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Inherited Thrombophilia and Risk of Thrombosis in Children with Cancer: a Single-center Experience[a]

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Abstract

Objectives. Thrombosis is an increasingly recognized complication of childhood malignancy and its treatment. The incidence and etiology of pediatric cancer-related thrombosis is still not well understood. The aim of this study was to evaluate the prevalence of common prothrombotic genetic conditions in children with cancer, the frequency of thrombosis, and the role of inherited thrombophilia in the development of thrombosis in a pediatric oncology population. **Patients and Methods.** Forty-seven children (36 treated for hematological malignancies and 11 for solid tumors) with a median age of 8.8. years (range 0.4 – 19.3 years) were included in the study. Genetic polymorphisms of Factor V Leiden (G1691A), prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T were determined by real-time polymerase chain reaction-based DNA analysis. **Results.** Four (8.5%) patients were heterozygous for Factor V Leiden, 3 (6.4%) were heterozygous for prothrombin G20210A mutation, and 3 (6.4%) were homozygous for MTHFR C677T mutation. All patients had implanted central venous catheters. Four (8.5%) children had documented thrombosis, three of which were in the upper venous system. Two of the four patients with thrombosis had Factor V Leiden heterozygosity. **Conclusions.** Thrombosis is an important complication of childhood cancer. The risk of thrombosis may be increased in patients with Factor V Leiden. In the absence of consensus guidelines, our results support the recommendation for thrombophilia screening in children with cancer.

Key Words: Inherited Thrombophilia ▪ Cancer ▪ Thrombosis ▪ Children,

Introduction

Thrombosis is a well-recognized complication of malignancy. It is estimated that up to 20% of all cancer patients develop thrombosis throughout the course of the disease, with an annual incidence rate of 0.5% compared to 0.1% in the general population (1, 2). There is substantially less knowledge about thrombosis in the pediatric cancer population, with reported rates varying from 2% to 16%, depending on the type of malignancy (3). Children with cancer and thrombosis have an increased risk of mortality, higher rates of recurrent thrombosis and thrombosis-related morbidity, and decreased quality of life (4, 5). The pathophysiology of pediatric cancer-related thrombosis is multifactorial, and may reflect prothrombotic genetic factors, and tumor-related and treatment-related factors (6). The role of inherited thrombophilia in the development of thrombosis in children with cancer is poorly investigated and still unclear.

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This study was undertaken to determine the prevalence of Factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphisms in children with hematological malignancies and malignant solid tumors, the frequency of cancer-associated thrombosis, and the role of inherited thrombophilic alterations in thrombotic events.

Patients and Methods

Patients

Forty-seven children (34 boys and 13 girls) with primary cancer consecutively admitted from January 1st, 2010 to December 31st, 2015 to the Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Centre Rijeka, Croatia, were included in the study. The following data were collected from medical records: gender, age at diagnosis, the type of cancer, previous and family history of thrombosis, insertion/type of a central venous catheter (CVC), and the presence/developmental time/site of thrombosis. Ethical approval was obtained from the institutional ethics board. Informed written consent was obtained from the parents of all patients.

Methods

The samples were taken from the peripheral blood in tubes containing EDTA. The genomic DNA was prepared from the whole blood with a NucleoSpin Blood kit (Macherey-Nagel GmbH & Co. KG, Düren, Germany). Genetic polymorphisms of Factor V G1691A (Factor V Leiden), Factor II-Prothrombin G20210A and MTHFR C677T were screened by real-time polymerase chain reaction (RT-PCR) on a Light Cycler® 1.5 Instrument, Roche Diagnostics, Germany. Tests were performed by binding specific DNA probes marked with fluorescent colors during PCR and melting curve analysis of marked PCR products, according to the manufacturer's instructions. Plasma homocysteine levels were not routinely assessed.

Statistical Analyses

Descriptive statistics were used to summarize the data. The results were compared with the relative frequencies of heterozygous and homozygous variants of each polymorphism in the general population. Fisher's exact test was used to compare the prevalence of Factor II and Factor V Leiden polymorphism between boys and girls with cancer, between children with hematological malignancies and solid tumors, and between patients with and without thrombotic events. The Chi-squared test was used to describe MTHFR genotype distribution in boys and girls with cancer, and between patients with hematological malignancies and solid tumors. A P value of <0.05 was considered statistically significant.

Results

The median age of the patients was 8.8 years (range 0.4 – 19.3 years). Thirty-six patients had hematological malignancies (acute lymphoblastic leukemia [ALL] = 26, acute myeloid leukemia = 2, non-Hodgkin lymphoma = 7, Hodgkin lymphoma = 1) and 11 patients had solid tumors (malignant brain tumor = 3, soft tissue sarcoma = 3, osteosarcoma = 2, Ewing sarcoma = 1, neuroblastoma = 1, nasopharyngeal carcinoma = 1). All patients had implanted CVC: 33 patients had tunneled catheters (Broviac®) and 14 had implantable ports (Port-a-cath®).

Three (6.4%) patients (all boys) had heterozygous Factor II G20210A mutation, while no homozygosity was detected. Heterozygous Factor V Leiden was identified in 4 (8.5%) children (2 boys and 2 girls) with cancer, and no homozygous Factor V Leiden was found. MTHFR C677T heterozygosity was present in 21 (44.7%) patients, and homozygosity in 3 (6.4%). Six (46.2%) girls and 15 (44.1%) boys were heterozygous for MTHFR C677T, while 1 (7.7%) girl and 2 (5.9%) boys were homozygous. There was no statistical significance in the prevalence of FII G20210A mutation (Fisher's exact test, P=0.550), Factor V G1691A mutation (Fisher's exact test, P=0.304),

and MTHFR C677T mutation (Chi-squared test, P=0.928) between male and female patients.

Two (5.6%) patients with hematological malignancies and one (9.1%) with a solid tumor had heterozygosity for Factor II G20210A mutation. Factor V Leiden heterozygosity was identified in 3 (8.3%) children with hematological malignancies, and in 1 (9.1%) with a solid tumor. A heterozygous MTHFR C667T mutation was identified in 16 (44.4%) children with hematological malignancies and in 5 (45.5%) children with solid tumors, while 2 (5.6%) patients with hematological malignancies and 1 (9.1%) with a solid tumor had MTHFR C667T homozygosity. No statistical significance was found in the prevalence of Factor II G20210A mutation (Fisher's exact test, P=0.560), Factor V Leiden (Fisher's exact test, P=01.000) and MTHFR C667T mutation (Chi-squared test, P=0.936) between patients with hematological malignancies and solid tumors. The previous or family history of thrombosis was negative in all patients.

Four (8.5%) children (all boys) had a documented thrombotic event during treatment: right axillar and brachial vein thrombosis in a patient with non-Hodgkin lymphoma; right brachial vein thrombosis in a patient with neuroblastoma; right subclavian, axillary and brachial vein thrombosis in a patient with nasopharyngeal carcinoma, and right atrial thrombosis in a patient with osteosarcoma. No patient had any recurrent thrombosis. Two patients had heterozygous Factor V Leiden (both combined with heterozygous but no homozygous MTHFR C677T mutation), and one patient had a heterozygous MTHFR C677T mutation. Heterozygosity for Factor V Leiden was statistically more frequent among patients with thrombotic events than in patients without thrombosis (50% versus 5.3%, Fisher's exact test, P=0.039), while there was no statistical difference in the prevalence of MTHFR C677T mutation between cancer patients with and without thrombosis (Fisher's exact test, P=0.332). Homocysteine levels were normal in all patients. In one patient no thrombophilia gene alteration was detected.

The characteristics of patients with thrombosis are shown in Table 1.

Discussion

In our study, thrombosis was documented in 4 of 47 (8.5%) children with cancer, which is substantially higher than in the general pediatric population. The incidence of thrombosis ranges from 0.14 to 0.21 per 10,000 children per year, and 0.2 to 0.6% among hospitalized pediatric patients (7). The majority of affected children have at least one underlying condition or trigger for thrombosis, the most common being CVC, inherited thrombophilia, malignancy, congenital heart disease, chronic neuromuscular disease, surgery, major trauma, immobility, estrogen-containing contraceptives, obesity, and severe infection (8-11).

Table 1. The Characteristics of Patients with Thrombosis

Patient number	Sex/Age at diagnosis (years)	Type of malignancy	Site of thrombosis	Time of thrombosis	CVC* type	CVC* duration (days)	Inherited thrombophilic factors
1	Male / 16.5	Non-Hodgkin lymphoma	Right axillar and brachial vein	During therapy	Broviac	52	Factor V Leiden heterozygous (MTHFR† C677T heterozygous)
2	Male / 15.6	Osteosarcoma	Right atrium	During therapy	Port-a-Cath	96	Factor V Leiden heterozygous (MTHFR† C677T heterozygous)
3	Male / 17.2	Nasopharyngeal carcinoma	Right subclavian, axillary and brachial vein	During therapy	Port-a-Cath	209	(MTHFR† C677 heterozygous)
4	Male / 2.4	Neuroblastoma	Right brachial vein	During therapy	Port-a-Cath	491	None

*Central venous catheter; †Methylenetetrahydrofolate reductase.

The association between thrombosis and pediatric cancer is well established, and overall, 25% of children with thrombosis have an underlying diagnosis of cancer (12). The reported prevalence of thrombosis in children with cancer ranges from 2 to 16%, while the occurrence of asymptomatic events is approximately 40% (13-19). The risk is highest in children with ALL, followed by sarcoma and lymphoma, and the lowest risk is in children with brain tumors (4, 20, 21). The occurrence of thrombosis in the current study is in agreement with the published data, although thrombosis was more frequent in children with solid tumors (3/11) compared to hematological malignancies (1/36).

The etiology of thrombosis in children with cancer is multifactorial and includes patient-related (inherited thrombophilia), disease-related and treatment-related factors. Cancer may be considered a hypercoagulable state. Tumor cells express tissue factor, procoagulant proteins, metalloproteases, and molecules that can induce direct and indirect activation of coagulation. Several additional mechanisms, such as inflammatory, immune, and angiogenic responses, are involved (22, 23). Major risk factors for thrombosis in children with hematological malignancies include the presence of CVC, older age, prothrombotic genetic defects, non-O blood group, obesity, and medications (asparaginase, concomitant use of steroids, anthracyclines) (4, 24-26). Proposed prothrombotic risk factors in children with solid tumors include the presence of CVC, age > 10 years, certain tumor types and sites, metastatic disease, thrombophilia, obesity, and type of treatment (surgery, radiation, anthracyclines, and platinum) (4, 17, 27). CVC is the most important risk factor (28). Reported rates of symptomatic catheter-related thrombosis range from 2.6 to 36.7%, and rates of asymptomatic catheter-related thrombosis range from 5.9 to 43% (3, 29). The pathogenesis of catheter-related thrombosis is not well characterized, and it may involve endothelial damage and local activation of blood coagulation (30). The most common sites are the upper venous system, and the lower extremities for non-catheter-related thrombosis (28, 31). Central nervous system thrombosis is more common in children with ALL, with approximately half of patients having sinus venous thrombosis (19, 28). The incidence of cerebral sinus venous thrombosis in pediatric ALL patients varies from 1.4 to 10.5% (32-35). Right atrial thrombosis is reported in 2% of patients with symptomatic thrombosis (36).

In our study, all patients had CVC in place, and all thrombotic events occurred during chemotherapy. All four patients were male, and three were adolescents. Three patients had upper extremity thrombosis, and one had right atrial thrombosis. Two patients (50%) had heterozygous Factor Leiden (combined with MTHFR C677T heterozygosity).

The contribution of inherited thrombophilia to the occurrence of thrombosis in cancer patients has been documented. The two most common genetic causes of thrombophilia identified to date are Factor V Leiden and prothrombin G20210A mutation (37, 38). MTHFR C677T heterozygosity is a very frequent polymorphism, but it only increases the risk of thrombosis when it results in hyperhomocysteinemia (39). A meta-analysis of 17 prospective studies comprising 1752 pediatric patients with ALL reported the overall thrombotic risk of 5.2%. Prothrombotic genetic defects were studied in 557 children. Thirty-one thrombotic events were observed in 113 children affected by at least one genetic alteration, pointing to an approximately 8-fold increased thrombotic risk (relative risk [RR]:8.5; 95% CI: 4.4-17.4) in patients with inherited thrombophilia (26). Similar results were reported by Nowak-Göttle et al., who documented venous thrombosis in 46.5% (27/58) of children with ALL carrying a prothrombotic defect, compared to 2.2% (5/131) of children with no identified prothrombotic defect ($P<0.0001$; chi-square 137.0). Homozygous MTHFR mutation with hyperhomocysteinemia was diagnosed in 12.5% (4/32) children with thrombosis, and in a further 9.4% (3/32) patients combined with Factor V Leiden or increased lipoprotein A concentrations. In addition, an increased risk of thrombotic complications was clearly demonstrated in leukemia patients with combined prothrombotic risk factors, compared to patients with single

alterations (40). The study by Knöfler et al. included 77 children with malignancies and in 11 (14%) of them catheter-related thrombosis was detected. Prothrombotic genetic defects were found in 23% (17/77) patients, and in 7 of 11 (64%) patients had thrombosis. Three children had combined defects (heterozygous Factor V G1691A combined with heterozygous prothrombin G20210A mutation, protein S deficiency or hyperlipoproteinemia), and 4 had a single defect (heterozygous Factor V G1691A, heterozygous prothrombin G20210A mutation, hyperlipoproteinemia, and protein C deficiency type I) (41). Ünal et al. evaluated inherited and acquired prothrombotic risk factors in 37 children with malignancies and thrombosis. Congenital defects were detected in 15 (40%) patients: 8 had heterozygous Factor V G1691A, 1 had heterozygous prothrombin G20210A mutation, 4 had lipoprotein(a) elevation, 1 had decreased protein S level, and 1 had decreased protein C level. The risk of thrombosis increased when accompanied by additional prothrombotic risk factors (42). A large population-based study in Israel of 1191 children with ALL reported venous thromboembolism in 89 (7.5%) children. Thrombophilia screening was performed in 584 children, and findings were positive in 84 (14.4%). Patients with thrombophilia had significantly more thrombotic events compared to children without thrombophilia ($p < 0.001$) (43). Other studies failed to show any impact of thrombophilic gene mutations on thrombosis risk in patients with cancer (28, 44-47). Thus, the impact of inherited thrombophilic markers on the development of thrombosis in pediatric oncology patients has not been completely clarified. Our study confirms the higher occurrence of symptomatic thrombosis in children with cancer. Two out of 4 children with thrombosis had heterozygosity for Factor V Leiden as an inherited prothrombotic risk factor.

Limitation of Study

Our study has several limitations, including retrospective design, the small number of patients, heterogenous underlying malignancies, and the limited panel of genetic prothrombotic traits tested. Moreover, no investigations for asymptomatic vessel occlusion were performed. This could result in underestimation of thrombotic events, which in turn leads to an overestimation of the role of inherited prothrombotic risk factors. Larger multicenter prospective studies, development of guidelines for thrombophilia screening, identification of high-risk groups, individualized reevaluation of additional prothrombotic risk factors and appropriate measures might help in the prevention and early intervention of thrombotic events.

Conclusion

Children with cancer are at increased risk for developing thrombosis secondary to disease- and treatment-related factors, and other poorly characterized conditions. The prevalence of inherited thrombophilia in our patients was within the prevalence in the healthy population, but fact that two out of four patients with thrombosis had documented congenital prothrombotic risk factors should not be overlooked. There is still much to be learned regarding the risk factors, prevention, and treatment of thrombosis in children with cancer. In the absence of consensus guidelines, our results support a recommendation for thrombophilia screening in this population.

What Is Already Known on This Topic:

Children with cancer constitute the largest subset of patients who experience thrombosis. The pathophysiology of pediatric cancer-associated thrombosis is multifactorial, and the role that inherited thrombophilia plays in the pathogenesis is largely unknown. Thrombosis is a serious condition that can lead to significant long-term morbidity, as well as early mortality. With over 80% cure rates of childhood cancer, strategies for prevention, early diagnosis, and optimal intervention of cancer-related thrombosis in pediatric patients are of great importance.

What This Study Adds:

This is the first study in the Republic of Croatia to investigate the frequency of thrombosis and the prevalence of common prothrombotic genetic defects in children with cancer, as well as to evaluate the role of inherited thrombophilia in the development of pediatric cancer-related thrombosis. Our results confirm that children with cancer experience increased risk of thrombosis. To identify patients at increased risk for thrombosis better, we suggest thrombophilia screening in the routine clinical care of children with cancer.

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Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-Associated Thrombosis: An Overview of Mechanisms, Risk Factors, and Treatment. Cancers (Basel). 2018;10(10):380. doi: 10.3390/cancers10100380.
2. Fernandes CJ, Morinaga LTK, Alves JL Jr, Castro MA, Calderaro D, Jardim CVP, et al. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019;28(151):180119. doi: 10.1183/16000617.0119-2018.
3. Ko RH, Thornburg CD. Venous Thromboembolism in Children with Cancer and Blood Disorders. Front Pediatr. 2017;5:12. doi: 10.3389/fped.2017.00012.
4. Athale UH, Yang JYK, Chan AKC. Thromboembolism in children with cancer. In: Pappo AS, O'Brien S, editors. UpToDate. Waltham, MA. [updated 2023 Mar 17; cited 2023 Nov 14]. Available from: https://www.uptodate.com/contents/thromboembolism-in-children-with-cancer.
5. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009;124(4):1001-8. doi: 10.1542/peds.2009-0768. Epub 2009 Sep 7.
6. Barg AA, Kenet G. Cancer-associated thrombosis in pediatric patients. Thromb Res. 2020;191 Suppl 1:S22-5. doi: 10.1016/S0049-3848(20)30392-3.
7. Albisetti M, Chan AKC. Venous thrombosis and thromboembolism (VTE) in children: Risk factors, clinical manifestations, and diagnosis. In: O'Brien S, editor. UpToDate. Waltham, MA. [updated 2022 Apr 11; cited 2023 Oct 30]. Available from: https://www.uptodate.com/contents/venous-thrombosis-and-thromboembolism-vte-in-children-risk-factors-clinical-manifestations-and-diagnosis/print.
8. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study. J Pediatr. 2011;159(4):663-9. doi: 10.1016/j.jpeds.2011.03.052. Epub 2011 May 19.
9. Takemoto CM, Sohi S, Desai K, Bharaj R, Khanna A, McFarland S, et al. Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. J Pediatr. 2014;164(2):332-8. doi: 10.1016/j.jpeds.2013.10.025. Epub 2013 Dec 12.
10. Giordano P, Grassi M, Saracco P, Molinari AC, Gentilomo C, Suppiej A, et al. Paediatric venous thromboembolism: a report from the Italian Registry of Thrombosis in Children (RITI). Blood Transfus. 2018;16(4):363-70. doi: 10.2450/2017.0075-17. Epub 2017 Jun 3.
11. Jinks S, Arana A. Venous thromboembolism in paediatrics. BJA Educ. 2019;19(9):305-12. doi: 10.1016/j.bjae.2019.05.003. Epub 2019 Jul 10.
12. Athale UH, Chan AK. Thromboembolic complications in pediatric hematologic malignancies. Semin Thromb Hemost. 2007;33(4):416-26. doi: 10.1055/s-2007-976177.
13. Lipay NV, Zmitrovich AI, Aleinikova OV. Epidemiology of venous thromboembolism in children with malignant diseases: a single-center study of the Belarusian Center for Pediatric Oncology and Hematology. Thromb Res. 2011;128(2):130-4. doi: 10.1016/j.thromres.2011.03.014. Epub 2011 Apr 13.
14. Athale U, Siciliano S, Thabane L, Pai N, Cox S, Lathia A, et al. Epidemiology and clinical risk factors predisposing to thromboembolism in children with cancer. Pediatr Blood Cancer. 2008;51(6):792-7. doi: 10.1002/pbc.21734.
15. Pelland-Marcotte MC, Pole JD, Kulkarni K, Athale U, Stammers D, Sabapathy C, et al. Thromboembolism Incidence and Risk Factors in Children with Cancer: A Population-Based Cohort Study. Thromb Haemost. 2018;118(9):1646-55. doi: 10.1055/s-0038-1668543. Epub 2018 Aug 13.
16. Athale U, Cox S, Siciliano S, Chan AK. Thromboembolism in children with sarcoma. Pediatr Blood Cancer. 2007;49(2):171-6. doi: 10.1002/pbc.21047.
17. Schiavetti A, Foco M, Ingrosso A, Bonci E, Conti L, Matrunola M. Venous thrombosis in children with solid tumors. J Pediatr Hematol Oncol. 2008;30(2):148-52. doi: 10.1097/MPH.0b013e31815f88b7.
18. Paz-Priel I, Long L, Helman LJ, Mackall CL, Wayne AS. Thromboembolic events in children and young adults with pediatric sarcoma. J Clin Oncol. 2007;25(12):1519-24. doi: 10.1200/JCO.2006.06.9930.
19. Piovesan D, Attard C, Monagle P, Ignjatovic V. Epidemiology of venous thrombosis in children with cancer. Thromb Haemost. 2014;111(6):1015-21. doi: 10.1160/TH13-10-0827. Epub 2014 Feb 13.
20. Athale UH, Nagel K, Khan AA, Chan AK. Thromboembolism in children with lymphoma. Thromb Res. 2008;122(4):459-65. doi: 10.1016/j.thromres.2007.12.006. Epub 2008 Jan 30.
21. Tabori U, Beni-Adani L, Dvir R, Burstein Y, Feldman Z, Pessach I, et al. Risk of venous thromboembolism in pediatric patients with brain tumors. Pediatr Blood Cancer. 2004;43(6):633-6. doi: 10.1002/pbc.20149.
22. Castle J, Blower E, Kirwan CC. Update on the role of circulating tumour cells in cancer-associated thrombosis. Thrombosis Update. 2021;5:100066. doi: https://doi.org/10.1016/j.tru.2021.100066.

23. Rubio-Jurado B, Sosa-Quintero LS, Guzmán-Silahua S, García-Luna E, Riebeling-Navarro C, Nava-Zavala AH. The prothrombotic state in cancer. Adv Clin Chem. 2021;105:213-42. doi: 10.1016/bs.acc.2021.03.001. Epub 2021 Apr 19.
24. Spavor M, Halton J, Dietrich K, Israels S, Shereck E, Yong J, et al. Age at cancer diagnosis, non-O blood group and asparaginase therapy are independently associated with deep venous thrombosis in pediatric oncology patients: A risk model. Thromb Res. 2016;144:27-31. doi: 10.1016/j.thromres.2016.05.015. Epub 2016 May 18.
25. Prasca S, Carmona R, Ji L, Ko RH, Bhojwani D, Rawlins YA, et al. Obesity and risk for venous thromboembolism from contemporary therapy for pediatric acute lymphoblastic leukemia. Thromb Res. 2018;165:44-50. doi: 10.1016/j.thromres.2018.02.150. Epub 2018 Mar 2.
26. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood. 2006;108(7):2216-22. doi: 10.1182/blood-2006-04-015511. Epub 2006 Jun 27.
27. Athale U. Thrombosis in pediatric cancer: identifying the risk factors to improve care. Expert Rev Hematol. 2013;6(5):599-609. doi: 10.1586/17474086.2013.842124.
28. Albisetti M, Kellenberger CJ, Bergsträsser E, Niggli F, Kroiss S, Rizzi M, et al. Port-a-cath-related thrombosis and postthrombotic syndrome in pediatric oncology patients. J Pediatr. 2013;163(5):1340-6. doi: 10.1016/j.jpeds.2013.06.076. Epub 2013 Aug 27.
29. Wiegering V, Schmid S, Andres O, Wirth C, Wiegering A, Meyer T, et al. Thrombosis as a complication of central venous access in pediatric patients with malignancies: a 5-year single-center experience. BMC Hematol. 2014;14(1):18. doi: 10.1186/2052-1839-14-18.
30. Dentali F, Gianni M, Agnelli G, Ageno W. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost. 2008;6(1):70-5. doi: 10.1111/j.1538-7836.2007.02823.x. Epub 2007 Nov 6.
31. Schoot RA, van de Wetering MD, Stijnen T, Tissing WJ, Michiels E, Abbink FC, et al. Prevalence of Symptomatic and Asymptomatic Thrombosis in Pediatric Oncology Patients With Tunneled Central Venous Catheters. Pediatr Blood Cancer. 2016;63(8):1438-44. doi: 10.1002/pbc.26036. Epub 2016 Apr 29.
32. Musgrave KM, van Delft FW, Avery PJ, Clack RM, Chalmers EA, Qureshi A, et al. Cerebral sinovenous thrombosis in children and young adults with acute lymphoblastic leukaemia - a cohort study from the United Kingdom. Br J Haematol. 2017;179(4):667-9. doi: 10.1111/bjh.14231. Epub 2016 Jul 8.
33. Ranta S, Tuckuviene R, Mäkipernaa A, Albertsen BK, Frisk T, Tedgård U, et al. Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia - a multicentre study from the Nordic Society of Paediatric Haematology and Oncology. Br J Haematol. 2015;168(4):547-52. doi: 10.1111/bjh.13162. Epub 2014 Oct 7.
34. Ghanem KM, Dhayni RM, Al-Aridi C, Tarek N, Tamim H, Chan AKC, et al. Cerebral sinus venous thrombosis during childhood acute lymphoblastic leukemia therapy: Risk factors and management. Pediatr Blood Cancer. 2017;64(12). doi: 10.1002/pbc.26694. Epub 2017 Jun 29.
35. El-Khoury H, Saifi O, Haddad S, Chahrour M, Ghanem KM, Mubarak Y, et al. Treatment-induced cerebral sinus venous thrombosis in childhood acute lymphoblastic malignancies: New risk factors to consider. Pediatr Blood Cancer. 2021;68(11):e29210. doi: 10.1002/pbc.29210. Epub 2021 Jul 29.
36. Athale UH, Chan AK. Thrombosis in children with acute lymphoblastic leukemia: part I. Epidemiology of thrombosis in children with acute lymphoblastic leukemia. Thromb Res. 2003;111(3):125-31. doi: 10.1016/j.thromres.2003.10.013.
37. Decousus H, Moulin N, Quenet S, Bost V, Rivron-Guillot K, Laporte S, et al. Thrombophilia and risk of venous thrombosis in patients with cancer. Thromb Res. 2007;120 Suppl 2:S51-61. doi: 10.1016/S0049-3848(07)70130-5. Erratum in: Thromb Res. 2008;123(1):187-90.
38. Horowitz N, Brenner B. Thrombophilia and cancer. Pathophysiol Haemost Thromb. 2008;36(3-4):131-6. doi: 10.1159/000175151. Epub 2009 Jan 27.
39. Khan S, Dickerman JD. Hereditary thrombophilia. Thromb J. 2006;4:15. doi: 10.1186/1477-9560-4-15.
40. Nowak-Göttl U, Wermes C, Junker R, et al. Prospective evaluation of the thrombotic risk in children with ALL carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors. Blood. 1999;93(5):1595-9.
41. Knöfler R, Siegert E, Lauterbach I, Taut-Sack H, Siegert G, Gehrisch S, et al. Clinical importance of prothrombotic risk factors in pediatric patients with malignancy--impact of central venous lines. Eur J Pediatr. 1999;158 Suppl 3:S147-50. doi: 10.1007/pl00014342.
42. Unal S, Varan A, Yalçin B, Büyükpamukçu M, Gürgey A. Evaluation of thrombotic children with malignancy. Ann Hematol. 2005;84(6):395-9. doi: 10.1007/s00277-005-1004-x. Epub 2005 Feb 26.
43. Barzilai-Birenboim S, Nirel R, Arad-Cohen N, Avrahami G, Ben Harush M, Barg AA, et al. Venous Thromboembolism and Its Risk Factors in Children with Acute Lymphoblastic Leukemia in Israel: A Population-Based Study. Cancers (Basel). 2020;12(10):2759. doi: 10.3390/cancers12102759.
44. Sifontes MT, Nuss R, Hunger SP, Wilimas J, Jacobson LJ, Manco-Johnson MJ. The factor V Leiden mutation in children with cancer and thrombosis. Br J Haematol.

1997;96(3):484-9. doi: 10.1046/j.1365-2141.1997.d01-2046.x.

45. Ruud E, Holmstrøm H, Natvig S, Wesenberg F. Prevalence of thrombophilia and central venous catheter-associated neck vein thrombosis in 41 children with cancer--a prospective study. Med Pediatr Oncol. 2002;38(6):405-10. doi: 10.1002/mpo.10062.
46. Mauz-Korholz C, Junker R, Gobel U, Nowak-Gottl U. Prothrombotic risk factors in children with ALL treated with delayed E. coli asparaginase (COALL-92 and 97 protocols). Thromb Haemost. 2000;83(6):840-3.
47. Mitchell LG, Andrew M, Hanna K, Abshire T, Halton J, Anderson R, et al. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer. 2003 Jan 15;97(2):508-16. doi: 10.1002/cncr.11042.