BASIC AND CLINICAL CANCER REPORTS | Volume 1, Issue 2 | 2026

Acute lymphocytic leukemia in Iranian Children; a Review

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Running title: Acute Lymphoblastic Leukemia in Iranian Children

Abstract

Acute Lymphoblastic Leukemia (ALL) is the most common cancer in children and a leading cause of cancer-related mortality among individuals younger than 20 years. It is a malignancy of the blood and bone marrow characterized by the uncontrolled production of immature white blood cells, known as lymphoblasts, which impair immune function and increase susceptibility to infections. Common symptoms include fatigue, recurrent infections, bruising, bleeding, and pallor. At diagnosis, leukemic cells may infiltrate the liver, spleen, lymph nodes, and mediastinal region. In some patients, ALL can spread to the central nervous system (CNS) or testes, requiring specialized treatment strategies. Diagnosis generally involves examination, blood tests, and bone marrow aspiration or biopsy.Over recent decades, survival outcomes for children with ALL have improved remarkably, increasing from below 10% in the 1960s to 90% today. These advances have resulted from improved understanding of disease biology, risk classification, supportive care, and treatment protocols. Continued research is expected to further improve survival and quality of life.In Iran, the incidence of ALL is approximately 2.25 cases per 100,000 children younger than 15 years, with higher rates among boys and a peak incidence at ages 2–5 years. Seasonal variation has also been reported, with higher incidence during spring and summer.Improving physician awareness, diagnostic capacity, treatment access, and research into genetic factors is essential for reducing disparities and achieving optimal outcomes for children with ALL worldwide.

Keywords: Acute Lymphoblastic Leukemia , Prevalence , Child, Survival , Iran

Introduction

Pediatric cancer is any childhood cancer that occurs between birth and 14 years of age, which commonly includes individuals under the age of 18 (1). Acute leukemia is the most prevalent children malignancy, accounting for over 28% of all pediatric cancers and (97%) of childhood leukemia and are categorized into different types (2) . The two most prevalent kinds in children are acute lymphocytic leukemia (ALL) comprising 75% of cases and acute myeloid leukemia (AML) accounting for 20% of cases (3, 4). Other types are including; Acute undifferentiated leukemia, making up less than 0.5% of cases , Acute mixed-lineage leukemia , Chronic myeloid leukemia represent a smaller percentage (3%) of childhood leukemia and include: Philadelphia chromosome , positive (Ph1 positive) myeloid leukemia and Juvenile myelomonocytic leukemia. Even though over 90% of children with ALL respond to therapy, making it the most prevalent childhood cancer, ALL remains a significant cause of death for both children and adults (5). It makes up approximately 15–25% of adult acute leukemias, and differs from the pediatric form regarding to biological characteristics (6). ALL is a heterogeneous hematologic disorder that causes the development of immature lymphoid cells in the bone marrow, peripheral blood, and other tissues (7). In fact, chromosome translocations, mutations, and aneuploidies in genes involved in cell cycle regulation and the generation of lymphoid cells are among the genetic abnormalities that cause ALL. Also, The malignant transformation of B- and T-lineage lymphoid precursors is the source of ALL (8, 9). The clinical presentation of ALL can be quite varied and often includes vague symptoms. Most patients initially exhibit fever, pallor, and easy bruising, which are early indicators of bone marrow suppression or hematological issues. Additionally, more than 60% of patients may show signs of organ enlargement, particularly in the spleen and liver. Many individuals also report a history of recurrent infections, fatigue, swollen lymph nodes, and skin rashes (10). The highest occurrence of ALL is observed in children aged 2 to 5 years, and it is more prevalent in boys compared to girls (11). The distribution of ALL categories includes B lineage (85%), T lineage (10-15%) and NK lineage (<1%) (12). Additionally, ALL is classified into three morphological subtypes known as ALL-L1, ALL-L2, and ALL-L3 according to the French-American-British (FAB) classification system (13). ALL-L1 cells have rough chromatin that are relatively small and their nuclei are characterized by a uniform population. Nuclear heterogeneity is a characteristic of ALL-L2 cells, which are bigger than ALL-L1 cells. Finally, ALL-L3 cells are distinguished by the prevalence of vacuoles inside the cell and are thus larger than ALL-L1. Typically, Their nuclei homogeneous (14). B-ALL/LBL (Lymphoblastic lymphoma) represents a tumor originating from precursor B cells, which are also referred to as B lymphoblasts. The majority of ALL cases belong to the B-cell lineage, accounting for approximately 80% to 85% of the total. From a clinical perspective, B-ALL commonly exhibits involvement of extramedullary tissues, such as the central nervous system (CNS), lymph nodes, spleen, liver, and testes (15). In contrast, the LBL variant demonstrates a preference for skin, soft tissue, bone, and occasionally lymph nodes (16). T-ALL/LBL refers to a type of neoplasm that arises from precursor T cells, which are also known as T lymphoblasts. In contrast to B-lymphoblastic processes, T-cell lineage accounts for only a small proportion (10%–15%) of all cases of ALL , while the majority of lymphoblastic lymphomas (LBLs) originate from T cells (85%–90%). Interestingly, there is a slightly higher incidence (25%) of T-ALL in the adult population (17). T-ALL has traditionally been recognized as a particularly aggressive form ALL (18).

The World Health Organization has established a novel classification system for ALL that focuses on cytogenetic and molecular attributes (Table 1) (8, 19).

Table 1. WHO classification of acute lymphoblastic leukemia/lymphoma

Table 1 ; The World Health Organization has established a novel classification system for ALL that focuses on cytogenetic and molecular attributes B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t (9; 22) (q34; q11.2); BCR-ABL1
B-lymphoblastic leukemia/lymphoma with t (v; 11q23); MLL rearranged
B-lymphoblastic leukemia/lymphoma with t (12; 21) (p13; q22) TEL-AML1 (ETV6-RUNX1)
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t (5; 14) (q31; q32) IL3-IGH
B-lymphoblastic leukemia/lymphoma with t (1; 19) (q23; p13.3); TCF3-PBX1
T-lymphoblastic leukemia/lymphoma

Acute leukemia is characterized by the presence of over 20% blasts in the bone marrow. Nevertheless, if it is not diagnosed and treated on time, it can rapidly advance and result in fatality within a matter of months (20). Recent

treatments for ALL now include new agents such as monoclonal antibodies, immunomodulators, and chimeric antigen receptor T cells (CAR-T). Additionally, a number of recently discovered medications have been designed to target specific molecular pathways associated with the proliferation of leukemic cells (21). In this review article, we decided to investigate the pathophysiology, prevalence, diagnosis, treatment and survival rate in Iranian children with acute lymphocytic leukemia.

Pathophysiology

Leukemia and other malignancies exhibit a common biological feature known as clonality. Molecular alterations are indispensable for the initiation of cancer, as they have the ability to modify the constituents of the signaling cascade. This can result in the generation of proliferative cues, prompting cell growth, DNA synthesis, and cellular division in an aberrant manner, even in the absence of physiological demand (22). The development of a malignant hematological disease is most likely caused by a mutation in a key gene that regulates cell division, proliferation, and/or survival in hematopoietic progenitor cells (23). Less than 5% of leukemia are inherited, and these cases involve a numerical chromosomal abnormality like 21 trisomy (24). Most mutations associated with leukemia are acquired and occur in a progenitor cell of the lymphoid lineage. When a mutation activates an oncogene, the encoded protein undergoes structural changes and typically exhibits increased transformative activity. It also stays in its active state and continues to communicate through the interaction of tyrosine and/or threonine kinases. These signals cause cells to continue proliferating endlessly (22, 25). Mutations that impair gene function can arise in tumor suppressor genes like TP53. On average, 8 percent of adult ALL patients and less than 3 percent of pediatric patients have TP53 mutations (26). ALL is frequently characterized by a large number of chromosomal abnormalities as well as structural rearrangements (translocations). Major cytogenetic abnormalities in B cell precursors are associated with a negative prognosis for ALL . These abnormalities include chromosome 8 trisomy in adult ALL patients (27) , hypodiploidy (28) , and t (9; 22) or Philadelphia chromosome, which is frequently directly correlated with age (29). They also include t (4; 11), which is related to the mixed lineage leukemia (MLL) gene and is common in childhood as well as myeloid leukemia (30). Furthermore, the genetic changes linked to ALL are primarily found in areas where oncogenes are present. Examples of these abnormalities include the MLL oncogene, which is associated with ALL in children; the t(8;14) translocation related to the deregulation of gene expression by the C-MYC oncogene; mutations in the TP53 tumor suppressor gene; and various deletions and inversions, such as deletions of the transcription factor PAX5, which occur in at least 30% of cases of B cell precursor ALL (31, 32) . It has been determined that ALL cell lines exhibit aberrant methylation of CpG islands in gene promoter regions. This is significant because methylation of CpG dinucleotides close to transcription initiation sites has the potential to inhibit the expression of genes (33). Tumor suppressor gene hypermethylation and oncogene hypomethylation, respectively, can thus lead to leukemia. Alterations in angiogenesis, signal transduction involving tyrosine kinase receptors, and the regulation of apoptosis are other important mechanisms contributing to the development of ALL (34, 35). One such example is the BCL2 gene, which codes for a cytoplasmic protein found in the mitochondria that promotes cell survival by preventing apoptosis (36). A growing body of research indicates that leukemogenesis is a multi-step process involving a sequence of steps and modifications to oncogenes, tumor suppressor genes, and microRNA genes in tumor cells (37, 38). Numerous microRNAs have been connected to the pathophysiology of ALL (39, 40). Given the large number of target cells that can undergo genetic modification, the molecular changes required for the development of leukemia are relatively rare events (23). It is crucial to note that, in the case of ALL, the terms "original cell" and "leukemic stem cell" must be used when discussing the genesis of cancer (41). While the exact etiology of ALL remains unknown, the multifactorial nature of the disease implies that risk factors, including genetic and/or environmental ones, play a role in its development. Three prominent hypotheses, however, point to the immune system's possible involvement in the etiology of ALL: late infection (42), population mix, and hygienic-sanitary (43). The immune system and ALL have a complicated relationship that involves the interaction of numerous elements, including cells, proteins, cytokines, and epithelial barriers. Variations in these cells' genes can also affect how immune responses develop and function, which can increase an individual's susceptibility to ALL (44, 45).

Prevalence of ALL in Iran

Cancer ranks as the third leading cause of death in Iran, following cardiovascular diseases and accidents (46). Additionally, the high mortality rate linked to leukemia's high incidence and prevalence causes high expenses for diagnosis and treatment in Iran (47). Scientists identify several viral, environmental, geographic, and genetic susceptibility risk factors as the causes of variances in ALL incidence in various cultures (48). During the studies conducted in recent years by Iranian researchers regarding cancer, they have found that the incidence of cancer in children has increased significantly for both male and female sex groups in a period of 8 years (2000-2008) And the highest incidence was related to ALL (49). Rahimi Pordanjani and his colleagues conducted a study in this regard and finally showed that the average incidence of ALL in 2014-2006 was 2.25 per 100,000 children under 15 years of age.

Their findings also indicated that the prevalence of ALL among Iranian children is lower than in developed countries; however, similar to many developing nations, the rate of new cases is rising quickly. In addition, they mentioned that the incidence of ALL in newly diagnosed boy's patients was higher than in girls, although the average annual incidence (during 2006-2014) was higher in girls than in boys. Finally, according to the results of newly identified cases, they stated that ALL was more common in spring and summer (the warm seasons of the year when the possibility of transmitting infectious pathogens is higher) and in addition, the prevalence of ALL in the northern and western provinces of Iran (including Zanjan, Kurdistan, and Kermanshah) showed low prevalence, moderate prevalence in the central provinces, and high prevalence in the southern and eastern provinces (including Fars, Kohkiloyeh and Boyar Ahmad) (48). On the other hand, studies have been conducted in this field by Iranian researchers who have shown that the incidence rate of ALL during the years 2003-2008 had a constant trend (50). Also, Hejazi and his colleagues conducted a study in 2010 in West Azerbaijan province of Iran for children under 15 years and showed that the incidence of acute leukemia did not follow a regular increase or decrease during the studied years (51). Also, researchers have conducted more studies on the prevalence of children with ALL in Iran and have reported results similar to previous studies. including Mehrvar et al., who examined children with acute leukemia admitted to MAHAK's Pediatric Cancer Treatment and Research Center and finally concluded that the peak incidence of ALL in children was 1-5 years old and in addition mentioned that ALL-L1 and Pre-B - ALL was one of the most common phenotypes in the group of ALL patients (52, 53). At the beginning of this study, we mentioned the risk factors associated with ALL, one of which is the environmental risk factor, and studies have been conducted in this regard in our country. Mirmohammadi and his colleagues in Yazd conducted a study with the aim of investigating environmental risk factors related to acute leukemia in children. In their study, they examined children with ALL, AML and non-Hodgkin's lymphoma referred to Yazd Hospital. They finally found that the frequency and prevalence of acute leukemia and non-Hodgkin's lymphoma in children whose fathers were painters, farmers or exposed to hydrocarbons was higher than normal children (54). Also, Zakarinia et al., colleagues conducted a study in this area with the aim of investigating the relationship between acute leukemia and exposure to pesticides and reached similar results (55). In general, extensive and comprehensive studies about the epidemiology, prevalence and frequency of ALL in recent years in Iran are limited and few. Since the studies reviewed in this article are related to the years 2000-2015, it is suggested to conduct more comprehensive studies on the prevalence, frequency and cases related to the epidemiology of ALL by Iranian researchers. Maybe in this way we can get deeper and more correct insights of this disease.

Diagnosis and Treatment

During the initial clinical assessment of acute leukemia, certain symptoms, including anemia, hemorrhaging, fatigue, bone pain, and numerous infections, may be observed due to the ineffective hematopoiesis and cytopenia caused by the infiltration of leukemic cells in the bone marrow, lymphatic node, and extramedullary cites. Pain in the extremities or joints can be a primary symptom in children(56, 57). Ehsan Shahverdi et al. conducted a study on 305 children under the age of 14 who were diagnosed with ALL. The study discovered that the initial clinical manifestations of ALL were sudden and acute, with fever and hepatomegaly being the most prevalent symptoms. Nevertheless, a substantial number of patients experienced symptoms that were not specific and It is imperative to identify these indicators in order to facilitate an early diagnosis(58). The peripheral blood and the presence of leukemic cells in the blood smear stained with Wright-Giemsa dye are assessed in the following step. Subsequently, after the initial examinations, additional thorough examinations are required, including the assessment of bone marrow aspiration or biopsy using techniques like immunophenotyping of leukemic cells with flow cytometry and immunocytochemistry (ICC) . Chromosomal abnormalities are observed in the overwhelming majority of instances with ALL. These abnormalities, which may indicate an abnormal number of chromosomes, chromosomal translocation, or chromosomal deletion, may provide valuable information on the disease's prognosis.(59, 60). Furthermore, chromosomal aberrations play an invaluable role in the diagnosis of leukemia, the classification of diseases, the choice of the right treatment, and the assessment of minimal residual disease. Molecular tests, such as reverse transcriptase real-time PCR (RTqPCR), and cytogenetic studies, including karyotype analysis and fluorescence in situ hybridization (FISH), are therefore strongly advised for the diagnosis of ALL(59, 61). In 2019, Gholamreza Bahoush et al. conducted research on children diagnosed with ALL with the goal of assessing cytogenetic results and their influence on prognosis. The research revealed that the mean survival rate among children with ALL was equivalent to that of European nations. Nevertheless, the administration of potent chemotherapy resulted in the deterioration of prognostic markers, and translocations provided indicators for predicting mortality(62). In the treatment of ALL , Overall Survival (OS) and Event-Free Survival (EFS) are two critical metrics used to assess the effectiveness of treatment. The present research findings have shown a significant rise in the survival rate of children with Acute Lymphoblastic Leukaemia (ALL), rising from 10% to 96%, which is a source of tremendous delight(63-65). Leukemia is often treated using a triphasic approach, consisting of three sequential therapy stages. During the

initial phase, induction takes place, this step is accomplished by the administration of steroid medication and the injection of cytostatic drugs. Afterwards, the procedure of consolidating remission is carried out, followed by a period of maintenance therapy lasting 2-5 years. (66). Nevertheless, the adverse effects of traditional therapies, such as severe toxicity, diminish the efficacy of therapy and, in some instances, result in the patient's death(67). Hence, ongoing research underscores the need of adjusting therapy regimens according to individual biological characteristics and embracing innovative therapeutic alternatives to achieve further enhancements. However, recent research has shown that novel strategies like target therapy, which involves using medications that target specific signaling cascades, or immunological methods like chimeric antigen receptor T (CAR-T) cells and bispecific T-cell engager (BiTE) can reduce treatment toxicity and significantly advance the goal of a 100% overall survival rate in pediatric acute lymphoblastic leukaemia (ALL)(67-69) . But also, Assessing the survival rates of patients following diagnosis and treatment, along with identifying the factors that impact these rates, are crucial metrics forthe management and assessment of the treatment approaches (70).

Because of this, the approach to promoting and developing treatment methods, as well as increasing survival rates, differs in developing countries due to insufficient accessibility to appropriate medical care and subsequent higher death rates attributed to toxic exposure(71). In recent years, supportive treatment in the USA has led to a significant improvement in the 5-year survival rate for patients with leukemia, reaching up to 70%. However, research shows that, compared to developed countries, Iran has a lower 5-year survival rate, and more recent studies have shown that the 5-year survival rate reaches 57% in ALL patients.(72, 73). In 2015, Mehdi Azad and his colleagues conducted a study to examine the treatment and diagnosis shortcomings of ALL in Iran. The results of their study indicated that the most significant factor influencing the treatment process for leukemia patients in Iran in comparison to developed countries is the absence of appropriate access to advanced diagnostic techniques, which subsequently prolongs the diagnosis process(74). In a separate study, Ramin Bakhshi Biniaz, et al. showed that the main reasons for inadequate treatment processes in Iran, which fall short of global standards, are the absence of advanced diagnostic facilities, cell and bone marrow banks, and high treatment costs, as stated by specialists(75). In contrast, the research suggests that treatment abandonment may be influenced by factors such as low family income, difficulties with transportation, the educational level of the father, a belief in the incurability of ALL , and reliance on spiritual approaches. These issues necessitate the adoption of treatment protocols that are not only effective but also have the potential to attracted the maximum cooperation of the patient and their family in the continuation of the treatment (76). In accordance with this objective, Hadi Hayati and his colleagues conducted a comparison of protocols United Kingdom (UK-ALL) and Berlin-Frankfurt-Munster (BFM-ALL), which are mainly used by oncologists in Iran. They examined these two protocols from the perspective of financial costs, health effects of utility, and QALY, and concluded that the UK ALL protocol is more preferable (77). Also, the study conducted by Ehsan Shahverdi et al. provides evidence that this procedure is a highly effective treatment technique, as indicated by the overall survival and recurrence rates(78). Hence, in developing countries like Iran, the treatment of acute leukemia in children prioritizes the establishment of structures for improved access to diagnostic tools and treatment standardization, taking into account all existing obstacles to receiving complete treatment .

Survival Rate of ALL in Iran

In this review study, the time interval between diagnosis and death due to cancer is considered as the survival rate of a patient with ALL (79). In fact, with the help of epidemiological indicators such as survival rates, the effectiveness of treatments can be calculated. survival analysis is the standard method to assessing the progress of cancer care and treatment, that serves as a suitable indicator of the efficacy of therapeutic, diagnostic, and other cancer interventions (80, 81). Many studies have been conducted to investigate the survival rate of cancer patients in the world and also in Iran. Each study reported a different survival rate according to the type of cancer. In the last several years, there has been a notable improvement in the survival rates of children cancers, which is probably due to the development of diagnostic tools and improved treatment protocols (82). As a result, from 2010 to 2014, Latin America had the greatest survival rate (93%), with 80% of that region located in Costa Rica and 76% in Argentina. Less than 70% of these youngsters survived in Colombia, Brazil, Shelby, and Peru; less than 60% did so in Ecuador and Mexico (83). As mentioned, several studies have been conducted in the field of survival rate in Iran in recent years. Based on the studies, laboratory and clinical symptoms can be used as prognostic factors at the time of diagnosis. In fact, identifying factors affecting survival (such as age, gender, and white blood cell count) is one of the main methods to improve the survival rate of cancer patients (84, 85). In a study conducted by Almasian-Hashiani et al., they investigated the effect of factors such as age, gender, immunophenotype, WBC count, platelet count, and history of relapse on the 5-year survival rate of ALL patients. In this study, it was found that factors such as disease recurrence, the frequency of recurrences, initial WBC count, gender, and immunophenotype significantly influenced patient survival rates. Notably, platelet count emerged as a positive prognostic factor for survival in patients with ALL (86). In Parvaneh et al.'s study, the 5-year survival rate of ALL patients was the same as the survival rate reported from several developing countries,

but much lower than that of developed countries; which can be due to differences in medical care, economic-cultural problems, insufficient knowledge in the field of treatment in developing countries. Finally, they concluded that children with leukemia who had a higher WBC count at diagnosis (WBC ≥ 50,000) and a history of relapse had a lower survival rate (87). Bordbar et al., did an 8-year follow-up on ALL children in Shiraz (the largest oncology center in Southern Iran). They reported that the cumulative 5-year overall survival was 86.4% in patients with ALL. Comparing the conditions of childhood ALL in this center to those in prior years and other regions of the nation, the study's findings demonstrated a significant improvement. This improvement could be mostly attributed to improved supportive care that lowers non-relapse mortality, updated treatment regimens, and multicolor flow cytometry monitoring of MRD. Also, they showed for the first time in this study that hepatomegaly (as a potential risk factor for lower survival in ALL patients) is associated with a 5 time increased risk of death in children with ALL (88) . One of the most serious and potentially fatal complications of tumor lysis syndrome (TLS) is the electrolyte and metabolic imbalances that lead to cardiac arrhythmia, seizures, multiorgan failure, and ultimately death. These disturbances also cause the disease to advance toward an adverse conclusion (89). In the study by Hosseini-Baharanchi, it was found that the 5-year survival rate for patients with ALL was 82%, while the disease-free survival rate was 88%. The research also revealed that children with a history of tumor lysis syndrome (TLS) faced a significantly higher risk of disease recurrence and mortality, being four times more likely to experience these outcomes compared to those in the high-risk group (90). Since other studies have also observed a significant association between TLS and high mortality in AML patients (91), They noted that this indicator could serve as a prognostic marker for patients with leukemia. Additionally, they discovered that girls with ALL had a lower risk of relapse compared to boys, which may be attributed to the influence of sex hormones.In addition, this study reported for the first time that higher hemoglobin and LDH levels and platelet count are associated with a higher risk of recurrence (90). In a study conducted by Noroozi et al., in West Azerbaijan, it was shown that the 1, 3 and 5 year survival rates in patients with no history of recurrence were 83.1%, 75.1% and 68% respectively and in those with a history of recurrence it was 82.5%, 73.2% and 65.2% respectively. In this study, they reported that family history had a significant effect on the survival rate of patients (92). In Saeedi's study, it was shown that CNS involvement is one of the most important prognostic markers in determining recurrence and death rates. In fact, they reported that the mortality rate in patients with CNS involvement was approximately 4.25 times more than in patients without CNS involvement (79).

Conclusion

While ALL is a formidable challenge, it is not a hopeless one. Advances in treatment and understanding have significantly improved survival rates, particularly in children. ALL is a relatively uncommon cancer, but its impact is significant. The worldwide incidence of ALL is estimated to be around 3 cases per 100,000 people per year. While the disease can affect individuals of all ages, it is particularly prevalent in children, making it the most common type of childhood cancer. Despite significant progress, challenges remain in the fight against ALL. Relapse, the return of leukemia after initial treatment, is a significant concern. Research efforts are focused on developing new therapies to improve outcomes for patients with relapsed ALL, as well as to find ways to prevent relapse altogether. The future of ALL treatment holds promise. Ongoing research is exploring the potential of immunotherapy, which utilizes the patient's immune system and gene therapy . Hope for the future is abundant. With advancements in understanding the disease's pathophysiology, the development of more effective therapies, and the relentless pursuit of cures through ongoing research, the outlook for individuals with ALL continues to improve.

Declarations

Competing Interests

The authors state that they have no known financial conflicts of interest or personal relationships that might have influenced the work presented in this paper.

Ethical approval

This article does not include any studies involving human participants or animals conducted by any of the authors .

Funding

The authors did not receive any financial assistance for the research, authorship, or publication of this article.

Availability of data and materials

Data sharing is not relevant to this article, as no new data were generated or analyzed in this study.

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