

MAJOR REASONS FOR HOSPITALIZATION TO ICU OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A LITERATURE REVIEW

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ABSTRACT

Relevance: Acute lymphoblastic leukemia (ALL) is a common malignancy in children. Approximately 85% of ALLs have B-cell origin, and 15% are T-cell ALLs. Many patients diagnosed with hematologic cancer will require hospitalization in the intensive care unit (ICU) at some point in their treatment.

The study aimed to study the available literature on clinical deterioration in patients with ALL admitted to the ICU, the clinical significance and prognostic value of causes of clinical deterioration, and adverse outcomes in patients with ALL staying in the ICU.

Methods: A descriptive cross-sectional study approach was used. We reviewed published sources from 2016 to 2023 to collect data on major reasons for ALL patients' hospitalization to ICU.

Results: First, the patient's age at the time of initial diagnosis of ALL is crucial. Cure rates for B-cell ALL are higher between 1 and 9 years of age than in other age groups. Second, the initial white blood cell count during diagnosis is a prognostic indicator. Third, the specific subtype of ALL also affects prognosis. The risk factors emphasize the importance of comorbidities and infectious diseases, as well as monitoring and managing pulmonary and cardiovascular function in patients to avoid hospitalization in the ICU. The main causes of hospitalization in the ICU are complications related to chemotherapy, infection, and unplanned hospitalizations. Compared to normal-risk patients, high-risk patients had a higher rate of OIT hospitalization in the ICU. It is important to control chemotherapy and infections to reduce the number of admissions to the ICU in this group.

Conclusion: Chemotherapy, concomitant and infectious diseases, hypoxia, and hemodynamic instability are reasons for hospitalization of these patients to ICU. The condition of various organs and systems shall be monitored.

Keywords: children, clinical deterioration, intensive care unit, acute lymphoblastic leukemia (ALL), critical conditions.

Introduction: Acute lymphoblastic leukemia (ALL) is one of the common malignant neoplasms (MNs) in childhood; it accounts for up to 80% of all leucosis. About 85% of ALL cases have B cell origin, and 15% have T cell origin [1]. ALL leads to anemia, leukocytosis, hyperleukocytosis, thrombocytopenia, leukopenia, neutropenia, or pancytopenia, and all these changes require extreme alertness in combination with clinical symptoms of ALL. The survival of children diagnosed with ALL has significantly improved over recent years. However, there are still patients who require admission to an intensive care unit (ICU) due to the worsening of their clinical condition. Timely detection of early warning signs of critical conditions in children with ALL before admission to ICU has vital importance [2]. Other criteria are clinically and physically important indicators of prognosis in ALL. They include age, number of leukocytes detected for the first time, genetic and immunophenotypic characteristics of the leukemic blast, and individual response to treatment [3]. Patients with ALL are admitted to ICU with various clinical symptoms, such as hyperthermia, hemorrhagic syndrome, sepsis, and respiratory and other organ failures. These clinical deteriorations are associated with infectious complications, toxicity of chemo-

therapy, or damage to the organ due to leukemia [4]. It is important to keep in mind that at a certain point of treatment, many patients diagnosed with "hematological cancer" might require hospitalization to ICU; this highlights the importance of using indicators for effective treatment selection [5]. Assessment of the number of residual leukemic blast cells in the bone marrow (minimal residual disease, MRD) at various stages of treatment of oncohematological patients is one of the main prognosis and risk stratification factors for ALL from B-lineage precursors [6]. The T-cell ontogenesis peculiarities allow unifying immunological approaches to assessing MRD at all stages of T-ALL therapy [7]. Neutrophilic granulocytes (NG) are an important component of the immune response. They have a wide range of mechanisms that promote the attraction of adaptive immune effectors to the site of inflammation, induction of their maturation, differentiation, proliferation, and activation. Impaired NG function can lead to inadequate activation of adaptive immune response effectors and the development of pathological conditions that threaten the life and health of patients [8]. It is worth noting that many patients suffer from immediate and long-term undesirable effects of antitumor treatment [9].

The study aimed to study the available literature on clinical deterioration in patients with ALL admitted to the ICU, the clinical significance and prognostic value of causes of clinical deterioration, and adverse outcomes in patients with ALL staying in the ICU.

Materials and Methods: A descriptive cross-sectional study approach was used. The authors searched PubMed, CyberLeninka, and Wiley for articles published in 2016-2023 to collect data on “early warning signs and causes of clinical deterioration in patients with ALL admitted to ICU.” The search was made using keywords such as “clinical deterioration,” “intensive care unit,” “acute lymphoblastic leukemia,” and “critical conditions.” Secondary data was collected from four studies. We collected both quantitative and qualitative data. The findings were presented in a Table and a graph. Quantitative data was presented as frequency rates or percentages; qualitative data – was in the nominal form.

Results:

Prognostic factors for ALL. Table 1 presents several prognostic factors that determine outcomes in children with ALL. Age at diagnosis is the first significant factor. E.g., children with B-cell ALL aged 1 to 9 years demonstrate better outcomes than other age groups. Initial white blood cell (WBC) count at diagnosis is the second prognostic indicator: WBC count >50,000 cells/mm³ indicates a higher risk to the patient. The ALL subtype also influences the prognosis since early B-cell ALL has a better prognosis than a mature B-cell leucosis (Burkitt’s disease). Besides, there are gender differences: girls have better chances for recovery than boys. Finally, the response to initial treatment is decisive since an early remission characterized by a significant decrease in cancer cell count within 1-2 weeks of chemotherapy expects a better overall prognosis.

Table 1 – Prognostic factors for ALL [10]

Prognostic factors	Outcomes
Age at diagnosis	Children with B-cell ALL aged 1 to 9 years demonstrate better out-comes.
WBC count	A higher risk is associated with a WBC count >50,000 cells/mm ³ at diagnosis.
ALL subtype	Early B-cell ALL has a better prognosis than a mature B-cell leucosis (Burkitt’s disease).
Gender	Girls might have a slightly better prognosis than boys.
Initial treatment	Early remission (a significant decrease in cancer cell count within 1-2 weeks of chemotherapy) expects a better prognosis.

Cohorts, admitted to ICU for ALL, in the study by Ranta S. et al. Fig. 1 provides research data on admission to ICU split by gender and cell type. In each category, they calculated those admitted to ICU and those who did not require ICU hospitalization. No differences by gender or mean age at admission to ICU

were registered among 637 patients in the Ranta et al. study. By type of precursors, 24.7% of patients with B-cell ALL and 56.6% of patients with T-cell ALL required admission to ICU. This data provides insight into the distribution of ICU admissions by gender, cell types, and mean age.

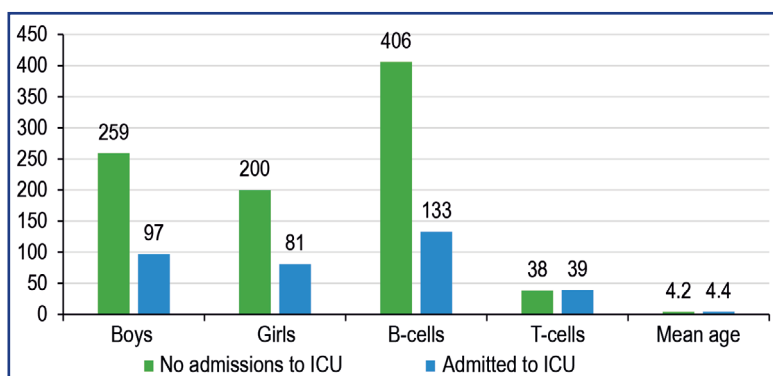


Figure 1 – Cohorts admitted to ICU [11]

Three major reasons for admission to ICU in the retrospective cohort study by Leahy A.B. et al. The research data in Table 2 indicates three major reasons for admission to ICU of children with ALL. Accordingly, 25.6% were admitted for factors related to chemotherapy. At that, high-risk patients had one median of admissions (0 to 23 range), with no patients with a standard risk of admission (0 to 21 range). Infection-related factors caused other 49.1% of cases, including three admissions on average among high-risk patients

(0 to 26 range) and two admissions on average among standard-risk patients (0 to 20 range). Unscheduled admissions accounted for 24.3%, including one admission on average among high-risk and standard-risk patients each (0 to 22 range). This evidences that factors related to chemotherapy and infections significantly contribute to ICU admission of children with ALL and highlights the importance of managing these aspects of care to reduce the risk of ICU admissions in this population.

Table 2 – Major reasons for admission to ICU [12]

Variable	All admissions	High-risk patients (median value)	Standard-risk patients (median value)
Chemotherapy-related factors	26.5%	1 (0-23 range)	0 (0-21 range)
Infection-related factors	49.1%	3 (0-26 range)	2 (0-20 range)
Unscheduled referral	24.3%	1 (0-22 range)	1 (0-22 range)

Discussion: Different studies show that some clinical and laboratory prognostic markers have lower prognostic value in B-ALL than T-ALL. At the same time, other criteria, like time to relapse or location of relapse, are important factors for survival with B-ALL [13]. Similar studies in low- and middle-income countries found the age, gender, and initial WBC count to be prognostic markers for ALL in children [14]. In a separate study, children below 15 years had a very good prognosis with ALL (the survival rate exceeded 85%), which got worse with age. An ALL relapse is still the main reason for cancer death in all ages [15]. The literature reviews showed that age at diagnosis, initial WBC count, ALL type and subtype, and initial response to treatment are important prognostic factors. Still, other factors like genetic abnormalities and relapse also play a role in determining prognosis. According to Dendir et al., comorbidities are typical risk factors for patients with ALL admitted to ICU since they contribute to higher ICU mortality [16]. In Ungar et al.'s study, infectious diseases were another reason for ICU admission [17]. Those risk factors emphasize the importance of monitoring and treating concomitant and infectious diseases and respiratory and cardiovascular disorders in patients to minimize ICU admissions. The above data describes major reasons for children with ALL admission to ICU. According to a study in Canada, cancer patients can require admission to ICU for bleeding or infection, usually during or after chemotherapy or bone marrow transplantation

[18]. Other reasons for ICU admissions are intracranial hemorrhage or brain infarction. Finally, septicemia or severe sepsis, a serious bloodstream infection, also often requires ICU care, even when mechanical ventilation is not needed [19].

In general, reasons for ICU admission vary depending on factors such as patient age and gender and hospital type and location. Still, Kalicińska et al. mentioned breathing, heart, kidney problems, and sepsis as common reasons for ICU admission and long stay [20]. Vijenthira et al. reported that reasons for ICU admission of patients with hematological malignancies included infections and febrile neutropenia, pain, elevated creatinine and lactate dehydrogenase, and decreased albumin [21]. In a nationwide cohort study in Denmark by Maeng et al., ICU admission of patients with ALL was associated with high mortality [22]. In the study by McLaughlin et al., respiratory rate and increase in FiO_2 compared to the baseline level 24 hours before ICU admission were statistically significant, suggesting that changes in these vital signs are most predictive for ALL treatment outcomes [23]. The above studies indicate that chemotherapy- and infection-related factors were major reasons for ICU admission. The findings show that managing chemotherapy-related factors and infections is important to reduce the ICU admission risk for patients with ALL.

Table 3 provides cumulative findings of the studies included in the analysis.

Table 3 – Reasons for ICU admission according to different studies

Variable	Leahy et al., 2018	Dendir et al., 2023	Society of Critical Care Medicine, 2023	Kalicińska et al., 2020	Vijenthira et al., 2020
Respiratory system		+	+	+	
Cardiac system		+		+	
Kidney system				+	+
Sepsis (infectious diseases)	+		+	+	+
Comorbidities		+			
Pain syndrome					+
Chemotherapy-related	+		+		
Bleeding			+		

Conclusion: In general, the search findings show the need for additional research on the reasons for ICU admission of children with hematological malignancies. The provided data summarizes the reasons for ICU admission: they are related to chemotherapy and infections, concomitant diseases, and respiratory, cardiac, and renal dysfunction. This data is important for patient management and treatment. Monitoring and treatment of concomitant and infectious diseases and dysfunction

of organs of various systems is vital to reduce or prevent the hospitalization to ICU of patients with ALL.

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АНДАТПА

ЖЕДЕЛ ЛИМФОБЛАСТИКАЛЫҚ ЛЕЙКЕМИЯМЕН АУЫРАТЫН БАЛАЛАРДЫ ҚАРҚЫНДЫ ЕМДЕУ БӨЛІМІНЕ ЖАТҚЫЗУДЫҢ НЕГІЗГІ СЕБЕПТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: Балалардағы қатерлі ісіктердің кең таралған түрлерінің бірі жедел лимфобласттикалық лейкемия (ЖЛЛ). Шамамен 85 пайызы В-жасушалы және 15 пайызы Т-жасушалы ЖЛЛ барлық жасағдайларынан. Гематологиялық қатерлі ісік диагнозы қойылған көптеген науқастар емдеудің белгілі бір кезеңінде қарқынды емдеу бөлімшесіне (ҚЕБ) жатқызуды қажет етеді.

Зерттеудің мақсаты – ҚЕБ-қа жатқызылған ЖЛЛ науқастарының клиникалық нашарлауы туралы өзекті әдеби деректерді зерттеу болып табылады. Олардың клиникалық маңыздылығы және ҚЕБ-ғы ЖЛЛ науқастардың клиникалық нашарлау себептері мен жасағымсыз нәтижелердің болжамдық мәні.

Әдістері: Колденең зерттеуге сипаттамалық тәсіл қолданылды. Біз 2016-2023 жылдар аралығында жарияланған дереккөздерді талдап, ЖЛЛ науқастарды ҚЕБ-ке жатқызудың негізгі себептері туралы деректерді жинадық.

Нәтижелер: Біріншіден, ЖЛЛ диагнозын алғаш рет қойғанда науқастың жасы өте маңызды. В-жасушалық ЖЛЛ емдеу басқа жас топтарына қарағанда 1 жастан 9 жасқа дейінгі аралықта жоғары нәтижелі. Екіншіден, диагноз қойылған кездегі лейкоциттердің бастапқы саны болжамды көрсеткіш болып табылады. Үшіншіден, ЖЛЛ-дің белгілі бір түрі емдеу болжамына әсер етеді. Тәуекел факторлар қосымша және жұқпалы аурулар, өкпе мен жүрек-қан тамыр жүйесінің функцияларын бақылаудың және басқарудың маңыздылығын атап көрсетеді. ҚЕБ жатқызудың келесі негізгі себептері химиотерапиямен, инфекциямен және жоспардан тыс ауруханаға жатқызумен байланысты асқынулар болып табылады. Қалыпты қауіпті науқастармен салыстырғанда, жоғары қауіпті науқастарда ҚЕБ жатқызу жиілігі жоғары болды. Осы топ арасында ҚЕБ жатқызуды азайту үшін химиотерапия мен инфекцияларды бақылау маңызды болып табылады.

Қорытынды: химиотерапия, қосымша және жұқпалы аурулар, гипоксия және гемодинамиканың тұрақсыздығы – бұл науқастарды ҚЕБ жатқызудың қосымша себептері. Әр түрлі органдар мен жүйелерді бақылау өте маңызды.

Түйінді сөздер: балалар, клиникалық нашарлау, қарқынды емдеу бөлімі, жедел лимфобласттық лейкозия, жағдайдың нашарлауы.

АННОТАЦИЯ

ОСНОВНЫЕ ПРИЧИНЫ ГОСПИТАЛИЗАЦИИ В ОТДЕЛЕНИЕ ИНТЕНСИВНОЙ ТЕРАПИИ ДЕТЕЙ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: Одним из распространенных видов злокачественных новообразований у детей является острый лимфобластный лейкоз (ОЛЛ). Примерно 85 процентов имеют В-клеточное происхождение и 15 процентов Т-клеточное ОЛЛ от всех случаев заболевания. Многим пациентам с диагнозом «гематологический рак» на определенном этапе лечения требуется госпитализация в отделения интенсивной терапии (ОИТ).

Цель исследования – изучение литературных данных о клинических ухудшениях пациентов с ОЛЛ, госпитализированных в ОИТ, определение клинической значимости и прогностической ценности причин клинического ухудшения и неблагоприятных исходов у пациентов с ОЛЛ, госпитализированных в ОИТ.

Методы: Использовался подход «описательное поперечное исследование». Авторы изучили источники, опубликованные с 2016 по 2023 годы, по основным причинам госпитализации в ОИТ пациентов с ОЛЛ.

Результаты: Во-первых, решающее значение имеет возраст пациента во время постановки первичного диагноза ОЛЛ. Излечение В-клеточного ОЛЛ выше в возрасте от 1 до 9 лет, чем в других возрастных группах. Во-вторых, начальное количество лейкоцитов на момент постановки диагноза служит прогностическим показателем. В-третьих, конкретный подтип ОЛЛ также влияет на прогноз. Факторы риска подчеркивают важность сопутствующих и инфекционных заболеваний, мониторинга и ведения функций легких и сердечно-сосудистой системы у пациентов во избежание госпитализации в ОИТ. Основными причинами госпитализации в ОИТ являются осложнения, связанные с химиотерапией, с инфекцией и внеплановые госпитализации. По сравнению с пациентами с нормальным риском, у пациентов с высоким риском частота госпитализации в ОИТ была выше. Чтобы уменьшить количество госпитализаций в ОИТ среди этой группы, важно контролировать химиотерапию и инфекции.

Заключение: Химиотерапия, сопутствующие и инфекционные заболевания, гипоксия и гемодинамическая нестабильность являются причинами госпитализации этих пациентов в ОИТ. Очень важен мониторинг различных органов и систем.

Ключевые слова: дети, клиническое ухудшение, отделение интенсивной терапии, острый лимфобластный лейкоз (ОЛЛ), критические состояния.

Transparency of the study: Authors are solely responsible for the content of this article.

Conflict of interest: Authors declare no conflict of interest.

Funding: The authors declare no funding or financing of the study.

Authors' inputs: contribution to the concept, the study design, execution of the study, interpretation of the study results – Kurakbaev E.B., Turdalieva B.S., Sarsekbaev E.S., Umbetov K.O.; preparation of the manuscript – Kurakbaev E.B.

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