Received: 24 February 2022 | Revised: 22 March 2022 | Accepted: 23 March 2022

DOI: 10.1002/jcla.24405

RESEARCH ARTICLE

WILEY

The relationship between *vitamin D receptor* gene and *TREM-1* gene polymorphisms and the susceptibility and prognosis of neonatal sepsis

Li Xiao[1,2] | Shengshun Que[3] | Lei Mu[4] | Rongxiu Zheng[1]

[1]Department of Pediatrics, Tianjin Medical University General Hospital, Tianjin, China

[2]Department of Neonatology, Hohhot First Hospital, Hohhot, China

[3]Department of Neonatology, Second Hospital of Tianjin Medical University, Tianjin, China

[4]Department of Geriatrics, Inner Mongolia People's Hospital, Hohhot, China

Correspondence
Rongxiu Zheng, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, China.
Email: rzheng@tmu.edu.cn

Funding information
This work was supported by Tianjin Key Medical Discipline(Specialty) Construction Project

Abstract

Objective: The objective of this was to study the relationship between vitamin D receptor (VDR) and triggering receptor expressed on myeloid cells 1 (TREM-1) gene single-nucleotide polymorphisms (SNP) and neonatal sepsis susceptibility and prognosis.

Methods: The blood of 150 neonatal sepsis patients and 150 normal neonates was collected, and genomic DNA was extracted. Sanger sequencing was used to analyze the genotypes of VDR rs739837 and TREM-1 rs2234246.

Results: Vitamin D receptor rs739837 locus GT, TT genotype, dominant model, and recessive model were all protective factors for sepsis ($0 < OR < 1$, $p < 0.05$). The risk of sepsis in carriers of the rs739837 G allele was 0.65 times that of the rs739837 T allele (95% CI: 0.50–0.83, $p < 0.001$), CT, TT, dominant model, and recessive model at rs2234246 were risk factors for sepsis ($OR > 1$, $p < 0.05$). The risk of sepsis in carriers of the rs739837 T allele was 1.38 times that of carriers of the C allele (95% CI: 1.16–1.61, $p < 0.001$). The polymorphisms of VDR gene rs739837 and TREM-1 gene rs2234246 were not significantly correlated with the survival of patients with neonatal sepsis ($p > 0.05$).

Conclusion: *Vitamin D receptor* gene rs739837 locus G>T is associated with a reduction in the risk of neonatal sepsis, TREM-1 rs2234246 C>T is associated with the increased risk of neonatal sepsis, but none of them was significantly associated with the prognosis of neonatal sepsis.

KEYWORDS
sepsis, single-nucleotide polymorphism, triggering receptor expressed on myeloid cells 1, vitamin D receptor

1 | INTRODUCTION

Neonatal sepsis is the main cause of death of newborns, especially premature infants. According to the statistics of epidemiology, the incidence rate of full-term infants is about 1%, the incidence rate of very low birth weight infants is as high as 20%, the mortality rate of early-onset sepsis is 13%, and the mortality rate of late-onset sepsis is 8.9%, which is extremely low, the mortality rate of very low birth weight infants can reach more than 20%.[1–3] In recent years, with the completion of the Human Genome Project and the development of

molecular genetics technology, researchers have begun to study the susceptibility of neonatal sepsis from a genetic perspective.

Vitamin D is a steroid derivative, which has the effect of maintaining calcium homeostasis and bone mineralization, as well as immune regulation.[4–6] Vitamin D has powerful antibacterial and anti-inflammatory properties, and vitamin D deficiency has been shown to be related to the risk of susceptibility to different infectious diseases (such as neonatal sepsis).[7,8] A meta-analysis of the association between vitamin D status in children and sepsis found a significant association between vitamin D deficiency and sepsis in children and newborns.[9] Siyah et al.[7] found that compared with the control group, full-term infants with late-onset sepsis and their mothers had lower levels of 25-hydroxyvitamin D. *Vitamin D receptor* gene polymorphism can affect individual vitamin D expression.[10,11] VDR is found in almost all immune cells, and some of its polymorphisms are found to be related to the increased incidence of autoimmune diseases.[12]

Triggering receptor expressed on myeloid cells 1 is a newly discovered immunoglobulin superfamily activated transmembrane receptor in recent years. It can trigger and expand the cascade effects of various inflammatory factors in the inflammatory response, and plays an important role in the formation of foam cells and the development of atherosclerosis.[13] Studies have found that serum soluble TREM-1 (sTREM-1) and *TREM-1* rs2234237 single-nucleotide polymorphisms are related to the prognosis of sepsis.[14] Therefore, TREM-1 may be a potential target for the prevention and treatment of sepsis.

Therefore, we hope to study the relationship between *VDR* and *TREM-1* gene polymorphisms and the susceptibility and prognosis of neonatal sepsis, and provide a theoretical basis for the prevention and treatment of neonatal sepsis.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 150 full-term neonatal sepsis patients with clinical symptoms, signs, and positive blood cultures admitted to our hospital from January 2018 to August 2021 were selected as the study subjects. The diagnostic criteria for neonatal sepsis were in accordance with the "Protocol for diagnosis and treatment of neonatal septicemia"[15] proposed by the Subspecialty Group of Neonatology Pediatric Society Chinese Medical Association in 2003. Another 150 cases of non-infected full-term newborns during the same period were selected as the control group. There were no infection-related risk factors before and during childbirth, no clinical infection symptoms, and no abnormalities in laboratory tests related to infection indicators. Exclusion criteria: (1) children with severe congenital malformations; (2) children with inherited metabolic diseases. This study was approved by the ethics committee of our hospital (IRB2021097-1.0), and one of the parents of all children has signed an informed consent form. Basic data of children in each group, including gestational age, day age, gender, birth weight, and mode of delivery, were collected.

2.2 | Gene polymorphism analysis

About 3 ml of venous blood was collected using EDTA anticoagulation tube, and genomic DNA was extracted using QIAmp® DNA blood Mini kit (Qiagen). The extracted genomic DNA was used as a template for PCR amplification of DNA containing ±20 bp upstream and downstream of the SNP locus. The sequence of the PCR amplification primers designed for rs739837 site was: 5′-TCCTGTCTGTTCCCTCAACA-3′ (forward primer); 5′-AGGGCCTTGCCCAGAGAT-3′ (reverse primer); the sequence of PCR amplification primers for rs2234246 site was 5′-AGGAAGGTGAGACGCTGACT-3′ (forward primer); 5′-GGAGGTAAA AGGCAGGGAGT-3′ (reverse primer). The total volume of each reaction system for PCR amplification was 20 μl: genomic DNA, 1 μl (about 200 ng); 10 × buffer, 2 μl; $MgCl_2$ (1.5 mmol/L), 1.5 μl; dNTPmix (200 μmol/L), 2 μl; PCR primer mix, 0.5 μl; 0.2 μl of Taq DNA polymerase; added double distilled water to 20 μl. Amplification conditions: predenaturation at 94°C for 5 min; denaturation at 94°C for 30 s, annealing at 58°C for 30 s, extension at 72°C for 30 min, 30 cycles; extension at 72°C for 10 min, the PCR products were purified by agarose gel electrophoresis and then subjected to Sanger sequencing. The sequencing results were compared with the sequences in the dbSNP database to determine the genotypes of *VDR* rs739837 and *TREM-1* rs2234246.

2.3 | Statistical analysis

In this study, SPSS 22.0 (IBM) statistical software was used for statistical analysis. The genotype distribution of *VDR* rs739837 locus and *TREM-1* rs2234246 locus of each group was detected by Hardy–Weinberg equilibrium. The measurement data conforming to the normal distribution were expressed by the mean ± standard deviation, the comparison between the two groups was analyzed by *t* test. The measurement data that did not conform to the normal distribution were expressed by the median (interquartile range) [M (P25, P75)], the comparison between two groups was performed by the Nemenyi method. Counting data were expressed in percentage (%); the chi-square test was used for comparison between groups. The continuous-corrected chi-square test was used if 1 ≤theoretical frequency < 5. Logistic regression was used to analyze the relationship between *VDR* rs739837 locus and *TREM-1* rs2234246 locus genotypes and neonatal sepsis. All tests were two-tailed, $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics

The clinical data of children in the control group and sepsis group are shown in Table 1. The results of statistical analysis showed that there were no statistically significant differences in birth weight, sex, delivery method, gestational age and age of children in the control group and sepsis patients ($p > 0.05$).

3.2 | The correlation between genetic polymorphism and sepsis

The different genotypes and genetic models of the *VDR* gene rs739837 and the *TREM-1* gene rs2234246 of the control group and neonatal sepsis are shown in Table 2. After adjusting for birth weight, sex, delivery way, gestational age and age, GT, TT genotype, dominant model, and recessive model at rs739837 were all protective factors for neonatal sepsis ($0 < OR < 1$, $p < 0.05$). The risk of neonatal sepsis in carriers of the rs739837 G allele was 0.65 times that of the T allele (95% CI: 0.50–0.83, $p < 0.001$), CT, TT genotype, dominant model, and recessive model at rs2234246 were risk factors for sepsis ($OR > 1$, $p < 0.05$). The risk of sepsis in carriers of the T allele was 1.38 times that of carriers of the C allele (95% CI: 1.16–1.61, $p < 0.001$).

3.3 | The correlation between gene polymorphism and neonatal sepsis after baseline data stratification

According to gender, the children were divided into male and female, the birth weight was divided into ≥3153.4 g (mean birth weight) group and <3153.4 g group, the delivery way was divided into vaginal delivery and cesarean section, and the gestational age was divided into ≥38 weeks and <38 weeks, and the correlation between the dominant model and recessive model and the risk of neonatal sepsis in different test groups were analyzed. The results showed that the dominant model at rs739837 locus in male, the recessive model in female, the dominant model in children with a birth weight ≥3153.4 g, the dominant and recessive models in children with cesarean section, and the dominant model in the children with gestational age ≥38 weeks and gestational

TABLE 1 Comparison of clinical data between the control group and the sepsis group

	Control group (n = 150)	Sepsis group (n = 150)	t/χ^2	p
Birth weight (g)	3116.46 ± 312.72	3190.34 ± 405.49	1.767	0.078
Sex [n (%)]			0.120	0.729
Male	79 (52.67%)	76 (50.67%)		
Female	71 (47.33%)	74 (49.33%)		
Delivery way [n (%)]			0.054	0.816
Vaginal	86 (57.33%)	84 (56.00%)		
Cesarean	64 (42.67%)	66 (44.00%)		
Gestational age (week)	37.85 ± 0.94	37.84 ± 1.05	0.087	0.931
Age (day)	11.51 ± 5.82	10.98 ± 5.63	0.802	0.423

TABLE 2 The correlation between the different genotypes, genetic models, and alleles of *VDR* rs739837 locus and *TREM-1* rs2234246 locus and neonatal sepsis

	Control (n = 150)	Sepsis group (n = 150)	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
rs739837						
GG	81 (54.00%)	110 (73.33%)	1.00 (reference)		1.00 (reference)	
GT	53 (35.33%)	34 (22.67%)	0.47 (0.28–0.79)	0.004	0.68 (0.49–0.91)	0.006
TT	16 (10.67%)	6 (4.00%)	0.28 (0.10–0.74)	0.007	0.47 (0.20–0.90)	0.013
GT + TT vs. GG			0.43 (0.26–0.69)	<0.001	0.64 (0.47–0.84)	0.001
TT vs. GG + GT			0.35 (0.13–0.92)	0.027	0.53 (0.22–0.99)	0.046
G	215 (71.67%)	254 (84.67%)	1.00 (reference)		1.00 (reference)	
T	85 (28.33%)	46 (15.33%)	0.46 (0.31–0.69)	<0.001	0.65 (0.50–0.83)	<0.001
rs2234246						
CC	102 (68.00%)	77 (51.33%)	1.00 (reference)		1.00 (reference)	
CT	42 (28.00%)	54 (36.00%)	1.70 (1.03–2.81)	0.036	1.31 (1.01–1.67)	0.049
TT	6 (4.00%)	19 (12.67%)	4.20 (1.60–11.00)	0.002	1.77 (1.22–2.18)	0.004
CT + TT vs. CC			2.02 (1.26–3.22)	0.003	1.40 (1.11–1.76)	0.005
TT vs. CC + CT			3.48 (1.35–8.98)	0.007	1.60 (1.12–1.93)	0.012
C	246 (82.00%)	208 (69.33%)	1.00 (reference)		1.00 (reference)	
T	54 (18.00%)	92 (30.67%)	2.02 (1.37–2.96)	<0.001	1.38 (1.16–1.61)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

age <38 weeks were all protective factors for sepsis (0 < OR < 1, $p < 0.05$) (Table 3). The dominant model at rs739837 locus in males, the dominant model in test children with birth weight <3153.4 g, the dominant model in vaginal delivery children, the recessive model in children with cesarean section, and the dominant model and the recessive model in children with gestational age ≥38 weeks were risk factors for neonatal sepsis (OR > 1, $p < 0.05$) (Table 4).

3.4 | The correlation between genetic polymorphism and the prognosis of patients with neonatal sepsis

The different genotypes and allele frequencies of *VDR* gene rs739837 locus and *TREM-1* gene rs2234246 locus and the prognosis and survival of patients with neonatal sepsis are shown in Table 5. The results showed that the genetic polymorphisms of *VDR* gene rs739837 and *TREM-1* gene rs2234246 were not significantly correlated with the prognosis and survival of patients with neonatal sepsis ($p > 0.05$).

3.5 | Serum 25 hydroxy vitamin D [25(OH)D] and sTREM-1 levels

The comparison of serum 25 hydroxyvitamin D [25(OH)D] and sTREM-1 levels between the control group and neonatal sepsis patients is shown in Figure 1. The analysis results showed that the serum 25(OH)D level of neonatal sepsis patients was significantly lower than that of the control group (Figure 1A), while the serum sTREM-1 level was significantly higher than that of the control group (Figure 1C), and the differences were statistically significant ($p < 0.01$). In addition, we separately analyzed the receiver operating curve (ROC) of serum 25(OH)D and sTREM-1 in the diagnosis of neonatal sepsis. The results showed that the area under the curve (AUC) for the diagnosis of neonatal sepsis in the former was as high as 0.966 (Figure 1B), the

TABLE 3 Correlation between different genetic models of rs739837 locus and neonatal sepsis after stratification of baseline data

	Control (n = 150)	Sepsis group (n = 150)	Adjusted OR (95% CI)	p
Sex				
Male				
GT + TT/GG	38/41	18/58	0.55 (0.35–0.83)	0.003
TT/GG + GT	5/74	4/72	0.83 (0.19–3.47)	0.777
Female				
GT + TT/GG	31/40	22/52	0.55 (0.28–1.08)	0.117
TT/GG + GT	11/60	2/72	0.17 (0.03–0.79)	0.016
Birth weight				
≥3153.4 g				
GT + TT/GG	18/22	6/43	0.28 (0.10–0.64)	0.001
TT/GG + GT	6/34	0/49	\	
<3153.4 g				
GT + TT/GG	51/59	34/67	0.73 (0.50–1.04)	0.082
TT/GG + GT	10/100	6/95	0.65 (0.22–1.89)	0.546
Delivery way				
Vaginal				
GT + TT/GG	39/47	31/53	0.81 (0.55–1.20)	0.336
TT/GG + GT	7/79	5/79	0.73 (0.21–2.48)	0.797
Cesarean				
GT + TT/GG	30/34	9/57	0.29 (0.14–0.57)	<0.001
TT/GG + GT	9/55	1/65	0.11 (0.01–0.78)	0.019
Gestational age				
≥38				
GT + TT/GG	48/60	27/75	0.60 (0.39–0.89)	0.010
TT/GG + GT	8/100	3/99	0.40 (0.08–1.59)	0.253
<38				
GT + TT/GG	21/21	13/35	0.54 (0.29–0.98)	0.043
TT/GG + GT	8/34	3/45	0.33 (0.07–1.26)	0.127

Abbreviations: CI, confidence interval; OR, odds ratio.

AUC of the latter in the diagnosis of neonatal sepsis was as high as 0.925 (Figure 1D), and both were potential markers for the diagnosis of neonatal sepsis.

In addition, we analyzed the serum 25(OH)D levels and sTREM-1 levels of neonatal sepsis patients with different prognosis, and the results are shown in Figure 2. The serum 25(OH)D level and sTREM-1 level of sepsis children in the death group were not significantly different from those of the surviving children ($p > 0.05$). Therefore, serum 25(OH)D levels and sTREM-1 levels may not be good indicators for predicting the prognosis of neonatal sepsis patients.

3.6 | Gene polymorphism and serum 25(OH)D and sTREM-1 levels

Subsequently, we compared the serum 25(OH)D and sTREM-1 levels of children with different genotypes at the rs739837 locus of the *VDR* gene and the rs2234246 locus of the *TREM-1* gene. The results are shown in Figure 3. The results showed that the genetic polymorphisms of *VDR* gene rs739837 and *TREM-1* gene rs2234246 were significantly correlated with serum 25(OH)D and sTREM-1 levels ($p < 0.01$). *VDR* rs739837 locus G > T variation was associated with increased serum 25(OH)D (Figure 3A,B), *TREM-1* rs2234246 locus C > T variation was associated with increased serum sTREM-1 level (Figure 3C,D).

4 | DISCUSSION

Neonatal sepsis is a systemic inflammatory response syndrome caused by infection, it is one of the common critical illnesses in the neonatal intensive care unit with a high morbidity and fatality rate.[16,17] From subclinical symptoms to atypical symptoms of severe focal or systemic infections, since the deterioration of the disease may be sudden and rapid, the early diagnosis and treatment

TABLE 4 Correlation between different genetic models of rs2234246 locus and neonatal sepsis after stratification of baseline data

	Control (n = 150)	Sepsis group (n = 150)	Adjusted OR (95% CI)	p
Sex				
Male				
CT + TT/CC	27/52	40/36	1.54 (1.04–2.30)	0.031
TT/CC + CT	4/75	11/65	2.86 (0.89–10.43)	0.087
Female				
CT + TT/CC	21/50	33/41	1.51 (0.95–2.45)	0.090
TT/CC + CT	2/69	8/66	3.84 (0.79–25.95)	0.116
Birth weight				
≥3153.4 g				
CT + TT/CC	14/26	25/24	1.46 (0.85–2.58)	0.193
TT/CC + CT	1/39	8/41	7.61 (0.91–63.69)	0.072
<3153.4 g				
CT + TT/CC	34/76	48/53	1.54 (1.07–2.23)	0.020
TT/CC + CT	5/105	11/90	2.40 (0.80–7.76)	0.139
Delivery way				
Vaginal				
CT + TT/CC	28/58	45/39	1.65 (1.12–2.43)	0.009
TT/CC + CT	4/82	9/75	2.30 (0.68–8.72)	0.231
Cesarean				
CT + TT/CC	20/44	28/38	1.36 (0.83–2.25)	0.255
TT/CC + CT	2/62	10/56	4.85 (1.06–31.76)	0.039
Gestational age				
≥38				
CT + TT/CC	34/74	48/54	1.50 (1.04–2.17)	0.030
TT/CC + CT	3/105	15/87	5.29 (1.51–22.76)	0.005
<38				
CT + TT/CC	14/28	25/23	1.56 (0.91–2.77)	0.115
TT/CC + CT	3/39	4/44	1.18 (0.25–5.61)	0.833

Abbreviations: CI, confidence interval; OR, odds ratio.

	Survival group (*n* = 136)	Death group (*n* = 14)	Adjusted OR (95%CI)	*p*
rs739837				
GG	99 (72.79%)	68 (78.57%)	1.00 (reference)	
GT	32 (23.53%)	51 (14.29%)	0.59 (0.09–2.59)	0.697
TT	5 (3.68%)	17 (7.14%)	1.67 (0.08–8.02)	0.602
G	230 (84.56%)	187 (85.71%)	1.00 (reference)	
T	42 (15.44%)	85 (14.29%)	0.92 (0.28–2.59)	0.872
rs2234246				
CC	11 (50.00%)	9 (64.29%)	1.00 (reference)	
CT	2 (37.50%)	3 (21.43%)	0.48 (0.10–1.81)	0.373
TT	1 (12.50%)	2 (14.29%)	0.90 (0.14–3.93)	0.890
C	24 (68.75%)	21 (75.00%)	1.00 (reference)	
T	4 (31.25%)	7 (25.00%)	0.75 (0.30–1.79)	0.640

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 5 Correlation between the different genotypes of *VDR* gene rs739837 locus and *TREM-1* gene rs2234246 locus and the survival of children with neonatal sepsis

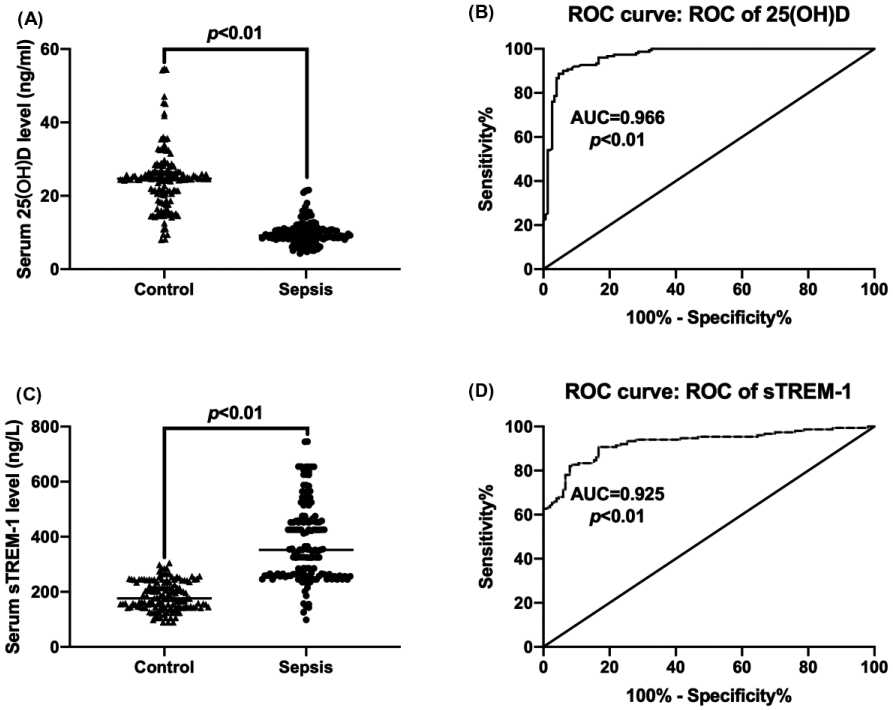

FIGURE 1 Serum 25-hydroxyvitamin D[25(OH)D] and sTREM-1 levels. (A) Comparison of serum 25(OH)D levels between the control group and sepsis group. (B) The receiver operating curve (ROC) of the serum 25(OH)D levels in the diagnosis of sepsis. (C) Comparison of serum sTREM-1 levels between the control group and sepsis group. (D) ROC of the serum sTREM-1 levels in the diagnosis of sepsis. AUC, area under the curve

of neonatal sepsis is very important. Early diagnosis and evaluation of the severity of the disease and its prognosis, and intervention are the key to effectively reducing the mortality rate. Identifying high-risk gene variants can predict the susceptibility and outcome of sepsis, which helps us to identify those children who are at high risk of death or severe complications and require prompt and active treatment.

In addition to the classic regulation of calcium and phosphorus metabolism, vitamin D also has new potential biological functions, such as protecting central nervous system function, anti-tumor, preventing cardiovascular diseases, autoimmune system diseases, diabetes, etc..[18,19] Vitamin D receptor (VDR) is a nucleophilic protein, a member of the steroid hormone/thyroid hormone receptor superfamily, and it mainly mediates the cellular effects of vitamin D in the body.[20] 1,25-dihydroxycholecalciferol, the main active metabolite of vitamin D, has a wide range of effects in the body. In addition to the classic regulation of calcium and phosphorus metabolism, when combined with VDR, vitamin D can also inhibit proliferation, promote differentiation, regulate immunity, inhibit cell necrosis, inhibit tumor infiltration and metastasis, and other non-calcium regulatory effects.[21–23]

In this study, we found that the serum 25(OH)D level of patients with sepsis was significantly lower than that of the control group, and the *VDR* rs739837 G > T allelic variation was correlated with the increase of serum 25(OH)D. Küchler et al.[24] found that the *VDR* mRNA expression level in samples of GG genotype in rs739837 was

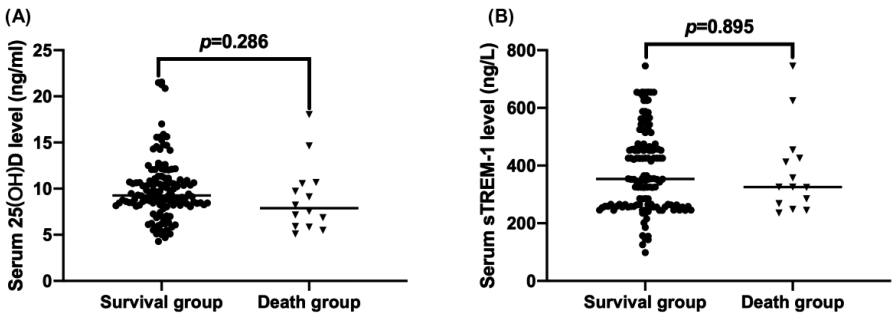

FIGURE 2 Comparison of serum 25(OH)D level (A) and sTREM-1 level (B) of neonatal septicemia patients in the survival group and the death group

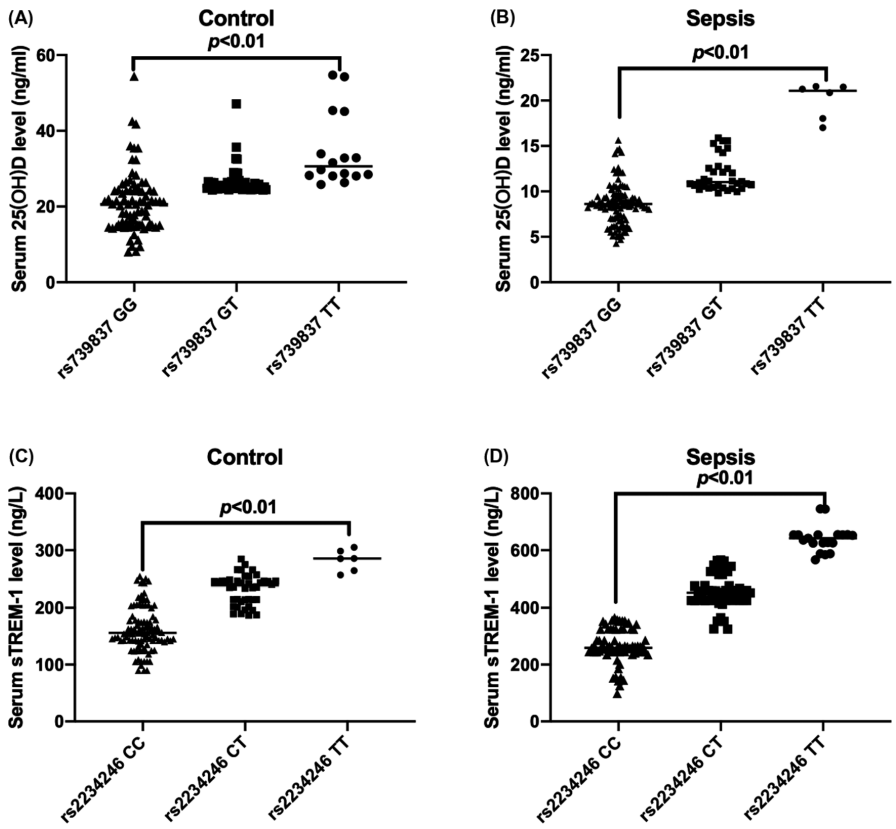

FIGURE 3 Comparison of serum 25(OH)D and sTREM-1 levels between different genotypes at the *VDR* rs739837 and the *TREM-1* rs2234246 in the control group and the sepsis group. (A) Comparison of serum 25(OH)D levels between different genotypes at the *VDR* rs739837 in the control group. (B) Comparison of serum 25(OH)D levels between different genotypes at the *VDR* rs739837 in the sepsis group. (C) Comparison of serum sTREM-1 levels between different genotypes at the *TREM-1* rs2234246 in the control group. D, Comparison of serum sTREM-1 levels between different genotypes at the *TREM-1* rs2234246 in the sepsis group

lower, which was consistent with the results of this study. 25(OH)D levels are closely related to neonatal sepsis. One possible reason is that vitamin D is an important micronutrient required by the body, involved in calcium and phosphorus metabolism, and is also a precursor of hormones. 1, 25-(OH)2D is considered to be a steroid hormone, which is involved in the regulation process of a variety of cell proliferation, differentiation, and immune function.[25] When the 25(OH)D level is insufficient, the body's immunity is low, and the neonates are prone to complicated infections because of the immature organ functions. 25(OH)D deficiency can reduce the activity of antimicrobial peptides by inhibiting the expression of antimicrobial peptides, thereby affecting the body's innate immunity and the ability of the host to defend against infection. The subjects of this study were neonates, whose immunity was lower than that of adults. When vitamin D was insufficient or deficient, infections and sepsis were more likely to occur.

Triggering receptor expressed on myeloid cells 1 is a member of the immunoglobulin superfamily associated with inflammation that has been discovered in recent years.[26] Its soluble form, sTREM-1 is often used in clinical diagnosis and condition judgment of various infectious diseases.[27–29] After the body is infected, TREM-1 falls off as the expression increases on the surface of activated neutrophils or macrophages,[26] so sTREM-1 can be detected in body fluids. During the infection process, sTREM-1 can be released into body fluids and is closely related to the severity of the infection, especially in patients with sepsis and bronchial bubble lavage fluid of patients with pneumonia, sTREM-1 is significantly increased.[30] In this study, we found that the serum sTREM-1 level of neonatal sepsis was significantly higher than that of the control group. *TREM-1* rs2234246 locus C > T allelic variants were associated with increased serum sTREM-1 levels. Aldasoro et al.[31] found that the minor allele T at rs2234246 was related to the increase of sTREM-1 levels.

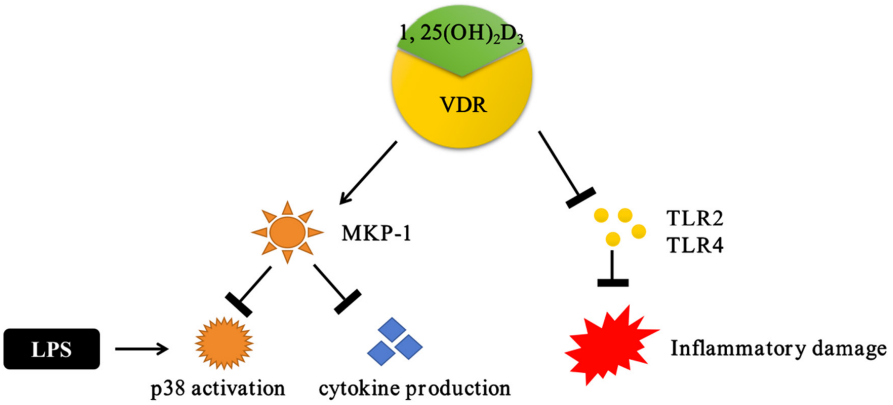

FIGURE 4 A potential mechanism of VDR in neonatal sepsis. LPS, lipopolysaccharide; MKP-1, MAPK phosphatase-1; TLR, toll-like receptors

However, this study also has some shortcomings. First of all, according to the allele frequencies of rs739837 locus and rs2234246 locus, the minimum sample sizes required for this study were 155 and 176 (the power was 0.8), but the sample size included in this study was 150, which was smaller than the minimum sample sizes. And there is no classification of the severity of sepsis, so further research is needed in a large sample size. Secondly, the mechanisms of the *VDR* gene rs739837 locus G > T allelic variation and 25(OH)D level and TREM-1 rs2234246 locus C > T allelic variation and serum sTREM-1 level have not been confirmed yet, and a potential mechanism of VDR in neonatal sepsis is shown in Figure 4 and requires further experiments to confirm.

5 | CONCLUSION

In summary, our study proved that the *VDR* rs739837 site G > T is associated with a reduction in the risk of neonatal sepsis, and *TREM-1* rs2234246 C > T is associated with the increased risk of neonatal sepsis, but they are not significantly related to neonatal prognosis. Moreover, *VDR* rs739837 G > T allele variation is associated with the increase of serum 25(OH)D, and *TREM-1* rs2234246 C > T allele variation is associated with the increase of the serum sTREM-1 level. Our study can provide a reference for the prevention and treatment of neonatal sepsis.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Rongxiu Zheng contributed to the experiment design, article draft, and data analysis. Li Xiao contributed to the experiment implementation and article draft. Shengshun Que and Lei Mu analyzed the data. All authors read and approved the final study.

CLINICAL TRIAL

Our clinical trial was registered (No. ChiCTR2200055627).

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. And supported data can be found on GitHub page (https://github.com/today2022/VDR-and-TREM-1).

ORCID

Rongxiu Zheng https://orcid.org/0000-0001-6118-0218

REFERENCES

1. Tiskumara R, Fakharee SH, Liu CQ, et al. Neonatal infections in Asia. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(2):F144-F148.
2. Mehta K, Bhatta NK, Majhi S, Shrivastava MK, Singh RR. Oral zinc supplementation for reducing mortality in probable neonatal sepsis: a double blind randomized placebo controlled trial. *Indian Pediatr*. 2013;50(4):390-393.
3. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics*. 2010;126(3):443-456.
4. van Driel M, van Leeuwen J. Vitamin D endocrinology of bone mineralization. *Mol Cell Endocrinol*. 2017;453:46-51.
5. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881-886.
6. Fleet JC. The role of vitamin D in the endocrinology controlling calcium homeostasis. *Mol Cell Endocrinol*. 2017;453:36-45.
7. Siyah Bilgin B, Gonulal D. Association between vitamin D level and community-acquired late-onset neonatal sepsis. *Arch Argent Pediatr*. 2020;118(4):265-272.
8. Hagag AA, El Frargy MS, Houdeeb HA. Therapeutic value of vitamin D as an adjuvant therapy in neonates with sepsis. *Infect Disord Drug Targets*. 2020;20(4):440-447.
9. Xiao D, Zhang X, Ying J, et al. Association between vitamin D status and sepsis in children: a meta-analysis of observational studies. *Clin Nutr*. 2020;39(6):1735-1741.
10. Gisbert-Ferrándiz L, Cosin-Roger J, Hernández C, et al. The vitamin D receptor Taq I polymorphism is associated with reduced VDR and increased PDIA3 protein levels in human intestinal fibroblasts. *J Steroid Biochem Mol Biol*. 2020;202:105720.
11. Al-Ghafari AB, Balamash KS, Al Doghaither HA. Relationship between serum vitamin D and calcium levels and vitamin D receptor gene polymorphisms in colorectal cancer. *Biomed Res Int*. 2019;2019:8571541.
12. Bizzaro G, Antico A, Fortunato A, Bizzaro N. Vitamin D and autoimmune diseases: is Vitamin D Receptor (VDR) polymorphism the culprit? *Isr Med Assoc J*. 2017;19(7):438-443.

13. Tammaro A, Derive M, Gibot S, Leemans JC, Florquin S, Dessing MC. TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives. *Pharmacol Ther*. 2017;177:81-95.
14. Su L, Liu C, Li C, et al. Dynamic changes in serum soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) and its gene polymorphisms are associated with sepsis prognosis. *Inflammation*. 2012;35(6):1833-1843.
15. Subspecialty Group of Neonatology Pediatric Society Chinese Medical Association. Protocol for diagnosis and treatment of neonatal septicemia. *Zhonghua Er Ke Za Zhi= Chin J Pediatr*. 2003;41(12):897-899.
16. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet*. 2017; 390(10104):1770-1780.
17. Kim F, Polin RA, Hooven TA. Neonatal sepsis. *BMJ*. 2020;371:m3672.
18. Bläuer M, Sand J, Laukkarinen J. Physiological and clinically attainable concentrations of 1,25-dihydroxyvitamin D3 suppress proliferation and extracellular matrix protein expression in mouse pancreatic stellate cells. *Pancreatology*. 2015;15(4):366-371.
19. Playford MP, Dey AK, Zierold C, et al. Serum active 1,25(OH)2D, but not inactive 25(OH)D vitamin D levels are associated with cardiometabolic and cardiovascular disease risk in psoriasis. *Atherosclerosis*. 2019;289:44-50.
20. Olabiyi AA, Passos DF, da Silva JL, Schetinger MR, Leal DB. Role of purinergic system and vitamin D in the anti-cancer immune response. *Life Sci*. 2021;287:120110.
21. Das A, Gopinath SD, Arimbasseri GA. Systemic ablation of vitamin D receptor leads to skeletal muscle glycogen storage disorder in mice. *J Cachexia Sarcopenia Muscle*. 2022;13(1):467-480.
22. Sun Q, Gao Y, Qiao L, Yuan Y, Liu Q. 25(OH)-vitamin D alleviates neonatal infectious pneumonia via regulating TGFbeta-mediated nuclear translocation mechanism of YAP/TAZ. *Bioengineered*. 2021;12(1):8931-8942.
23. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet*. 2014;383(9912):146-155.
24. Küchler EC, Schröder A, Teodoro VB, et al. The role of 25-hydroxyvitamin-D3 and vitamin D receptor gene in human periodontal ligament fibroblasts as response to orthodontic compressive strain: an in vitro study. *BMC Oral Health*. 2021;21(1):386.
25. Becker AL, et al. The role of the vitamin D receptor in the pathogenesis, prognosis, and treatment of cutaneous melanoma. *Front Oncol*. 2021;11:743667.
26. Liu T, Chen S, Xie X, et al. Soluble TREM-1, as a new ligand for the membrane receptor Robo2, promotes hepatic stellate cells activation and liver fibrosis. *J Cell Mol Med*. 2021;25(24):11113-11127.
27. Backes FN, de Souza A, Bianchin MM. Biomarkers in the prognostic evaluation of ischemic stroke: is there benefit in the measurements of TREM-1 and TREM-2 in the acute phase? *Clin Biochem*. 2021;98:10-16.
28. Jiang J, Wang X, Cheng T, Han M, Wu X, Wan H. Dynamic monitoring of sTREM-1 and other biomarkers in acute cholangitis. *Mediators Inflamm*. 2020;2020:8203813.
29. Wright SW, Lovelace-Macon L, Hantrakun V, et al. sTREM-1 predicts mortality in hospitalized patients with infection in a tropical, middle-income country. *BMC Med*. 2020;18(1):159.
30. Qin Q, Liang L, Xia Y. Diagnostic and prognostic predictive values of circulating sTREM-1 in sepsis: a meta-analysis. *Infect Genet Evol*. 2021;96:105074.
31. Aldasoro Arguinano A-A, Dadé S, Stathopoulou M, et al. TREM-1 SNP rs2234246 regulates TREM-1 protein and mRNA levels and is associated with plasma levels of L-selectin. *PLoS One*. 2017;12(8):e0182226.

How to cite this article: Xiao L, Que S, Mu L, Zheng R. The relationship between *vitamin D receptor* gene and *TREM-1* gene polymorphisms and the susceptibility and prognosis of neonatal sepsis. *J Clin Lab Anal*. 2022;36:e24405. doi:10.1002/jcla.24405