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Host genetic factors modulating dengue virus: a systematic review of *TLR* polymorphisms

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Abstract

Background Dengue virus (DENV) infection is a substantial global public health burden, affecting ~ 390 million people every year, with a mortality rate of ~ 2.5% of those requiring hospitalization. Despite implementing vaccination and outbreak controls, DENV infection incidence continues to rise, particularly in endemic tropical and subtropical regions. Toll-like receptors (*TLR*s), as key components of the innate immune system, play a crucial role in recognizing DENV and initiating immune responses. Genetic variations, such as single-nucleotide polymorphisms (SNPs), in *TLR* genes may alter their function and expression levels, which in turn affect an individual's susceptibility to dengue and the severity of the disease. Defining these associations is critical for dengue risk stratification, prognosis, treatment strategies, and vaccine development. Currently, no review has comprehensively defined these associations; therefore, this study aimed to systematically evaluate *TLR* gene variants and their association with DENV infection susceptibility and severity.

Methods A systematic search was performed across major databases, including PubMed/MEDLINE, EMBASE, Scopus, and Web of Science, covering reports published up to April 20, 2025. Prospective or retrospective observational studies (case-control and cohort) investigating the association between *TLR* SNPs and dengue susceptibility and severity were included. Descriptive data were independently extracted by two reviewers using a standardized workflow, and bias risk was assessed using an adapted Newcastle-Ottawa Scale for case-control studies.

Results Eight case-control studies from India, Mexico, Colombia, and Indonesia met the inclusion criteria from an initial 65 records. All the included studies were assessed as having acceptable quality. Although studies demonstrate heterogeneity in their methods, *TLR3* rs3775291 and rs3775290, *TLR4* rs4986790 and rs4986791, and *TLR7* rs179008 and rs3853839 were among the most studied SNPs that exhibited correlation with dengue susceptibility and/or severity.

Conclusion Certain SNPs in *TLR3*, *TLR4*, *TLR7*, *TLR8*, and *TLR9* demonstrate associations with dengue susceptibility. All of these, except *TLR4* and *TLR9*, demonstrated some correlation with severity and/or certain clinical outcomes. The heterogeneity and limitations of the reviewed studies, as indicated by finding discrepancies, highlight the complexity of these genetic associations. Therefore, further large-scale, multi-ethnic prospective studies with standardized methodologies and functional validation are required to clarify the role of *TLR* SNPs in dengue pathogenesis.

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Clinical trial number Not applicable.

Keywords Dengue, Dengue susceptibility, Dengue severity, Toll-like receptor SNPs, Toll-like receptor

Background

The dengue virus (DENV) causes dengue fever, a viral, mosquito-borne infection that substantially affects public health. The clinical manifestations of this tropical infectious disease range from mild to severe, and it presents with plasma leakage and considerable hemorrhage because of platelet depletion, which can ultimately lead to organ failure due to shock. The World Health Organization (WHO) updated the dengue classification in 2009 to enhance its clinical sensitivity, thereby enabling the early detection of severe disease. The three new classifications are dengue without warning signs, dengue with warning signs, and severe dengue [1–3]. According to the WHO, using a cartographic approach, it was estimated that approximately 390 million people are affected by dengue infection annually [4], resulting in around 96 million clinical manifestations and approximately 500,000 hospitalizations, with a mortality rate of around 2.5% for hospitalized cases [5]. Real-world data from the WHO Global Dengue Surveillance from August 2024 to July 2025 reported 6,108,584 dengue cases worldwide, with a total of 4,740 deaths. Most of these cases originated from regions of the Americas, including Brazil and Mexico, which reported 3,180,580 and 62,927 cases, respectively. The second most affected region was countries in Southeast Asia, with Indonesia having the highest incidence, reporting 90,776 new cases and 393 deaths [6].

The worldwide incidence of DENV infections has been increasing over recent decades, with tropical and subtropical regions experiencing the highest infection rates due to their favorable climatic conditions for *Aedes* mosquito growth, particularly *Aedes aegypti*, the primary vector responsible for DENV transmission [2, 7]. Thus, the rise of DENV infection is associated with a considerable proportion of the global population, nearly half, who are currently living in endemic tropical areas for dengue infection, particularly in the tropical and subtropical regions of Asia, the Americas, and Africa [4, 8]. The primary preventive measures against dengue have been implemented through the development of vaccines. The latest vaccine developed and widely available for dengue is TAK-003, a live-attenuated tetravalent vaccine that was built on a dengue virus serotype 2 (DENV-2) backbone. This two-dose vaccine has been approved in numerous countries, including Indonesia and Brazil, as well as across the European Union, for preventing dengue caused by any serotype, regardless of an individual's previous exposure status. While TAK-003 has demonstrated an acceptable safety profile, it remains under continuous supervision through ongoing and post-licensure studies to further assess its long-term safety and effectiveness [9].

The early innate immune response is the first line of defense against most viral infections, including DENV. The intricate balance of the host's immune response plays a crucial role in responding to viral infections, in which balanced inflammation and repairing mechanisms are pivotal in the process of clearing the infection without detrimental effects to the host [10]. A key component within a human's innate immune system is the activation of the pattern recognition receptors (PRRs) family, such as Toll-like receptors (*TLR*s), which play a critical role in recognizing pathogen-associated molecular patterns (PAMPs). *TLR*s are expressed in immune cells (e.g., dendritic cells and macrophages) and non-immune cells (e.g., fibroblasts and endothelial cells) [11].

*TLR*s act as key receptors for the initiation of innate immune responses against single-stranded RNA (ssRNA) viruses, such as DENV. Examples of other RNA viruses include influenza A virus, severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), and SARS-CoV-2, which is commonly studied for its infection susceptibility and outcomes associated with *TLR* variants [12]. Specific *TLR*s, such as *TLR3*, *TLR7*, *TLR8*, and *TLR9*, function in identifying viral remnants, including foreign or viral genetic materials. Moreover, *TLR3* recognizes dsRNA, while *TLR7* and *TLR8* preferentially detect ssRNA, with all three implicated in the antiviral immune response [13, 14]. Furthermore, *TLR4* responds to non-structural proteins, such as non-structural protein 1 (NS1), thus further highlighting the critical role of *TLR*s in modulating the immune outcomes following DENV infection [15].

Moreover, genetic variations in *TLR* genes may influence an individual's susceptibility to dengue infections as well as their severity, as certain specific single-nucleotide polymorphisms (SNPs) in *TLR* genes (e.g., *TLR3*, *TLR4*, *TLR7*, *TLR8*, and *TLR9*) have been shown to affect their receptor function and expression levels, thereby disrupting the intricate balance of the immune response [10]. Studies have linked *TLR* SNPs to altered immune responses in patients with dengue, suggesting that these genetic variations may predispose individuals to severe dengue phenotypes by modulating their inflammatory responses [15, 16]. In addition, genome-wide association studies have further demonstrated a strong association between genetic variants and dengue susceptibility and severity, as determined by polygenic risk scoring [17].

Defining these associations and identifying the existence of these SNPs in specific populations can aid patient risk stratification, prognosis, and precise

treatments. This would enable the identification of individuals predisposed to rapid disease progression or poor outcomes and those who may require early clinical interventions or more aggressive treatments. Thus, potentially facilitating the optimal allocation of healthcare resources by prioritizing susceptible populations in dengue-endemic regions [16].

Therefore, to comprehensively evaluate and synthesize findings on the association of *TLR* SNPs with DENV infection susceptibility and/or severity across populations, an updated systematic review of the available literature on the subject was conducted. Although a few systematic reviews have been published on the association between SNPs in several genes and dengue [18–20], until recently, no one has comprehensively studied the *TLR* genes. Thus, this review focused on *TLR* SNPs, as one of the important PRR families of receptors of the human innate immune system, and their association with DENV infection susceptibility and severity.

Methods

Search strategy The review's research question aimed to determine whether there was an association between *TLR* genetic variants and dengue susceptibility and/or severity. The population consisted of patients with dengue and healthy controls from all countries. The exposure was the presence of *TLR* SNPs. The comparison was made between the genetic variants found in patients with dengue and those in healthy controls or between the different clinical classifications of dengue. The outcome was to determine whether certain SNPs were associated with an increased or decreased risk of dengue infection (i.e., susceptibility) or the development of more severe forms of the disease (i.e., severity). A protocol for this review was submitted to PROSPERO (registration no. CRD420250642381). The systematic search was performed on PubMed/MEDLINE and EMBASE through the Ovid, Scopus, and Web of Science databases. The search, which also searched through preprint servers, dissertations, and institutional repositories but yielded no relevant grey literature, covered literature published up to April 20, 2025. The search keywords (Appendix A) were based on the research question.

Inclusion and exclusion criteria The **s**tudy designs in this review include prospective or retrospective observational studies, such as case-control and cohort studies, investigating the association between certain genetic variants or SNPs in *TLR* genes and dengue susceptibility and/or severity. In vivo, in vitro, or other preclinical functional studies; studies that were not available in English; or studies that were reviews, editorials, commentaries, book chapters, conference abstracts, or congress communications are excluded. In addition, reports that lacked methodological detail (not reproducible) and/or did not present key findings regarding the *TLR* genetic variants' influence on dengue susceptibility and/or severity were also excluded following abstract and full-text screening.

Quality assessment The risk of bias in the selection of cases and controls, the comparability of the groups, and the ascertainment of exposure were assessed using the Newcastle-Ottawa Scale (NOS) scoring for case-control studies. The scale utilizes a scoring system to evaluate study quality, and the total number of stars awarded was used to determine the overall quality. The studies were stratified into three groups: a score of 0–3 indicates high risk, a score of 4–6 indicates moderate risk, and a score of 7–9 indicates low risk [21].

Data extraction Two reviewers (DSC and PGP) independently performed the data extraction for this study, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [22]. Using a standardized data extraction workflow in Rayyan, a web-based tool for systematic reviews [23], the reviewers systematically gathered data from the included studies and organized them based on their bibliographic information (study title, authors, publication year, journal, and country), study characteristics (eligibility criteria and sample size), participant information (age, sex, and ethnicity), and outcome measures (overall and stratified by subgroups). Following the removal of duplicates, the reviewers screened the titles and abstracts. Further full-text screening was performed to exclude reports without relevant key findings. Any disagreements between DSC and PGP were resolved by including a third, independent reviewer. All excluded full-text articles were documented, along with the reasons for their exclusion.

Results

Using our search strategy, we initially identified 65 articles related to dengue, and after removing duplicates, 28 articles remained. The independent screening excluded 15 articles that were not original full-length articles (e.g., conference abstracts, reviews, books, and proceedings). A full-text review was performed on the remaining 13 articles, of which five were excluded because of a non-relevant study design or objectives. In total, eight studies investigating the role of *TLR* SNPs in dengue were included in this review. Figure 1 presents the PRISMA flow diagram outlining the screening and selection process.

This systematic review synthesized findings from eight case-control studies examining SNPs in the TLR genes. These included studies on the TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9 genes. The included studies were all case-control studies published between 2011 and 2021. Diverse endemic geographical areas for dengue were also

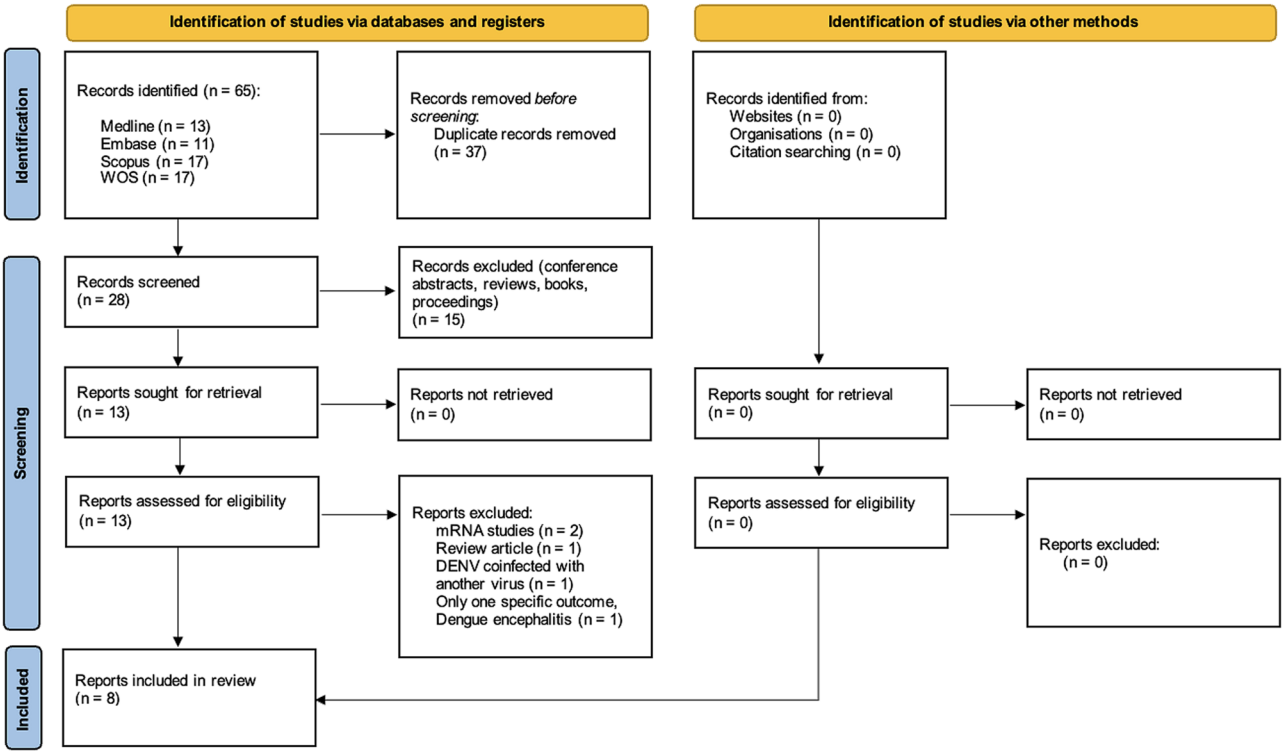


Fig. 1 PRISMA 2020 flow diagram showing the process of study selection. A total of 65 records were identified through database searches (Medline, Embase, Scopus, and Web of Science). After removing 37 duplicates, 28 records were screened, of which 15 were excluded based on title and abstract. The full reports of the remaining thirteen reports were then assessed for eligibility, with 5 subsequently excluded. Eight studies were included in the final review. No additional records were identified through other sources

included in this review, as the reviewed reports include populations from India (North, West, and East regions), Mexico, Colombia, and Indonesia. The sample sizes varied across the studies, with a balanced distribution of cases and controls in most studies, ranging from 98 to 201 patients/cases with dengue and 98 to 200 healthy controls. The mean participant age, gender distribution, clinical form/diagnostic test, and SNP detection method are summarized in Table 1. The most commonly used clinical classification of dengue severity in the included studies was the WHO 1997/1999 guidelines (DF, DHF, DSS), with two studies using the updated WHO 2009 classification (severe/non-severe).

Quality assessment results The assessment results of the NOS checklist for the included case-control studies are shown in Fig. 2; Table 2. For the proper case definition, representativeness of the cases, control selection, control definition, case-control comparability, and outcome assessment using validated methodologies, case-control studies were evaluated in accordance with the NOS criteria [21]. All studies were deemed low risk of bias as they scored seven (7) or higher. The cases and controls in every study were well described. In addition, all the studies took into consideration the appropriate methods for evaluating the outcomes or results; therefore, the score of outcome/exposure ascertainment was consistently high except for one study, due to variability in the DENV infection confirmation method among the case group [27]. Several studies were given less score within the comparability domain [25, 28, 29], as they may lack adequate adjustment for key confounders such as age, sex, and ethnicity, and some lacked a clear definition for controls (Table 2). However, the high median score of all studies indicates a low risk of bias across the included reports.

Discussion

This systematic review synthesized findings from eight case-control studies that examined SNPs in *TLR* genes. NOS assessment indicated that all reviewed studies were of good quality (Table 3; Fig. 2). The studies were geographically diverse, originating from India, Colombia, Mexico, and Indonesia. Collectively, the analyzed population consisted of 2,525 individuals, including 1,294 patients with dengue and 1,231 healthy controls, with patient enrollment predominantly occurring between 2001 and 2016. The genetic testing methodologies varied, primarily including PCR-RFLP, Sanger sequencing, and TaqMan SNP genotyping assays, which were used to analyze SNPs in *TLR2*, *TLR3*, *TLR4*, *TLR7*, *TLR8*, and *TLR9*.

Table 1 Study characteristics

No	Authors	Year	Ethnicity	Country of Study	Study Type	Number of Samples (WHO Criteria Used)	Age Distribution	Gender Distribution	Case and Control Definition	Method of Genotyping	Hardy-Weinberg Equilibrium Status
1	Posadas-Mondragón A, et al. [13]	2020	Admixed American (AMR)	Mexico	Case-control study	65 DHF patients, 100 DF patients, 89 general population (GP) subjects (WHO 1997)	**Cases** mean age: 39.85 +/- 14.07 **Controls**: mean age: 49.52 +/- 22.99	**Cases** male = 88, female = 77. **Controls**: male = 30; female = 59	**Case**: clinical diagnosis, laboratory confirmed by serology and identification of the viral genome. **Control**: healthy adults in the same health units at the same time with case group	Real-time PCR (Applied Biosystems)	Yes, except *TLR7*-rs3853839 and *TLR4*-rs4986790
2	Singh AK et al.[A] [24]	2021	South Asian	India (North India)	Case-control study	98 dengue cases, 98 healthy controls (WHO 2009)	**Cases**: mean age: 37.70 +/- 0.81 **Controls**: mean age: 35.98 +/- 0.77	**Cases**: male = 62, female = 36 **Controls**: male = 59; female = 39	**Case**: lab confirmed dengue infection (serum samples was positive for either anti dengue IgM or DV-nonstructural 1 antigen (NS1Ag) or both). **Control**: age and sex matched normal healthy volunteers residing in similar geographic area and negative for markers of dengue virus infection	Sanger sequencing	Yes
3	Singh AK, et al.[B] [25]	2021	South Asian	India	Case-control study	98 dengue cases (84 non-severe, 14 severe), 98 healthy controls (WHO 2009)	**Cases**: mean age: 37.70 +/- 0.81) **Controls**: mean age: 35.98 +/- 0.77	**Cases**: male = 62, female = 36 **Controls**: male = 59; female = 39	**Case**: laboratory confirmed by ELISA for anti-dengue IGM and non-structural-1 antigen (NS1Ag) **Control**: same geographical regions and laboratory confirmed negative for dengue virus infection.	Sanger sequencing	Yes
4	Mukherjee S & Tripathi A [26]	2019	South Asian	India	Case-control study	201 dengue infected patients and 157 healthy controls (WHO 2009)	**Cases**: mean age: 32.01+/- 14.7 **Controls**: mean age: 36.2 +/- 11.8)	**Cases**: male = 113 female = 78 **Controls**: male = 78; female = 79	**Case**: clinical symptoms and signs as per WHO criteria of dengue infection, laboratory confirmed by anti-dengue-IgM ELISA/ dengue-NS1ELISA/quantitative RT-PCR. **Control**: healthy age-matched unrelated individuals of same ethnicity, without any signs and history of other infections and without dengue infection as tested by anti-dengue-IgM ELISA/dengue-NS1 ELISA/quantitative RT-PCR,"	PCR-RFLP	Yes, except *TLR7*-rs3853839
5	Avendano-Tamayo EA, et al. [27]	2019	Admixed American (AMR)	Colombia	Case-control study	191 dengue cases and 101 controls (WHO 1997, WHO 2009)	**Cases**: mean age: 25 +/- 15.8 **Controls**: mean age: N/A	**Cases**: male = 142; female = 150 **Controls**: N/A	**Case**: laboratory confirmed through at least one out of three tests ELISA IgM/ IgM seroconversion/ RT-PCR. **Control**: subjects without prior records of dengue and tested negative in the ELISA IgM specific for DENV.	PCR-RFLP	Yes
6	Sharma S, et al. [15]	2016	South Asian	India	Case-control study	120 dengue infected (63 DF, 57 DHF/DSS) and 200 healthy controls (WHO 1997)	**Cases**: mean age: 33.47+/-14.66 **Controls**: mean age: 32,54+/- 9.22	**Cases**: male = 90; female = 30 **Controls**: male = 140, female = 60	**Case**: clinical symptoms and signs as per WHO guidelines and detection of NS1 antigen, IgM and IgG antibodies by ELISA (Bio-Rad, Marnes-La-Coquettee, France) in serum **Control**: same ethnicity, age, and gender with neither signs nor a previous history of dengue infection"	PCR-RFLP, Real-time RT-PCR (for mRNA)	Yes

Table 1 (continued)

No	Authors	Year	Ethnicity	Country of Study	Study Type	Number of Samples (WHO Criteria Used)	Age Distribution	Gender Distribution	Case and Control Definition	Method of Genotyping	Hardy-Weinberg Equilibrium Status
7	Djamiatun K, et al. [28]	2011	South East Asian	Indonesia	Case-control study	201 children with DHF and 179 healthy controls (mostly Javanese) (WHO 1997)	**Cases**: mean age: 7,31 **Controls**: mean age: N/A	**Cases**: N/A **Controls**: N/A	**Case**: laboratory confirmed by capture and indirect enzyme-linked immunosorbent assays (Focus Technologies, Cypress, CA) for dengue-specific IgM and IgG. **Control**: healthy control who had no history of DHF/DSS"	PCR-RFLP	Yes
8	Alagarasu K, et al. [29]	2015	South Asian	India	Case-control study	120 dengue cases (87 DF, 33 DHF) and 109 healthy controls (WHO 1999)	**Cases** mean age: 31,3 +/- 13 **Controls**: mean age: 29 +/- 8	**Cases** male = 73; female = 47 **Controls**: male = 67; female = 42	**Case**: hospitalisation for dengue, laboratory confirmed by dengue specific IgM Capture ELISA **Control**: healthy control	Taqman genotyping assays (PCR-RFLP for *TLR7*)	Yes

Several particular *TLRs* (*TLR3*, *TLR4*, *TLR7*, *TLR8*, and *TLR9*) and their association with dengue susceptibility and/or severity were investigated across the multiple included studies, as these genes were involved in the innate immunity response to viral infection. From all the included studies, a total of 18 SNPs were found to have a meaningful association with dengue susceptibility and/or severity or were studied in more than 1 study (Table 3). Notably, the *TLR2* gene was only studied in one study by Singh et al.[A] (2021) [24], and no significant association was observed. TLRs that were not the focus of this study, such as *TLR5* and *TLR6*, are generally not considered primary mediators in antiviral defense because their established ligands are predominantly non-viral components. Specifically, TLR5 is known to recognize bacterial flagellin, and TLR6 functions as a heterodimer with TLR2 to detect various bacterial lipoproteins and fungal cell wall components [31–33].

There is a growing body of evidence on the molecular insights behind the role of *TLR* SNPs, specifically regarding dengue infection; however, the exact mechanism remains unclear. The evidence of how each *TLR* gene's variants may influence or alter their receptor function and inflammatory response is discussed below.

TLR3

TLR3 recognizes viral dsRNA, a common replication intermediate for many viruses [34], including the DENV. Upon activation, *TLR3* triggers a downstream signaling pathway that leads to the production of type I interferons (IFN-1), thereby initiating inflammatory and antiviral responses. Therefore, dysregulation or SNPs in *TLR3* may contribute to increased susceptibility or severity of dengue fever [13, 34]. Notably, specific well-studied variants, such as *TLR3*: rs3775291, have probable pathway and molecular changes. However, two other synonymous and non-coding variants in the same gene, rs3775290 and rs3775296, respectively, are frequently co-inherited with rs3775291, which may disturb its independent association with the outcomes.

*TLR*3 rs3775290 (C > T) demonstrates a complex association among different populations with regard to dengue susceptibility. Interestingly, rs3775290 (C > T) is a synonymous SNP (F459F), meaning that it has no implication on the amino acid sequence. Its observed associations with disease might be attributed to its strong linkage disequilibrium with the below-discussed functional rs3775291 (L412F) variant [35, 36]. However, synonymous SNPs in this region could influence pre-mRNA splicing, thus potentially resulting in altered protein isoforms with modified functions. In addition, the presence of a less common codon might decelerate protein translation and affect the rate of mRNA degradation, thereby affecting the overall quantity and correct folding of the



Fig. 2 NOS Assessments results in traffic light plot. The top panel shows the assessment for each study across three domains. The bottom panel presents the overall percentage of studies with good (green), some concerns (yellow), and low (red) quality. Adapted from McGuinness et al. (2020) [30]

Table 2 Newcastle-Ottawa Scale (NOS) quality assessment

No	Authors	Year	Study Type	Selection (Max 4)	Comparability (Max 2)	Outcome/ Exposure (Max 3)	Total Score (Max 9)	Quality Comments
1	Posadas-Mondragón A, et al.	2020	Case Control	4	2	3	9	Good quality, defined age criteria for case/controls, adjusts for normal hematic biometry test
2	Singh et al. [A]	2021	Case Control	4	2	3	9	Good quality, adjusts for age-sex matched controls, also those residing in similar geographic area
3	Singh et al. [B]	2021	Case Control	4	1	3	8	Good quality, adjusts for similar geographic area and laboratory markers, but lacks age- and sex-matching
4	Mukherjee S & Tripathi A	2019	Case Control	4	2	3	9	Good quality, adjusts for similar geographic area and laboratory markers, also age- and sex-matched
5	Tamayo EA, et al.	2019	Case Control	4	2	2	8	Good quality, adjusts for a similar geographic area, age-matched, defined and included multiple ethnicites adjustments
6	Sharma S, et al.	2016	Case Control	4	2	3	9	Good quality, adjusts for similar geographic area, age- and sex-matched, adjusts for ethnicities
7	Djamiatun K, et al.	2011	Case Control	3	1	3	7	Good quality, adjusts for ethnicity, but lacks definition of controls, lacks adjustments for age and sex
8	Alagarasu K, et al.	2015	Case Control	3	1	3	7	Good quality, sex-matched but lacks adjustments for age and ethnicity, lacks controls definition

TLR3 protein; however, there is no clear functional evidence for these mechanisms [37, 38].

Among the three studies that assessed rs3775290, Singh et al.[B] (2021) found no significant association, while Mukherjee et al. (2019) found that the CC (wild-type) genotype may have increased susceptibility to dengue and was correlated with the WHO-defined warning signs (hemorrhagic manifestation) within the Eastern Indian population. Interestingly, Tamayo et al. reported a different risk allele or allele substitution (G > A) [25–27]. The differing risk alleles (C vs. A) across the populations (Indian vs. Colombian) strongly suggest population-specific effects or linkage with other functional variants, especially as rs3775290 (F459F) is a synonymous change [27]. Similarly, the T (variant) allele of rs3775290 has been associated with a higher susceptibility to severe Hand, Foot, and Mouth Disease caused by Human Enterovirus 71 [39]. Furthermore, the heterozygous CT genotype has also been suggested as a susceptibility risk factor for chronic Hepatitis C Virus (HCV) infection [40].

Another SNP in *TLR3*, rs3775291 (C > T substitution), which results in a leucine to phenylalanine substitution

Table 3 Key findings

Gene	SNP	Author, Year	Key Findings	Conclusion
TLR3	rs3775290 (C > T)	Avendaño Tamayo et al., 2019 (G > A substitution)	The A allele was associated with an increased risk of dengue in a Colombian Mestizo population (OR = 2.33, $p = 0.005$). The AA genotype was also linked to increased risk in the total study population (OR = 2.48, $p = 0.033$) [27].	Complementary/reverse strand allele may be used in genotyping (G > A). Variant Allele as susceptibility risk allele.
		Mukherjee et al., 2019	The CC genotype (OR = 4.15, 95% CI 1.86–9.24, $p = 0.0002$) and the C allele ($p = 0.04$) were associated with increased susceptibility to dengue. The CC genotype was found to be present in significantly higher frequency among dengue patients exhibiting WHO-defined warning sign [26].	Wild type allele (C) as susceptibility risk allele (C > T).
		Singh et al. [B], 2021	No significant association was observed between genotypes or alleles of this SNP and dengue risk in a North Indian population [25].	No significant difference found/no association
	rs3775291 (C > T)	Singh et al. [B], 2021	The mutant TT genotype (OR = 4.34, $p = 0.031$) and the mutant T allele (OR = 2.17, $p = 0.003$) were more frequent in dengue cases, indicating increased risk in a North Indian population [25].	Homozygote variant (TT) allele and T allele carriers, both may have higher susceptibility to dengue
		Alagarasu et al., 2014	The T allele frequency was lower in patients with Dengue Hemorrhagic Fever (DHF) compared to those with Dengue Fever (DF) (OR = 0.39, $p = 0.015$) and healthy controls (OR = 0.41, $p = 0.018$), suggesting a protective role against severe disease. Difference in allele frequency on healthy controls versus all cases (DHF + DF), or susceptibility, was not studied [29].	T (variant) allele as severity protective allele
		Posadas Mondragón et al., 2020	No direct association was found with dengue susceptibility or severity. However, the C/C genotype was more likely in dengue patients with low leukocytes and high monocytes [13].	No significant difference found/no association
	rs3775296 (C > A)	Singh et al. [B], 2021	The frequency of heterozygous (CA) and mutant (A) alleles was higher in dengue cases than in controls, but the association was not statistically significant [25].	No significant difference found/no association
TLR4	rs4986790 (A > G or Asp299Gly) & rs4986791 (C > T or Thr399Ile)	Singh AK et al. [A], 2021	Heterozygous genotypes were more common in North Indian dengue cases: AG (Asp299Gly) (OR = 2.40, $p = 0.02$) and CT (Thr399Ile) (OR = 2.09, $p = 0.037$). Their respective mutant alleles, G (OR = 2.35, $p = 0.009$) and T (OR = 2.36, $p = 0.006$), were also associated with increased risk [24].	Heterozygote variant allele carriers, both independently or together as a haplotype, may have higher susceptibility to dengue
		Sharma et al., 2016	Heterozygous genotypes for both Asp299Gly (OR = 1.70, $p = 0.042$) and Thr399Ile (OR = 2.17, $p = 0.024$) conferred increased susceptibility to dengue. The Ile/Gly haplotype was associated with disease risk (OR = 3.15, $p = 0.035$).	Heterozygote variant allele carriers, both independently or together as a haplotype, may have higher susceptibility to dengue
		Djamiatun et al., 2011	No significant association of the 299/399 SNPs was found with DHF/DSS in Indonesian children [13, 28].	No significant difference found/no association
		Posadas Mondragón et al., 2020	No significant association was found for these SNPs with the clinical forms of dengue in a Mexican population [13].	No significant difference found/no association
	rs2737190 (G > A)	Posadas Mondragón et al., 2020	The GG (wild-type) genotype reduced susceptibility to dengue infection (OR = 0.34, $p = 0.038$), suggesting a protective effect [13].	G (wild-type) allele may reduces susceptibility to dengue
	rs11536865 (G > C)	Posadas Mondragón et al., 2020	The GC genotype was associated with protection from dengue, may reduces susceptibility (OR = 0.19, $p = 0.0092$) [13].	Heterozygote variant allele (GC) carriers may have lower susceptibility to dengue compared to wild-type (GG). Homozygote CC not assessed.

Table 3 (continued)

Gene	SNP	Author, Year	Key Findings	Conclusion
TLR7	rs5741880 (G > T)	Mukherjee et al., 2019	The GT genotype was correlated to a decreased risk of dengue infection (OR = 0.45, $p = 0.046$) [26].	Heterozygote variant allele (GT) carriers may have lower susceptibility to dengue compared to wild-type (GG). No significant difference found/no association compared to homozygote TT.
	rs179010 (C > T)	Mukherjee et al., 2019	The CT genotype was correlated to a decreased risk of dengue infection (OR = 1.01, $p = 0.02$) [26].	Heterozygote variant allele (CT) carriers may have lower susceptibility to dengue compared to wild-type (CC). No significant difference found/no association compared to homozygote CC.
	rs179008 (A > T)	Mukherjee et al., 2019 (A > C substitution)	The CC genotype (OR = 2.89, $p = 0.01$) and C allele ($p = 0.01$) were associated with increased susceptibility, but AC heterozygote variant were associated with reduced susceptibility (OR = 0.12, $p = 0.02$). Furthermore, the CC/C genotype was strongly associated with the development of WHO-defined warning signs ($p < 0.0001$) [26].	Different variant allele used in Genotyping (A > C instead of A > T). Homozygote variant allele (CC) and C (variant) allele carriers may have higher susceptibility to dengue compared to wild-type (AA), but may have reduced susceptibility among heterozygote (AC) carriers.
		Singh et al. [B], 2021	The heterozygous AT genotype (OR = 2.12, $p = 0.034$) and the T allele (OR = 1.90, $p = 0.021$) were associated with an increased risk of dengue infection [25].	Heterozygote variant allele (AT) carriers may have higher susceptibility to dengue compared to wild-type (AA). No significant difference found/no association compared to homozygote TT.
		Posadas Mondragón et al., 2020	No significant association was found with dengue clinical forms, but the AA genotype was associated with high monocyte levels in Mexican women with dengue [13].	No significant difference found/no association
		Alagarasu et al., 2014	This SNP was observed at a very low frequency in the Western Indian study population, which precluded statistical analysis [29].	N/A
	rs179009 (C > T)	Singh et al. [B], 2021	The heterozygous CT genotype was found in a higher frequency in dengue cases compared to controls (OR = 2.04, $p = 0.040$), indicating increased risk [25].	Heterozygote variant allele (CT) carriers may have higher susceptibility to dengue compared to wild-type (CC). No significant difference found/no association compared to homozygote TT.
	rs3853839 (C > G)	Mukherjee et al., 2019	The CC genotype (OR = 2.01, $p = 0.004$) and the C allele ($p = 0.0002$) were associated with increased susceptibility to dengue [26].	Homozygote wildtype allele (CC) carriers may have higher susceptibility to dengue compared to variant allele (GG). No significant difference found/no association compared to heterozygote CG.
		Posadas Mondragón et al., 2020	No significant association with clinical forms of dengue was found [13].	No significant difference found/no association
TLR8	rs3764880 (A > G)	Mukherjee et al., 2019	For rs3764880, the AA genotype was associated with increased susceptibility to dengue (OR = 2.58, $p = 0.004$), while the AG genotype was associated with a lower risk ($p < 0.0001$). The AA/A genotype was also associated with developing warning signs ($p < 0.0001$) [26].	Homozygote wild-type allele (AA) and A allele carriers may have higher susceptibility to dengue compared to variant (GG), but reduced susceptibility among heterozygote (AG) carriers. The variant allele also associated with dengue warning signs or (severe) form.
	rs3764879 (C > G)	Mukherjee et al., 2019	For rs3764879, no significant difference was observed [26].	No significant difference found/no association
	rs3764879 & rs3764880 haplotype	Alagarasu et al., 2014	The C-A haplotype was observed at a higher frequency in male patients with DF compared to healthy male controls ($p = 0.025$) [29].	Among male, C-A haplotype carriers may have higher susceptibility to dengue (DF only, DHF not accounted) compared to GG haplotypes. No significant difference found among different haplotypes in female.
	rs5744080 (C > T)	Mukherjee et al., 2019	The CC genotype (OR = 2.49, $p = 0.001$) and the C allele ($p < 0.0001$) demonstrated a marked association with increased dengue susceptibility. *TLR8* rs5744080 CC/C was found to be present in significantly higher frequency among dengue patients exhibiting WHO-defined warning sign [26].	Homozygote wild-type allele (CC) and C allele carriers may have higher susceptibility to dengue compared to variant allele (TT).

Table 3 (continued)

Gene	SNP	Author, Year	Key Findings	Conclusion
TLR9	rs187084 (C > T)	Singh et al. [B], 2021	The heterozygous CT genotype (OR = 1.97, $p = 0.046$) and the mutant T allele (OR = 1.91, $p = 0.014$) were significantly associated with an increased risk of dengue infection [25].	Heterozygote variant allele (CT) carriers may have higher susceptibility to dengue compared to wild-type (CC). No significant difference found/no association compared to homozygote TT.
	rs5743836 (C > T)	Singh et al. [B], 2021	An association was found with the heterozygous CT genotype (OR = 2.38, $p = 0.009$) and the mutant T allele (OR = 2.29, $p = 0.0018$), both indicating increased risk of dengue infection [25].	Heterozygote variant allele (CT) carriers may have higher susceptibility to dengue compared to wild-type (CC). No significant difference found/no association compared to homozygote TT.

(L412F), has been frequently studied; however, these have yielded variable findings. Observing its association with dengue susceptibility, Singh et al.[B] (2021) reported that the TT genotype significantly increased susceptibility to DENV infection [25]. On the other hand, Alagarasu et al. (2014) found no differences between the case and control groups. However, in terms of DENV severity, the author found that the frequency of the T allele was significantly lower in patients with dengue hemorrhagic fever (DHF) compared to those with dengue fever (DF) and healthy controls in the Western Indian population [29]. The author postulated that the L412F change was "possibly altering" and noted that phenylalanine-containing *TLR3* (T allele) binds less dsRNA, which reduces nuclear factor-kappa B (NF-κB) activation, potentially leading to a more balanced inflammatory response against severe dengue [29].

Functional studies further define that the L412F substitution occurs in the ectodomain of *TLR3*. This change does impair *TLR3* signaling, thereby reducing NF-κB activation by approximately 30–50% [35, 41]. Leucine 412 is situated just next to the glycosylated "asparagine" residue, and its glycan moiety contacts with dsRNA, and the L412F variant, which causes substitution of leucine with phenylalanine, may affect the glycosylation of asparagine or the dsRNA-N-glycosyl moiety interaction, leading to reduced signaling activity, decreased activation of interferon regulatory factor 3 (IRF-3) and NF-κB, and subsequently lower type I IFN production [42]. This has also been reported to reduce the cell-surface expression of *TLR3* and its dsRNA binding capacity [36]. Posadas-Mondragón et al. (2020) found no meaningful association of the rs3775291 SNP in Mexican adults with either DENV susceptibility or severity but observed interactions with hematological parameters; for instance, the C/C genotype was more likely in patients with dengue who have low leukocytes and high monocytes [13]. Similarly, Singh et al.[B] (2021) did not find any significant difference between the genotype frequency of severe vs. non-severe dengue. The seemingly contradictory associations of rs3775291 detailed above highlight the need for further research, as its functional impact may be population-specific or modulated by other genetic or environmental factors [13].

Another report identified an association between *TLR* SNPs and a specific severe outcome of DENV, dengue encephalitis (DE). Verma et al. (2024) highlighted that *TLR3* was significantly expressed in central nervous system cells, including astrocytes, microglia, and T cells. As the dsRNA-sensing function of *TLR3* is crucial for the antiviral response, the author postulated that modifications in *TLR3* genes, such as the L412F SNP, could alter their receptor functions, potentially making patients with DENV infection more susceptible to inflammation, leading to a higher risk of developing DE [43]. This SNP has also been implicated in several RNA viruses, other than DENV, thus highlighting their broad roles in innate immunity against a wide range of viral infections. Previous studies have associated *TLR3* rs3775291 (L412F) with outcomes in several flaviviruses and neurotropic viruses. Biyani et al. (2015) demonstrated that the *TLR3* gene variant genotype (Phe/Phe–TT) was more prevalent in patients with Japanese encephalitis (JE) as compared to the controls [44]. This SNP has also been associated with symptomatic Human Cytomegalovirus (HCMV) infection in children, with the heterozygous CT genotype conferring an increased risk [36]. Moreover, the L412F variant has been implicated in outcomes of HCV infection in liver transplant recipients and tick-borne encephalitis (TBE) [36, 42]. In the context of COVID-19, while one study in a Brazilian cohort found no significant association [35], another report linked this SNP to an increased relative risk of severe symptoms in children [45].

TLR3 rs3775296 (C > A) was only studied by Singh et al.[B], who noted a higher, but not significant, frequency of the heterozygous CA genotype and the mutant A allele in dengue cases in North India compared with those in the control group [25]. This SNP is located within the 5' untranslated region (UTR) or promoter region of *TLR3*. Variations in this region can potentially affect gene expression levels by altering transcription factor binding or mRNA stability. Furthermore, it was found to be in moderate linkage disequilibrium with rs3775291; thus, its

association may also be attributed to the previously discussed SNP [36]. Reports have also described the association of this SNP with other RNA virus infections, where it was associated with reduced Human T-cell Lymphotropic Virus 1 (HTLV-1) infection susceptibility (i.e., a protective factor) [46]. Moreover, another study revealed that the heterozygous genotype of rs3775296 conferred an increased relative risk of HCMV infection (p = 0.042) [36].

TLR4

Although *TLR4* is known to recognize bacterial lipopolysaccharide (LPS), it has also been shown to be activated by DENV NS1, thus leading to an inflammatory response to DENV [47]. It recognizes PAMPs, particularly the DENV NS1, leading to the activation of inflammatory pathways that can exacerbate dengue symptoms. Circulating NS1 is associated with activation of immune cells, such as in vivo mouse cells and in vitro human peripheral blood mononuclear cells [48]. Genetic variations in *TLR4* may further modulate these responses, making some individuals more susceptible to severe dengue outcomes than others [13, 47]. *TLR4* activation leads to the release of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which is mediated by the MyD88-dependent and TRIF-dependent pathways, as well as type 1 IFN [49]. *TLR4* has also emerged as a promising target for drug development because of its interaction with NS1, as its dysregulation can have adverse outcomes, including hyperinflammation, sepsis, and target organ or tissue damage [11]. These consequences may impair the endothelial cell barrier integrity, which is associated with vascular leakage in dengue [48, 50].

One of the most studied innate immunity SNPs is the *TLR4* Asp299Gly (rs4986790) SNP, which interferes with *TLR4* signal transduction; thus, it is expected to affect host susceptibility to infections and microbial invasions [51]. Moreover, structural analysis of *TLR4* Asp299Gly has revealed that it impairs *TLR4* binding to its ligands [52]. Moreover, these missense SNPs, rs4986790 (A > G or Asp299Gly) and rs4986791 (C > T or Thr399Ile), are frequently co-inherited. Sharma et al. (2016) found that in a North Indian population, individuals who are heterozygous for Asp299Gly and Thr399Ile had increased susceptibility to dengue infection. The G and T variant (T399I) alleles were both also more frequently identified in patients with dengue; thus, they are associated with the risk of infection [15]. Singh et al.[A] (2021) similarly reported that heterozygous genotypes AG (rs4986790) and CT (rs4986791) were significantly more common in North Indian patients with dengue compared to the control group [24]. However, Djamiatun et al. (2011) found no significant association of these SNPs with DHF/DSS in Indonesian Javanese children, where the variant haplotype was rare [28]. Functionally, Sharma et al. (2016) observed higher *TLR4* mRNA expression in DF compared to that in the DHF/DSS and control groups, but this expression did not differ significantly between the *TLR4* genotypes, which suggests that these SNPs might impair *TLR4* function rather than its expression level [15]. D299G and T399I are both located in the extracellular domain of *TLR4*. These variants, particularly D299G, are associated with a reduced inflammatory response to bacterial LPS [53]. The D299G variant can alter *TLR4* structure, limit its interaction with LPS, CD14, and MD-2, decrease *TLR4* surface expression, and suppress downstream signaling via NF-κB and IRF3 [28, 54]. However, the functional impact may be population-specific because of differing haplotype frequencies and linkage patterns [55].

Several SNPs in the promoter region of *TLR4* were studied by Posadas-Mondragón et al. (2020) among Mexican individuals. Patients with dengue had a lower probability of presenting with the *TLR4*-rs2737190-G/G and *TLR4*-rs11536865-G/C genotypes and had a high probability of presenting with the TACG haplotype but a lower probability of presenting with the TGCG haplotype in the *TLR4* compared to individuals in the general population [13]. The GG genotype has been associated with a higher expression of *TLR4*, as well as an increased production of IL-6 and TNF-α upon LPS stimulation, suggesting an improved immune response capability, which might explain its protective role in dengue [56]. Further in silico analysis suggests that the SNPs, as mentioned earlier, could alter the binding sites for transcription factors such as HNF-1B, HOX D9/10, progesterone receptors (for rs2737190), or glucocorticoid receptors (for rs11536865) observed in HIV infection. These variants may also potentially influence *TLR4* expression, though this requires further functional validation [57]. However, the rs11536865 SNP among liver donors was associated with liver graft failure, particularly in HCV-positive recipients, which suggests that it modulates *TLR4* activity and inflammatory responses to viral infection [58].

TLR7

TLR7 and *TLR8* recognize single-stranded viral RNA (ssRNA) fragments in endosomes [59]. Emerging evidence, although the latter has been studied less, suggests that they are implicated in modulating inflammatory responses, which may impact the clinical outcomes of patients with dengue [13].

The *TLR7* gene is located on the X chromosome, and SNPs resulting from a mutation principally influence the antimicrobial host immunity [60]. Immune cells bearing a *TLR7*-null mutation show severe impairment in sensing ssRNA and release of inflammatory mediators, such

as TNF-α or IFN-γ [61]. For *TLR7* rs179008, two different variant alleles have been reported (A > C and A > T). Singh et al.[B] found that the AT (A > T substitution) heterozygous genotype increased an individual's risk of developing dengue, and the T allele was more frequently observed in cases in North India [25]. Conversely, Mukherjee et al. (2019) found that the CC genotype (A > C substitution) increased susceptibility in the Eastern Indian population; the CC/C genotype was also strongly associated with warning signs [26]. Alagarasu et al. (2014) reported a very low frequency of this SNP in the Western Indian population [29]. Posadas-Mondragón et al. (2020) noted interactions in Mexican women, where the A/A genotype was associated with high monocyte levels. This non-synonymous SNP is predicted to affect splicing [13] and has been associated with accelerated HIV-1 disease progression and higher viral loads, particularly in men. In women, it was associated with increased HIV-1 susceptibility [62]. The Q11L substitution (glutamine to leucine at amino acid 11) occurs in the N-terminal region of *TLR7*. Moreover, carriers of the Gln11Leu allele have been demonstrated to secrete significantly less IFN-α following *in vitro TLR7* activation [63]. This variant has been associated with persistent HTLV-1 infection, in which the G allele carriers had higher *TLR7* expression and IFN-α levels [64]. This suggests that this variant may impair *TLR7* signaling and reduce cytokine production in response to viral infection, thereby increasing an individual's susceptibility.

The heterozygous CT genotype of *TLR7* rs179009 (C > T) was found to be associated with a higher risk of dengue infection in North Indian individuals [25]. However, according to the ClinVar database, this variant was reported as an A-to-G substitution [65]. In the context of other viral infections, the AG genotype of this SNP was associated with a reduced risk of HIV-1 infection [62]. This c.4–151 A > G SNP has also been associated with severe clinical outcomes in COVID-19 pneumonia and ICU admission. Its association with various viral outcomes may suggest that it impacts *TLR7* gene regulation, although it is an intronic SNP [66].

For *TLR7* rs3853839 (C > G), Mukherjee et al. (2019) found an association of the C/C genotype and C allele with increased susceptibility to or dengue infectivity in the Eastern Indian population [26]. Similarly, Posadas-Mondragón et al. (2020) noted that among women, patients with DHF, leukopenia (low levels of leukocytes), and high levels of total IgG and IgG1 were observed in patients harboring the C/C genotype of this SNP, with a similar pattern observed for Chikungunya virus infection [13]. This SNP is located within the 3' UTR of *TLR7*, and the G allele has been associated with increased *TLR7* mRNA and protein expression [64, 67]. Interestingly, the opposing GG genotype was also associated with higher susceptibility to COVID-19 and was linked to disease severity and poor clinical outcomes, as the G allele was more prevalent in cases than in the controls [67].

Moreover, Mukherjee et al. (2019) found that specific heterozygous genotypes of other *TLR7* SNPs (rs5741880 GT, rs179010 CT) offered protection against dengue susceptibility in the Eastern Indian population [13]. This further indicates the variability of the phenotypic impacts of genetic variants within *TLR7*.

TLR8

TLR8 rs3764880 (A > G), a non-synonymous variant that is predicted to be damaging and affect splicing, exhibited complex associations. Mukherjee et al. (2019) reported that in the Eastern Indian population, the AA genotype increased dengue risk, while the AG genotype was protective; the AA/A genotype was strongly linked to warning signs [26]. Furthermore, Alagarasu et al. (2014) found that the C-A haplotype (rs3764879-rs3764880) increased DF risk in Western Indian males [29]. Posadas-Mondragón et al. (2020) found interactions in Mexican women patients with DHF, where high monocyte and IgG levels were associated with the A/A genotype [13]. Mukherjee et al. (2019) also associated this SNP's CC genotype and C allele with susceptibility and the CC/C genotype with warning signs in the Eastern Indian population [26]. Functional SNPs of *TLR8* are associated with susceptibility to other flaviviruses, including HCV. The data indicate that variations in *TLR8* genes may modulate immune responses during HCV infection, where *TLR8* SNPs altered the transcriptional activity, mRNA stability, NF-κB activation via CLO75 stimulation, and pro-inflammatory cytokine expression [68].

TLR9

TLR9 typically senses CpG DNA, but emerging evidence has demonstrated its activation in dendritic cells in response to RNA viral infections such as DENV [69]. Currently, there is no clear evidence on the functional mechanism of how variants in this gene affect dengue; however, allelic variation located within the promoter region of the *TLR9* locus has been shown to alter the receptor function by regulating its expression [70]. Moreover, within plasmacytoid dendritic cells, *TLR9* specifically identifies mitochondrial DNA, which sets off signaling cascades that involve the NF-κB and MAPK p38 pathways. This activation results in the generation of a Th2 immune response against DENV. A lack of *TLR9* signaling may be a contributing factor to the severity of the disease experienced, as patients with severe dengue symptoms exhibit less IFN-α production in response to *TLR9* ligand activation than those with milder symptoms. This suggests that healthy *TLR9* function is crucial for generating a strong immune response to DENV and

that weakened *TLR9* activity may be linked to worsening disease outcomes [71]. In the context of other RNA virus infections, *TLR9* variants have been linked to endothelial cell dysfunction, resulting from the increased release of mitochondrial DNA during viral infection-induced cell stress, which acts as a Damage-Associated Molecular Pattern (DAMP) and potentially exacerbates inflammation, as observed in SARS-CoV-2, another RNA virus [72].

Singh et al.[B] found that in the North Indian population, heterozygous CT genotypes for *TLR9* rs187084 may increase dengue risk, as this genotype was significantly more frequent in cases than in the controls [25]. This SNP heterozygous CT genotype was also associated with neonatal HCMV infection [73]. The SNP is located within the promoter region of *TLR9*, which may affect or alter the Sp1 binding site [24]. Thus, in line with the previously mentioned mechanisms, the variant allele of this SNP may be tightly associated with *TLR9* signaling regulation to potentially reduce its activity, thus increasing an individual's susceptibility to dengue.

Moreover, Singh et al.[B] found a similar CT heterozygous genotype at another SNP (*TLR9* rs5743836), which also increased dengue risk and was associated with cytomegalovirus (CMV) reactivation in patients who underwent hematopoietic cell transplantation and with human CMV infection in infants [74]. It has also been reported to be associated with the viral set point in HIV infection [75]. Previous studies suggest that this promoter SNP affects *TLR9* transcriptional activity, as the C allele has been shown to create a putative NF-κB binding site and increase *TLR9* transcription, with the CC genotype demonstrating higher promoter activity in luciferase assays [74, 75].

Overall, some distinct associations between alleles were observed. In *TLR8* rs3764880, the AA genotype and the A allele have been associated with increased susceptibility; however, the heterozygote AG genotype was associated with a markedly reduced susceptibility compared to that of the GG genotype. Several inconsistent findings may be attributed to the different populations studied and variable sample sizes. For example, a variant in *TLR3*, the SNP rs3775290, exhibited conflicting results: one study in a Colombian population found the A allele increased dengue risk, while another study in an Indian population found another allele, the C allele, increased dengue susceptibility [26, 27]. Similarly, in *TLR7* rs179008, most studies found that the CC genotype and C allele increased susceptibility, while Mukherjee et al. (2019) found that the heterozygous AT genotype and T allele were associated with increased risk. A separate study noted a potential difference in the allele designation for rs179008, using an A > C substitution instead of A > T (Table 3) [13, 25, 26, 29].

Clinical and public health implications

Dengue is a worldwide public health concern because of its widespread distribution, which results in recurring epidemics and a steady increase in cases. Identifying SNPs that cause or exacerbate dengue can help researchers develop vaccinations and identify early indicators that facilitate the prediction of the disease's clinical course [76]. Understanding the dynamic interactions at different points of infection (temporal variability) of the regulation of these pathways and molecular interactions within *TLR*-mediated signaling during DENV infection may facilitate the development of therapeutic procedures against specific viral targets, as well as the potential of including *TLR* agonists within the vaccine design [16] It has been shown that dengue subunit vaccines consisting of recombinant DENV2 envelope domain III combined with *TLR* agonists induced a strong immunological signature that involved immune cell trafficking, IFNs, and proinflammatory and T-cell responses; however, only partial protection was obtained against viral challenge [77]. Therapeutically, *TLR3* agonists have been shown to enhance the immune system's antiviral responses. For instance, the activation of *TLR3* was linked to decreased DENV replication in hepatoma cells through the induction of IFN-β [78]. In vivo studies have shown that administering *TLR3* agonists, as well as *TLR7*/8 agonists, can reduce the viral load and stimulate an antibody-mediated immune response, which is critical in fighting viral infections [79]. These findings suggest that integrating the genetic profiling of *TLR* and elucidating its signaling pathways could be a promising modality to enhance the protective capacity of flavivirus vaccines and stimulate antiviral antibody responses [80].

Despite the preliminary nature of these findings, they carry important potential for practical and public health applications. Knowledge of the relevant *TLR* SNPs could be used for clinical risk stratification. Furthermore, identifying individuals with high-risk genotypes upon diagnosis could aid clinicians in predicting prognosis and prioritizing patients who require closer monitoring for the warning signs of severe dengue. From a public health policy perspective, this genetic information could guide resource allocation. For example, during outbreaks or for the rollout of new dengue vaccines, public health officials could prioritize genetically identified vulnerable groups for early vaccination, targeted vector control, and prompt clinical intervention.

Limitations

This study is the first to collectively present *TLR* gene SNP studies related to dengue severity and susceptibility. A limitation of this systematic review is that a quantitative meta-analysis to calculate a pooled measure of the association was not performed. Furthermore,

the available evidence among published records is still limited, as this review only identified eight retrospective case-control studies. The number of individuals in each analysis subgroup (e.g., DF vs. DHF/DSS or DF vs. healthy controls) in the reviewed studies was limited for comparisons, which may produce unstable estimates of effect, observed from wide confidence intervals of some data [81–83]. However, several of the reviewed studies did perform sample size calculations based on expected odds ratios and minor allele frequencies to achieve a certain power for detecting associations with the overall dengue susceptibility [15]. This is also due to the considerable heterogeneity observed across the included studies in terms of their diverse populations (e.g., Indian, Mexican, and Colombian), varied genotyping methodologies (e.g., PCR-RFLP and Sanger sequencing), and genotype/allele count reporting. Moreover, variations in the WHO guidelines used for dengue classification (e.g., 1997 vs. 2009) may affect severity categorizations and comparisons in several reports. Some studies also lack rigorous dengue screening in the controls, as the controls were defined by routine check-ups with normal hematology parameters but lacked specific dengue serology tests for dengue infection biomarkers [13].

Furthermore, the exclusion of non-English studies may introduce language bias, as it prevents the reporting of important findings in other languages. The absence of more robust prospective cohort studies or clinical trials means that the findings may be subject to inherent biases, such as selection and recall bias. Genetic ancestry may also confound the association between *TLR* variants and dengue clinical outcomes [18]. Many of the investigations failed to establish clear causal relationships between the studied *TLR* SNPs and the observed clinical outcomes, thus leaving a gap in understanding how these genetic variations may influence disease progression or patient responses. In addition, the included studies did not account for the different DENV serotypes that can influence disease severity.

Future research

This review fills a critical knowledge gap by synthesizing the current, although preliminary, evidence on *TLR* SNPs and dengue susceptibility and/or severity. While no single SNP has universally or consistently demonstrated reliable predictive ability, there is compelling evidence, supported by the mechanistic roles of *TLR*s, that indicates its potential role as a crucial determinant of dengue outcomes. The majority of these findings are from case-control studies that require further validation in larger, multiethnic, prospective cohorts. Furthermore, additional evidence from functional studies is required to explain how these SNPs alter the immune response to DENV. In addition, functional analyses are essential to elucidate the molecular mechanisms by which these SNPs affect *TLR* expression, their signaling cascades, and the subsequent antiviral response.

Future research should include larger-scale, multiethnic prospective studies with standardized classifications, robust genotyping, and ancestry adjustment to identify robust evidence of the association between *TLR* variants and DENV severity and susceptibility. Furthermore, integration of functional analyses assessing the impact of *TLR* variants on receptor expression, signaling, cytokine/IFN production, and viral replication, especially for the different DENV serotypes, would provide a more comprehensive understanding of dengue immunopathogenesis. In addition, the incorporation of a wider array of *TLR* and other related genes may further define gene-gene interactions and the implicated pathways of the innate immune system in DENV infection.

Conclusions

Overall, this review highlights that certain SNPs in the *TLR3*, *TLR4*, *TLR7*, *TLR8*, and *TLR9* genes exhibit an association with susceptibility to dengue and/or severity of the disease, as well as clinical outcomes across different populations. These genetic variants can alter immune responses by affecting receptor expression, signaling pathways, and/or binding capacity. The genetic alterations of these receptors may reduce inflammatory signaling pathways, leading to a balanced inflammatory state and acting as protective factors, but they can also drive hyperinflammation and tissue damage via the hyperactivation of inflammatory cytokines, such as TNF-α and IL-6. Some studies also link these SNPs to hematological changes, such as variations in leukocyte and monocyte counts in patients with dengue. Future research may benefit from larger, multiethnic cohort studies to establish robust evidence on the association between *TLR* SNPs and DENV susceptibility and/or severity. Functional studies are also crucial for bridging the molecular evidence to implementation of *TLR*-based dengue precision medicine, such as TLR agonists in vaccine development and therapeutic management.

Appendix A: Search keywords

Embase and MEDLINE through OVID

(dengue or "dengue fever" or "dengue hemorrhagic fever").ti, ab. AND.
("toll-like receptor*" or *TLR** or *TLR*).ti, ab. AND.
(SNPs or SNP or SNP or "molecular mechanism" or "differential expression" or SNP* or "genetic variant*" or mutation).ti, ab. AND.
(susceptibility or severity).af.

Web of science (WOS)

TS=(dengue OR "dengue fever" OR "dengue hemorrhagic fever") AND.
TS=("toll-like receptor*" OR *TLR** OR *TLR*) AND.
TS=(SNPs OR SNP OR SNP OR "molecular mechanism" OR "differential expression" OR "genetic variant*" OR mutation*) AND.
TS=(susceptibility OR severity).

Scopus

TITLE-ABS(dengue OR "dengue fever" OR "dengue hemorrhagic fever") AND.
TITLE-ABS("toll-like receptor*" OR *TLR** OR *TLR*) AND.
TITLE-ABS(SNPs OR SNP OR SNP OR "molecular mechanism" OR "differential expression" OR "genetic variant*" OR mutation*) AND.
ALL(susceptibility OR severity).

Abbreviations

DENV	Dengue virus
TLR	Toll-like receptor gene
SNP	Single-nucleotide polymorphism
DF	Dengue fever
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
WHO	World Health Organization
PRRs	Pattern recognition receptors
PAMPs	Pathogen-associated molecular patterns
ssRNA	Single-stranded RNA
SARS-CoV-1	Severe acute respiratory syndrome coronavirus-1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
dsRNA	Double-stranded RNA
NS1	Nonstructural protein 1
PROSPERO	International Prospective Register of Systematic Reviews
WOS	Web of Science
RoB	Risk of Bias
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PCR	Polymerase Chain Reaction
PCR-RFLP	Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
RT-PCR	Reverse Transcription Polymerase Chain Reaction
LPS	Lipopolysaccharide
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
MyD88	Myeloid differentiation primary response 88
TRIF	TIR domain-containing adaptor inducing IFN-β
DE	Dengue encephalitis
JE	Japanese encephalitis
TBE	Tick-borne encephalitis
HCMV	Human Cytomegalovirus
HCV	Hepatitis C Virus
COVID-19	Coronavirus Disease 2019
UTR	Untranslated region
HTLV-1	Human T-cell Lymphotropic Virus 1
NF-κB	Nuclear Factor-kappaB
IRF-3	Interferon Regulatory Factor 3
IFN-β	Interferon – beta
IFN-α	Interferon-alpha
DAMPs	Damage-Associated Molecular Patterns
CMV	Cytomegalovirus
HIV	Human Immunodeficiency Virus

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Author contributions

DSC defined the research questions and initiated a preliminary literature search. PGP, DSC, and HN defined the search keywords and conducted the systematic literature search. PGP and DSC filtered and screened records from systematic searches. PGP, DSC, DP, and ISL extracted and synthesized the relevant findings from the records and contributed to the manuscript. HN provided a critical appraisal and review. All authors reviewed the final manuscript.

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Data availability

All data generated or analyzed during this study are included in the submission. The raw data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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