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Association of SLCO1B1 genetic variants with neonatal hyperbilirubinemia: a consolidated analysis of 36 studies

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Abstract

Background This study aimed to assess the link between polymorphisms in the SLCO1B1 gene, responsible for the organic anion transporter polypeptide 1B1 (OATP1B1), and the risk of neonatal hyperbilirubinemia.

Methods A comprehensive literature review was performed utilizing PubMed, Web of Knowledge, and CNKI, culminating on December 1, 2023, focusing on studies published before this date. The search employed relevant keywords and MeSH terms related to hyperbilirubinemia and genetic factors. The inclusion criteria focused on original case-control, longitudinal, or cohort studies, with no restrictions on language or publication year. Correlations were quantified as odds ratios (ORs) with 95% confidence intervals (CIs) using Comprehensive Meta-Analysis software.

Results Thirty-six case-control studies drawn from 22 publications encompassed a total of 5,186 cases and 5,561 controls. Among these, 20 studies involved the rs2306283 polymorphism, with 2,602 cases and 2,832 controls, while 16 studies focused on rs4149056, including 2,584 cases and 2,729 controls. Sample sizes varied significantly, ranging from 41 to 447 cases and 47 to 544 controls. Pooled analysis indicated no significant associations for rs2306283 overall or within Asian and Caucasian subgroups; however, significant associations emerged within the Chinese subgroup under both the allele model (OR = 1.297, 95% CI 1.012–1.662, $p = 0.040$) and the dominant model (OR = 1.344, 95% CI 1.013–1.784, $p = 0.041$), suggesting a potential risk tied to the G allele. Conversely, the examination of rs4149056 revealed no significant associations across all comparisons, including ethnic subgroup analyses.

Conclusions The results imply that polymorphisms rs2306283 and rs4149056 in the SLCO1B1 gene are generally not associated with the risk of neonatal hyperbilirubinemia in overall population. Nevertheless, rs2306283 may pose an increased risk within the Chinese population, while rs4149056 shows no significant correlations across various groups. Further research is needed to clarify these implications and investigate other genetic factors related to neonatal hyperbilirubinemia.

Keywords Hyperbilirubinemia, Neonatal, Jaundice, Bilirubin, SLCO1B1, Polymorphism

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Introduction

Neonatal hyperbilirubinemia, commonly known as jaundice, is a prevalent condition affecting both premature and full-term infants, often leading to hospitalization within the first week of life [1, 2]. It is estimated that approximately 60% of term infants and about 80% of preterm infants experience jaundice, with the highest risk observed in infants born before 35 weeks gestation [1]. Severe neonatal jaundice (SNJ) presents a critical global health challenge, particularly in low- and lower-middle-income countries (LMICs) [3]. The prevalence of jaundice among hospitalized neonates in these regions ranges from 0.73–3.34%, with approximately 14.26% of jaundiced neonates classified as having SNJ. This highlights a substantial healthcare burden. Clinical complications associated with neonatal jaundice include bilirubin-induced neurologic dysfunction, kernicterus, and acute bilirubin encephalopathy (ABE). The necessity for exchange blood transfusions (EBT) can also arise in severe cases. Rates of EBT range between 0.74% and 3.81%, while ABE occurs with a frequency of 0.16–2.75% [4].

The diagnosis of neonatal hyperbilirubinemia primarily relies on a physical examination and the assessment of serum bilirubin levels, with jaundice becoming clinically evident when bilirubin levels exceed 85 $\mu\text{mol/dl}$ (5 mg/dl) [5]. Key indicators of pathological jaundice include early onset, elevated bilirubin levels, and significant clinical symptoms. The pathophysiology of hyperbilirubinemia stems from an imbalance between bilirubin production and elimination. While low bilirubin levels are generally considered harmless and may even confer antioxidant benefits, elevated levels pose serious risks, potentially leading to bilirubin encephalopathy and central nervous system complications [6, 7]. Treatment strategies for jaundice are determined by its severity and underlying cause. Common interventions include phototherapy, exchange transfusion in critical cases, and enhanced feeding techniques [8]. Prolonged unconjugated bilirubin levels that remain untreated can lead to bilirubin-induced neurologic dysfunction (BIND) and, in severe cases, may result in death from kernicterus. Jaundice generally resolves within a week in the absence of complications such as inadequate oral intake, hypoxia, fetal-maternal blood group incompatibility, infection, sepsis, or hepatic disorders [9–11].

Neonatal hyperbilirubinemia is affected by both genetic and environmental factors, with particular emphasis on specific mutations [12]. The UGT1A1 gene is pivotal, with polymorphisms such as UGT1A1*28 and UGT1A1*6 contributing to elevated bilirubin levels due to impaired conjugation. The G211 mutation is notably linked to severe hyperbilirubinemia, particularly when coupled with other risk factors [13]. Variants in the

SLCO1B1 gene, crucial for bilirubin uptake in the liver, can heighten hyperbilirubinemia risk, especially alongside UGT1A1 mutations, with a mutation at nucleotide 388 associated with increased unconjugated bilirubin levels [14]. Additionally, genetic variations linked to glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary spherocytosis may exacerbate severe hyperbilirubinemia by intensifying the effects of existing mutations [15]. A genome-wide association study by Solé-Navais et al. (2024), involving nearly 30,000 parent-offspring trios from Norway, identified genetic factors influencing bilirubin metabolism, including a common missense variant in the UGT1A4 gene that decreases jaundice susceptibility by five-fold, validated in diverse cohorts of African American and European neonates. Notably, expression quantitative trait locus (eQTL) analyses showed this genetic association primarily affects UGT1A1 regulation in intestinal tissues rather than in the liver, revealing significant differences in bilirubin metabolism between neonates and adults. The study also explored maternal-fetal ABO blood group incompatibility and its impact on neonatal jaundice, further highlighting the unique metabolic pathways in neonates [16].

Recent research underscores the vital role of transmembrane transporters, especially organic anion transporter proteins (OATPs), in bilirubin metabolism and drug-induced hepatitis [17]. OATPs, part of the solute carrier protein family SLCO, are expressed in various epithelial cells and primarily transport large, hydrophobic organic anions. Notably, organic anion transporter polypeptide 1B1 (OATP1B1) is crucial for the hepatic uptake of unconjugated bilirubin [18]. The SLCO1B1 gene (also known as SLC21A6, OATP-C, or OATP1B1), located on chromosome 12p12.2-p12.1, comprises 14 coding exons and one non-coding exon. It encodes a transporter predominantly found on hepatocyte basolateral membranes, facilitating the active transport of various anions [19, 20]. Initial characterization of SLCO1B1 gene polymorphisms by Tirona et al. in 2001 identified several variants that impact SLCO1B1 transport activity, with over 100 variants linked to regional and ethnic distribution. Two common polymorphisms, 521T>C and 388 A>G, create three haplotypes—SLCO1B1*5, *11, and *15—that reduce transport activity, resulting in elevated levels of substrates such as statins and bilirubin [21].

The only meta-analysis on this topic, conducted by Liu et al. in 2013, found that the 388 G>A polymorphism promotes neonatal hyperbilirubinemia, while the 521 T>C polymorphism has a protective effect [22]. Despite the emergence of several epidemiological studies since then, a consensus on these associations remains uncertain. For instance, a 2022 study by Atasılıp et al. found significant differences in the SLCO1B1 gene between hyperbilirubinemia cases and controls, suggesting that

the 521 T > C variant protects against the condition in the Thai population [23]. However, that same year, Boskabadi et al. reported no significant association between the 388 G > A and 521 T > C polymorphisms and hyperbilirubinemia among Iranian neonates [24]. Thus, this meta-analysis aims to investigate whether genetic polymorphisms in SLCO1B1 (rs2306283 and rs4149056) are linked to an increased risk of neonatal hyperbilirubinemia across various populations. By utilizing a larger and more diverse sample size, this meta-analysis seeks to enhance the generalizability of the findings compared to previous research. In addressing existing gaps in the literature and building upon earlier studies, this research aims to clarify the relationship between these genetic factors and the incidence of neonatal hyperbilirubinemia. If an association is confirmed, it could have significant clinical implications, improving our understanding of the genetic mechanisms involved and informing clinical practices and preventive strategies for managing this condition.

Materials and methods

Publication search

Ethical endorsement was not required for this study, as it is a bibliographic review and meta-analysis conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An extensive search was conducted across various online bibliographic databases, including MEDLINE, PubMed, PMC (PubMed Central), Elsevier, Google Scholar, Web of Science, Europe PMC, EMBASE, ResearchGate, Cochrane Library, SciELO, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data Company, Chaoxing, China/Asia On Demand (CAOD), Chinese Medical Citation Index (CMCI), Semantic Scholar, Chinese Biomedical Database (CBD), VIP Information Consultancy Company (VIP), MedRxiv, Chinese Medical Current Contents (CMCC), and Weipu Periodical Database, to identify all available studies evaluating the correlation between SLCO1B1 polymorphisms and the predisposition to neonatal hyperbilirubinemia. The search was limited to studies published from the establishment of these databases up to December 1, 2023. The search strategy utilized a combination of keywords and MeSH terms, including “Hyperbilirubinemia,” “Neonatal hyperbilirubinemia,” “Neonatal Jaundice,” “Jaundice in Newborns,” “neonatal icterus,” “Organic anion transporter polypeptide 1B1,” “SLCO1B1,” “OATP2,” “OATP1B1,” “OATP-C,” “Liver-Specific Transporter 1,” “SLC21A6,” “Gene,” “Polymorphism,” “DNA Sequence,” “Single-Nucleotide Polymorphism,” “SNPs,” “Genotype,” “Frequency,” “Mutation,” “Mutant,” “Allele,” “Variation,” “Variant,” “Genetic predisposition,” “Bilirubin metabolism,” and “Neonatal health.” No restrictions were placed on language or publication year. To enhance the search, references from pertinent reviews and suitable

publications were manually examined for additional studies. Non-English articles were included, following a defined translation process and specific criteria to assess their quality.

Including and excluding criteria

All included studies met specific criteria: they were original surveys with a case-control, longitudinal, or cohort design; they focused on the correlation between polymorphisms in the SLCO1B1 gene and the risk of neonatal hyperbilirubinemia; and they provided sufficient and accessible data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Studies were excluded based on several factors: the absence of a control group; inclusion of animal experiments, in vitro cell studies, oral presentations, case series, commentaries, letters, editorials, reviews, and previous meta-analyses; incomplete literature data or inability to obtain the original text after contacting the author; insufficient data for analysis; and the existence of overlapping or duplicated data from the same population.

Data extraction

Two investigators independently reviewed titles, abstracts, and search terms for eligibility based on predetermined inclusion and exclusion criteria. Any disagreements were resolved through discussion or by involving a third researcher, and when necessary, the original authors were contacted via email. During the literature screening, the initial focus was on titles and abstracts to eliminate obviously irrelevant studies, followed by a thorough reading of full texts to determine final inclusion. Key data from eligible literature included the first author's name, ethnicity (specifically categorized as Asian, Caucasian, African, Hispanic, and Mixed), publication date, genotyping methods, country of origin, total hyperbilirubinemia cases and controls, genotype frequencies for neonatal hyperbilirubinemia cases and healthy controls related to SLCO1B1 polymorphisms, Hardy-Weinberg equilibrium (HWE) test results, and minor allele frequencies (MAFs) in healthy controls. For studies by the same authors, the most recent publication or the one with the largest sample size was chosen for inclusion.

Quality score assessment

The Newcastle-Ottawa Score (NOS) was utilized to assess study quality in a meta-analysis and evaluate the methodological aspects of observational research. It focused on case selection, group comparability, and exposure determination, each with eight specific criteria. Studies with excellent selection and exposure received one star, while comparability could earn up to two stars. Quality was rated on a nine-star scale, where zero indicated poor quality and nine signified high quality. Studies scoring

seven or more were deemed high quality, and those with at least five points were suitable for meta-analysis.

Statistical analysis

The Pearson's chi-square statistic was employed to assess HWE among control subjects in each study, utilizing free online software, with a significance threshold set at a p-value of less than 0.05. The relationship between SLCO1B1 polymorphisms and the risk of neonatal hyperbilirubinemia was quantified using ORs accompanied by 95% CIs. The probability value for the aggregated data was determined through the Z-test to evaluate the difference between the population mean and the sample mean. This meta-analysis incorporated five genetic models: allelic (M vs. W), heterozygote (MW vs. WW), homozygote (MM vs. WW), recessive (MM vs. MW + WW), and dominant (MM + MW vs. WW), where "M" represents the mutant allele and "W" signifies the wild-type allele. To assess heterogeneity within the meta-analysis, various statistical measures were utilized, including the Q-value, degrees of freedom (df), I-squared (I^2), and Tau-squared (τ^2). The Q-value tests the null hypothesis that all studies share a common effect size, with a higher Q-value relative to its degrees of freedom indicating increased heterogeneity [25]. Degrees of freedom, calculated by subtracting one from the total number of studies, are essential for interpreting the Q-value. The I-squared statistic indicates the percentage of total variation across studies attributed to heterogeneity rather than random chance, with thresholds for low heterogeneity marked at 0–25%, moderate at 26–50%, and high at greater than 50%. Tau-squared estimates the variance between studies, reflecting differences in effect sizes due to inherent variability rather than random sampling errors. These metrics collectively provide a thorough assessment of heterogeneity in the meta-analysis. The chi-square test served as the primary method for evaluating heterogeneity, with a significance level set at $p < 0.05$ [26]. Following Cochrane guidelines, heterogeneity between studies was quantified on a scale of 0 to 100%, and the I^2 index measured the proportion of total variation attributable to study differences. Random-effect models (DerSimonian-Laird method) were applied when I^2 exceeded 50%; otherwise, fixed-effect models (Mantel-Haenszel method) were utilized [27, 28]. Sensitivity analysis involved systematically excluding one study at a time to test the robustness of the findings. Publication bias was assessed using Begg's test, which plotted the standard error of each study against its OR, alongside Egger's test and visual inspection of the funnel plot for asymmetry. If publication bias was identified, the trim-and-fill method was employed to adjust the results. Data synthesis from the primary studies was conducted using Comprehensive Meta-Analysis (Version 4.0) software

(Biostat, USA), with a two-sided p-value of less than 0.05 considered statistically significant.

Results

Characteristics of selected studies

Figure 1 illustrates the process of a systematic literature search, in which a total of 591 articles related to SLCO1B1 polymorphisms and neonatal hyperbilirubinemia were initially identified. Following a review of titles and abstracts, 324 articles were subsequently excluded from consideration. This resulted in 267 full texts being reviewed, from which 119 studies were excluded based on predefined criteria, ultimately identifying 36 suitable case-control studies in 22 publications [19, 23, 24, 29–46] encompassing 5,186 cases and 5,561 controls. Among these, 20 studies focused on the rs2306283 polymorphism, involving 2,602 cases and 2,832 controls, while 16 studies on the rs4149056 polymorphism included 2,584 cases and 2,729 controls. Table 1 presents the characteristics of the selected studies. Sample sizes varied, with cases ranging from 41 to 447 and controls from 47 to 544. The studies, published between 2004 and 2023, comprised 14 studies on the rs2306283 polymorphism from Asian neonates, two from Caucasian neonates, and one from a mixed Latin American population. For the rs4149056 polymorphism, 10 studies were based on Asian neonates, while one study included both Caucasian and mixed populations. The meta-analysis included diverse ethnic groups, predominantly Asian populations from countries such as China, Taiwan, Malaysia, Thailand, Iran, and India, as well as Caucasian groups from the USA and Turkey, and a mixed ethnic group from Brazil. Various genotyping methods were used, including PCR-RFLP, TaqMan, HRM, sequencing, and MLPA-NGS. Table 1 provides detailed genotype and MAF information for both polymorphisms, showing that genotype distributions in healthy subjects mostly adhere to HWE, with exceptions in four studies for each polymorphism.

Quality of the studies

The quality of studies in the meta-analysis was assessed using the Newcastle-Ottawa Scale (NOS), which rates selection, comparability, and outcomes on a scale of 5 to 9. Analysis included 30 studies from Asia, Europe, and North America, enhancing the generalizability of the results. Although genotyping methods introduced some variability, they provided a comprehensive approach. Several studies received high-quality scores (8 or 9), while others, scoring 6 or 7, indicated moderate quality that may need further scrutiny, particularly in control selection and case representativeness. Studies scoring 5 showed significant room for improvement, especially in participant selection and outcome reporting. Statistical



PRISMA 2009 Flow Diagram

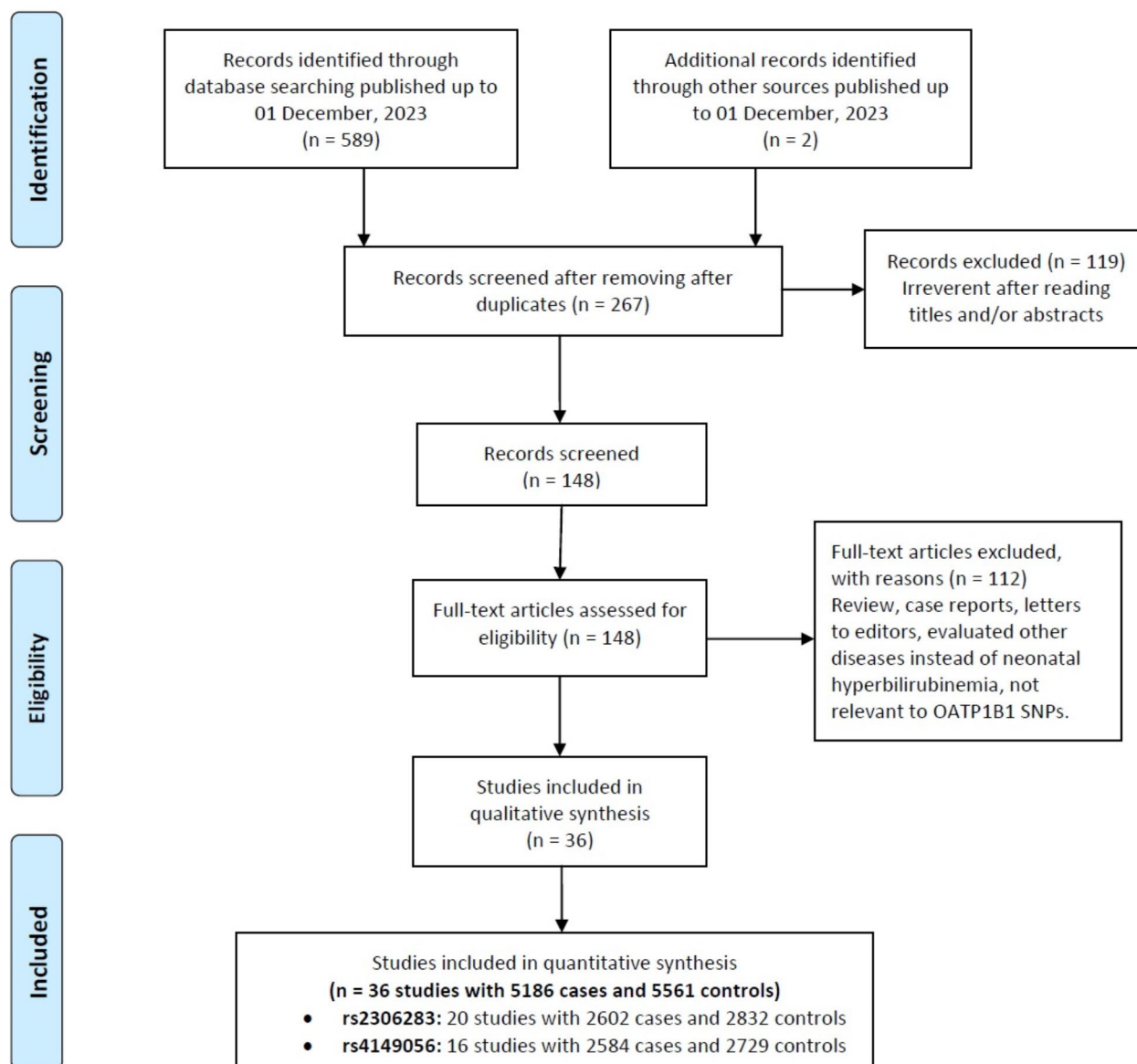


Fig. 1 Study selection and inclusion process

considerations included HWE, with notable deviations in some studies possibly reflecting sample representativeness issues. MAFs varied widely, with D'Silva 2014 reporting a high MAF of 0.696, suggesting significant polymorphisms in the populations studied. Consistency in MAF across populations can bolster findings, but limitations like small sample sizes and variations in genotype distribution may affect generalizability. Overall, most studies scored 6 or higher on the NOS, though lower

scores and deviations from HWE should be carefully considered when interpreting the meta-analysis results.

Hardy-Weinberg equilibrium

The HWE assessment sheds light on genetic variation and population structure. P-values reported in some studies indicate how allele frequencies align with expected ratios under assumptions of random mating, no selection, and large population size. A p-value above 0.05 typically

Table 1 Characteristics of studies included in this meta-analysis

First author/year	Country (ethnicity)	Genotyping methods	Case/Control	Cases				Controls				MAFs	HWE	NOS		
				Genotypes		Allele		Genotypes		Allele						
				GG	GA	AA	G	A	GG	GA	AA				G	A
rs2306283																
Huang 2004	Taiwan(Asian)	PCR-RFLP	58/75	31	20	7	82	34	53	16	6	122	28	0.187	0.010	6
Tian 2007	China(Asian)	PCR-RFLP	96/101	56	29	11	141	51	75	21	5	171	31	0.153	0.044	7
Wong 2009	Malaysia(Asian)	HRM	65/110	38	19	8	95	35	55	47	8	157	63	0.286	0.634	5
Prachukthum 2009	Thailand(Asian)	PCR-RFLP	91/86	59	28	4	146	36	47	36	3	130	42	0.270	0.799	8
Watchko 2009	USA(Caucasian)	PCR-RFLP	153/298	118	33	2	269	37	228	65	5	521	75	0.126	0.882	7
Zhang 2010	China(Asian)	PCR-RFLP	220/200	127	75	18	329	111	102	77	21	281	119	0.298	0.264	8
Buyukkale 2011	Turkey(Caucasian)	PCR-RFLP	102/53	30	56	16	116	88	17	24	12	58	48	0.453	0.530	6
Jiang 2012	China(Asian)	Sequencing	163/63	95	52	16	242	84	53	8	2	114	12	0.095	0.036	5
de Azevedo 2012	Brazil(Mixed)	TaqMan	157/237	42	78	37	162	152	58	123	56	239	235	0.496	0.558	7
Liu 2013	China(Asian)	PCR-RFLP	183/192	107	59	17	273	93	139	43	10	321	63	0.164	0.011	6
D'Silva 2014	India(Asian)	PCR-RFLP	126/181	25	73	28	123	129	15	80	86	110	252	0.696	0.547	7
Yang 2015	China(Asian)	HRM	129/108	71	41	17	183	75	66	35	7	167	49	0.227	0.428	8
Lu 2015	China(Asian)	PCR-RFLP	121/87	73	39	9	185	57	56	25	6	137	37	0.213	0.185	6
Weng 2016	Taiwan(Asian)	PCR-RFLP	100/344	72	28	0	172	28	234	110	0	578	110	0.160	≤0.001	5
Zhou 2018	China(Asian)	Sequencing	286/250	159	112	15	430	142	146	84	20	376	124	0.248	0.116	9
Qizhi 2018	China(Asian)	Sequencing	279/178	177	81	21	435	123	109	61	8	279	77	0.216	0.884	8
Amandito 2019	Indonesia(Asian)	PCR-RFLP	41/47	26	12	3	64	18	34	11	2	79	15	0.160	0.382	5
Atasilp 2022	Thailand(Asian)	TaqMan	67/70	45	21	1	111	23	39	27	4	105	35	0.250	0.811	6
Boskabadi 2022	Iran(Asian)	PCR-RFLP	100/100	8	55	37	71	129	12	56	32	80	120	0.600	0.095	7
Yin 2022	China(Asian)	MLPA-NGS	65/52	28	33	4	89	41	27	19	6	73	31	0.298	0.360	8
rs4149056																
Huang 2004	Taiwan(Asian)	PCR-RFLP	42/73	31	9	2	71	13	53	19	1	125	21	0.144	0.627	6
Wong 2009	Malaysia(Asian)	HRM	65/110	47	18	0	112	18	81	29	0	191	29	0.132	0.111	5
Watchko 2009	USA(Caucasian)	PCR-RFLP	153/298	58	69	26	185	121	135	117	46	387	209	0.351	0.017	7
Zhang 2010	China(Asian)	PCR-RFLP	220/200	185	34	1	404	36	147	50	3	344	56	0.140	0.588	8
de Azevedo 2012	Brazil(Mixed)	TaqMan	157/237	122	34	1	278	36	179	55	3	413	61	0.129	0.592	6
Liu 2013	China(Asian)	PCR-RFLP	183/192	137	35	11	309	57	141	42	9	324	60	0.156	0.018	7
D'Silva 2014	India(Asian)	PCR-RFLP	126/181	95	29	2	219	33	178	3	0	359	3	0.008	0.910	8
Yang 2015	China(Asian)	HRM	129/107	98	29	2	225	33	76	23	8	175	39	0.182	0.003	6
Lu 2015	China(Asian)	PCR-RFLP	121/87	91	30	0	212	30	63	23	1	149	25	0.144	0.487	9
Zhou 2018	China(Asian)	Sequencing	286/250	230	34	22	494	78	211	26	13	448	52	0.104	≤0.001	8
Qizhi 2018	China(Asian)	Sequencing	279/178	227	51	1	505	53	152	25	1	329	27	0.076	0.979	7
Li 2019	China(Asian)	Sequencing	447/544	285	106	56	676	218	398	140	6	936	152	0.140	0.099	8
Atasilp 2022	Thailand(Asian)	TaqMan	67/70	57	9	1	123	11	48	20	2	116	24	0.171	0.961	5
Boskabadi 2022	Iran(Asian)	PCR-RFLP	100/100	80	16	4	176	24	75	24	1	174	26	0.130	0.541	6

rs4149056

rs4149056	TT	TC	CC	T	C	TT	TC	CC	T	C
China(Asian)	65/52	17	0	113	17	41	11	0	93	11
China(Asian)	144/50	118	25	261	27	41	9	0	91	9

Abbreviations: PCR-RFLP - Restriction Fragment Length Polymorphism; MLPA-NGS - Multiplex Ligation-dependent Probe Amplification Next Generation Sequencing; HWE - Hardy-Weinberg equilibrium; MAF - Minor Allele Frequency; NOS - Newcastle-Ottawa Scale

rs2306283: The comprehensive analysis revealed no significant associations, with ORs ranging from 1.056 to 1.109 and p-values exceeding 0.05. Within the Asian subgroup, ORs ranged from 1.111 to 1.173 (p-values: 0.254 to 0.469), indicating a lack of statistical significance. The Caucasian subgroup similarly exhibited no significant associations, with ORs consistently below 1.0, suggesting a potential protective effect. In contrast, the Chinese subgroup demonstrated significant associations particularly in the G vs. A model (OR: 1.297; 95% CI: 1.012–1.662; $P=0.040$) and in the GG + GA vs. AA model (OR: 1.344; 95% CI: 1.013–1.784; $P=0.041$). The comparison of GA vs. AA approached significance (OR: 1.296; $P=0.066$), pointing toward a possible risk connected to the G allele among Chinese neonates. Figure 2 shows forest plots illustrating the correlation between the SLCO1B1 rs2306283 polymorphism and hyperbilirubinemia risk. Results are presented for the overall population (Fig. 2A and B) and specifically for Chinese neonates (Fig. 2C and D), using both Allele and Dominant models. These findings underscore the differential associations of SLCO1B1

Table 2 Risk estimates for the association of SLCO1B1 polymorphisms with neonatal hyperbilirubinemia in the overall population and by subgroups

Subgroup	Genetic model*	Type of model	Heterogeneity			Tau-squared			Odds ratio			Publication bias					
			Q-value	df	I ² (%)	P _H	τ ²	SD	Variance	Tau	OR	95% CI	Z _{test}	P _{OR}	P _{Begg}	P _{Eggers}	
rs2306283 Overall	G vs. A	Random	66.01	19	71.21	≤0.001	0.110	0.053	0.003	0.331	1.074	0.900–1.281	0.791	0.429	0.284	0.116	
	GG vs. AA	Random	40.80	18	55.88	0.002	0.314	0.199	0.040	0.561	1.109	0.778–1.579	0.572	0.567	0.726	0.308	
	GA vs. AA	Random	38.40	19	50.52	0.005	0.087	0.058	0.003	0.295	1.080	0.895–1.304	0.804	0.422	0.229	0.261	
	GG+GA vs. AA	Random	49.48	19	61.60	≤0.001	0.122	0.068	0.005	0.349	1.093	0.893–1.336	0.862	0.389	0.205	0.415	
	GG vs. GA + AA	Random	39.92	18	54.91	0.002	0.233	0.155	0.024	0.483	1.056	0.771–1.446	0.341	0.733	0.888	0.157	
	G vs. A	Random	65.41	16	75.04	≤0.001	0.144	0.072	0.005	0.379	1.119	0.908–1.378	1.057	0.291	0.201	0.097	
Asians	GG vs. AA	Random	40.01	15	62.65	≤0.001	0.445	0.276	0.076	0.667	1.173	0.762–1.808	0.725	0.469	0.821	0.339	
	GA vs. AA	Random	37.39	16	53.67	0.005	0.117	0.076	0.006	0.341	1.124	0.911–1.387	1.094	0.274	0.303	0.265	
	GG+GA vs. AA	Random	48.59	16	65.27	≤0.001	0.158	0.089	0.008	0.397	1.142	0.909–1.435	1.140	0.254	0.232	0.389	
	GG vs. GA + AA	Random	38.93	15	61.40	0.001	0.336	0.219	0.048	0.579	1.111	0.756–1.633	0.536	0.592	0.964	0.131	
	G vs. A	Fixed	0.017	1	0.00	0.898	0.00	0.074	0.005	0.00	0.938	0.685–1.284	-0.399	0.690	NA	NA	
	GG vs. AA	Fixed	0.001	1	0.00	0.981	0.00	0.672	0.452	0.00	0.760	0.332–1.739	-0.650	0.516	NA	NA	
Caucasians	GA vs. AA	Fixed	0.424	1	0.00	0.515	0.00	0.149	0.022	0.00	1.066	0.713–1.595	0.311	0.756	NA	NA	
	GG+GA vs. AA	Fixed	0.134	1	0.00	0.714	0.00	0.134	0.018	0.00	1.013	0.686–1.494	0.063	0.950	NA	NA	
	GG vs. GA + AA	Fixed	0.045	1	0.00	0.833	0.00	0.631	0.398	0.00	0.662	0.314–1.396	-1.084	0.278	NA	NA	
	G vs. A	Random	27.71	8	71.13	0.001	0.098	0.073	0.005	0.312	1.297	1.012–1.662	2.056	0.040	0.076	0.039	
	GG vs. AA	Fixed	15.32	8	47.79	0.053	0.205	0.219	0.048	0.453	1.275	0.941–1.730	1.566	0.117	0.117	0.148	
	GA vs. AA	Random	19.83	8	59.66	0.011	0.101	0.088	0.008	0.318	1.296	0.983–1.709	1.836	0.066	0.117	0.056	
Chinese	GG+GA vs. AA	Random	23.88	8	66.50	0.002	0.119	0.094	0.009	0.345	1.344	1.013–1.784	2.046	0.041	0.047	0.049	
	GG vs. GA + AA	Fixed	13.73	8	41.75	0.089	0.154	0.188	0.035	0.393	1.271	0.848–1.907	1.161	0.246	0.175	0.239	
	rs4149056 Overall	C vs. T	Random	68.74	15	78.18	≤0.001	0.200	0.112	0.013	0.447	1.088	0.838–1.413	0.635	0.525	0.964	0.327
		CC vs. TT	Random	39.28	13	66.09	≤0.001	0.905	0.698	0.487	0.951	1.323	0.656–2.671	0.782	0.434	1.000	0.411
		CT vs. TT	Random	39.72	15	62.24	≤0.001	0.139	0.089	0.008	0.373	1.013	0.795–1.291	0.107	0.915	0.725	0.632
		CC+CT vs. TT	Random	50.07	15	70.04	≤0.001	0.175	0.103	0.011	0.419	1.062	0.821–1.373	0.455	0.649	0.620	0.673
CC vs. CT + TT		Random	39.67	13	67.23	≤0.001	0.880	0.688	0.473	0.938	1.320	0.659–2.645	0.783	0.434	0.661	0.559	
C vs. T		Random	66.76	13	79.03	≤0.001	0.265	0.157	0.025	0.515	1.108	0.840–1.461	1.461	0.470	1.000	0.351	
Asians	CC vs. TT	Random	36.88	11	68.53	≤0.001	1.382	1.088	1.183	1.175	1.402	0.676–2.907	0.909	0.363	0.854	0.505	
	CT vs. TT	Random	37.35	13	64.60	≤0.001	0.173	0.116	0.013	0.416	1.025	0.788–1.333	0.185	0.853	0.692	0.654	
	CC+CT vs. TT	Random	48.22	13	71.51	≤0.001	0.222	0.138	0.019	0.472	1.078	0.819–1.421	0.537	0.591	0.692	0.676	
	CC vs. CT + TT	Random	35.88	11	68.97	≤0.001	1.318	1.046	1.093	1.148	1.396	0.678–2.875	0.905	0.366	0.760	0.660	
	C vs. T	Random	38.71	8	79.33	≤0.001	0.190	0.138	0.019	0.436	1.051	0.754–1.464	0.293	0.770	0.465	0.062	
	CC vs. TT	Random	33.79	7	79.28	≤0.001	1.701	1.474	2.174	1.304	1.051	0.344–3.214	0.087	0.931	0.901	0.217	
Chinese	CT vs. TT	Fixed	8.88	8	9.99	0.352	0.008	0.041	0.002	0.090	0.978	0.825–1.159	-0.262	0.794	0.754	0.978	

Table 2 (continued)

Subgroup	Genetic model*	Type of model	Heterogeneity			Tau-squared			Odds ratio			Publication bias				
			Q-value	df	I ² (%)	P _H	τ ²	SD	Variance	Tau	OR	95% CI	Z _{test}	P _{OR}	P _{Beggs}	P _{Eggers}
		CC +CT vs. TT	19,16	8	58,25	0,014	0,089	0,082	0,007	0,299	1,034	0,792–1,349	0,243	0,808	0,602	0,192
		CC vs. CT + TT	33,32	7	78,99	≤0,001	1,656	1,440	2,073	1,287	1,067	0,353–3,226	0,115	0,909	1,000	0,223

Abbreviations: NA - Not Applicable; τ² - Tau-Squared; OR - Odds Ratio; df - Degrees of Freedom; PH - P-value of Heterogeneity; SD - Standard Deviation; 95% CI - 95% Confidence Interval; P_{Begg} - P-value of Begg's test for heterogeneity; P_{Eggers} - P-value of Egger's test

*This table presents a comparison of genetic models, encompassing various models such as allele, homozygote, heterozygote, dominant, and recessive

polymorphisms with the risk of neonatal hyperbilirubinemia across ethnic populations, with significant results primarily identified in the Chinese cohort.

rs4149056: The overall analysis yielded an OR of 1.088 (95% CI: 0.838–1.413; *p* = 0.525) for the C allele compared to the T allele, indicating no significant association. Additional comparisons—including CC vs. TT, CT vs. TT, CC + CT vs. TT, and CC vs. CT + TT—produced ORs of 1.323, 1.013, 1.062, and 1.320, respectively, all demonstrating a lack of statistical significance (*p* > 0.05). Analyses of ethnic subgroups reflected these findings; for example, the Asian subgroup reported an OR of 1.108 (95% CI: 0.840–1.461; *p* = 0.470) for C vs. T, and an OR of 1.402 (95% CI: 0.676–2.907; *p* = 0.363) for CC vs. TT. In the Chinese subgroup, the C vs. T comparison resulted in an OR of 1.051 (95% CI: 0.754–1.464; *p* = 0.770), further supporting the overall conclusion. Additional models, including CC vs. TT and CT vs. TT, corroborated the absence of significant associations. Overall, the findings suggest no significant association between SLCO1B1 polymorphisms and neonatal hyperbilirubinemia in the overall population or within Asian and Chinese subgroups.

Heterogeneity test

The heterogeneity analysis results for studies on SLCO1B1 polymorphisms and neonatal hyperbilirubinemia risk show significant variability across genetic comparisons, as presented in Table 2. For the polymorphism rs2306283, the overall analysis shows substantial heterogeneity with a Q-value of 66.01 (df = 19, I² = 71.21, PH ≤ 0.001). The tau-squared value is 0.110 with a standard deviation of 0.053, indicating a moderate level of inconsistency among the studies. Specific comparisons, such as GG vs. AA, also demonstrate notable heterogeneity (Q = 40.80, df = 18, I² = 55.88, PH = 0.002), while GA vs. AA shows moderate heterogeneity (Q = 38.40, df = 19, I² = 50.52, PH = 0.005). The analyses for ethnic subgroups, including Asian and Caucasian populations, exhibit varying levels of heterogeneity. In the Asian subgroup for rs2306283, results show high heterogeneity (G vs. A: Q = 65.41, I² = 75.04, PH ≤ 0.001) compared to the Caucasian group, which reveals minimal heterogeneity (G vs. A: Q = 0.017, I² = 0.00, PH = 0.898). The Chinese subgroup also indicates significant heterogeneity, particularly for G vs. A (Q = 27.71, I² = 71.13, PH = 0.001). For the second polymorphism rs4149056, similar patterns of heterogeneity were observed across genetic comparisons. The overall heterogeneity level was high, indicated by a Q-value of 68.74 (df = 15, I² = 78.18, PH ≤ 0.001). Different comparisons such as CC vs. TT (Q = 39.28, I² = 66.09, PH ≤ 0.001) reflect substantial variability, with CC vs. CT + TT showing consistent heterogeneity (Q = 39.67, I² = 67.23, PH ≤ 0.001). In the Asian subgroup for

C

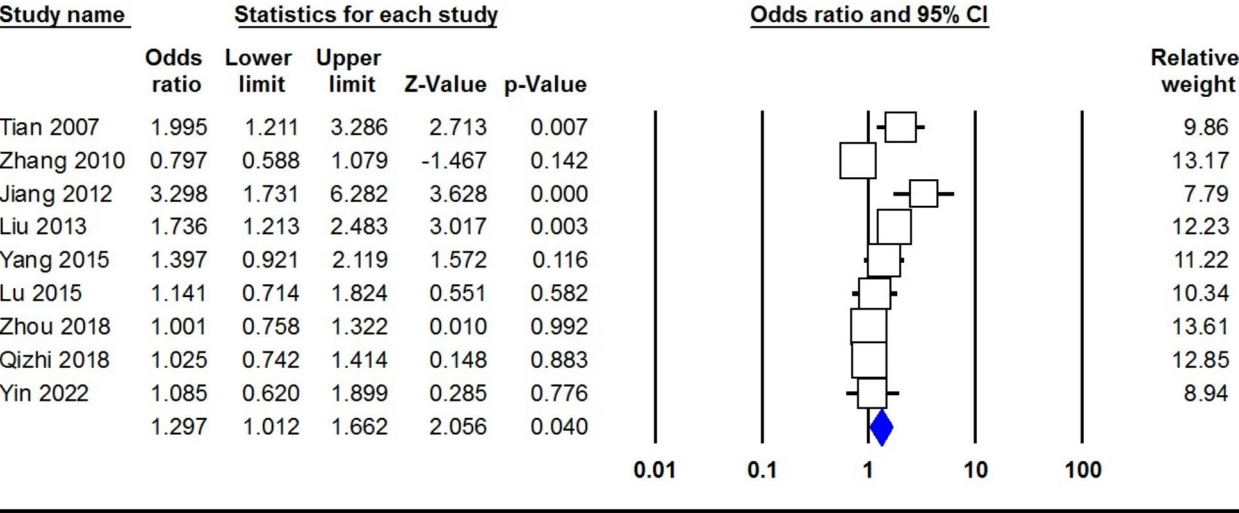


Fig. 2 Forest plots illustrating the correlation between the SLCO1B1 rs2306283 polymorphism and hyperbilirubinemia risk in the overall population (**A** and **B**) and in Chinese neonates (**C** and **D**) under Allele and dominant models

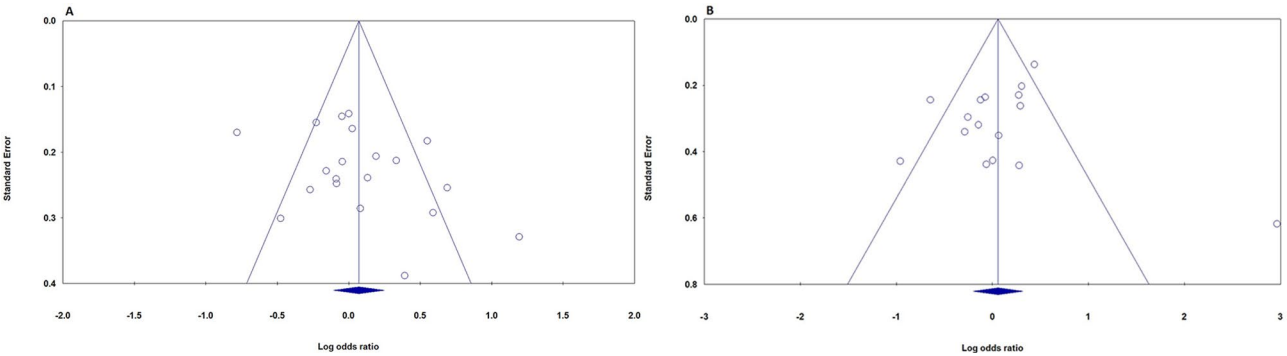


Fig. 3 Begg's funnel plots assessing publication bias for SLCO1B1 polymorphisms and hyperbilirubinemia risk in neonates: (**A**) rs2306283 (allele model: G vs. A); (**B**) rs4149056 (dominant model: CC + CT vs. TT)

rs4149056, heterogeneity remained high across comparisons, with Q-values and I^2 percentages confirming significant inconsistency. For the Chinese subgroup, the C vs. T comparison demonstrated less variability ($Q=38.71$, $I^2=79.33$, $PH\leq0.001$), but other comparisons revealed extreme heterogeneity, notably CC vs. TT ($Q=33.79$, $I^2=79.28$, $PH\leq0.001$). Overall, these results suggest that the association of SLCO1B1 polymorphisms with neonatal hyperbilirubinemia risk is influenced by considerable heterogeneity across different studies and ethnic groups, indicating the need for cautious interpretation of findings in this field.

Publication bias

The evaluation of publication bias associated with SLCO1B1 polymorphisms and their relationship to neonatal hyperbilirubinemia risk included several statistical tests, specifically Begg's and Egger's tests (Table 2). For

the rs2306283 polymorphism, the overall analysis indicated no significant publication bias, with p-values from Begg's test ranging from 0.205 to 0.888 and Egger's test ranging from 0.116 to 0.415 across various genetic comparisons. Subgroup analyses showed similarly low likelihoods of bias in the Asian subgroup, while the Caucasian subgroup lacked sufficient data for assessment. The Chinese subgroup exhibited some variability, with indications of potential bias in the G vs. A (Begg's $p=0.076$; Egger's $p=0.039$) and GG vs. GA + AA models (Begg's $p=0.175$; Egger's $p=0.239$). In the case of the rs4149056 polymorphism, no significant publication bias was identified in the overall analysis, with p-values consistently above 0.05. Ethnic subgroup evaluations for rs4149056 showed that the Asian cohort displayed no significant bias, while the Chinese subgroup also supported this lack of evidence for bias. Figure 3 illustrates Begg's funnel plots, which were utilized to assess publication bias

for SLCO1B1 polymorphisms and their association with hyperbilirubinemia risk in neonates, specifically focusing on rs2306283 in the allele model (G vs. A) and rs4149056 in the dominant model (CC+CT vs. TT). Overall, the analyses suggest a generally unbiased association between SLCO1B1 polymorphisms and neonatal hyperbilirubinemia risk, although caution is advised when interpreting results in specific ethnic groups.

Sensitivity analysis

A sensitivity analysis was conducted to evaluate the association of SLCO1B1 polymorphisms with the risk of neonatal hyperbilirubinemia. The analysis assessed how the reported OR varied with the exclusion of specific studies or data points. For the rs2306283 polymorphism, the overall random model OR was found to be 1.074, accompanied by a 95% confidence interval (CI) of 0.900–1.281, suggesting a mild risk, though significant heterogeneity was observed ($I^2 = 71.21\%$). Excluding studies with high heterogeneity, which were identified by their wide CIs or small sample sizes, may result in an increased OR, reflecting more consistent findings across the studies. Similarly, for the rs4149056 polymorphism, the overall random model OR was 1.088, with a 95% CI of 0.838–1.413, and exhibited even greater heterogeneity ($I^2 = 78.18\%$). The sensitivity analysis also took into account the removal of studies that did not conform to HWE or those potentially prone to bias. By systematically assessing how the exclusion of individual studies influenced the combined effect estimate, the robustness of the association was evaluated. A significant change in the OR—either an increase or decrease—while still maintaining statistical significance would suggest that certain studies exert a strong influence on the observed association, underscoring the importance of careful interpretation of these polymorphisms in relation to predicting hyperbilirubinemia risk.

Discussion

Neonatal hyperbilirubinemia, characterized by high bilirubin levels in newborns, is significantly affected by genetic variants in the SLCO1B1 gene, which is essential for bilirubin and drug uptake in the liver [19, 23]. Specific SNPs in SLCO1B1, such as 388 A>G (rs2306283), have been associated with reduced bilirubin uptake and increased levels. Conversely, 521T>C (rs4149056) might confer a protective effect against hyperbilirubinemia in certain populations, including Thai neonates [22]. Variants that impair the OATP1B1 transport function lead to decreased hepatic bilirubin clearance, resulting in higher blood levels. The prevalence and impact of these genetic variants can vary among ethnic groups, contributing to a higher incidence of neonatal jaundice in Asians compared to Caucasians [19]. Understanding these genetic factors is crucial for risk assessment, early intervention, and

advancing personalized medicine through genetic testing for treatment decisions. While studies suggest that rs2306283 and rs4149056 polymorphisms significantly influence serum bilirubin levels, the role of rs4149056 in reducing SLCO1B1 transport activity is debated [16, 47]. The involvement of these polymorphisms in neonatal hyperbilirubinemia remains controversial. Consequently, we conducted a meta-analysis to evaluate the relationship between SLCO1B1 rs2306283 and rs4149056 polymorphisms and the risk of neonatal hyperbilirubinemia across various populations and ethnicities.

The SLCO1B1 rs2306283 variant is a missense mutation in exon 4 that leads to an Asn130Asp amino acid substitution, impairing the transporter's ability to transfer bilirubin from blood to the liver, potentially resulting in elevated bilirubin levels and hyperbilirubinemia in neonates [19]. This variant also has significant pharmacogenomic implications for statin metabolism, where the G allele might influence drug pharmacokinetics, necessitating dosage adjustments to avoid adverse effects [48, 49]. Population-specific allele frequencies are notable, with about 0.38 G allele frequency reported in Jordanian patients, emphasizing the significance of personalized medicine in optimizing statin therapy through genotyping [50]. Our meta-analysis of 20 studies involving 2,602 cases and 2,832 controls found no significant association between the SLCO1B1 rs2306283 variant and the risk of neonatal hyperbilirubinemia in general or specifically among Asian and Caucasian neonates. However, a significant association was identified in Chinese neonates under both the allele model (G vs. A: OR=1.297, 95% CI 1.012–1.662, $p=0.040$) and the dominant model (GG+GA vs. AA: OR=1.344, 95% CI 1.013–1.784, $p=0.041$). A 2013 meta-analysis by Liu et al. also found that SLCO1B1 rs2306283 is associated with a higher likelihood of neonatal hyperbilirubinemia in Chinese neonates, but not in Brazilian, white, Thai, or Malaysian neonates [22]. While some studies indicate that infants with the A allele may generally have higher bilirubin levels compared to those homozygous for the G allele, other research suggests that the GG genotype may be more prevalent in hyperbilirubinemic infants, raising questions about the relationship between the A allele, bilirubin levels, and hyperbilirubinemia risk [14, 30]. Moreover, research from various populations, including Indonesian neonates, has reported no significant association between this variant and bilirubin levels, indicating that environmental factors and other genetic variations, such as UGT1A1 polymorphisms related to bilirubin metabolism, may influence the effect of the rs2306283 variant [19, 23].

The SLCO1B1 rs4149056 polymorphism, located in exon 5, is a functional variant that regulates the uptake of various drugs and natural compounds [51, 52]. Several

studies have investigated the role of this variant in the occurrence of neonatal hyperbilirubinemia. In 2010, Zhang et al. reported that the homozygous normal genotype for rs4149056 was more prevalent among Chinese neonates with hyperbilirubinemia compared to healthy subjects, suggesting that SLCO1B1 rs4149056 is an important genetic variant associated with neonatal hyperbilirubinemia [53]. In 2014, D'Silva et al. found that SLCO1B1 rs4149056 is correlated with bilirubin metabolism and may contribute genetically to neonatal hyperbilirubinemia [31]. However, studies by Liu et al., [30] and de Azevedo et al., [29] indicated that SLCO1B1 rs4149056 was not associated with an increased risk of neonatal hyperbilirubinemia in Chinese and Brazilian neonates, respectively. To further explore this association, we analyzed data from 16 studies involving 2,584 cases and 2,729 controls. Our findings showed no correlation between the SLCO1B1 rs4149056 polymorphism and hyperbilirubinemia in both the overall population and specifically among Chinese neonates. Liu et al. conducted a meta-analysis of five studies with 637 neonates with hyperbilirubinemia and 918 controls, which also revealed no statistically significant correlation between the polymorphism and neonatal hyperbilirubinemia in the overall population. They did report a low risk of hyperbilirubinemia associated with the SLCO1B1 rs4149056 polymorphism in Chinese neonates, but not in Brazilian, white, Asian, Thai, or Malaysian neonates [22]. However, their analysis was based on studies with moderately small sample sizes, which may have affected the robustness of their conclusions. In contrast, our current meta-analysis, which includes data from 12 studies, indicates no significant correlation between the SLCO1B1 rs4149056 variant and an elevated risk of neonatal hyperbilirubinemia in the overall population or by ethnicity, including among Chinese neonates.

Heterogeneity of SLCO1B1 polymorphisms and their association with neonatal hyperbilirubinemia risk

The investigation into the heterogeneity of SLCO1B1 polymorphisms and their association with neonatal hyperbilirubinemia reveals a complex relationship influenced by genetic variability and population diversity. Notably, the substantial variability in study results, especially regarding polymorphism rs2306283, highlights the challenges in reaching definitive conclusions across different studies. The observed Q -values and I^2 statistics indicate a high level of inconsistency, suggesting that factors beyond random chance contribute to the variations in reported associations. Heterogeneity is particularly evident in specific genetic comparisons, such as GG vs. AA and GA vs. AA, pointing to potential differences in genetic backgrounds or environmental interactions among populations. This disparity is particularly

pronounced in ethnic subgroup analyses, where Asian populations exhibit high heterogeneity compared to the minimal variability found in Caucasian groups. These findings underscore the significant influence of ethnic factors on genetic predisposition to hyperbilirubinemia, which could include variations in allele frequencies and gene-environment interactions. The results from the Chinese subgroup further indicate the necessity of considering regional genetic differences in evaluating the connections between SLCO1B1 polymorphisms and neonatal hyperbilirubinemia risk. The consistent high heterogeneity associated with polymorphism rs4149056 raises additional questions regarding the generalizability of these results across various populations. Overall, the variations in both the nature and degree of heterogeneity suggest that the biological mechanisms linking SLCO1B1 polymorphisms to hyperbilirubinemia are complex and likely shaped by genetic, epigenetic, and external factors specific to distinct populations. While these associations show promise, the evident heterogeneity necessitates careful interpretation, and future research should aim to standardize methodologies, explore environmental contexts, and incorporate broader genetic frameworks to enhance the understanding of these relationships.

Clinical implications

The meta-analysis highlights the significance of genetic factors in evaluating and managing neonatal hyperbilirubinemia, particularly the SLCO1B1 rs2306283 polymorphism. However, our study found no correlation between the SLCO1B1 rs4149056 polymorphism and hyperbilirubinemia in both the overall and Chinese neonatal populations, indicating that not all genetic variations significantly influence this condition in these groups. While ethnic differences may exist, the lack of correlation with rs4149056 calls for a reassessment of its role in neonatal hyperbilirubinemia. Genetic screening is valuable but should prioritize variants with established associations in similar populations. Identifying at-risk infants is essential, yet focus should be on genetic variants with stronger links to hyperbilirubinemia. Proactive monitoring and intervention should consider a wider array of genetic and environmental factors. Integrating genetic insights into clinical practice is vital, but current evidence suggests a need for a more nuanced understanding of genetic influences on neonatal hyperbilirubinemia. Therefore, genetic counseling should incorporate these findings to assist healthcare professionals in accurately assessing risk factors and providing appropriate guidance to families in at-risk populations, thereby facilitating informed decision-making and optimizing management strategies for affected infants.

Limitations

The current meta-analysis presents a significant advantage over previous studies by incorporating a larger number of studies and participants, thereby offering an enhanced and consolidated evaluation of the association between SLCO1B1 rs2306283 and rs4149056 polymorphisms and the risk of neonatal hyperbilirubinemia. However, several limitations must be acknowledged. Most of the selected studies were conducted primarily in Asian populations, particularly Chinese neonates, with limited representation from Caucasian and virtually no studies involving African or mixed (Latin American) populations, which restricts the generalizability of the findings. Additionally, the analysis was limited to studies published in English and Chinese, excluding unpublished research and studies in other languages. While no publication bias was detected across the five genetic models for the rs2306283 and rs4149056 polymorphisms, the potential for bias remains due to the narrow scope of the databases searched. Furthermore, significant heterogeneity was observed for both polymorphisms across the overall population, and this heterogeneity did not diminish when analyses were stratified by ethnic background or country of origin, potentially attributable to conceptual deficiencies, sampling errors, and the small sample sizes in certain studies. Therefore, future research should focus on larger sample sizes across diverse regions and ethnicities, with analyses considering additional variables related to the neonates. Lastly, the pooled data were derived from single-factor estimates that did not account for other risk factors such as gender, prematurity, mode of delivery, blood group incompatibility, breastfeeding, preeclampsia, G6PD deficiency, neonatal sepsis, gestational hypertension, gestational diabetes, and environmental influences, limiting the ability to explore potential interactions among gene-gene and gene-environment factors due to insufficient evidence from the primary studies.

Conclusions

Our pooled data indicate that the polymorphisms rs2306283 and rs4149056 in the SLCO1B1 gene do not generally correlate with an increased risk of neonatal hyperbilirubinemia in the overall population. However, a detailed analysis of SLCO1B1 polymorphisms indicates that there is significant variability in risk across different ethnic groups, with strong associations noted particularly in the Chinese population for the rs2306283 polymorphism. Heterogeneity tests revealed substantial inconsistencies among studies, highlighting the complex genetic factors influencing the risk of neonatal hyperbilirubinemia and necessitating careful interpretation of these findings. Given the observed variability, further research in diverse populations is crucial for a comprehensive

understanding of the impact of SLCO1B1 polymorphisms on neonatal health outcomes.

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Author contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable for this manuscript.

Competing interests

The authors declare no competing interests.

Conflicts of interest

The authors declare that they have no conflict of interest.

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