RESEARCH ARTICLE

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Effect of *XRCC1 Arg399Gln* Gene Polymorphism on Survival in Lymphoblastic Leukemia

Asel Usenova[1]*, Stalbek Akhunbaev[1], Emil Makimbetov[2], Abdurakhman Vaninov[1]

Abstract

Introduction: The relevance of the research of the article is conditioned upon the problem of the development of molecular genetic diagnostics to determine the effectiveness of treatment for acute lymphoblastic leukemia in children. The purpose of the article is to identify the polymorphism parameters of the *P53 Arg72Pro* and *XRCC1 Arg399Gln* genes in acute lymphoblastic leukemia with criteria for determining the survival rates of sick children. **Materials and methods:** Methods for the study of the identified problem are the study of the medical histories of children with acute leukemia, which allowed selection of the necessary contingent of patients for further genetic study of their frozen blood, where the genomic part of deoxyribonucleic acid was isolated from the frozen blood in a standard way using molecular biological research when performing a polymerase chain reaction. **Results:** The article presents the results of a study that shows that in children with acute lymphoblastic leukemia, the frequency of genotypes of the *XRCC1 Arg399Gln* gene is variable. The most common genotypes are Arg/Gln and Arg/Arg, approximately 48% each. The Gln/Gln genotype is less common. Relapse-free survival of children with the Arg/Gln and Gln/Gln genotypes was the highest, slightly lower rates were noted with the Arg/Arg genotype. **Conclusion:** It was identified that the frequency of genotypes of the *XRCC1 Arg399Gln* gene can be a predictor of prognosis in acute lymphocytic leukemia in children, which can be considered when choosing treatment tactics, and this has practical significance for the field of medicine.

Keywords: Oncology- gene polymorphism-bleukemia- pediatrics- medicine

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Introduction

In recent years, there has been an increase in patients suffering from cancer. If a few decades ago cancer affected people in middle and old age to a greater extent, and in patients under 20 it practically did not occur, now there is a sharp change in the situation. Modern statistics show that cancer affects people at any age, including children (Rodriguez et al., 2021). There are several factors that have contributed to the increased incidence of cancer in children and young people. One factor is exposure to environmental toxins and carcinogens, such as pollution, radiation, and chemicals. Lifestyle factors such as poor diet, lack of physical activity, and obesity may also contribute to the development of cancer (Burkitbayev ZK et al., 2017; Andersen et al., 2023). More than 174 thousand cases of newly diagnosed oncological diseases in children under 14 years of age are observed annually in the world, and these figures tend to increase, which is identified when comparing statistics in recent years. Among the children's population, the majority of malignant tumors were detected in the hematopoietic organs, of which acute lymphoblastic leukemia (ALL) is the most common type of malignant tumor. According to various data, ALL occupies 20 to 25% of the structure of pediatric oncopathology. However, in the age group of 0-4 years, acute leukemia accounts for up to 36% of all malignant tumors. Cancer is also the first place in terms of patient mortality, more lives are claimed only by the causes of violent death, and this is official data from the World Health Organisation (FDA Approvals…, 2018).

Modern treatment often allows prolonging the standard of living for this disease for 5 years or more, but often after several years of remission, a relapse of the disease occurs, and patients, knowing these facts, have a life at the stage of stable condition overshadowed by the expectation of a possible resumption of the disease. Cancer brings into the life of a child and his family many problems in the degree of medical support, psychological, social, ethical and economic (Practical Geriatric Assessment, 1997). After all, at the moment, cancer treatment at a qualitative level is available only in developed countries and is expensive, which makes it inaccessible to many in need. In fact, the statistics on the incidence and survival rates of patients

*[1]Special Surgical Disciplines Department, International Higher School of Medicine, Bishkek, Kyrgyz Republic. [2]Department of Therapy, International Higher School of Medicine, Bishkek, Kyrgyz Republic. *For Correspondence: asel.usenova@yahoo.com*

with ALL are significantly underestimated, as they are based solely on data collected from highly developed countries that have access to effective ALL treatment methods. And the situation in low- and middle-income regions has no comforting indicators in terms of the cure of patients, but the full picture is not known, because all data on the incidence of cancer is not fully collected. Almost 90% of children live in low-income countries, and in low- and middle-income countries the population is younger and, consequently, a larger proportion of children with cancer than in high-income countries, but sick children cannot undergo professional treatment. They do not have the opportunity to do this, and there are no publicly available elements of professional medical care in these regions (Arber, 2019; Bullinger et al., 2017).

The objectives of the study "Effect of *XRCC1 Arg399Gln* Gene Polymorphism on Survival in Lymphoblastic Leukemia" are:

1. To determine the frequency of genotypes of the *XRCC1 Arg399Gln* gene in patients with lymphoblastic leukemia.

2. To identify whether the *XRCC1 Arg399Gln* gene polymorphism affects the survival rates of patients with lymphoblastic leukemia.

3. To evaluate the relationship between the *XRCC1 Arg399Gln* gene polymorphism and the response to specialized treatment in lymphoblastic leukemia.

Materials and Methods

The diagnostic criteria of this scientific and medical study were determined by the methods of studying medical histories to select the necessary contingent of patients within the framework of a confirmed clinical diagnosis of acute lymphoblastic leukemia. Then their biomaterial was collected, which at the time of the study was frozen blood, and with the help of a polymerase chain reaction of deoxyribonucleic acid (DNA) synthesis, which was carried out on a specialised apparatus to isolate the necessary genomic DNA. This was carried out by a generally accepted and standard method using phenol-chloroform extraction. In the described method, the lysis of erythrocytes, which belong to non-nuclear blood cells, is observed, which occurs at the buffer level, where there is a sucrose content, triton X-100 in the parameter 1%, 5mM MgCl2 and 10mM tris HCl. After removal of the destroyed leukocytes, which belong to non-nuclear cells of white blood cells, lysis of sodium dodecyl sulfate (SDS) is observed, and protein kinase K, subsequent degradation of proteins is carried out. The resulting leukocyte lysate is treated with organic reagents such as phenol, a mixture of phenol and chloroform and pure chloroform, which are necessary to remove the protein phase. Deoxyribonucleic acid is precipitated using cold 96% ethanol and salt, as 4M NaCl, and subsequently, this is dissolved in deionized water (DDH2 O) (Miranda-Filho et al., 2018). In the future, the necessary accounting was made of the results obtained in the gel-documenting system GelDoc IF (UVP UK). The two genes *XRCC1 Arg399Gln* and *P53 Arg72Pro* with the corresponding genotypes were analyzed.

The resultant data obtained during the study were processed using the Statistica 10 program. Quantitative indicators were analysed with median calculation (Me), and the Kraskel-Wallis criterion was used to statistically assess the level of reliability ($p < 0.05$) of independent groups. The obtained results of the study are displayed using a graphical image in diagrams and tables. The medical study was conducted based on the pediatric Hematology Department of the National Center of Oncology and Hematology of the Ministry of Health of the Kyrgyz Republic, located in Bishkek. 75 children aged 4 to 12 years who were treated for acute lymphoblastic leukemia in the period from 2014 to 2017 were examined. The medical examination of the biomaterial of the selected children took place within the framework of informed consent signed by parents or legal representatives following the relevant bioethics standards.

The scientific and medical study of the identified problem was carried out in three stages, where at the first stage is an analytical and theoretical study of scientific, research and methodological literature on aspects related to the development and treatment of acute limblastic leukemia, and the polymorphism of the *P53 Arg72Pro* and *XRCC1 Arg399Gln* genes associated with its course, including the factors of change, was carried out as a result of the treatment of patients and considering the survival of children at their level. During the study of the existing theoretical and practical aspects, an actual problem, purpose, and research methods were identified and an active work plan was drawn up. In the second stage, a genetic study of the biomaterial of a selected group of children with acute lymphoblastic leukemia was carried out, for their inherent level of polymorphism of the genes in question, and then an analysis of the results was made, and conclusions were formulated. In the third stage, the obtained results and conclusions were refined and systematised.

Results

In recent decades, genetic engineering has been actively developed, methods for isolating the composite human genome have been gradually improved, and the factors of influence of individual genes and their role in the body have been studied. After all, it is known that human DNA contains the entire spectrum of knowledge about all components of the body (Schuurhuis et al., 2018). The process of genetic engineering involves identifying a specific gene or DNA sequence of interest, isolating it, and inserting it into the genome of the target organism using various techniques such as gene editing, gene splicing, or transgenic technology. The new genetic information can be inherited by the organism's offspring, leading to the spread of the desired trait through a population or species (Lewis et al., 2022).

So, the whole DNA carries all the knowledge about a particular person, and thanks to this property, many scientists have learned to reproduce the appearance and details of creatures on the line of belonging to their DNA, which stood out from even the smallest part of the found fragment of any biomaterial. Modern achievements in

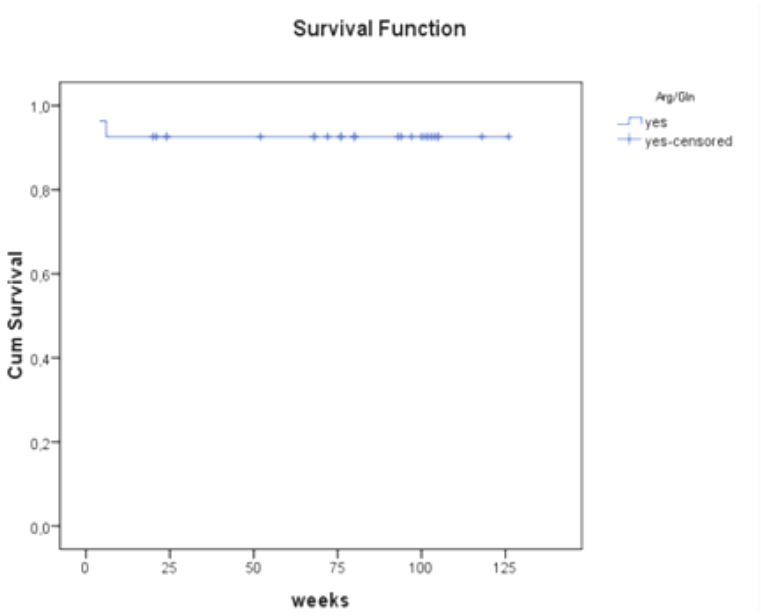

Figure 1. Overall and Relapse-Free Survival of Children with ALL with the Arg/Gln genotype of the *XRCC1 Arg399Gln* gene

genetic engineering have achieved great results, and a large number of the necessary equipment has been created in the accents of technical, biological, and chemical reagents, and this development continues to this day. It is widely used and becomes available in the field of medical research, and even on the bases of standard clinical laboratories in the territories of medical centers or hospitals. This leads to an increase in genetic research, which is gradually being introduced into various fields of practical medicine (DiNardo and Wei, 2020). The availability of various genetic studies at the present stage of the development of medical science allows expanding the direction of gene diagnostics against the background compared with other laboratory studies, such as biochemical blood analysis, which is carried out in any medical laboratory. The high possibilities of genetic research that have appeared require a detailed study of the various components of the genome at an important level to identify various indicators that would allow determining factors inherent in various diseases or norms (LeBlanc and Erba, 2019).

The human genome carries the image of all its components, at the cellular, tissue, organ, and system level and the whole image, which is determined by the totality of all systems in the values of their smallest details. The genome is a complex entity that is made up of both integral structures and the tiniest details. The organism itself, from the aspects of considering the norm, has clear constants that are studied in the disciplines of normal physiology and normal anatomy, and any pathology is, this or that deviation from the norm. It is known that pathology can be detected at the level of a cell, tissue, organ, or system, where an organism's disease will be observed in any case. And treatment factors will already depend on how much they affect changes in various functions that will be displayed in pathological syndromes, and patient complaints (Ollila et al., 2018). Also, considering the existing relationships, various correlations between functional parameters and biochemical manifestations are known. Which have been studied in detail at the moment, both from the norm and pathology, and conditioned upon this there are elements of generally accepted laboratory diagnostics. Genetic analyses, which of all existing methods are the most profound and determine the essence of the gene relationship in the parameter of their influence not only on the life of a particular person, or patient but also on his future generation in the fact of procreation. Since the modified genome will be reflected on whole DNA systems, in the already existing modified level of further reproduction, in the form of gene modifications and changes (Jamy et al., 2020).

Table 1. *XRCC1 Arg399Gln* Genotype Distribution in Children with Acute Lymphoblastic Leukemia in Kazakhstan

Genotype	Number of Children	Percentage
Gln/Gln	7	9.30%
Arg/Gln	32	42.70%
Arg/Arg	36	48.00%

Table 2. Mean follow-up Time or Median in Children with ALL *XRCC1 Arg399Gln* Gene with Arg/Gln genotype and Arg/Arg genotype

	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Arg/Gln				
Overall	117.037	6.099	105.083	128.991
Arg/Arg				
Overall	141.007	12.567	116.377	165.638

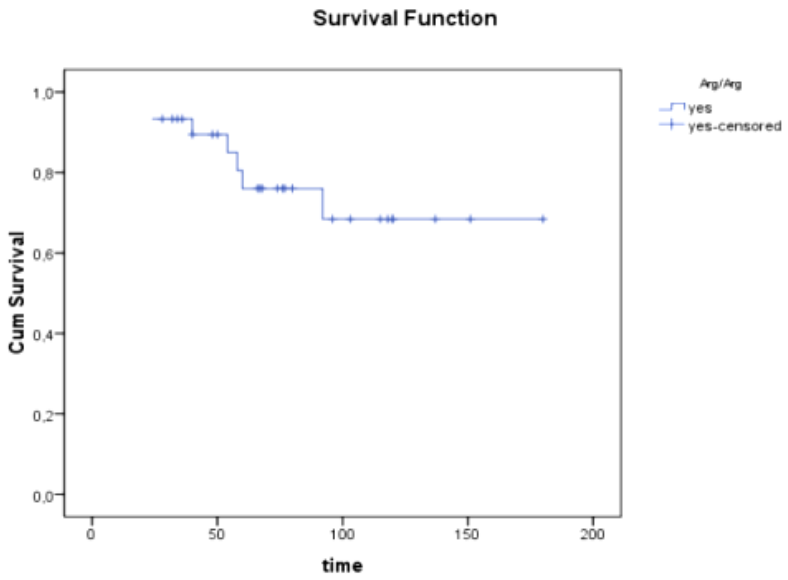

Figure 2. Relapse-Free Survival of Children with ALL with the Arg/Gln genotype of the *XRCC1 Arg399Gln* Gene

The genome of a healthy person is a constant value, and it is the existing set of genes in a certain sequence, number and type that will reflect the health of the individual. Any change in the human genome will be expressed in a disease, in one way or another, and then it will depend on the type of its modification, and any variant in its change will provoke the appearance of this or that pathology (Wei et al., 2020). The conception of a child against the background of an altered genome will determine in him an already indicative variant of the genome of a healthy person changed from the norm in all aspects, and this system is known as the inheritance of various diseases that develop and intensify from generation to generation, both against the background of gene change and the strengthening of genotype pathology, which, in fact, with the passage of time leads to the strengthening of this fact in the progenitors of the genus (DiNardo et al., 2020a). Children born with genetic features have certain pathologies, both in appearance and systemic diseases, which are manifested either from their birth or in the factor of their growth and development, which rapidly increase under adverse external circumstances, such as radiation or chemical exposure in various forms, which are by they are the starting bases for the activation of various diseases that are already embedded in the human genotype (Sallman et al., 2021).

Considering that a healthy genome is a constant, and only it allows a person to be born with the correct anatomical structure of all cells, tissues, organs, vital activity systems and a properly proportioned human skeleton, as the main and supporting part responsible for the movement and representation of the entire human structure (Hasserjian et al., 2020). Then it is a healthy image of a person with a full understanding

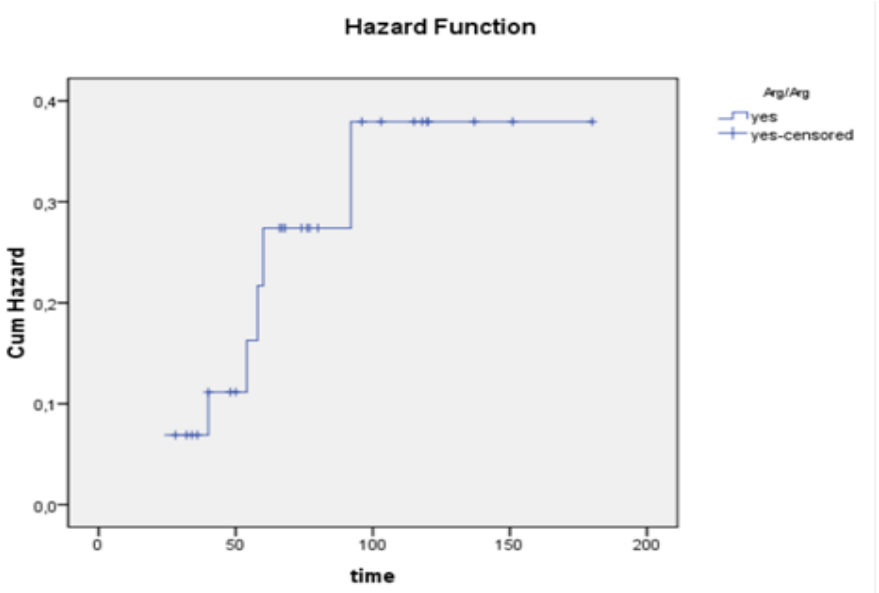

Figure 3. Risk of Relapse in Children with ALL with the Arg/Gln Genotype of the *XRCC1 Arg399Gln* Gene

that is embedded in healthy DNA, and any change in it can be considered a factor in the development of the disease. Genetic engineering at the present stage can influence genes by isolating certain genes and replacing them with others, and all this changes the appearance of DNA. This will allow in the future carrying out various genetic procedures at the public level, both diagnostic and therapeutic against the background of genetic engineering in each medical center. And acute lymphatic leukemia is a disease that annually claims many lives, including children, and there is an importance in studying the appearance of polymorphism of the *XRCC1 Arg399Gln* and *P53 Arg72Pro* genes with it (Candoni et al., 2017).

This medical study created a model to determine polymorphism types of *XRCC1 Arg399Gln* and *P53 Arg72Pro* genes and their interrelations with life expectancy and treatment effectiveness in acute lymphoblastic leukemia (ALL) in children. The study involved theoretical and laboratory aspects, including the polymerase chain reaction of DNA synthesis. The obtained values were statistically processed, and the necessary polymorphism parameters of the genes were determined to control the treatment process of children with ALL at the prognostic level. This study provides important aspects to improve medical support for treating ALL in children. A scientific and medical study examined 75 sick children with confirmed acute lymphoblastic leukemia in the age category up to 12 years, of which there were 48 boys and 27 girls.

Thus, the clinical characteristics of children are presented above, which corresponds to the necessary parameters for further genetic and molecular research, which allows for identifying polymorphism of the *XRCC1 Arg399Gln* and *P53 Arg72Pro* genes in acute lymphoblastic leukemia. The choice of this category of genes in the study was made as a result of the already existing knowledge that the XRCC1 gene has the function of stabilising the entire genome, and given that it is very important in the gene chain, and characterises the factors of its cell cycle, including maintaining the genome constant, which collectively is responsible for human health (Voso et al., 2019). Its polymorphism in the form of Arg399Gln disrupts the protein structure at the cellular level, leading to a characteristic replacement of one substance in the substance to another, where arginine, necessary for the consideration of the norm, is replaced by glycine, which essentially makes the properties and structure of the cell different. This means that a violation has already occurred, and the progress of violations in the future in other biochemical and functional connections, where there is a decrease in the activity of this protein, and as a result, the assembly of the repair complex will be sharply reduced. This mechanism leads to the development of cancer, including acute lymphoblastic leukemia. The P53 gene in the human body plays the role of the guardian of the genome, it is responsible for the protective function, and when the whole DNA image is violated or damaged, it is modified, and its polymorphism develops, which weakens the human genome and activates the development of a tumor. Its polymorphism in the form of Arg72Pro is a suppressor of tumor tissue growth (Majothi et al., 2020).

Discussion

The above is confirmed by various studies, such as the results of a meta-analysis of researchers that have shown that the polymorphism *XRCC1 Arg399Gln* may be associated with an increased risk in children with ALL among the Asian population. The existing MDM2 SNP309 G allele was associated with an increased risk of acute myeloid leukemia. In addition, the polymorphisms of codon 72 P53 and MDM2 SNP309 were not previously associated with age and other studied clinical parameters. And an element like the homozygous MDM2 SNP309 GG genotype may be a factor of genetic susceptibility in the pathogenesis of the disease. But it is described that mutations of the P53 tumor suppressor gene could not be detected often, both in acute myeloblastic leukemia and in ALL, approximately 5-10% and 2-3%, respectively. The XRCC1 repair gene has been described in some malignant tumors, but has not been practically studied in ALL children. The totality of the description reflects that research in the field of gene modifications is just beginning to be studied in detail. And notably, a different ratio of genes is possible and reflects different variants of the course of diseases, which follows from the above model of genome disorders and the development of various pathologies that at one stage or another affect the genome, and actively develop and modify under the influence of external triggers, which leads to DNA disruption (Megias-Vericat et al., 2020). Gene mutations determine known and new diseases, including deformities. Studying human genome components can identify disease features, like cancer and ALL, and aid future laboratory indicators. Genetic analysis can predict ALL components and treatment effects, valuable for practical medicine (Molica et al., 2020).

Based on this position, a model was developed to determine the indicators of genetic and molecular studies, which allows for identifying polymorphism of the genes *XRCC1 Arg399Gln* and *P53 Arg72Pro* in ALL, to predict the survival parameters of children with ALL and to determine the degree of positive criteria that will reflect the recovery of the body, which will contribute to the stabilisation of the state in remission in ALL against the background of the ongoing treatment patients. This will further optimise and expand laboratory methods for the study of children with acute lymphoblastic leukemia at an accessible level of blood analysis and in the factor of its DNA study. Considered at a qualitative level, it will strengthen the diagnostic base of oncological diseases, and will allow purposefully conducting and selecting treatment methods that would successfully affect the genome of ALL patients. This would allow identifying the variability in the frequency of genotypes of the *XRCC1 Arg399Gln* gene in children with ALL, among which the Arg/Gln and Arg/Arg genotypes are most common in corresponding indicators of 48%. The Gln/Gln genotype was detected less frequently in children with ALL. The determined survival rate of patients with acute lymphoblastic leukemia against the background of the absence of recurrence of cancer with the Arg/Gln and Gln/Gln genotypes was the highest, and with the Arg/Arg genotype, its values were observed at a

level lower. And the frequency of detection of genotypes of the *XRCC1 Arg399Gln* gene can be used in practical medicine as a predictor of prognosis in children with ALL. These indicators and criteria should also be considered when choosing treatment tactics as a qualitative indicator of their effectiveness.

Further, at the control stage of the study, the results of a gene-molecular study were analysed to determine the polymorphism indicators of the genes in question. It was identified that *XRCC1 Arg399Gln* was analyzed in 75 cases in children with ALL. At ALL, Gln/Gln was detected in 7 (9.3%). The Arg/Gln allele was detected in 32 children (42.7%), and Arg/Arg in 36 patients (48.0%) (Table 1).

Table 2 shows the overall survival of children with ALL belonging to the *XRCC1 Arg399Gln* gene and the Arg/Gln genotype. The mean follow-up time or median was 117.037± 6.099 weeks. At the same time, the 95% confidence interval (CI) was equal to 105.083 (lower bound); 128.991 (upper bound) weeks. There were no cases of relapse in this group. When studying the survival rates in children with ALL associated with the Arg/Arg genotype of the same gene as *XRCC1 Arg399Gln*, the data were obtained, which are reflected in Table 2. This genotype was found with approximately the same frequency in ALL as Arg/Gln. The average follow-up time was 141.007 ± 12.567 weeks, which was slightly longer than in the previous observation. At the same time, 95% CI was 116.377; 165.638.

There were no deceased patients in this subgroup of the studied, and the overall 128-week survival rate, which was 29 months, was 91.0%, as shown in Figure 1. However, the relapse-free survival rate was lower and amounted to 67%, as shown in Figure 2.

Next, the risk function was calculated. This is the probability of a critical outcome, such as death, failure, and other similar parameters, in a time interval, provided that the critical event has not yet occurred at the time. During the study, this is the time of relapse, as shown in Figure 3.

The frequency of occurrence of the Gln/Gln genotype of the *XRCC1 Arg399Gln* gene in children with ALL was low and was detected in only 7 children. The average follow-up time was 121 weeks, and no relapses were observed in children. Analysis of all the results obtained suggests that the survival rate of children with the Arg/Gln and Gln/Gln genotypes is high, and the frequency of *XRCC1 Arg399Gln* genotypes can be used to determine the effectiveness of the treatment method and to make a prognosis for ALL.

The obtained results of the study allow asserting that it is successful, and the identified qualitative indicators, with the timely introduction into practical medicine to help patients with ALL, will successfully develop gene laboratory studies in healthcare to significantly improve the provision of oncological care to patients. In this study, its correctness was ensured, since the characteristics, parameters of the studies and the data obtained were comparable in the study correctly. The analysis of the results of the study allowed determining that the data obtained can significantly expand and improve the field of medical support in the treatment of cancer patients.

Despite medical progress, oncological diseases remain a significant cause of mortality, highlighting the need for improving the situation. Genetic diagnostic methods based on a healthy genome can investigate aspects related to genome pathology caused by DNA disorders (Turganbekova AA et al., 2017; Carter et al., 2020; DiNardo et al., 2020b).

In conclusions, genetic and molecular research is expanding practical medicine, particularly in the diagnosis and treatment of oncological diseases, including acute lymphoblastic leukemia (ALL). Gene-molecular studies on stabilizer genes such as *XRCC1 Arg399Gln* and *P53 Arg72Pro* can determine the survival rates of ALL children and create effective treatment plans. The results of the work reflected that among the types of the variability of the *XRCC1 Arg399Gln* gene, the Arg/Gln and Arg/Arg genotypes occur most often in children with ALL, within 48% of each. The Gln/Gln genotype is less common. The survival rate of children with ALL is highest with the Arg/Gln and Gln/Gln genotypes, and in this case, there is also a long-term remission of the disease. With the Arg/Arg genotype, the revealed degree of survival is less. Determination of the frequency of genotypes of the *XRCC1 Arg399Gln* gene is a predictor of the prognosis of the course of ALL diseases, and they can also be used as a criterion for the effectiveness of its treatment. Determining the frequency of genotypes of the *XRCC1 Arg399Gln* gene can predict the prognosis of ALL and improve treatment effectiveness. This study contributes to improving medical care for cancer patients.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

Study limitations

The study was conducted in a specific population of children with acute lymphoblastic leukemia, which may limit the generalizability of the findings to other populations. Further research in diverse populations is needed to validate the study findings.

Conflicts of Interest

The authors declare no conflict of interest.

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