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Review

Genetic variants associated with dengue hemorrhagic fever. A systematic review and meta-analysis

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A B S T R A C T

Dengue hemorrhagic fever (DHF) is a severe condition resulting from the dengue virus, with four serotypes known as DEN-1, DEN-2, DEN-3, and DEN-4. Genetic variations play a crucial role in influencing susceptibility to DHF. Therefore, this investigation conducted a meta-analysis to uncover genetic changes that might have remained undetected in individual studies due to small sample sizes or methodological differences. Among 2212 initially identified studies, 23 were deemed suitable for analysis based on PRISMA guidelines. Toll-like receptors (TLR) and CD209 showed significant association with DHF (odds ratios: TLR=0.56, CD209 =0.55), indicating protective effects. However, tumor necrosis factor (TNF) and human leukocyte antigen (HLA) did not exhibit a statistically significant relationship with DHF. This study emphasizes the relevance of TLR and CD209 in DHF susceptibility and resistance across diverse geographical locations.

Contents

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Introduction

Dengue fever was the second most prevalent tropical contagious disease in 1998 after malaria, with 100 million cases reported. Annually, 500,000 cases of dengue fever accounted for a 1:20 mortality ratio. Moreover, the pattern of dengue infection from 1780 to 1940 was characterized by sporadic events but with significant outbreaks. However, dengue virus infection became endemic during this time in various tropical regions. Furthermore, the cases of dengue declined in the years 2020–2022, due to the COVID-19 pandemic and the lower rate of incidence reported. While, in 2023, an unexpected rise in dengue cases was observed. There have been over five million recorded cases and more than 5000 deaths associated with dengue in over 80 countries and territories throughout five areas monitored by the World Health Organization (WHO). The regions of Africa, the Americas, Southeast Asia, the Western Pacific, and the Eastern Mediterranean have a global presence (WHO 2023 report). All through World War II, disruptions in South Asia and the Pacific zone led to an increase in the spread of mosquito-borne infections, and the transmission of various dengue serotypes accompanied the pandemic of dengue. Infection with these serotypes caused a dengue hemorrhagic fever (DHF) epidemic in southern Asian countries as a newly emerging disease [1]. Several factors could influence these outbreaks, including the presence of the dengue virus, the density of mosquito populations, and the presence of a susceptible human population. DHF outbreaks can cause substantial mortality and morbidity, which could put a strain on healthcare services, especially in regions with limited resources. Controlling the mosquito population, improving access to appropriate medical care, and raising public awareness about DHF and its transmission are all effective ways to prevent and control DHF outbreaks [2]. The first known DHF epidemic was found in Manila, Philippines, in 1953–54. This was followed by cases in Thailand (1958), Malaysia (1960–62), Singapore (1960–62), Vietnam (1963), Indonesia (1969), Burma (1970), Kampuchea, Laos (1985), and China (1985) [2–5]. India and Sri Lanka reported the first cases of DHF in 1988, followed by French Polynesia in 1990, Pakistan in 1992, and Bangladesh in 2000. This began the larger DHF outbreak [2,6].

The dengue virus is the primary agent behind dengue fever, a tropical disease transmitted by mosquitoes. The infection was carried on with the sting of a female Aedes aegypti mosquito that was previously plagued with the disease. The virus responsible for dengue is commonly known as dengue virus (DENV), which comprises four serotypes: (1) DENV-1, (2) DENV-2, (3) DENV-3, and (4) DENV-4. DENVs are single-stranded RNA viruses with a positive genetic strand, and they are members of the family Flaviviridae. Clinically, as per dengue severity, it is classified as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) [7]. High fever, severe headache, joint and muscle pain, and rashes are all symptoms of DF. The most effective strategy to prevent dengue is to minimize mosquito bites and eliminate mosquito breeding grounds. Although there is no cure for dengue at the moment, early identification and rapid supportive care can significantly control the health of those afflicted with the disease [8].

DHF is a fatal variant of dengue fever transmitted through the sting of an infected Aedes mosquito. Here, severe headache, high fever, extreme muscle and joint pain, nausea, vomiting, skin rashes, and bleeding from the gums, nose, or beneath the skin are the common symptoms of DHF. However, suppose it is left untreated for a longer time. In that case, DHF can result in dengue shock syndrome, which is characterized by severe abdominal pain, prolonged vomiting, short breathing, rapid pulse rate, and low blood pressure. Moreover, dengue shock syndrome can be fatal if treatment is delayed. However, early detection and prompt medication can mitigate the health risk caused associated with DSS [2,8].

Moreover, infection with a single dengue serotype might produce CD4 + memory T cells with cross-reactivity to other dengue serotypes. On the other hand, CD8 + T cells have an inherent cytotoxic activity that is directed specifically toward the dengue virus. T lymphocytes CD4 + generate numerous cytokines that include interferon (IFN-g), IL-2, IL-4, IL-5, IL-6, IL-10, and lymphotoxins. Moreover, Infected monocytes could generate cytokines/chemokines such as TNF- and IL-1, which are known to activate vascular endothelial cells and cause vascular leakage9. It was also hypothesized that a rise in tandem effects of mediators that include TNF, IL-2, IL-6, IFN-g, PAF, C3a, C5a, and histamine could potentially lead to plasma leakage, increased vascular permeability, shock, and a malfunction of the coagulation system, all these could potentially result to hemorrhage [9,10].

Several factors, including genetic predisposition, can influence the severity of DHF symptoms. Several studies have shown the impact of genetic variation on the susceptibility of DHF. A population sample from Thailand was used in a study that demonstrated a genetic mutation in the genes for tumor necrosis factor (TNF), and interleukin 10 (IL-10) was associated with an increased chance of developing coronary heart disease [11]. Another study showed the involvement of TNF, interferon-gamma (IFNG) and IL-10 genetic variation with increased susceptibility to DHF in the Brazilian population [12]. Here, immunopathogenesis showed that the host immune system mounted an immune response to the virus by producing cytokines and antibodies. In some cases, the antibodies produced against the virus can bind to the virus, which enhances its infectivity and leads to a more severe condition [13]. Moreover, Loke et al. (2001) determined that CD8 T cell responses constrained by HLA class I play a role in both immunopathology and protection in DHF [14]. Carvalho et al. (2014) showed changes in the innate immune response of DHF patients (TLR4 expression and sensitivity in CD14 + cells, along with TNF-/NO production) are inversely proportional to NS1 serum levels and illness stage and severity [15]. Pablan et al. (2017) showed that DC-specific ICAM-3 grabbing non-integrin (DC-SIGN) CD209–336 G/A is polymorphic and can be affected by DHF. In another study, Tassaneetrithep et al. (2003)

demonstrated that dendritic cells could be protected against infection by using antibodies against DC-SIGN (CD209). Therefore, DC-SIGN (CD209) should be researched further as a possible novel therapeutic target for preventing and treating dengue fever [16].

Therefore, in this meta-analysis, we investigated the relationship of genetic factors (HLA, DC-SIGN (CD209), TNF, and TLR) with dengue hemorrhagic fever (DHF) and parameterized their statistical significance.

Materials and methods

A meta-analysis of dengue hemorrhagic fever with the association of genetic variants was performed based on the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements.

Search approach

The investigation was carried out to collect relevant articles. These articles were searched on various electronic databases that include (1) Web of Science (WOS), (2) PubMed, and (3) grey literature from health websites. In the literature search process, the advanced search option of the database was used to retrieve the studies citing DHF caused by the dengue virus and associated genetic factors. The keywords used in the search were: [(genetic variation) OR (genetic factor) OR (genetic markers) OR (genetic analysis) OR (SNP) OR (single nucleotide polymorphism)] OR (genetic susceptibility) OR (genome-wide association) OR (genetic variability) OR (gene identity) OR (disease susceptibility) OR (polymorphism)] AND [(Dengue virus infection) OR (Dengue hemorrhagic fever) OR (Dengue shock syndrome) OR (Haemorrhagic Dengue)] all field criteria were used to search the articles, whereas in PubMed, article/abstract criteria were used with the keywords mentioned above.

Screening of the studies

The retrieved data were imported in comma-separated value (CSV) format. The duplicate files were removed, and the resultant studies were further screened according to their titles and abstracts. Case-control studies, cohort studies, and observational studies that demonstrated an association between genetic variants and DHF were considered inclusion criteria. Three basic kinds of studies have played a vital role: case-control studies, cohort studies, and observational studies. Case-control studies aim to find potential genetic risk factors by comparing the genetic variants of individuals with DHF (Dengue Hemorrhagic Fever) to those without the condition. Cohort studies longitudinally study groups to examine the impact of varying genetic compositions on the progression of DHF. Observational studies aim to follow people' health and genetics without any intervention in order to identify natural relationships between genetic variants and DHF. The objective of these investigations is to comprehensively comprehend the impact of genetic variations on the probability of getting DHF, which is crucial for formulating specific preventative and therapy approaches. The exclusion criteria include studies that did not contain information about genetic variants and their association with DHF. The complete flow of article screening is presented in Fig. 1.

Data extractions

Further, the data mined from the collected articles for meta-analysis consisted of (a) the name of the author or study, (b) the year of publication, (c) the country, (d) the total number of cases exposed and affected, (e) the total number of cases controlled and unaffected, and (f) the distribution of genes and their associated alleles.

Statistical investigation

The meta-analysis was carried out using RevMan 5.4.1 to generate the forest plot for each selected gene using the data collected from selected studies on that gene. The degree of correlation between genetic variation and DHF was determined using the inverse variance-weighted mean of the odd ratio (OR) logarithm with 95% confidence intervals. Here, the I2 parameter is the percentage of overall variation that can be attributed to heterogeneity between studies, as compared to random error or coincidence.

Results

DHF is a severe stage of dengue fever instigated by an infection with the dengue virus. Numerous factors, including genetics and the environment, can influence the severity of DHF symptoms. Certain genetic variants can increase an individual's susceptibility to DHF, as studies in diverse populations demonstrate. It was observed that the genetic factors that affect blood clotting regulation, such as certain variants of the platelet glycoprotein TAP and the HPA gene polymorphism, were allied with an increased threat of DHF [17]. Other studies have identified correlations between variants in genes that regulate the immune response, including the gene for tumor necrosis factor (TNF) and the likelihood of DHF [11]. Similarly, in this analysis, genes named human leukocyte antigen (HLA) classes I and II, toll-like receptors (TLR), TNF, and DC-SIGN (CD209) were found to perform crucial roles in susceptibility and protection against DHF. Moreover, it is indispensable to understand that the specific gene alleles associated with an increased risk of emerging DHF vary with the population set.

Here, statistical evaluations were used to investigate the relationship between the genetic variants of the HLA, TNF, TLR, and DC-SIGN (CD209) genes with the susceptibility to and protection against DHF. The proportions of infected patients and healthy subjects were compared statistically for selected four genes. The degree of association between genes and the DHF was estimated through odd ratios (OR), heterogeneity (I2), and the overall size effect (P-value). In this analysis, a higher number of studies were found and collected for HLA and TNF gene alleles. The selected cases pertaining to HLA I and II reported 757 infected and 913 healthy individuals, while the study pertaining to TNF reported 844 patients and 1057 control cases. In addition, there were 122 affected cases and 289 control cases for the TLR gene and 178 affected cases and 224 control cases for the CD209 gene considered in this meta-analysis. Fig. 2 shows the statistical analysis outcome illustrated using forest plots, elucidating the odds ratio with class interims and the associated P-value of these genes. Moreover, explaining the existence bias for the publication showed through the funnel plot in Fig. 3. Fig. 3(a) the funnel plot of HLA gene studies exhibits significant symmetry with respect to the line of no effect (RR=1), indicating little presence of publication bias. The clustering of studies at the top demonstrates diverse levels of accuracy, which is a common characteristic of lower sample sizes. In summary, there is no definitive evidence of asymmetry, which could suggest the presence of systematic bias or heterogeneity. Fig. 3(b) the funnel plot analysis of TNF gene studies reveals a symmetrical distribution centred on the line of no effect, indicating minimal or negligible publication bias. The concentration of study at the top suggests a combination of larger and smaller studies with different levels of precision. All studies are located close to the apex of the funnel, indicating the absence of outliers or extreme effects. The plot suggests a uniform effect size across studies with varying sample sizes. Fig. 3(c) the funnel plot for TLR gene study suggests the presence of publication bias or other small-study effects. This is supported by the uneven distribution of studies on the right side of the no-effect line (RR=1). The plot indicates a dearth of research with small sample sizes and high standard errors on the left side, indicating a potential inclination to select and publish

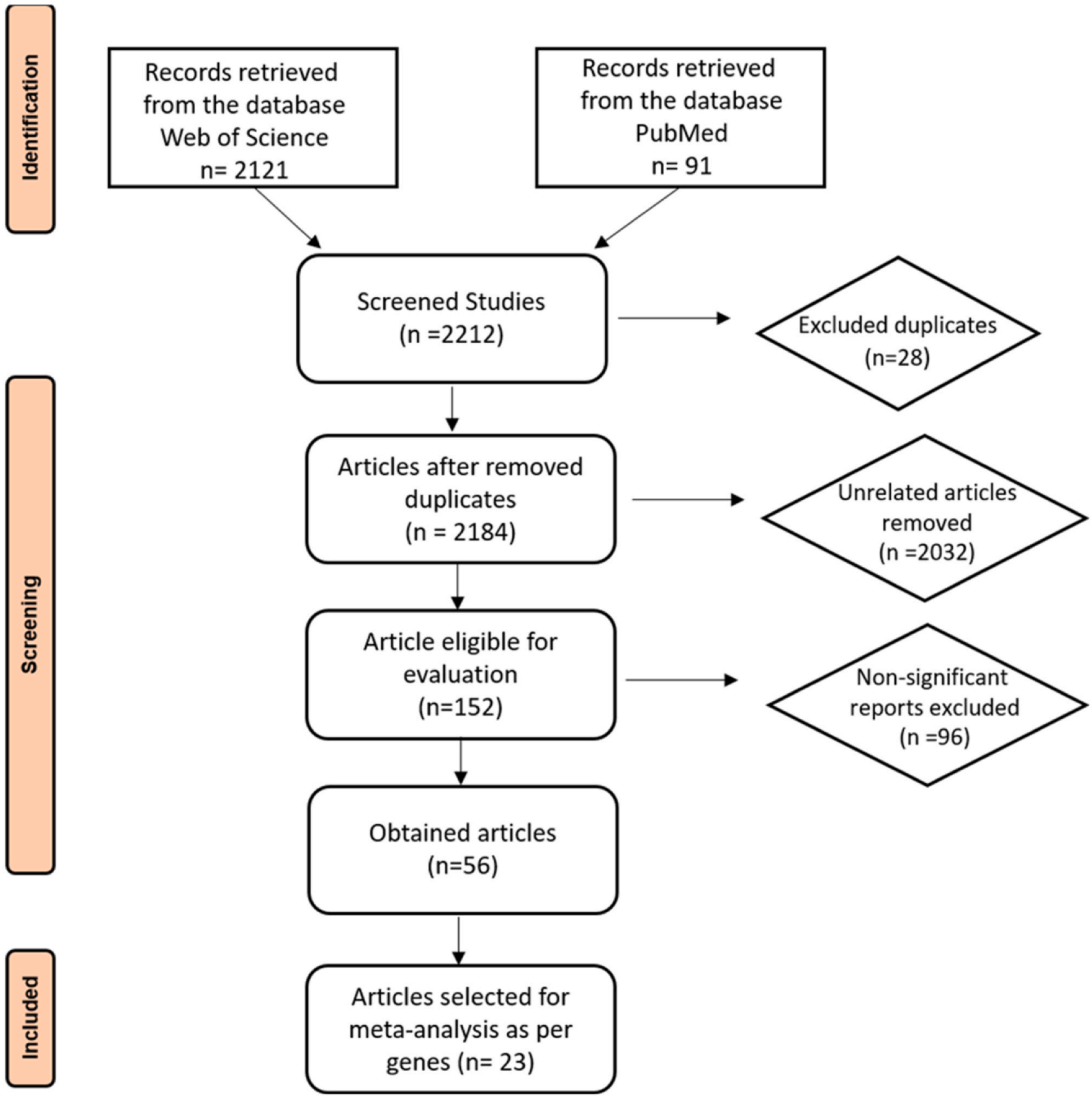

Fig. 1. Schematic diagram illustrating the search strategy. This PRISMA flowchart illustrates the phases of article selection that eventually identified 23 articles that qualified for inclusion in the meta-analysis review.

studies with favourable or significant outcomes. The clustering of studies in the upper-middle region indicates that the majority of the studies that were included possess a moderate to high degree of accuracy. The lack of investigation on the bottom left quadrant may suggest the absence of studies with conclusions that are not statistically significant. Fig. 3(d) the funnel plot for study on the CD09 gene indicates a distribution that is highly symmetrical around the line of no effect. This pattern is commonly associated with low publication bias. Nevertheless, there is a subtle signal of imbalance with a lower number of studies on the left side, which could imply the possibility of small-study effects or publication bias. The distribution of research across different degrees of precision is moderate, although additional studies are required at the lower end of precision to validate the symmetry. The plot suggests the need for further inquiry into potential biases, despite the generally consistent reporting across different sample sizes.

HLA class I and II

Nine studies were included to observe the association between the HLA genes and DHF [14,18–25]. The meta-analysis was carried out using RevMan 5.4.1 on a random model to generate the statistical parameters. Fig. 2(a) shows the forest plot for the HLA gene. The analysis estimated an odd ratio of 0.62 [0.27, 1.42], heterogeneity: $Tau^2 = 1.34$; $Chi^2 = 154.43$, df = 7 ($P < 0.00001$); $I^2 = 95\%$, and overall effect: $Z = 1.14$ ($P = 0.25$). This indicates that the estimated probabilities of the outcome were 0.62 times lower in the exposure group than in the control group. The 95% confidence interval (CI) for OR ranged from 0.27 to 1.42, indicating low OR estimation precision in the studies. Moreover, the OR jumped to the value of 1 in this 95% CI, which signifies that there might be a high risk for DHF patients associated with HLA genetic variants (exposed cases). Heterogeneity (I^2) was calculated at 95%, which indicates considerable variability among the individual studies.

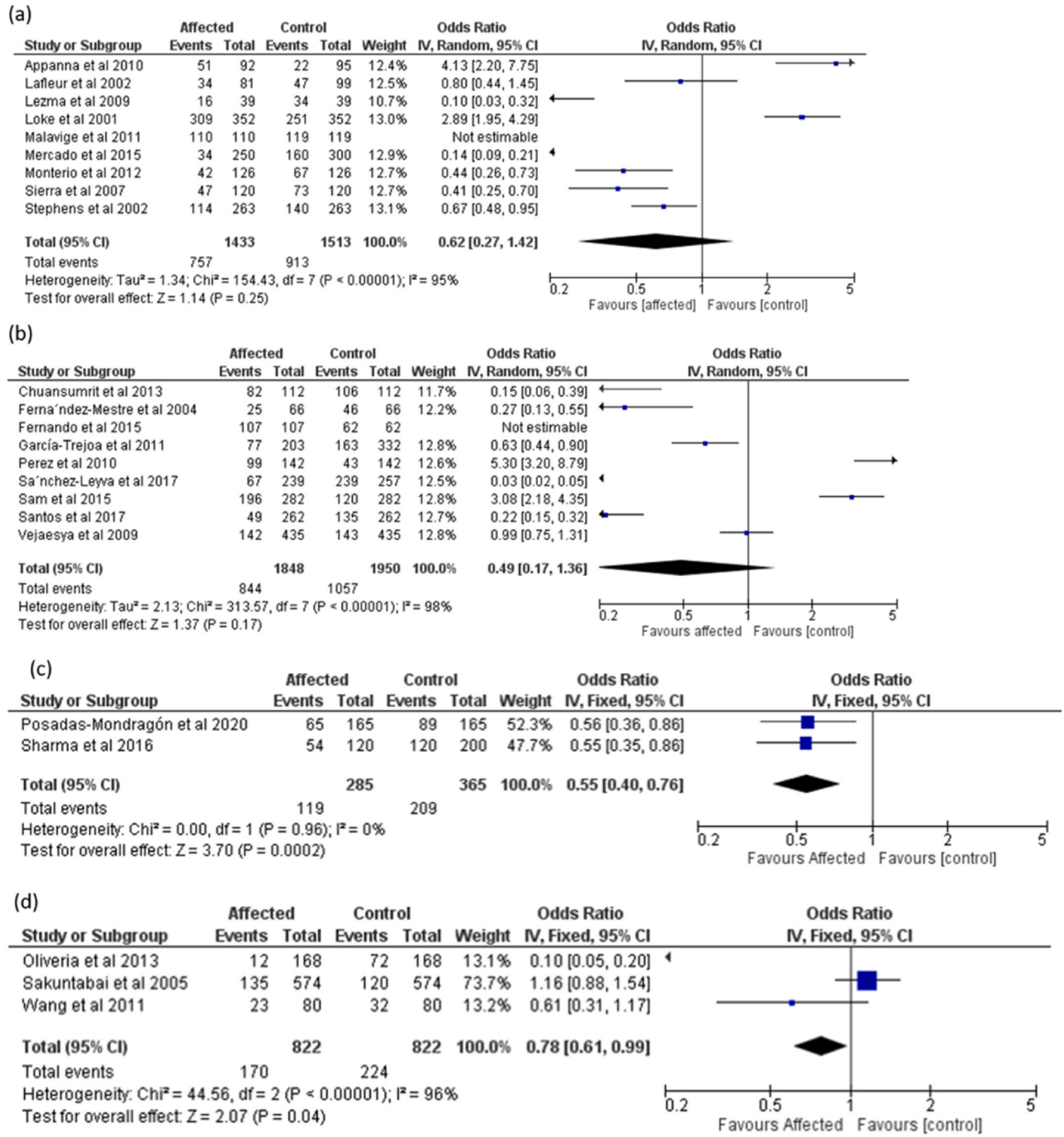

Fig. 2. Meta-analysis of genetic variation associated with DHF condition. The RevMan tool was used for the meta-analysis of gene count data collected from published articles on DHF subjects. The odds ratio (OR) for the most severe form of association is given for each gene model (a) HLA and (b) TNF, (c) TLR and (d) DC-SIGN(CD209).

In a meta-analysis, heterogeneity is the variation in findings that may be related to demographic, intervention, comparator, outcome measure, risk of bias, research technique, healthcare systems, and other variables. The Tau² and Chi² values estimate additional statistics on the heterogeneity. A high Chi² value and a significant P-value ($P < 0.00001$) indicate the heterogeneity among the studies was statistically significant. Moreover, a Z-value of 1.14 and a corresponding P-value of 0.25 represent a test for the overall effect of the HLA gene on DHF. The P-value of 0.25 is greater than 0.05, indicating that there is not enough evidence to disprove the null theory and conclude that there is no statistical association between HLA and DHF. In conclusion, the meta-analysis suggests no significant relationship was found between HLA and DHF, as indicated by the effect size, confidence interval, and overall effect test results. However, as per an individual study, it was observed that there was a positive relationship with DHF. The alleles associated with the selected studies were HLA*B13, HLA-DRB1 * 04, HLA-DQB1 * 302, HLA-A, HLA-DRB1 * 08, HLA-A, DRB1, HLA-A* 01, HLA-B* 15, and A* 31, as presented in Table 1.

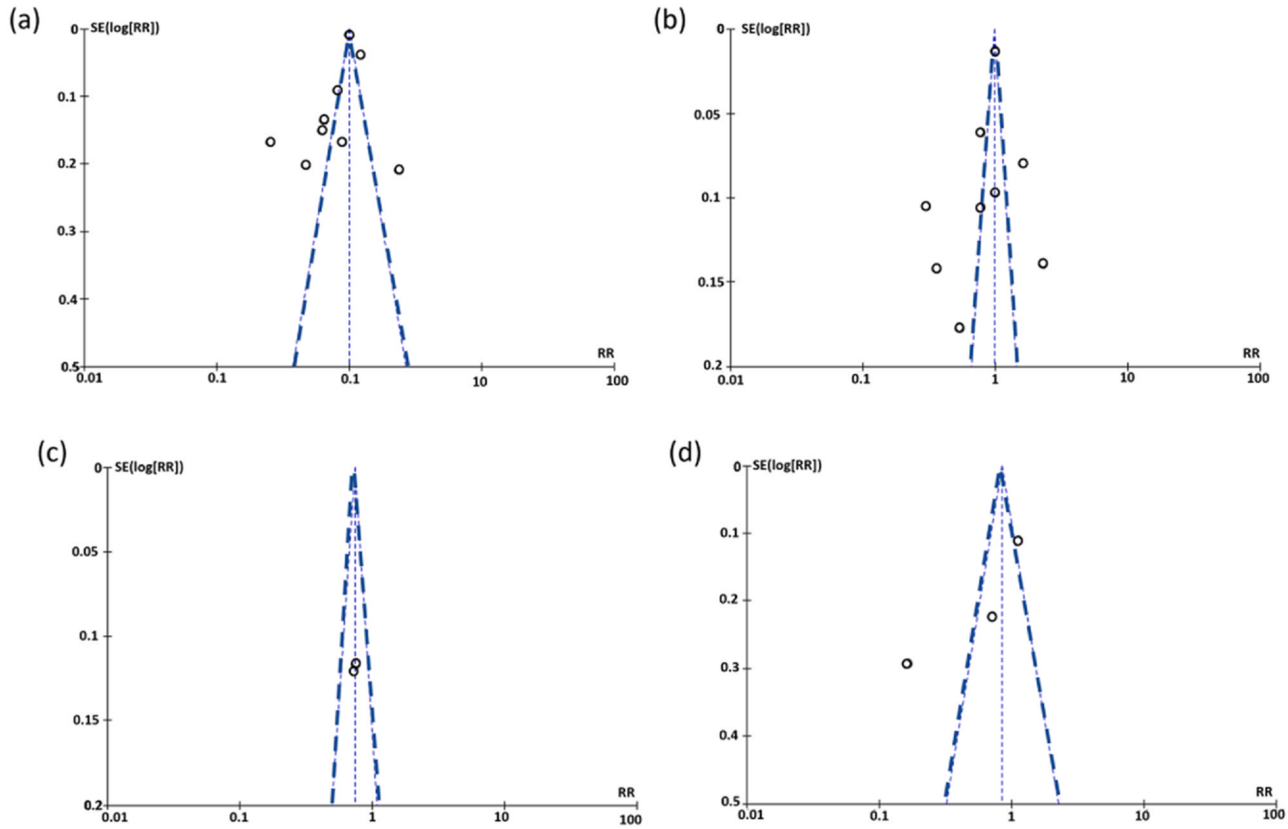

Fig. 3. Funnel plot representation of studies (a) HLA vs DHF, outcome: 1.1 HLA susceptibility (b) TNF vs DHF, outcome: 2.1 TNF susceptibility (c) TLR vs DHF, outcome: 3.1 TLR susceptibility (d) CDO9 vs DHF, outcome: 4.1 CDO9 susceptibility.

Table 1
Dissemination of HLA genes between control and affected DHF cases.

Studies	Countries/ ethnic population	DHF	Control	Total	Gene
Appanna et al. [18]	Malaysia	51	95	92	HLA*B13
Lezama et al. [19]	Mexican Mestizo	16	34	39	HLA-DQB1 * 302
Lafleur et al. [20]	Mexico	34	99	81	HLA-DRB1 * 04
Loke et al. [14]	Vietnam	309	251	352	HLA-A
Malavige et al. [21]	Srilanka	110	119	110	HLA-DRB1 * 08
Mercado et al. [22]	Philippines	34	300	250	HLA-A, DRB1
Monteiro et al. [23]	Brazil	42	67	126	HLA-A* 01
Sierra et al. [24]	Cuban	47	189	120	HLA B* 15, A* 31
Stephens et al. [25]	Thai	114	140	263	HLA Class1

TNF-α

TNF-alpha's relationship with the DHF condition was investigated in nine studies [11,26–33]. TNF-alpha 308 A, TNF-alpha, and TNF-alpha 238 are among the genes and alleles associated with the selected studies, as other cytokines, including IFN, IL-6, TGF Beta1, IL-10, IL-10, IL-2, and the LTA haplotype, as listed in Table 2. The meta-analysis was carried out in RevMan 5.4.1 using a random model, and a forest plot was generated that showed an odd ratio of 0.49 [0.17, 1.36] heterogeneity: $Tau^2 = 2.13$, $Chi^2 = 313.57$, df = 7 ($P < 0.00001$); $I^2 = 98\%$; and overall effect: Z = 1.37 (P = 0.17). This indicates that the estimated odds of outcome (DHF condition) in the exposure group (variants in the TNF gene) were 51% lower than in the reference group. This meant that people with different TNF genotypes were at lower risk of developing DHF, and there was a link between TNF genetic variants and the condition. The 95% CI in OR was [0.17, 1.37], indicating that the study's precision in OR estimation was low and the interval was relatively large. Moreover, the OR crossed the value of 1 in the 95% CI, which signifies that there might be a high risk for DHF patients associated with TNF genetic variants (exposed cases). Here, I^2 was calculated at 98%, which indicates the considerable variability among the studies collected in this analysis. In a meta-analysis, heterogeneity is the variation in findings that may be related to demographic, intervention, comparator, outcome measure, risk of bias, research technique, healthcare systems, and other variables. The Tau^2 and Chi^2 values estimate additional statistics on the heterogeneity. A high Chi^2 value and a significant P-value ($P < 0.00001$) indicate that the heterogeneity is statistically significant. Moreover, a Z-value of 1.36 and a corresponding P-value of 0.17 represent a test for the overall effect of the TNF gene on DHF. The P-value of 0.17 is greater than 0.05, indicating that there is insufficient evidence to cast off the null hypothesis and conclude that there is no statistical association between TNF and DHF. In conclusion, the statistical analysis suggests no significant relationship was found between variation in the TNF gene and DHF, as indicated by the effect size, confidence interval, and overall effect test results. However, as per an individual study, it was observed that there was a positive relationship between TNF and DHF in some cases.

Table 2
Distribution of TNF genes between control and affected DHF cases.

Studies	Countries/ ethnic population	DHF	Control	Total	Gene
Chuansumrit et al. [26]	Bangkok	82	106	112	TNF-alpha 308 A
Fernandez-Mestre et al. [27]	-	25	46	66	TNF-alpha
Fernando et al. [28]	Srilanka	107	62	107	TNF-alpha 308
García-Trejo et al. [29]		77	332	203	TNF-alpha 238, TNF-alpha 308
Perez et al. [11]	Cuban	99	43	142	TNF-alpha 308
Sam et al. [30]		196	120	282	TNF-alpha 308
Sanchez-Leyva et al. [31]	Mexico	67	257	239	TNF-alpha 308
Santos et al. [32]	Brazilian	49	135	262	TNF-alpha 308
Vejbaesya et al. [33]	Ethnic Thais	142	143	435	TNF-alpha

TLR

Only two studies were found and used in this analysis to understand the association between TLR gene variants and DHF [34,35]. These studies included different members of TLR. These were: TLR4 (Asp299Gly and Thr399Ile), TLR3, TLR7, and TLR8 as listed in Table 3. The meta-analysis was performed using a fixed model and a generated forest plot that showed an odd ratio of 0.55 [0.40, 0.76], heterogeneity: $Chi^2 = 0.00$, $df = 1$ ($P = 0.96$); $I^2 = 0\%$, and overall effect: $Z = 3.70$ ($P = 0.0002$). The 95% CI for OR was between 0.40 and 0.76, indicating that the precision of the OR estimation was high in the study due to the small interval size. Moreover, the OR value is less than 1 in the 95% CI which signifies that there might be less risk for DHF patients associated with TLR genetic variants (exposed cases) or that exposure might be a protective factor against DHF. Here, I2 = 0% suggests no heterogeneity due to the smaller number of studies considered. Moreover, a P value of 0.0002 showed a statistically significant association between TLRs and DHF.

DC-SIGN promoter CD209 gene

Three studies were selected to understand the association between CD209 gene variants and the DHF condition [36–38]. These studies included the CD209–336A/G alleles of this gene, as listed in Table 4. The meta-analysis showed a 0.78 [0.61, 0.99] odd ratio, heterogeneity: $Chi^2 = 44.56$, $df = 2$ ($P < 0.00001$); $I^2 = 96\%$ and an overall impact size of $Z = 2.07$ ($P = 0.04$). The result showed a significant association between CD209 and DHF, as depicted by the low P-value. The odd ratio of 0.78 at the 95% confidence interval ranged from 0.61 to 0.99, suggesting that individuals with CD209 variants may have a 32% less likely to develop DHF. The I2 value of 96% and heterogeneity statistic (Chi2 = 44.56, df = 2, P 0.00001) show that there is substantial variation in the findings across studies. The overall impact size Z of 2.07 with a P value of 0.04 specifies that the association between CD209 and DHF is statistically significant. The meta-analysis indicated that individuals with CD209 may have a lower risk of DHF than those without the gene. However, substantial variation was detected across studies, and additional studies may be required to understand the causes of this variation and further confirm the association.

Discussions

Numerous case controls and meta-analyses have been performed to understand the association between various genetic variants and DHF [32,39]. The current study examined four genes associated with DHF, including HLA classes I and II, TNF, TLR, and DC-SIGN (CD209). Here, the affected cases and controls were taken from the selected study to investigate the data. Following the findings of the meta-analysis conducted on the HLA, no statistically significant correlation exists between the DHF and the HLA, which has been shown as a cumulative impact from the chosen studies. However, several studies found that HLA class I and II alleles were susceptible to and protective against DHF [10,40]. Similarly, in the investigated HLA studies, Appanna et al. (2010) showed an odd ratio of 4.16 with 95% CI values of (2.20. 7.75) that indicated high precision in OR estimation. Moreover, the OR was higher than 4.16 (> 1), which signifies that there might be a 4.16-fold higher risk for DHF patients associated with HLA genetic variants (exposed cases) found in the Malaysian population. Furthermore, evaluating these potential relationships in a larger population requires exploration. Moreover, another selected study conducted by Loke et al. (2001) showed an odd ratio of 2.89 with a confidence interval of 1.95–4.29. This indicates that the OR value was greater than 1, indicating the odds of exposure (genetic variants in HLA) among the affected individuals. The probabilities of exposure were greater than among the controls. This suggested the HLA variant may be a risk factor for the DHF observed in the Vietnamese population. However, other factors are also considerable, including study design, sample size, and potential confounding variables that must be considered to draw more definitive conclusions. This demonstrated that more specific studies were required to investigate the HLA and DHF associations to comprehend the complicated genetic foundations underlying severe dengue infection completely. It is also suggested that HLA-alleles associated with greater vulnerability to DHF can differ among populations. The TNF-α meta-analysis found a negative association with DHF (OR = 0.49, 95% confidence interval [0.17, 1.37], p-value = 0.17), and the outcome was not statistically significant that showed a high level of heterogeneity ($I^2 = 98\%$). This means elevated TNF levels may not be related to DHF in the selected studies. However, it was observed that Perez et al. (2010), one of the investigated studies in the TNF meta-analysis, showed an odd ratio of 5.30 (3.20–8.79), indicating a 5.3 times higher risk of DHF that can be caused by variants of TNF- α. This suggested the TNF variant might be a threat factor for the DHF in the given set of populations. Another study by Sam et al. (2015) found a higher OR of 3.08, indicating that TNF variation is linked to an increased risk of DHF. In this case, the relatively large interval [2.18 to 4.35] indicates that the estimate involves a certain degree of uncertainty. This could result from multiple factors, including data variability or a comparatively small sample size. This finding demands more specific studies to understand their association, as selected individual studies showed both a positive and negative relationship with DHF. On the other hand, the meta-analysis of two studies investigating the relationship between

Table 3
Distribution of TLR genes between control and affected DHF cases.

Studies	Countries/ ethnic population	DHF	Control	Total	Gene
Posadas-Mondragón et al. [34]	Mexico	65	89	165	TLR3, TLR4, TLR7, and TLR8
Sharma et al. 2016 [35]	Lucknow, India	54	200	120	TLR4 (Asp299Gly and Thr399Ile)

Table 4
Distribution of DC-SIGN CD209 genes between control and affected DHF cases.

Studies	Countries/ ethnic population	DHF	Control	Total	Gene
Oliveira et al. [36]	Para, Brazil	12	72	168	CD209 – 336A/G
Sakuntabhai et al. [37]	Thailand	23	32	80	CD209
Wang et al. [38]	Taiwan	135	120	574	CD209 – 336A/G

TLRs and DHF found it to be statistically significant. The result showed no heterogeneity due to the small set of studies considered. Lastly, the meta-analysis of three studies investigating the relationship between the CD209 gene and DHF showed a statistically significant negative association with a high level of heterogeneity. This means individuals with a certain allelic variation in the CD209 gene may be less likely to develop DHF. Overall, the meta-analysis results suggest a possible association between these genetic factors and DHF, but the heterogeneity and lack of studies contribute to it being difficult to reach definitive conclusions. Several alleles were found to have a positive relationship with DHF; however, in a few instances, these associations were not found to be statistically significant. To substantiate these conclusions, additional research must be conducted.

Conclusion

Here, the meta-analysis was performed that showed there was a statistically significant link between TLR and the DHF condition and CD209 and the DHF condition. Furthermore, the meta-analysis results showed no statistically significant association between HLA alleles, TNF, and the DHF condition. Moreover, the odd cumulative ratio for all genes was less than one, but in certain studies, it crossed 1. Further, the study has important practical consequences for healthcare professionals. It emphasises the significance of genetic variables in the vulnerability to Dengue Hemorrhagic Fever (DHF). Healthcare professionals should possess knowledge on the correlation between particular genetic indicators, such as TLR and CD209, and the susceptibility to developing DHF. This comprehension can direct more individualised methods for evaluating, preventing, and potentially, managing plans for patients in places susceptible to dengue. Nevertheless, the study proposes additional investigation, indicating that the implementation of clinical practices should be informed by continuous findings in this developing field of research.

Institutional review board statement

Not applicable.

Informed consent statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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