepsy were found in 7% of the patients. Neurological recovery was achieved to a considerable extent in patients with thrombosis, but it is stated that detailed neurological and neuropsychological tests should be applied to these

patients for optimal neurological examination.[27] Consequently, it was accepted as an expected result that the sequelae rates would show a wide distribution.

The use of LMWH is recommended in the treatment of CNS thrombosis.[28] In our study, it was observed that LMWH treatment was continued for about 6 months without any bleeding complications. Side effects that would terminate the treatment were not reported in our patients with thrombosis and bleeding. In the presence of thrombocytopenia and coagulopathy, it is recommended to continue the treatment by correcting the coagulation disorder and thrombocytopenia in patients requiring anticoagulant therapy.[29]

Few studies have been conducted on thrombosis prophylaxis in patients with leukemia.[19,28,30] Currently, there is insufficient evidence to recommend thrombosis prophylaxis in newly diagnosed ALL patients.[9,16] The use of LMWH, which was started after the first thrombosis in our patients, lasted for an average of 6 months. Secondary antithrombotic prophylaxis was continued to prevent the recurrence of thrombosis during the intensive active chemotherapy period. Thrombosis recurrence occurred in 3% of our patients despite prophylaxis. In addition, the continuation of anticoagulant therapy is important, as the development of chronic thrombosis will increase morbidity in these patients. In the literature, it has been reported that treatment with LMWH for a minimum of 3 months and until L-asparaginase therapy is over with major radiologic improvement seems to be effective and feasible.[31] It is thought to have a positive prophylactic effect.[32] New oral anticoagulants (NOACs) such as rivaroxaban can be used in some thromboembolic disorders. Results of the EINSTEIN-Jr CVT study showed that rivaroxaban is effective and safe in pediatric CVT.[33] PREVAPIX-ALL is the first study of NOACs use in primary thrombosis prophylaxis in patients with pediatric ALL. The results of the PREVAPIX-ALL study were presented at ISTH 2022. Apixaban decreases VTE risk in obese patients.[34]

It has been reported that the development of thrombosis in ALL patients negatively affects the prognosis.[35] On the other hand, it has been shown that there was no significant difference in terms of event-free survival or overall survival in a study published by the Dana Farber Group of adult and pediatric patients, which investigated how the discontinuation of asparaginase affected prognosis.[36] CNS thrombosis can be severe and life-threatening, and the overall mortality of CSVT is reported to be between 10% and 21%.[37,38] In a recent study, morbidity was reported as 25% and mortality as 6.3% in cases who had CSVT during pediatric ALL treatment.[39] This result also indicates the importance of early treatment where there may be death related to thrombosis in patients with ALL.

The retrospective design was a limitation of our study. As the data of ALL patients without thrombosis were not analyzed, comparisons to determine risk factors could not be made. Genetic tests were not performed in all centers. Furthermore, our study included only the results of a homogeneous group of ALL patients designed as a multicenter study. To our knowledge, it is the largest study in the literature.

In conclusion, CNS thrombosis is a rare complication that can affect the arterial and venous systems in patients with ALL. CNS thrombosis may be seen more intensely in the first 2 months of chemotherapy protocols. Anticoagulant treatment for thrombosis achieves remarkable clinical and radiological improvement in patients. LMWH provides safe and effective treatment for these patients. Patients with leukemia, especially those receiving induction chemotherapy, should be carefully monitored for clinical findings suggestive of CNS thrombosis to initiate appropriate treatment with rapid diagnosis and to minimize morbidity and mortality rates.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Zeliha Guzelkucuk https://orcid.org/0000-0003-1462-6867
Deniz Yılmaz Karapınar https://orcid.org/0000-0002-1637-4678
Sema Aylan Gelen https://orcid.org/0000-0002-8473-8146
Alper Ozcan https://orcid.org/0000-0002-6100-1205
Arzu Akyay https://orcid.org/0000-0002-4480-7784
Nihal Karadas https://orcid.org/0000-0002-0019-7347
Hale Oren https://orcid.org/0000-0001-5760-8007
Zuhre Kaya https://orcid.org/0000-0002-3798-7246
Serap Karaman https://orcid.org/0000-0002-7428-3897
Yesim Oymak https://orcid.org/0000-0002-6908-8309
Ersin Toret https://orcid.org/0000-0002-6379-8326
Melike Sezgin Evim https://orcid.org/0000-0002-4792-269X

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How to cite this article: Guzelkucuk Z, Karapınar DY, Gelen SA, et al. Central nervous system thrombosis in pediatric acute lymphoblastic leukemia in Turkey: A multicenter study. *Pediatr Blood Cancer*. 2023;70:e30425.
https://doi.org/10.1002/pbc.30425