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The role of routing in the diagnosis of acute leukemia in children: an observational retrospective non-randomized study

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ABSTRACT

BACKGROUND: Acute leukemia is the commonest malignancy of childhood with an incidence rate of about 55–62 per 1 million under 18 years of age. Early diagnosis of acute leukemia is difficult due to the non-specificity of primary symptoms, which are often hidden under the "masks" of other diseases. This problem is especially relevant for regions with a population of up to 100 thousand people, where a case of acute leukemia in children occurs every 2–5 years causing too low oncological alertness among pediatricians.

AIM: Assess the delay in diagnosis depending on the areas of residence in the Tver region and area remoteness from the Tver Regional Clinical Children's Hospital (Tver, Russia).

MATERIALS AND METHODS: The analysis included 35 patients hospitalized in the Department of Oncology and hematology of the Tver Regional Clinical Children's Hospital for the period from 2018 to 2023. The diagnoses were: acute lymphocytic leukemia (C91.0) — 30 (86%) patients, acute myeloid leukemia (C92) — 3 (9%) patients, and acute leukemia of unspecified cell type (C95.0) — 2 (5%) patients. The mean age was 61 months (5.1 years). Thrombocytopenia and anemia at the time of diagnosis were found in 76% and 78%, respectively. Leukocytosis (> 20×10^9/L) was observed in 58%, leukopenia (<3.5×10^9/L) in 15% of patients. In 97% of cases blasts (2% to 95%) were detected in peripheral blood. In the city of Tver (Group 1) and the Tver region (Group 2), 16 (46%) and 19 (54%) patients were identified, respectively. The mean age of patients in Group 1 is 28.6 months, and in Group 2 — 72.3 months (p=0.1).

RESULTS: In Groups 1 and 2, acute lymphocytic leukemia was diagnosed in 14 (88%) and 16 (84%), respectively (p=0.6); acute myeloid leukemia — in 1 (6%) and 2 (11%), respectively (p=0.7); acute leukemia of unspecified cell type — in 1 (6%) and 1 (5%) cases, respectively (p=0.95). Delay of diagnosis in the general group (n=35) was observed as follows: <2 weeks — in 21 (60%) cases; 2–4 weeks — in 7 (20%) cases; 4–8 weeks — in 4 (11%) cases: >8 weeks — in 3 (9%) cases. Comparison of the time of delayed diagnosis among patients living in the city of Tver versus the Tver region yielded following results: <2 weeks in 7 (44%) vs 13 (68%) cases; 2–4 weeks — in 6 (38%) vs 3 (17%), 4–8 weeks — in 1 (6%) vs 1 (5%); >8 weeks — in 2 (12%) vs 2 (10%) cases, respectively (p=0.37). There was no significant impact of the distance of the residence place from the level 3 children's hospital providing specialized care on the time of diagnosis. With the patients' distance of <50 km from the clinic, the diagnosis delay of <2 weeks, 2–4 weeks, 4–8 weeks and >8 weeks was observed in 36%, 36%, 21% and 7% of cases, respectively. With the distance of 50–100 km, the diagnosis was made in the period of 2–4 weeks in 100% of cases. With the removal of >100 km the diagnosis delay of <2 weeks, 2–4 weeks, 4–8 weeks, >8 weeks was observed in 30%, 30%, 20% and 20%, respectively (p=0.78).

CONCLUSION: The distance from the third-level hospital did not affect the period of diagnosis of acute leukemia in children. We believe this is achieved by holding daily on-line conferences with country hospitals and out-patient departments followed by the rapid hospitalization of children with suspected oncohematological disorders in the specialized department.

Keywords: acute leukemia; children; delay in diagnosis; distance; third-level hospital.

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Роль маршрутизации в диагностике острого лейкоза у детей: обсервационное ретроспективное нерандомизированное исследование

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АННОТАЦИЯ

Обоснование. Острый лейкоз — наиболее распространённая злокачественная патология у детей: 55–62 на 1 млн населения до 18 лет. Ранняя диагностика затруднена ввиду неспецифичности первичных симптомов, особенно в регионах с населением до 100 тыс. человек, где случай острого лейкоза у детей диагностируется 1 раз в период от 2 до 5 лет и где отсутствует онкологическая настороженность среди врачей поликлинического звена.

Цель. Оценить влияние маршрутизации на сроки установления диагноза «острый лейкоз» на примере Тверской области.

Материалы и методы. В анализ включено 35 пациентов, госпитализированных в отделение онкогематологии Детской областной клинической больницы (г. Тверь) за период с 2018 по 2023 год с диагнозами: острый лимфобластный лейкоз (C91.0) — 30 (86%) пациентов, острый миелоидный лейкоз (C92) — 3 (9%) пациента, и лейкоз с неопределённым клеточным типом (C95.0) — 2 (5%) пациента. Средний возраст пациентов составил 61 мес. (5,1 года). Тромбоцитопения и анемия на момент диагноза обнаруживались у 76% и 78% соответственно. Лейкоцитоз (>20×10^9/л) наблюдался у 58%, лейкопения (<$3{,}5\times10^9$/л) — у 15% пациентов. В 97% случаев в периферической крови определялись бласты от 2% до 95%. В г. Тверь (Группа 1) и Тверской области (Группа 2) выявлено 16 (46%) и 19 (54%) больных соответственно. Средний возраст пациентов в Группе 1 — 28,6 мес., а в Группе 2 — 72,3 мес. (p=0,1).

Результаты. В Группах 1 и 2 острый лимфобластный лейкоз был диагностирован в 14 (88%) и 16 (84%) случаях соответственно (p=0,6), острый миелоидный лейкоз — в 1 (6%) и 2 (11%) случаях соответственно (p=0,7), и лейкоз с неопределённым клеточным типом — в 1 (6%) и 1 (5%) случае соответственно (p=0,95). В общей группе (n=35) отсрочка диагноза на срок <2 недель наблюдалась в 21 (60%) случае, на срок 2–4 недели — в 7 (20%) случаях, на срок 4–8 недель — в 4 (11%) случаях, и на срок >8 недель — в 3 (9%) случаях. При сравнении двух групп пациентов, проживающих в городе и в области, отсрочка диагноза на срок <2 недель отмечена в 7 (44%) случаях в Группе 1 против 13 (68%) случаев в Группе 2; на срок 2–4 недели — в 6 (38%) против 3 (17%) случаев; на срок 4–8 недель — в 1 (6%) против 1 (5%) случая; на срок >8 недель — в 2 (12%) против 2 (10%) случаев соответственно (p=0,37).

Не отмечено достоверного влияния удалённости места проживания пациентов от детского учреждения 3-го уровня, оказывающего специализированную помощь, на время постановки диагноза. При расстоянии <50 км отсрочка диагноза на сроки <2 нед., 2–4 нед., 4–8 нед. и >8 нед. наблюдалась в 36%, 36%, 21% и 7% случаев соответственно. При удалении на расстояние 50–100 км диагноз был поставлен в период 2–4 недели в 100% случаев. При проживании пациентов на расстоянии >100 км отсрочка диагноза на сроки <2 нед., 2–4 нед., 4–8 нед. и >8 нед. наблюдалась в 30%, 30%, 20% и 20% соответственно (p=0,78).

Заключение. Удалённость от Детской областной клинической больницы г. Твери не оказала влияние на срок постановки диагноза «острый лейкоз» у детей. Отсутствие негативного влияния этого фактора достигается проведением ежедневных конференций с лечебными учреждениями области и быстрой госпитализацией детей с подозрением на онкогематологическую патологию в профильное отделение.

Ключевые слова: острый лейкоз; дети; задержка в постановке диагноза; расстояние; медицинское учреждение 3-го уровня.

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BACKGROUND

The treatment outcomes of children with acute leukemia (AL) have improved significantly over the years, owing to several clinical trials [1, 2]. The use of risk-adapted specific therapy and improvements in accompanying therapy protocols have significantly reduced the relapse rate and treatment-related mortality in patients with AL [3]. Despite improvements in the treatment outcomes of children and young adults with AL, certain socioeconomic and healthcare organization issues and the type of healthcare facility providing this care can affect treatment outcomes [4–6].

In 2017, the World Health Organization published "Guidelines for the Early Detection of Cancer" to strengthen early detection programs worldwide. In this article, "delay" is classified into patient delay (from symptom onset to first visit to a physician, presentation interval) and healthcare delay which is further divided into diagnosis establishment delay (from initial visit to a physician to confirmed diagnosis, diagnostic interval) and treatment delay (from confirmed diagnosis to treatment initiation, therapeutic interval) [7]. The duration of each of the three stages of early diagnostics is ideally no more than 30 days for all types of malignancies in children and adults. Most studies revealed that the interval from symptom onset to chemotherapy initiation for children with AL is less than 60 days [8–13]. However, with a reduction in the total time to early diagnosis of AL to 30 days or less, relapse-free and overall survival of patients significantly increases [5, 13].

A factor influencing the delay in diagnostics at stage 2 is the distance from the patient's place of residence to the healthcare facility with pediatric oncologists and hematologists who can provide specialized care [4, 13, 14]. The current study provides basis for cancer control programs that will systematically eliminate challenges in the timely provision of pediatric oncological care at each stage.

AIM

This study aimed to identify the correlation between the distance from the place of residence of children diagnosed with AL to the Children's Regional Clinical Hospital (CRCH) of Tver Region (level 3 institution) and delay in establishing the diagnosis of the disease.

MATERIALS AND METHODS

Study design

An observational retrospective non-randomized study was conducted.

Eligibility criteria

The criteria for inclusion of patients in the study were age <18, confirmed AL diagnosis, and voluntary informed consent of parents/legal representatives for participation of patients in the study and publication of results.

The exclusion criteria was refusal to participate in the study.

Conditions and duration of the study

The analysis included 35 patients aged <18 years available for analysis and hospitalized in the oncohematology department of the CRCH between 2018 and 2023 with a confirmed diagnosis of AL.

Description of medical intervention

Acute lymphoblastic leukemia (ALL, C91.0) was diagnosed in 30 cases (86%), acute myeloid leukemia (C92) in 3 cases (9%), and leukemia of undetermined cell type (C95.0) in 2 cases (5%).

The initial blood analysis showed the following results:

- Thrombocytopenia and anemia at diagnosis in 76% of patients in group 1 and 78% in group 2.
- Platelet concentration: thrombocytopenia; 50–99×10^9/L in 50% of patients, 20–49×10^9/L in 37.5%, and <20×10^9/L in 12.5%.
- Severe anemia (<70 g/L) in 47% of patients.
- Leukocyte concentration: leukocytosis (>20×10^9/L) in 58% of patients, leukopenia (<3.5×10^9/L) in 15%, and hyperleukocytosis (>100×10^9/L) in 14%. The average concentration of leukocytes was 261.6×10^9/L (126–470). In 27% of cases, the concentration of leukocytes in the peripheral blood was within the normal reference values, and in 97% of cases (*n*=34), blasts were detected in the peripheral blood of 2–95% of cases.

All patients were transferred to one of the Federal Children's Oncology Centers immediately after the provisional diagnosis was made because performing a full diagnostics on site was impossible. The average transfer period was 4.2 (1–9) days. Bone marrow puncture was performed in 27 (77%) patients. Myelography was conducted if no blasts in the periphery in the presence of cytopenia were found in the clinical blood test and if the patient did not exhibit characteristics determining high risk and therapeutic urgency (e.g., bleeding grade III and higher, hyperleukocytosis, organ dysfunction). In the presence of risk factors, patients were urgently transferred to a specialized federal center.

The clinical presentation mainly showed hepatosplenomegaly (58%) and lymphadenopathy (54%). Infectious syndrome with fever necessitating antibacterial therapy was noted in 23% of patients. Hemorrhagic syndrome of grade III and higher, requiring transfusion of blood-derived products, was observed in 12% (*n*=4) of patients.

According to the distance from the place of residence to the CRCH, patients were distributed into the following groups:

- Group 1: Tver: "0" kilometers
- Group 2: Tver Region: <50 km, 51–99 km, and >100 km.

By the delay in diagnosis from the onset of the first symptoms, four groups were identified:

- Group 1: <2 weeks
- Group 2: 2–4 weeks
- Group 3: 4–8 weeks
- Group 4: >8 weeks

Subgroups analysis

The average age of patients was 61 months (5.1 years). The gender ratio was 17 boys (46%) and 18 girls (54%). In Tver (group 1) and Tver Region (group 2), 16 (46%) and 19 (54%) patients were identified, respectively. The average age of patients was 28.6 months in group 1 and 72.3 months in group 2 (p=0.1).

Ethics committee

The study was approved by the Local Ethics Committee of the Children's Regional Clinical Hospital of Tver Region on February 20, 2024 (No. 125284).

Statistical processing

Statistical data processing was performed using Microsoft Excel 2019 (Microsoft Inc., USA). In the variation series with the distribution, the Student's t-test was utilized to identify the significant differences between the two groups. The differences were considered significant at p <0.05.

RESULTS

In groups 1 and 2, the following distribution of AL forms was revealed:

- Acute lymphoblastic leukemia in 14 (88%) and 16 (84%) patients (p=0.6)
- Acute myeloid leukemia in 1 (6%) and 2 (11%) patients (p=0.7)
- Leukemia of undetermined cell type in 1 (6%) and 1 (5%) patients (p=0.95)

The delay in diagnosis averaged 21 (6–62) and 18 (5–64) days in groups 1 and 2, respectively. In the overall group (n=35), a delay in diagnosis of less than 2 weeks was noted in 21 (60%) cases, of 2–4 weeks in 7 (20%) cases, of 4–8 weeks in 4 (11%) cases, and of more than 8 weeks in 3 (9%) cases.

When comparing the delay in diagnostics indicator between groups 1 and 2, the following results were obtained:

- Less than 2 weeks: 7 (44%) versus 13 (68%) cases (p=0.15)
- 2–4 weeks: 6 (38%) versus 3 (17%) cases (p=0.16)
- 4–8 weeks: 1 (6%) versus 1 (5%) case
- More than 8 weeks: 2 (12%) versus 2 (10%) cases

The difference between AL patients in groups 1 and 2 was not significant (p=0.37).

Among patients in group 2, the distance of the place of residence from the children's institution level 3 providing specialized care (CRCH) had no significant effect on the time of diagnosis. When patients were located <50 km from the CRCH, the delay in diagnostics was the following:

- <2 weeks (36% of patients)
- 2–4 weeks (36% of patients)
- 4–8 weeks (21% of patients)
- >8 weeks (7% of patients)

With a distance of 50–100 km, diagnosis was made within 2–4 weeks in 100% of cases.

The delay in diagnostics when patients lived >100 km from the CRCH was as follows:

- Less than 2 weeks in 30%
- 2–4 weeks in 30%
- 4–8 weeks in 20%
- More than 8 weeks in 20% (p=0.78)

DISCUSSION

Delay in diagnosis and treatment has been described in various studies with different results depending on the type of cancer studied. AL is diagnosed quickly compared with other types of cancer in children [5, 15]. However, the results may vary significantly depending on the country income level and healthcare organization system.

Most studies have noted a negative impact of delay from the onset of the first symptoms to the time of diagnosis on overall and relapse-free survival and early mortality during therapy [4–6, 12, 13]. In a group of 166 pediatric patients with acute lymphoblastic leukemia, a significant improvement in survival was observed in children whose overall treatment delay was <30 days, compared with those whose overall treatment delay was 30–120 days (86.4 versus 60%; p=0.02). Moreover, the average time interval from the onset of symptoms to the start of chemotherapy (overall delay) was 53.5 (38–93.5) days. Only 13.3% of patients started treatment within 30 days after the onset of symptoms [13]. Gardie et al. reported that acute lymphoblastic leukemia was diagnosed within 30 days in only 66% of children studied, which had a negative impact on the therapy results [15]. A similar negative impact was revealed in a Chinese study [6].

In the current study, the interval from the onset of the first symptoms to the time of diagnosis was 19 (5–64) days, and an excess of the diagnostic interval by more than 30 days was found in only 20% of patients. Thus, our data positively correlate with studies conducted in Brazil, Mexico, and Nicaragua, where the median of the overall

delay is 30–35 days, and with data from Japan and China (median: 20 and 21 days, respectively) [6, 9, 11, 16, 17].

In most cases, an increase in the distance from the place of residence to a medical institution capable of making a diagnosis negatively affects the results of therapy and is directly related to an extended diagnostic interval. In a study in Greece, higher mortality rate was reported among children living 50 km or more from a treatment center compared with those living within 50 km (mortality ratio: 1.77; 95% confidence interval (CI): 0.93–3.37; *n*=293) [18]. Youlden et al. revealed higher mortality rates among children with leukemia living in remote areas compared with those in major cities in Australia (relative risk: 1.52; 95% CI: 1.11–2.08; *n*=6,289) [19]. In a recent analysis of pediatric and young adult (up to 39 years) patients in the North American National Cancer Database, Rotz et al. showed higher survival among those living within 50 miles (80 km) of the cancer center compared with those living more than 50 miles away from it (83 versus 77%; p <0.001) [4]. In a univariate analysis of 288 children with AL, late diagnostics was noted in 45% of cases when living 100 km or less away from the hospital and in 55% of cases when the distance from the hospital was more than 100 km. The relative risk of a delay in diagnosis of more than 30 days was 1.62 (95% CI: 1.01–2.58; *p*=0.04) [9].

In contrast, not all studies noted the association between the distance of residence and outcome of AL therapy. Janitz et al. did not observe differences between distance-to-care categories and relapse-free survival in children and adolescents aged ⩽20 years with acute lymphoblastic leukemia (*n*=275). However, in this study, an increased risk of relapse was noted when the patient lived more than 121 km (75 miles) from the treatment center [20].

The present study did not detect an effect of the distance from the patient's place of residence to the medical facility level 3 on the delay in diagnosis of AL in children. Among children living 100 km or more from the CRCH, the average delay in diagnosis was 20 [6–62] days compared to 19 [5–64] days in those living less than 100 km from it (*p*=0.97). Interestingly, among patients living in Tver, diagnosis was made within 30 days in 72% of patients, whereas among those in Tver Region, the diagnosis was made within this period in 85% of patients. The average delay in diagnosis in Tver and Tver region was 21 and 18 days, respectively (*p*=0.58). The higher frequency of early (<4 weeks) detection of AL in the districts of Tver Region compared to that in the city can be elucidated by the fact that doctors in the districts, when faced with abnormal blood test results or an unexplained deterioration in the patient's health, attempt to immediately transfer the patient to the CRCH, where there is a pediatric oncologist. In contrast, city patients are first examined at the city clinic; then, they are often hospitalized in level 2 institutions and only then transferred to the CRCH.

Study limitations

First, considering the child population of Tver Region, the average incidence of all types of AL was 3 per 100 thousand individuals, which is slightly lower than the average for children aged <18 years [21]. Thus, it can be assumed that some patients living in the border of the Moscow and Leningrad regions visit directly the federal pediatric oncology institutions when pathological symptoms appear, bypassing the CRCH. Second, the distance to the level 3 medical facility is geocoded from the postcode level of the patient's actual residential address and does not take into account how long it took the patient to reach the primary care medical facility or whether the patient was elsewhere at the time of disease onset.

ADDITIONAL INFORMATION

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Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. Dolgopolov IS — development of research design, data collection, analysis of literary sources, text editing; Rykov MYu — development of research design, data collection, analysis of literary sources, editing and writing of text.

REFERENCES

1. Zwaan CM, Kolb EA, Reinhardt D, et al. Collaborative Efforts Driving Progress in Pediatric Acute Myeloid Leukemia. *J Clin Oncol.* 2015;33(27):2949–2962. doi: 10.1200/JCO.2015.62.8289

2. Pui CH, Yang JJ, Hunger SP, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *J Clin Oncol.* 2015;33(27):2938–2948. doi: 10.1200/JCO.2014.59.1636

3. Alexander TB, Wang L, Inaba H, et al. Decreased relapsed rate and treatment-related mortality contribute to improved outcomes for pediatric acute myeloid leukemia in successive clinical trials. *Cancer.* 2017;123(19):3791–3798. doi: 10.1002/cncr.30791

4. Rotz SJ, Wei W, Thomas SM, Hanna R. Distance to treatment center is associated with survival in children and young adults with acute lymphoblastic leukemia. *Cancer.* 2020;126(24):5319–5327. doi: 10.1002/cncr.33175

5. Brand NR, Qu LG, Chao A, Ilbawi AM. Delays and Barriers to Cancer Care in Low- and Middle-Income Countries: A Systematic Review. *Oncologist.* 2019;24(12):e1371–e1380. doi: 10.1634/theoncologist.2019-0057

6. Dai Q, Liu R, Wang Y, et al. Longer Time Intervals From Symptom Onset to Diagnosis Affect the Overall Survival in Children With Acute Lymphoblastic Leukemia. *Journal of Pediatric Hematology/Oncology.* 2021;44:285–292. doi: 10.1097/MPH.0000000000002344

7. *Guide to cancer early diagnosis.* Geneva: World Health Organization; 2017.

8. Flytkjær Virgilsen L, Møller H, Vedsted P. Cancer diagnostic delays and travel distance to health services: A nationwide cohort study in Denmark. *Cancer Epidemiol.* 2019;59:115–122. doi: 10.1016/j.canep.2019.01.018

9. Lins MM, Amorim M, Vilela P, et al. Delayed diagnosis of leukemia and association with morbid-mortality in children in Pernambuco, Brazil. *J Pediatr Hematol Oncol.* 2012;34(7):271–276. doi: 10.1097/MPH.0b013e3182580bea

10. Begum M, Islam MJ, Akhtar MW, Karim S. Evaluation of delays in diagnosis and treatment of childhood malignancies in Bangladesh. *South Asian J Cancer.* 2016;5(4):192–193. doi: 10.4103/2278-330X.195343

11. Fajardo-Gutiérrez A, Sandoval-Mex AM, Mejía-Aranguré JM, et al. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer. *Med Pediatr Oncol.* 2002;39(1):25–31. doi: 10.1002/mpo.10100

12. Baker JM, To T, Beyene J, et al. Influence of length of time to diagnosis and treatment on the survival of children with acute lymphoblastic leukemia: a population-based study. *Leuk Res.* 2014;38(2):204–209. doi: 10.1016/j.leukres.2013.11.014

13. Hailu A, Mekasha A, Hailu D, et al. Impact of delay prior to treatment in Ethiopian children with acute lymphoblastic leukemia. *Pediatric Health Med Ther.* 2023;14:147–157. doi: 10.2147/PHMT.S406181

14. Sergentanis T, Dessypris N, Kanavidis P, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia: results from the Nationwide Registry for Childhood Hematological Malignancies in Greece. *Eur J Cancer Prev.* 2013;22(5):473–479. doi: 10.1097/CEJ.0b013e32835c7f69

15. Gardie Y, Wassie M, Wodajo S, et al. Delay in diagnosis and associated factors among children with cancer admitted at pediatric oncology ward, University of Gondar comprehensive specialized hospital, Ethiopia: a retrospective cross-sectional study. *BMC Cancer.* 2023;23(1):469. doi: 10.1186/s12885-023-10873-8

16. De Angelis C, Pacheco C, Lucchini G, et al. The experience in Nicaragua: childhood leukemia in low income countries—the main cause of late diagnosis may be "medical delay". *Int J Pediatr.* 2012;2012. doi: 10.1155/2012/129707

17. Tamefusa K, Ochi M, Ishida H, et al. Delayed diagnostic interval and survival outcomes in pediatric leukemia: A single-center, retrospective study. *Eur J Haematol.* 2023. doi: 10.1111/ejh.14162

18. Charalampopoulou A, Petridou E, Spyridopoulos T, et al. An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece. *Eur J Cancer Prev.* 2004;13(5):397–401. doi: 10.1097/00008469-200410000-00007

19. Youlden DR, Baade PD, Valery PC, et al. Differentials in survival for childhood cancer in Australia by remoteness of residence and area disadvantage. *Cancer epidemiology, biomarkers & prevention.* 2011;20(8):1649–1656. doi: 10.1158/1055-9965.Epi-11-0432

20. Janitz AE, Barber R, Campbell JE, et al. Measuring disparities in event-free survival among children with acute lymphoblastic leukemia in an academic institute in Oklahoma, 2005-2019. *Cancer Epidemiol.* 2022;81:102275. doi: 10.1016/j.canep.2022.102275

21. Cancer Stat Facts: Childhood Leukemia [Internet]. National Cancer Institute. [cited 2024 Mar 10]. Available from: https://seer.cancer.gov/statfacts/html/childleuk.html

СПИСОК ЛИТЕРАТУРЫ

1. Zwaan C.M., Kolb E.A., Reinhardt D., et al. Collaborative Efforts Driving Progress in Pediatric Acute Myeloid Leukemia // J Clin Oncol. 2015. Vol. 33, N 27. P. 2949–2962. doi: 10.1200/JCO.2015.62.8289

2. Pui C.H., Yang J.J., Hunger S.P., et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration // J Clin Oncol. 2015. Vol. 33, N 27. P. 2938–2948. doi: 10.1200/JCO.2014.59.1636

3. Alexander T.B., Wang L., Inaba H., et al. Decreased relapsed rate and treatment-related mortality contribute to improved outcomes for pediatric acute myeloid leukemia in successive clinical trials // Cancer. 2017. Vol. 123, N 19. P. 3791–3798. doi: 10.1002/cncr.30791

4. Rotz S.J., Wei W., Thomas S.M., Hanna R. Distance to treatment center is associated with survival in children and young adults with acute lymphoblastic leukemia // Cancer. 2020. Vol. 126, N 24. P. 5319–5327. doi: 10.1002/cncr.33175

5. Brand N.R., Qu L.G., Chao A., Ilbawi A.M. Delays and Barriers to Cancer Care in Low- and Middle-Income Countries: A Systematic Review // Oncologist. 2019. Vol. 24, N 12. P. e1371–e1380. doi: 10.1634/theoncologist.2019-0057

6. Dai Q., Liu R., Wang Y., et al. Longer Time Intervals From Symptom Onset to Diagnosis Affect the Overall Survival in Children With Acute Lymphoblastic Leukemia // Journal of Pediatric Hematology/Oncology. 2021. Vol. 44. P. 285–292. doi: 10.1097/MPH.0000000000002344

7. Guide to cancer early diagnosis. Geneva : World Health Organization, 2017.

8. Flytkjær Virgilsen L., Møller H., Vedsted P. Cancer diagnostic delays and travel distance to health services: A nationwide cohort study in Denmark // Cancer Epidemiol. 2019. Vol. 59. P. 115–122. doi: 10.1016/j.canep.2019.01.018

9. Lins M.M., Amorim M., Vilela P., et al. Delayed diagnosis of leukemia and association with morbid-mortality in children in Pernambuco, Brazil // J Pediatr Hematol Oncol. 2012. Vol. 34, N 7. P. 271–276. doi: 10.1097/MPH.0b013e3182580bea

10. Begum M., Islam M.J., Akhtar M.W., Karim S. Evaluation of delays in diagnosis and treatment of childhood malignancies in Bangladesh // South Asian J Cancer. 2016. Vol. 5, N 4. P. 192–193. doi: 10.4103/2278-330X.195343

11. Fajardo-Gutiérrez A., Sandoval-Mex A.M., Mejía-Aranguré J.M., et al. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer // Med Pediatr Oncol. 2002. Vol. 39, N 1. P. 25–31. doi: 10.1002/mpo.10100

12. Baker J.M., To T., Beyene J., et al. Influence of length of time to diagnosis and treatment on the survival of children with acute lymphoblastic leukemia: a population-based study // Leuk Res. 2014. Vol. 38, N 2. P. 204–209. doi: 10.1016/j.leukres.2013.11.014

13. Hailu A., Mekasha A., Hailu D., et al. Impact of delay prior to treatment in Ethiopian children with acute lymphoblastic leukemia // Pediatric Health Med Ther. 2023. Vol. 14. P. 147–157. doi: 10.2147/PHMT.S406181

14. Sergentanis T., Dessypris N., Kanavidis P., et al. Socioeconomic status, area remoteness, and survival from childhood leukemia: results from the Nationwide Registry for Childhood Hematological Malignancies in Greece // Eur J Cancer Prev. 2013. Vol. 22, N 5. P. 473–479. doi: 10.1097/CEJ.0b013e32835c7f69

15. Gardie Y., Wassie M., Wodajo S., et al. Delay in diagnosis and associated factors among children with cancer admitted at pediatric oncology ward, University of Gondar comprehensive specialized hospital, Ethiopia: a retrospective cross-sectional study // BMC Cancer. 2023. Vol. 23, N 1. P. 469. doi: 10.1186/s12885-023-10873-8

16. De Angelis C., Pacheco C., Lucchini G., et al. The experience in Nicaragua: childhood leukemia in low income countries—the main cause of late diagnosis may be "medical delay" // Int J Pediatr. 2012. Vol. 2012. doi: 10.1155/2012/129707

17. Tamefusa K., Ochi M., Ishida H., et al. Delayed diagnostic interval and survival outcomes in pediatric leukemia: A single-center, retrospective study // Eur J Haematol. 2023. doi: 10.1111/ejh.14162

18. Charalampopoulou A., Petridou E., Spyridopoulos T., et al. An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece // Eur J Cancer Prev. 2004. Vol. 13, N 5. P. 397–401. doi: 10.1097/00008469-200410000-00007

19. Youlden D.R., Baade P.D., Valery P.C., et al. Differentials in survival for childhood cancer in Australia by remoteness of residence and area disadvantage // Cancer epidemiology, biomarkers & prevention. 2011. Vol. 20, N 8. P. 1649–1656. doi: 10.1158/1055-9965.Epi-11-0432

20. Janitz A.E., Barber R., Campbell J.E., et al. Measuring disparities in event-free survival among children with acute lymphoblastic leukemia in an academic institute in Oklahoma, 2005-2019 // Cancer Epidemiol. 2022. Vol. 81. P. 102275. doi: 10.1016/j.canep.2022.102275

21. Cancer Stat Facts: Childhood Leukemia [Internet]. National Cancer Institute. [дата обращения: 10.03.2024]. Доступ по ссылке: https://seer.cancer.gov/statfacts/html/childleuk.html

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