Arch Argent Pediatr. 2026;e202611089

Correlation of *MTHFR* (methylenetetrahydrofolate reductase) gen polymorphism, folate and neonatal hyperbilirubinemia

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ABSTRACT

Objective. Investigate the distribution of methylenetetrahydrofolate reductase (*MTHFR*) genotypes in newborns with hyperbilirubinemia and explore their correlation with folate concentration and bilirubin elevation.

Methods. Neonates with hyperbilirubinemia were categorized into mild, moderate, and severe elevation groups based on total bilirubin levels. *MTHFR* C677T genotype (CC wild-type, CT heterozygous mutant, TT homozygous mutant) was detected using PCR fluorescent probe and folate by chemiluminescence assay. Chi-square tests, ANOVA, and ordered logistic regression were used for analysis.

Results. A total of 132 neonates were included. The moderate and severe elevation groups predominantly exhibited the CT genotype (54.9% and 58.8%), while the mild elevation group predominantly showed the CC genotype (43.3%). The mutant (CT+TT) proportions in the moderate and severe groups were 76.5% and 90.2%, respectively, greater than the 67.1% reported in a large-scale Chinese investigation. Genotype (χ^2 = 13.665, *P* = 0.008) and allele (χ^2 = 6.081, *P* = 0.048) distributions differed significantly among groups. Folate levels were significantly lower in the mutant genotype than in the wild-type (t = 2.162, *P* = 0.032). Ordered logistic regression analysis indicated a negative correlation between folate levels and the degree of hyperbilirubinemia (*P* ≤0.001). TT (95% CI: 1.012–1.974, *P* = 0.042) and CT (95% CI: 1.069–1.823, *P* = 0.014) genotypes were identified as risk factors for elevated bilirubin.

Conclusion. *MTHFR* C677T polymorphism and serum folate levels are associated with the severity of neonatal hyperbilirubinemia. *MTHFR* C677T mutation may exacerbate bilirubin metabolism disorders by inhibiting folate metabolism and promoting homocysteine accumulation, offering potential references for disease risk assessment.

Keywords: *methylenetetrahydrofolate reductase (NADPH2); polymorphism, genetic; homocysteine; folate; hyperbilirubinemia, neonatal.*

doi: http://dx.doi.org/10.5546/aap.2026-11089.eng

To cite: Zhang Z, Bai W, Duan Y, Liu H, Guo P. Correlation of *MTHFR* (metilenetetrahydrofolate reductase) gene polymorphim, folate and neonatal hyperbilirubinemia. *Arch Argent Pediatr.* 2026;e202611089. Online ahead of print 23-JUL-2026.

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Funding*: This study was supported by Bengbu Municipal Science and Technology Innovation Guidance Project (20220107).*

Conflict of interest*: None.*

Received*: 3-13-2026*
Accepted*: 5-21-2026*

INTRODUCTION

Over 80% of neonates are affected with hyperbilirubinemia (HP), one of the most prevalent clinical illnesses in infants.[1,2] Neonatal hyperbilirubinemia is primarily characterized by elevated unconjugated bilirubin (UCB). In the bloodstream, unconjugated bilirubin mostly attaches itself to albumin and travels as a complex. Because of its high molecular weight and water solubility, albumin not only acts as a stable transporter for UCB but also sterically hinders its ability to move freely across cell membranes, preventing large quantities of UCB from entering tissue cells and causing harmful damage.[3] Consequently, albumin is a crucial regulating factor in the binding and distribution of UCB. Albumin's ability to bind UCB under normal settings is significantly greater than the increased amounts seen in children with hyperbilirubinemia. However, changes in the affinity between serum albumin and UCB may play a major role in causing aberrant UCB elevation under specific clinical situations.[4]

Elevated serum homocysteine (Hcy) levels can modify specific amino acid residues in albumin, causing homocysteinylation and altering the spatial conformation of albumin. This competitively inhibits the binding of unconjugated bilirubin (UCB) to albumin, leading to the development of hyperbilirubinemia.

The metabolism of homocysteine is dependent on folate; MTHFR is the rate-limiting enzyme in the folate metabolic pathway,[5] and C677T is its most common mutation site.[6] Following mutation, three genotypes exist: CC (wild type), CT (heterozygous mutant), and TT (homozygous mutant). Mutation can lead to reduced enzyme activity, impaired folate utilization and homocysteine accumulation.[7] It remains unclear whether the *MTHFR* C677T genetic polymorphism and folate levels influence bilirubin metabolism by affecting homocysteine levels.

To test this hypothesis, this study investigated the correlation between the distribution of *MTHFR* C677T genotypes, serum folate and homocysteine levels, and the degree of elevated bilirubin in newborns, with the aim of providing new evidence for research into the mechanisms of this condition and clinical intervention.

METHODS

Materials collection

The study included 132 infants with hyperbilirubinemia who were admitted to Bengbu First People's Hospital's Neonatal Department between January 2023 and December 2025. Criteria for inclusion: (1) neonatal unconjugated hyperbilirubinemia; (2) age ≤7 days; (3) availability of enough heparin-anticoagulated and EDTA-anticoagulated blood samples to satisfy all testing needs. Criteria for exclusion: (1) low birth weight (less than 2500 g) or concurrent newborn feeding intolerance; (2) verified hemolytic illness in neonates, such as Rh hemolysis or ABO hemolysis; (3) hemolysis, coagulation, or other disorders impacting test results in blood samples; (4) incomplete clinical information; (5) premature newborns. According to blood total bilirubin (TBIL) levels, the severity of the disease was divided into three groups:[8] mild elevation group, (TBIL ≤221 μmol/L), moderate elevation group, (221 <TBIL <342 μmol/L), and severe elevation group, (TBIL ≥342 μmol/L).

Detection of TBIL and Hcy concentrations

To separate plasma, heparin-anticoagulated venous blood obtained from pediatric patients that same day was centrifuged for seven minutes at 3500 rpm. A Beckman AU5831 fully automated biochemical analyzer was used for the detection. The detection procedure closely adhered to the operating manuals for the equipment and reagent kit, and all of the reagents utilized were produced by Beijing Jiqiang Biological Co., Ltd. Materials for internal quality control were provided by Landau Diagnostics Ltd. in the United Kingdom.

Folate concentration testing

Collect pediatric patients' EDTA-anticoagulated blood, then centrifuge it for ten minutes at 3500 rpm. Use the Magilumi X8 chemiluminescent immunoassay analyzer from New Industries to test the following after plasma separation. Shenzhen New Industries Biomedical Engineering Co., Ltd. provided the reagents.

MTHFR gene polymorphism detection

To detect *MTHFR* gene polymorphisms, collect 400 μL of pediatric patients' EDTA-anticoagulated whole blood and store it at -80 ºC. The PCR fluorescent probe method was used to detect *MTHFR* gene polymorphisms, and Shenzhen Huizhong Biotechnology Co., Ltd. provided the reagents. The Shanghai Hongshi PCR Amplifier was used as the detecting device.

Statistical methods

The statistical program SPSS 22.0 was used to

analyze the data. Quantitative data with a normal distribution were represented as mean ± standard deviation. The independent samples t-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons between three groups, pairwise comparisons between groups were performed using the LSD-t test. Categorical data were expressed as rates. Chi-square testing was used for intergroup comparisons. The Hardy-Weinberg equilibrium test was used to evaluate the representativeness of the sample. The association between genotype, folate, Hcy, and the level of increased newborn bilirubin was investigated using ordered logistic regression analysis. The *P* values <0.05 indicated statistically significant differences.

RESULTS

Comparison of three groups' homocysteine and folate concentration levels

A total of 132 neonates were included; mild elevation group, 51 cases, moderate elevation group, 51 cases and severe elevation group, 30 cases. Compared to the mild and moderate elevation groups, the severe elevation group's Hcy level was significantly higher (*P* = 0.001). Compared to the mild and moderate elevation groups, the severe elevation group's folate level was significantly lower (*P* ≤0.001) (*Table 1*).

MTHFR genotype and allele frequency distribution in three groups

The distribution of *MTHFR* C677T genotypes revealed that the wild-type genotype was mostly present in the mild elevation group, whereas the heterozygous mutant genotype was primarily found in the moderate elevation and severe elevation groups. There were statistically significant differences across the three groups (χ^2 = 13.665, *P* = 0.008). Additionally, there were significant changes in allele frequency (χ^2 = 6.081, *P* = 0.048) (*Table 2*).

The test of Hardy-Weinberg equilibrium

The theoretical frequencies for TT, CT, and CC in the C677T variation were determined for each of the three groups using the formula $(T+C)^2 = T^2 + 2TC + C^2 = 1$ (T: actual frequency of T, C: actual frequency of C). With these theoretical and actual frequencies, $\chi^2 = \sum$ (actual frequency - theoretical frequency)^2/theoretical frequency was used to calculate the chi-square value. The calculated chi-square value was used to compute the *P*-value in Excel (*P* = CHIDIST [chi-square value, 2]). Results showed that the genotype distributions in the mild elevation group (χ^2 = 4.394, *P* = 0.111), moderate elevation group

Table 1. Comparison of three groups' homocysteine and folate concentration levels (X ± SD)

Group	Number of cases (male/female)	Folate (ng/mL)	Homocysteine (mmol/L)
Mild elevation group	30 (13/17)	13.28 ± 4.38[c]	10.39 ± 3.47[c]
Moderate elevation group	51 (28/23)	11.63 ± 4.98[c]	12.02 ± 4.68[c]
Severe elevation group	51 (30/21)	7.75 ± 5.26[ab]	14.05 ± 3.97[ab]
χ^2/F	1.865	13.915	7.721
P	0.394	≤0.000	0.001

a: Compared with the Mild elevation group, P <0.05; b: Compared with the moderate elevation group, P <0.05; c: Compared with the severe elevation group, P <0.05; χ^2/F:chi-square test/degrees of freedom.

Table 2. *MTHFR* genotype and allele frequency distribution in three groups

		C677T				
		Genotype frequency n (%]			Allele frequency n (%)	
Group	Cases	CC	CT	TT	C	T
Mild elevation group	30	13 (43.3)	9 (30)	8 (26.7)	35 (58.3)	25 (41.7)
Moderate elevation group	51	12 (23.5)	28 (54.9)	11 (21.6)	52 (51)	50 (49)
Severe elevation group	51	5 (9.8)	30 (58.8)	16 (31.4)	40 (39.2)	62 (60.8)
χ^2		13.665			6.081	
P		0.008			0.048	

(χ^2 = 0.494, *P* = 0.781), and severe elevation group (χ^2 = 2.790, *P* = 0.250) all conformed to Mendelian inheritance laws (all *P* >0.05). This suggests that there is no discernible selection bias in the sample and that the subjects in this study are well representative of the population.

Comparison of TBIL, folate, and homocysteine levels between mutant and wild-type groups

Based on the *MTHFR* C677T genotype, all participants were divided into wild-type (CC) and mutant (CT+TT) groups. The levels of TBIL, folate, and Hcy were then compared between the two groups. Results showed that the mutant group had significantly higher TBIL and Hcy levels than the wild-type group, with statistically significant differences (*t* = -3.688, -2.414; *P* ≤0.001, 0.017). The mutant group also had significantly lower folate levels than the wild-type group, with a statistically significant difference (*t* = 2.162; *P* = 0.032) (*Table 3*).

Folate and homocysteine levels comparison of various genotypes in each group

Children with varied *MTHFR* C677T genotypes in the mild, moderate, and severe elevation groups showed significant differences in folate and Hcy levels (all *P* <0.05) according to intragroup stratified analysis (*Figure 1, Figure 2*).

Table 3. Comparison of total bilirubin, folate, and homocysteine between mutant and wild-type groups (X ± S)

Group	Total bilirubin (μmol/L)	C677T Folate (ng/mL)	Homocysteine (mmol/L)
Wild-type	246.38 ± 83.69	14.30 ± 5.53	10.74 ± 3.69
Mutant	311.81 ± 84.60	11.30 ± 6.87	12.92 ± 4.46
t	-3.688	2.162	-2.414
P	≤0.001	0.032	0.017

Figure 1. Folate level comparison of various genotypes in each group

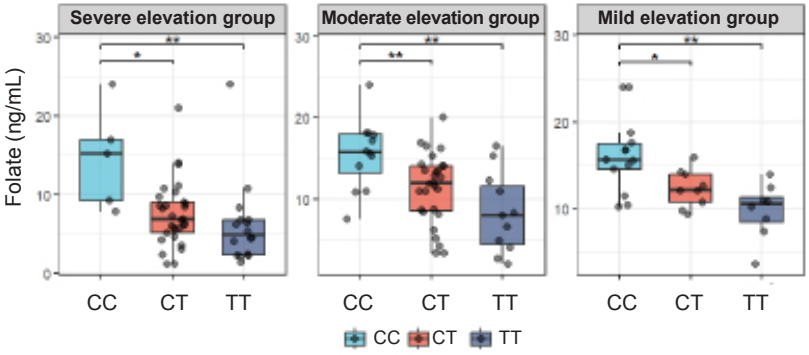
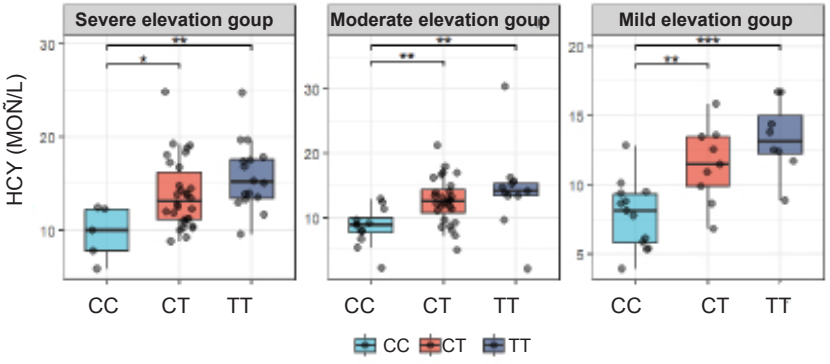


Figure 2. Homocysteine level comparison of various genotypes in each group



Factors linked to elevated total bilirubin levels in neonates: an ordered logistic regression analysis

Ordered logistic regression analysis: folate, Hcy, and C677T genotype (TT = 1, CT = 2, CC = 3) were independent factors, while the dependent variable was the total bilirubin elevation severity in neonates (mild elevation = 1, moderate elevation = 2, severe elevation = 3). Results indicated: the *MTHFR* C677T TT genotype (95%CI: 1.012–1.974, *P* = 0.042) and CT genotype (95%CI: 1.069–1.823, *P* = 0.014) were linked to the degree of elevated bilirubin, indicating risk factors for bilirubin elevation. The results showed a negative correlation between folate concentration and bilirubin elevation (95%CI: -0.159 to -0.054, *P* ≤0.001) and a positive correlation between homocysteine concentration and bilirubin elevation (95%CI: 1.024 - 2.180, *P* = 0.037) (*Table 4*).

DISCUSSION

Neonatal hyperbilirubinemia is one of the common causes of hospitalization within the first 1-2 weeks after birth, with nearly 90% of newborns exhibiting varying degrees of elevated bilirubin levels clinically. Bilirubin has two biological impacts, according to research:[9-11] when it is present in sufficient amounts, it acts as an endogenous antioxidant, shielding different cells from oxidative damage. However, chronically high bilirubin levels can cause apoptosis, inflammatory reactions, and oxidative stress, which can lead to pathological damage to organs and tissues such as the heart, kidneys, and brain.[12-14] For clinical prevention and therapy, it is crucial to clarify the pathophysiology of newborn hyperbilirubinemia and to develop useful risk assessment indicators and therapeutic targets.

The results of this study indicate that the *MTHFR* C677T gene mutation is relatively common. Overall, the proportions of the mutant allele (CT+TT) in the mild, moderate, and severe groups were 56.7%, 76.5%, and 90.2%, respectively, whilst the T allele frequencies were 41.7%, 49.0%, and 60.8%, respectively. Compared with data from a large-scale study conducted in 2013 involving 15 357 Chinese adults across 10 provinces (CT 43.9%, TT 23.2%),[15] mutation frequencies were higher in our study population, particularly among children with moderate to severe hyperbilirubinemia. These findings suggest that the *MTHFR* C677T mutation may be closely associated with the onset or severity of this condition.

According to the study's findings, among *MTHFR* C677T genotypes, the CT genotype is more common in the group with moderate-to-severe hyperbilirubinemia, and the CC genotype is more common in the group with mild hyperbilirubinemia. The total bilirubin level was substantially higher in the mutant genotype group than in the wild-type genotype group (*P* <0.001). Comparisons of folate levels showed that the group with severe hyperbilirubinemia had lower levels than the groups with mild and moderate hyperbilirubinemia; the mutant genotype group's folate levels dropped by 21% in comparison to the wild-type group. However, the relationship between folate levels, newborn hyperbilirubinemia, and *MTHFR* gene polymorphisms has not been investigated in any prior studies. In comparison to *MTHFR* 677 CC homozygotes, Molloy[16] revealed that TT homozygotes had an 18% drop in red blood cell folate concentration, while CT heterozygotes had a nearly 10% loss.

According to the study's findings, the severe elevation group had higher homocysteine (Hcy) levels than the mild and moderate elevation groups. Hcy levels in the mutant type were 20.3% higher than those in the wild type. In addition to being associated with higher serum Hcy, Barjaktarovic M[17] discovered that newborn hyperbilirubinemia also exhibits a certain correlation with neonatal cerebrovascular and cardiovascular accidents. Zhang Yuchao[18] demonstrated that Hcy levels in the *MTHFR* 677 TT and CT genotypes were significantly higher than in the CC genotype.

Table 4. Factors linked to elevated total bilirubin levels in neonates

Independent variable		B	SE	Wald value	*P*	95%CI
Folate		-0.107	0.027	15.734	≤0.001	(-0.159, -0.054)
Homocysteine		0.402	0.193	4.339	0.037	(1.024, 2.180)
C677T	TT	0.346	0.170	4.12	0.042	(1.012, 1.974)
(CC = 0)	CT	0.334	0.136	6.00	0.014	(1.069, 1.823)

This study suggests the following pathogenic mechanism in light of these data and theoretical underpinnings. Theory: the *MTHFR* C677T mutation lowers MTHFR enzyme activity, blocking pathways involved in folate metabolism and resulting in inadequate generation of 5-methyltetrahydrofolate. This impairs Hcy methylation conversion, resulting in elevated serum Hcy levels. Through homocysteinylation (S- or N-homocysteinylation), Hcy can alter the structure of albumin.[19,20] Research has confirmed that the key binding sites for albumin and bilirubin are lysine residues 28 and 569, which are precisely the same sites where Hcy binds to albumin.[21] This suggests that the sites involved in bilirubin binding and those altered by Hcy share a significant amount of overlap. Consequently, increased Hcy may bind to important albumin sites in a competitive manner, changing the folding state and spatial configuration of the protein. This results in an aberrant rise of blood bilirubin because albumin's binding affinity for unconjugated bilirubin (UCB) is decreased, which hinders its effective transport to the liver for processing.

This mechanism preliminarily establishes the pathological chain: "*MTHFR* C677T mutation → folate metabolism abnormality → Hcy accumulation → impaired albumin binding function → elevated bilirubin." It offers a fresh viewpoint on the pathophysiology of hyperbilirubinemia in neonates.

In this study, the correlation between elevated Hcy and hyperbilirubinemia ($P = 0.010$) was statistically less significant than that for folate ($P \leq 0.001$), which may suggest that the independent effect of Hcy is less pronounced than that of folate. We speculate that this may stem from: 1) The *MTHFR* C677T mutation directly affects the efficiency of folate metabolism, and folate levels are a more direct and sensitive metabolic indicator in this pathway. As a downstream product, Hcy concentrations are influenced by multiple factors (such as vitamin B12 and B6 status, etc.); consequently, its linear relationship with bilirubin levels may be partially diluted. 2) Non-linear or threshold effects: We speculate that the modification of Hcy binding to albumin may not follow a simple linear dose-response relationship, but rather involves a 'threshold'. Only when Hcy accumulation exceeds a certain critical threshold (such as the significant elevation observed in the group with severe hyperhomocysteinemia) does it significantly affect the capacity of albumin to bind bilirubin. In the groups with mild to moderate hyperhomocysteinemia, the elevation in Hcy is insufficient to trigger marked functional changes.

Folic acid can improve albumin's capacity to bind bilirubin and lower homocysteine (Hcy) levels.[22] Furthermore, by reducing anomalies in folate metabolism brought on by mutations, high-dose folic acid supplementation may improve brain development.[23,24] More research is necessary to determine whether folic acid therapy may be used as a novel therapeutic approach for neonatal hyperbilirubinemia.

Limitations and future directions of this study

By examining the relationships between Hcy, folate levels, and *MTHFR* gene variants, this study offered preliminary information about the roles of several variables in the pathophysiology of neonatal hyperbilirubinemia. But there are still certain restrictions: First, the sample size for this cross-sectional, single-center investigation was somewhat small, which would have affected the results' stability and statistical power. To further validate the findings, future research should involve multicenter studies and a larger sample size. Second, the impact of other genetic loci or gene-gene interactions on the disease was not taken into account in this study, which solely looked at the *MTHFR* gene C677T polymorphism. For example, Gilbert's syndrome is a recognized genetic cause of neonatal unconjugated hyperbilirubinemia, with the most common contributing factor being a polymorphism in the *UGT1A1* gene. In this study, the *UGT1A1* genotype may act as a confounding factor or an effect modifier; a joint analysis of *MTHFR* and *UGT1A1* gene polymorphisms could be conducted in future studies to assess potential gene–gene interactions. Furthermore, this study did not perform thorough studies of variables that can affect neonatal folate levels, such as mother nutritional status during pregnancy or newborn folate intake. These variables should be examined further in future studies since they might interact with genetic polymorphisms.

To summarize, newborn hyperbilirubinemia is tightly linked to blood homocysteine (Hcy) and folate levels as well as the *MTHFR* C677T polymorphism. Neonatal hyperbilirubinemia may be more severe in those with the *MTHFR* C677T CT and TT genotypes, and folate insufficiency and increased Hcy levels are probably significant risk factors for the development and course of

the condition. These results give a scientific foundation for clinical early screening, risk assessment, and focused therapies, as well as fresh insights into the pathophysiology of newborn hyperbilirubinemia.

CONCLUSIONS

Serum folate/Hcy levels and the *MTHFR* C677T genetic variant are closely associated with the severity of neonatal hyperbilirubinemia. The *MTHFR* C677T mutation may exacerbate bilirubin metabolism issues by inhibiting folate metabolism and promoting homocysteine accumulation, serving as a marker for assessing disease risk and prevention. ■

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