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Dengue Virus Infection and Skin Manifestations: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Dengue virus infection is a severe systemic condition primarily transmitted by its main vector, *Aedes aegypti*. Skin rash may be the initial symptom in patients with dengue virus infection, which could be helpful for clinical diagnosis. This research aimed to evaluate the prevalence of skin manifestations associated with dengue virus infection worldwide.

Materials & Methods: Electronic resources such as Scopus, Medline (via PubMed), and Web of Science were searched to identify studies focusing on skin manifestations in patients with dengue virus infection between 2000 and 2024. Statistical analysis was conducted using Stata software, and sources of heterogeneity were assessed using I^2.

Findings: A total of 24 papers (six prevalence studies and 18 case reports/case series) were included. A meta-analysis of prevalence studies revealed that skin manifestations were reported in patients with dengue virus infection in three countries (India, Pakistan, and France), with an overall prevalence of 63.2% (95% CI: 54.4-71.1) among 962 dengue virus-infected patients. Analysis of case reports/case series showed that among 19 dengue virus-infected cases, skin rash and thrombocytopenia were the most common skin manifestations and laboratory indications, respectively.

Conclusion: Dengue virus infection could result in various dermal manifestations with distinct clinical symptoms and laboratory findings. These skin involvements may aid in the timely diagnosis of patients with dengue virus infection.

Keywords: Dengue virus, Skin manifestation, Systematic review, Meta-analysis

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Introduction

Dengue virus is an enveloped, single-stranded, positive-sense RNA genome, belonging to the family Flaviviridae (genus Orthoflavivirus). Four different serotypes of dengue virus have been identified globally, which could be distinguished by their antigenic differences [1]. Recent research has revealed that the RNA polymerase in dengue virus is an error-prone, RNA-dependent enzyme that lacks a proofreading mechanism, which results in approximately one mutation per round of genome replication, leading to genetic diversity and the emergence of various serotypes of dengue virus. Additionally, genetic recombination has also been suggested to contribute to intra-serotype genetic variation in dengue virus [2].

Dengue virus is known as the most rapidly spreading mosquito-borne infection in the world. Due to urbanization and climate change, the global burden of this disease is projected to increase as the virus spreads to new geographical regions [3].

This virus is primarily transmitted by *Aedes* mosquitoes, especially *A. aegypti*, *A. albopictus*, *A. polynesiensis*, and *A. scutellaris* [4]. While mosquitoes are most active during dusk and dawn, *Aedes* mosquitoes are anthropophilic and could bite indoors during the day. The virus has no harmful effects on the mosquito, and the mosquito remains infected for the rest of its life [5]. Symptoms of dengue virus infection include fever, headache, muscle and joint pains, and skin rashes similar to measles. In severe cases, abnormal manifestations of pulmonary, gastrointestinal, and cardiac diseases have been reported [4]. Rarely, the disease could progress into dengue hemorrhagic fever (DHF), which could lead to bleeding, thrombocytopenia, and leakage of blood plasma, potentially resulting in dengue shock syndrome (DSS) with dangerously low blood pressure [6]. Diagnostic methods for detecting dengue virus in humans include reverse transcriptase-polymerase chain reaction (RT-PCR), Enzyme-Linked Immunosorbent Assay (ELISA), NS1 antigen detection, hemagglutination inhibition (HI), and immunochromatography [7].

Skin rash occurs in 50-82% of patients with dengue virus infection, typically appearing 3 to 4 days after the onset of fever. The rash may start as flushing erythema before developing into a maculo-papular or morbilliform eruption, sometimes forming "white islands in a red sea" or Herman's rash. It usually begins on the palms of the hands and feet before spreading to the arms, legs, and trunk, remaining without scaling for a period [8, 9]. Itching and swelling may also occur in some patients due to immune system responses. Hemorrhagic skin manifestations like petechiae and purpura are more common in DHF and DSS [10, 11].

Treatment for dengue virus infection involves oral support and hydration for mild to moderate cases, while severe cases may require intravenous electrolytes or blood transfusion [12]. Skin rashes could serve as clinical manifestations of dengue virus infection and may aid in improving diagnostic methods.

Objectives: This study aimed to analyze patients with skin manifestations caused by dengue virus infection through a systematic review and comprehensive meta-analysis.

Materials and Methods

Literature search: This meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and included a comprehensive literature search in Medline (PubMed), Scopus, and Web of Science (WOS). A structured search strategy was developed using Boolean operators, parentheses, truncations, and medical subject headings

Table 1) Frequency of skin manifestations among dengue virus-infected cases in various subgroups

Patients with Skin Manifestations Associated with Dengue Virus Infection	Prevalence% (95% CI)	No. of Studies	No. of Dengue virus Infected Cases with Skin Manifestations	I-Squared
Overall	63.2 (54.4-71.1)	6	606	84.83%

(MeSH). The core PubMed search combined controlled vocabulary and free-text terms as follows: "dengue" [13] OR "dengue virus" [13] OR "dengue hemorrhagic fever" OR "dengue fever" OR "dengue virus infection" OR "dengue shock syndrome" AND "skin diseases" [13] OR "cutaneous manifestation" OR "skin rash" OR dermatolog OR "mucocutaneous manifestation". Equivalent Boolean-based strategies were adapted for searching Scopus and WOS. Complete and precise search strings for all databases are provided in Supplementary Table 1. Filters were applied to restrict results to human studies published in English between January 2000 and December 2024, and duplicates were removed electronically and verified manually.

Eligibility criteria: Original research studies reporting skin manifestations associated with dengue virus infection were eligible if they contained sufficient scientific data, including diagnostic methods and study location. Exclusion criteria were animal studies, articles on dengue virus infection without dermatologic findings, narrative or systematic reviews, meta-analyses, conference abstracts, editorial correspondence, duplicate publications, and studies not published in English. Two independent reviewers screened titles, abstracts, and full texts to determine study eligibility, and disagreements were resolved by consensus.

Data extraction: During the data extraction process, all critical information was gathered and categorized as follows: period of sample collection, date of publication, country, number of patients with dengue virus infection, number of patients with skin manifestations associated with dengue virus infection, type of skin symptoms, diagnostic methods used for dengue virus, and clinical manifestations. The quality of the studies included was assessed by two reviewers using an adapted version of the Joanna Briggs Institute (JBI) checklist [14].

Statistical analysis: All statistical calculations were conducted using Stata 18.0 software to analyze the frequency of skin manifestations in patients with dengue virus infection worldwide. Statistical heterogeneity was assessed using the Q-test and the I^2 statistical methods. In cases of low heterogeneity (I^2 = 0–25%), a fixed-effect model was deemed suitable. For moderate (I^2 = 25–75%) or high heterogeneity (I^2 > 75%), a random-effects model was typically used. A p-value of less than 0.05 was considered statistically significant.

Findings

Characteristics of included studies: Initially, 327 papers were found through the literature search. After removing duplicates, 220 articles remained for screening. Of these, 167 articles were excluded due to irrelevant titles and abstracts (e.g., skin manifestations caused by dengue virus infection were not specifically mentioned (n=64), retrospective nature of the articles (n=92), and use of previously collected data (n=11)). After full-text review, six prevalence studies were selected for final analysis (Figure 1). The characteristics of the analyzed studies could be found in Supplementary Table 2.

Frequency of skin manifestations among patients with dengue virus infection based on prevalence studies: To standardize reporting across highly variable primary articles, a working definition of "skin manifestations" was proposed, defined as any clinically documented cutaneous abnormality occurring during dengue infection, including both primary lesions (e.g., macules, papules, and petechiae) and secondary changes (such as erythema, morbilliform eruptions, and desquamation). Out of the six articles that discussed skin manifestations among dengue virus-infected cases, five were conducted in Asia and one in Europe (France) (Supplementary Table 2). All six included studies had a moderate risk of bias (Supplementary Table 3). The results showed that all published studies reporting dermal manifestations in dengue virus-infected patients were published over only 6 of the past 24 years, with the highest number of records in 2012, 2014, and 2024, respectively (Figure 2). After meta-analysis of prevalence studies, it was found that the incidence of cutaneous symptoms among patients with dengue virus infection was reported in three countries (India, Pakistan, and France), with an overall frequency of 63.2% (95% CI: 54.4–71.1) among 962 dengue virus-infected cases (Table 1).

Figure 3A presents the forest plot of the meta-analysis. The pooled prevalence of skin manifestations was 63.2% (95% CI: 54.4–

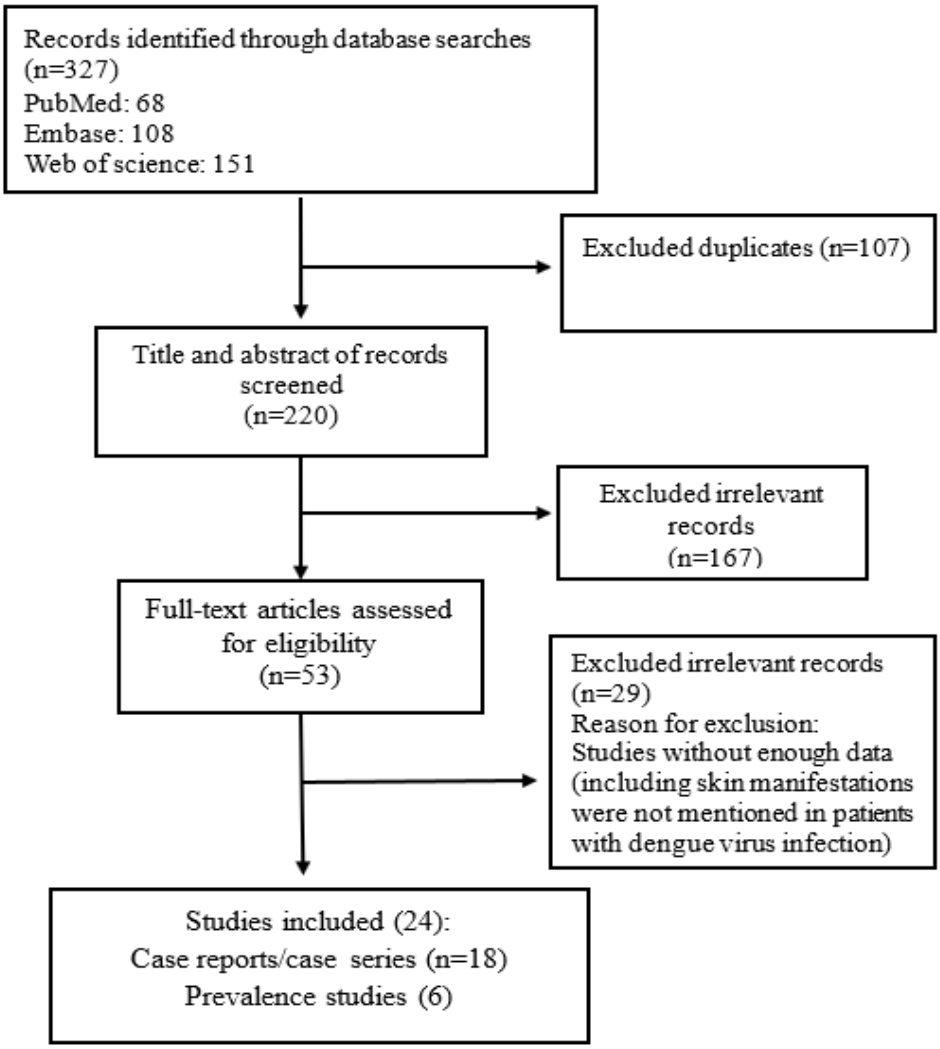


Figure 1) Flow chart of study selection for inclusion in this systematic review and meta-analysis (2000-2024)

71.1). A random-effects model was used due to substantial heterogeneity among the studies (I^2 = 84.83%, τ^2 = 0.16; Q-test: p < .001). The funnel plot (Figure 3B) and Galbraith plot (Figure 3C) were used to visually assess potential heterogeneity and publication bias.

Frequency of skin manifestations among patients with dengue virus infection based on case reports/case series: For

Table 2) Summary of the case reports and case series findings

Variables	Number of Studies	Number of Patients with Skin Manifestations
Study design		
Case reports	17	17
Case series	1	2
Types of skin manifestations		
Yellowish discoloration of the skin	1	1
Rash	6	6
Petechial rash	1	1
Erythematous rash	2	2
Maculopapular rash	1	1
Chik sign	1	1
"White islands in a sea of red" rash pattern	2	2
Erythema	1	1
Macular morbilliform erythema	1	1
Erythroderma	1	1
Hyperpigmented lesion	1	1
Vasculitic skin lesion	1	1
Hemorrhagic skin lesions	1	2
Clinical findings		
Fever	4	4
Fatigue	1	1
Myalgia	2	2
Nausea	2	2
Vomiting	1	1
Headache	1	1
Chills	1	1
Bone pain	1	1
Conjunctiva hemorrhage	1	1
Dry cough	1	1
Dengue encephalopathy	1	1
Diarrhea	1	2
Hepatomegaly	2	2
Splenomegaly	1	1
Underlying diseases		
Hepatitis A virus coinfection	2	2

Variables	Number of Studies	Number of Patients with Skin Manifestations
Laboratory parameters		
Hemophagocytic lymphohistiocytosis	1	1
Leukocytosis	1	1
Leukopenia	2	3
Neutrophilia	1	1
Lymphocytopenia	1	1
Thrombocytopenia	11	12
Elevated CRP	1	1
High Prothrombin time	1	1
High creatine kinase	2	2
Elevated LDH	1	1
Elevated ALT	2	2
Elevated AST	2	2
Diagnostic methods		
Serological tests	11	11
RT-PCR assay	2	2
Both serological and RT-PCR methods	3	3
Not reported (NR)	2	3

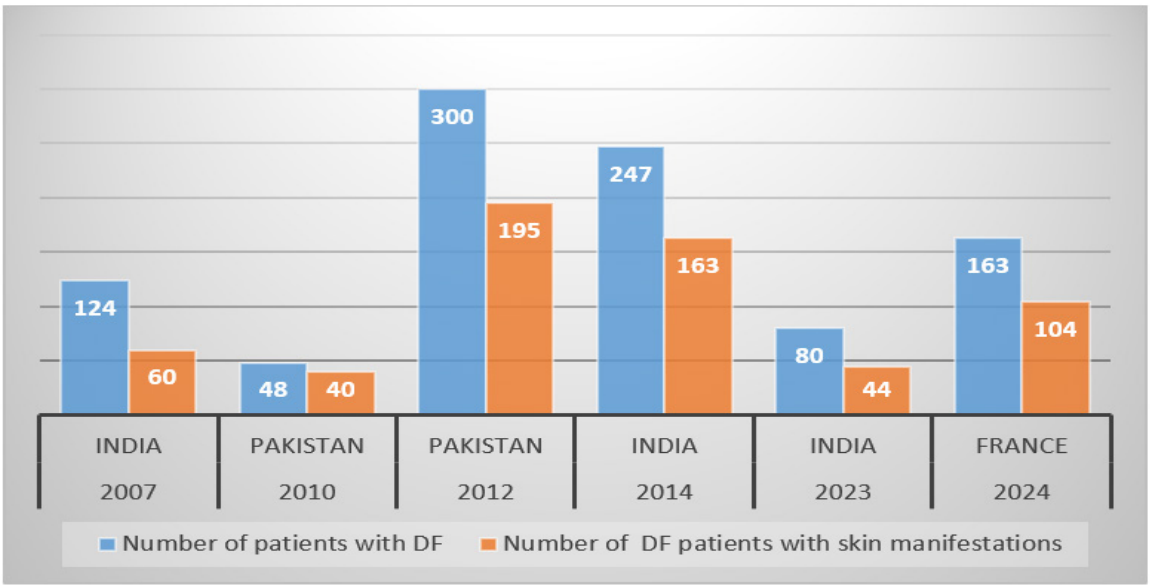
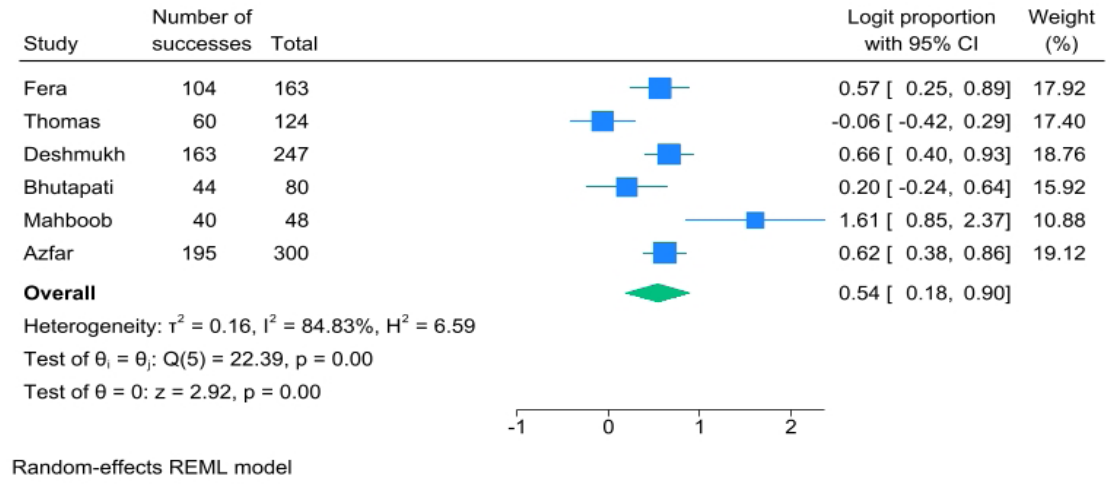


Figure 2) Temporal trend of dengue fever (DF) cases with cutaneous manifestations in different countries. Skin manifestations were reported in a considerable proportion of DF cases, peaking during major outbreaks (notably in Pakistan in 2012 and India in 2014) and then declining in more recent years.

consistency with the prevalence analysis, all reported skin findings were reclassified into the same three predefined categories (exanthematous, hemorrhagic/vascular, and pigmentary/other). This approach reduced confusion between primary and secondary lesions and allowed a more standardized comparison across heterogeneous case reports.

To illustrate the spectrum of possible dermatological presentations, published case reports and case series were analyzed de-



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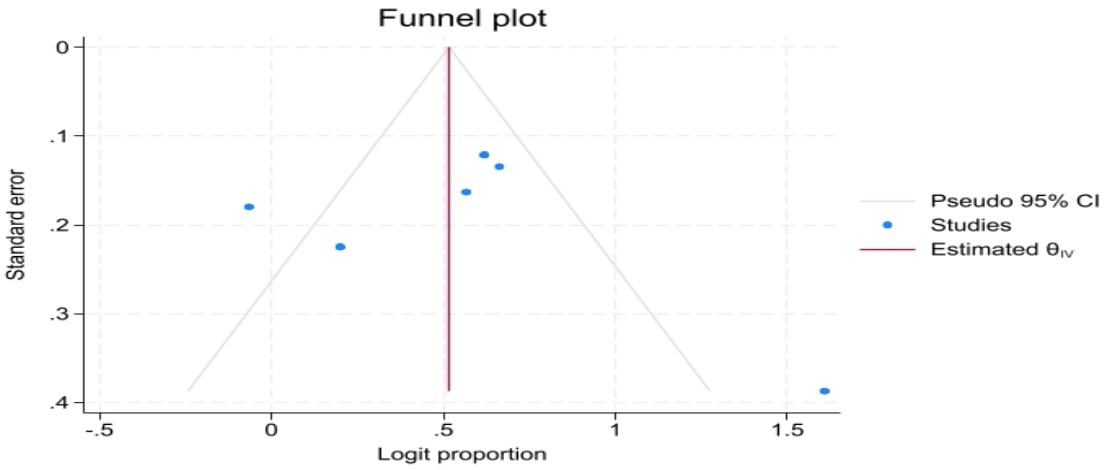

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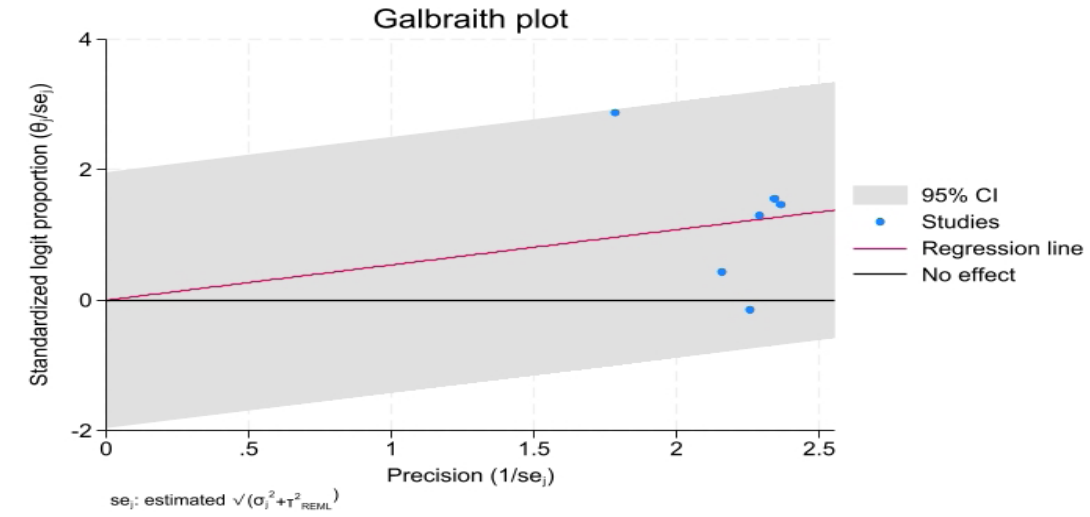

C

Figure 3) Forest plot (A), Funnel plot (B), and Galbraith plot (C) of the meta-analysis on the prevalence of skin manifestations among patients with dengue virus infection worldwide

scriptively. It is critical to emphasize that the following statistics are derived from a non-representative sample of published cases subject to significant reporting bias. They are presented here to describe the range of reported findings and must not be interpreted as prevalence estimates.

After assessing the prevalence articles, case reports/case series papers with sufficient data on skin-related symptoms among dengue virus-infected cases were analyzed. The characteristics of these studies are represented in Supplementary Table 4.

According to the results, 13 different types of skin manifestations were observed among 19 dengue virus-infected patients in 13 countries (Table 2). These cases were mostly in India and Austria (three cases each), followed by Japan and Taiwan (two cases each). No articles were conducted in Africa and Oceania.

Among dengue virus-infected individuals whose sex was known, ten patients with dermal manifestations were female, and seven were male, with an average age of 37 years. Rash (n=6), erythematous rash (n=2), "white islands in a sea of red" rash pattern (n=2), and hemorrhagic skin lesions (n=2) were among the types of skin manifestations reported.

Furthermore, clinical findings among these patients were investigated. The results showed that 12 types of clinical symptoms were reported. Fever (n=4), myalgia (n=2), nausea (n=2), and hepatomegaly (n=2) were the most commonly reported symptoms.

Moreover, comorbidities were also investigated. Only two patients with dengue virus infection also suffered from hepatitis A virus (HAV) infection. Laboratory tests revealed that thrombocytopenia (n=12) and leukopenia (n=3) were the most frequently reported abnormalities.

In terms of diagnosis, this viral infection was predominantly diagnosed by serological tests (n=11), followed by polymerase chain reaction (PCR) (n=2). In three patients, these methods were utilized to identify the virus. However, the other three patients were diagnosed based on clinical findings and laboratory parameters, not molecular or serological tests. Only five studies mentioned the treatment process of patients, which included albumin replacement, administration of antipyretics and vitamin K, blood transfusions, and ascites puncture (n=1); gamma globulin transfusion, plasma transfusion, and administration of anti-inflammatory and antipyretic drugs (n=1), and supportive treatment (n=3) (Table 2).

Discussion

Despite the fact that the first observed dengue epidemic occurred in Southeast Asia and then progressively spread to Latin America, present data suggest that the burden of dengue is now identical in both locations [3]. This study demonstrated that all case reports and case series related to dengue virus infection were conducted in 13 countries from three different continents, with the majority of them reported in Asian countries. Female patients made up a larger proportion of dengue cases than males, and the mean age of patients was approximately 37 years**.** Saleem and Shaikh (2008) reported that youth were more vulnerable to dengue virus infection, with the youngest and oldest patients being 11 and 42 years old, respectively [15].

To reduce inconsistency in dermatological terminology across studies, a structured classification system was applied, distinguishing primary exanthematous lesions, hemorrhagic/vascular findings, and pigmentary/other atypical manifestations. Similar to other RNA viruses [16], there may be different types of skin manifestations caused by dengue virus. Scientists suggest that around half of dengue virus-infected cases

present cutaneous symptoms [17]. This review could be considered the first meta-analysis study on skin manifestations associated with dengue virus infection, providing a precise evaluation of relevant prevalence studies as well as case reports and case series. However, the pooled prevalence estimates of 63.2% (95% CI: 54.4–71.1) derived from the meta-analysis of prevalence studies should be interpreted with caution due to considerable statistical heterogeneity (I^2 = 84.83%; Table 1). This high heterogeneity reflects substantial variation among the included studies, likely stemming from differences in diagnostic criteria for dengue infection, definitions of specific skin manifestations, study populations (e.g., age groups, clinical settings), and geographical factors such as circulating dengue virus serotypes. Despite this variability, which underscores the challenge of deriving a single precise estimate, our synthesis confirms that cutaneous involvement is a common and clinically significant feature of dengue infection.

Among the published case reports and case series analyzed, rash was the most frequently described manifestation, noted in 31.57% of these reported cases. However, this figure likely reflects reporting bias towards significant manifestations and should not be interpreted as the true prevalence among all dengue patients.

According to Wu et al. (2000), dengue virus appears to initially target skin dendritic cells during arthropod-to-human transmission [18]. In theory, scientists have hypothesized that the appearance of a skin rash following dengue virus infection could be associated with damaged small blood vessels. More specifically, flavivirus infection of vascular endothelium could lead to a range of complications, including perivascular edema, endothelial swelling, and mononuclear cell infiltration. These pathological changes could trigger immune responses through the release of pro-inflammatory cytokines, ultimately exacerbating tissue damage [19, 20]. Additionally, activation of T-cells and cutaneous dendritic cells has been proposed as a contributing factor in the development of dengue shock syndrome [21]. Clinicians have demonstrated that these skin manifestations are non-specific and highly variable. Dengue virus non-structural protein 1 (NS1) is a virulence factor that damages endothelium, leading to vascular injury and increased permeability [22]. Pathogenically, virus-host cell interaction is thought to trigger the release of chemical mediators and subsequent immunological responses that may contribute to skin rash development [23]. According to clinical reports, there are two stages of dengue virus infection-linked skin rash occurrence [17]. The first phase occurs within 24-48 hours following the onset of dengue infection. Initially, the face, neck, and chest become flushed, and 3-6 days after the fever, a widespread macular rash develops, with islands of normal skin with petechial lesions. As the fever subsides, the rashes become accompanied by generalized pruritus and exfoliation of the skin [17].

On the other hand, studies have shown that dengue virus infection could cause widespread, non-blanching erythematous rashes while causing macules and patches of normal skin. Scientists have referred to this phenomenon as the “white islands in a sea of red” rash pattern. In this review, this type of rash appeared in 10.52% of patients with dengue virus infection. These abnormalities are often observable during defervescence and gradually resolve within about one week. According to recent scientific findings, multiple factors contribute to the emergence of these manifestations, including dengue virus replication in skin-resident immune cells (like Langerhans

cells), primary cutaneous infection, and complex host-pathogen interactions [8]. The appearance of the "white islands in a sea of red" rash has been suggested as a useful diagnostic sign, potentially indicating hyper-permeable capillaries and fluid leakage [24, 25]. Additionally, this characteristic rash is often regarded as a hallmark of dengue defervescence, which could make it a helpful marker for distinguishing dengue virus infection from other febrile illnesses with similar presentations.

Another clinical symptom worth noting is the observation of skin hyperpigmentation, which was prevalent among Black/African American patients following the administration of immunomodulatory drugs. Studies have indicated that hyperpigmentation is 11.6 times more likely to occur in Black/African American cases compared to other ethnicities.

These pigmentary changes, reported primarily in the context of exposure to immunomodulatory drugs, typically develop early in the course of treatment and often persist long-term, even after medication discontinuation [26]. According to this review, hyperpigmented lesions were observed in a Colombian patient with dengue fever infection. Furthermore, a pooled global prevalence of 2.5% has been reported for dengue and chikungunya coinfection [27]. Hyperpigmentation observed in chikungunya has been attributed to increased intra-epidermal melanin, which could be dispersed or retained following the viral infection. Some researchers have proposed that chikungunya-related hyperpigmentation may be a form of post-inflammatory hyperpigmentation. This condition could be exacerbated by exposure to ultraviolet (UV) radiation, which aligns with the observation that facial lesions are most common, as the face is frequently exposed to sunlight [13, 28]. Sangal et al. (2024) further supported the association between dengue fever and chikungunya-like signs and hyperpigmented lesions [29].

In a systematic review and meta-analysis study conducted by Kharwadkar and Herath (2024), fever, headache, myalgia, chills, and arthralgia were reported as the most common symptoms of dengue cases (97.45,81.62, 74.20, 65.29, and 57.47%, respectively) [30]. Similarly, in the present study, fever was the most commonly reported clinical symptom in dengue virus-infected patients with skin manifestations.

Among laboratory parameters, thrombocytopenia was the most common laboratory abnormality reported in patients with dengue virus infection. In line with this finding, Adaneh and Getawa (2021) investigated coagulation abnormalities in dengue virus infection in their meta-analysis and discovered that the overall prevalence of thrombocytopenia in dengue virus-infected cases was 70.29% [31]. Researchers have suggested that thrombocytopenia could play a vital role in the severity of dengue virus infection. According to their theory, dengue virus could affect bone marrow cells, leading to the inhibition of hematopoietic cell function.

Moreover, scientists have reported that most point-of-care diagnostic methods for detecting non-structural protein 1 (NS1) antigen do not provide acceptable levels of sensitivity, particularly in patients with secondary dengue infections. However, the interpretation of available serological tests could be challenging due to their complexity. In areas where multiple flaviviruses co-circulate, cross-reaction with immunoglobulin G (IgG) complicates the interpretation of serological tests [32].

The findings indicated that in patients with skin manifestations caused by dengue infection, virus identification was primarily done through serological tests. Clinicians prefer to use serological tests to diagnose dengue virus infection, as these assays are easier to

use compared to cell culture and RNA detection techniques. Scientific reports show distinct patterns of antibody responses to primary or secondary dengue infections. In primary infections, IgM could be detected after 5 days, while IgG could be traced within 10-15 days. In secondary infections, IgM may be detectable earlier but at lower titers compared to primary infections, while IgG is already present and increases rapidly [33].

This study had several limitations that should be acknowledged. First, the most significant limitation was the geographical focus of the included prevalence studies, which were mainly from Asia (specifically India and Pakistan), with one study from France. Although the analysis of case reports spanned 13 countries across three continents, the pooled prevalence estimates were heavily influenced by data from a single region. This limits the global generalizability of the findings, as genetic, environmental, and immunological factors influencing dengue presentation may vary across different populations and endemic regions. Consequently, the pooled prevalence estimates of 63.2% may not accurately reflect the true global epidemiology.

Additionally, differences in diagnostic assays and testing protocols (e.g., NS1 antigen tests, RT-PCR sensitivity, and serological cross-reactivity) limit the comparability of prevalence estimates across studies.

Second, quantitative data pooling from case reports and case series is inherently susceptible to reporting bias.

These publications typically document severe, unusual, or diagnostically challenging presentations and thus are not representative of the broader dengue patient population. Therefore, the frequencies of specific manifestations derived from these sources (e.g., rash types) should be interpreted as a descriptive illustration of the possible clinical spectrum rather than as generalizable prevalence estimates.

Third, as noted in the descriptive analysis, some cases were diagnosed based on clinical and laboratory parameters without definitive molecular or serological confirmation. This introduces a potential for misclassification bias, where non-dengue illnesses with similar presentations could have been included, possibly leading to an overestimation of the frequency of skin manifestations attributed to dengue.

Fourth, a significant gap in our analysis is the lack of data on dengue virus serotypes. The included studies did not systematically report this information, preventing a serotype-specific analysis. This is a crucial limitation because different serotypes (DENV-1 to DENV-4) are known to vary in virulence and could manifest with distinct clinical severity and rash patterns.

Finally, as noted in the discussion, the high statistical heterogeneity (I^2 = 84.83%) observed among the prevalence studies indicates substantial underlying variability, likely due to differences in diagnostic criteria, study design, and population characteristics, further cautioning against over-interpreting a single summary estimate.

Future multi-regional, prospective studies with standardized diagnostic and reporting protocols are needed to establish a truly global and representative understanding of the dermatological spectrum of dengue infection.

Conclusion

This study underscores the importance of recognizing skin manifestations as a significant clinical feature of dengue virus infection, which could aid in early diagnosis and management. However, the limited number of studies and geographical disparities in reports suggest the need for further research, particularly in underrepresented regions, to better

understand the global epidemiology and clinical spectrum of dengue-related skin manifestations.

Abbreviations:
DHF: Dengue hemorrhagic fever
DSS: Dengue shock syndrome
HAV: Hepatitis A virus
PCR: Polymerase chain reaction
NS: Non-structural protein
ELISA: Enzyme-Linked Immunosorbent Assay
NS1: Nonstructural protein 1
HI: Hemagglutination inhibition
COVID-19: Coronavirus disease 2019

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