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# *MTHFR* GENE POLYMORPHISM AND ITS IMPACT ON HOMOCYSTEINE LEVELS IN PEDIATRIC BURKITT LYMPHOMA PATIENTS FROM AZERBAIJAN: EXPLORING ASSOCIATIONS WITH THE FOLATE CYCLE

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**Abstract.** This study investigated the metabolic profile in children with Burkitt's lymphoma and MTHFR C677T polymorphism, with an emphasis on homocysteine and B vitamin levels. Among 67 patients, the heterozygous CT genotype was detected in 47.6% and the homozygous TT genotype in 10%, whereas among 20 healthy control subjects, these figures were 30% and 15%, respectively. Despite the higher frequency of the CT genotype in patients, no statistically significant difference was found (p=0.299). Patients had significantly elevated homocysteine levels (38.3 ± 2.89 μmol/L versus 14.8 ± 0.34 μmol/L in the control group). Vitamin B6 and B9 levels were significantly reduced and vitamin B12 levels were moderately reduced. ROC analysis showed high diagnostic value for homocysteine (AUC = 0.857), while vitamins B6, B9 and B12 had limited discriminatory power. These results indicate that the C677T polymorphism contributes to impaired one-carbon metabolism, with hyperhomocysteinemia and vitamin deficiency. Given the method of assessing antifolate activity, the MTHFR genotype may influence response to therapy and toxicity. This highlights the potential of genotype-guided nutritional support to improve outcomes in children with lymphoma.

***Keywords:*** *MTHFR, Burkitt lymphoma, homocysteine, folate cycle, pediatric oncology, polymorphism.*

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## 1. Introduction

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate cycle, responsible for catalyzing the conversion of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5methyltetrahydrofolate (5-MTHF). This process is critical for the remethylation of homocysteine into methionine, which is a precursor to S-adenosylmethionine (SAM), a primary methyl group donor for DNA methylation and other essential cellular processes. Zarembska et al. (2024) and Dadashova et al. (2025) and have reported that dysregulation in MTHFR activity can result in elevated homocysteine levels. This is associated with an increased risk of several pathologies, including cancers, cardiovascular diseases and neural tube defects.

Folate metabolism plays a central role in DNA synthesis, repair and the maintenance of genomic stability. Genetic polymorphisms in folate cycle enzymes, such as *MTHFR*, can disrupt these processes leading to the accumulation of homocysteine and a predisposition to various diseases, including non-Hodgkin's lymphoma and other malignancies (Wang *et al*., 2024) have implicated the *MTHFR* C677T polymorphism in altering enzyme activity, which may influence folate metabolism and DNA methylation.

According to Kotur et al. (2020), Shen et al. (2021), Tan et al. (2023) and elevated homocysteine levels, a consequence of this polymorphism, are associated with an increased risk of lymphoma and may also negatively affect the metabolism of methotrexate, a key chemotherapeutic agent in the treatment of Burkitt lymphoma.

In Azerbaijan, over the past 10 years, there has been an increase in the incidence of oncological diseases, particularly hematopoietic system disorders in children, including leukemias and lymphomas. Bagirov et al. (2018) report that over the past 10 years, the incidence of leukemia in children in Azerbaijan has increased by an average of 3.39% per year. From 2012 to 2023, 1,533 children with various oncological diseases were admitted to the National Oncology Center of Azerbaijan (Aliyev & Ismail-zade, 2023).

Despite the growing interest in genetic factors affecting disease progression and treatment response, studies on their impact in the pediatric population of Azerbaijan remain limited. Moreover, the role of *MTHFR* polymorphisms and their potential influence on methotrexate treatment outcomes in these patients are not well understood.

Although there is a wealth of data in the world literature on the role of MTHFR C677T polymorphism in carcinogenesis and its effect on the efficacy of methotrexate, there are virtually no such studies for the Azerbaijani paediatric population. It is unclear how common this polymorphism is in children with Burkitt's lymphoma in Azerbaijan and how it affects homocysteine levels, vitamin B metabolism and treatment outcomes. This gap in knowledge determines the relevance of our study.

This study aims to investigate the *MTHFR* C677T polymorphism in pediatric Burkitt lymphoma patients in Azerbaijan, exploring its relationship with homocysteine levels and folaterelated vitamin deficiencies. We aim to assess how these genetic and biochemical variations may influence disease progression and treatment response, which may contribute to a deeper understanding of pathogenesis and the potential development of personalized therapeutic approaches that take patients' genetic characteristics into account.

## 2. Materials and Methods

The study included 67 patients with Burkitt lymphoma, aged 5 to 13 years, who were undergoing treatment at the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan. The diagnosis was confirmed through clinical, immunohistochemical and molecular genetic studies. The control group was selected mainly from children from the same region with similar social conditions.dietary habits, minimizing confounding effect. Inclusion criteria: children aged 5 to 13 years, diagnosed with Burkitt lymphoma confirmed through clinical, immunomorphological and cytogenetic studies, were included in the study. All participants had no prior treatment, including chemotherapy, radiotherapy or immunotherapy. Exclusion criteria: participants were excluded from the study if they had other types of lymphomas, had previously received any form of chemotherapy, radiotherapy or immunotherapy or were aged over 18 years.

Patients were included in the study sequentially from among those admitted to the Azerbaijan National Oncology Centre with a confirmed diagnosis of Burkitt's lymphoma during the study period. The control group consisted of healthy children of comparable age who underwent routine examinations.

Nutritional status was assessed using dietary history (questioning parents about dietary patterns and the consumption of foods rich in B vitamins) and the analysis of

biochemical parameters, including serum levels of vitamins B6, B9, B12 and homocysteine.

Vitamin supplementation during chemotherapy was not standardized; additional vitamins were prescribed only when clinically indicated, at the discretion of the attending physician. This approach reflected actual clinical practice at our centre.

*MTHFR* C677T gene polymorphism analysis was performed using real-time PCR. DNA was isolated from peripheral blood cells by cell lysis with protease K to degrade DNA-associated proteins, followed by DNA purification through centrifugation and ethanol precipitation. This method ensured the isolation of high-quality DNA suitable for further molecular analyses, including sequencing and PCR. The *MTHFR* C677T gene polymorphism was analyzed in the molecular genetic laboratory of the National Oncology Center. Homocysteine levels were measured in plasma (μmol/L) using a chemiluminescent immunoassay on an automated analyzer, with a reference range of 5-15 μmol/L. Vitamin $B_9$ (folate) and $B_{12}$ levels were quantified using chemiluminescent immunoassays, while vitamin $B_6$ (pyridoxal-5'-phosphate) levels were measured by high-performance liquid chromatography (HPLC). Results for vitamins are expressed in ng/mL. These biochemical analyses were conducted in the research laboratory of Azerbaijan Medical University.

Statistical analysis was performed using STATISTICA 12.0 software. Data are presented as mean ± standard error (SE). The Mann-Whitney U-test was used to compare the control group with the patient groups. Statistical significance was defined as $p < 0.05$. The odds ratio (OR) and 95% confidence intervals (CI) for the association between *MTHFR* gene polymorphisms and the patient groups were calculated using the Chi-square test ($\chi^2$). The Chi-square test was also used to assess the statistical significance of differences between the groups and odds ratios with their 95% confidence intervals were computed to estimate the strength of the association.

All participants, being minors, provided informed written consent through their legal guardians or parents. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki for medical research involving human subjects.

## 3. Results

The analysis of the *MTHFR* C677T polymorphism revealed the presence of the heterozygous CT variant in 47.6% of Burkitt lymphoma patients, compared to 30% in the control group ($p = 0.299$, $\chi^2 = 1.08$, OR = 2.10, 95% CI = 0.69-6.40). The TT genotype was found in 10% of patients, versus 15% of controls ($p = 1.000$, $\chi^2 = 0.00$, OR = 0.92, 95% CI = 0.20-4.20). The remaining patients had the wild-type CC genotype (Figure 1).

The analysis of the MTHFR C677T polymorphism showed that the heterozygous CT genotype was present in 47.6% of Burkitt lymphoma patients (n=32/67) and in 30.0% of controls (n=6/20). The difference was not statistically significant ($\chi^2 = 1.08$, OR = 2.10, 95% CI = 0.69-6.40, $p = 0.299$).

The TT genotype was detected in 10.4% of patients (n=7/67) and in 15.0% of controls (n=3/20), also without statistical significance ($\chi^2 = 0.00$, OR = 0.92, 95% CI = 0.20-4.20, $p = 1.000$).

The remaining cases corresponded to the wild-type CC genotype (41.8% in patients and 55.0% in controls) (Figure 1, Table 1).

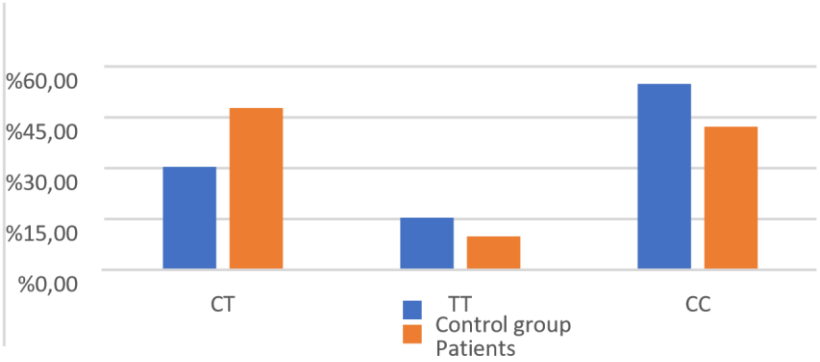


**Figure 1.** Genotype frequency distribution

**Table 1.** Distribution of MTHFR C677T genotypes in patients with Burkitt's lymphoma and in the control group

| Group | CC (n,%) | CT (n,%) | TT (n,%) |
|---|---|---|---|
| Patients (n=67) | 28 (41.8%) | 32 (47.6%) | 7 (10.4%) |
| Control (n=20) | 11 (55.0%) | 6 (30.0%) | 3 (15.0%) |

While the statistical significance for the CT and TT genotypes was not strong, the OR value of 2.10 for the CT genotype suggests a potential association between the heterozygous CT variant and the elevated homocysteine levels observed in this patient cohort. Despite the p-value being above 0.05, the trend observed here is consistent with findings from other studies indicating that the *MTHFR* C677T polymorphism may influence homocysteine metabolism, particularly in the context of lymphoma.

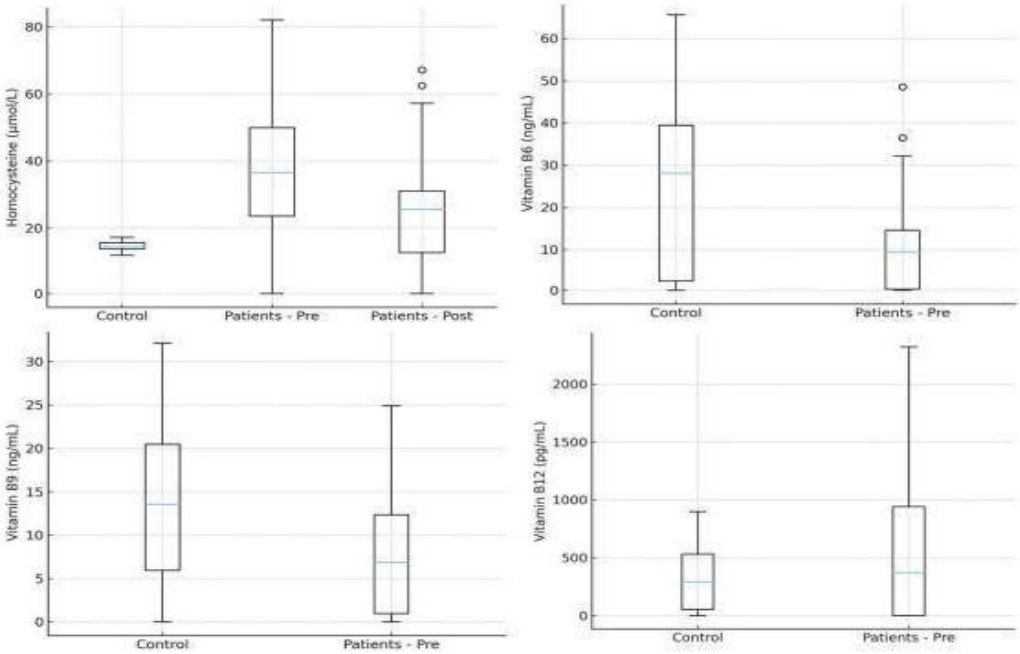


**Figure 2.** ROC curves for biomarkers in pediatric Burkitt lymphoma

Homocysteine levels were significantly elevated in the patient group, being 2.6 times higher than in the control group ($p < 0.05$). Detailed analysis showed that the

increase in homocysteine levels was particularly prominent in patients with the CT heterozygous genotype, while no significant change in homocysteine concentration was observed in patients with the TT variant. Elevated homocysteine levels suggest that the *MTHFR* C677T mutation may impair methylenetetrahydrofolate reductase activity, which plays a crucial role in converting homocysteine to methionine. This, in turn, contributes to the accumulation of homocysteine, supporting the hypothesis that the *MTHFR* C677T mutation may disrupt normal folate metabolism, consistent with findings in the literature (Wang *et al*., 2024). To assess possible changes in folate metabolism in patients with Burkitt's lymphoma, this study measured levels of vitamins B6, B9 and B12 (Figure 2). Vitamin B6 concentrations were severely diminished (7.50 ± 1.30 ng/mL vs. 20.5 ± 5.32 ng/mL in controls; $p = 0.05$). Vitamin B9 (folate) levels were also substantially decreased (6.02 ± 1.08 ng/mL compared to 12.2 ± 2.10 ng/mL in controls; $p = 0.05$). Vitamin B12 levels were mildly reduced (350 ± 110 pg/mL vs. 409 ± 112 pg/mL in controls).

## 4. Discussion

The literature provides data indicating that in Chinese and European paediatric cohorts, the frequency of the TT genotype is 12-18% (Ponti *et al*., 2021; Shen *et al*., 2020), while in our cohort it was 10%, which indicates regional differences.

The concentration of vitamin B6 in the patient group was reduced by more than twofold compared to the control group. This may indicate a disruption in the transsulfuration pathway of homocysteine metabolism, which is dependent on vitamin B6. Vitamin B6 deficiency could impair the conversion of homocysteine to cysteine, leading to the accumulation of homocysteine and possibly increasing the risk of cardiovascular and neurological diseases, as reported by other studies (Spinneker *et al*., 2007; Bajic *et al*., 2022). Possible causes for reduced vitamin B6 levels include inadequate dietary intake, impaired absorption or metabolism of vitamin (Wilson *et al*., 2019). Similarly, vitamin B9 (folate) levels were also reduced by approximately twofold in patients with Burkitt lymphoma compared to the control group. This suggests a deficiency in the active form of folate, 5-MTHF, which is essential for the normal methylation of homocysteine to methionine. We hypothesize that folate deficiency in these patients may be due to impaired MTHFR enzyme function, which reduces the conversion of folate into its active form. Folate deficiency is known to lead to homocysteine accumulation, which increases the risk of cardiovascular disease (Li *et al*., 2016; Abhinand *et al*., 2017; Loria *et al*., 2000). Additionally, the deficiency could be related to low dietary intake or poor folate absorption (Khan & Jialal, 2023).

While vitamin B12 levels were slightly lower in the lymphoma group, the decrease was less pronounced than for vitamins B6 and B9. Nevertheless, vitamin B12 plays a crucial role in the methylation of homocysteine to methionine and its deficiency could impair this process, contributing to elevated homocysteine concentrations. A possible cause of vitamin B12 deficiency may be impaired transport and intracellular metabolism, including defects in vitamin carriers or dysfunction of enzymes involved in its activation and utilization by the body (Giammarco *et al*., 2024). Homocysteine levels exhibit good discriminative power in differentiating pediatric Burkitt lymphoma patients from healthy controls (AUC (Area Under Curve): 0.857). This finding suggests that homocysteine can serve as a reliable biomarker for the identification of Burkitt lymphoma in pediatric populations. Its elevated levels reflect significant metabolic disturbances associated with

the disease. Vitamin B6, B9 and B12 demonstrate low AUC values (<0.5), indicating limited capability to distinguish between patients and healthy individuals based on their concentrations. Despite their physiological importance in the folate cycle and one-carbon metabolism, these vitamins do not serve as effective diagnostic markers for pediatric Burkitt lymphoma. Vitamins B6, B9 and B12, although metabolically significant, these markers alone lack diagnostic efficacy for this condition.

In pediatric lymphoma patients, comprehensive evaluation of biochemical parameters offers valuable insights into the systemic impact of malignancy and the associated metabolic alterations. In this cohort, several key biochemical markers, including liver enzymes (ALT, AST), lactate dehydrogenase (LDH), renal function indicator (Creatinine), hemoglobin (Hb), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were assessed to delineate the metabolic and inflammatory profile characteristic of lymphoma.

ALT and AST levels exhibited significant variability across patients, indicating potential hepatic involvement either due to disease progression, paraneoplastic effect (Khalifa *et al*., 2025). Although ALT, AST and LDH are not directly related to folate metabolism, the inclusion of these data allows for a more detailed discussion of systemic disorders in Burkitt's lymphoma, complementing the basic analysis of MTHFR-homocysteine-vitamin.

LDH levels were notably elevated among most patients, consistent with increased cellular turnover and tissue breakdown, hallmarks of aggressive lymphomas like Burkitt lymphoma. Elevated LDH is widely recognized as a prognostic indicator in hematological malignancies, correlating with tumor burden and disease activity (Kyriakidis *et al*., 2024).

Creatinine levels remained predominantly within the normal physiological range, suggesting preserved renal function in the majority of patients at the time of biochemical assessment. This is clinically relevant, especially considering the potential nephrotoxicity associated with certain chemotherapeutic agents (Rahiman *et al*., 2022).

Hemoglobin (Hb) measurements revealed considerable inter-patient variability, with several patients demonstrating reduced levels indicative of anemia. Shen et al. (2020) conducted a multicenter study in Shanghai, demonstrating that anemia in lymphoma patients may result from bone marrow infiltration, chronic disease processes or treatment-related myelosuppression. Markers of inflammation, namely ESR and CRP, displayed a broad range of values, with elevated levels in a subset of patients. These markers reflect the systemic inflammatory response often accompanying malignancy and may serve as adjunct indicators of disease activity or complications such as infection or treatment-related toxicity (Adams *et al*., 2015).

Collectively, these biochemical parameters provide a critical snapshot of the physiological disruptions occurring in pediatric lymphoma patients (Figure 3). Monitoring these markers not only aids in evaluating baseline health status but also facilitates the detection of organ dysfunction, guides therapeutic interventions and helps predict treatment outcomes.

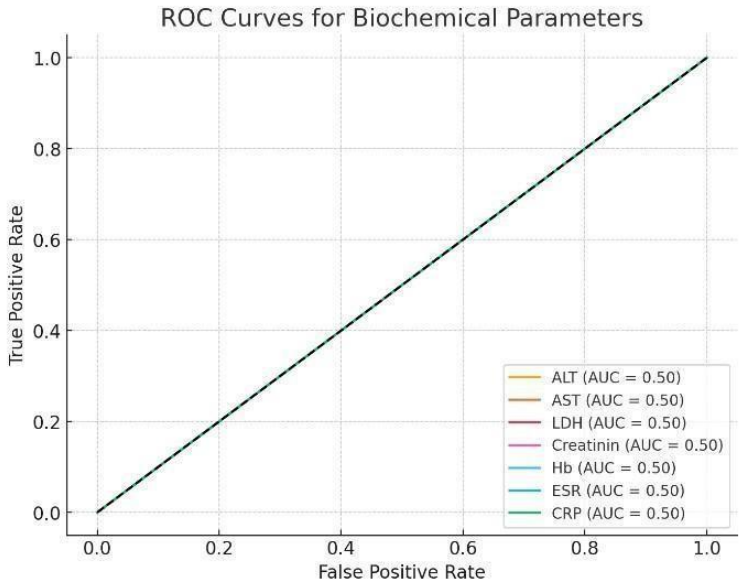


**Figure 3.** Summary of biochemical parameters in pediatric lymphoma patients

The collective data highlight significant metabolic disturbances in pediatric Burkitt lymphoma patients, particularly in those carrying the *MTHFR* C677T mutation. Metabolic processes involved in folate-dependent one-carbon metabolism, including the conversion of 5,10methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF), are finely regulated at the molecular level by enzymatic activity. These transformations are critically dependent on the conformational stability and catalytic efficiency of enzymes such as methylenetetrahydrofolate reductase (MTHFR). Our study highlights the complex interaction between the *MTHFR* C677T polymorphism, plasma homocysteine levels and folate-related vitamin status in pediatric patients with Burkitt lymphoma and is consistent with findings from other researchers (Liu *et al*., 2012).

We revealed significantly elevated levels of plasma homocysteine in patients harboring the C677T mutation. This observation reflects the impaired enzymatic function of MTHFR due to the thermolabile nature of the variant allele, resulting in reduced conversion of 5,10-MTHF to 5MTHF, which is essential for the remethylation of homocysteine to methionine. Consequently, the accumulation of homocysteine is recognized as a biochemical hallmark of disrupted onecarbon metabolism, contributing to DNA strand breaks, oxidative stress, impaired methylation and potentially carcinogenesis (Menezo *et al*., 2022; Geissler *et al*., 2024).

In malignancies such as Burkitt lymphoma, characterized by a high proliferative index, elevated homocysteine may exacerbate genomic instability and accelerate disease progression. Furthermore, sustained hyperhomocysteinemia has been associated with endothelial dysfunction and prothrombotic states, factors that may increase the risk of complications in pediatric oncology populations (Rong *et al*., 2024; Lu *et al*., 2021). Together, these deficits exacerbate the risk of DNA hypomethylation, which has been linked to oncogene activation and tumorigenesis, as well as chemotherapy resistance. As a crucial cofactor for methionine synthase, vitamin $B_{12}$ supports the remethylation of homocysteine; however, its relatively stable concentrations may be attributed to sufficient baseline levels, dietary intake or medical supplementation protocols during chemotherapy (Geissler *et al*., 2024). To better understand potential hepatotoxic effects during treatment, data from experimental studies on doxorubicin-induced hepatotoxicity

were also considered (Panahova *et al*., 2025). Importantly, methotrexate the cornerstone of Burkitt lymphoma treatment - acts as a competitive inhibitor of dihydrofolate reductase (DHFR), thereby depleting intracellular tetrahydrofolate pools and impairing purine and thymidylate synthesis. In patients with preexisting folate cycle dysfunction due to the *MTHFR* C677T variant, methotrexateinduced folate depletion may be more profound, potentially increasing drug-related toxicity and reducing therapeutic efficacy (Lu *et al*., 2021). This pharmacogenetic interaction underscores the critical need for individualized treatment approaches based on genetic and biochemical profiling (Ayad *et al*., 2014).

The observations made in this study are consistent with. Lim et al. (2007) linking *MTHFR* polymorphisms to increased lymphoma risk, altered folate metabolism and variable treatment outcomes. Our study uniquely contributes by demonstrating dynamic biochemical changes, providing a deeper understanding of metabolic adaptation. These findings highlight potential opportunities for targeted interventions, such as genotype-guided folate and vitamin supplementation, to improve therapeutic tolerance and efficacy.

Furthermore, although the elevated odds ratio for the CT genotype did not achieve statistical significance in our sample, it suggests a potential association between heterozygosity and disrupted homocysteine metabolism. This warrants further investigation in larger, multicenter cohorts to clarify the genetic contribution of *MTHFR* variants to lymphoma pathophysiology and treatment response. The coexisting deficiencies in vitamins B6 and B9 further amplify the disruption of the methylation cycle. Vitamin B6, as a coenzyme for cystathionine β-synthase (CBS), facilitates the transsulfuration pathway, offering an alternative mechanism for homocysteine clearance. A deficiency in B6 not only hinders this compensatory mechanism but may also be reflective of increased metabolic turnover or inadequate dietary intake in the context of malignancy. Similarly, vitamin B9 (folate) plays a direct role in methyl group donation and nucleotide biosynthesis. Reduced serum folate levels likely result from both increased cellular demand and impaired folate recycling due to MTHFR activity (Sartor *et al*., 2023).

In our study, we observed a tendency for the MTHFR C677T polymorphism to be associated with altered homocysteine levels and impaired folate metabolism. However, it should be emphasized that any discussion of the potential influence of this polymorphism on methotrexate toxicity within the framework of the present work remains hypothetical, as no direct clinical data on toxicity manifestations were analyzed. To validate these assumptions, further prospective studies are required, including stratification of patients by genotype and evaluation of chemotherapy toxicity profiles.

In addition, our findings should be interpreted in the context of gene-environment interactions. It is well established that dietary intake of folates and B-vitamins can substantially modify the biochemical effects of MTHFR polymorphisms. In Azerbaijan, where mandatory folate fortification of food products is not implemented and dietary habits differ from those in other regions, the role of nutritional factors may be particularly relevant. Considering these regional characteristics may provide deeper insights into the mechanisms of one-carbon metabolism disturbances and improve the accuracy of data interpretation.

The ROC analysis performed for homocysteine and vitamins provided preliminary insights into the possible diagnostic value of these markers. However, considering the

limited sample size and the absence of cross-validation, the results should be interpreted solely as exploratory and require confirmation in larger-scale studies.

## 5. Conclusion

In pediatric patients with Burkitt lymphoma carrying the *MTHFR* C677T polymorphism, a significant increase in homocysteine levels was observed, indicating disrupted folate metabolism. Homocysteine demonstrated high diagnostic accuracy (AUC = 0.857), while vitamins B6, B9 and B12 showed insufficient specificity and sensitivity to serve as independent diagnostic markers.

These findings highlight the importance of integrating genetic and metabolic indicators to improve diagnostic precision and guide individualized treatment strategies.

A limitation of the study is the relatively small, geographically localized sample, which may affect the generalizability of the results. Further research is needed to clarify the clinical implications of these metabolic alterations and to optimize therapeutic approaches.

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