RESEARCH ARTICLE

CYP2C9 rs1057910 Genotype and Its Association with Paraclinical Characteristics in Gout Patients in the Northeast Region of Vietnam

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Abstract

BACKGROUND: Celecoxib and lesinurad are medications used in the management of gout, and their metabolism is significantly influenced by genetic variations in the CYP2C9 enzyme. *CYP2C9*3* (rs1057910) is associated with reduced CYP2C9 activity. This study investigated the association between *CYP2C9* rs1057910 genotype and paraclinical characteristics in gout patients from the Northeast region of Vietnam.

METHODS: A total of 139 gout patients were recruited and their paraclinical characteristics including red blood cell, hemoglobin, hematocrit, white blood cell, neutrophil, lymphocyte, platelet, glucose, urea, creatinine, uric acid, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were collected. The *CYP2C9* rs1057910 genotypes were identified by Sanger sequencing method of PCR products, analyzed with BioEdit software, and verified using the NCBI dbVar database. Statistical analyses were performed using SPSS.

RESULTS: The cohort was predominantly male (93.5%), with female patients showing a significantly higher mean age (70.33±10.64 years) than males (51.81±14.93 years, $p<0.001$). This study showed significant positive correlations between uric acid concentration, creatinine (r=0.201, $p=0.018$) and platelet count (r=0.169, $p=0.046$). The wild-type homozygous *CYP2C9*1/*1* genotype was found in 92.09% of patients; the *CYP2C9*1/*3* and *CYP2C9*3/*3* genotypes were identified in 7.19% and 0.72%, respectively. No significant differences in most paraclinical parameters were observed between genotype groups, except for HDL-C levels, which were significantly higher in *CYP2C9*3* carriers ($p=0.000$).

CONCLUSION: This study showed that the *CYP2C9*3* carrier is significantly associated with higher HDL-C levels compared to the *CYP2C9*1/*1* in gout patients. This finding suggests that the *CYP2C9*3* variant may influence lipid metabolism in a way that promotes a more favorable lipid profile, which are considered protective against cardiovascular disease.

KEYWORDS: *CYP2C9* gene, *CYP2C9*3*, *CYP2C9* rs1057910 genotype, gout patients, paraclinical characteristics

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Introduction

Gout is a long-term and advancing type of inflammatory arthritis that results from the buildup of monosodium urate crystals in the joints, triggered by consistently high levels of uric acid in the blood. It commonly presents with acute, excruciating joint pain, swelling, and redness most often in the big toe but can affect other joints over time.(1) Contributing factors to gout include diets rich in purines,

alcohol intake, excess body weight, impaired kidney function, and inherited genetic traits.(2) If left untreated, gout can lead to serious consequences such as chronic arthritis, joint deformity, tophi formation (deposits of urate crystals in soft tissues), and even irreversible joint damage.(3) Furthermore, gout is associated with an increased risk of cardiovascular disease, kidney stones, and chronic kidney disease, highlighting the importance of early diagnosis and long-term management with urate-lowering therapies.(4) The incidence of gout in Vietnam has been increasing and affecting younger individuals, rising from approximately 0.14% of the population in 2003 to 1.0% (about 940,000 patients) in 2014.(5,6)

The treatment of gout focuses on managing acute flare-ups and preventing future attacks by controlling serum uric acid levels. Acute gout flare-ups are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids to alleviate pain and control inflammation.(1,7) Gout treatment involves the use of medications that lower uric acid levels, such as allopurinol, pegloticase, lesinurad and others.(8-10) Additionally, herbal extracts have been studied for their ability to regulate blood urate levels.(11) In addition, lifestyle modifications including reducing the intake of purine-rich foods, limiting alcohol consumption, maintaining hydration, and managing weight are also essential components of gout management.(2) Cytochrome P450 2C9 (CYP2C9) is a key liver enzyme involved in the metabolism of various clinically important drugs, including NSAIDs, anticoagulants such as warfarin, and uricosuric agents like lesinurad. Genetic polymorphisms in the *CYP2C9* gene significantly affect enzyme activity, leading to interindividual variability in drug metabolism. The most common variant alleles, *CYP2C9**2 (rs1799853) and *CYP2C9**3 (rs1057910), are associated with reduced enzymatic activity compared to the wild-type *CYP2C9**1 allele.(12) Celecoxib and lesinurad is significantly influenced by genetic variations in the CYP2C9 enzyme. Individuals with reduced-function alleles, such as *CYP2C9**2 and *CYP2C9**3, exhibit decreased metabolic activity, leading to higher plasma concentrations of celecoxib. This can increase the risk of adverse effects, and dose adjustments may be necessary for these patients.(7,13) While celecoxib provides greater gastrointestinal safety than many other NSAIDs, it still poses significant risks, including serious cardiovascular events like heart attacks and strokes, as well as gastrointestinal complications such as bleeding, ulcers, and perforations.(7) Lesinurad, a urate transporter inhibitor, is also metabolized by CYP2C9. Patients who are poor metabolizers due to *CYP2C9* polymorphisms may experience increased exposure to lesinurad, elevating the risk of renal-related adverse events and cardiovascular complications. Therefore, understanding a patient's *CYP2C9* genotype can guide dosing strategies and improve the safety and efficacy of gout treatment.(8)

Globally, the *CYP2C9**2 allele is most prevalent in Middle Eastern populations, with frequencies reaching up to 18.1%, followed by South European populations at 16.5%. In contrast, East Asian populations, including Vietnamese, have a very low or absent frequency of the *CYP2C9**2 allele, with frequencies approaching 0%.(14,15) Regarding the *CYP2C9**3 allele, it is most abundant in Emiratis (21.3%) and South Asian populations (up to 11.9%), followed by South European populations at 10.1%. In East Asian populations, including Vietnamese, the frequency of *CYP2C9**3 is also low, with studies reporting frequencies of approximately 2.2% in the Vietnamese Kinh population.(14,16) Recently, it was reported that *CYP2C9**3 accounted for 3.23% in Kinh, Tay, Muong, H'Mong, Nung ethnic. The number of individuals carrying the non-functional *CYP2C9**3 allele existing in a heterozygous state accounted for 7% in the Kinh people of Vietnam.(15) Understanding the distribution of these alleles is crucial for personalized medicine approaches, especially in populations with low frequencies of these variants, where standard dosing may be appropriate.(14) In addition to the Kinh ethnic group, the Northeast region of Vietnam is home to various ethnic minorities, including the Tay, Mong, Nung, Dao and others.(17) Moreover, several meta-analyses have shown that blood lipid parameters can predict major cardiovascular events and mortality risk.(18,19) The association between the *CYP2C9**3 variant and hyperlipidaemia has been studied in Chinese patients with hyperlipidaemia and epilepsy.(20,21) Furthermore, functional variants of *CYP2C9* associated with hematological consequences during treatment have been investigated in patients undergoing angioplasty and stenting for cardiovascular disease, as well as in breast cancer patients.(22,23) Therefore, genotype and allele frequency of *CYP2C9* rs1057910 and its association with paraclinical characteristics in gout patients living in Vietname were deteremined to develop testing solutions to support treatment in Vietnam.

Methods

Subjects Recruitment

The subjects were unrelated 139 gout patients randomly recruited from between January 2023 and June 2024 at

Thai Nguyen General Hospital, Vietnam. The diagnosis of gout was made by clinicians based on etiology, medical history, clinical symptoms, complications, laboratory tests, imaging, and histopathological findings.(24) All participants were informed about the purpose of the study, and written informed consent was obtained. Participant privacy was strictly protected. The study protocol was approved by the Human Ethics Committee of Thai Nguyen General Hospital, Ministry of Health of Vietnam (Approval No. 882/HDDD-BVTWTB).

Paraclinical Characteristics Analysis

Analysis of subjects' paraclinical characteristics including red blood cell, hemoglobin, hematocrit, white blood cell, neutrophil, lymphocyte, platelet, glucose, urea, creatinine, uric acid, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and light-density lipoprotein cholesterol (LDL-C) were carried out at Thai Nguyen General Hospital in accordance with the standard operating procedures (SOPs) established by the Ministry of Health of Vietnam (25), and the data were obtained for this study.

Total Genomic DNA Extraction, PCR, PCR Product Direct Sequencing and Genotype Analysis

Genomic DNA extraction, PCR amplification, and Sanger sequencing of PCR products were performed according to a previous report.(26) Primers used for PCR and sequencing of the *CYP2C9* gene (exon 7) were designed based on the GenBank reference sequence NG_008385. The forward primer was 5′-CCTGAATTGCTACAACAAATGTGCC-3′ and the reverse primer was 5′-ACCTAAGAGTAGCCA AACCAATCTTG-3′, yielding a 500 bp PCR product. All primers were synthesized and supplied by PHUSA Biochem, Can Tho, Vietnam. Genotyping of the SNP rs1057910 in the *CYP2C9* gene was conducted using BioEdit sequence alignment software (BioEdit, Raleigh, NC, USA), and results were verified using the NCBI Database of Genomic Structural Variation (dbVar).

Statistical Analysis

Allele and genotype frequencies, as well as clinical test results, were calculated using direct counting methods. Differences in allele and genotype distributions, as well as clinical test outcomes, between this study and previous reports were considered statistically significant when $p<0.05$ and the odds ratio (OR) was within a 95% confidence interval. All statistical analyses were performed using SPSS 25.0 software (IBM Corporation, Armonk, NY, USA).

Results

Age, Gender and Paraclinical Characteristics of Study Subjects

The age, gender and clinical characteristics of 139 gout subjects living in the Northeast region of Vietnam were shown in Table 1 and Table 2. The average age of male subjects was 51.81±14.93 years old, while the average age of female subjects was higher at 70.33±10.64 years old. The overall mean age of all subjects was 53.01±15.35 years old. A statistically significant difference between male and female age distributions was observed, with a $p<0.001$ (Table 1). The results revealed that serum uric acid, a key biomarker for gout, was significantly elevated in the gout subjects, with an average level of 507.45±94.97 µmol/L, compared to the normal rank of 150–420 µmol/L. Most hematological parameters such as red blood cell count, hematocrit, lymphocyte percentage, and platelet count, along with biochemical markers including blood glucose, kidney function indices (urea and creatinine), and cardiovascular-related lipids (total cholesterol, HDL-C, and LDL-C) were within normal limits in the study population. While minor variations were observed between the study group and normal rank, only one parameter showed a marked elevation, which was the triglyceride level. Normal reference for triglyceride was <1.7 mmol/L; however, in this current study, gout subjects exhibited a mean triglyceride level of 2.84±1.83 mmol/L exceeding the diagnostic threshold for hypertriglyceridemia and measuring approximately 1.65 times higher than the upper limit of the normal rank (Table 2).

Association between Uric Acid Concentration with Paraclinical Characteristics

For the correlation of uric acid with other paraclinical characteristics, most parameters showed weak correlations

Table 1. Age and gender characteristics in study gout subjects.

Age (year)	Gender		Total
	Male	Female	
n (%)			
≤40	36 (100.0)	0 (0.0)	36 (25.9)
41-59	57 (96.6)	2 (3.4)	59 (42.4)
≥60	37 (84.1)	7 (15.9)	44 (31.7)
Total	130 (93.5)	9 (6.5)	139 (100.0)
Mean±SD	51.81±14.93	70.33±10.64	53.01±15.35

There are significant difference with $p<0.001$.

Table 2. Paraclinical characteristics of gout subjects.

Test Parameters	Subjects (Mean±SD)	Normal Range
Hematological test		
Red blood cells (10^{12}/L)	5.433±1.987	4.2-6.3
Hemoglobin (g/L)	14.0±20.2	12-18
Hematocrit (%)	41.94±3.73	37-51
White blood cells (10^{9}/L)	10.25±3.93	4.4-10.9
Neutrophil (%)	53.9±27.4	37-80
Lymphocytes (%)	19.59±15.80	10-58.5
Platelet (10^{12}/L)	272.6±114.6	140-440
Blood biochemistry test		
Glucose (µmol/L)	5.87±1.55	3.9-6.4
Total cholesterol (mmol/L)	5.11±1.2	<5.2
Triglyceride (mmol/L)	2.81±1.78*	<1.7
HDL-C (mmol/L)	1.35±0.37	1-1.5
LDL-C (mmol/L)	2.56±0.77	<3.4
Urea (µmol/L)	5.72±1.28	2.5-7.7
Creatinine (µmol/L)	93.28±19.11	53-120
Uric acid (µmol/L)	507.45±94.97*	150-420

*The mean±SD values is outside the normal value.

with uric acid levels, and the majority were also showing statistically non-significant results. Correlation of platelet count with uric acid levels demonstrated a modest positive correlation (r=0.169) with a statistically significant p=0.046 (p<0.05), suggesting a potential association. Similarly, creatinine had the highest positive correlation with uric acid (r=0.201) and is also statistically significant (p=0.018), indicating a likely relationship between renal function and uric acid levels. Other variables such as red blood count, hemoglobin, hematocrit, white blood cells, neutrophils, lymphocytes, glucose, urea, total cholesterol, triglyceride, HDL-C, and LDL-C all exhibited weak correlations (r values were close to zero) and non-significant p-values (p>0.05), implying no strong linear association with uric acid concentration. Overall, only creatinine and platelet count that were significantly correlated with uric acid levels in the gout subjects (Table 3).

Genotype and Allele Frequencies of SNP rs1057910 in the CYP2C9 Gene

An illustration of nucleotide sequencing used to identify the *CYP2C9* rs1057910 genotype was presented in Figure 1 and their frequencies were calculated as showed in Table 4. The top panel shows the *CYP2C9**1/*1 genotype, which was homozygous for the wild-type allele (*CYP2C9**1), represented by the A nucleotide sequence in the standard peak. The middle panel displayed the *CYP2C9**1/*3 genotype, which was heterozygous for the *CYP2C9*, with a nucleotide change from A to C at position 1075 (c.1075A>C), leading to a protein substitution of isoleucine to leucine at position 359 (p.Ile359Leu). The mutation was indicated by a mixed peak at a specific nucleotide position, suggesting the presence of both *CYP2C9**1 and *CYP2C9**3 alleles. The bottom panel represents the *CYP2C9**3/*3 genotype, which was homozygous for the mutated allele (*CYP2C9**3), indicated by the C nucleotide sequence in the standard peak at the corresponding position. The arrows highlight the specific nucleotide positions where these variations occur.

Table 4 presented the allele and genotype frequencies of the SNP rs1057910 in the *CYP2C9* gene. The most common genotype observed was *CYP2C9**1/*1, found in 128 subjects, accounting for 92.09% of the sample. The heterozygous genotype *CYP2C9**1/*3 was present in 10 subjects (7.19%), while the homozygous mutant genotype CYP2C9*3/*3 was rare, occurring in only 1 subject (0.72%). Subjects carrying at least one *CYP2C9**3 allele account for 7.91%. In terms of allele frequencies, the wild-type *CYP2C9**1 allele was predominant at 95.68%, whereas the *CYP2C9**3 variant allele had a frequency of 4.32%.

Association between CYP2C9 rs1057910 Genotype, Paraclinical Characteristics with Gender Characteristics

Comparison of paraclinical characteristics between male (n=130) and female (n=9) subjects were presented in Table 5. Statistical analysis revealed that male subjects had

Table 3. Correlation between uric acid concentration with paraclinical characteristics.

Paraclinical Characteristics	r	p-value
Red blood cells (10^{12}/L)	-0.008	0.929
Hemoglobin (g/L)	-0.052	0.545
Hematocrit (%)	-0.048	0.574
White blood cells (10^{9}/L)	0.005	0.953
Neutrophil (%)	-0.026	0.762
Lymphocytes (%)	0.079	0.355
Platelet (10^{12}/L)	0.169	0.046*
Glucose (mmol/L)	0.008	0.927
Urea (µmol/L)	0.159	0.061
Creatinine (µmol/L)	0.201	0.018*
Total cholesterol (mmol/L)	-0.037	0.669
Triglyceride (mmol/L)	-0.073	0.392
HDL-C (mmol/L)	0.025	0.771
LDL-C (mmol/L)	-0.029	0.738

r: correlation coefficient. *p<0.05 is considered statistically significant.

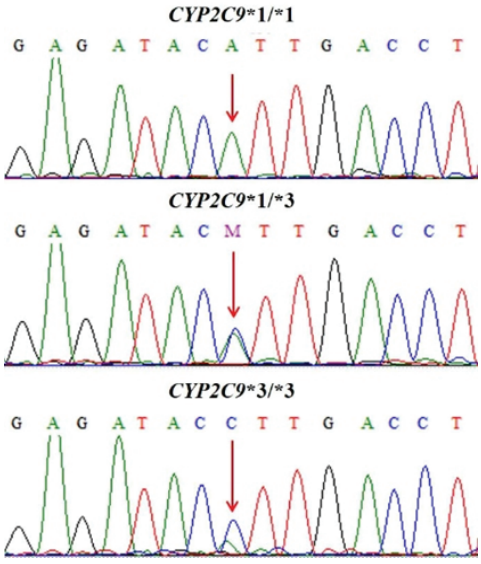

Figure 1. Sequence of SNP rs1057910 of *CYP2C9*. *CYP2C9**1/*1: wild type homozygous for the *CYP2C9*; *CYP2C9**1/*3: heterozygous for the *CYP2C9*; *CYP2C9**1/*3: mutant homozygous for the *CYP2C9*.

significantly higher levels of red blood cells (p=0.022), hemoglobin (p=0.002), hematocrit (p=0.001), neutrophil (p=0.009), and lymphocytes (p=0.005) compared to female subjects. Conversely, females subjects had significantly higher levels of urea (p=0.015) and HDL-C (p=0.040) than male patients. No significant gender differences were found in white blood cells, platelet, glucose, creatinine, uric acid, total cholesterol, triglyceride and LDL-C levels (p>0.05). Table 6 showed the association between the *CYP2C9* rs1057910 genotype and gender characteristics. Among 139 subjects, the *CYP2C9**1/*1 genotype was observed in 128 subjects (92.1%), including 119 males (91.5%) and all 9 females (100%). The variant genotype group (*CYP2C9**X/*3) was found exclusively in males (8.5%) and was absent in females. Statistical analysis revealed no significant association between *CYP2C9* rs1057910 genotype distribution and gender (p=0.62).

Association between rs1057910 CYP2C9 Genotype with Paraclinical Characteristics

In this study, we analyzed and compared paraclinical characteristics between subjects with the *CYP2C9**1/*1 genotype and those carrying at least one *CYP2C9**3 allele (*CYP2C9**X/*3), which correspond to normal and reduced metabolism of celecoxib, respectively. The analyzed hematology parameters include red blood cells, hemoglobin, hematocrit, white blood cells, neutrophil, lymphocytes, and platelet while the mean values for each parameter slightly differ between the genotype groups, none of the comparisons reached statistical significance (all p>0.05). For example, red blood cells was 5.13×10^{12}/L for *CYP2C9**1/*1 and 5.02×10^{12}/L for *CYP2C9**X/*3 (p=0.780), and platelet levels were 277.27×10^{12}/L and 248.99×10^{12}/L respectively (p=0.227). These findings suggest that the *CYP2C9* rs1057910 polymorphism does not have a significant impact on the hematological profile in the studied population (Table 7). Across most blood chemistry parameters including glucose, urea, creatinine, total cholesterol, triglyceride and LDL-C, there were no statistically significant differences observed between the genotypes (p>0.05). However, a significant difference was found in HDL-C levels, which was subjects with the *CYP2C9**1/*1 genotype had a mean HDL-C level of 1.25 mmol/L, whereas those with the *CYP2C9**X/*3 genotype had a significantly higher mean of 1.61 mmol/L (p=0.000). This finding suggested a potential influence of the *CYP2C9* rs1057910 variant on HDL-C levels in gout subjects.

Discussion

This is the first study to investigate the association between the SNP rs1057910 in the *CYP2C9* gene and paraclinical characteristics in 139 randomly selected gout patients living in the Northeast region of Vietnam (Table 1). The cohort is markedly male-dominated, with 130 males (93.5%) and

Table 4. Allele and genotype frequencies of SNP rs1057910 of *CYP2C9* in gout subjects.

Gene	Polymorphism	Nucleotide Change	Protein Change	Genotypes and Alleles	n	Frequencies
CYP2C9	rs1057910	c.1075A>C	p.Ile359Leu	*1/*1	128	92.09
				*1/*3	10	7.19
				*3/*3	1	0.72
				*1	202	95.68
				*3	12	4.32

n: number of subjects. *1/*1: wild type homozygous for the *CYP2C9*; *1/*3: heterozygous for the *CYP2C9*; *1/*3: mutant homozygous for the *CYP2C9*.

Table 5. Association between paraclinical characteristics with gender characteristics.

Paraclinical Characteristics	Gender	n	Mean	SD	Minimum	Maximum	*p*-value
Red blood cells (10^{12}/L)	Male	130	5.19	1.30	3.40	14.00	0.022*
	Female	9	4.18	0.69	3.29	5.18	
Hemoglobin (g/L)	Male	130	140.26	17.62	98	227	0.002*
	Female	9	121.33	11.29	104	134	
Hematocrit (%)	Male	130	41.93	4.79	29.80	56.00	0.001*
	Female	9	36.27	3.65	31.20	41.00	
White blood cells (10^{9}/L)	Male	129	9.98	4.27	5.00	45.80	0.971
	Female	9	10.03	4.01	4.30	15.90	
Neutrophil (%)	Male	129	50.70	25.22	2.50	85.70	0.009*
	Female	9	27.32	30.66	2.40	83.01	
Lymphocytes (%)	Male	130	19.98	12.87	0.50	70.10	0.005*
	Female	9	7.61	9.40	0.90	29.70	
Platelet (10^{12}/L)	Male	130	275.36	72.34	2.23	440.00	0.845
	Female	9	270.33	103.92	118.00	457.00	
Glucose (mmol/L)	Male	130	10.22	43.03	1.66	496.00	0.762
	Female	9	5.85	1.45	4.77	8.51	
Urea (µmol/L)	Male	130	6.17	3.05	2.47	29.26	0.015*
	Female	9	8.81	3.75	4.53	15.05	
Creatinine (µmol/L)	Male	130	102.38	34.40	45.80	276.24	0.312
	Female	9	114.44	35.55	71.57	178.16	
Uric acid (µmol/L)	Male	130	523.30	89.26	67.30	953.30	0.476
	Female	9	501.25	93.12	375.70	700.60	
Total Cholesterol (mmol/L)	Male	130	5.07	1.05	3.13	10.03	0.417
	Female	9	5.37	1.13	3.43	7.30	
Triglyceride (mmol/L)	Male	130	2.82	1.63	0.55	10.21	0.305
	Female	9	2.25	1.01	0.81	4.28	
HDL-C (mmol/L)	Male	130	1.26	0.30	0.71	3.39	0.040*
	Female	9	1.49	0.45	1.05	2.52	
LDL-C (mmol/L)	Male	130	2.77	0.86	0.57	7.77	0.541
	Female	9	2.95	0.54	2.01	3.78	

n: number of subjects; SD: standard deviation. *p<0.05 is considered statistically significant.

only 9 females (6.5%), aligning with previous research demonstrating a significantly higher prevalence of gout in men compared to women.(1,6,27) Interestingly, the gender disparity decreases with age: while all patients aged ≤40 years were male, the proportion of females increased to 15.9% in the ≥60 years group, suggesting a delayed onset or diagnosis of gout in women likely due to the urate-lowering effects of estrogen prior to menopause.(28) The mean age

Table 6. Association between *CYP2C9* rs1057910 genotype with gender characteristics.

Genotype	Gender		Total (n=139)	*p*-value
	Male (n=130)	Female (n=9)		
*1/*1	119 (91.54%)	9 (100%)	128 (92.09%)	0.620
*X/*3	11 (8.46%)	0 (0%)	11 (7.91%)	

n: number of subjects. *p<0.05 is considered statistically significant. *1/*1: wild type homozygous for the *CYP2C9*; *1/*3: heterozygous for the *CYP2C9*; *1/*3: mutant homozygous for the *CYP2C9*; *X could be either *1 or *3 alelle.

Table 7. Association between *CYP2C9* rs1057910 genotype with paraclinical characteristics.

Paraclinical Characteristics	Genotypes	n	Mean	SD	Minimum	Maximum	*p*-value
Red blood cells (10^{12}/L)	*1/*1	128	5.13	1.34	3.29	14.00	0.780
	*X/*3	11	5.02	0.51	4.32	5.70	
Hemoglobin (g/L)	*1/*1	128	139.34	18.07	98	227	0.490
	*X/*3	11	135.45	15.64	101	154	
Hematocrit (%)	*1/*1	128	41.67	5.03	29.80	56.00	0.379
	*X/*3	11	40.31	3.37	33.40	45.00	
White blood cells (10^{9}/L)	*1/*1	127	10.09	4.35	4.30	45.80	0.334
	*X/*3	11	8.79	2.60	6.00	14.40	
Neutrophil (%)	*1/*1	127	49.51	26.08	2.40	85.70	0.610
	*X/*3	11	45.30	27.69	3.50	74.30	
Lymphocytes (%)	*1/*1	128	19.19	12.97	0.50	70.10	0.976
	*X/*3	11	19.07	14.09	1.70	42.60	
Platelet (10^{12}/L)	*1/*1	128	277.27	74.12	2.23	440.00	0.227
	*X/*3	11	248.99	74.68	182.00	457.00	
Glucose (mmol/L)	*1/*1	128	10.26	43.36	1.66	496.00	0.758
	*X/*3	11	6.20	1.83	4.12	9.93	
Urea (µmol/L)	*1/*1	128	6.40	3.27	2.47	29.26	0.472
	*X/*3	11	5.68	0.99	4.20	7.08	
Creatinine (µmol/L)	*1/*1	128	104.77	35.15	54.90	276.24	0.060
	*X/*3	11	84.42	16.87	45.80	103.16	
Uric acid (µmol/L)	*1/*1	128	524.45	91.25	67.30	953.30	0.247
	*X/*3	11	491.83	57.33	415.50	593.60	
Total Cholesterol (mmol/L)	*1/*1	128	5.09	1.06	3.13	10.03	0.939
	*X/*3	11	5.07	0.98	3.53	7.39	
Triglyceride (mmol/L)	*1/*1	128	2.82	1.62	0.55	10.21	0.292
	*X/*3	11	2.29	1.31	0.75	4.50	
HDL-C (mmol/L)	*1/*1	128	1.25	0.25	0.71	2.52	0.000*
	*X/*3	11	1.61	0.69	1.03	3.39	
LDL-C (mmol/L)	*1/*1	128	2.78	0.86	0.57	7.77	0.921
	*X/*3	11	2.76	0.61	1.94	4.30	

n: number of subjects; SD: standard deviation. *$p<0.05$ is considered statistically significant. *1/*1: wild type homozygous for the *CYP2C9*; *X/*3: mutation homozygous and heterozygous for the *CYP2C9*; *X could be either *1 or *3 alelle.

of female patients (70.33±10.64 years) was significantly higher than that of male patients (51.81±14.93 years), with a highly significant p-value ($p<0.001$), reinforcing the observation that gout tends to present later in life in women. These findings are consistent with broader epidemiological literature indicating that both gender and age are critical factors in the pathogenesis and clinical presentation of gout.(2) Previous studies have shown that gout is a chronic systemic inflammatory disease, often accompanied by conditions such as dyslipidemia, cardiovascular disease, fatty liver disease, and kidney disease.(29,30) In this study, we compared paraclinical characteristics of gout patients with normal rank (Table 2). The results showed elevated white blood cells counts (10.25±3.93×10^{9}/L), neutrophils percentages (53.9±27.4 %), and platelet levels (272.6±114.63×10^{12}/L), suggesting a systemic inflammatory response commonly observed during gout flares.(2) The most notable abnormalities were found in lipid metabolism and renal function markers. Triglyceride levels were markedly elevated (2.81±1.78 mmol/L), exceeding the normal upper limit (<1.7 mmol/L), which is consistent with the dyslipidemia frequently associated with gout (28). While total cholesterol, HDL-C, and LDL-C levels remained within normal rank, elevated triglyceridelevels persist as a notable metabolic concern. Hypertriglyceridemia is more frequently found in individuals with gout compared to those without the

condition.(31) It is recognized as a risk factor for gout, with blood total cholesterol levels showing a positive correlation with uric acid levels.(32) Morever, hypertriglyceridemia is a risk factor for cardiovascular disease.(33) These associations underline the importance of comprehensive metabolic assessment and management in gout patients not only to control uric acid levels but also to mitigate cardiovascular risk. Serum uric acid levels in the study population were significantly elevated (507.45±94.97 µmol/L), confirming hyperuricemia, the central feature of gout pathophysiology. (1) The resuls of this study did not show a positive correlation between uric acid and triglyceride levels in gout patients (Table 3). Correlation analysis between uric acid concentration and various paraclinical parameters revealed mostly weak and statistically insignificant associations. However, platelet and creatinine levels showed significant positive correlations with uric acid (r=0.169, p=0.046; and r=0.201, p=0.018, respectively). The correlation with creatinine supports the hypothesis that impaired renal clearance contributes to elevated uric acid levels (34), while the association of uric acid with platelet count may reflect correlation of gout disease with severe atherosclerosis and as a predictor of acute myocardial infarction.(35,36) However, its clinical relevance remains uncertain and warrants further investigation. Other parameters including white blood cells, glucose, triglyceride, and HDL-C did not show significant correlations, in contrast to some previous studies that have reported associations between hyperuricemia and components of metabolic syndrome.(37)

Overall, the findings in this current study suggest that while uric acid shows limited correlation with most paraclinical indices, its relationship with renal markers remains clinically significant. Notably, paraclinical characteristics between male and female gout patients showed several statistically significant gender-related differences (Table 5). Red blood cells, hemoglobin, and hematocrit levels were significantly higher in males compared to females (p=0.022, p=0.002, and p=0.001, respectively), consistent with known physiological differences in erythropoiesis between genders.(1,2) Additionally, neutrophil and lymphocytes percentages also differed significantly (p=0.009 and p=0.005), suggesting possible gender-based variations in inflammatory responses in gout.(3) Blood uric acid levels were significantly elevated in females (p=0.015), possibly indicating differences in renal function or protein metabolism.(4) HDL-C was significantly higher in females (p=0.040), aligning with established patterns in lipid metabolism.(5) These findings highlight the importance of considering gender-specific physiological and biochemical differences in the clinical assessment and management of gout patients.

In the studied group of gout patients, the wild-type homozygous genotype (*CYP2C9**1/*1) was predominant with 92.09%, individuals carrying at least one *CYP2C9**3 allele accounted for 7.91% (Table 4), a proportion consistent with previous studies conducted in Asian populations and in Vietnam.(12,15,16,38) Comparisons with these earlier studies show slight differences in allele and genotype frequencies; however, these differences were not statistically significant (p>0.05). The CYP2C9 enzyme plays a critical role in metabolizing various drugs, including NSAIDs, lesinurad which are commonly used in gout treatment. The presence of the *CYP2C9**3 allele, even at a low frequency, may have pharmacogenetic implications by altering drug metabolism and increasing the risk of adverse effects.(7,8). Thus, these findings highlight the importance of incorporating genetic polymorphism screening into personalized treatment strategies for gout. *CYP2C9**3 frequency in patients with hyperlipidaemia was significantly lower than that in controls.(20) The results of this study indicated differences in the *CYP2C9* rs1057910 genotype between male and female gout patients. There was no *CYP2C9**3 allele detected in female gout patients. The association of *CYP2C9**3 with female gender characteristics in patient groups needs to be further investigated.

Paraclinical characteristics are routinely used by clinicians for diagnosis and monitoring of treatment effectiveness. We analyzed and compared these parameters between patients with the *CYP2C9**1/*1 genotype and those carrying at least one *CYP2C9**3 allele (*CYP2C9**X/*3) (Table 7). The results showed that most parameters did not significantly differ between the two genotype groups (p>0.05), a statistically significant difference was observed in HDL-C levels (p=0.000), with *CYP2C9**X/*3 carriers showing higher HDL-C concentrations (1.61±0.69 mmol/L) compared to the *CYP2C9**1/*1 group (1.25±0.65 mmol/L). For lipid profile, a study in patients with epilepsy showed that those carrying the *CYP2C9**X/*3 genotype had significantly lower levels of triglyceride, total cholesterol, LDL-C, and HDL-C compared to patients with the *CYP2C9**1/*1 genotype.(21) In contrast, in our study, there were no differences in triglyceride, total cholesterol, and LDL-C levels while HDL-C levels were significantly higher. In other hand, increasing HDL-C has been hypothesised that have an effect on antiinflammation action, inflammatory status (39,40) and reducing risk of cardiovascular mortality (18,19). This may suggest a potentially protective lipid profile associated with the *CYP2C9**1/*3 genotype,

although the clinical implications require further investigation. Previous studies have shown that individuals with the *CYP2C9**X/*3 genotype who use celecoxib and lesinurad experience adverse effects related to the cardiovascular, gastrointestinal, and renal systems.(7,8) In additional, another study indicated that the role of HDL-C is not only dependent on its concentration but also on its quality.(39) However, gout patients carrying *CYP2C9**X/*3 genotype has high HDL-C levels in this study. Therefore, further research is needed to clarify the relationship between HDL-C levels, *CYP2C9* rs1057910 genotype, the use of celecoxib and lesinurad in inflammation control, uric acid reduction and risk for cardiovascular, in order to develop effective treatment strategies for gout.

Conclusion

The results of this study showed there are gender and age differences in gout onset and highlighted the metabolic abnormalities like hypertriglyceridemia and impaired renal function. A significant positive correlation between uric acid concentration, creatinine and platelet count were revealed in gout patients. Although uric acid levels did not differ by genotype, but *CYP2C9**3 carrier is significantly associated with higher HDL-C levels compared to the *CYP2C9**1/*1 in gout patients. These results contribute to a more nuanced understanding of how genetic and metabolic factors intersect in gout and may inform future approaches to risk stratification and personalized management.

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Authors Contribution

LTV and YTTH drafted the manuscript; YTN, VVN and HTN performed the lab experiments; THD and THP collect the clinical data; YTTH and HTN conception and design of the work. All the authors reviewed and edited the manuscript and agreed on the final form.

Conflict of Interest

The authors disclose no conflicts.

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